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April 2024

Eye to the future: is the proposed EU General Pharmaceutical Legislation ready to support pharmaceutical innovation?

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Abbreviations

Abbreviation	Explanation
AI	Artificial Intelligence
AMR	Antimicrobial Resistance
ATMP	Advanced Therapy Medicinal Product
CAT	Committee on Advanced Therapies
CBG-MEB	College ter Beoordeling van Geneesmiddelen (Medicines Evaluation Board)
CHM	Commission on Human Medicine (UK)
CHMP	Committee for Medicinal Products for Human Use
COMP	Committee on Orphan Medicinal Products
DCM	Decentralised Manufacturing
EAHP	European Association of Hospital Pharmacists
EC	European Commission
ECJ	European Court of Justice
EMA	European Medicines Agency
EU	European Union
EUA	Emergency Use Authorisation
FDA	US Food and Drug Administration
GDP	Good Distribution Practice
GMP	Good Manufacturing Practice
HE	Hospital Exemption
HMA	Heads of Medicines Agencies
HUMN	High Unmet Medical Needs
HTA	Health Technology Assessment
IGJ	Health and Youth Care Inspectorate
IND	Investigational New Drug
MA	Marketing Authorisation
MAH	Marketing Authorisation Holder
MHRA	UK Medicines and Healthcare products Regulatory Agency

Ministry of VWS	Ministry of Health, Welfare and Sports
ML	Machine Learning
NCA	National Competent Authority
NHS	National Health Service
PDCO	Paediatric Committee
PIP	Paediatric Investigation Plan
PRAC	Pharmacovigilance Risk Assessment Committee
PRIME	PRIority Medicines scheme
RCT	Randomised Controlled Trial
RWD	Real World Data
RWE	Real World Evidence
SAWP	Scientific Advice Working Party
SME	Small and Medium-sized Enterprises
SoHO	Substances of Human Origin
UK	United Kingdom
UMN	Unmet Medical Needs
US	United States
ZonMw	Netherlands Organisation for Health Research and Development

Management summary

Background

In April 2023, the European Commission (EC) published legislative proposals for the revision of the European Union (EU) General Pharmaceutical Legislation. The revision would merge various pieces of legislation into one Directive and one Regulation, simplifying and replacing existing legislation. Purpose of the revised legislation is to (1) ensure that all patients throughout the EU have prompt and equitable access to safe, effective, and affordable pharmaceuticals, (2) maintain an environment that is supportive of research, development, and production of medicines in Europe, fostering innovation and competitiveness, (3) significantly reduce administrative burdens and authorisation application times, (4) guarantee a consistent supply of medicines to patients, regardless of their location within the EU, (5) address critical issues such as antimicrobial resistance (AMR) and the presence of pharmaceuticals in the environment through a comprehensive One Health approach and (6) promote the environmental sustainability of medicines. Member States have been given time to evaluate the proposals and measures contained therein. Negotiations between Member States on these proposals have started in the first half of 2024.

The Dutch Ministry of Health, Welfare and Sports (Ministry of VWS) has requested a Quickscan of the proposals to assess whether the draft EU General Pharmaceutical Legislation is fit for purpose to assess innovative medicines for marketing authorisation, and whether there are possibilities to further revise the system for a positive impact on innovation and access to medicine in Europe and the Netherlands. The focus of the Quickscan has been on the regulatory aspects for authorisation, i.e. the legal and technical framework for the assessment of new medicines needed to grant marketing authorisation. Other aspects of the legislation, in particular those concerning regulatory incentives, were outside of the scope and are being looked at in a separate process.

Methodology

The Quickscan started with a 'horizon scan' of trends in pharmaceutical innovation and their (future) interaction with the regulatory framework for assessment and authorisation. This process was informed by a literature review and stakeholder interviews. Stakeholders included national competent authorities, pharmaceutical product developers (including large companies, small and medium-size enterprises and academic institutes), technology transfer offices, research funders, patient federations, academic experts and health professionals.

From the analysis of interview data, five key areas in the legislation were identified where changes have been proposed that may impact innovation and access to medicines and that were felt to merit further attention by the Dutch government in the negotiation process. These key issues were then discussed with stakeholders in a series of workshops, supported by additional desk research, to explore potential amendments to the proposals or clarify areas of concern.

Running in parallel, four case reports were prepared of the regulatory frameworks in other jurisdictions (US, UK, Singapore, China). Findings from these have been used as illustrations and potential lessons for the development of the EU framework.

Findings

Advancements in, among others, biomedical science, data analysis methods, and manufacturing techniques are reshaping the landscape of pharmaceutical care. Whilst some developments can be readily absorbed by the existing regulatory system, others may stretch its limits. The major changes in pharmaceutical development can be seen in the context of three macro-trends: personalised medicine, data-driven drug discovery and point-of-care manufacturing. These trends are expected to bring important changes to the way in which medicines are developed, produced and administered to patients. It is important that the regulatory framework is properly equipped to enable innovative medicines to move through all the regulatory processes with sufficient ease and speed, whilst maintaining the high standards of quality, safety and efficacy set by the current system.

Building further from these (and other) trends, interviewees identified possible bottlenecks in various areas of the proposed legislation. In consultation with the client and the guidance committee supporting this Quickscan, it was agreed to focus the remainder of the Quickscan on the following five areas:

- Regulatory acceptance of new ways to generate (clinical) evidence;
- Derogations from the marketing and/or manufacturing authorisation;
- Restructuring of the EMA Scientific Committees;
- Support for non-commercial pharmaceutical developers;
- Drug repurposing.

1. *Regulatory acceptance of new ways for generating evidence*

The trend towards personalised medicine, aided by advances in data analytics, means that the traditional route of collecting clinical evidence needed for regulatory assessment through randomised controlled trials is no longer always feasible or even appropriate. This requires developers and regulators to find new ways of generating the evidence that is needed to demonstrate that a medicine is safe and effective for the specific patients for whom it is intended. This includes, for instance, the use of Real-World Data (RWD) and Real-World Evidence (RWE) in regulatory decision-making, potentially supported by novel data analytics techniques using Artificial Intelligence (AI).

To find the appropriate balance between high standards of evidence and timely access to innovative medicines, several measures have already been introduced. The conditional marketing authorisation route was adopted through legislation and has been in use since 2006. The European Medicines Agency (EMA) has piloted adaptive pathways for medicines in areas of high unmet need. The Data Analysis and Real-World Interrogation Network (DARWIN EU) was set up to provide high-quality, validated real-world data and support regulatory decision-making. The proposed legislation now adds the concept of "regulatory sandboxes" and provides new instructions on adapted dossier requirements. Regulatory sandboxes are to provide a structured context for experimentation, with close coordination between regulators and developers. The concept has been cautiously welcomed but many questions remain concerning its exact focus and implementation, as well as how experiences derived from it will be embedded into the regulatory framework. It is therefore recommended that the Ministry of VWS supports the introduction of regulatory sandboxes but encourages the EMA and Commission to further develop it through guidance and implementing acts. The EMA should furthermore be requested to engage with regulators and developers to clarify the concept and identify suitable use cases.

Through the proposals, the Commission is also seeking to promote the principles of replacement, reduction and refinement of animal testing in pharmaceutical research and development. Implementation of these principles in practice, however, is likely to require further collaboration between the EMA, the research community and product developers to encourage the validation of new models that is needed for their regulatory acceptance.

Recommendations in this area are: (1) *Developing guidance on the sandbox concept and identifying relevant 'use cases'* and (2) *Assess need for further action to encourage use and acceptance of new models to support replacement, reduction and refinement of animal testing in pharmaceutical product development.*

2. *Derogations from the marketing and/or manufacturing authorisation*

Pharmacy preparation refers to a situation wherein a medicine is produced directly by a pharmacist rather than sourced from a licensed pharmaceutical wholesaler/distributor. It is typically done in situations where there is no suitable licensed medicine, for instance because a patient needs a different dosage or formulation than that which is commercially available or, in nuclear medicine, because of the short half-life of many isotopes. In the new legislative proposals, the basic conditions for the use of pharmacy preparations have remained the same, but a clause has been added to specify that magistral formulation may be used also to prepare products in advance "on the basis of the estimated medical prescriptions within that hospital for the following seven days" in "duly justified cases". Industry has voiced concerns that broadening of the scope for preparing magistral formulations could open the door for more widespread use of pharmacy preparations, or could reduce the quality of medicine production, although the current amendment itself is unlikely to have that effect. The proposed legislation does not lift the restriction that pharmacy preparations may be provided only to the patients of the preparing pharmacy and not be distributed to other pharmacies. This restriction is known to limit patient access to medicines as not all pharmacies have the capacity to prepare. An amendment to the legislation to allow distribution under certain conditions, such as the absence of licensed alternatives, would provide the legal basis sought by the Dutch government to allow distribution of pharmacy preparations.

A so-called *Hospital Exemption (HE)* exempts ATMPs from the need for a marketing authorisation. Currently, a HE license can be granted by the competent authority of a Member State if the product is prepared on a non-routine basis according to specific quality standards, is used within the same Member State in a hospital under the exclusive professional responsibility of a medical practitioner and complies with an individual medical prescription. Since the development of ATMPs will grow in importance, new treatments could increasingly be produced under a HE license. This gives rise to questions about quality assurance (of production) and standardisation, evidence generation (on safety and efficacy) and possible market distortion with a potential disincentive for industry to invest in the development of ATMPs. Additionally, despite the framework being provided by an EU Regulation, there is substantial variation between Member States on its interpretation and application. To address some of these issues, the proposed legislation maintains the HE in much the same form but introduces further rules with regards to notification, quality standards (e.g. manufacturing done in accordance with quality standards equivalent to GMP requirements) and data collection.

The expected increase in the use of the HE route may also contribute to uneven access to innovative ATMPs across the EU, as the capacity to produce ATMPs in a pharmacy or hospital setting is not present everywhere in equal measure. Yet, the legislation prohibits production of medicines under a HE license for treatment of patients in another Member State. Allowing for

parallel distribution of medicines produced under a HE license to other Member States would lead to more equitable access to treatment between Member States. At the same time, it is important that such distribution is tightly regulated to protect patient safety whilst maintaining a fair and competitive market for ATMPs.

None of the jurisdictions considered in this Quickscan appears to have a dedicated framework in place for allowing the production and supply of ATMPs without a marketing authorisation license. Special measures do exist, however, for the use of investigational medicines, including ATMPs. In the UK, the MHRA is introducing a one-of-a-kind framework to allow the manufacture of innovative medicines at the point of care to ensure the supply to patients through clinical trial studies to marketing authorisation.

The general trend towards more personalised medicines is driving pharmaceutical manufacturing away from large-scale production to smaller batch manufacturing close to the patient, including with the aid of new techniques such as 3-dimensional printing. Under the current EU legislation, all of these locations would require their own manufacturing authorisation and GMP certification, registration in the marketing authorisation dossier and would be subject to inspections. This could increase the regulatory burden to an unsustainable level. In 2017, special guidelines on GMP were introduced that include guidance on the use of 'decentralised sites' for manufacturing of ATMPs. The legislative proposal for a new Directive now extends this concept of decentralised manufacturing to other medicines provided the product is covered by a marketing authorisation and decentralised sites fall under the responsibility of a qualified central site. Similar issues concerning quality assurance and standardisation of production as seen with HE products apply in the context of decentralised manufacturing, but additional questions have also been raised regarding distribution of responsibilities and liability involving new, and as yet largely untested, technologies. Implementing legislation covering such issues has not yet been presented.

Recommendations in this area are: (3) *Create an EU-wide legal basis for distribution of pharmacy preparations between pharmacies;* (4) *Further increase transparency on application of the HE framework across Member States;* (5) *Protect the ability of Member States to set national rules and conditions concerning the application of the HE framework* (6) *Permit the (conditional) parallel distribution of products produced under a hospital exemption within the EU;* (7) *Encourage the use of conventional regulatory pathways over the HE route;* and (8) *Monitor the development of implementing legislation and evaluate experiences with DCM.*

3. Restructuring of EMA scientific committees

The regulatory assessment of medicines is performed by the Committee for Medicinal Products for Human use (CHMP). The CHMP is made up of experts from each Member State and is assisted by various scientific advisory committees. Dedicated committees have been set up to support the assessment of the safety of medicines (Pharmacovigilance Risk Assessment Committee, PRAC), orphan medicines (Committee for Orphan Medicinal Products, COMP), medicines used to treat children (Paediatric Committee, PDCO) and for ATMPs (Committee on Advanced Therapies, CAT). The Commission is seeking to simplify the current structure, improve efficiency and reduce administrative costs. It is hereto proposing to replace the COMP, PDCO and CAT with working parties. These working parties will be made up of selected experts and support the CHMP but will no longer have formal decision-making powers of their own. Among stakeholders in the Netherlands the rationale for this restructuring is not widely recognised and

concerns exist that it will ultimately lead to loss of important expertise within the EMA. This loss could, in turn, negatively affect the EMA's ability to deal with innovations. It is unclear whether the working parties would be proactively involved in development of guidance and strategy in their areas of expertise to the same extent the committees currently are. The restructuring could also reduce opportunities for knowledge sharing and regulatory capacity development for National Competent Authorities. There is precedent from other jurisdictions where smaller committees and expert panels appear to be an effective way of providing the required expertise to make decisions related to the safety, quality, safety, and efficacy of medicines. However, whether such a structure would similarly be able to fulfil the needs of the EMA, the Member States and pharmaceutical developers is as yet unclear. This proposal therefore merits further clarification of expected responsibilities and operational details.

Recommendations in this area are: (9) *Withhold support for the proposed restructuring of EMA Scientific Committees until assurances are in place that the new structure can adequately take over its responsibilities;* (10) *Request an intermediate evaluation of the new organisational structure (if adopted);* (11) *Ensure knowledge sharing and regulatory capacity development within and between NCAs.*

4. Support for non-commercial operators

A significant share of medical research and development is done by academia, research institutes and not-for-profit organisations. Such non-commercial entities tend to have less experience with the clinical development stages and with the regulatory processes needed to get to a marketing authorisation. To support pharmaceutical product developers, the EMA offers (against a fee, with fee waivers and reductions available) scientific advice and protocol assistance to give guidance on the best methods and study designs that are required to generate the evidence used in the scientific evaluation for marketing authorisation. This advice is considered useful, but there is a sense that the nature of the advice is still too formal for inexperienced developers to be optimal. To improve this, it is proposed to set up a dedicated 'Academia Office' to support not-for-profit entities with early scientific advice. Its tasks will be similar to that of the existing SME Office. Among stakeholders, closer interaction between the EMA and inexperienced developers is welcomed but the distinction that would be drawn between non-profit entities and SMEs on the other hand raises questions about potential distortion of competition and unfair advantages for academic developers. In practice, this distinction may prove difficult to make. It is therefore uncertain whether the creation of a dedicated Academia Office is preferable over an expansion of the services of the existing SME Office to a wider range of developers. This requires further discussion and potentially a broader consultation of stakeholders to assess the risks and benefits of different options.

Recommendation in this area is: (12) *Request clarification on the rationale behind the Academia Office and on how it is envisaged to function.*

5. Drug repurposing

The repurposing of existing medicines for new indications can have positive impacts on both the availability of treatments and on the affordability of healthcare. Exploration of existing data sets, aided by the use of AI, may allow for the identification of new treatment populations without the need to extensively repeat all preclinical and clinical research, and could therefore be a way of developing new treatments at greater speed and reduced costs.

At present, there are important hurdles to the use of repurposed medicines in clinical practice, stemming from the fact that new indications are frequently not added to the marketing authorisation. The proposed legislation wants to stimulate drug repurposing by bringing new indications for repurposed medicines 'on-label'. It will hereto be offering additional data protection for registration of a new indication and provide the possibility for not-for-profit entities to submit evidence to the EMA to support a registration. The proposed change would make it mandatory for marketing authorisation holders of the product concerned to file a submission for a variation to the authorisation following a positive opinion by the EMA. Whilst the intent to promote registration of new indications is considered good, there are concerns that the mandatory registration of a variation could lead to market withdrawals if the costs and risks associated with the variation do not outweigh the benefits to the authorisation holder. It is therefore feared the measure would have unintended consequences and hinder rather than stimulate access to medicines. There are also questions concerning the legality of imposing registration of a new indication on marketing authorisation holders based on data they did not generate or submit. Several alternatives were explored with stakeholders, though each likely to encounter both practical and legal difficulties. It is therefore recommended that the mandatory filing for a variation is removed from the proposal and alternative means are sought to stimulate and support repurposing, both in a European and in a national context.

Recommendations for this area are: (13) *Remove the requirements for mandatory registration of new indications (Regulation Art. 48(2));* (14) *Encourage additional actions to support repurposing and registration of new indications;* (15) *Consider the need for changes in the national policies and framework to support reimbursement of repurposed medicines.*

Conclusions

With these proposals for revision of the EU general pharmaceutical legislation, the Commission has shown significant ambition and a readiness to introduce rather substantial changes into the legislation. It opens up significantly greater space for innovations. Important new concepts introduced in the proposals to this effect include the use of regulatory sandboxes and adaptive frameworks, a greater place for RWD/RWE in regulatory decision-making and decentralised manufacturing. These additions are highly relevant in ensuring that innovations in, for instance, the development of ATMPs and personalised medicines can navigate the regulatory processes more predictably.

Many of the introduced measures have deliberately been formulated rather open and technology-agnostic. This has the benefit that the legislation will, at least in theory, be able to accommodate a broad range of innovations. At the same time, it leaves a degree of uncertainty among regulators and developers as to when and how some of these new measures may be used. Such uncertainty could lead to reluctance to use the full scope of the opportunities offered given the high costs and risks involved in pharmaceutical development. For the measures to be effective, active and open dialogue between developers and regulators is needed to provide sufficient predictability of how the framework would be applied.

Access to innovative medicines depends on a number of factors, starting with the efficiency with which regulatory process for assessment and authorisation are conducted. The proposals aim to accelerate the approval of innovative medicines through administrative simplification and improved procedural efficiency. The proposed reduction in the review timelines for the application for a marketing authorisation may be considered an important step in this direction. The proposed restructuring of the EMA scientific committees, however, raises

concerns that this administrative simplification may come at a cost to the system in terms of loss of expertise and, consequently, less adaptive ability to future innovation.

The revised legislation is seeking to introduce some changes that would affect the ability of patients to access medicines through alternative regulatory pathways, namely pharmacy preparations and the hospital exemption for ATMPs. The proposals maintain the basic criteria under which these routes may be used but introduces new rules that are intended to improve oversight and protect quality standards. The legislation also introduces the concept of decentralised manufacturing to accommodate such technological developments as 3D-printing of medicines. The proposals, however, could benefit from inclusion of additional rules that would permit, under strict conditions, distribution of pharmacy preparations and hospital exemption products to places without the required manufacturing capabilities. Measures and conditions could simultaneously be introduced that would encourage producers of such products to seek registration and follow more conventional regulatory routes.

The challenges facing the EU regulatory system are by no means unique; other jurisdictions are similarly exploring how best to ensure their frameworks are kept up-to-date and able to deal with innovations. There is already close collaboration between, for instance, the US FDA, the UK's MHRA and the EMA, to help ensure that mutual learnings will inform the future development of additional guidance and implementing legislation. The current proposals for the new EU general pharmaceutical legislation appear to already offer much space for innovative types of medicines and methodologies, with sufficient openness to potentially accommodate as yet unknown scientific advances. Ultimately, however, the success of the legislation may depend as much, or more, on the capacity of the regulatory system to properly apply the space for innovation the new legislation provides as it does on the legal texts itself.

Managementsamenvatting

Achtergrond

In april 2023 heeft de Europese Commissie (EC) wetgevingsvoorstellen voor de herziening van de Algemene Farmaceutische Wetgeving van de Europese Unie (EU) gepubliceerd. Met de beoogde herziening worden verschillende stukken wetgeving samengevoegd tot één richtlijn en één verordening, waardoor de bestaande wetgeving wordt vereenvoudigd en vervangen. Doelen van de herziene wetgeving zijn (1) ervoor te zorgen dat alle patiënten in de hele EU snelle en eerlijke toegang hebben tot veilige, effectieve en betaalbare geneesmiddelen, (2) een klimaat te handhaven dat onderzoek, ontwikkeling en productie van geneesmiddelen in Europa ondersteunt en innovatie en concurrentievermogen bevordert, (3) de administratieve lasten en de duur voor de aanvraag van een handelsvergunning aanzienlijk te verminderen, (4) een consistente levering van geneesmiddelen aan patiënten garanderen, ongeacht waar deze zich in de EU bevinden, (5) essentiële kwesties zoals antimicrobiële resistentie en de aanwezigheid van geneesmiddelen in het milieu aan te pakken door middel van een alomvattende "One Health"-aanpak en (6) de duurzaamheid van geneesmiddelen (op milieugebied) te bevorderen. De lidstaten hebben de tijd gekregen om de daarin vervatte voorstellen en maatregelen te evalueren. De onderhandelingen tussen de lidstaten over deze voorstellen zijn in de eerste helft van 2024 van start gegaan.

Het Nederlandse Ministerie van Volksgezondheid, Welzijn en Sport (VWS) heeft Technopolis gevraagd een Quickscan uit te voeren van de voorstellen van de Commissie om te beoordelen of het ontwerp van de EU Algemene Farmaceutische Wetgeving geschikt is om innovatieve geneesmiddelen te beoordelen voor een handelsvergunning en of er mogelijkheden zijn om het systeem verder te herzien om een (groter) positief effect te krijgen op innovatie en toegang tot geneesmiddelen in Europa en Nederland. De focus van de Quickscan lag op de regelgevingsaspecten voor toelating, d.w.z. het wettelijke en technische kader voor de beoordeling van nieuwe geneesmiddelen dat nodig is voor het verlenen van een handelsvergunning. Andere aspecten van de wetgeving, met name die betrekking hebben op innovatieprikkels, vielen buiten de reikwijdte van de Quickscan en worden in een afzonderlijk proces bekeken.

Methodologie

Binnen de Quickscan is allereerst, op basis van literatuurstudie en interviews met belanghebbenden, een 'horizon scan' uitgevoerd naar trends in farmaceutische innovatie en hun mogelijke (toekomstige) interactie met het regelgevend kader voor beoordeling en toelating. De geïnterviewden partijen waren (vertegenwoordigers van) de nationale bevoegde instanties, ontwikkelaars van farmaceutische producten (kleine, middelgrote en grote bedrijven en academische instellingen), technologie transfer bureaus van universiteiten, onderzoeksfinanciers, patiënten federaties, academische deskundigen en professionals uit de gezondheidszorg.

Uit de interviews kwamen vijf belangrijke gebieden in de wetgeving naar voren waarvoor wijzigingen zijn voorgesteld die van invloed kunnen zijn op innovatie en toegang tot geneesmiddelen, en waar, volgens de respondenten, de Nederlandse regering nadere aandacht zou moeten besteden in het onderhandelingsproces. Deze gebieden zijn vervolgens nader besproken met belanghebbenden in een reeks workshops en aangevuld met verder literatuuronderzoek, om mogelijke alternatieven voor de voorstellen te onderzoeken of punten van zorg te verduidelijken.

Parallel hieraan zijn de regelgevingskaders in andere jurisdicties (VS, VK, Singapore, China) bestudeerd. De bevindingen hiervan zijn ter illustratie en als mogelijke inspiratie voor de verdere uitwerking van het EU-kader in de rapportage verwerkt.

Bevindingen

Vooruitgang in onder andere de biomedische wetenschap, methoden voor gegevensanalyse en farmaceutische productietechnieken hebben grote invloed op het landschap van de farmaceutische zorg. Terwijl sommige ontwikkelingen gemakkelijk door het bestaande regelgevende systeem kunnen worden geabsorbeerd, zullen anderen wellicht de grenzen ervan oprekken. De belangrijkste farmaceutische ontwikkelingen kunnen worden gezien in de context van drie macrotrends: 'personalised medicine', datagestuurde ontdekking van geneesmiddelen en zogenaamde 'point-of-care' productie. Deze trends zullen naar verwachting belangrijke veranderingen teweegbrengen in de manier waarop geneesmiddelen worden ontwikkeld, geproduceerd en toegediend aan patiënten. Het is belangrijk dat het regelgevingskader voldoende is toegerust om innovatieve geneesmiddelen met voldoende gemak en snelheid door alle regelgevingsprocessen te laten gaan, terwijl de hoge kwaliteits-, veiligheids- en werkzaamheidsnormen van het huidige systeem gehandhaafd blijven.

Voortbouwend op deze (en andere) trends hebben de geïnterviewden mogelijke knelpunten van de voorgestelde wetgeving geïdentificeerd op verschillende gebieden. In overleg met de opdrachtgever en de begeleidingscommissie die deze Quickscan heeft ondersteund, is besloten om het resterende deel van de Quickscan specifiek te richten op de volgende vijf gebieden:

- Acceptatie van nieuwe manieren om (klinisch) bewijs te genereren;
- Uitzonderingen op de handels- en/of fabricagevergunning;
- Herstructurering van de wetenschappelijke comités van het EMA;
- Ondersteuning voor niet-commerciële farmaceutische ontwikkelaars;
- 'Drug repurposing' of herpositionering van bestaande geneesmiddelen.

1. *Acceptatie van nieuwe manieren om bewijs te genereren*:

'Personalised medicine' (gepersonaliseerde geneeskunde of precisiegeneeskunde) gaat om het toedienen van medicijnen op basis van een specifiek profiel van een patiënt. De traditionele route van het verzamelen van het benodigde klinisch bewijs van werking van medicijnen op basis van RCTs (Randomised Controlled Trials of gerandomiseerde gecontroleerde onderzoeken) is daardoor niet altijd meer haalbaar of geschikt. Hierdoor moeten ontwikkelaars en regelgevers nieuwe manieren vinden om het bewijs te genereren dat een geneesmiddel veilig en effectief is voor de specifieke patiënten voor wie het bedoeld is. Dit omvat bijvoorbeeld het gebruik van Real-World Data (RWD) en Real-World Evidence (RWE) bij regelgevende besluitvorming, mogelijk ondersteund door nieuwe technieken voor gegevensanalyse met behulp van kunstmatige intelligentie (AI).

Verschillende maatregelen zijn al ingevoerd om te helpen de juiste balans te vinden tussen enerzijds voldoende bewijslast en anderzijds snelle toegang tot innovatieve geneesmiddelen. Zo is het sinds 2006 mogelijk om een middel in de handel te brengen op basis van een voorwaardelijke vergunning, waarbij aanvullende gegevens dienen te worden verzameld na de initiële markttoelating. Daarnaast heeft het Europees Geneesmiddelenbureau (EMA) proefprojecten uitgevoerd met adaptieve trajecten voor geneesmiddelen in gebieden met

een grote onvervulde behoeften ('high unmet needs'). Het *Data Analysis and Real-World Interrogation Network* (DARWIN EU) is opgezet om gevalideerde RWD van hoge kwaliteit te leveren en de besluitvorming over markttoelating te ondersteunen. De voorgestelde wetgeving voegt daar nu het concept van proeftuinen ("regulatory sandboxes ") aan toe en stelt nieuwe instructies voor aangepaste dossiervereisten voor. Deze proeftuinen moeten, in goede samenwerking tussen regelgevers en ontwikkelaars, een gestructureerde context bieden voor experimenten. Veldpartijen zijn gematigd optimistisch over het concept, al leven er nog veel vragen over de precieze focus en implementatie ervan, en over de manier waarop de opgedane ervaringen zullen worden ingebed in de wetgeving. Daarom wordt aanbevolen dat het ministerie van VWS de invoering van de proeftuinen in principe steunt, maar tegelijkertijd het EMA en de Commissie aanmoedigt om het concept verder te ontwikkelen door middel van richtlijnen en uitvoeringsbesluiten. De EMA moet daarnaast worden aangemoedigd om samen te werken met regelgevers en ontwikkelaars om het concept te verduidelijken en geschikte 'use cases' te identificeren.

Aanbevelingen op dit gebied zijn: (1) *Het ontwikkelen van een leidraad voor het 'regulatory sandbox' concept en het identificeren van relevante 'use cases'* en (2) *Het beoordelen van de behoefte aan verdere actie om het gebruik en de acceptatie van nieuwe modellen aan te moedigen ter ondersteuning van de vervanging, vermindering en verfijning van dierproeven.*

2. *Afwijkingen van de vergunning voor het in de handel brengen en/of de fabricage*:

Apotheekbereiding ('pharmacy preparation') verwijst naar een situatie waarin een apotheker zelf een geneesmiddel bereid in plaats van dit in te kopen bij een farmaceutische groothandel/distributeur. Dit gebeurt vooral in situaties waarin er geen geschikt geneesmiddel op de markt is, bijvoorbeeld omdat een patiënt een aangepaste dosering of formulering nodig heeft of, in de nucleaire geneeskunde, vanwege de korte halfwaardetijd van veel isotopen. In de nieuwe wetsvoorstellen zijn de basisvoorwaarden voor het gebruik van apotheekbereidingen hetzelfde gebleven, maar is er een clausule toegevoegd om te specificeren dat magistrale bereidingen ook mogen worden gebruikt om producten vooraf te bereiden "op basis van de geschatte recepten binnen dat ziekenhuis voor de volgende zeven dagen" in "gerechtvaardigde gevallen". De industrie heeft haar bezorgdheid geuit dat het vergroten van de ruimte voor magistrale bereidingen de deur open kan zetten voor een grootschaliger gebruik van apotheekbereidingen, of de kwaliteit van de medicijnproductie in gevaar zou kunnen brengen, hoewel. het niet aannemelijk lijkt dat de huidige wijziging dit effect zal hebben. De voorgestelde wetgeving heft immers de beperking niet op dat apotheekbereidingen alleen mogen worden verstrekt aan patiënten van de bereidende apotheek en niet mogen worden doorgeleverd aan andere apotheken. Het is bekend dat deze beperking de toegang van patiënten tot geneesmiddelen vermindert, omdat niet alle apotheken de capaciteit hebben om bereidingen te maken. Een wijziging van de wetgeving om doorlevering onder bepaalde voorwaarden toe te staan, zoals het ontbreken van erkende alternatieven, zou de door de Nederlandse regering gewenste rechtsgrondslag bieden om doorlevering van apotheekbereidingen toe te staan.

Voor geneesmiddelen voor geavanceerde therapieën (ATMPs) kan een vrijstelling van de handelsvergunning worden verleend in de vorm van een zogenaamde '*Hospital Exemption' (HE)*. Deze vrijstelling stelt een ziekenhuis in staat het middel in de eigen apotheek te bereiden. Momenteel kan een HE-vergunning worden verleend door de bevoegde instantie van een lidstaat als het product op niet-routinematige basis wordt bereid volgens vastgelegde

kwaliteitsnormen, binnen dezelfde lidstaat in een ziekenhuis wordt gebruikt onder de exclusieve professionele verantwoordelijkheid van een arts en op basis van een op naam gesteld recept. Aangezien de ontwikkeling van ATMP's steeds belangrijker zal worden, is het de verwachting dat nieuwe behandelingen steeds vaker onder een HE-licentie zullen worden geproduceerd. Dit roept vragen op over kwaliteitsborging (van de productie) en standaardisatie, het genereren van bewijs (over veiligheid en werkzaamheid) en mogelijke marktverstoring waarbij de industrie haar interesse zou kunnen verliezen om te investeren in de ontwikkeling van ATMP's. Bovendien bestaan er, ondanks het feit dat de wetgeving op EU-niveau is vastgesteld, aanzienlijke verschillen tussen de lidstaten wat betreft de interpretatie en toepassing ervan. Om enkele van deze problemen aan te pakken, handhaaft de voorgestelde wetgeving de HE weliswaar in vrijwel dezelfde vorm, maar worden verdere regels ingevoerd met betrekking tot kennisgeving, kwaliteitsnormen (bv. fabricage volgens kwaliteitsnormen die gelijkwaardig zijn aan de GMP-vereisten) en gegevensverzameling.

De verwachte toename van het gebruik van de HE-route zorgt mogelijk voor ongelijke toegang tot innovatieve ATMP's in de EU, aangezien de capaciteit om ATMP's te produceren in een apotheek of ziekenhuis niet overal in gelijke mate aanwezig is. Toch verbiedt de wetgeving de productie van geneesmiddelen met een HE-vergunning voor de behandeling van patiënten in een andere lidstaat. Indien parallelle distributie naar andere lidstaten van geneesmiddelen die onder een HE-vergunning zijn geproduceerd wel zou worden toegestaan, zou dit kunnen bijdragen aan een evenwichtigere toegang tot behandeling tussen de lidstaten. Tegelijkertijd is het belangrijk dat deze distributie strikt gereguleerd is om de veiligheid van patiënten te beschermen, en om een eerlijke en concurrerende markt voor ATMP's te behouden.

Geen van de nationale jurisdicties die in deze Quickscan zijn onderzocht, lijkt over een specifiek kader te beschikken om de productie en levering van ATMP's zonder vergunning voor het in de handel brengen toe te staan. Wel bestaan er speciale maatregelen voor het gebruik van geneesmiddelen voor onderzoek, waaronder ATMP's. Zo werkt in het Verenigd Koninkrijk de MHRA aan een specifiek kader om de productie van innovatieve geneesmiddelen op de plaats van zorg mogelijk te maken, zodat de levering aan patiënten via klinische studies tot aan de vergunning voor het in de handel brengen verzekerd is.

Meer algemeen zorgt de opkomst van gepersonaliseerde geneeskunde voor een verschuiving van grootschalige productie van geneesmiddelen naar productie in kleinere batches op locaties dichter bij de patiënt. Dit kan onder meer dankzij nieuwe technieken zoals 3D-printen. Onder de huidige EU-wetgeving zouden al deze locaties hun eigen fabricagevergunning en GMP-certificering nodig hebben, zouden ze moeten worden opgenomen in het dossier van de handelsvergunning en onderworpen worden aan inspecties. Dit zou de regeldruk tot een onhoudbaar niveau kunnen verhogen. In 2017 werden speciale GMP-richtlijnen geïntroduceerd met daarin, onder meer, instructies voor het gebruik van 'gedecentraliseerde locaties' voor de productie van ATMP's. Het wetgevingsvoorstel voor een nieuwe richtlijn breidt dit concept van gedecentraliseerde fabricage nu uit tot andere geneesmiddelen, mits voor het product een handelsvergunning is verleend en gedecentraliseerde locaties onder de verantwoordelijkheid van een gekwalificeerde centrale locatie vallen. Vergelijkbare kwesties met betrekking tot kwaliteitsborging en standaardisatie van de productie als bij HE-producten zijn van toepassing in de context van gedecentraliseerde fabricage, maar er zijn ook extra vragen gerezen over de verdeling van verantwoordelijkheden en aansprakelijkheid met betrekking tot nieuwe, en tot nu toe grotendeels ongetoetste, technologieën. Er is nog geen uitvoeringswetgeving met betrekking tot dergelijke kwesties ingediend.

De aanbevelingen op dit gebied zijn (3) *Creëer een EU-brede rechtsgrondslag voor de doorlevering van apotheekbereidingen;* (4) *Vergroot de transparantie over de toepassing van het HE-kader in alle lidstaten verder;* (5) *Bescherm de mogelijkheid van lidstaten om nationale regels en voorwaarden vast te stellen met betrekking tot de toepassing van het HE-kader* (6) *Sta de (voorwaardelijke) parallelle distributie binnen de EU toe van producten die zijn geproduceerd onder een ziekenhuisvrijstelling;* (7) *Stimuleer het gebruik van conventionele reguleringstrajecten in plaats van de HE-route;* en (8) *Monitor de ontwikkeling van uitvoeringswetgeving en evalueer ervaringen met gedecentraliseerde productie*.

3. Herstructurering van wetenschappelijke comités van EMA

De beoordeling van geneesmiddelen wordt uitgevoerd door de Commissie voor geneesmiddelen voor menselijk gebruik (CHMP). De CHMP bestaat uit experts uit elke lidstaat en wordt bijgestaan door verschillende wetenschappelijke adviescomités. Speciale comités zijn opgericht ter ondersteuning van de beoordeling van de veiligheid van geneesmiddelen (Risicobeoordelingscomité voor geneesmiddelenbewaking, PRAC), voor weesgeneesmiddelen (Comité voor weesgeneesmiddelen, COMP), voor geneesmiddelen voor pediatrisch gebruik (Pediatrisch Comité, PDCO) en voor ATMP's (Comité voor geavanceerde therapieën, CAT). De Commissie wil de huidige structuur vereenvoudigen, de efficiëntie verbeteren en de administratieve kosten terugdringen door drie van de comités (COMP, PDCO en CAT) te vervangen door werkgroepen. Deze werkgroepen zullen bestaan uit geselecteerde deskundigen, en zullen de CHMP ondersteunen maar zelf geen formele beslissingsbevoegdheid meer hebben. Belanghebbenden in Nederland herkennen de onderliggende motivatie hiertoe slechts in beperkte mate en zijn bezorgd dat de herstructurering uiteindelijk zal leiden tot verlies van belangrijke expertise binnen de EMA. Dit verlies zou op zijn beurt een negatieve uitwerking kunnen hebben op het vermogen van het EMA om op innovaties in te spelen. Het is momenteel nog onduidelijk of de werkgroepen actief betrokken zullen worden bij de ontwikkeling van richtlijnen en strategieën binnen hun domein, in dezelfde mate als de comités dat nu zijn, en hoe. De herstructurering zou ook de mogelijkheden voor het delen van kennis en de ontwikkeling van expertise binnen de nationale bevoegde instanties kunnen beperken. Er zijn precedenten uit andere nationale jurisdicties waar kleinere comités en deskundigenpanels een effectieve manier blijken te zijn om de vereiste deskundigheid te bieden voor het nemen van beslissingen over de veiligheid, kwaliteit, veiligheid en werkzaamheid van geneesmiddelen. Het is echter nog onduidelijk of een dergelijke structuur ook aan de behoeften van het EMA, van de lidstaten en van farmaceutische ontwikkelaars kan voldoen. Hiertoe zullen de verwachte verantwoordelijkheden en operationele details van dit voorstel eerst verder moeten worden uitgewerkt of toegelicht.

De aanbevelingen op dit gebied zijn (9) *Geen steun verlenen aan de voorgestelde herstructurering van de wetenschappelijke comités van het EMA totdat er garanties zijn dat de nieuwe structuur de verantwoordelijkheden adequaat kan overnemen;* (10) *Vragen om een tussentijdse evaluatie van de nieuwe organisatiestructuur (indien aangenomen);* (11) *Zorgen voor kennisdeling en ontwikkeling van expertise binnen en tussen nationale bevoegde instanties.*

4. Ondersteuning voor niet-commerciële exploitanten

Een aanzienlijk deel van het onderzoek dat leidt tot de ontwikkeling van nieuwe geneesmiddelen wordt uitgevoerd door academische instellingen, onderzoeksinstituten en non-profitorganisaties. Dergelijke niet-commerciële entiteiten hebben doorgaans minder ervaring met de klinische ontwikkelingsfasen en met de processen die nodig zijn om een handelsvergunning te verkrijgen. Om ontwikkelaars van farmaceutische producten te ondersteunen, biedt de EMA (tegen betaling, waarbij kortingen en vrijstellingen mogelijk zijn) wetenschappelijk advies en protocolassistentie omtrent de beste methoden en onderzoeksopzetten voor het verzamelen van de gegevens benodigd voor aanvraag van een handelsvergunning. Dit advies wordt over het algemeen als nuttig ervaren, maar de aard van het advies wordt toch vaak nog gezien als te formeel voor minder ervaren ontwikkelaars om optimaal te zijn. Om dit te verbeteren stelt de Commissie voor om een speciaal 'Academia Office' op te richten om non-profit organisaties te ondersteunen met vroegtijdig wetenschappelijk advies. De taken van dit bureau zullen vergelijkbaar zijn met die van het bestaande mkb-bureau. Onder belanghebbenden wordt een nauwere interactie tussen het EMA en minder ervaren ontwikkelaars toegejuicht, maar het onderscheid dat zou worden gemaakt tussen non-profitorganisaties en het mkb roept tevens vragen op over mogelijke concurrentieverstoring en oneerlijke voordelen voor academische ontwikkelaars. In de praktijk is dit onderscheid mogelijk moeilijk te maken Het is daarom onzeker of de oprichting van een specifiek academisch bureau te verkiezen is boven een uitbreiding van de diensten van het bestaande mkb-bureau tot een bredere doelgroep. Dit vereist verdere discussie en mogelijk een verdere raadpleging van belanghebbenden om de risico's en voordelen van verschillende opties te beoordelen.

Aanbeveling op dit gebied is: (12) *Verzoek om opheldering over de beweegredenen achter het Academia Office en over de manier waarop het zou moeten functioneren.*

5. Herpositionering van geneesmiddelen

Soms kunnen geneesmiddelen die al langer op de markt zijn ook worden gebruikt bij de behandeling van andere aandoeningen dan die waarvoor het middel in eerste instantie is ontwikkeld. Dit wordt wel geneesmiddel herpositionering, of ‘drug repurposing’, genoemd. Herpositionering van bestaande geneesmiddelen kan positief zijn voor zowel de beschikbaarheid van behandelingen als voor de betaalbaarheid van de gezondheidszorg doordat het traject van ontwikkeling en registratie aanzienlijk sneller kan worden doorlopen. Verkenning van bestaande datasets, geholpen door het gebruik van AI, kan de identificatie van nieuwe behandelingspopulaties mogelijk maken zonder dat al het preklinisch en klinisch onderzoek moet worden herhaald, en kan daarom een manier zijn om nieuwe behandelingen sneller en tegen lagere kosten te ontwikkelen.

Momenteel zijn er belangrijke belemmeringen in de praktijk voor de herpositionering van geneesmiddelen, die voortkomen uit het feit dat nieuwe indicaties vaak niet aan de bestaande handelsvergunning worden toegevoegd. De voorgestelde wetgeving wil herpositionering van geneesmiddelen stimuleren door nieuwe indicaties 'on-label' te brengen, dat wil zeggen: deze toe te voegen aan de handelsvergunning. De wetgeving zal extra gegevensbescherming bieden voor de registratie van een nieuwe indicatie en zal non-profitorganisaties de mogelijkheid bieden bewijsmateriaal bij het EMA in te dienen ter ondersteuning van een registratie. De voorgestelde wijziging zou houders van een handelsvergunning van het betrokken product verplichten een aanvraag in te dienen voor een wijziging van de vergunning na een positief advies van het EMA. Hoewel het de bedoeling

is om de registratie van nieuwe indicaties te bevorderen, bestaat de vrees dat deze verplichte registratie van een wijziging kan leiden tot het uit de handel nemen van producten als de kosten en risico's van de wijziging niet opwegen tegen de voordelen voor de vergunninghouder. Daarom wordt gevreesd dat de maatregel onbedoelde gevolgen zal hebben en de toegang tot geneesmiddelen eerder zal belemmeren dan stimuleren. Er zijn ook vragen over de rechtmatigheid van het opleggen van de registratie van een nieuwe indicatie aan houders van een handelsvergunning op basis van gegevens die zij niet hebben gegenereerd of ingediend. Samen met belanghebbenden zijn verschillende alternatieven verkend, die naar verwachting echter stuk voor stuk op praktische en juridische problemen zullen stuiten. Daarom wordt aanbevolen om de verplichte indiening van een wijziging uit het voorstel te schrappen en te zoeken naar alternatieve middelen om herpositionering te stimuleren en te ondersteunen, zowel in een Europese als in een nationale context.

Aanbevelingen op dit gebied zijn: (13) *Schrap de vereisten voor verplichte registratie van nieuwe indicaties (Verordening art. 48(2));* (14) *aanvullende acties aanmoedigen om herbestemming en registratie van nieuwe indicaties te ondersteunen;* (15) *Overweeg de noodzaak van wijzigingen in het nationale beleid en kader om de vergoeding van hergebruikte geneesmiddelen te ondersteunen.*

Conclusies

Met deze voorstellen voor de herziening van de algemene geneesmiddelenwetgeving van de EU heeft de Commissie blijk gegeven van aanzienlijke ambitie en van de bereidheid om vrij ingrijpende wijzigingen in de wetgeving aan te brengen. Er wordt aanzienlijk meer ruimte gecreëerd voor innovaties. Belangrijke nieuwe concepten die daartoe in de voorstellen zijn geïntroduceerd, zijn het gebruik van proeftuinen en adaptieve kaders, een grotere plaats voor RWD/RWE in de besluitvorming en gedecentraliseerde productie. Deze toevoegingen zijn van groot belang om ervoor te zorgen dat innovaties, in bijvoorbeeld de ontwikkeling van ATMP's en gepersonaliseerde geneesmiddelen, voorspelbaarder door de registratieprocedures kunnen navigeren.

Veel van de ingevoerde maatregelen zijn opzettelijk vrij open en technologieneutraal geformuleerd. Dit heeft als voordeel dat de wetgeving, althans in theorie, een breed scala aan innovaties kan verwerken. Tegelijkertijd zorgt het voor een zekere mate van onzekerheid bij regelgevers en ontwikkelaars over wanneer en hoe sommige van deze nieuwe maatregelen kunnen worden gebruikt. Deze onzekerheid zou kunnen leiden tot terughoudendheid om de geboden mogelijkheden volledig te benutten, gezien de hoge kosten en risico's die gepaard gaan met de ontwikkeling van geneesmiddelen. Willen de maatregelen effectief zijn, dan is een actieve en open dialoog tussen ontwikkelaars en regelgevers nodig om voldoende voorspelbaarheid te bieden over de manier waarop het kader zal worden toegepast.

De toegang tot innovatieve geneesmiddelen hangt af van een aantal factoren, te beginnen met de efficiëntie waarmee de procedures voor markttoelating worden uitgevoerd. De voorstellen zijn bedoeld om de goedkeuring van innovatieve geneesmiddelen te versnellen door administratieve vereenvoudiging en grotere efficiëntie van de procedures. De voorgestelde verkorting van de beoordelingstermijnen voor de aanvraag van een handelsvergunning kan als een belangrijke stap in deze richting worden beschouwd. De voorgestelde herstructurering van de wetenschappelijke comités van het EMA doet echter vrezen dat deze administratieve vereenvoudiging ten koste van het systeem zal gaan in

termen van verlies van deskundigheid en, bijgevolg, minder aanpassingsvermogen aan toekomstige innovatie.

De herziene wetgeving beoogt enkele veranderingen aan te brengen die van invloed zouden zijn op de mogelijkheid van patiënten om geneesmiddelen te verkrijgen via alternatieve routes, namelijk apotheekbereidingen en de ziekenhuisvrijstelling voor ATMP's. De voorstellen handhaven de basiscriteria waaronder deze routes kunnen worden gebruikt, maar introduceren nieuwe regels die bedoeld zijn om het toezicht te verbeteren en de kwaliteitsnormen te beschermen. De wetgeving introduceert ook het concept van gedecentraliseerde productie om rekening te houden met technologische ontwikkelingen zoals het 3D-printen van geneesmiddelen. De voorstellen zouden echter baat kunnen hebben bij de opname van aanvullende regels die, onder strikte voorwaarden, de doorlevering van apotheekbereidingen en HE-producten naar plaatsen zonder de vereiste productiecapaciteit toestaan. Tegelijkertijd kunnen maatregelen en voorwaarden worden ingevoerd die producenten van dergelijke producten aanmoedigen om registratie aan te vragen en conventionelere routes te volgen.

De uitdagingen waarmee het regelgevingssysteem van de EU wordt geconfronteerd zijn zeker niet uniek; andere landen onderzoeken op vergelijkbare wijze hoe ze hun kaders het best up-to-date kunnen houden en in staat kunnen stellen om te gaan met innovaties. Er wordt bijvoorbeeld al nauw samengewerkt tussen de EMA, de Amerikaanse FDA en de Britse MHRA om ervoor te zorgen dat ieders ervaring de toekomstige ontwikkeling van aanvullende richtlijnen en uitvoeringswetgeving informeert. De huidige voorstellen voor de nieuwe algemene EU-wetgeving op farmaceutisch gebied lijken al veel ruimte te bieden voor innovatieve geneesmiddelen en methoden, met voldoende openheid ruimte te bieden aan nog onbekende wetenschappelijke ontwikkelingen. Uiteindelijk zal het succes van de wetgeving echter evenveel, of zelfs meer, afhangen van het vermogen van het systeem om de ruimte voor innovatie die de nieuwe wetgeving biedt goed toe te passen dan van de wetteksten zelf.

1 Introduction

1.1 Background of the EU legislation

In the late 1950s and early 1960s the use of thalidomide[1] by pregnant women resulted in thousands of miscarriages and the birth of more than 10,000 children with severe deformities worldwide. This tragedy sparked the creation of marketing authorisation procedures for the assessment of the efficacy and safety of new medicines which came into force in Europe in 1965. Over the years, these procedures developed into a set of regulations, shaping a single European market for medicines, aimed at ensuring that all patients throughout the European Union (EU) have prompt and equitable access to safe, effective, and affordable medicines. With the advancement of the EU as a single market, a European Medicines Agency (EMA) was set up in 1995 to harmonise the work of existing national regulatory bodies, known as 'national competent authorities' (NCAs). The EMA plays a crucial role in the implementation of the EU regulatory system for pharmaceutical products. It is nowadays responsible for the regulatory assessment for authorisation of nearly all innovative medicines marketed in the EU.

The legislative backbone of today's EU regulatory system for medicines is formed by the EU General Pharmaceutical Legislation, which consists of a Directive (Directive 2001/83/EC) and a Regulation (Regulation (EC) No 726/2004). In part because of the strict EU regulatory framework[2], the costs for bringing pharmaceuticals to market have increased significantly. These costs have further limited the financial incentives to develop pharmaceuticals for smaller markets, such as that for rare diseases. In response, the EU has introduced the EU Orphan Regulation (Regulation (EC) No 141/2000)), which offers regulatory incentives to developers of designated orphan medicinal products. Additional legislation has also been adopted to encourage development of products for specific patient groups (i.e. the Regulation on medicinal products for paediatric use (EC) No 1901/2006) or to provide regulatory guidance for new types of products (i.e. the Regulation on Advanced Therapy Medicinal Products (EC) No 1394/2007). Together, these pieces of legislation form the EU regulatory system for pharmaceuticals[3].

Although the EU legislative framework has in places been amended to reflect changes in the field of medicinal product development, the EU General Pharmaceutical Legislation itself is 20 years old. A 2023 evaluation of this legislation, along with preceding evaluations of the EU Orphan and Paediatric Regulations, identified several areas for potential improvement to

[1] Thalidomide was initially sold as a medication to treat, among other things, nausea and vomiting in early pregnancy.

[2] It should be recognised that the United States and other jurisdictions similarly have put in place stringent regulatory frameworks that require demonstration of efficacy and safety before medicines are approved for marketing.

[3] Additional legislation exists concerning pharmacovigilance (Regulation (EU) No 1235/2010 and Directive 2010/84/EU), conditional marketing authorisations (Regulation (EU) No 507/2006), protection of the integrity of the supply chain (Directive 2011/62/EU, 'Falsified Medicines Directive'), variations to the terms of marketing authorisation (Regulation (EC) No 1234/2008), clinical trials (Regulation (EU) No 536/2014), colouring matters in medicinal products (Directive 2009/35/EC) and manufacturing of medicines (Regulation (EU) No 1252/2014 and Directive (EU) 2017/1572, 'Good Manufacturing Practice Directive'). Implementing and delegated acts further support the legislative framework.

further direct innovation and support access to medicines[4,5,6,7,8]. The legislative framework was therefore deemed in need of revision to ensure that it is made future-proof and able to accommodate future innovations and scientific developments. In April 2023, the European Commission (EC) published legislative proposals to revise the EU General Pharmaceutical Legislation and merge various pieces of legislation into one new Directive and one new Regulation, simplifying and replacing the existing legislation[9]. The new Directive would contain all the requirements for authorisation, monitoring, labelling and regulatory protection, placing on the market and other regulatory procedures for all medicines authorised at EU and national level. The Regulation would set specific rules (on top of the ones in the Directive) for medicines authorised at EU level, in particular the most innovative ones. It would furthermore set the rules on coordinated management of critical shortages and security of supply of critical medicines, as well as rules governing the EMA.

This proposed legislation has several key objectives. First and foremost, it aims to strengthen a single market for medicines, ensuring that all patients throughout the EU have prompt and equitable access to safe, effective, and affordable pharmaceuticals. Additionally, it strives to maintain an environment that is supportive of research, development, and production of medicines in Europe, fostering innovation and competitiveness. To streamline processes and expedite access to medicines, the legislation aims to significantly reduce administrative burdens and authorisation times. It also focuses on enhancing availability and guaranteeing a consistent supply of medicines to patients, regardless of their location within the EU. Furthermore, the legislation addresses critical issues such as antimicrobial resistance (AMR) and the presence of pharmaceuticals in the environment through a comprehensive One Health approach. Finally, it seeks to promote the environmental sustainability of medicines, aligning with broader sustainability goals.

The Commission hopes that the new legislation will be sufficiently future-proof and sustainable to accommodate not only the current state-of-the-art of drug development, but also innovations resulting from technologies that today are only in the early stages of development or even non-existent. According to the European Commission, the new legislation promotes innovation in a number of ways:

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[4] European Commission (2023). Commission Staff Working Document: Impact Assessment Report SWD(2023) 192 final. Available at: https://health.ec.europa.eu/document/download/027a1084-0540-4bb6-b669-aa6cf3887684_en?filename=swd_2023_192_1_ia_en.pdf.

[5] Varnai P, Davé A, Simmonds P, et al. (2023) *Study in support of the evaluation and impact assessment of the EU general pharmaceuticals legislation – Impact assessment report*, European Commission, Directorate-General for Health and Food Safety, Publications Office of the European Union. https://data.europa.eu/doi/10.2875/00611

[6] Commission Staff Working Document Evaluation. Joint evaluation of Regulation (EC) No 1901/2006 of the European Parliament and of the Council of 12 December 2006 on medicinal products for paediatric use and Regulation (EC) No 141/2000 of the European Parliament and of the Council of 16 December 1999 on orphan medicinal products. (2020) European Commission. https://health.ec.europa.eu/system/files/2020-08/orphan-regulation_eval_swd_2020-163_part-1_0.pdf.

[7] De Jongh T, van Belle J, de Ruiter A, et al. (2020). *Study to support the evaluation of the EU Orphan Regulation.* European Commission Directorate General for Health and Food Safety.

[8] Schiffers, K., Varnai, P., Birov, S. et al., (2018). *Study on the economic impact of the Paediatric Regulation, including its rewards and incentives – Final report (redacted version)* European Commission, Directorate-General for Health and Food Safety, Publications Office. https://data.europa.eu/doi/10.2875/662696.

[9] The new legislation would replace the EU General Pharmaceutical Legislation, as well as the EU Orphan Regulation and EU Paediatric Regulation.

- Many measures have been proposed to support the development of innovative medicines: the authorisation process for new medicines will be sped up, thanks to simplified procedures and a revamped EMA structure.
- Early scientific advice by EMA will improve the quality of applications and tailored scientific support will be provided to small and medium-sized enterprises (SME). Learning from the COVID-19 experience, "rolling reviews" (i.e., a phased reviews of data as they become available), and temporary emergency marketing authorisations for health emergencies will be introduced.
- Regulatory 'sandboxes' allow testing new regulatory approaches for novel therapies under real world conditions. The use of real-world evidence and health data is also facilitated. The regulatory framework will be more agile to accommodate scientific advances, digitalisation, artificial intelligence and cutting-edge products.
- Special provisions and incentives for repurposing make it easier for researchers and not-for-profits to develop their research into authorised medicines.
- Companies marketing innovative medicines will have a minimum period of regulatory protection of 8 years, which includes 6 years of data protection and 2 years of market protection. Companies may benefit of additional periods of protection, increasing the total period up to maximum 12 years, while it is maximum of 11 years today. These additional periods of protection can be obtained if the companies launch the medicine in all Member States (+2 years), if the medicine addresses an unmet medical need (+6 months), or if comparative clinical trials are conducted (+6 months). A further year of data protection can be granted if the medicine can treat other disease(s) too.
- For medicines for rare diseases, the standard duration of market exclusivity will be 9 years. Companies can benefit from additional periods of market exclusivity if they address a high unmet medical need (1 year), launch the medicine in all Member States (+ 1 year), or develop new therapeutic indications for an already authorised orphan medicine (up to 2 extra years). The regulatory protection periods can add up to maximum 13 years while today the maximum is 10 years.
- A number of future-proofing measures will ensure that the regulatory system can keep pace with scientific and technological progress. This also comprises promoting innovative methods, including those aimed at reducing animal testing.

1.2 Aim of this Quickscan

The Commission published its proposals for revision of the legislation in April 2023. Member States have been given time to evaluate the proposals and measures contained therein. This provides an opportunity to consider, and possibly propose, adaptations to better fit the measures with the set objectives through negotiations with other Member States and Parliament to come to a final text for approval by Parliament and Council. The Dutch Ministry of Health, Welfare and Sports (Ministry of VWS), acting on behalf of the Dutch government, is spearheading the discussions in the Netherlands concerning the new EU legislation, from the perspective that the current proposal will have enduring implications as the changes are intended to prepare the EU for the coming 10 to 20 years of pharmaceutical development. The goal of the Ministry of VWS is to ensure access to therapies and technologies for patients in the Netherlands and the EU, now and in the future.

To provide the Ministry of VWS with input, ZonMw (the Netherlands Organisation for Health Research and Development) has requested a Quickscan of the draft proposals for the new

European general pharmaceutical legislation[10]. The main question of the Quickscan has been whether the draft EU general pharmaceutical legislation is fit for purpose to assess innovative medicines for marketing authorisation, and whether there are possibilities to further revise the legislation for a positive impact on innovation and access to medicine in Europe and the Netherlands.

The focus of the Quickscan has been on the regulatory aspects for authorisation, i.e. the legal and technical framework for the assessment needed to grant marketing authorisation for medicines. These aspects intersect with other elements of the legislation, such as innovation incentives and measures focused on improving patient access to medicines (e.g. tackling shortages, health technology assessment). However, these latter aspects were generally out of scope (see also Section 1.3). Because of the Quickscan's focus on the framework's ability to support and stimulate innovation, the emphasis was on (future) innovative pharmaceuticals, excluding generic medicines and biosimilars from consideration[11].

This Quickscan explores the following questions:

- Is the proposed legislation appropriate and future-proof? What is the regulatory impact on the innovation chain from preclinical to clinical research and marketing authorisation?
- How and to what extent do the proposed adjustments address existing bottlenecks and opportunities in the regulatory system to facilitate access to innovative medicines?
- How do key opportunities and bottlenecks in EU laws and regulations compare with the regulatory system in other countries with leading systems?
- What further possibilities are there to exploit the identified opportunities through adjustments in new EU laws and regulations?

To help answer these questions, the Quickscan has collected perspectives from stakeholders in the Netherlands. These perspectives have been analysed alongside broader contextual information obtained through the analysis of academic literature and other relevant documents. This report contains the results of these efforts.

Where applicable, concrete recommendations are offered to the Ministry of VWS to amend the legislative proposals or otherwise seek clarifications and assurances concerning the implementation of the proposed framework. It is herein understood that the proposed legislation will be accompanied by implementing guidance and additional legislation that has not yet been adopted.

1.3 Analytical framework

An analytical framework was developed to structure and visualise the proposed changes in the legislation across different phases of pharmaceutical development (See Figure 1). The agreed focus of the Quickscan is highlighted in green and particularly concerns changes in the regulatory framework for marketing authorisation and manufacture of medicines. By contrast, proposed changes that relate to incentives for research and innovation, on the one hand, or to availability and economic assessment of medicines on the other hand, were not considered in scope of this Quickscan (grey sections). This means that issues such as changes

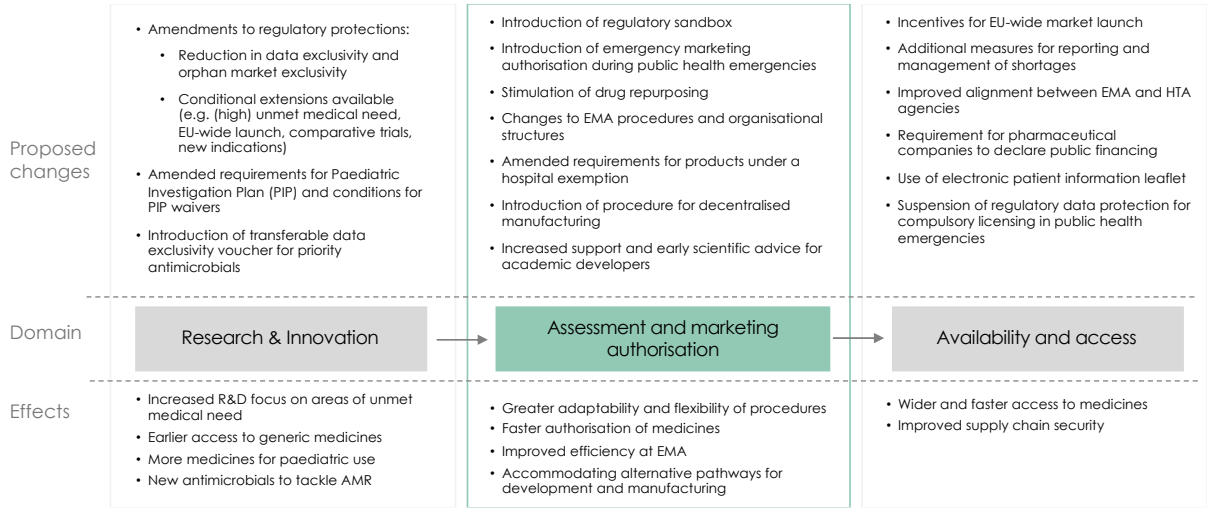
[10] The Quickscan is conducted under the supervision of the ZonMw Regulatory Pandemic Preparedness programme.

[11] Repurposing is, however, considered in scope as it involves a measure of innovation due to the need for additional clinical evidence generation and the new use for the product itself.

to the system for regulatory incentives (data exclusivity, market protection and orphan market exclusivity) were *outside* the scope.

The choice to focus the Quickscan on this particular area of the legislative proposals originated with the Dutch Health Research Council and Ministry of VWS. That, however, should not be interpreted to mean that these issues are not considered of high importance by the Ministry of VWS. In fact, their importance means that that the Ministry of VWS is conducting a separate consultation with the field – in parallel to this Quickscan – to inform its position in respect to the modulation of regulatory protections. Issues that primarily fall within the national competences of Member States, involving health technology assessment and national systems for decision-making on reimbursement and pricing policies, were similarly outside the scope of the study. This again does not signal that the importance of these issues is not recognised, but it should be kept in mind that the purpose of the present Quickscan was to provide input for negotiations with other Member States on issues that transcend national policies. The Ministry of VWS is in regular dialogue with national stakeholders to discuss ways of supporting innovation and access to medicines in the Netherlands.

Figure 1 Analytical framework showing key changes in the proposals for the EU general pharmaceutical legislation in connection to the focus of the Quickscan

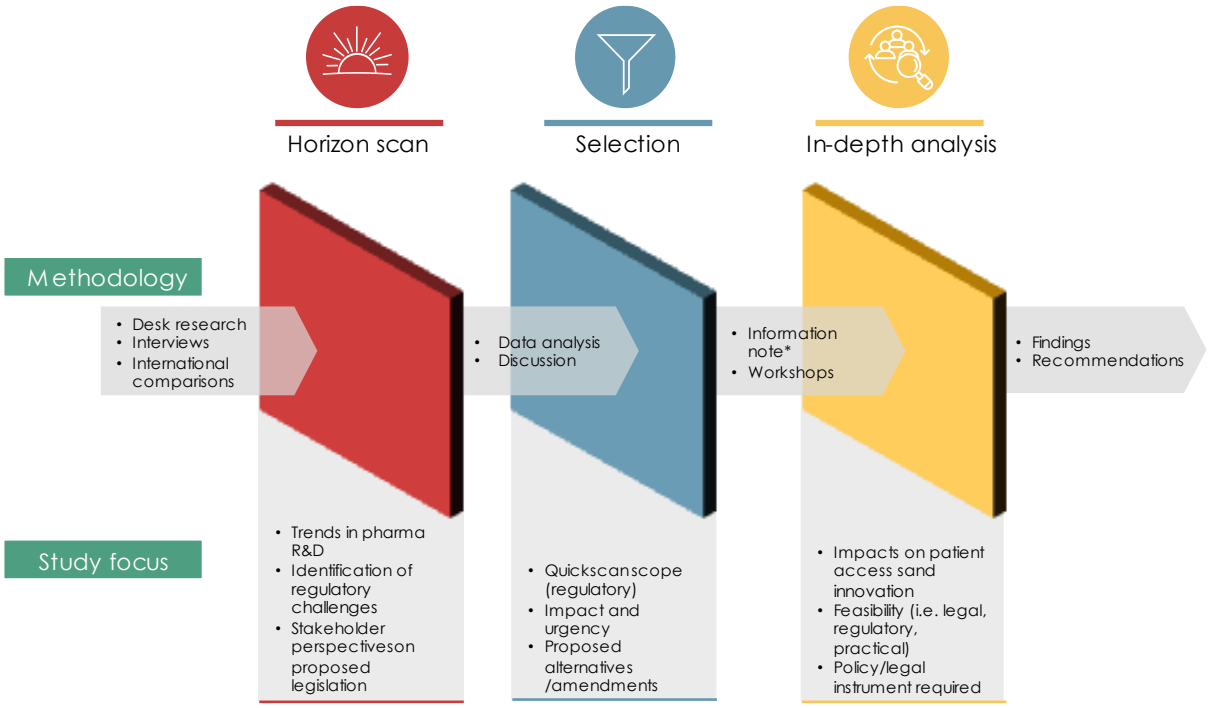


1.4 Methodological approach

The Quickscan was conducted through a three-phased process (Figure 2). It started with a 'horizon scan' of trends in pharmaceutical innovation and their (future) interaction with the regulatory framework for assessment and authorisation. This process was informed by desk research and stakeholder interviews. The results of this process have been presented in Chapter 2 of this report. Running in parallel, a series of case reports was prepared on the basis of desk research of the regulatory frameworks in three other jurisdictions. Findings from these cases have been incorporated at various points throughout the report as illustrations and potential lessons for the development of the EU framework.

This high-level scan was followed by a filtering stage wherein a selection was made of key areas for further in-depth exploration in the final stage through discussion with stakeholders and formulation, where applicable, of concrete recommendations.

Figure 2 Methodological approaches and stages of the Quickscan



Source: Technopolis (2024). *Refers to the note prepared by the study team on selected key issues and shared in advance with workshop invitees.

1.4.1 Phase 1: Horizon scan of pharmaceutical innovation and its regulatory implications

In the first phase of the work, a high-level exploration was done of how the field of pharmaceutical innovation may be expected to change in the years and decades to come and what challenges this, in turn, may pose to the regulatory framework for medicines. Purpose of this was to better understand in what ways the proposed EU legislation may, or may not, be suited to address already identified bottlenecks and to accommodate pharmaceutical innovation. To this end, data were collected through desk research as well as from interviews with selected stakeholders. The exploration was supported by development of a series of profiles of the regulatory frameworks in the UK, US, Singapore and – to a lesser extent – China.

Desk study

The desk study helped to build an overview of current and expected developments in the field of pharmaceutical research and innovation. Sources were gathered from academic literature (through searches in the Pubmed database of medical literature) and grey literature, using search terms related to the EU general pharmaceutical legislation, concepts related to specific proposed changes, identified innovations and names of specific Dutch and European stakeholder groups. Additionally, websites of key stakeholder organisations were searched to identify position papers and other relevant documentation.

Interviews with stakeholders

A list of potential interviewees was prepared, in consultation with the client and guidance committee. The selection of interviewees was designed to represent a broad range of interests in and perspectives on the proposed legislation and was done prior to the identification of the

key issues on which the in-depth analysis in the next phase of the study focused. An overview of the stakeholders consulted is provided in Appendix A.

Semi-structured interviews were conducted to gather information from these stakeholders on their experiences with the intersection between pharmaceutical innovation and the regulatory framework and collect their perspectives and expectations concerning the legislative proposals. Interviewees were asked for reflections on existing regulatory hurdles and opportunities as well as on expected future issues with regulatory processes.

In total, 33 interviews were held with 31 stakeholders representing the pharmaceutical industry, non-governmental organisations, and regulatory organisations in the Netherlands. The scope and duration of this Quickscan necessarily limited the number of interviews that could be done, such that only a relatively small number of participants for each stakeholder group could be included. To further supplement their perspectives, documentation published by organisations and associations representing the interests of these groups was also included in the analysis. The insights from the interviews and desk study were jointly used to develop an overview of potential issues with the proposed legislation.

International comparison

Four case reports were prepared, providing an international comparison of the regulatory frameworks in other countries with the intent to draw potential lessons and examples from these. The countries comprised 1) the United States (US), selected as a large pharmaceutical market, 2) the United Kingdom (UK), selected to review the recent, post-Brexit review and update of a regulatory framework, 3) Singapore, selected as a non-Western country with a 'flexible' framework to promote innovation, and 4) China, selected as a non-Western country with a remarkable level of innovation in the field of ATMPs. The case study for each individual country consisted of a description of the regulatory system and key marketing authorisation pathways, the structure and organisation of expertise in the regulatory agency, and experiences to date with assessing medicines. In addition, specific attention was paid to issues in the proposed EU legislation identified during the interviews. The case studies were conducted on the basis of a review of regulatory agency websites, grey literature and/or policy documents, and, where necessary, peer-reviewed literature. The findings from the case studies were used to provide international context and examples for the analytical sections of this report.

1.4.2 Phase 2: Selection of key areas for in-depth exploration

The work performed in the first phase of the Quickscan resulted in a wide-ranging overview of developments in pharmaceutical research and innovation and potential issues these innovations may encounter when moving from the development stage through to marketing authorisation. To bring more focus to the findings and recommendations offered to the Ministry of VWS, a selection of key areas for further in-depth exploration was performed. For this, several considerations were applied. Specifically, it was assessed:

- Whether the identified issues related to aspects covered by the EU General Pharmaceutical Legislation;
- Whether the identified issues fell within the agreed scope of the Quickscan;
- To what extent the identified issues can be expected to impact pharmaceutical innovation and access to medicine within the foreseeable future;
- Whether any recommendations can be offered to add, remove or amend specific aspects of the proposed legislation.

This assessment was made by the study team on the basis of information collected in the first phase of the work. The resulting short-list of key topics was clustered around five main areas for further exploration in the final phase of the project. These areas were presented to the Guidance Committee that supported the conduct of the Quickscan. With the endorsement of the Guidance Committee, these five key areas were selected as the basis for further discussion with stakeholders to support the formulation of recommendations offered to the Ministry of VWS. The five key areas selected, as presented in Chapter 3 of this report, concerned:

- Regulatory acceptance of new ways to generate (clinical) evidence;
- Derogations from the marketing and/or manufacturing authorisation;
- Restructuring of the EMA Scientific Committees;
- Support for non-commercial pharmaceutical developers;
- Drug repurposing.

The selection process necessarily means that not all potential areas of tension in the legislative proposals have been discussed in detail in this report. A brief overview of some remaining issues has been included in Appendix B to ensure these issues are brought to the attention of the Ministry of VWS. However, these issues were not part of the activities conducted in Phase 3 of the project and therefore have not been explored with stakeholders in a broader forum. As such, it was not possible to offer sufficiently balanced and actionable recommendations in these areas.

1.4.3 Phase 3: In-depth discussion of key areas for development of recommendations

The final phase of the project centred on a more in-depth exploration of the key issues selected in the previous phase. Its purpose was to further identify whether and how the proposed legislation seeks to address these issues and reflect with stakeholders on the desirability and feasibility of potential alternatives. This, in turn, informed the formulation of actionable recommendations. Data collection in this phase of the study centred on documentation analysis and a set of stakeholder workshops.

Preparation of workshop information note and stakeholder workshops

All interviewees who participated in the first phase of the Quickscan were asked whether they would be interested in participating in a workshop along with other stakeholders at a later stage of the project. Those who expressed interest were invited to participate in one of three possible online workshops, all with the same duration and agenda.

To allow workshop participants to better prepare, a workshop information note was prepared corresponding to each of the five selected key areas (Appendix C). This note contained a description of the main issues, expected trends and identified bottlenecks in the existing regulatory framework. Additionally, it was outlined how the proposed legislation seeks to address the issue, including references to the applicable passages in the legislative texts. Where specific suggestions for amendment had already been offered by stakeholders during the first phase of the project, these were included in the note as well. The note was shared with all invited workshop participants several days in advance of the workshops.

Based on confirmed attendance, it was decided to proceed with two rather than three workshops. Each workshop took place over 90 minutes, in the form of a moderated online discussion. Notes from the workshops were included in the analysis. Parties that could not attend either of the workshops but had requested to be allowed to submit a written response

to the information note were given opportunity to do so. Their written responses were included in the analysis as well, along with any further submitted comments from workshop participants.

Formulation of recommendations

All data sources were brought together to inform, where applicable, the development of actionable recommendations to the Ministry of VWS as input for the Member State negotiations on the proposed legislation. Different viewpoints and interests of stakeholders were carefully considered in the development of these recommendations, aiming to strike an appropriate balance between interests whilst also considering the feasibility of the recommendations from a legal and regulatory perspective. The goal of these recommendations was to allow a future-proof regulatory system in support of innovation and access to medicine.

1.4.4 Deviations in our approach from original plan

Throughout the study the approach was adapted to optimise data collection. Initially, it had been planned to follow a Delphi-like approach with a survey for broad stakeholder groups prior to the interview rounds and a survey after the interviews to work towards a consensus on key challenges and opportunities. This approach was adapted to reduce the burden on stakeholders and allow more in-depth interviews with relevant stakeholders.

2 Trends in drug development and their regulatory implications

Advancements in biomedical science, data analysis methods, and manufacturing techniques are reshaping the landscape of pharmaceutical care. Whilst some developments can be readily absorbed by the existing regulatory system, others may stretch its limits. This study has aimed to identify those developments that may push against these boundaries of the regulatory framework as it stands today. Whilst there are many individual technologies and techniques being developed that have the potential to change the face of medicine, for the purposes of this report these have been clustered around three macro-trends: 1) personalised medicine, 2) data-driven drug discovery, and 3) point-of-care manufacturing. Each of these trends is presented in the following paragraphs.

It should be noted that important developments are happening also in the area of medical devices and drug-device combination products, whereby medicines are integrated with delivery systems. Medical devices are, however, regulated by separate pieces of EU legislation: the Medical Devices Regulation (Regulation (EU) 2017/745) and the In-Vitro Diagnostic Regulation (Regulation (EU) 2017/746). Drug-device combination products may fall either under the EU general pharmaceutical legislation or under the MDR, depending on whether the medicinal product is considered an integral part of the product or ancillary to the device[12]. The MDR and IVDR became applicable only in 2021 and 2022 respectively and are not part of the current proposals for revision. Therefore, developments that would fall (mainly) under these regulations have not been included in this report.

2.1 Personalised medicine

Personalised medicine is a therapeutic approach that uses an individual's genotype and phenotype information to customise therapies or preventive care[13]. It is driven by the increasing recognition of individual characteristics influencing predisposition to a disease, disease progression and medication efficacy. Genetic makeup plays a crucial role, with some individuals being more susceptible to severe side effects or requiring different doses or even treatments due to genetic variations. The evolving understanding of individual factors in health and disease, aided by the collection and analysis of large volumes of health data (Section 2.2) is contributing to rapid progress in the field of personalised medicine[14].

One particular class of therapies to consider in the context of personalised medicine are the so-called Advanced Therapy Medicinal Products (ATMPs). They can be classified into three main types: gene therapy medicines, somatic-cell therapy medicines, and tissue-engineered

[12] Regulation (EU) 2017/745, Article 1(8): "Any device which, when placed on the market or put into service, incorporates, as an integral part, a substance which, if used separately, would be considered to be a medicinal product as defined in point 2 of Article 1 of Directive 2001/83/EC, including a medicinal product derived from human blood or human plasma as defined in point 10 of Article 1 of that Directive, and that has an action ancillary to that of the device, shall be assessed and authorised in accordance with this Regulation. However, if the action of that substance is principal and not ancillary to that of the device, the integral product shall be governed by Directive 2001/83/EC or Regulation (EC) No 726/2004 of the European Parliament and of the Council, as applicable. […].

[13] 'Personalised Medicine'. Source: https://health.ec.europa.eu/medicinal-products/personalised-medicine_en. accessed 4 December 2023.

[14] 'Application of Personalised Medicine: Opportunities and Challenges | RIVM' <https://www.rivm.nl/en/news/application-of-personalised-medicine-opportunities-and-challenges> accessed 4 December 2023.

medicines[15]. ATMPs can address diseases where more traditional medicines have fallen short, and a more targeted approach is required. Much is expected, for instance, of novel gene editing techniques, such as CRISPR-Cas9, that could allow for the customisation of treatments to a person's genetic profile. Meanwhile, advances in nanotechnology and biomolecular engineering may also hold great potential for the field of personalised medicine by offering new ways of testing, producing, or even delivering medicines. Although personalised medicine may have much to offer for patients, it also brings with it new questions and challenges for the functioning of the regulatory framework, particularly in regard to the scientific evaluation and quality assurance of medicines.

The existing regulatory framework for the scientific evaluation and authorisation of medicines is founded on the notion that treatments are developed for relatively homogeneous patient populations and that the same medicine, possibly with variations in dosage, can be used for a significant proportion of patients with a particular disease. The scientific evaluation of medicines has therefore been developed largely around the standards set by the randomised controlled trial (RCT), whereby efficacy must be demonstrated as a statistically significant treatment effect across the trial population. However, one of the inherent issues with personalised treatments is that they may benefit only a rather small sub-set of the total treatment population. This can make it challenging to identify and enrol sufficient numbers of patients into clinical trials. Consequently, regulators may have to perform their scientific evaluation on the basis of more limited evidence than has been the case in the past[16]. The challenge is even more pronounced for treatments that are derived from a patient's own material, such as with autologous cell therapies, whereby each treatment is essentially unique. This uncertainty extends to the assessment of cost-effectiveness, which many countries require to decide on reimbursement of expensive therapies. One of the important debates is therefore what role Real World Data (RWD) and Real World Evidence (RWE) may play in supporting the further assessment of medicines[17], including personalised treatments, that have been (conditionally) approved on the basis of limited evidence from clinical studies. it is the acceptability of this evidence for regulatory decision making in different use cases across the product life that has become the subject of intense debate.

The link that personalised medicine makes between a drug's mechanism of action and a patient's genetic characteristics can also have other implications for the design of a trial, by changing the relationship between a treatment and a specific indication. Traditionally, a drug candidate will be tested in a population of patients all diagnosed with the same disease. However, in oncology, some treatments can target specific genetic mutations that can be expressed in different types of cancer ('tumour agnostic'). These treatments therefore could benefit patients based on their genetic tumour profile rather than on the location of their

[15] 'Advanced Therapy Medicinal Products: Overview | European Medicines Agency'. https://www.ema.europa.eu/en/human-regulatory-overview/advanced-therapy-medicinal-products-overview#, accessed 6 December 2023; Article 2.1(a) of the ATMP Regulation (Regulation (EC) No 1394/2007).

[16] On the other hand, the personalised nature of the treatment can also mean that, within a sub-set of patients, the treatment effect observed is greater than for a conventional drug as the study population may include fewer no/low responders.

[17] Real World Data may be defined as "routinely collected data relating to a patient's health status or the delivery of health care from a variety of sources other than traditional clinical trials", whilst Real World Evidence can be defined as "the information derived from analysis of RWD". Cave A, Kurz X, Arlett P (2019). Real-World Data for Regulatory Decision Making: Challenges and Possible Solutions for Europe. Clinical Pharmacology & Therapeutics. 106(1), p.36-39. https://doi.org/10.1002/cpt.1426.

tumours. Development of such tumour agnostic therapies thus benefits from the enrolment of patient populations selected on the basis of biomarkers rather than on the type of cancer, using innovative trial designs such as basket designs[18].

Regulators like the EMA are cognisant of these developments and have developed guidance on the design of complex trials[19]. They are also conducting experiments with (regulator-led) use of RWD/RWE in regulatory decision-making[20]. However, it may be expected that, with the rise of personalised medicine, the use of new types of data and novel trial designs will increase and give rise to additional questions. It is therefore important that there is clarity between regulators and developers on the acceptability of clinical data for regulatory and reimbursement decision making. Chapter 3 of this report further explores whether and how the proposed new legislation may be able to adapt to these new ways of generating clinical evidence, including the role of RWD/RWE, to support the regulatory assessment of innovative medicines.

Further challenges for the field of personalised medicine arise after the development stage with the manufacturing process. The regulatory framework was developed at a time that the production of medicines was almost exclusively the domain of pharmaceutical companies. Procedures for assuring the quality of medicines have thus been designed with industrial manufacturing processes in centralised facilities in mind. However, when medicines are tailored to patient characteristics, centralised manufacturing may no longer be feasible from both a logistical and an economic perspective. Personalised medicines, in particular ATMPs, are therefore often produced at the point-of-care in hospital settings. The specific issues associated with this development are discussed further in Section 2.3.

The move towards personalised medicine is already visible today, but to unlock its full potential, several important hurdles still need to be cleared. These extend beyond the regulatory framework and include a need for better access to biomarker tests, and guidance on how and when to use these tests in support of personalised treatment[21]. Thus, whilst it is important to ensure that the regulatory framework is brought up to date to deliver on the promises of personalised medicine, action in other areas will be needed as well.

2.2 Data-driven drug discovery

In the two decades since the adoption of the EU general pharmaceutical legislation, the field of drug discovery has undergone a data revolution with vast amounts of new data being generated. This revolution has been enabled by scientific advances in, for instance, genetics and bioimaging but also by improvements in digital technology and data analytics.

One important class of data is that of so-called 'omics' data. Omics refers to techniques used in biological profiling, including genomics (the study of the structure and function of the

[18] Mark Sigman, 'Introduction: Personalized Medicine: What Is It and What Are the Challenges?' https://doi.org/10.1016/j.fertnstert.2018.04.027, accessed 4 December 2023.

[19] Complex clinical trials – Questions and answers, version 2022-05-23. (2022) European Commission, European Medicines Agency and Heads of Medicines Agencies. https://health.ec.europa.eu/system/files/2022-06/medicinal_qa_complex_clinical-trials_en.pdf.

[20] Real-world evidence framework to support EU regulatory decision-making: report on the experience gained with regulator-led studies from September 2021 to February 2023. (2023) HMA, EMA. https://www.ema.europa.eu/system/files/documents/report/real-world-evidence-framework-support-eu-regulatory-decision-making-report-experience-gained_en.pdf.

[21] Unlocking the potential of precision medicine in Europe. (2021) IQN Path, European Cancer Patient Coalition, EFPIA. https://www.efpia.eu/media/589727/unlocking-the-potential-of-precision-medicine-in-europe.pdf.

genome), transcriptomics (the study of the change in RNA to understand changes in gene expression), proteomics (the study of protein expression), metabolomics (the study of metabolite profiling), and epigenomics (the study of changes in gene functions). Leveraging omics data allows pharmaceutical developers to cut down on the time and cost of drug discovery, boosting the likelihood of successfully introducing new and effective drugs to the market. Omics data have several specific applications within drug development that can help accelerate timelines. First, they aid researchers in pinpointing new drug targets by offering a clearer picture of the molecular mechanisms underlying diseases. They can also help to identify specific mechanisms relevant to certain patient groups. Second, omics data are instrumental in creating predictive models. These models assist in identifying potential drug candidates and predicting their efficacy and safety[22].

Notwithstanding recent advancements in the field of omics technologies, there are still significant technical challenges involved with handling large volumes of this complex and heterogenous data. An important role herein may be expected to be played by Artificial intelligence (AI) and machine learning (ML) methods. AI/ML methods have been applied in drug discovery for 15 to 20 years but, with the adoption of deep learning and other advances in computing, their application has become increasingly sophisticated[23]. Big data processing and analytics techniques are, among other things, enabling the use of 'multi-omics' studies whereby data from different biomolecular levels are integrated for a more holistic perspective[24]. The pharmaceutical industry is embracing AI/ML mainly to reduce overall attrition and development costs. At every step of drug discovery and development there is a proactive exploration using ML algorithms and software. These tools can assist in, for instance, identifying new targets, providing stronger evidence for links between targets and diseases, improving the design of small-molecule compounds, deepening understanding of disease mechanisms, developing new biomarkers and refining the analysis of biometric, pathology and imaging data[25]. By creating *in silico* prediction models (i.e. computer-based analyses and simulations), the failure rate during the drug development process may be decreased. This can result in a significant and beneficial impact on both financial and scientific aspects of drug development, as well as increase the efficiency of the process[26].

It is widely expected that AI/ML techniques will be used more and more to help analyse RWD. The trend towards development of medicines for smaller patient populations (i.e. personalised medicine, rare diseases) means that the generation of evidence on the effectiveness and safety of medicines has begun to shift from the clinical trial setting to post-authorisation settings. Increasingly, medicines are being brought to market on the basis of Phase II studies rather than the traditional Phase III studies. This means that additional data need to be collected once the medicine is already in use in uncontrolled and heterogeneous patient populations. Analysis of

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[22] Matthews, H., Hanison, J., & Nirmalan, N. "Omics"-informed drug and biomarker discovery: opportunities, challenges and future perspectives. (2016). Proteomes >accessed January 15th, 2024

[23] Sheela Kolluri and others, 'Machine Learning and Artificial Intelligence in Pharmaceutical Research and Development: A Review' (2022) 24 The AAPS journal <https://pubmed.ncbi.nlm.nih.gov/34984579/> accessed 4 December 2023.

[24] Ivanisevic T, Sewduth RN. Multi-Omics Integration for the Design of Novel Therapies and the Identification of Novel Biomarkers. Proteomes. 2023 Oct 20;11(4):34. doi: 10.3390/proteomes11040034.

[25] Vamathevan, J., and others, Applications of machine learning in drug discovery and development. (2019). Nature reviews Drug discovery. > accessed January 15th.

26 Réda, C., Kaufmann, E., & Delahaye-Duriez, A. Machine learning applications in drug development. (2020). Computational and structural biotechnology journal. > accessed January 15th.

such data is far more complex than that of conventional trial data due to many potentially confounding factors and the comparatively unstructured way in which it is collected. AI/ML offers a means to detect patterns in drug responses and identify subgroups of patients within these complex data sets. Whilst this generation of RWE can be crucial in allowing regulators to decide whether (sub-groups of) patients actually benefit from a medicine and if a product is safe, it can be challenging for regulators to understand how such evidence was generated and whether it is sufficiently robust to support assessment (see Section 3.1).

Another noteworthy area where AI/ML techniques are expected to prove valuable is in the repurposing of existing medicines for new indications. Using learning algorithms, it is possible to reuse existing data sets to identify new associations between medicines and diseases[27,28]. This can involve use of data generated during the initial drug discovery phases (e.g. omics data) but also data collected post-approval from electronic health records. Using *in silico* methods has the potential of significantly speeding up the development process as critical steps, such as safety studies, can be significantly shortened or even omitted as these have already been performed for previous indications. It is hoped that, with the aid of AI-powered methodologies, drug repurposing will lead to faster, cheaper, and more efficient development of treatments. Yet another application for AI/ML methods lies in the substitution of animal studies with *in silico* approaches[29].

While AI/ML has the potential to enhance drug discovery and support regulatory decision-making, understanding its strengths and weaknesses is crucial to mitigate associated risks. For one, since patient health and safety are directly impacted, sound statistical judgment and in-depth knowledge of AI/ML techniques are essential to distinguish between correlation and causation. Challenges exist also around the quality and representativeness of data sets on which models have been trained, transparency of algorithms and in ensuring that data are processed properly[30]. Because of this, guidelines for AI development and use in medicinal products are important, covering areas such as data provenance, reliability, transparency, pharmacovigilance and real-world monitoring of patient functioning[31]. From a regulatory perspective, the main questions currently centre on the acceptability of data that has been generated with the support of *in silico* models or AI-aided analysis techniques[32].

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[27] Zong, N., Wen, A., Moon, S. *et al.* Computational drug repurposing based on electronic health records: a scoping review. *npj Digit. Med.* **5**, 77 (2022). https://doi.org/10.1038/s41746-022-00617-6

[28] Issa NT, Stathias V, Schürer S, Dakshanamurthy S. Machine and deep learning approaches for cancer drug repurposing. Semin Cancer Biol. 2021 Jan;68:132-142. doi: 10.1016/j.semcancer.2019.12.011. Epub 2020 Jan 3. PMID: 31904426; PMCID: PMC7723306.

[29] Vora LK, Gholap AD, Jetha K, Thakur RRS, Solanki HK, Chavda VP. Artificial Intelligence in Pharmaceutical Technology and Drug Delivery Design. Pharmaceutics. 2023 Jul 10;15(7):1916. doi: 10.3390/pharmaceutics15071916.

[30] José Jiménez-Luna and others, 'Artificial Intelligence in Drug Discovery: Recent Advances and Future Perspectives' (2021) 16 Expert Opinion on Drug Discovery 949 <https://www.tandfonline.com/doi/abs/10.1080/17460441.2021.1909567> accessed 4 December 2023.

[31] John P Santa Maria, Yuan Wang and Luiz Miguel Camargo, 'Perspective on the Challenges and Opportunities of Accelerating Drug Discovery with Artificial Intelligence' (2023) 3 Frontiers in Bioinformatics 1121591; 'Artificial Intelligence in Medicine Regulation | European Medicines Agency' <https://www.ema.europa.eu/en/news/artificial-intelligence-medicine-regulation> accessed 4 December 2023

[32] Askin S, Burkhalter D, Calado G, El Dakrouni S. Artificial Intelligence Applied to clinical trials: opportunities and challenges. Health Technol (Berl). 2023;13(2):203-213. doi: 10.1007/s12553-023-00738-2.

2.3 Point-of-care manufacturing

Most medicines today are produced in industrial manufacturing facilities under tightly controlled conditions. Medicines manufacturing is heavily regulated, under the EU Good Manufacturing Practice guidelines[33], and pharmaceutical manufacturers are subject to frequent inspections and routine batch testing to ensure the quality and consistency of products. However, a potentially disruptive trend in the pharmaceutical manufacturing industry involves the development of innovative methods that enable point-of-care manufacturing, bringing the production process closer to the patient. One of the techniques enabling this shift is that of three-dimensional (3D) printing, an additive manufacturing technology that allows detailed 3D structures to be created using computer-aided design. Compared to traditional methods, 3D printing makes it easier to create complex structures, engineer specific pharmacokinetic behaviours and faster to produce small batches of medicines[34]. Whilst 3D printing is not expected to substitute the large-scale commercial manufacturing of medicines, its potential applications lie in the ability to customise doses, forms, and how medicines are released into the body. This aligns with the growing emphasis on personalised medicine (see Section 2.1). As 3D printing machines become more affordable and easier to use, it may be expected that point-of-care manufacturing will become more common[35].

Although studies have already demonstrated the feasibility of 3D printing in clinical settings,[36] its implementation still faces significant hurdles, including legal, regulatory, ethical, and organisational ones[37]. The lack of quality testing methods for ensuring accurate dosage and safety in particular is an important challenge as the existing regulatory framework was not designed with point-of-care manufacturing in mind[38]. Other areas of concern relate to the responsibility for pharmacovigilance and liability in case of production problems that affect the medicine's safety or efficacy.

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[33] Commission Delegated Regulation (EU) No 1252/2014 of 28 May 2014 supplementing Directive 2001/83/EC of the European Parliament and of the Council with regard to principles and guidelines of good manufacturing practice for active substances for medicinal products for human use; Commission Directive (EU) 2017/1572 of 15 September 2017 supplementing Directive 2001/83/EC of the European Parliament and of the Council as regards the principles and guidelines of good manufacturing practice for medicinal products for human use; Commission Delegated Regulation (EU) 2017/1569 of 23 May 2017 supplementing Regulation (EU) No 536/2014 of the European Parliament and of the Council by specifying principles of and guidelines for good manufacturing practice for investigational medicinal products for human use and arrangements for inspections.

[34] Netta Beer and others, 'Scenarios for 3D Printing of Personalized Medicines - A Case Study' (2021) 4 Exploratory Research in Clinical and Social Pharmacy 100073; Shanshan Wang and others, 'A Review of 3D Printing Technology in Pharmaceutics: Technology and Applications, Now and Future' (2023) 15 Pharmaceutics </pmc/articles/PMC9962448/> accessed 4 December 2023.

[35] Huanbutta K, Burapapadh K, Sriamornsak P, Sangnim T. Practical Application of 3D Printing for Pharmaceuticals in Hospitals and Pharmacies. Pharmaceutics. 2023 Jul 4;15(7):1877. doi: 10.3390/pharmaceutics15071877.

[36] LR Jaidev Chakka and Shanthi Chede, '3D Printing of Pharmaceuticals for Disease Treatment' (2022) 4 Frontiers in Medical Technology 1040052.

[37] Beer and others (n 8).

[38] Akm Khairuzzaman, 'Regulatory Perspectives on 3D Printing in Pharmaceuticals' (2018) 31 AAPS Advances in the Pharmaceutical Sciences Series 215 <https://link.springer.com/chapter/10.1007/978-3-319-90755-0_11> accessed 4 December 2023.

Alongside additive manufacturing techniques like 3D printing, other developments in biotechnology are also driving a move towards point-of-care manufacturing. These include the use of tissue engineering and the production of cell- and gene-based therapies[39].

2.4 Conclusions

Collectively, the aforementioned trends are expected to bring important changes to the way in which medicines are developed, produced and administered to patients. It is hoped that these changes will, in time, translate into more effective, safer, and more affordable health care and better treatment outcomes for patients. However, for these positive effects to materialise, it is important that the regulatory framework is properly equipped to enable innovative medicines to move through all the regulatory processes with sufficient ease and speed, whilst maintaining the high standards of efficacy and safety set by the current system. Specific questions arising out of the discussed trends include:

- What evidentiary standards are appropriate in the context of development of medicines for small patient populations?
- How can new types of data, in particular RWD/RWE, best be used in regulatory decision-making?
- How can new methodologies for the generation of evidence (e.g. computer modelling) be used in regulatory decision-making?
- How can the quality and safety of medicines produced outside of the standard paradigms of the marketing and manufacturing authorisation be adequately protected?
- Is there sufficient knowledge and capacity within the regulatory system, at both the European and national levels, to properly assess innovative products and processes?
- How can the regulatory system foster broad and equitable access to innovative medicines or medicines developed using innovative methodologies?

These questions, to a large extent, underpin the analysis provided in the next chapter of this report within the five key areas that were identified.

[39] Harrison RP, Ruck S, Medcalf N, Rafiq QA. Decentralized manufacturing of cell and gene therapies: Overcoming challenges and identifying opportunities. Cytotherapy. 2017 Oct;19(10):1140-1151. doi: 10.1016/j.jcyt.2017.07.005. Epub 2017 Aug 7. PMID: 28797612.

3 Future-proofing the regulatory framework

The evaluation and impact assessment that were conducted for the proposed EU pharmaceutical legislation suggest that most stakeholders consulted find that the current framework is insufficiently flexible to accommodate important innovations and is in need of revision[4]. Stakeholders interviewed for this Quickscan corroborate that developments such as those discussed in Chapter 2 do not always fit well within the current scope set out by the legislation and experience unintended effects as a consequence.

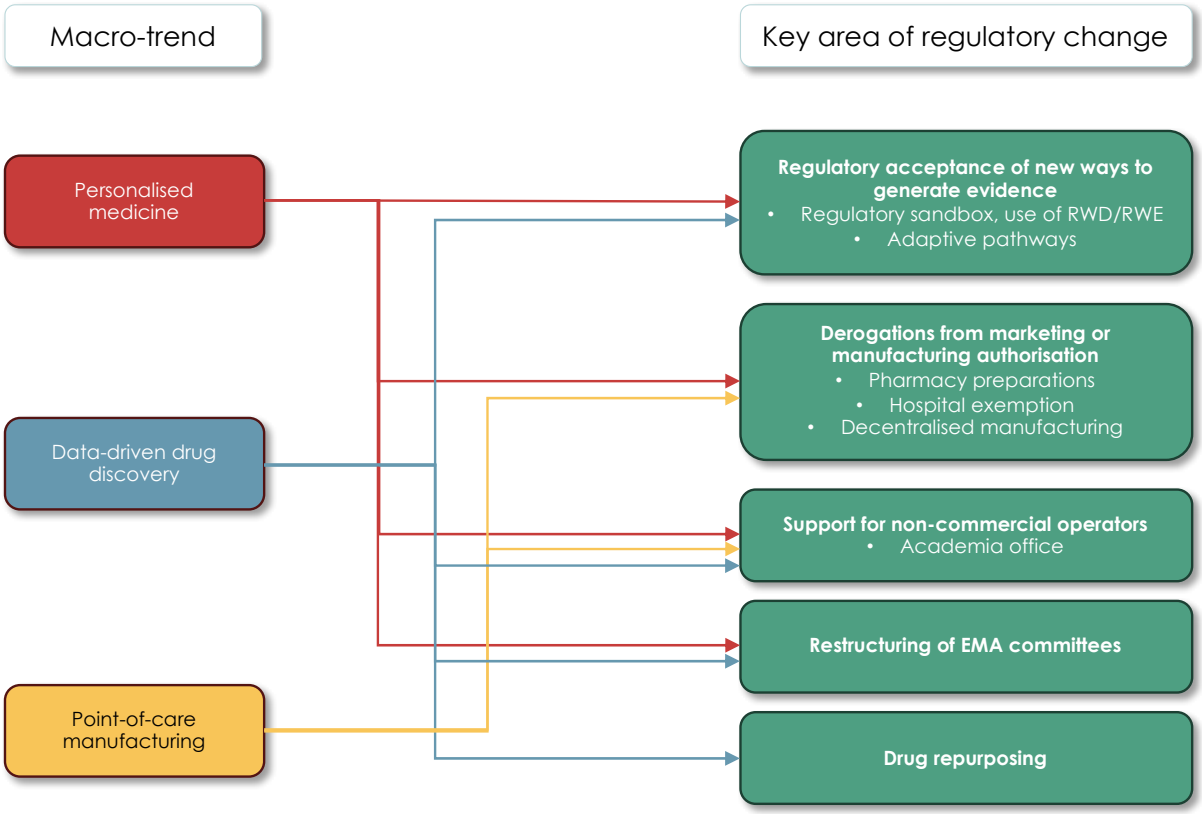
Acknowledging these concerns, the current legislative proposals uphold all of the core tenets of the current regulatory system but, at the same time, introduce new regulatory concepts and modify existing procedures to increase the adaptive ability of the regulatory framework. This includes measures such as the introduction of regulatory sandboxes and decentralised manufacturing, stimulation of drug repurposing, changes to the structure of the EMA's scientific advisory committees and increased support for non-commercial product developers.

The following sections of this chapter discuss some of the proposed changes to the regulatory framework centred on five key areas and links these to the three macro-trends discussed before. The selected areas are:

6. Regulatory acceptance of new ways for generating evidence
7. Derogations from the marketing and/or manufacturing authorisation
8. Restructuring of EMA scientific committees
9. Support for non-commercial operators
10. Drug repurposing

As detailed in Section 1.3, the selection of these five areas was based on their relationship to the scope of the Quickscan, the (perceived) importance and urgency of the potential impact of the suggested changes and on whether any alternatives to the proposed changes had been identified that could be further discussed with stakeholders. Figure 3 illustrates the relation between the macro-trends, on the one hand, and the identified five key areas of changes in the legislative proposals, on the other. It should, however, be recognised that the relations shown are only those that have the most direct relevance to the issues discussed in this report and that, in a different context, other relations could also be suggested.

Figure 3 Relations between the macro-trends in drug development and the key areas of changes in the regulatory framework included in this Quickscan.

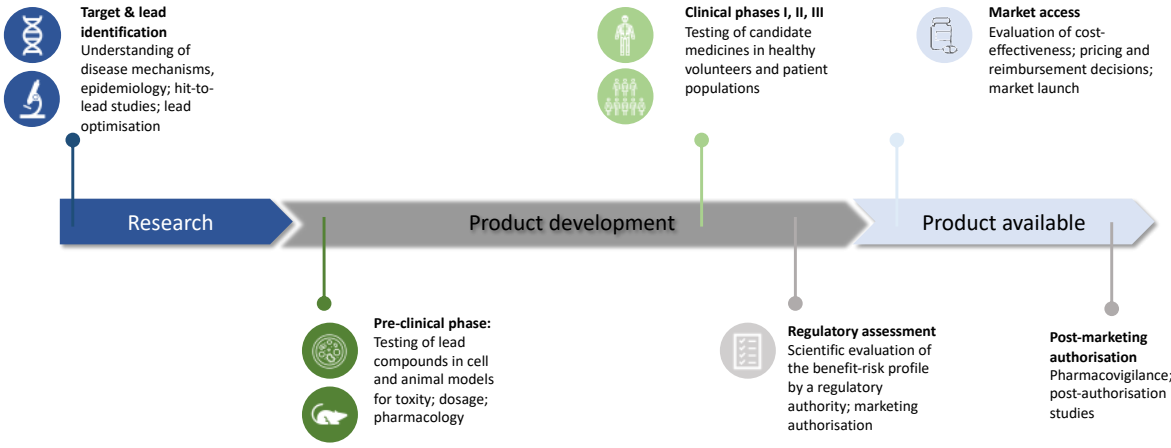


Each of the following sections of this report addresses one of the five key areas and the proposed changes to the regulatory framework contained therein. A brief background to the issues is presented, followed by a summary of the changes the legislative proposals are seeking to introduce. Next, the perspective from interviewed stakeholders on these suggested changes are presented, along with a brief illustration of how similar issues may be addressed in other jurisdictions. Each section concludes with a reflection on the proposed changes and any potential alternatives and, where appropriate, offers recommendations to the Ministry of VWS for action during the upcoming negotiation processes.

3.1 Regulatory acceptance of new ways for generating evidence

Traditionally, medicinal product development has followed a mostly linear path. It starts with the discovery of promising lead compounds and from there progresses through the phases of preclinical and clinical development (Figure 4). The data generated in the clinical development phases will form the dossier upon which the scientific regulatory assessment is performed to support an application for a marketing authorisation. The principal source of this clinical evidence has historically been the RCT. These trials must be conducted according to pre-approved protocols and involve a sufficient number of patients. If the generated clinical evidence supports the application for a marketing authorisation, the process normally results in a full approval for use of the medicine for the indication(s) specified in the application. A separate assessment may follow to determine the medicine's cost-effectiveness over existing treatments for the purposes of decision-making on pricing and reimbursement. Additional data is also still collected after the authorisation for the purpose of pharmacovigilance.

Figure 4 Pathway of medicinal product development



Source: The potential impact of the unitary Supplementary Protection Certificate on access to health technologies (2023), de Jongh TE, Kamphuis B, Bostyn S, Radauer A.

This paradigm of evidence generation is, however, increasingly being challenged by, on the one hand, scientific and technological developments, such as those around personalised medicine and data-driven drug discovery (Section 2.1 and 2.2 respectively), and, on the other, a public desire for faster access to innovative medicines. These developments mean that regulators may be expected to base their assessment on smaller and less mature data sets, such as Phase II data only. This brings with it an inherently greater risk but has the potential benefit of offering patients earlier access to treatments for serious conditions. The regulatory framework and EMA have thus far responded to this in several ways, including by:

- Introducing a **conditional marketing authorisation** pathway, whereby medicines that address unmet medical needs can be approved on the basis of less comprehensive data than normally required provided that agreed conditions are met within defined timelines[40,41]. These conditions may include the conduct of post-authorisation studies. The conditional authorisation is annually reassessed, after which it can be either renewed, converted to a standard authorisation or be revoked.
- Piloting **adaptive pathways**, allowing for iterative development and the incorporation of real-world data into the assessment[42]. The concept has thus far focused on areas of high unmet medical need. Following an initial pilot project, the EMA has been further exploring adaptive pathways in the context of parallel scientific advice with bodies for Health Technology Assessment (HTA).

[40] Conditional Marketing Authorisation. European Medicines Agency. https://www.ema.europa.eu/en/human-regulatory-overview/marketing-authorisation/conditional-marketing-authorisation.

[41] Commission Regulation (EC) No 507/2006 of 29 March 2006 on the conditional marketing authorisation for medicinal products for human use falling within the scope of Regulation (EC) No 726/2004 of the European Parliament and of the Council.

[42] Adaptive pathways. European Medicines Agency. https://www.ema.europa.eu/en/human-regulatory-overview/research-development/adaptive-pathways.

- Setting up the **Data Analysis and Real World Interrogation Network (DARWIN EU)** to provide high-quality, validated real-world data and support regulatory decision-making[43].

Furthermore, as previously mentioned in Section 2.1, the EMA has been gaining experience with regulator-led use of RWD/RWE in regulatory decision-making and has developed guidance on the use of innovative trial designs. More recently, the EMA has published a **reflection paper on the use of artificial intelligence** in the lifecycle of medicines, including in the generation of non-clinical and clinical evidence to inform regulatory assessment[44]. With the current legislative proposals, the Commission is seeking to build on these experiences and incorporate lessons learned into legislation.

3.1.1 Proposed legislative changes

In a concept paper prepared at the request of the Commission to inform the development of the current proposals, experts of the EMA and the Heads of Medicines Agencies (HMA) have stated that "advances in technologies and methodologies and availability of real-world data (RWD) have prompted a need to allow for broader range of study designs and data sources to inform decision making" and that there are "specific situations where regulatory questions benefit from complementary approaches such as real-world evidence (RWE)"[45]. The experts expect that the creation and development of the European Health Data Space will create new opportunities for the use of RWD and RWE. They therefore advise that the revised legislation should provide adequate legal provisions to enable the use of RWE as a supporting tool in regulatory decision-making. At the same time, it is recommended that this space is created without adding detailed technical provisions into the legislative text as this may quickly become out of date. Instead, provisions should be included in implementing texts and guidance.

Throughout the proposals, the Commission echoes this awareness of the need for regulatory flexibility to accommodate innovation. For instance, in the preamble to the proposed Regulation, it explicitly states that regulatory decision-making on the development, authorisation and supervision of medicinal products may be supported by access and analysis of data generated outside of clinical studies[46]. This recognition of the growing importance of RWD/RWE is most clearly exemplified by

[43] Data Analysis and Real World Interrogation Network (DARWIN EU). European Medicines Agency. https://www.ema.europa.eu/en/about-us/how-we-work/big-data/data-analysis-real-world-interrogation-network-darwin-eu.

[44] Reflection paper on the use of Artificial Intelligence (AI) in the medicinal product lifecycle (13 July 2023). European medicines Agency. https://www.ema.europa.eu/en/documents/scientific-guideline/draft-reflection-paper-use-artificial-intelligence-ai-medicinal-product-lifecycle_en.pdf.

[45] 08 Concept paper for EC on RWE including registries. Experts from EMA/HMA. https://health.ec.europa.eu/document/download/624cd58f-d680-404c-b676-8b65871b3d00_en?filename=mp_revision_concept-papers_compendium_en.pdf.

[46] Ad (60): "Regulatory decision-making on the development, authorisation and supervision of medicinal products may be supported by access and analysis of health data, including real world data, where appropriate, i.e. health data generated outside of clinical studies. The Agency should be able to use such data, including via the Data Analysis and Real World Interrogation Network (DARWIN) and the European Health Data Space interoperable infrastructure. Through these capabilities the Agency may take advantage of all the potential of supercomputing, artificial intelligence and big data science to fulfil its mandate, without compromising privacy rights. Where necessary the Agency may cooperate with the competent authorities of the Member States towards this objective."

the introduction of a "**regulatory sandbox**" (Table 1). Regulatory sandboxes are said to "provide a structured context for conducting experiments" and allow for the testing of innovative technologies, products, services, adaptive clinical trials or methods in real-world settings. They can advance regulation through proactive learning. The sandboxes would function for a limited time and within a restricted part of a sector or area under regulatory oversight, while ensuring the necessary safeguards.

Table 1 Overview of proposed changes regarding regulatory acceptance of new ways for generating evidence

Current	**Proposed**
None	Regulation • Chapter IX (Article 113, Article 114, and Article 115) 1. The Commission may set up a regulatory sandbox pursuant to a specific sandbox plan, based on a recommendation of the Agency and pursuant to the procedure set out in paragraphs 4 to 7, where all the following conditions are met: - it is not possible to develop the medicinal product or category of products in compliance with the requirements applicable to medicinal products due to scientific or regulatory challenges arising from characteristics or methods related to the product; - the characteristics or methods referred to in point (a) positively and distinctively contribute to the quality, safety or efficacy of the medicinal product or category of products or provide a major advantage contribution to patient access to treatment. […] 4. Where the Agency considers it appropriate to set up a regulatory sandbox for medicinal products which are likely to fall under the scope of this Regulation, it shall provide a recommendation to the Commission. The Agency shall list eligible products or category of products in that recommendation and shall include the sandbox plan referred to in paragraph 1. The Agency shall not recommend to set up a regulatory sandbox for a medicinal product that is already advanced in its development programme. 5. The Agency shall be responsible for developing a sandbox plan based on data submitted by developers of eligible products and following appropriate consultations. The plan shall set out clinical, scientific and regulatory justification for a sandbox, including the identification of the requirements of this Regulation, [revised Directive 2001/83/EC] and Regulation (EC) 1394/2007 that cannot be complied with and a proposal for alternative or mitigation measures, where appropriate. The plan shall also include a proposed timeline for the duration of the sandbox. Where appropriate, the Agency shall also propose measures in order to mitigate any possible distortion of market conditions as a consequence of establishing a regulatory. 6. The Commission shall, by means of implementing acts, take a decision on the set up of a regulatory sandbox taking into account the recommendation of the Agency and the sandbox plan pursuant to paragraph 4. […]

None	Directive • Section 5 Adapted Dossier Requirements, Article 28 (+ Annex VII) 1. Medicinal products listed in Annex VII shall be subject to specific scientific or regulatory requirements due to the characteristics or methods inherent to the medicinal product, when: (a) it is not possible to adequately assess the medicinal product or category of medicinal products applying the applicable requirements due to scientific or regulatory challenges arising from characteristics or methods inherent to the medicinal product; and (b) the characteristics or methods positively impact the quality, safety and efficacy of the medicinal product or category of medicinal product or provide a major contribution to patient access or patient care.
Directive 2010/63/EU (remains in effect) • Article 4 Principle of replacement, reduction and refinement 1. Member States shall ensure that, wherever possible, a scientifically satisfactory method or testing strategy, not entailing the use of live animals, shall be used instead of a procedure.	Regulation • Article 6(5) Centralised marketing authorisation application The marketing authorisation applicant shall demonstrate that the principle of replacement, reduction and refinement of animal testing for scientific purposes has been applied in compliance with Directive 2010/63/EU with regard to any animal study conducted in support of the application. The marketing authorisation applicant shall not carry out animal tests in case scientifically satisfactory non-animal testing methods are available.

Sources: Proposal for a regulation of the European Parliament and of the Council laying down Union procedures for the authorisation and supervision of medicinal products for human use and establishing rules governing the European Medicines Agency, amending Regulation (EC) No 1394/2007 and Regulation (EU) No 536/2014 and repealing Regulation (EC) No 726/2004, Regulation (EC) No 141/2000 and Regulation (EC) No 1901/2006 (proposed); Proposal for a directive of the European parliament and of the Council on the Union code relating to medicinal products for human use, and repealing Directive 2001/83/EC and Directive 2009/35/EC; Directive 2010/63/EU of the European Parliament and of the Council of 22 September 2010 on the protection of animals used for scientific purposes. Text in green denotes an addition to the legislative text that has no counterpart in the current legislation.

Article 28 of the proposal for a new Directive also provides new instructions on **adapted dossier requirements** in cases where it is not possible to adequately assess the product using the normal requirements due to "scientific or regulatory challenges arising from characteristics or methods inherent to the medicinal product". Thus far, Annex VII to the Directive only identifies "phage-containing medicinal products, in cases where the medicinal product has a variable composition depending on the specific clinical context" as falling within the scope of this provision but the proposals would empower the Commission to amend this list to take account of scientific and technical progress. More detailed rules concerning the marketing authorisation and supervision of products developed under adapted requirements still need to be laid down at a later date in a delegated act. The results of the regulatory sandboxes may also be used to inform the future application of adapted frameworks.

Whilst there are no specific provisions in the proposed legislation that reference the use of AI/ML methodologies in regulatory decision-making, in the preamble to the Regulation it is stated that the EMA "may take full advantage of all the potential of supercomputing, artificial intelligence and big data science to fulfil its mandate". Additionally, it is stated that animal tests should not be performed "in cases where scientifically satisfactory non-animal testing methods are available" (for products going through the centralised marketing application), suggesting that

computer modelling studies may be acceptable in lieu of animal testing provided the models used are considered scientifically satisfactory.

3.1.2 Perspectives from the field

It is widely agreed that the regulatory framework must provide sufficient space for, on the one hand, experimentation and flexibility but, on the other, clearly demarcate its 'lines in the sand', i.e. the minimum standards of evidence below which a regulator should not accept applications. This requires, among other things, proper validation of new methods (e.g. adaptive clinical trials, use of real-world evidence, in silico models) and guidance on how and when these may be used in regulatory decision-making. The regulatory sandbox could, at least in theory, offer this space for experimentation in a controlled environment. However, different stakeholders have varying understandings of the concept of the regulatory sandbox, as it has been proposed, with uncertainty around when and how it may be applied. Many have stated it is as yet a vague concept and that it is not clear what problems it seeks to address. Without a clearer understanding of what to expect, they feel unable to reflect on the utility of the regulatory sandbox.

Interviewed industry stakeholders interviewed generally appear cautiously optimistic, welcoming the additional space it creates for experimentation and for early dialogue between developers and regulators. However, some feel that, by limiting the sandbox environment to medicines, an opportunity may be missed to look more holistically at pharmaceutical innovation, including diagnostics and data processing techniques. Others would welcome more clarity on what the governance structure surrounding the sandbox will look like and on the rules that will be in place to protect patient safety. Questions exist also about how the EMA or the Commission will incorporate experiences with the sandbox into its routine assessment procedures, or possibly into the adapted frameworks respectively, to avoid the emergence of parallel regulatory routes.

The uncertainty about the purpose and functioning of the sandbox concept extends to the Dutch NCA, the Medicines Evaluation Board (CBG-MEB). The CBG-MEB indicates that, from past experience, it has not yet identified any situations where guidelines and scientific advice would have been insufficient and in which such a sandbox could have been helpful. It therefore does not (yet) hold high expectations about its utility but is open to learning from experiences with its application, recognising that new innovations may bring new challenges.

Because of the current unclarity about how the regulatory sandbox concept may be applied, it is difficult to determine whether it will assist with addressing existing regulatory questions, such as those around the use of RWE in regulatory decision-making. Various stakeholders have indicated that perhaps the main bottlenecks to regulatory acceptance of innovations lie not in how the regulatory framework has been formulated but in how it is applied in practice. In particular, it was signalled that regulatory authorities may lack the expertise and capacity to properly understand these innovations. It would therefore be important that, alongside the introduction of regulatory sandboxes, initiative is taken to further develop that regulatory capacity.

3.1.3 Experiences in other jurisdictions

Other countries are also exploring the use of regulatory sandboxes. The Singapore Ministry of Health, for instance, has launched the Licensing Experimentation and Adaptation Programme (LEAP) as a regulatory sandbox initiative designed to engage early with industries, particularly those pioneering innovative services in telemedicine and mobile medicine, to jointly develop

risk mitigation strategies prior to licensing. They plan to expand the use of regulatory sandboxes to other novel and innovative healthcare services. Also the regulatory authority of Canada, Health Canada, has been piloting a regulatory sandbox concept for advanced therapeutic products[47,48]. It is as yet unclear, though, at what stage this pilot is or what experiences have been gained from it thus far that could be used to inform the design of future sandbox projects in the EU. The United States does not have a regulatory sandbox, though it has been argued that the emergency use authorisations (EUA) could be considered as such. The EUA process allows the FDA to authorise a product under less strict evidence standards, where the benefit-risk analysis framework allows the FDA to tailor EUA requirements to the specific circumstances for its use.

As for the incorporation of RWD/RWE into regulatory decision-making, both the United Kingdom and the United States have been exploring how best to do this. The US FDA as well as the UK Medicines and Healthcare products Regulatory Agency (MHRA) have issued guidance on the use of real-world data and evidence in clinical trials. The FDA also hosts an RWE programme to evaluate the potential use of RWE to support labelling changes, including adding or modifying the indication.

The use of AI/ML techniques has likewise been receiving attention in other jurisdictions. In the US, the FDA has already experimented with AI techniques to assist with regulatory decision-making, such as for molecular modelling, virtual humans and patient-specific models, and to simulate clinical trials. It has furthermore tested AI in post-market surveillance and adverse event reporting. The success and appropriateness of these tools are not clear yet, with some calling into question how these are incorporated into the FDA's decision-making. In the UK, the MHRA announced its intention to launch 'AI-Airlock'. AI-Airlock is planned to be a regulatory sandbox for AI developers, allowing them to generate evidence for the AI-in-healthcare technologies and work together with the MHRA to identifying and managing evidence requirements.

3.1.4 Recommendations

Developing guidance on the sandbox concept and identifying relevant 'use cases'

Whilst the proposed concept of a 'regulatory sandbox' has been cautiously welcomed by many, much is still unclear about how it will work in practice and what type of innovations it may help. It is therefore not possible at this stage to suggest and evaluate specific amendments to the text of the legislative proposals.

However, this needed clarity on how the sandbox may work or on how experiences gained through it will be incorporated into the regulatory framework, for instance through further development of the adaptive frameworks concept, need not be laid down in the legislative proposal itself. Rather, **it is recommended that this is developed as the concept matures**

[47] Health and Biosciences: Targeted Regulatory Review – Program and Policy and Initiatives and Novel Regulatory Approaches. Health Canada. https://www.canada.ca/en/health-canada/corporate/about-health-canada/legislation-guidelines/acts-regulations/targeted-regulatory-reviews/health-biosciences-sector-regulatory-review/policy-program-initiatives-novel-regulatory-approaches.html. Last updated January 2021.

[48] Health Canada's controversial 'regulatory sandbox': Enabling innovation or lowering the bar for safety? (4 November 2021) Apostolides M. Healthydebate. https://healthydebate.ca/2021/11/topic/health-canadas-regulatory-sandbox/.

through delegated acts and guidance documents. This will require regular and transparent communication by parties involved with sandbox projects on the experiences gained and dialogue with regulators and developers.

To ensure that the proposed sandbox concept has relevance, it will be important to elaborate examples of potential 'use cases' that would allow medicines developers to understand whether it would apply to their situation. The Agency may hereto draw inspiration from examples such as Singapore's LEAP initiative and the UK's AI-Airlock initiative. It is **recommended that the Dutch Ministry of VWS supports the introduction of the Regulatory Sandbox concept. Additionally, it could take initiative to open up dialogue with the EMA and NCAs in other Member States on which problems could benefit from the concept and suggest use cases**.

Validation of new models for research and guidance on their regulatory acceptability

The Commission aims to promote the principle of replacement, reduction and refinement of animal testing in pharmaceutical research and development. It does so by, in Article 6(5) of the proposal for a new Directive, requiring applicants for a marketing authorisation to demonstrate they have not carried out animal tests when a scientifically satisfactory non-animal model is available. It is, however, often unclear to developers whether such models are indeed already considered 'scientifically satisfactory' by a regulator. This has so far slowed down the use of non-animal techniques, which in turn as the result of hindering the practical validation of these models.

It is neither practical nor desirable for the EU general pharmaceutical legislation to specify which models are or are not 'scientifically satisfactory' since this will be highly dependent on context and further scientific advances. Rather, the EMA must work closely with the research community and product developers to ensure its regulatory assessment procedures do not contradict the Commission's intentions in this regard by insisting on results from animal models when acceptable alternatives exist. The EMA needs to continue its work on **refining the already existing guidelines on the principles of regulatory acceptance of "3R testing approaches"**. A concept paper for revision of these guidelines was published in November 2023, alongside the start of a public consultation[49]. This consultation will close at the end of February 2024. Its findings may suggest a need for changes to the legislative framework are needed. Given the EMA's current framing of the process, however, it is more likely that any outcomes from the process will result in updating of existing guidance documents rather than the EU general pharmaceutical legislation. Since EU guidelines are a legally non-binding instrument, it is unclear whether such a revision would be sufficient to truly encourage greater use of non-animal methods in pharmaceutical development. It is therefore **recommended that, once published, the Ministry of VWS takes note of the outcomes of the consultation and, on the basis of this, assesses at what legislative level further action may be needed**.

3.2 Derogations from the marketing and/or manufacturing authorisation

One of the main objectives of the EU General Pharmaceutical Legislation is to ensure the safety, efficacy and quality of medicines available on the EU market by requiring authorisations for the marketing as well as the manufacturing and wholesale of medicines. There are, however, several possible exemptions from these requirements. The following sections consider the two

[49] https://www.ema.europa.eu/en/documents/scientific-guideline/concept-paper-revision-guideline-principles-regulatory-acceptance-3rs-replacement-reduction-refinement-testing-approaches_en.pdf

main exemptions: pharmacy preparations and the hospital exemption (sections 3.2.1 and 3.2.2 respectively). The following section of this report discusses how the proposed revision to the legislation will deal with these exemptions and what impact may be expected from changes to these from the perspectives of patient access and innovation. A final section of this chapter looks into the issue of decentralised manufacturing (DCM)(section 3.2.3). Here, the requirement for a manufacturing authorisation is not entirely voided but a system of delegated responsibilities is introduced.

3.2.1 Pharmacy preparations

Pharmacy preparation (alternatively: compounding) refers to a situation wherein a medicine is produced directly by a pharmacist rather than sourced from a licensed pharmaceutical wholesaler/distributor. The preparation of medicines is a basic pharmacy skill and is fairly common practice, particularly for simpler products. It is typically done in situations where there is no suitable licensed medicine, for instance because a patient needs a different dosage or formulation than that which is commercially available. This may be the case, for instance, in the field of neonatal and paediatric medicine when there are no age-appropriate formulations on the market[50]. Pharmacy preparation is also common in nuclear medicine, because of the short half-life of many isotopes which requires that these medicines are produced close to the patient. Many medical isotopes, especially those used in diagnosis of rare tumours, are not even commercially produced and are available only through compounding at the hospital. The need for pharmacy preparation of nuclear medicines is expected to grow further due to increased use of both diagnostic and therapeutic radionuclides, especially in the context of personalised medicine[51].

The legal basis for pharmacy preparations is currently provided by Article 3 of Directive 2001/83/EC, which describes a series of exemptions from the Directive, including the requirement for a marketing or manufacturing authorisation. A distinction is herein made between 'magistral formulae' and 'officinal formulae', with the latter requiring that the preparation is done in accordance with the prescriptions of a recognised pharmacopoeia (Table 2). To provide further guidance on the interpretation of the legislation and to establish standards for safety and quality assurance of medicines, in 2011 the Council of Europe adopted a (non-binding) resolution on the use of pharmacy preparations[52]. Among other things, the resolution encouraged Member States to, if necessary, amend their national legislation to ensure its alignment with the Resolution. The conditions under which pharmacy preparations are permitted have been the subject of litigation. However, in a 2015 ruling, the European Court of Justice (ECJ) stated that the legislation must be narrowly interpreted and confirmed that pharmacy preparations may not be distributed to other pharmacies[53]. In 2016, a new Council Resolution was adopted, confirming the principles of the 2011 Resolution[54]. Neither Resolution explicitly discusses the issue of distribution from preparing to non-preparing pharmacies.

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[50] See, for example, https://repub.eur.nl/pub/112858/Proefschrift-AC-van-der-Vossen.pdf

[51] Ligtvoet A, Scholten C, Davé A, King R, Petrosova L, Chiti A, Goulart De Medeiros M, Joerger A. (2021) Study on sustainable and resilient supply of medical radioisotopes in the EU. Therapeutic radionuclides. Technopolis Group.

[52] Resolution CM/Res AP(2011)1

[53] Joint cases C-544/13 and C-545/13 *Abcur v Apoteket* (2015).

[54] Resolution CM/Res(2016)1 on quality and safety assurance requirements for medicinal products prepared in pharmacies for the special needs of patients (succeeding Resolution CM/ResAP(2011)1).

Pharmacies in the Netherlands are not formally allowed to prepare medicines for patients other than those registered with that pharmacy, consistent with the ECJ's ruling. However, the Ministry VWS, together with the Dutch Health and Youth Care Inspectorate (IGJ), has issued an instruction ("Circular Letter") stating the restriction on distribution ("collegiaal doorleveren") will not be enforced as long as the preparation and distribution are compliant with instructions in the letter[55]. This includes mandatory notification of the distribution to allow the IGJ to monitor the practice. The current national guidance on enforcement expires on 24 August 2024 but is expected to be replaced by a new policy measure to this same effect[56]. By contrast, for nuclear medicines pharmacy preparation is still permitted only for patients of the pharmacy where the medicine is prepared.

In the Netherlands, pharmacy preparations may exceptionally also be used in case of shortages, but only after the IGJ has determined this to be the best solution (rather than, for example, therapeutic substitution or importation) and has given formal approval.

3.2.1.1 Proposed legislative changes

In a concept paper exploring the need for updating of core definitions, experts of the EMA/HMA re-examined the definitions of the terms 'magistral formula' and 'officinal formula'[57]. This was done in light of emerging types of medicinal products (e.g. bacteriophages) that could lead to disparities in the interpretation of the provisions. It was, however, recommended not to change the definition of "magistral formulation" but provide minor clarification to that of the officinal formula. These recommendations are reflected in the text of the proposed Directive but have no significant bearing on the scope of the exemptions.

The basic conditions for the use of pharmacy preparations have remained the same, but with one notable addition (Article 1, paragraph 6)(Table 2). Thus far, magistral formulations could only be prepared and dispensed on the basis of a prescription for an individual patient. In the proposed Directive, a clause has been added to specify that magistral formulation may be used also to prepare products in advance "on the basis of the estimated medical prescriptions within that hospital for the following seven days" in "duly justified cases". This would facilitate production at a somewhat larger scale than before so that the pharmacy may hold a week's worth of stock. The proposal maintains the limitation that pharmacies may only prepare medicines for their own patients.

Table 2 Overview of proposed changes regarding pharmacy preparations

Current	**Proposed**
Directive 2001/83/EC • Article 3 This Directive shall not apply to:	Directive • Article 1, Paragraph 5 The Directive shall not apply to:

[55] Inspectie Gezondheidszorg en Jeugd. https://www.igj.nl/publicaties/circulairen/2023/07/25/circulaire-handhavend-optreden-bij-collegiaal-doorleveren-van-eigen-bereidingen-door-apothekers-kopie.

[56] Inspectie Gezondheidszorg en Jeugd. *Collegiaal doorleveren van eigen bereidingen*. https://www.igj.nl/zorgsectoren/geneesmiddelen/beschikbaarheid-van-geneesmiddelen/collegiaal-doorleveren.

[57] 05. Concept paper on Core definitions. Experts of the EMA/HMA. https://health.ec.europa.eu/document/download/624cd58f-d680-404c-b676-8b65871b3d00_en?filename=mp_revision_concept-papers_compendium_en.pdf.

1. Any medicinal product prepared in a pharmacy in accordance with a medical prescription for an individual patient (commonly known as the magistral formula). 2. Any medicinal product which is prepared in a pharmacy in accordance with the prescriptions of a pharmacopoeia and is intended to be supplied directly to the patients served by the pharmacy in question (commonly known as the officinal formula). 3. Medicinal products intended for research and development trials. 4. Intermediate products intended for further processing by an authorised manufacturer. 5. Any radionuclides in the form of sealed sources. 6. Whole blood, plasma or blood cells of human origin.	a. medicinal products prepared in a pharmacy in accordance with a medical prescription for an individual patient ('magistral formula'); b. medicinal products prepared in a pharmacy in accordance with a pharmacopoeia and intended to be supplied directly to the patients served by the pharmacy in question ('officinal formula') c. investigational medicinal product as defined in Article 2, paragraph 5, of Regulation (EU) No 536/2014 Paragraph 6: Medicinal products referred to in paragraph 5, point (a), may be prepared in duly justified cases in advance by a pharmacy serving a hospital, on the basis of the estimated medical prescriptions within that hospital for the following seven days.

Sources: Directive 2001/83/EC (current) and Proposal for a Directive of the European Parliament and of the Council on the Union code relating to medicinal products for human use, and repealing Directive 2001/83/EC and Directive 2009/35/EC (proposed). Text in green indicates an addition in the proposed legislation compared to the current legislation, whilst text in red has been removed and no longer has a direct counterpart in the proposals.

3.2.1.2 Perspectives from the field

Among contributing stakeholders, there is broad consensus that pharmacy preparations can be a useful or even essential solution in situations where there is no suitable licensed product on the market. As such, the inclusion of this exemption in the legislative text is undisputed. There are, however, different viewpoints on the degree to which the proposed text provides the right conditions for the use of pharmacy preparations. On the one hand, there is concern, particularly among pharmaceutical companies, that the slight broadening of the scope for preparing magistral formulations under Article 1(6) could open the door for more widespread use of pharmacy preparations, including by specialised compounding pharmacies[58]. If the increased space is used also to prepare medicines for which there is a licensed product on the market, this could have the effect of undercutting that market. However, given that the proposed Article 1(6) limits the preparation to patients *within* the hospital and that the amount produced cannot exceed the estimated number of prescriptions during a 7-day period, the possibility for such extended use appears very limited. No clarity has been offered on how the phrase "in duly justified cases" may be interpreted. Here too, though, there are no indications this could be used to significantly stretch the conditions under which pharmacy preparations may be used. Rather, it appears to refer to instances whereby logistical or practical factors would favour less frequent preparation of somewhat larger batches over frequent preparation of very small batches. The total amount of the product prepared as a pharmacy preparation would likely not be impacted.

Industry stakeholders have additionally voiced concerns about the fact that pharmacy preparations are not subject to the same stringent quality control measures as industrially prepared medicines and that therefore their safety and effectiveness cannot be guaranteed to the same level. These concerns, whilst in themselves legitimate, are not fuelled by changes

[58] It should be noted that the Dutch Network of Specialised Compounding Pharmacies ("Netwerk Gespecialiseerde Bereidingsapotheken) was not consulted as part of this quickscan. The network has not published any formal reactions to the proposed legislation.

in the proposed legislation since the basic criteria under which pharmacy preparation is permitted will remain the same. Rather, the concerns appear to arise from a fear that Member States are increasingly looking towards pharmacy preparations as a way of producing low-cost alternatives to licensed medicines. For instance, in a 2017 report, the Council of Public Health & Society advised the Dutch government to encourage the use of pharmacy preparations to ensure the availability and affordability of medicines[59]. Pharmacy preparations have also been recognised as a possible solution to help mitigate shortages[60].

One issue raised by some parties involved in pharmacy preparations is the restriction on the supply of such preparations to patients other than those directly served by the pharmacy in question. The European Association of Hospital Pharmacists (EAHP), for instance, has called on health authorities to facilitate the delivery of pharmacy preparations *between* hospitals, which is seen as a way of facilitating patient access to treatments that need to be prepared in specialised centres[60,61]. The Dutch Society for Nuclear Medicine has similarly called for permitting distribution of nuclear medicines to other pharmacies[62]. Although the IGJ was approached for participation in this study, no input from their side was received. Their position on the current proposals regarding this issue is therefore not known. However, the IGJ has previously indicated, together with the Ministry of VWS, they would like to see a European legal framework that expressly allows distribution of pharmacy preparations to other pharmacies[63]. The minister of VWS has reiterated this position in his response to questions on the issue in October 2023[64]. The proposed wording around pharmacy preparations in the new legislation does not offer this additional legal space and even explicitly upholds the existing restriction. As such, the proposed Directive likely does not fulfil the needs of the IGJ and Ministry of VWS.

Whilst the IGJ and Ministry of VWS have indicated a desire for a legal basis for distribution of pharmacy preparations, industry stakeholders are generally not in favour of a further extension of the legal framework. They argue that the Dutch government's existing instruction has proven effective and sufficient. It is feared that an amendment into EU legislation to allow distribution by compounding pharmacies, similar to the situation in the UK and US (see Section 3.2.1.3), could lead to large scale preparation of medicines outside of the standard regulatory pathways. Such a move can therefore be expected to meet with strong industry opposition. It is important to recognise, though, this opposition is mainly linked to the possibility of pharmacy preparations being used as an alternative to licensed (industrially prepared) medicines – particularly if done for the purposes of cost-savings – rather than to their use in cases where a product is compounded to meet individual patient requirements (e.g. adapted

[59] Development of new medicines: better, faster, cheaper. (2017) Raad voor Volksgezondheid en Samenleving.

[60] EAHP Position Paper on Pharmacy Preparations and Compounding. (2022) The European Association of Hospital Pharmacists

[61] Le Brun PPH. (2019) Preparation has a future! European Journal of Hospital Pharmacy 26:300.

[62] It should be noted that the special position of nuclear medicines derives from the conditions set by the "Circulaire Handhavend optreden bij collegiaal doorleveren van eigen bereidingen door apothekers" of the IGJ and is not the direct result of EU legislation.

[63] https://www.igj.nl/zorgsectoren/geneesmiddelen/geneesmiddelen-zonder-handelsvergunning/collegiaal-doorleveren.

[64] Kamerbrief betreft: "verzoek om reactie op initiatiefnota over 'Geneesmiddelen weer binnen bereik' van het lid Van den Berg (CDA)". 9 Oktober 2023. E. Kuipers, minister van Volksgezondheid, Welzijn en Sport. https://open.overheid.nl/documenten/41e165e7-14d8-427f-9055-8b1b26a6cfb1/file.

formulations/dosages). The opposition could therefore be mitigated if the right conditions are established under which distribution could be allowed.

3.2.1.3 Experiences in other jurisdictions

In the United Kingdom, medicines prepared by a pharmacist (known as 'specials') are regulated under an exception in the Human Medicines Regulations 2012[65]. To manufacture an unlicensed product, a 'Specials' Manufacturing Authorisation' is required. A 'special' can be prescribed in some cases (e.g. when the medicine has not been commercially manufactured or if it has been discontinued, for example). Pharmacists can either formulate it themselves or have a pharmaceutical specials manufacturer do so.

In the United States, under the Compounding Quality Act of 2013, certain medicinal products may be prepared by pharmacies or at 'outsourcing facilities' on a per patient basis without FDA market approval. This is only used where there is no appropriate FDA-approved medicine. Medicines produced by a compounding pharmacy without or prior to receiving a prescription may be introduced into "interstate commerce", meaning that they can be distributed to anywhere within the United States[66].

3.2.1.4 Recommendations

Create an EU-wide legal basis for distribution of pharmacy preparations between pharmacies

Pharmacy preparations have a clear and largely undisputed role within health care, provided this is done within the regulatory boundaries that simultaneously protect patient safety and the pharmaceutical market for authorised medicines. The Commission's proposal for a new directive (Article 1, paragraph 6) slightly increases the regulatory space for the preparation of magistral formulations by allowing pharmacists to prepare medicines not solely on the basis of an already issued prescription but also on the basis of the estimated medical prescriptions for the following seven days. It is unlikely that the extended scope this provides for advance preparation and limited stock keeping will pose a threat to patient safety, or that it will lead to unfair market competition for authorised medicines. Rather, it may reasonably be expected to enable more efficient preparation and ease of access for patients in cases where it would be impractical to prepare smaller batches. As such, **the Dutch government should welcome this legislative addition, which appears in line with the Ministry's recognition of the importance of pharmacy preparations in ensuring patient access to medicine**.

The current proposal, however, falls short of the Dutch government's stated desire for a regulatory framework that would legally allow for distribution by a preparing pharmacy to other (non-preparing) pharmacies, as is allowed in the UK and US. In the Netherlands, this practice is currently permitted only through a special instruction on enforcement but lacks a legal basis. The Ministry and IGJ have made their position clear that they consider an EU-wide legal basis preferable over the current situation.

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[65] Medicines & Healthcare products Regulatory Agency: The supply of unlicensed medicinal products ("specials"). MHRA Guidance Note 14. https://assets.publishing.service.gov.uk/media/645e19f5ad8a03000c38b3bc/The_supply_of_unlicensed_medicinal_products__special_GN14.pdf.

[66] https://www.help.senate.gov/imo/media/Section-by-Section_PCQA.pdf

From a patient's rights perspective, there are clear arguments in favour of allowing distribution of pharmacy preparations between pharmacies[67]. Most importantly, for specialised products – including those based on radioisotopes – only a limited number of pharmacies may have the required compounding capabilities or access to the raw materials needed. In such cases, distribution may be the only viable way for pharmacies without these capabilities or materials to provide their patients access to important medicines. Allowing for products to be made in specialised compounding facilities and be distributed from there to non-preparing pharmacies also has potential benefits in terms of quality assurance and cost-efficiency. At the same time, from the perspectives of fair competition and promoting innovation, it is not desirable that compounding pharmacies are enabled to compete with producers and distributors of licensed medicines. It is therefore important to maintain clear limits on the distribution of pharmacy preparations to avoid the emergence of a parallel market that does not fall under the same regulatory requirements and oversight provided for by the EU legislation.

This balance between interests is at present reflected in the Dutch instruction, which condones the distribution of pharmacy preparations only if there is no adequate licensed alternative on the market[55]. The IGJ, together with the CBG-MEB, also seeks to encourage preparing pharmacies to file for a marketing authorisation, when appropriate. In this way, it recognises that in certain situations pharmacy preparations are the best or even only solution for patients and that access to such preparations should be facilitated as much as possible, whilst also emphasising the importance of the conventional regulatory pathways for authorisation.

In itself, it could be reasoned that the Dutch instruction offers sufficient regulatory space to protect the interest of Dutch patients and that, since the proposed revisions to the EU legislation do not materially affect the practice, the present situation could be sustained as is. On the other hand, the absence of a legal basis in the EU regulatory framework makes the Dutch practice vulnerable to legal challenges. Given that in past the ECJ has ruled to confirm the strict interpretation of the exception accorded to pharmacy preparations and that the current proposals do not change the basic conditions, it must be assumed the legal space for large scale production and distribution of pharmacy preparations will not change with the proposed revisions. Whilst thus far the Dutch instruction has not been challenged, it is an open question whether this situation will be allowed to continue. For more legal certainty in the future, it would therefore be preferable if the EU framework would be more aligned with current Dutch practice. **It is therefore recommended that the Dutch government proposes amendment of Art. 1 Para. 5(b) of the new Directive to provide an EU-wide legal basis for distribution of pharmacy preparations, outlining the conditions under which such should be allowed, similar to the existing Dutch instruction on enforcement**.

Specifically, this would require an amendment to Art. 1 Para. 5(b) of the proposed Directive to replace the wording "intended to be supplied directly to the patients served by the pharmacy in question" with an alternative that additionally allows patients of other dispensing pharmacies to be served if further conditions are met, namely:

- There is no licensed alternative medicinal product available on the market;
- The pharmacotherapeutic rationale is demonstrated;
- Product dossiers are available;

[67] Scheepers, H. (2017). Pharmacy preparations: European quality standards and regulation . [Doctoral Thesis, Maastricht University]. Datawyse / Universitaire Pers Maastricht. https://doi.org/10.26481/dis.20170517hs

- Production complies with Good Manufacturing Practice (GMP);
- Neither the preparing nor the dispensing pharmacy is allowed to advertise for unlicensed medicines.

3.2.2 Hospital exemption for ATMPs

Regulation (EC) No. 1394/2007 ('the ATMP Regulation), which was adopted in 2007, prescribes that all ATMPs must proceed through the EMA's centralised procedure to obtain a marketing authorisation. Some ATMPs, though, are highly specialised and used to treat rare conditions affecting very few patients. These small patient populations can make the commercialisation of treatments unattractive, to the point where parties are not incentivised to make the investments needed for clinical development and apply for a marketing authorisation. Furthermore, some treatments must be produced from a patient's own cells or tissue (autologous therapies). This requires their preparation close to the patient, typically at the site of treatment. Because of such factors, the marketing authorisation route is not always feasible for ATMPs, necessitating an alternative pathway to realise patient access to such treatments.

The space for this is provided by Article 28(2) of the ATMP Regulation, which introduces an amendment to Directive 2001/83/EC[68]. This article lays down the conditions for application of a so-called Hospital Exemption (HE), which exempts certain ATMPs from the need for a centralised marketing authorisation. Instead, it places the power to grant authorisation for manufacturing of these products with the competent authority of the Member States. The HE may be granted only if a product is prepared:

(i) on a non-routine basis according to specific quality standards

(ii) used within the same Member State in a hospital under the exclusive professional responsibility of a medical practitioner,

(iii) in order to comply with an individual medical prescription for a custom-made product for an individual patient

In the preamble to the ATMP Regulation, the Commission emphasises that for products under the HE the "relevant Community rules related to quality and safety" must be upheld. Nevertheless, the HE does not require the existence of an equivalent product with a marketing authorisation and is, in fact, frequently used for the preparation of treatments for which there is no authorised version. Therefore, therapies provided under the HE may not always have been subjected (yet) to a rigorous evaluation to determine their safety and efficacy. The use of potentially unproven therapies raises some ethical concerns and should therefore be done only as a measure of last resort when there are no other treatment options available for a patient[69]. Because of the potentially greater risks associated with the use of medicines produced outside of the highly regulated pathways for marketing authorisation and manufacturing, the HE pathway must be seen as an exception to be used with great restraint. The exception is nonetheless very important, as for some unmet needs it can represent the only route for patients to access innovative ATMPs.

[68] Directive 2001/83/EC forms part of the current EU general pharmaceutical legislation.

[69] Cuende N, Ciccocioppo R, Forte M, Galipeau J, Konomou L, Levine BL, Srivastava A, Zettler PJ. (2022) *Patient access to and ethical considerations of the application of the European Union hospital exemption rule for advanced therapy medicinal products*. Cytotherapy 24: 686-690.

Since the hospital exemption clause is an amendment to a Directive, it requires transposition into national legislation. Member States may include additional evaluation criteria and requirements in their national legislation to further regulate the implementation of the exemption. In the Netherlands, the IGJ may grant a hospital exemption for ATMPs if they are prepared "according to a prescription for a made-to-order medicine used for a particular patient on a non-routine basis according to specific quality standards […] in a hospital under the exclusive professional responsibility of a doctor"[70]. The IGJ has specified that this means the preparation may be done for no more than 10 patients and that the product may only be released by the hereto Qualified Person if that person is in possession of a prescription note and completed doctor's statement[71]. The product must furthermore be prepared in accordance with the GMP principles by the Qualified Person, who is also responsible for pharmacovigilance and traceability of both the product and the patient. Annually and at the end of treatment any side effects and adverse events must be reported to the IGJ (with serious cases requiring immediate notification). An exemption will not be granted if there are alternatives (authorised or non-authorised) with the same or similar effect. The IGJ places no specific requirements on demonstration of efficacy or on the generation of clinical evidence.

Currently, there is substantial variation between Member States on the interpretation and application of the HE, with some countries effectively prohibiting the practice and others having a relatively 'liberal' interpretation. A 2020 study on the HE pathway in 7 EU countries, for instance, found that whilst regulatory conditions for use of the HE were relatively favourable in Finland, Italy and the Netherlands, conditions in Belgium and Germany were not[72,73]. Variability includes the clinical evidence base, with some countries requiring demonstration of safety and efficacy before granting a HE license, whilst others do not. There is at present no central repository of information on how many HE licenses have been granted (or refused), where they have been granted and for which products. This lack of transparent, comprehensive and comparable information is an important barrier to a more harmonised application of the regulatory framework across the EU. In the Netherlands, the responsibility for evaluation of applications for a HE license rests with the IGJ. Manufacturing under a HE license is limited to a specified number of patients or batches (with a permit granted for a maximum of one year).

It is worth highlighting that the space created by the hospital exemption means that the role of product developer has been shifting somewhat from pharmaceutical and biotech companies to academic and non-profit parties. Such non-commercial operators typically have less experience with the regulatory processes involved with developing and manufacturing a new medicine. Consequently, they may be in greater need of regulatory advice and support than traditional medicinal product developers.

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[70] Geneesmiddelenwet Hoofdstuk 4. De handelsvergunning voor geneesmiddelen. Art. 40.3.d.

[71] Vragen en antwoorden over de hospital exemption voor ATMPs. Dutch Health and Youth Care Inspectorate. https://www.igj.nl/publicaties/vragen-en-antwoorden/vragen-en-antwoorden-over-de-hospital-exemption-voor-atmp%E2%80%99s.

[72] Coppens DGM, Hoekman J, De Bruin ML, Slaper-Cortenbach ICM, Leufkens HGM, Meij P, Gardarsdottir H. (2020) *Advanced therapy medicinal product manufacturing under the hospital exemption and other exemption pathways in seven European Union countries*. Cytotherapy 22; 592-600.

[73] Coppens DG, Gardarsdottir H, Bruin ML, Meij P, Gm Leufkens H, Hoekman J. Regulating advanced therapy medicinal products through the Hospital Exemption: an analysis of regulatory approaches in nine EU countries. Regen Med. 2020 Aug;15(8):2015-2028. doi: 10.2217/rme-2020-0008.

3.2.2.1 Proposed legislative changes

In the previously discussed concept paper on core definitions[57], EMA/HMA experts reflect on the definition of some of the concepts that relate to the scope of Directive 2001/83/EC and the derogations from this directive. At present, the Directive applies only to products that are "prepared industrially or manufactured by a method involving an industrial process" but not to products "prepared on a non-routine basis". The ATMP Regulation extends this derogation also to ATMPs prepared on a non-routine basis[74]. However, neither legislative act defines what is to be understood by 'industrial'. The EMA/HMA experts note that this has led to different approaches in the interpretation of whether the derogation is applicable. Additionally, they highlight that the term might be overly restrictive within the dynamic field of medicines. It was therefore suggested to remove the phrase 'prepared industrially or manufactured by a method involving an industrial process' from the legislation, and to focus only on the derogations (taking an "all-in except if specifically excluded" approach). This recommendation was taken up in the proposals for revision of the legislation which maintain the phrase "non-routine basis" for the derogation but no longer refer to industrial process to demarcate the scope of the legislation (Table 3). The concept papers clarify that this removal has no further bearing on the scope of the derogation itself. It should therefore be understood that the criteria for applicability of the HE have not changed in the proposed revisions.

The EMA/HMA experts furthermore recommend a harmonisation of oversight between Member States of the HE clause and a requirement of "some proof of safety and efficacy (similar to what would be required for an early clinical trial)". In line with these recommendations, the proposed legislation maintains the HE in much the same form as before, but introduces further rules with regards to notification, quality standards and data collection. First, to obtain better oversight of how, when and where the HE is being used, and what the experiences with this are, it is proposed to make it mandatory for national competent authorities to inform the EMA of any approvals granted or revoked for use of the exemption. This will enable more central collection of information on use of the HE compared to the current situation and enable the EMA to prepare periodic reports on experiences with the HE.

A second important change is the requirement that all manufacturing is done in accordance with quality standards equivalent to GMP requirements[75] and that data are collected on use, safety and efficacy. NCAs will be responsible for overseeing these aspects and for annually relaying the obtained data to the EMA, which will maintain a central repository of the data.

Table 3 Overview of proposed changes regarding the hospital exemption

Current	**Proposed**
ATMP Regulation No 1394/2007 • Preamble	Directive • Article 2

[74] Preamble to Regulation (EC) No 1394/2007, ad. 6.

[75] As opposed to the previous, more general, requirement that "specific quality standards" must be met.

… The scope of this Regulation should be to regulate advanced therapy medicinal products which are intended to be placed on the market in Member States and either prepared industrially or manufactured by a method involving an industrial process, in accordance with the general scope of the Community pharmaceutical legislation laid down in Title II of Directive 2001/83/EC. Advanced therapy medicinal products which are prepared on a non-routine basis according to specific quality standards, and used within the same Member State in a hospital under the exclusive professional responsibility of a medical practitioner, in order to comply with an individual medical prescription for a custom-made product for an individual patient, should be excluded from the scope of this Regulation whilst at the same time ensuring that relevant Community rules related to quality and safety are not undermined. • Article 28 (2), amending Directive 2001/83/EC "Any advanced therapy medicinal product, […], which is prepared on a non-routine basis according to specific quality standards, and used within the same Member State in a hospital under the exclusive professional responsibility of a medical practitioner, in order to comply with an individual medical prescription for a custom-made product for an individual patient. Manufacturing of these products shall be authorised by the competent authority of the Member State. Member States shall ensure that national traceability and pharmacovigilance requirements as well as the specific quality standards referred to in this paragraph are equivalent to those provided for at Community level in respect of advanced therapy medicinal products […]"	1. "… this Article shall apply to advanced therapy medicinal products prepared on a non-routine basis in accordance with the requirements set in paragraph 3 and used within the same Member State in a hospital under the exclusive professional responsibility of a medical practitioner, in order to comply with an individual medical prescription for a custom-made product for an individual patient ('advanced therapy medicinal products prepared under hospital exemption'). 2. The manufacturing of an advanced therapy medicinal product prepared under hospital exemption shall require an approval by the competent authority of the Member State ('hospital exemption approval'). Member States shall notify any such approval, as well as subsequent changes, to the Agency. The application for a hospital exemption approval shall be submitted to the competent authority of the Member State where the hospital is located. 3. Member States shall ensure that advanced therapy medicinal products prepared under hospital exemption comply with the requirements equivalent to the good manufacturing practices and traceability for advanced therapy medicinal products referred to in Articles 5 and 15 of Regulation (EC) No 1394/2007 32 respectively, and with pharmacovigilance requirements equivalent to those provided for at Union level pursuant to [revised Regulation (EC) No 726/2004]. 4. Member States shall ensure that data on the use, safety and the efficacy of advanced therapy medicinal products prepared under hospital exemption is collected and reported by the hospital exemption approval holder to the competent authority of the Member State at least annually. The competent authority of the Member State shall review such data and shall verify the compliance of advanced therapy medicinal products prepared under hospital exemption with the requirements referred to in paragraph 3. 5. If a hospital exemption approval is revoked due to safety or efficacy concerns the competent authority of the Member States that approved the hospital exemption shall inform the Agency and the competent authorities of the other Member States. The competent authority of the Member State shall transmit the data related to the use, safety and efficacy of an advanced therapy medicinal product prepared under the hospital exemption approval to the Agency annually. The Agency shall, in collaboration with the competent authorities of Member States and the Commission, set up and maintain a repository of that data.

Sources: ATMP Regulation No 1394/2007 (current) and Proposal for a Directive of the European Parliament and of the Council on the Union code relating to medicinal products for human use, and repealing Directive 2001/83/EC and Directive 2009/35/EC (proposed). Text in green indicates additions in the proposed legislation compared to the current legislation. Text in red indicates an element in the current legislation that has been removed or replaced in the proposed legislation.

3.2.2.2 Perspectives from the field

Whilst the proposed legislative text does not offer any substantive changes to the conditions under which the HE may be used, these conditions are the subject of ongoing discussion. This discussion is fuelled by widespread expectations that the development of ATMPs will increase in importance, accelerated by the trend towards personalised medicine, and mark a shift in how patients in future may be treated. This creates the possibility that new treatments will

increasingly be produced outside of the traditional paradigms for medicinal product development and manufacturing. *In extremis*, this could mean that a pathway that was expressly designed as an exemption evolves into a new 'normal'. Whilst such a future may still be largely hypothetical, already the present situation gives rise to questions about quality assurance and standardisation, evidence generation and possible market distortion. More specifically:

- A key concern voiced, not only by representatives of the innovative pharmaceutical industry but also by academic experts, involves potential problems around standardisation of production and quality assurance of products made under a HE. Pharmaceutical industry stakeholders indicate that they are held to different standards than academic developers. In that regard, the proposed amendment (Article 2, paragraph 3) that will require that ATMPs produced under a HE must meet requirements equivalent to the GMP standards that apply to industry may be considered a relevant addition to the legislation which addresses an existing concern. Additionally, the centralisation of information on the use of the HE through mandatory reporting to the EMA may allow greater sharing of information among holders of a HE license and improve standardisation. At the same time, it is conceivable that the raising of the bar will make it harder for non-commercial developers and slow down innovation coming out of academia.
- A further concern stems from the investigational nature of many treatments produced under the HE pathway, as it essentially allows these products to be fast-tracked from the lab to the patient without following the standard route of building the clinical evidence base needed for scientific evaluation and regulatory assessment. This raises the spectre of patients being treated with products that have not been vetted for safety and efficacy in the same way that they would have been had they gone through the process of applying for a centralised marketing authorisation. Products used without a marketing authorisation also do not fall under the same post-authorisation requirements for patient monitoring and collection of data that could be helpful in further product development. This situation is suboptimal from both a patient-perspective and a broader system-perspective.
- Pharmaceutical developers consider the different evidentiary and regulatory standards applied to holders of a marketing authorisation (usually industry) and of a HE license (often academia/hospitals) unfair competition and a potential disincentive for industry to invest in the development of ATMPs. New requirements in the proposed legislation (Article 2 paragraph 4) may go some way towards levelling the playing field by requiring holders of a HE license to collect and report, at least annually, data on use, safety and efficacy to the NCA. As the proposal does not offer specifics on the standards for this data, it cannot be fully determined whether this would bring the data collection requirements on HE license holders on par with those that apply to marketing authorisation holders. In the current proposal for new Directive (Article 2, paragraph 7), the Commission indicates such details will be laid down further in implementing acts that have not yet been published[76]. The strengthened requirement that HE products must be produced according to GMP standards similarly may reduce existing differences in standards applied to industry and academia/hospitals.

While the above concerns may, at least to an extent, be addressed by the current legislative proposal, a separate issue has been raised concerning the continued prohibition of import and

[76] The study team is not aware of the stage in which this process currently may be.

export of products manufactured under a HE license between Member States. Several patient and advocacy organisations, academics and medical professionals are advocating for its removal, to allow preparation of products not only for use "within the same Member State" (Article 2, paragraph 1) but for treatment of patients in other Member States as well. The main arguments in support of this proposal are rooted in uneven access to innovative ATMPs across the EU. There are several reasons for this, including:

- The production of ATMPs can be very complex and the skills base and resources needed for hospitals to manufacture products under a HE license are not present equally in all Member States.
- Because the treatment populations are often small, local production of ATMPs can be very inefficient and costly. This can make it economically unfeasible for parties to manufacture medicines at a small scale, even under the HE pathway.
- Localisation of clinical trials. Patients in countries where there are more clinical trials will have greater access to investigational treatments, including ATMPs[77].

Removing the restriction on use of products prepared under a HE license in another Member State would allow for products to be centrally prepared in a standardised manner in the hereto most qualified site and be transported from there to patients in other Member States. This could improve the quality of production and increase patient access, whilst economies of scale could have the additional benefit of lowering the cost of treatment.

The IGJ, as the authority responsible for approving HE licenses in the Netherlands, did not respond to our request for participation in this study. It is therefore not possible to provide their perspective on the current amendments concerning the HE or on the feasibility of removing territorial restrictions.

3.2.2.3 Experiences in other jurisdictions

None of the jurisdictions considered in this Quickscan appears to have a dedicated framework in place for allowing the production and supply of ATMPs without a marketing authorisation or manufacturing license. Special measures do exist, however, for the use of investigational medicines, including ATMPs.

In the United States, the Federal Right to Try Act of 2018 creates a framework for patients to access investigational therapies, including products that have been designated as Regenerative Medicine Advanced Therapies, outside of the FDA's expanded access programme. Use of a medicine through this act is exempt from FDA requirements for authorisation, though the manufacturer must comply with FDA requirements for investigational medicines and report to the FDA on various aspects (number of doses, adverse events etc.). To obtain the exemption, an Investigational New Drug (IND) application must be filed[78]. Three types of IND exist (Box 1). The 'treatment IND' most closely matches the conditions applied in the EU to the HE although it explicitly ties the exemption to the further conduct of clinical work,

[77] Where clinical trials are conducted, in turn, depends on such factors as: presence of research infrastructures and academic hospitals, national laws and frameworks for the conduct of clinical research, capacity of local health systems to diagnose, treat and manage patients within the trial.

[78] Investigational New Drug Application. USFDA. https://www.fda.gov/drugs/types-applications/investigational-new-drug-ind-application)

unlike in the existing EU framework. The IND may be commercial or for research (non-commercial) purposes.

Under Federal law, in the US a medicine must be the subject of an approved marketing application before it may be transported or distributed across state lines. The grant of an IND, however, provides an exemption from this legal requirement and allows for the medicine to be shipped across state lines for investigational purposes.

Box 1 Types of Investigational New Drug application in the United States

- **Investigator IND**: submitted by a physician who both initiates and conducts an investigation, and under whose immediate direction the investigational drug is administered or dispensed. A physician might submit an investigator IND to propose studying an unapproved drug, or an approved product for a new indication or in a new patient population.
- **Emergency Use IND**: allows the FDA to authorise use of an experimental drug in an emergency situation that does not allow time for submission of an IND […]. It is also used for patients who do not meet the criteria of an existing study protocol, or if an approved study protocol does not exist.
- **Treatment IND**: submitted for experimental drugs showing promise in clinical testing for serious or immediately life-threatening conditions while the final clinical work is conducted, and the FDA review takes place.

In the United Kingdom, the MHRA is introducing a one-of-a-kind framework to allow the manufacture of innovative medicines at the point of care to ensure the supply to patients through clinical trial studies to marketing authorisation[79,80]. This plan will apply to all point-of-care products manufactured in the UK, including ATMPs. The framework will ensure there are no undue regulatory barriers, while maintaining quality and safety standards. Legislation is being introduced to support this framework but the framework itself has not yet been released.

3.2.2.4 Recommendations

In light of the above considerations, the following recommendations are offered for the Dutch government to consider in respect to the hospital exemption for ATMPs.

Further increase transparency on application of the HE framework across Member States

The regulatory space offered through the HE serves an important role in providing patients access to innovative and investigational therapies. However, the pathway has thus far been used very differently across the EU, without central oversight on which products are produced under a HE, where and when or what the experiences with these products are. The proposed legislation's new requirements aim to enhance transparency on this by mandating data collection and reporting on the use, safety, and efficacy of ATMPs approved under a HE. The

[79] Medicines and Healthcare products Regulatory Agency (2023). Press release: UK to introduce first-of-its-kind framework to make it easier to manufacture innovative medicines at the point of care. Available at: https://www.gov.uk/government/news/uk-to-introduce-first-of-its-kind-framework-to-make-it-easier-to-manufacture-innovative-medicines-at-the-point-of-care

[80] Medicines and Healthcare products Regulatory Agency (2023). Consultation outcome: Consultation on Point of Care manufacturing. Available at: https://www.gov.uk/government/consultations/point-of-care-consultation/consultation-on-point-of-care-manufacturing

information relayed to NCAs would be collected centrally by the EMA on an annual basis. These changes are widely welcomed but some stakeholders feel they may not yet go far enough as access to this information would be accessible only to the regulatory agencies and collected just once a year. Some interviewed stakeholders have suggested that at least the information on where and which products have been produced under a hospital exemption could be made available to other interested parties, such as physicians, patient organisations and industry, as well. From the perspective of patients and their physicians, this information could aid in identifying where treatment options may be available. Regular publication of data on potential safety concerns or (lack of) efficacy with HE products could also support more informed decision-making when considering treatment with these products. From an industry perspective, the information could be used in identifying market needs.

The desirability or feasibility of such third-party transparency has not been further explored with other stakeholders. In general, however, greater transparency would appear to be in the public interest, provided data disclosure is done in full consideration of all privacy and data protection rules. This could mean that information shared with third parties is limited to the organisational details of HE license applicants, the outcomes of the application and a description of the treatment for which the license is granted, including for how many treatments. By contrast, any information about treatment outcomes should remain confidential. **It is recommended that the Dutch government proposes an additional article to require periodic sharing of relevant data collected by the EMA on the grant (or refusal) of HE licenses with third parties.**

Protect the ability of Member States to set national rules and conditions concerning the application of the HE framework

Some stakeholders have expressed concern about a further push to harmonise application of the HE framework across Member States. The regulatory environment in the Netherlands has been assessed as relatively 'motivating' for use of the HE pathway, as evidenced by the comparatively greater number of licenses granted in the Netherlands than in other EU countries[72]. Motivating factors include short application timelines and a regulatory mandate that favours the HE over other exemption pathways. Some stakeholders fear that this situation could be in jeopardy if harmonisation efforts go in the direction of more restrictive application of the framework. They therefore urge the Dutch government to resist any attempts by other actors – either during the negotiations on the proposal or in a separate process – to further limit the scope of the HE.

Whereas the current proposals offer no indication of a movement in this direction, it is possible that the negotiations will bring up new suggestions for amendments to the text that would impact on the practice in the Netherlands. **It is thus recommended the Dutch government carefully monitors the negotiation discussions for any further modifications to the HE framework and is clear in its position on the regulatory space it wishes to protect at a national level for this practice. More specifically, it is recommended this space is not significantly curtailed compared to the current situation.**

Permit the (conditional) parallel distribution of products produced under a hospital exemption within the EU

From the perspective of patient access to treatment, the continued prohibition on the export and import of treatments prepared under the HE runs somewhat counter to the Commission's stated aim of "*addressing unequal patient access of medicinal products*" through the revision

of the EU general pharmaceutical legislation. It is therefore justified to consider the motivations behind this prohibition and assess whether these outweigh potential advantages of its removal.

Neither the original ATMP Regulation nor the current proposal for revision of the legislation provide an explicit motivation for including the wording "within the same Member State" into the legislative text. Given the legislation's general objective of guaranteeing a high level of public health by ensuring the quality, safety and efficacy of medicinal products for EU patients, it may be assumed that the restriction stems from concerns about the ability to do so if these products are used outside of the Member State where they have been produced. Alternatively, the restriction may have been motivated by concerns that, without it, the hospital exemption could make the European environment less attractive for the innovative pharmaceutical industry.

There are of course legitimate concerns about the ability to maintain product integrity and assure the quality of treatment when products are moved across considerable distances, possibly requiring handling by multiple parties along the supply chain. ATMPs are complex and often fragile products that require careful handling by qualified experts and may need special care, such as refrigeration, to maintain product quality. These aspects are much harder to control when the product must be transported from one Member State to another than if a product is used within the same facility where it is produced. Nonetheless, these concerns by themselves should not be considered sufficient to justify a blanket prohibition on import/export of *all* ATMPs produced under a HE. Rather, they merit a case-by-case assessment to determine whether a particular product or class of products can be transported from one specified location to another under conditions whereby the product integrity can be sufficiently guaranteed. This assessment should be accompanied by the establishment of a chain of custody to specify which party has responsibility for the product at what point. The parallel distribution of biological medicines (e.g. mRNA vaccines) is by itself not new and there are specialised distributors that can manage such transport in compliance with Good Distribution Practice (GDP) guidelines.

In this light, it is also worth noting that in the EU the transport of blood, cells and tissue across Member State borders is already permitted. These types of products share many of the characteristics of ATMPs. A new Regulation on substances of human origin (SoHO), for which the text was recently provisionally agreed, even explicitly underlines the importance of "the cross-border exchange of SoHO"[81]. The Regulation addresses potential safety concerns by indicating that "quality control is a key element of a quality management system that is critical for the safe release of SoHO for human application or for distribution or export." The fact that the United States allow for the transport of investigational ATMPs across state lines if an IND has been granted further underscores that the need for transportation itself is insufficient ground for a full prohibition on import/export, given the even greater distances that may need to be covered in the US than within the EU.

Although it has not been explicitly articulated in any identified policy documents or position papers, another plausible concern arising from the cross-border transport of HE products could pertain to the capacity in the importing Member State to administer the product properly and conduct the necessary clinical management of patients treated with it. Here too, though, a

[81] Proposal for a Regulation on standards of quality and safety for substances of human origin intended for human application and repealing Directives 2002/98/EC and 2004/23/EC. (30 January 2024) European Commission. https://data.consilium.europa.eu/doc/document/ST-5389-2024-INIT/en/pdf.

case-by-case assessment conducted at the level of the facility where the product would be used would appear to be a more proportionate response.

A separate argument potentially motivating a ban on cross-border use of the HE may be found in the need to protect the 'exceptional' nature of the pathway. Allowing for HE products to be transported to other Member States could be viewed as diluting this exceptionality by allowing the product to be used at a wider scale. This argument can be countered by the recognition that, also under the proposed revisions, the conditions for grant of a HE license still require that the product is "prepared on a non-routine basis" and only in case there is "an individual medical prescription for a custom-made product for an individual patient". These conditions already apply equally in all Member States and therefore the total number of patients for whom preparation of a HE product would be permissible would be unaffected. Rather, removal of the restriction would enable patients in countries where the capacity for HE preparation of a particular product is lacking to enjoy the same access as patients in countries where that capacity is available. Thus, whilst indeed the number of patients treated with HE products could increase, the exceptional nature of the pathway would still apply in equal measure as today.

Based on the above considerations, **it is recommended that the Dutch government suggests or supports an amendment of the legislative proposals concerning the hospital exemption to lift the prohibition on the cross-border movement of products prepared under a HE license within the EU.** This would, at a minimum, require removing the words "used within the same Member State" from Article 2 of the proposed Directive, although this move would preferably be accompanied by further wording to set out the broad conditions under which such movement may be permissible. These broad conditions could include, at a minimum, the following elements:

- To be allowed to treat patients with a product prepared under a HE license in another Member State, the responsible treatment facility must apply for a special 'parallel import license for HE products' with the NCA in their own country. The NCA must assess the application to:
  - establish if the same criteria that apply to HE licenses nationally have been fulfilled, including those concerning 'preparation on a non-routine basis' and for an individual medical prescription.
  - determine whether the quality and safety of the product can be sufficiently guaranteed during transport (possibly with explicit reference to GDP guidelines) and whether an appropriate chain of custody has been established.
  - determine whether the treatment facility has adequate capacity to administer the product and conduct the clinical management of the patient.
- Obligations on holders of a parallel import license for HE products concerning the data collection and sharing of information with the NCA should be comparable to those on holders of a nationally issued HE license.

The NCA must share this information with the EMA in the same manner as for HE licenses.

To further protect the exceptional nature of the pathway, additional criteria could be considered that would limit the grant of a parallel import license for HE products to situations where import is the only viable option for access or is otherwise preferable over local production. Additionally, allowing for parallel distribution of HE products between Member States should not create a situation whereby variation in the national legislation concerning HE products is misused to apply for HE licenses in countries where they are most easily obtained rather than in those countries where the product is needed. It should also be avoided that the

possibility is misused to create a commercial market for HE products. Possible conditions to achieve this could take the following form:

- A treatment facility applying for a parallel import license for HE products must demonstrate that:
  - it does not itself have the required capabilities and/or resources to produce the product to the same standards as that of the product it wishes to import, nor do these capabilities and resources exist elsewhere within that Member State.
  - the required capabilities and/or resources could not be obtained through transfer of know-how and technology within a timeframe that does not unduly delay treatment or endanger the patient.
- An HE license may only be granted if there is a nationally identified need for the product and production may not be done solely for the purpose of parallel distribution to another Member State.
  - Parallel distribution of HE products is only allowed on a non-profit basis. The producer may request reimbursement for the costs of manufacturing and transport only.

Useful lessons for the development of further guidance could perhaps be drawn from the parallel distribution of centrally approved medicines within the EU. Here, the EMA is responsible for checking regulatory compliance of parallel distributors. However, the study authors have insufficient knowledge of the processes concerned with this form of parallel distribution to offer specific recommendations in the context of HE products. Rather, **it is recommended that further discussions with experts from the EMA and NCAs, as well as with HE license holders and applicants are held to develop the necessary guidance and criteria**.

Given that the current restriction is embedded in the proposal for a new Directive, its removal would require a direct amendment to this legislative text (Article 2, paragraph 1). The suggested conditions could either be included directly into the Directive or be part of implementing legislation or guidelines. It is important to ensure that the basic framework conditions apply equally in all Member States. It is furthermore relevant to note that striking the restriction from a legislative text at Union level would only serve to no longer formally *prohibit* cross-border movement of products approved under a hospital exemption but would not mandate individual Member States to allow these products to be imported and used (or reimbursed) within their own countries (as these decisions fall under national competencies). Further conditions or restrictions on the parallel distribution of HE products may therefore be set at Member State level in national legislation.

Encourage the use of conventional regulatory pathways over the HE route

Although the HE route serves a clear purpose from the perspective of patient access to treatment, the EU general pharmaceutical framework was developed to promote the generation of evidence on effectiveness and safety and protect patients by requiring regulatory approval. As such, whenever possible, conventional access pathways should always be preferred over the HE route and product developers should be motivated to generate the clinical evidence necessary to support an application for a marketing authorisation. The Commission's expressed intent to set up a dedicated Academia Office may prove to be an important tool in supporting this. Also, the new Clinical Trials Information System (CTIS) that is being developed will be useful in matching patients to ongoing clinical trials.

Industry actors have suggested that, to protect the exceptional nature of the HE route, its use should be limited to situations where:

- there is an unmet medical need;
- there is no (centrally) authorised product on the market;
- there is no relevant ongoing clinical trial, or a patient is not eligible for these trials;
- the product cannot be obtained through other exemption routes, such as named-patient basis access or compassionate use programmes.

Although these suggestions objectively have merit, considering the importance of stimulating the generation of evidence and not undercutting (commercial) innovation, in practice there is only limited overlap between manufacturing under HE and commercial development[72]. Thus, the pathways tend to be complementary rather than overlapping. Adding such limitations directly into EU legislation may therefore be unnecessary. Instead, it should be left to Member States to set further conditions on the issuance of a HE license and take into consideration national contextual factors (e.g. availability of treatment alternatives; capacity of the health system to conduct clinical management). Rather than formally embed these conditions into (national) legislation, the NCA (in the case of the Netherlands, the IGJ) may **consider the availability of alternative treatments or clinical trials in its assessment of an HE license application**. It may also be left to national regulatory authorities to require HE license holders to develop the clinical dossiers needed to support an application for a regular marketing authorisation.

3.2.3 Decentralised manufacturing

Aside from simple manipulations (e.g. dissolving a powder into a solution or dilution of a product), most steps in the production of a medicine fall under the scope of GMP requirements. This means, among other things, that manufacturing may only be done in facilities that are in possession of a manufacturing authorisation and are subject to regular inspections. Manufacturing is therefore typically performed at a limited number of sites that are all listed in the marketing authorisation. However, this manufacturing paradigm has begun to shift with the advent of, among others, additive manufacturing techniques such as 3D-printing of medicines (as described in Section **Error! Reference source not found.**) and point-of-care manufacturing o f products derived from a patient's own material.

The general trend towards more personalised medicines is driving pharmaceutical manufacturing away from large-scale production to smaller batch manufacturing close to the patient. This may mean that some, or even all, of the production steps are performed in locations, such as hospitals and pharmacies, that are not typical pharmaceutical manufacturing facilities. Under the current EU legislation, all of these locations would require their own manufacturing authorisation, GMP certification and registration in the marketing authorisation dossier and would be subject to inspections. The further anticipated trend towards smaller scale production of medicines may thus increase the regulatory burden to an unsustainable level.

Recognising that centralised manufacturing is not always possible, but that the current regulatory system is insufficiently equipped to handle these new manufacturing paradigms, the proposed legislation will allow more space for decentralised manufacturing.

3.2.3.1 Proposed legislative changes

Because of the complexity of ATMPs, in 2017 special guidelines on GMP were introduced that include guidance on the use of 'decentralised sites' for manufacturing of ATMPs. For other product categories there has been no mention of the concept of decentralised manufacturing thus far. The guidance for ATMPs also does not offer details on, for instance, the authorisation requirements for decentralised sites. Seeing a need for further guidance in this area, the

EMA/HMA have advocated for a risk-based and flexible regulatory approach for a range of products – including not only ATMPs but also 3D printed chemical products – to allow their production "in close proximity to the patient" in decentralised locations[82]. They specify that only products "with short shelf life or where there is a clear clinical advantage to administrate the product to patients at point of care should be eligible for DCM."

This EMA/HMA advice has been taken up in the legislative proposal for a new Directive, which offers a derogation from the requirement for a manufacturing authorisation for decentralised sites (Table 4). Instead, decentralised sites will fall under the responsibility of a qualified central site. The product must, nonetheless, be covered by a marketing authorisation[83]. The proposed text offers no further specifications on the conditions for when a product is eligible for DCM. In the aforementioned concept paper, the EMA/HMA also recommends specific guidance is developed for additive manufacturing to ensure consistency and quality of production. It is presumed such detailing will be provided in further guidance that has not yet been published. As such, the current legislative proposals only serve to introduce the broad concepts needed to permit DCM within the confines of the EU regulatory framework but do not offer any operational detailing. The EMA/HMA has recommended that considerations involving the criteria when a product will be eligible for DCM and the different modes to decentralised manufacture "should be given in the legislation and in GMP/quality guidance to ensure that consistent regulatory interpretation is achieved across all member states". More specifically, it is indicated that for this purpose new GMP/GDP guidance should be developed, with corresponding revisions in the Compilation of Community Procedures on Inspections and Exchange of Information.

[82] 04. Concept paper for EC on New manufacturing methods. https://health.ec.europa.eu/document/download/624cd58f-d680-404c-b676-8b65871b3d00_en?filename=mp_revision_concept-papers_compendium_en.pdf.

[83] Making this derogation distinct from the derogations offered by the hospital exemption for ATMPs or pharmacy preparations where a marketing authorisation is not a requirement.

Table 4 Overview of proposed changes regarding decentralised manufacturing

Current	Proposed
Directive 2001/83/EC • Article 40 1. Member States shall take all appropriate measures to ensure that the manufacture of the medicinal products within their territory is subject to the holding of an authorization. […] 2. The authorization referred to in paragraph 1 shall be required for both total and partial manufacture, and for the various processes of dividing up, packaging or presentation. However, such authorization shall not be required for preparation, dividing up, changes in packaging or presentation where these processes are carried out, solely for retail supply, by pharmacists in dispensing pharmacies or by persons legally authorized in the Member States to carry out such processes. Guidelines on GMP for ATMPs (2017) • 11.3.3 Batch release process in cases of decentralised manufacturing "There may be cases where manufacturing of the ATMP needs to take place in sites close to the patient […]. In such cases, manufacturing of the ATMPs may need to be decentralised to multiple sites so as to reach to patients across the EU ("decentralised manufacturing"). This scenario may occur both in the context of authorised ATMPs as well as in the context of investigational ATMPs. […] A 'central site', which should be established in the EU, should be identified. The central site is responsible for the oversight of the decentralised sites."	Directive Chapter XI • Article 142. 1. Member States shall take all appropriate measures to ensure that the manufacture of the medicinal products within their territory is subject to authorisation (the "manufacturing authorisation"). 2. The manufacturing authorisation referred to in paragraph 1 shall be required for both total and partial manufacture, and for the various processes of dividing up, packaging or presentation. 3. By derogation from paragraph 2, the manufacturing authorisation shall not be required for the following: i) preparation, dividing up, changes in packaging or presentation where these processes are carried out, solely for retail supply, by pharmacists in dispensing pharmacies or by persons legally authorised in the Member States to carry out such processes; or ii) decentralised sites carrying out manufacturing or testing steps under the responsibility of the qualified person of a central site referred to in Article 151(3). • Article 148: Registration and listing process of decentralised sites Guidelines on GMP for ATMPs (2017) will remain.

Sources: Directive 2001/83/EC and Guidelines on Good Manufacturing Practice specific to Advanced Therapy Medicinal Products (2017)(current) and Proposal for a directive of the European parliament and of the Council on the Union code relating to medicinal products for human use, and repealing directive 2001/83/EC and directive 2009/35/EC (proposed). Text in green indicates an addition in the proposed legislation compared to the current legislation.

3.2.3.2 Perspectives from the field

The issues raised in connection to decentralised manufacturing are largely the same as those discussed under the 'hospital exemption' (Section 3.2.2.2) regarding quality assurance and standardisation of production. Additional questions are being raised regarding distribution of responsibilities and liability around new, and as yet largely untested, technologies such as 3-dimensional printing (Section 2.3). If, for instance, in the course of 3D printing of medicines a problem occurs with the printing device that diminishes the quality of the medicinal product, is the liability with the producer (or owner[84]) of the printing device or with the centralised site under whose supervision the manufacturing was done? Whilst the proposed legislative framework outlines the general obligations on manufacturing authorisation holders, and by

[84] It is conceivable that 3D printers for medicines will be used by hospitals and pharmacies on a rental basis.

extension centralised sites, it remains to be seen whether this will suffice for entirely new manufacturing paradigms. It may well be that litigation and decisions by the ECJ are needed to provide further guidance on the interpretation of the legislation.

In the Netherlands, additive manufacturing techniques such as 3D printing of medicines are being piloted but it appears that they are not yet used in clinical practice[85]. As such, there is little practical experience that would allow the IGJ, as the regulatory authority responsible, or other parties to assess the fitness of the proposed regulatory framework in the context of these novel production techniques. This lack of practical experience likely explains why stakeholders have been largely quiet on this issue in the legislative proposals.

3.2.3.3 Experiences in other jurisdictions

In 2015, the FDA approved the first medicine manufactured using 3D printing technology: Spritam (levetiracetam), an anti-epileptic. The 3D printing technique enables this product to be created in a porous formulation that is far more easily dissolved than conventional formulations. In the EU, thus far only the conventional formulation has been approved. However, whilst the FDA has issued guidance on technical considerations for medical devices made using 3D printing techniques, it does not appear to have a specific framework in place for decentralised manufacturing or 3D-printing of medicines.

3.2.3.4 Recommendations

Monitor the development of implementing legislation and evaluate experiences with DCM

The introduction of the concept of decentralised manufacturing into the EU general pharmaceutical legislation is a sound reaction to the emergence of new manufacturing paradigms focused on small-scale production of personalised products close to the patient. As such, the proposed revisions are in line with the recommendations offered by regulatory authorities. They provide the necessary legal basis for further development of DCM in regulatory practice. However, in the absence of the corresponding guidance that will offer more details on the application of DCM in practice, it is difficult to assess whether the proposed legislation can offer the required balance between regulatory flexibility and safeguarding the basic tenets of the pharmaceutical legislation regarding safety and efficacy of medicines.

The choice to lay down the specifics concerning implementation of DCM in guidance, rather than directly in the legislative proposals, is justified as such guidance can be more easily updated and adjusted to remain in step with technological developments. As such, the current proposals do not appear to contain any significant points of contention or concern on this issue. Nonetheless, **it is recommended that the Dutch government already explores the Commission's intents regarding future guidance documents to determine whether this would align with its own needs**. Additionally, it may **insist on a periodic report by the Commission on the experiences with DCM to assess whether the regulatory framework requires further revision**.

[85] 3D printing is, however, already more common in the production of medical devices, such as prosthetics or implants.

3.3 Restructuring EMA Scientific Committees

The scientific evaluation of medicines to determine whether a medicine is safe and efficacious and therefore eligible for a marketing authorisation is performed by the **Committee for Medicinal Products for Human use (CHMP)**. The CHMP is made up of experts acting on behalf of each of the NCAs in the Member States (with one member and one alternate), complemented by experts to provide additional expertise in a particular scientific area. The CHMP is supported in its tasks by a number of dedicated scientific committees. These include[86]:

- The **Committee for Orphan Medicinal Products** (COMP) deals with medicines that are being developed to diagnose, prevent, or treat rare diseases. The COMP advises the EC on the granting of an initial orphan designation during the development process, which allows a sponsor access to incentives such as protocol assistance. At the time of marketing authorisation, the COMP assesses whether the developed product fulfils all the requirements to be marketed as a designated orphan medicine, which would entitle the sponsor to orphan market exclusivity. Whilst the formal decision to grant an orphan designation is made by the EC, the recommendation of the COMP herein is usually followed. The COMP comprises one representative from each EU Member State or EEA-EFTA State, three members representing patients' organisations nominated by the EC, and three members of the EC. The committee meets for three days every month.
- The **Paediatric Committee** (PDCO) was created to support the implementation of the Paediatric Regulation (Regulation (EC) No 1901/2006). Its main role is to assess the content of paediatric investigation plans (PIPs), which determine the studies that companies must carry out in children when developing a medicine. The PDCO consists of scientific experts nominated by the Member States,[87] representatives of patients' associations and representatives of healthcare professionals. The PDCO meets for four days once a month.
- The **Committee for Advanced Therapies** (CAT) is responsible for advising the CHMP – through preparation of a draft opinion – on each application for a marketing authorisation for an ATMP. The CAT can also, upon request by the EMA's Executive Director, prepare opinions on any scientific matter relating to ATMPs. Analogous to the COMP and PDCO, the CAT is made up of representatives from each Member State, as well as representatives of patients' organisations and clinicians. The CAT meets once a month.
- The **Pharmacovigilance Risk Assessment Committee (PRAC)** is responsible for assessing all aspects of risk management of medicines and providing recommendations on pharmacovigilance and risk management systems. The PRAC consists of scientific experts nominated by the Member States, complemented by independent scientific experts, representatives of patients' organisations and representatives of healthcare professionals nominated by the Commission. The PRAC meets for four days every month.

The scientific committees for their part can request advice on regulatory procedures from EMA working parties and scientific advisory groups. Members of these are drawn from a pool of experts coming from NCAs and academic institutions maintained by the EMA[88]. The working parties may support the drafting of scientific guidelines and produce strategic plans based on

[86] Scientific committees also exist for medicinal products for Veterinary Use and Herbal Medicinal Products, but these fall outside of the scope of this Quickscan.

[87] Unlike in the COMP, in the PDCO Member State nominate one member and one alternate.

[88] Working parties and other groups. European Medicines Agency. https://www.ema.europa.eu/en/committees/working-parties-other-groups.

the EMA priorities. In 2022, EMA revised the structures and procedures for the working parties, organising these around five domains: quality; non-clinical; methodology; clinical; and veterinary.

Depending on the characteristics of a particular medicine, a single product may be assessed by up to five committees. For instance, developers of an ATMP for the treatment of a rare disease affecting children will have dealings with the CAT, COMP, PDCO, PRAC and CHMP at various stages throughout the development and assessment process. Although the evaluation of the EU Orphan and Paediatric Regulations found no major issues in the cooperation between the various committees, several potential inefficiencies were identified[89]. These related primarily to the different timelines used by different committees. Developers also noted some inconsistencies in the outcomes of procedures.

It is worth noting that, with the increase in the number of designated orphan medicines, the workload of the COMP in particular has increased substantially over time. The associated burden of this, in turn, also has an impact on NCAs as they receive no financial compensation for the work performed by the national delegates to the COMP.

3.3.1 Proposed legislative changes

In response to the potential inefficiencies and inconsistencies arising from the current EMA structures, the Commission is seeking to bring administrative simplification with the new legislation. In the impact assessment that was conducted to inform the revision structural simplification of the EMA as regards to the committees was presented as a way of reducing the administrative costs for both public authorities and businesses. This was presented as a 'horizontal measure', included in all policy options considered, but without further elaboration of what the simplification would entail.

In the legislative proposals this structural simplification was concretised as a reorganisation of the CAT, COMP and PDCO[90] into 'working groups, working parties and a pool of experts who are organised based on different domains', whilst only the CHMP and PRAC will remain as Committees (

[89] Commission Staff Working Document Evaluation. Joint evaluation of Regulation (EC) No 1901/2006 of the European Parliament and of the Council of 12 December 2006 on medicinal products for paediatric use and Regulation (EC) No 141/2000 of the European Parliament and of the Council of 16 December 1999 on orphan medicinal products. (2020) European Commission. https://health.ec.europa.eu/system/files/2020-08/orphan-regulation_eval_swd_2020-163_part-1_0.pdf.

[90] As well as the Committee for Herbal Medicinal Products.

Table 5). The exact structure of these working parties and working groups has not been elaborated on, although it is indicated that they will mostly consist of members appointed by the Member States based on their expertise and of external experts. Member States that are not represented in a working party may request to attend meetings as an observer. Contrary to the present situation, the working parties will function only in a supporting capacity and will have no mandate to make decisions or issue formal recommendations. Alongside this restructuring, it is proposed to transfer the formal power to grant or refuse orphan designations from the European Commission to the EMA.

Table 5 Overview of proposed changes regarding the restructuring of the EMA Scientific Committees

Current	Proposed
EU Orphan Regulation (EC) No 141/2000 • Article 4 2. A Committee for Orphan Medicinal Products, hereinafter referred to as 'the Committee', is hereby set up within the Agency. 3. The task of the Committee shall be: i) (a) to examine any application for the designation of a medicinal product as an orphan medicinal product which is submitted to it in accordance with this Regulation; ii) (b) to advise the Commission on the establishment and development of a policy on orphan medicinal products for the European Union; iii) (c) to assist the Commission in liaising internationally on matters relating to orphan medicinal products, and in liaising with patient support groups; iv) (d) to assist the Commission in drawing up detailed guidelines. 4. The Committee shall consist of one member nominated by each Member State, three members nominated by the Commission to represent patients' organisations and three members nominated by the Commission on the basis of a recommendation from the Agency. The members of the Committee shall be appointed for a term of three years, which shall be renewable. They may be accompanied by experts. Paediatric Regulation (EC) No 1901/2006 • Article 4 1. The Paediatric Committee shall be composed of the following members: a. five members, with their alternates, of the Committee for Medicinal Products for Human Use […]; b. one member and one alternate appointed by each Member State whose national competent authority is not represented through the members appointed by the Committee for Medicinal Products for Human Use; c. three members and three alternates appointed by the Commission, on the basis of a public call for expressions of interest, after consulting the European Parliament, in order to represent health professionals; d. three members and three alternates appointed by the Commission, on the basis of a public call for expressions of interest, after consulting the European Parliament, in order to represent patient associations. […] • Article 6 1. The tasks of the Paediatric Committee shall include the following: a. to assess the content of any paediatric investigation plan for a medicinal product submitted to it in accordance with this Regulation and formulate an opinion thereon; b. to assess waivers and deferrals and formulate an opinion thereon; c. at the request of the Committee for Medicinal Products for Human Use, a competent authority or the	Regulation • Recitals (p. 26-27) (33) To optimise the functioning and efficiency of the regulatory system, the structure of the Agency's scientific committees is simplified and reduced to two main Committees for medicinal products for human use, the Committee for Medicinal Products for Human Use (CHMP) and Pharmacovigilance Risk Assessment Committee (PRAC). (34) The simplification of procedures should not have an impact on standards or the quality of scientific evaluation of the medicinal products to guarantee the quality, safety and efficacy of medicinal products. It should also allow for the reduction of the scientific evaluation period from 210 days to 180 days. (35) The Agency's scientific committees should be able to delegate some of their evaluation duties to working parties which should be open to experts from the scientific world and appointed for this purpose, whilst retaining complete responsibility for the scientific opinions issued by them. (36) The expertise of the Committee for Advanced Therapies (CAT), the Committee for Orphan Medicinal Products (COMP), the Paediatric Committee (PDCO) and Committee for Herbal Medicinal Products (HMPC) is retained through working groups, working parties and a pool of experts who are organised based on different domains and who are giving input to the CHMP and PRAC. The CHMP and PRAC consists of experts from all Member States while working parties consist in majority of experts appointed by the Member States, based on their expertise, and of external experts. The model of rapporteurs remains unchanged. Representation of patients and health care professionals, with expertise in all areas, including rare and paediatric diseases, is increased at the CHMP and PRAC, in addition to the dedicated working groups representing patients and health care professionals. (37) Scientific committees like the CAT have been instrumental to ensure expertise and capacity building in an emerging technological field. However, after more than 15 years, advanced therapy medicinal products are now more common. The full integration of their assessment in the work of the CHMP will facilitate the assessment of medicinal products within the same therapeutic class, independent of the technology on which they are based. It will

applicant, to assess compliance of the application for a Marketing Authorisation with the agreed paediatric investigation plan concerned and formulate an opinion thereon; d. at the request of the Committee for Medicinal Products for Human Use or a competent authority, to assess any data generated in accordance with an agreed paediatric investigation plan and formulate an opinion on the quality, safety or efficacy of the medicinal product for use in the paediatric population; e. […] 3. When carrying out its tasks, the Paediatric Committee shall consider whether or not any proposed studies can be expected to be of significant therapeutic benefit to and/or fulfil a therapeutic need of the paediatric population. The Paediatric Committee shall take into account any information available to it, including any opinions, decisions or advice given by the competent authorities of third countries. ATMP Regulation (EC) 1394/2007, Chapter 7 • Article 21 1. The Committee for Advanced Therapies shall be composed of the following members: a. five members or co-opted members of the Committee for Medicinal Products for Human Use from five Member States, with alternates either proposed by their respective Member State or, in the case of co-opted members of the Committee for Medicinal Products for Human Use, identified by the latter on the advice of the corresponding co-opted member. These five members with their alternates shall be appointed by the Committee for Medicinal Products for Human Use; b. one member and one alternate appointed by each Member State whose national competent authority is not represented among the members and alternates appointed by the Committee for Medicinal Products for Human Use; c. two members and two alternates appointed by the Commission, on the basis of a public call for expressions of interest and after consulting the European Parliament, in order to represent clinicians; d. two members and two alternates appointed by the Commission, on the basis of a public call for expressions of interest and after consulting the European Parliament, in order to represent patients' associations. […] 2. All members of the Committee for Advanced Therapies shall be chosen for their scientific qualification or experience in respect of advanced therapy medicinal products. For the purposes of paragraph 1(b), the Member States shall cooperate, under the coordination of the Executive Director of the Agency, in order to ensure that the final composition of the Committee for Advanced Therapies provides appropriate and balanced coverage of the scientific areas relevant to advanced therapies, including medical devices, tissue engineering, gene therapy, cell therapy, biotechnology, surgery, pharmacovigilance, risk management and ethics. […] • Article 23 The Committee for Advanced Therapies shall have the following tasks:	also ensure that all biological medicinal products are assessed by the same committee. • Explanatory Memorandum Responsibility for adopting decisions on orphan designations will be transferred from the Commission to the Agency to provide a more effective and efficient procedure.

a. to formulate a draft opinion on the quality, safety and efficacy of an advanced therapy medicinal product for final approval by the Committee for Medicinal Products for Human Use and to advise the latter on any data generated in the development of such a product; b. to provide advice, pursuant to Article 17, on whether a product falls within the definition of an advanced therapy medicinal product; c. at the request of the Committee for Medicinal Products for Human Use, to advise on any medicinal product which may require, for the evaluation of its quality, safety or efficacy, expertise in one of the scientific areas referred to in Article 21(2); d. to provide advice on any question related to advanced therapy medicinal products, at the request of the Executive Director of the Agency or the Commission; e. to assist scientifically in the elaboration of any documents related to the fulfilment of the objectives of this Regulation; f. at the Commission's request, to provide scientific expertise and advice for any Community initiative related to the development of innovative medicines and therapies which requires expertise in one of the scientific areas referred to in Article 21(2); g. to contribute to the scientific advice procedures referred to in Article 16 of this Regulation and in Article 57(1)(n) of Regulation (EC) No 726/2004.	

Sources: EU Regulation (EC) No 141/2000, EU Regulation (EC) No 1901/2006 and EU Regulation 1394/2007 (current) and Proposal for a directive of the European parliament and of the Council on the Union code relating to medicinal products for human use, and repealing directive 2001/83/EC and directive 2009/35/EC (proposed). Text in green indicates a material addition in the proposed legislation compared to the current legislation, whereas text in red denotes articles that are proposed for removal from the legislation.

In recital 32 of the proposals the Commission explains that there are several reasons behind the decision to restructure the committees. First, it is noted that both EMA scientific committees and competent authorities of the Member States are faced with an increasing number of procedures to be conducted within the appropriate timeframe and which require additional resources. New challenges are experienced in the assessment of innovative and complex medicinal products, especially in the form of capacity limitations. These were first observed during the COVID-19 pandemic but may become more frequent.

Furthermore, as explained earlier, in the current structure multiple scientific committees can be involved in assessing a single medicinal product. The Commission indicates that "experience with the functioning of the regulatory system has shown that the existing European Medicines Agency multi-scientific committee structure often creates complexity in the scientific assessment process among committees, duplication of work and non-optimised use of expertise and resources." The restructuring is hoped to address both the capacity constraints and optimise the use of resources.

A related reason may be that, due to their respective responsibilities, there may be an appearance of inconsistency between recommendations issued by different committees if these recommendations relate to similar issues. For instance, whilst the CHMP may deem a product eligible for the PRIority MEdicines (PRIME) scheme based on its expected therapeutic advantage, the COMP may deem the product not to offer 'significant benefit' over existing treatments and issue a negative recommendation on an orphan designation.

3.3.2 *Perspectives from the field*

Among interviewed stakeholders, there was very limited recognition of the suggested drivers behind the proposed restructuring of the scientific committees. Consistent with earlier findings arising out of the evaluation of the EU Orphan and Paediatric Regulations, these stakeholders did not observe major issues with the current structure, although not all had sufficiently close familiarity with their processes to have a well-informed opinion on the matter. This could be because a lot of the work the committees do is not very visible to the outside world. For instance, if the COMP is set to issue a negative opinion on an orphan designation, a sponsor may withdraw its application without it becoming public information. Therefore, to the outside world, it may appear as if the COMP only issues positive opinions whereas in reality, it has more of a gatekeeping role.

Some interviewees with close knowledge of the work of the committees suggested that the issue of seemingly inconsistent decisions by different committees may not be rooted in the existence of multiple committees as much as it is in the fact that their activities involve multiple, seemingly similar yet non-identical, concepts. For instance, the COMP determines whether a medicine offers 'significant benefit' on a different basis from that which is used to determine eligibility for PRIME. At the same time, both assessments are considered a signal of the EMA's assessment of the medicine's therapeutic importance. As long as such underlying differences between regulatory concepts exist, it is possible for different procedures to lead to diverging outcomes, regardless of what body conducts the evaluation. The legislative proposals do not suggest any changes to the assessment criteria for orphan designation or a redefinition of associated regulatory concepts and thus would not directly tackle this issue[91].

Whereas the rationale behind the restructuring is not broadly accepted by stakeholders, it is clear that various stakeholders are very worried about the proposed restructuring of the committees into working parties. They consider committees like the COMP and CAT to have important expertise and to play a very valuable role in the EU regulatory system. There is strong concern that abolishing the committees and replacing them with working parties will lead to the loss of this valuable expertise. To what extent this may occur will depend heavily on how the working parties will be structured. Given that a drive for improved efficiency is one of the motivations behind the change, it is likely that the working parties will be smaller than the committees. This will indeed create the risk that experience will not be used to the same extent. Also, by nominating members from each Member State to the committees, the committees serve as a tool for building capacity in NCAs. When, by contrast, working parties will consist only of members who are selected on the basis of already existing expertise, this opportunity for learning and capacity development may become lost. Although these effects may not be felt immediately, as the working parties and the pool of experts will initially likely consists of many of the same people as are in the current committees, they may become clearer in future. Questions exist also on the extent to which patient representatives will have a place in the new structure.

Another main concern among many stakeholders is that, unlike the current committees, the role of the working parties will be mainly responsive rather than proactive. The working parties will be involved only at the initiative of the CHMP but it is unclear whether they will be given a mandate to engage in more strategic activities, such as developing guidance documents and

[91] Except for the removal of the possibility to apply for orphan designation if the sponsor can establish that "without incentives it is unlikely that the marketing of the medicinal product in the Community would generate sufficient return to justify the necessary investment" (Art. 3.1(a) of Regulation (EC) 141/2000).

quality standards. The CAT in particular is considered to play an important role in these activities. Whilst the limited number of ATMPs authorised to date has meant that the role of the CAT in advising the CHMP on authorisations has not yet been very large, the committee also plays an active role in developing the knowledge and expertise that is needed to help develop these therapies by maintaining early contacts with developers of ATMPs[92]. Such work is important to ensure that the regulatory framework remains adapted to the realities of innovations coming through the system. If the committee were to disappear, as is currently planned, this work will still need to be done. It may be questioned whether the CHMP, which is already under pressure, will have the time, resources, and expertise to do this work. It may then have to rely instead on *ad hoc* expert groups, which may impair the expertise development in the EMA.

At the CBG-MEB, the potential impacts of the proposed restructuring were still being examined at the time of data collection. Their main questions revolve around its possible effects on NCAs in terms of the workload on examiners and on the division of responsibilities between the EMA secretariat and the CHMP[93]. Questions exist also around whether, with the transfer of responsibilities, the new structure would be able to adequately fulfil its duty to provide checks and balances on the regulatory system. However, there is a sense that the current proposals lack the level of operational detailing that would be needed to accurately make these assessments and take an informed position on the feasibility of the restructuring. The CBG-MEB therefore could not yet express an opinion for or against the proposed restructuring but rather seeks more insight into how it would be implemented.

3.3.3 Experiences in other jurisdictions

While the EMA's structure is unique, other countries do use committees and expert panels to ensure that enough expertise is present to ensure decisions related to the safety, quality, and efficacy of medicines. In the US, for instance, the FDA has 47 technical and scientific advisory committees, although their recommendations are non-binding and the committees are thus more similar in their mandate to the EMA Working Parties. The committees are made up of a much smaller group of experts than the EMA committees, consisting of around nine members selected on the basis of their expertise.

3.3.4 Recommendations

Withhold support for the proposed restructuring of EMA Scientific Committees until assurances are in place that the new structure can adequately take over its responsibilities

The proposed replacement of the CAT, COMP and PDCO with working parties that advice directly to the CHMP has raised serious questions about whether and how the valuable expertise of these committees will be retained in the new system. The current proposals in this regard offer insufficient information about their expected composition and responsibilities as the restructuring has only been presented in the explanatory memorandum and the recitals but has not yet been detailed in the legislative articles. This leaves it unclear how tasks currently performed by the committees will be reassigned. For instance, the proposed Regulation states

[92] Celis, Patrick. (2010). CAT - The new committee for advanced therapies at the European Medicines Agency. Bundesgesundheitsblatt, Gesundheitsforschung, Gesundheitsschutz. 53. 9-13. 10.1007/s00103-009-0998-y.

[93] Members of the CHMP are representatives of National Competent Authorities (NCAs) of all EU Member States. Therefore, changes in the workload of the CHMP directly affect the NCAs.

that "for the purpose of establishing whether the orphan designation criteria are fulfilled, the Agency may consult the Committee for Medicinal Products for Human Use or one of its working parties" but does not specify how the EMA will take up this responsibility internally or what capacity the EMA has in-house to do this. Likewise, there is no clarity on whether the working parties will be given a mandate to advise the Commission (and EMA) on more strategic matters, in liaising with patient groups or in developing scientific guidance in the way the committees currently do. If such responsibilities are not delegated to the new working parties but rather will be integrated with the other tasks of the CHMP, there are warranted concerns about the CHMP's capacity to adequately fulfil these responsibilities.

In its justification for the proposed restructuring, the Commission points towards growing capacity limitations with the assessment of innovative and complex products. It is unclear, though, how it expects this new structure would address these limitations. Rather, without a formal role in the assessment processes for the working parties, there is the danger that crucial expertise currently housed in the committees is no longer drawn upon in a systematic and consistent manner and that the burden on the CHMP increases. This could negatively impact the EMA's overall capacity to be flexible and responsive to innovations in the areas of expertise of the committees as the CHMP may lack the necessary expertise. All of these unresolved questions cast serious doubt on the appropriateness of the proposed restructuring.

Notwithstanding these major concerns, it is conceivable that smaller working parties – working directly under the CHMP – will bring some of the desired efficiency gains and reduce costs. Experience at the US FDA, where technical and scientific advisory committees are formed of a much smaller group of experts than the EMA committees, also shows that an advisory structure based on expert groups of limited size can work and still be accommodating of innovation. At the same time, it should be recognised that – unlike in the US where regulatory assessment is fully centralised within the FDA – the EMA committees serve a dual purpose in that they not only bring expertise from the Member States to the EMA, but also do the converse by providing the NCAs with a platform for knowledge sharing and learning. Restructuring into working parties, with membership based solely on expertise and without consideration for Member State representation, could result in a loss of this second function. Whilst this concern may not very much affect the CBG-MEB, which is widely considered a well-respected NCA with a lot of in-house expertise, it almost certainly would affect other Member States.

Based on the above considerations, it must be concluded that, with these proposals, the Commission has not yet sufficiently explained how or why it expects the new structure to yield benefits over the current one, nor how it intends to mitigate any negative consequences from the restructuring. **It is therefore recommended that the Ministry of VWS withholds its support for the proposed restructuring of the EMA scientific committees until it has received more detailed information and assurances about the composition, roles and responsibilities of the new working parties and their relation to the CHMP.** Specifically, the Ministry of VWS should request clarification on:

- The expected number, size and composition of working parties formed;
- The criteria for selecting members of the working parties, in particular the role of Member State representation;
- What tasks currently performed by the scientific committees will be transferred to the CHMP and which ones will be performed by members of the working parties;
- The role of patient representatives within the working parties (additional to patient representation in the CHMP);
- How and when the CHMP would be required to involve the working parties;

- What role the working parties will play in advising the Commission and EMA on subject-specific matters, including development of guidelines and regulatory strategy;
- The function of the 'pool of experts' and its complementarity to the working parties;
- How the working parties and CHMP will be resourced to ensure they have the needed capacity and expertise to perform their respective tasks.

The impact assessment published by the Commission suggests that streamlining of procedures, including "better coordination within the regulatory network" will deliver benefits to both industry and regulators but is not specific on the nature or magnitude of these potential benefits in relation to specific measures. As it has previously been indicated that the current committee structure places a heavy burden on NCAs, the proposed restructuring could have certain benefits for these organisations, but these cannot be properly estimated from the available information. It should therefore be clarified further what the implications of the proposed new structure will be for NCAs in terms of costs and workload.

Answers to the above questions should allow the Ministry of VWS to understand whether the proposed restructuring can offer the necessary balance between efficiency and quality, considering not only current regulatory assessment needs but also the ability to continuously refine the regulatory framework in line with medical and scientific advances. Only if it has obtained sufficient assurances that the new structure will be equipped to fulfil its tasks to the same or a better standard as currently the case, should the Ministry support the proposals.

At present, the operational detailing on the existing committees is contained within the respective regulations for orphan medicinal products (EC No 141/2000), paediatric products (EC No 1901/2006) and ATMPs (EC 1394/2007). Given that the legislative proposal for a new regulation is expected to replace the first two and amend the latter, it would be logical to include a similar level of detail directly into this proposal as well. It is, however, also possible for this information to be laid down in a separate implementing regulation, that would follow adoption of this proposal. In such a case, it would nonetheless be pertinent that the broad outlines of what the implementing legislation would contain are already decided upon prior to adoption of the new regulation.

Request an intermediate evaluation of the new organisational structure (if adopted)

The proposals foresee in a comprehensive evaluation of the revised legislation only after at least 15 years from the deadline of its transposition. From the perspective of measuring the legislation's impact on innovation and patient benefit, this long time horizon is realistic. However, one may expect certain impacts to be observable much sooner. The suggested restructuring is a significant change to the regulatory system that would affect regulators and developers almost immediately and which could have major consequences for the efficient functioning of the system. It would therefore be sensible for the Ministry of VWS to **request the Commission to agree to an evaluation with a limited scope of this aspect of the revised legislation sooner, potentially after the first 3 to 5 years of implementation**.

Ensure knowledge sharing and regulatory capacity development within and between NCAs

Whilst the main purpose of the committee structure is not to deliver knowledge and expertise to the Member States, the importance of this secondary function should not be underestimated. Medical and technological advances in drug development are moving faster than regulators can keep up with. Stakeholders already observe that NCAs frequently lack expertise on certain pharmaceutical innovations, which slows down their regulatory acceptance. Without further action, this knowledge gap will only widen in future. Whilst the

proposed revision of the EU General Pharmaceutical Legislation may be an essential step in future-proofing the EU regulatory system, its success will depend to a large extent on whether it can be effectively implemented. Hereto, regulatory capacity development at all levels of the system, including at Member State level is urgently needed. If the current committee structure, in which all Member States are represented in all committees, is abandoned in favour of a structure with smaller groups of experts, other means should be found to take over this function. It is therefore **recommended that the Ministry of VWS, together with other Member States, calls upon the Commission to identify and fund suitable instruments for further advancing the field of regulatory science in the EU and help strengthen the capacity of NCAs**.

3.4 Support for non-commercial operators

Not all medicinal product development is conducted by large pharmaceutical companies. Particularly in earlier stages, a significant share of research is done by academia, research institutes, not-for-profit organisations, and small start-ups. Increasingly, though, also later stages research is performed by non-commercial operators. Academic institutions, for instance, play a growing role in the development of ATMPs[94,95,] as well as in drug repurposing[96]. Such non-commercial entities tend to have less experience with the clinical development stages and with the regulatory processes needed to get to a marketing authorisation. As a result, early-stage research is frequently not designed with those next stages in mind and parts of the research may need to be redone in order to progress. When trials need to be redone, this not only leads to extra costs but also places an unnecessary burden on patients who participate in the research.

To support pharmaceutical product developers, the EMA offers scientific advice and protocol assistance to give guidance on the best methods and study designs that are required to generate the evidence used in the scientific evaluation for marketing authorisation. Scientific advice is normally given by the Scientific Advice Working Party (SAWP)[97]. For developers of medicines for rare diseases, protocol assistance is also available through which more specific information connected to the criteria for designation as an orphan medicine can be obtained. Scientific advice is given only in direct response to specific questions and the SAWP cannot deviate from this to offer unsolicited input to developers. This is done to ensure that the scientific advice remains impartial, and all developers are given equal access to information. The advice given remains confidential during the development process but is published after a medicine obtains a marketing authorisation.

Scientific advice and protocol assistance are both non-binding and open to any product developer, although it tends to be most valuable for less experienced and smaller developers.

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[94] Priesner C, Hildebrandt M. Advanced Therapy Medicinal Products and the Changing Role of Academia. Transfus Med Hemother. 2022 May 16;49(3):158-162. doi: 10.1159/000524392. PMID: 35813600; PMCID: PMC9209977.

[95] Rommel W, Coppens D. The potential for academic development of medicines in Europe: case study of advanced therapy medicinal products (January 2023). European Cancer League Access to Medicines Task Force. https://www.cancer.eu/wp-content/uploads/2023-03-23-Policy-paper_The-potential-for-academic-development-of-medicines-in-Europe.pdf.

[96] Van den Berg S, de Visser S, Leufkens HGM, Hollak CEM. Drug repurposing for rare diseases: a role for academia. (2021). Front.Pharmacol. 12. https://doi.org/10.3389/fphar.2021.746987.

[97] In the case of medicines that are intended to treat, prevent or diagnose a disease causing a declared public health emergency, scientific advice is instead given by the CHMP based on recommendation of the Emergency Task Force. Source: https://www.ema.europa.eu/en/human-regulatory-overview/research-and-development/scientific-advice-and-protocol-assistance.

The EMA charges a fee for scientific advice, although fee waivers and reductions are available to academic sponsors and SME[98]. The EMA has a dedicated office to support SME developers by providing incentives and support. Academic developers share many of the same qualities as SME sponsors in terms of their limited experience with pharmaceutical development and regulatory processes, and lack of dedicated resources for this. Nonetheless, academic hospitals have tended to fall outside of the eligibility criteria for SME support as they are often too large to be considered SME.

Whilst developers from industry and academia alike consider the scientific advice offered by the EMA very valuable, there is a sense that the nature of the advice is still too formal for inexperienced developers to be optimal, and that the EMA takes an overly 'arm's length' approach to its relationship with such developers. These parties may not always know what specific questions to ask, whilst the SAWP is precluded from proactively offering advice unless it is in response to a specific question. This creates a situation whereby study designs can remain suboptimal, possibly resulting in a need to repeat trials or even rejection of the marketing application, even though the regulator might have been able to prevent this had it been allowed to volunteer relevant information. As such, there is a sense that the way in which the EMA engages with first-time and inexperienced developers could be improved.

3.4.1 Proposed legislative changes

Whilst the legislative proposals make no direct reference to academic developers, the staff working document and legislative financial statement accompanying the proposals indicate that the EMA will be expected to create an 'Academia Office' to support not-for-profit entities by providing them free of charge early scientific advice within six months of adoption of the proposals (Table 6). Its tasks will be similar to that of the SME office.

The Commission's intent to create this office is somewhat unexpected as this suggestion had not been explored in any of the options considered in the impact assessment for the revision. In the proposals the Commission also offers no explanation of why it considers such an office necessary or whether it has explored other options.

Table 6 Overview of proposed changes regarding non-commercial operators

Current	**Proposed**
None	Regulation, Legislative Financial Statement 1.5.1 Regarding the enhanced regulatory support, the Agency shall set up within 6 months of adoption a coordination mechanism to enable parallel scientific advice with health technology assessment and regulatory bodies for medical devices. Within the same period, the Agency shall create an Academia Office, a secretariat to support not-for-profit entities by providing them free of charge early scientific advice. 3.2.3.1 The requested FTE are necessary to set up the Academia Office at EMA that will be managing the procedures. The tasks of the office will be similar to the tasks of the SME office and will include procedural and administrative assistance to "not-for-profit" entities, including direct assistance and briefing meetings on regulatory strategy, providing fee waivers and reductions to eligible entities, provide free-of-charge

[98] Since 19 June 2020, applicants from the academic sector are eligible to receive free protocol assistance for developing orphan medicines. Source: https://www.ema.europa.eu/en/human-regulatory-overview/research-and-development/scientific-advice-and-protocol-assistance/requesting-scientific-advice-or-protocol-assistance-ema#ema-inpage-item-10290.

	translations of the product information in all EU languages for initial EU marketing authorisations, provide training and education to "not-for-profit" entities, etc.

Sources: Proposal for a regulation of the European parliament and of the Council laying down Union procedures for the authorisation and supervision of medicinal products for human use and establishing rules governing the European Medicines Agency, amending Regulation (EC) No 1394/2007 and Regulation (EU) No 536/2014 and repealing Regulation (EC) No 726/2004, Regulation (EC) No 141/2000 and Regulation (EC) No 1901/2006 (proposed). Text in green indicates an addition in the proposed legislation compared to the current legislation.

3.4.2 Perspectives from the field

Although in the initial set of interviews stakeholders were not asked specifically to comment on the proposed setup of an 'Academia Office', discussions about the role of EMA more generally confirm the relevance of increased support for academia. There is a perceived need for earlier and more informal dialogue between the regulator and new developers. Although it is recognised that there should remain a clear separation between regulatory assessors and developers to protect the independence and integrity of the assessment, it would be welcomed if the EMA could engage more proactively with academia than it does with commercial parties.

There is some concern, however, that the new Academia Office may draw an unjustifiably sharp distinction between academia on the one hand and small commercial operators on the other. Many SMEs are spin-offs or spinouts[99] from academic institutions and the line between academia and such companies is not always clear cut: individuals may simultaneously hold positions at the university and at a spin-off/out, a spin-off/out may use research facilities owned by the university, or the university may have a financial interest in the spin-off/out (e.g. through licensing of IP or royalties). The question then is how such organisations may be classified and at what point an entity progresses from being part of 'academia' to being an 'SME'. Furthermore, the needs of both types of entities, as well as their know-how and access to resources, may be very similar. As such, some parties have suggested that the new Academia Office may create a false dichotomy between the two and unfairly favour academia. In the absence of further information on how the distinction may be made between academia, new spin-offs/outs and somewhat more mature start-ups remains speculative whether there are grounds for concern about unfair treatment.

A further issue raised in discussions was the feasibility for the EMA to engage more proactively with developers and share potentially relevant information outside of the confidential context of the scientific advice process. This could be done, for instance through public Question & Answer documents and guidance on issues that may be relevant for a broader pool of developers. Naturally, this would require a careful balancing of interests to, on the one hand, protect the rights of developers to keep specific information related to their research confidential and, on the other hand, serve broader societal interests by sharing information that could speed up the development of treatment and improve the quality of research.

3.4.3 Experiences in other jurisdictions

Several industry stakeholders suggest that the ecosystem in the US is more conducive to fostering partnership between industry and academia and that, in general, academia in the US is more engaged in pharmaceutical product development than that in the Netherlands. There is a desire to see more of a similar ecosystem develop here as well ("Boston on the North

[99] Spin-offs are entities that formally are still subsidiaries of the parent organisation, whilst spinouts are completely independent. The distinction is, however, of little relevance in the context here discussed.

Sea"). Whilst the factors needed for this are varied and mostly out of the scope of this quickscan, increased regulatory support for academic and other non-commercial developers could be part of the equation.

In the US, the CDER Small Business and Industry Assistance provides a single channel for technical assistance to small pharmaceutical companies through meetings, workshops, and information materials. A fee waiver exists for small business applicants submitting their first FDA application. No information was identified regarding whether the FDA offers dedicated scientific advice or other support for academic developers as well. Similarly, in the UK, the MHRA offers payment easements or fee waivers for scientific advice requests to applicants who fulfil requirements as an SME, but it is not clear whether any specific support is also offered to non-commercial operators.

In Singapore, in 2021, the HSA set up an Innovation Office as a pilot to provide a conducive regulatory environment that will also support the development of the biomedical sector. The Innovation Office provides scientific and regulatory advice to researchers, academia, biotechnology companies, and pharmaceutical companies with an interest in early-stage clinical product development, and with the intent to pursue product registration in Singapore. The Office enables individuals, researchers or companies to proactively engage with the HSA on regulatory requirements and seek early guidance on technical or scientific issues that need to be considered during product development.

3.4.4 Recommendations

Request clarification on the rationale behind the Academia Office and on how it is envisaged to function

Non-commercial operators, including academia and charitable organisations, play an important role in medicinal product development. Progress in the field of personalised medicine, in particular the development of ATMPs, and the increased attention for drug repurposing are likely to further increase their role. However, they typically lack the resources and know-how of commercial developers that are needed to progress the development process from its early stages through clinical evaluation and regulatory assessment. As such, there is a clear rationale behind the Commission's intent to expand the regulatory support offered to this type of developers by setting up an Academia Office. However, it is unclear why the Commission is choosing to set up an entirely new office for academic developers, rather than open up the services of the already existing SME Office to academic and other non-commercial developers. The distinction between academia (and other non-commercial operators) on the one hand and commercial developers on the other can be challenging to make, particularly in the context of entities that have only recently been spun out of academia and that still maintain strong ties there. The legislative proposals offer scant details on how the Academia Office would function, who would be eligible for its services or what fees will be levied. Also, no information is available on how the Academia Office would be expected to cooperate with the SME Office.

Having two separate offices could mean that it is unclear to which office developers operating on this interface must turn for support or that they could fall under different offices at different points in the development stage, depending on the formal status of their organisation. This could lead to inefficiencies in the process. Furthermore, providing different services to academic developers, or providing similar services at a different rate, than to other inexperienced developers could be considered market distortion by favouring one group over the other. It is therefore important to ensure that the set-up of an Academia Office is done with

due consideration of these factors. The current proposals offer insufficient information to assess whether that is currently the case. As the possibility of an Academia Office has also not been included in the stakeholder consultations nor in the impact assessment supporting the proposals, it is not clear whether this arrangement is best suited to the needs of developers. It will therefore be essential that the Commission further clarifies its intentions regarding this new office, specifying its expected tasks and responsibilities, eligibility criteria, fee structure and connection to the SME Office. This is needed to ensure that the office is fit-for-purpose and does not lead to unfair competition.

The study authors do not have the legal expertise to assess whether the mere mention of the Academia Office in the Financial Statement accompanying the proposals by itself provides sufficient legal basis for its establishment or whether additional legislative acts are needed for this. Presumably, at least a separate Regulation, similar to Regulation (EC) No 2049/2005 regarding the payment of fees to, and the receipt of administrative assistance from, the Agency by micro, small and medium-sized enterprises, will be needed. In this case, it is possible that Member States will be given further opportunity to discuss some of the topics raised above. However, these discussions may focus only on some of the operational detailing of the Office and already presume the need for its establishment itself as generally accepted. Thus, rather than wait until further details have been worked out, it would be useful for Member States to first have clarity on whether an Academia Office itself the most appropriate solution is. **It is recommended that the Ministry of VWS requests clarification from the Commission and EMA on why it considers an Academia Office preferable over other solutions, such as opening up the services of the SME Office to academic developers.**

3.5 Drug repurposing

The repurposing of existing medicines for new indications is an important development that can have positive impacts on both the availability of treatments, including for patients with rare diseases, and on the affordability of healthcare as these medicines often are no longer under patent or regulatory protection. Repurposing can happen for a) an active substance that has never received a marketing authorisation, b) a medicine with a marketing authorisation and active intellectual property or regulatory protection, c) a medicine with marketing authorisation with expired intellectual property or regulatory protection or d) a medicine that was never subject to intellectual property or regulatory protection[100]. As touched upon in the discussion about the potential of data-driven drug discovery (Section 2.2), the expectation is that drug repurposing will grow in importance as a way of developing new treatments at greater speed and reduced costs. Exploration of existing data sets may allow for the identification of new treatment populations without the need to extensively repeat all preclinical and clinical research. This type of research is often performed in the clinical setting, by academic groups.

Whilst repurposing of medicines holds much promise, there are significant hurdles to its implementation in practice. At present, use of medicines for indications other than those for which they were developed is often done through 'off-label' prescribing. This is because the addition of a new indication to the product label requires the marketing authorisation holder

[100] van der Pol, K.H., Aljofan, M., Blin, O. *et al.* Drug Repurposing of Generic Drugs: Challenges and the Potential Role for Government. *Appl Health Econ Health Policy* 21, 831–840 (2023). https://doi.org/10.1007/s40258-023-00816-6

to submit an application for a 'variation'[101] to the competent authority. Particularly for older, products that are not, or no longer, under any form of market protection there may be little or no incentive for the authorisation holder to do so as this requires the marketing authorisation holder to submit a full dossier of documentation to support the application, including updates to existing information, and pay the fees associated with submitting a variation. Consequently, even if results from studies have shown that a medicine can be safely and effectively repurposed for another indication, this information is not always added to the regulatory file and the product information. This in turn may have the consequence that the medicine may not be reimbursed for treatment in indications for which the medicine has not been registered[102]. From a regulatory perspective, the main challenges associated with drug repurposing lie not in the readiness of the framework to accommodate developments in science or technology but rather in how to facilitate access for patients, simultaneously ensuring that such new applications are suitably subjected to regulatory assessment and registration.

3.5.1 Proposed legislative changes

With the legislative proposals, the Commission is issuing a signal that it wants to stimulate drug repurposing by further extending the data protection for registration of a new indication[103,104]. Simultaneously, it wants to promote access to repurposed medicines through bringing drug repurposing 'on-label' by providing the possibility for "an entity not engaged in an economic activity ('not-for-profit entity')" to submit evidence to support the registration of a new therapeutic indication expected to fulfil an unmet medical need to the EMA (Article 48 of the Regulation)(Table 7). If, after evaluation, the EMA issues a positive opinion all marketing authorisation holders of the product concerned must file a submission for variation of the authorisation to register the new indication.

These additions to the legislation follow most of the recommendations by experts of the EMA/HMA in their concept paper on generics and biosimilars[105]. Herein, reflections are offered on the added value of an independent regulatory procedure dedicated to repurposing. Whilst it was deemed that the existing pathways are sufficiently adapted for repurposed applications, both in the context of the marketing authorisation application and subsequent variations, several other suggestions were offered aimed at stimulating the registration of new indications,

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[101] In line with Commission Regulation (EC) No 1234/2008 ('Variation Regulation'), this concerns a 'Type-II variation". Type-II variations are defined as a major variation that may have a significant impact on the quality, safety or efficacy of a medicinal product.

[102] Pricing and reimbursement policies are a national competence of the Member States. Therefore, whether off-label use may, under certain conditions, be reimbursed depends on the specifics of national frameworks.

[103] Proposal for a new Directive, Article 84: "1. A regulatory data protection period of four years shall be granted for a medicinal product with respect to a new therapeutic indication not previously authorised in the Union, provided that: a) adequate non-clinical or clinical studies were carried out in relation to the therapeutic indication demonstrating that it is of significant clinical benefit, and b) the medicinal product is authorised in accordance with Articles 9 to 12 and has not previously benefitted from data protection, or 25 years have passed since the granting of the initial marketing authorisation of the medicinal product concerned."

[104] This aspect of the proposals is, however, outside of the scope of this Quickscan as it focuses on provision of incentives rather than on purely regulatory aspects of the framework. It has therefore not been further discussed in this report.

[105] 02. Concept paper for EC on Generics and Biosimilar. Experts from EMA/HMA. *12. Dedicated regulatory pathway for repurposing*. https://health.ec.europa.eu/document/download/624cd58f-d680-404c-b676-8b65871b3d00_en?filename=mp_revision_concept-papers_compendium_en.pdf.

noting this should be done without relaxing evidentiary standards or placing a disproportionate burden on regulators. One such suggestions was the introduction of new "incentives in terms of regulatory protection and/or reimbursement", in line with the Commission's current proposal. Other proposals were:

- Creation of a dedicated platform of interactions between different stakeholders or specific scientific support;
- Analyse and, where possible, remove or reduce challenges with regulatory requirements for a marketing authorisation for applicants interested in repurposing (e.g. requirements for paediatric investigations);
- Enhanced legal provisions to mandate or enforce marketing authorisation holders to keep their product information up to date with newly available evidence even when not generated by them, taking into account questions of liability and obligations;
- Have a mechanism for regulatory agencies to perform assessment of data generated by academia/not-for-profit organisations when relevant to support product information updates.

With the addition of Article 48 to the proposed Regulation, the Commission is responding to the latter two recommendations.

Table 7 Overview of proposed changes regarding drug repurposing

Current	**Proposed**
Regulation (EC) No 726/2004 • Article 14.11 […] medicinal products for human use which have been authorised in accordance with the provisions of this Regulation shall benefit from an eight-year period of data protection and a ten-year period of marketing protection, in which connection the latter period shall be extended to a maximum of 11 years if, during the first eight years of those ten years, the marketing authorisation holder obtains an authorisation for one or more new therapeutic indications which, during the scientific evaluation prior to their authorisation, are held to bring a significant clinical benefit in comparison with existing therapies. Directive 2001/83/EC • Article 10(1) […] A generic medicinal product authorised pursuant to this provision shall not be placed on the market until ten years have elapsed from the initial authorisation of the reference product. […] The ten-year period referred to in the second subparagraph shall be extended to a maximum of eleven years if, during the first eight years of those ten	Regulation • Article 48 1. An entity not engaged in an economic activity ('not-for-profit entity') may submit to the Agency or to a competent authority of the Member State substantive non-clinical or clinical evidence for a new therapeutic indication that is expected to fulfil an unmet medical need. The Agency may, at the request of a Member State, the Commission, or on its own initiative and on the basis of all available evidence make a scientific evaluation of the benefit-risk of the use of a medicinal product with a new therapeutic indication that concerns an unmet medical need. The opinion of the Agency shall be made publicly available and the competent authorities of the Member States shall be informed. 1. In cases where the opinion is favourable, marketing authorisation holders of the medicinal products concerned shall submit a variation to update the product information with the new therapeutic indication. 2. Article 81(2), point (c) of [revised Directive 2001/83/EC] shall not apply for variations under this Article. Directive • Article 81 1. The regulatory data protection period shall be six years from the date when the marketing authorisation for that medicinal product was granted in accordance with Article 6(2). For marketing authorisations that belong to the same global marketing authorisation the period of data protection shall start from the date when the initial marketing authorisation was granted in the Union. Subject to a scientific evaluation by the relevant competent authority, the data protection period referred to in paragraph 1 shall be prolonged by: […] 12 months, where the marketing authorisation

years, the marketing authorisation holder obtains an authorisation for one or more new therapeutic indications which, during the scientific evaluation prior to their authorisation, are held to bring a significant clinical benefit in comparison with existing therapies. • Article 10(5) In addition to the provisions laid down in paragraph 1, where an application is made for a new indication for a well-established substance, a non-cumulative period of one year of data exclusivity shall be granted, provided that significant pre-clinical or clinical studies were carried out in relation to the new indication.	holder obtains, during the data protection period, an authorisation for an additional therapeutic indication for which the marketing authorisation holder has demonstrated, with supporting data, a significant clinical benefit in comparison with existing therapies. • Article 84 1. A regulatory data protection period of four years shall be granted for a medicinal product with respect to a new therapeutic indication not previously authorised in the Union, provided that: a) adequate non-clinical or clinical studies were carried out in relation to the therapeutic indication demonstrating that it is of significant clinical benefit, and b) the medicinal product is authorised in accordance with Articles 9 to 12 and has not previously benefitted from data protection, or 25 years have passed since the granting of the initial marketing authorisation of the medicinal product concerned. 2. The data protection period referred to in paragraph 1 may only be granted once for any given medicinal product. 3. During the data protection period referred to in paragraph 1, the marketing authorisation shall indicate that the medicinal product is an existing medicinal product authorised in the Union that has been authorised with an additional therapeutic indication.

Source: Directive 2001/83/EC of the European Parliament and of the Council of 6 November 2001 on the Community code relating to medicinal products for human use(current); Regulation (EC) No 726/2004 of the European Parliament and of the Council of 31 March 2004 laying down Community procedures for the authorisation and supervision of medicinal products for human and veterinary use and establishing a European Medicines Agency (current); Proposal for a regulation of the European Parliament and of the Council laying down Union procedures for the authorisation and supervision of medicinal products for human use and establishing rules governing the European Medicines Agency, amending Regulation (EC) No 1394/2007 and Regulation (EU) No 536/2014 and repealing Regulation (EC) No 726/2004, Regulation (EC) No 141/2000 and Regulation (EC) No 1901/2006. Text in green indicates an addition in the proposed legislation that has no counterpart in the current legislation; text in red reflects provisions that would be impacted by the proposed changes.

3.5.2 Perspectives from the field

Whilst interviewed stakeholders generally welcome the Commission's efforts to promote drug repurposing and increase registration of new indications, there are questions on all sides about the effectiveness as well as concerns about unintended consequences of the measures included in the proposals, in particular the mandatory submission of variations by marketing authorisation holders (Article 48(2)) in case of a favourable assessment by the EMA on the basis of data submitted by a party other than the holder of the authorisation.

Filing for a variation of the authorisation – and subsequently maintaining that authorisation – is not without costs to a marketing authorisation holder[106]. As most repurposed medicines concern older, off-patent products for which profit margins may already be small, mandating submission of a variation could push the costs over the point where it is no longer commercially interesting for marketing authorisation holders. In response, they may opt to withdraw the authorisation completely rather than submit a variation. Stakeholders from academia and patient organisations are thus worried that, rather than supporting on-label use (and enabling reimbursement), the measure could backfire and make the product unavailable even for off-label use. If marketing authorisation holders choose to withdraw their authorisation rather than submit a variation, the preparation of a new marketing authorisation application by another

[106] The NHS estimated the cost of a variation in an existing marketing authorisation to be around £163,000. NHS (2021)

party (such as that which has submitted the data supporting the registration of an additional indication to the EMA) may be unlikely. This is because a large proportion of repurposing research for off-patent/generic products is performed by academic researchers, who may not be interested in becoming marketing authorisation holders nor have the expertise or funding to engage with regulatory procedures[107,108]. Some stakeholders are therefore arguing that filing for variation of the authorisation should only be mandatory for products that are still under regulatory protection and be optional for all other products, whereas industry favours removal of the mandatory registration all together.

It has also been indicated there is a need for further clarification of which entity would be responsible for submitting a variation and to which products the variation should apply: the proposals place the responsibility for submitting a variation on the marketing authorisation holder, but do not clarify if there would need to be a different process for older products with multiple generic versions on the market. Further concerns include issues around the enforceability of the proposed four years of data protection, highlighting how generic medicines may still be prescribed (off-label) even if this data protection is in place, and the potential for implementation bottlenecks around registration and reimbursement of repurposed medicines.

Some concern has been voiced regarding the offer of four additional years of data protection for adding a new indication to the label. There are concerns that this creates a risk of 'hijacking' of academic research by industry. The proposal does not specify to what extent the applicant must have engaged in the collection and analysis of original data or whether it would be acceptable for an applicant to file for a new indication on the basis of (academic) literature. In the latter case, the applicant would be given access to a potentially very valuable incentive for minimal effort. However, as the introduction of regulatory incentives was outside of the scope of this Quickscan, these concerns have not been further explored.

The CBG-MEB has not articulated a position on any of the proposed measures regarding drug repurposing. The Dutch Healthcare Institute, responsible for advising the government on reimbursement, does recognise the current difficulties with registration of new indications and considers the Commission's plans to offer additional data protection for new indications generally positive and likely to benefit patients. It has, however, not commented on the risks associated with the ability for third parties to submit data to support the registration of a variation, nor suggested alternative options for stimulating registration.

3.5.3 Experiences in other jurisdictions

The US has similar issues to the European system for the process for repurposed, off-patent products: the process is less clear than for on-patent products and often, these medicines are

[107] Van der Pol, K.H., Aljofan, M., Blin, O. *et al.* Drug Repurposing of Generic Drugs: Challenges and the Potential Role for Government. *Appl Health Econ Health Policy* **21**, 831–840 (2023). https://doi.org/10.1007/s40258-023-00816-6

[108] Verbaanderd C, Rooman I, Meheus L, Huys I. On-Label or Off-Label? Overcoming Regulatory and Financial Barriers to Bring Repurposed Medicines to Cancer Patients. Front Pharmacol. 2020 Jan 31;10:1664. doi: 10.3389/fphar.2019.01664. PMID: 32076405; PMCID: PMC7006723.

used off-label without FDA approval[109]. An additional six months of exclusivity is given if a repurposed medicine treats a rare disease[110].

In the UK, adding a new indication for a medicine that is still under market protection can be rewarded in much the same way as is currently the case in the EU: if the MHRA deems the variation to have a significant clinical benefit and the application is submitted within the first eight years of market protection, an extension of one extra year can be given[111]. In 2021, the MHRA set up the Medicines Repurposing Programme to identify opportunities and provide support for adding a variation to the label of a generic or biosimilar medicine. In a 2021 report, the National Health Service (NHS) recognised that a generic manufacturer may not recover costs by applying for a variation, and new incentives are needed which, ideally, do not affect price competition[111]. No incentive currently exists, though there are efforts to still encourage variation applications. These include:

- The exploration of establishing a fund which can support the licensing process for repurposed products in priority areas.
- The introduction of the Repurposed Medicine Programme, which seems to facilitate and encourage the licensing of repurposed medicines[111]. The Programme can appoint a working group to assist with applying for a licensing variation or with evidence generation.
- A pilot scientific advice meeting with potential repurposed medicine candidates.

Both the US FDA and the UK MHRA are seeking to use and evaluate RWE to support labelling changes, including adding or modifying the indication[112]. The MHRA has indicated the Early Access to Medicines Scheme may be used to collect real-world data to generate further evidence for licensing applications[113]. The CURE Drug Repurposing Collaboratory, a public private partnership on behalf of the FDA and the National Center for Advancing Translational Sciences, seeks to use real-time data shared by clinicians to inform clinical trials and, potentially, labelling of medicines[114]. The data in question is collected via an app, where clinical practitioners can report novel uses of existing medicines.

3.5.4 Recommendations

Repurposing of existing medicines can offer a valuable solution to some of the existing inefficiencies in drug development and speed up the development of cost-effective

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[109] Duke Margolis Center for Health Policy (2023). Drug Repurposing for Pandemic Innovation: Establishing an Effective and Efficient Ecosystem. Available at: https://healthpolicy.duke.edu/sites/default/files/2023-06/Drug%20Repurposing%20for%20Pandemic%20Innovation.pdf

[110] Everylife Foundation for Rare Diseases (2015). Press Release: Senate Introduces the OPEN ACT. Available at: https://everylifefoundation.org/press-release-senate-introduces-the-open-act/

[111] NHS (2021). Opportunities to Repurpose Medicines in the NHS in England. Available at: https://www.england.nhs.uk/wp-content/uploads/2021/03/B0342-oportunities-to-repurpose-medicines-in-the-nhs-in-england.pdf

[112] FDA (2018). Framework for FDA's Real-World Evidence Program. Available at: https://www.fda.gov/media/120060/download#:~:text=FDA%20will%20explore%20strategies%20for,tools%2C%20wearables%2C%20and%20biosensors

[113] NHS (2021). Opportunities to Repurpose Medicines in the NHS in England. Available at: https://www.england.nhs.uk/wp-content/uploads/2021/03/B0342-oportunities-to-repurpose-medicines-in-the-nhs-in-england.pdf

[114] FDA.gov (2020). CURE ID App Lets Clinicians Report Novel Uses of Existing Drugs. Available at: https://www.fda.gov/drugs/science-and-research-drugs/cure-id-app-lets-clinicians-report-novel-uses-existing-drugs

treatments. However, there are currently few incentives to encourage adding new indications to a medicine's marketing authorisation, which is needed to bring use on-label and allow for reimbursement. The Commission's intents to address some of the challenges with repurposing, through offering additional data protection and by enabling third parties to submit evidence supporting a variation to the EMA, are considered laudable. However, the instruments proposed for this may run into practical as well as legal problems and even pose a threat for the availability of medicines.

Remove the requirements for mandatory registration of new indications (Regulation Art. 48(2))

From a legal perspective, it can be questioned whether marketing authorisation holders can lawfully be forced to submit a variation and maintain a marketing authorisation on a product, following a favourable opinion by the EMA, particularly if:

- They have not been involved in generating and/or analysing the evidence submitted to the EMA by a third party to support the filing;
- They have pre-existing evidence from (own) clinical studies that is inconsistent with that submitted by the third party, and which has not yet been taken into account by the EMA, and which would affect the assessment of the product's safety and efficacy in relation to the new indication;
- There is no procedure in place to enable marketing authorisation holders to review the third-party data or oppose the EMA's assessment of this;
- There are legitimate concerns related to liability and/or economic viability of the product that place the marketing authorisation holder at undue financial or legal risk.

These considerations, and potentially others, mean that the legislative text as proposed under Article 48(2) of the Regulation may not hold up under legal challenge. However, even without these legal questions, there are grounds for the concern that the proposed mandatory registration of new indications will jeopardise the market availability of products that are no longer under regulatory protection and for which profit margins tend to be narrow. Studies on shortages of medicines have repeatedly shown that economic factors are a major cause of market withdrawals, especially for generic medicines[115]. Adding further regulatory costs could accelerate such withdrawals and achieve the opposite of the Commission's intentions.

Two potential alternatives to the current proposals were explored in discussion with stakeholders. The first was amending the text of Article 48(2) to maintain the requirement of mandatory filing for a variation but limiting it to products that are still under regulatory protection. This may address some of this risk but, at the same time, may also render the entire article largely ineffective. For innovative products that are still under regulatory protection, submitting a variation is already inherently more attractive due to greater profit potential and therefore more commonly done. Limiting the obligation to these products is therefore unlikely to solve the bigger problem of insufficient registration of new indications for older, off-patent medicines.

As another alternative, representatives of patient organisations suggested allowing the EMA to add the variation to the 'core summary of product characteristics (core SmPC)' of a generic

[115] De Jongh TE, Becker D, Boulestreau M et al., *Future-proofing pharmaceutical legislation – Study on medicine shortages – Final report (revised)* (2021), European Commission, Directorate-General for Health and Food Safety, Publications Office of the European Union. https://data.europa.eu/doi/10.2875/211485.

product directly rather than require Marketing Authorisation Holders (MAHs) to submit a variation, thus removing the issue of the regulatory costs from the equation. Industry representatives, however, indicated this would likewise not be legally tenable as it would impose a responsibility for post-authorisation data collection and a liability for use of the product in an indication that the MAH has not themselves evaluated or approved. Another complication arising from centrally adding an indication to the SmPC for *all* generic versions of a product relates to the incentive offered in the form of additional data protection under Article 84 of the proposed Directive. Offering this incentive to all current MAHs would effectively render it unenforceable and thereby meaningless. This could even act as a disincentive for industry to participate in academic research into drug repurposing. Although the question of the legality of this alternative could not be answered, the likelihood of legal challenges and additional difficulties in its implementation means that this suggestion also could not be recommended.

In the absence of viable amendments that would mitigate the risks associated with mandatory registration of new indications, it is thus **recommended the Ministry of VWS proposes to fully remove Article 48(2) mandating marketing authorisation holders to submit a variation** in case of a positive opinion by the EMA. Although this removal may render the remaining parts of the Article, allowing for the submission of third-party data to the EMA, far less meaningful, its potential benefits may not outweigh the associated risks.

Encourage additional actions to support repurposing and registration of new indications

Given that actions to stimulate repurposing contained in the current proposals by the Commission to stimulate repurposing may be legally unenforceable as well as have unintended consequences, **the Commission should be urged to explore other avenues to achieve its objectives**. This may be done, for instance, by reducing financial barriers to submission of a variation or supporting industry-academia research collaborations that aim to lead to registration, such as by making submission of a variation in case of positive outcomes a condition of EU research grants in this field. It is worth noting that suggestions to this same effect issued by EMA/HMA experts do not appear to have been taken up in the current proposals. However, such alternatives need not be included in the legislative proposals for the EU general pharmaceutical legislation but could be part, for instance, of the EMA fee system or an amendment to Regulation (EC) No 1234/2008 ('Variation Regulation').

Consider the need for changes in the national policies and framework to support reimbursement of repurposed medicines

Although outside of the direct focus of this Quickscan, an issue that has been flagged in this Quickscan is the necessity for models for national reimbursement of repurposed medicines. Currently, in the Netherlands insurers only reimburse off-label use of medicines for products that have *not* been placed on a list of medicines for which reimbursement has been restricted to the listed indication[116,117]. Products on this list may still be reimbursed for off-label use if they

[116] Farmacotherapeutisch Kompas: niet-geregistreerde indicaties. https://www.farmacotherapeutischkompas.nl/algemeen/niet-geregistreerde-indicaties.

[117] Overheid.nl (2024). Regeling zorgverzekering. Bijlage 2. https://wetten.overheid.nl/BWBR0018715/2024-04-11/0#Bijlage2.

meet certain criteria[118]. In such cases, the National Health Care Institute advises insurers on whether the criteria for reimbursement have been met. These restrictions on reimbursement for off-label use are a result of national policy. It would thus be pertinent if, alongside discussions on the question of how best to encourage registration of new indications for repurposed medicines at Union level, the Ministry considers whether any changes to the national policies and frameworks for reimbursement of repurposed medicines are in order.

[118] "The right to reimbursement [for off-label use of products included in Annex 2] applies only if: the insured suffers from a disease that occurs in less than 1 in 150,000 inhabitants in the Netherlands, 2) and the efficacy of that medicine for that indication has been scientifically substantiated; and no treatment is possible in the Netherlands for that condition with any medicine registered in the Netherlands for that indication." https://www.farmacotherapeutischkompas.nl/algemeen/niet-geregistreerde-indicaties#section-vergoeding-van-geneesmiddelen-die-op-bijlage-2-zijn-opgenomen-bij-niet-geregistreerde-indicaties.

4 Conclusions

The EU regulatory system is under pressure due to the need to assess more and more complex innovations. With the proposed revisions to the existing EU General Pharmaceutical Legislation, the Commission is trying to provide a framework that simultaneously achieves the objectives of fostering innovation and competitiveness and enhancing availability of and access to medicines.

Among the stakeholders participating in this Quickscan there is broad recognition of the need to re-evaluate the present regulatory framework and ensure it is future-proofed to accommodate innovation. Yet, the Commission's proposals hereto have received mixed reviews: some stakeholders recognise the difficulty in putting forward a regulatory framework to suit all needs or praise specific measures, but others are concerned about the legislation's impacts on innovation and patient access. Industry stakeholders have even suggested the proposed package of measures may drive innovation out of Europe and towards other established markets, such as the US or China, or settings which are cheaper for R&D, such Latin America or South Africa.

This Quickscan has collected these different perspectives and weighed them against the practical and legal feasibility of the proposed measures and their expected impacts. Based on this, an assessment was made of whether the proposed package of measures creates a framework that may reasonably be expected to be ready to support the pharmaceutical innovations of tomorrow and provide patients timely access to medicines. The following sections offer reflections on the different questions addressed by the Quickscan.

Is the proposed legislation appropriate and future-proof? What is the regulatory impact on the innovation chain from preclinical to clinical research and marketing authorisation?

With these proposals for revision of the EU general pharmaceutical legislation, the Commission has shown significant ambition and a readiness to introduce rather substantial changes into the legislation. Although the backbone of the regulatory framework remains intact, it opens up significantly greater space for innovations in fields such as biomedical sciences, engineering, digital technology and data analytics. Important new concepts introduced in the proposals to this effect include the use of regulatory sandboxes and adaptive frameworks, a greater place for RWD/RWE in regulatory decision-making and decentralised manufacturing. These additions are highly relevant in ensuring that innovations in, for instance, the development of ATMPs and personalised medicines can navigate the regulatory processes more predictably.

The Commission's plans to offer greater support to non-commercial developers may also offer an important stimulus for the development of highly innovative products, as cutting-edge innovation often comes from this direction. Whether the creation of a separate Academia Office is the most appropriate vehicle for this support, however, is open for debate as the line between academia and small commercial developers is often not clear-cut. Some further discussion on the right modality of regulatory support is therefore warranted, notwithstanding its obvious relevance to academic developers.

The Commission shows itself cognisant of the fact that innovation can be quick and unpredictable and that it is not possible for regulators to anticipate how a specific field will develop. As such, many of the introduced measures have deliberately been formulated rather open and technology-agnostic. Also, some of the definitions used in parts of the legislation have been updated to remove potentially restrictive concepts. This openness has the benefit that the legislation will, at least in theory, be able to accommodate a broad range of

innovations. At the same time, it leaves a degree of uncertainty among regulators and developers as to when and how some of these new measures may be used. It is conceivable that, as a result of this uncertainty, parties will be reluctant to seek out the full space offered by the legislation and still hold on to old paradigms. Developers have indicated that, even within the existing regulatory framework, regulators have sometimes been reluctant to consider certain innovations and that opening up the regulatory space alone will not be sufficient to address the underlying issues of unfamiliarity and risk averseness. This instead will require strengthening of the regulatory capacity among competent authorities and systematic dialogue between regulators and developers. Ultimately, whereas the changes to the regulatory framework suggested by the Commission may go a long way towards promoting its readiness for future innovations, its true test will lie in the ability of the supporting systems to implement the framework.

Last, it should be emphasised that the concerns voiced by, in particular, industry stakeholders about the proposals' potential detrimental impacts on innovation stem primarily from the Commission's intent to modulate the existing system of regulatory incentives. As these incentives were, however, not within the scope of this Quickscan the effects of such changes have not been considered here. It is nonetheless important to understand that access to medicines not only requires that products can move through the regulatory system without undue barriers, but also that there are sufficient stimuli in the system to drive innovation to areas of greatest need. Without such stimuli the chain of innovation may ultimately no longer produce the needed outputs, even if the regulatory system would be fully equipped to assess them.

How and to what extent do the proposed adjustments address existing bottlenecks and opportunities in the regulatory system to facilitate access to innovative medicines?

One of the main objectives of the proposed revisions is to improve access to innovative medicines. Such access depends on a number of factors, starting with the efficiency with which regulatory process for assessment and authorisation are conducted. Although the measure was not explored in detail in this Quickscan, the proposed reduction in the review timelines for the application for a marketing authorisation may be considered an important step towards faster access. The proposed administrative simplification in the organisational structure of the EMA, by replacing the current scientific advisory committees (CAT, COMP and PDCO) with working parties, has likewise been presented as a way of removing inefficiencies and bottlenecks in the existing processes for the regulatory assessment of innovative medicines. Based on the data collected for this Quickscan, however, it may be considered uncertain whether this restructuring will indeed have the envisioned effect or whether this can be achieved without simultaneous loss of important expertise within the system. This, in the long run, could reduce the system's ability to fulfil its tasks and slow down access to innovation rather than facilitate it.

The revised legislation is furthermore seeking to introduce some changes that would affect the ability of patients to access medicines through alternative regulatory pathways, such as pharmacy preparations, hospital exemptions for ATMPs and decentralised manufacturing. By allowing for the preparation of a limited stock of medicines in advance, it would become easier, faster and potentially cheaper for pharmacies to supply patients with compounded medicines. Meanwhile, additions to the regulatory framework governing the production of ATMPs under a hospital exemption are intended to ensure that these products meet high quality standards and that appropriate data is collected on their effectiveness, which may be used in further development. Though these additions are introduced to protect the ability of

patients to access treatments that may not be available through the customary regulatory pathways, the legislation maintains a number of restrictions that, if removed, could further increase patient access. Specifically, these concern the possibility of allowing for distribution of pharmacy preparations to non-preparing pharmacies and allowing for the parallel distribution of products prepared under a hospital exemption between Member States. These suggested additions should not be viewed as a general call to increase the overall regulatory space accorded to pharmacy preparations or products under a hospital exemption. It is recommended that the same basic criteria, under which these exemptions may be used that are already in effect, should be maintained and due consideration should always be given to whether other regulatory routes are preferable. The additions would, however, address an important issue of inequitable access to treatment affecting patients across the EU.

As before, an answer to the question at hand would not be complete without consideration of factors outside of the scope of this Quickscan. A large majority of stakeholders has emphasised that the main bottlenecks for timely access to innovative medicines at the moment lie at the level of pricing and reimbursement decisions by Member States. The Dutch government especially is herein seen as a strong rate-limiting factor, with mechanisms such as the 'lock procedure' (known, in Dutch, as "de Sluis") being heavily criticized. More generally, it is observed that there is often a discrepancy between the requirements of the EMA and of national HTA organisations in the type of information requested to support the respective assessments. As the EU has limited competence to act in this area, it is clear that improvements in the EU regulatory system intended to accelerate access will have only limited relevance on the overall availability of medicines, if factors further downstream are not simultaneously addressed at the level of the Member States.

How do key opportunities and bottlenecks in EU laws and regulations compare with the regulatory system in other countries with leading systems?

The challenges facing the EU regulatory system are by no means unique; other jurisdictions are similarly exploring how best to ensure their frameworks are kept up-to-date and able to deal with innovations. The use of regulatory sandboxes, for instance, is being tested also in Singapore and Canada, whilst the US and UK are seeking ways for the introduction of RWD/RWE into regulatory decision-making through guidance and pilot programmes. Lessons from these initiatives have not yet been widely shared and they cannot be readily compared to the proposals for the EU legislation. There is, however, already close collaboration between the US FDA, MHRA and EMA, making it likely that mutual learnings will inform the future development of additional guidance and implementing legislation. Stakeholders have nonetheless suggested the EU continues to lag behind its American counterparts in modernising its regulatory framework.

What further possibilities are there to exploit the identified opportunities through adjustments in new EU laws and regulations?

This Quickscan has identified several distinct areas where it is believed that specific adjustments to the revised EU legislation would be useful to support innovation and promote access to innovative medicines. The specific recommendations to this effect have already been discussed in greater detail in Chapter 3 but are briefly reiterated here. Specifically, it is recommended that the Dutch government proposes:

- Amendment of Article 1, Paragraph 5(b) of the new Directive to provide an EU-wide legal basis for distribution of pharmacy preparations, outlining the conditions under which such should be allowed, similar to the existing Dutch instruction on enforcement. (Section 3.2.1.4);

- Addition of a clause to Article 2 of the proposed Directive, requiring the EMA to periodically share relevant data collected by the EMA on the grant (or refusal) of licenses for a hospital exemption with third parties. (Section 3.2.2.4);
- Amendment of Article 2, Paragraph 1 of the proposed Directive to lift the prohibition on the cross-border movement of products prepared under a hospital exemption license within the EU. (Section 3.2.2.4);
- Full removal of Article 48(2) of the proposed Regulation mandating marketing authorisation holders to submit a variation, following a positive opinion by the EMA. (Section 3.5.4).
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Furthermore, it is recommended that support is withheld for the proposed restructuring of the EMA scientific committees pending further discussion with the Commission, given the strong concerns from the field and the limited information about the new organisational structure (Section 3.3.4). Only if sufficient assurances are obtained that the restructuring will not have an undue negative impact on the overall functioning of the regulatory system, should this change be accepted. Also the question of the appropriateness of an Academia Office as the preferred mechanism of offering regulatory support to academic developers should be resolved before lending support to this proposal (Section 3.4.4).

Complementing these recommendations concerning specific elements of the legislative proposals, several broader suggestions are offered for areas where the Ministry of VWS may want to seek further clarification from the Commission or discuss pertinent issues with other Member States. These concern:

- Expectations regarding how and when the regulatory sandbox concept may be applied and how experiences with it will be used to inform future developments of the regulatory framework. (Section 3.1.4);
- A potential need to update existing guidelines on the principles of regulatory acceptance of "3R testing approaches" following the publication of outcomes on a public consultation on this matter expected later this year. (Section 3.1.4);
- Further development of guidance to support decentralised manufacturing and periodic reporting on experiences. (Section 3.2.3.4);
- Identification of appropriate mechanisms and funds to advance the field of regulatory science in the EU and help strengthen the capacity of NCAs. (Section 3.3.4).

These discussions are by themselves not essential to inform the Ministry's position during the upcoming negotiations and therefore can take place at a later stage and in a different setting. They are nonetheless relevant to support the future implementation of the revised legislation.

Appendix A Participating organisations

Table 8 Overview of conversation partners

#	Category	Organisation
1	Government	Dutch Health Care Institute (Zorginstituut Nederland)
2	Government	Medicines Evaluation Board (College ter Beoordeling van Geneesmiddelen)
3	Regulatory consultant	DADA
4	Patient federation	Vereniging Samenwerkende Ouder- en Patiëntenorganisaties (VSOP)
5	Patient federation	Nederlandse Federatie van Kankerpatiëntenorganisaties (NFK)
6	Company or trade association	Vereniging Innovatieve Geneesmiddelen (VIG)
7	Company or trade association	HollandBIO
8	Company or trade association	Necstgen
9	Company or trade association	ProQR Therapeutics
10	Company or trade association	Simmunext
11	Company or trade association	Trained Therapeutic Discovery
12	Company or trade association	ArgenX
13	Company or trade association	Janssen
14	Company or trade association	Lenticure
15	Company or trade association	Pfizer
16	Company or trade association	Organon
17	Company or trade association	Associatie van Contract Research Organisaties Nederland (ACRON)
18	Clinical Research Organisation	Center for Human Drug Research
19	Infrastructure for innovation	Health-Holland
20	Knowledge/technology transfer office	Technology Transfer Office Erasmus MC
21	Knowledge/technology transfer office	Knowledge Transfer Office KNAW
22	Knowledge infrastructure / academic organisation	ONCODE
23	Knowledge infrastructure / academic organisation	DARE-NL
24	Knowledge infrastructure / academic organisation	Leiden University Medical Center
25	Knowledge infrastructure / academic organisation	Medicijn voor de maatschappij
26	Professional association	NVNG
27	Professional association	ESDPPP

#	Category	Organisation
28	Research funder	KWF Kankerbestrijding
29	Research funder	Hartstichting
30	Private Equity	Holland Capital
31	Advocacy organisation	Wemos

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Table 9 Overview of workshop participants

Workshop #	Category	Organisation
1	Research funder	Kongingin Wilhelmina Fonds
1	Patient federation	Nederlandse Federatie van Kankerpatiëntenorganisaties
1	Patient federation	Vereniging Samenwerkende Ouder- en Patiëntenorganisaties
2	Infrastructure for innovation	Health-Holland
2	Professional association	ESDPPP
2	Clinical Research Organisation	DCRF
2	Company or trade association	Janssen
2	Company or trade association	Pfizer

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Appendix B Additional reflections on regulatory changes

As indicated previously, in the course of our data collection stakeholders raised several more regulatory issues for potential consideration by the Dutch government. As these issues were not explored in the workshops with stakeholders, they have not been included in the main report. Nonetheless, we feel they merit being brought to the attention of the Ministry of VWS and have therefore included these here.

B.1 Temporary Emergency Marketing Authorisation

At present, the main regulatory pathway for (temporarily) allowing the supply of previously unauthorised medicines in the context of a public health emergency is the conditional marketing approval (CMA). CMA helps to fast-track the approval, once a positive benefit-risk ratio has been established, on the basis of less comprehensive sets of data than normally would be required, provided that the data collection is completed post-authorisation. The system relies on robust post-authorisation safeguards and controls. The mechanism was, however, not designed for the specific context of public health emergencies and rather has been used mainly in situations where large-scale collection of data cannot be done (e.g. for rare diseases) and in cases whereby the advantages of early access outweigh the risks of remaining uncertainty. The EMA sets conditions regarding post-authorisation data collection on the authorisation and will review periodically whether these conditions have been met, in order to decide whether the conditional approval can be converted into a regular marketing authorisation.

With the legislative proposals, the Commission envisages a new mechanism: that of the Temporary Emergency Marketing Authorisation (TEMA). This mechanism is intended to provide a faster way of authorising useful medicines during a declared public health emergency. During a public health emergency, the Commission may grant a TEMA for medicinal products intended for the treatment, prevention or medical diagnosis of a serious or life-threatening disease or condition which are directly related to the public health emergency[119]. A TEMA may be granted only after the recognition of a public health emergency at Union level, which is when:

- No alternative method of treatment, prevention, or diagnosis is authorised or adequately accessible within the Union. In cases where such a method is available, the temporary emergency authorisation of the medicinal product would contribute to addressing the public health crisis;
- The Agency provides an opinion that determines the medicinal product's potential effectiveness in treating, preventing, or diagnosing the disease or condition directly associated with the public health emergency. Additionally, it assesses that the known and potential benefits of the product outweigh its known and potential risks, considering the threat posed by the public health emergency[120].

[119] Proposed Regulation Article 30

[120] Proposed Regulation Article 31

The TEMA will end when the Commission terminates the recognition of a public health emergency[121]. When the authorisation ends there is still allowance for a transitional period, the supply of the medicinal product to patients who are already being treated with it[122].

The TEMA will be granted on a coordinated EU-level, rather than a Member State-by-Member State basis but will run alongside Member State powers. The TEMA could in some circumstances provide an additional regulatory tool at EU level, giving more flexibility to EMA to respond to emerging threats and protect public health[123].

Stakeholders, particularly those from the pharmaceutical industry, are generally positive about how the EMA handled regulatory processes for assessment of vaccines and medicines for use in the COVID-19 crisis. Nonetheless, they have questions about how the new TEMA mechanism would work, particularly once the Commission terminates the recognition of a public health emergency. For example, they wonder whether any products approved through a TEMA will then automatically be granted a CMA or whether the authorisation will be terminated completely, and an entirely new application must be filed. It is therefore advised that the Ministry of VWS seeks clarification from the Commission on the transitional processes for products granted a TEMA once the declared public health emergency is terminated.

B.2 Unmet medical needs (UMN)

Despite many new medicines being approved every year, there remain many therapeutic areas, especially in the field of rare diseases, where there are no effective methods to prevent or treat a condition. The Commission aims to draw more development of medicinal products to these areas of unmet medical need by offering regulatory incentives. The already existing Priority Medicines (PRIME) scheme, run by the EMA, is an instrument to enhance support for the development of medicines that target an unmet medical need. Through PRIME the EMA has gained experience with the provision of early scientific and regulatory support to developers of certain medicinal products that, based on preliminary evidence, are likely to address an unmet medical need and are considered promising at an early stage of development.

The proposed legislation aims to give extra incentives for development of treatments that address high unmet medical needs (HUNM). Under the proposed revisions, the normal duration of market exclusivity would be set at nine years, with an exception for Orphan Medical Products if it is assessed to address a HUMN, which will then get ten years[124,125]. An orphan medicinal product shall be considered as addressing a high unmet medical need when:

- There is no medicinal product authorised in the Union for such condition or where the applicant demonstrates that the orphan medicinal product will bring exceptional therapeutic advancement;
- The use of the orphan medicinal product results in a meaningful reduction in disease morbidity or mortality for the relevant patient population[126].

[121] Proposed Regulation Article 34

[122] Proposed Regulation Article 37

[123] Cavaleri, M., Sweeney, F., González-Quevedo, R., & Carr, M. (2021). Shaping EU medicines regulation in the post COVID-19 era. The Lancet Regional Health - Europe, 9, 100192. https://doi.org/10.1016/j.lanepe.2021.100192.

[124] Proposed Regulation Article 71

[125] Proposed Regulation Article 69

[126] Proposed Regulation Article 70

The goal of this measure is to make it more attracting to develop treatments for rare diseases and shift more research and investment to areas of HUMN.

Interviewees acknowledged that there is still a substantial group of (rare) diseases that has no effective treatment. However, there are conflicting opinions concerning the definition of unmet medical needs. Some interviewees argue that a well-formulated definition is required in order to actually give incentives to certain treatments. Clarity on this definition is considered especially important for developers as it is associated with possible financial rewards and therefore a way of attracting investment. Other interviewees, however, are concerned that a very demarcated definition of UMN results in the exclusion of more incremental innovations. With the new legislation, they claim that companies may hesitate to invest in certain innovations, when these do not fit within the framework of unmet medical needs. Therefore, they argue that a certain degree of flexibility is needed. Whilst the data collected as part of this Quickscan offer no specific suggestions for modification or further elaboration of the above proposed definition, it is clear that the issue will likely form a trigger point for discussion during the upcoming negotiation process. It is therefore advisable that the Ministry of VWS formulates a clear position on the proposed definitions for (H)UMN under the proposed legislation and their linkage to regulatory incentives, such that it may support this position during the negotiations.

Appendix C Workshop discussion papers

C.1 Restructuring of EMA scientific committees

Background: Depending on product characteristics, various EMA scientific committees may be involved in the assessment of a single medicinal product. The different procedures of these committees, and the interactions between them, have been said to lead to duplication of work, inconsistent assessments, and delays in the overall procedure. To improve the overall efficiency, the proposals for revision of the EU general pharmaceutical legislation therefore include dissolving the following scientific committees: Committees for Advanced Therapies (CAT), Committee for Orphan Medicinal Products (COMP) and Paediatric Committee (PDCO)[127]. These committees, which currently comprise representatives of each Member State, will be replaced by 'working parties'. The working parties will mostly consist of experts appointed by the Member States based on their expertise and of external experts. Member States that are not represented in a working party may request to attend meetings as an observer. Contrary to the present situation, the working parties will function only in a supporting capacity and will have no mandate to make decisions or issue formal recommendations. Alongside this restructuring, it is proposed to transfer the power to grant or refuse orphan designations from the European Commission to the EMA.

Reaction from the field:

Existing inefficiencies and inconsistencies in the working methods of the EMA are recognized by several parties, supporting the rationale behind a restructuring. At the same time, various organisations, notably including those representing the interests of patients, have expressed concerns that the change will lead to a loss of expertise. This may, in turn, have a knock-on effect on the expertise available at the Member State level with national competent authorities. Moreover, there is concern that working parties will only be able to act *ad hoc* and in a reactionary manner rather than proactively develop strategies and guidance.

A related concern is that the restructuring of committees and transfer of responsibilities from the European Commission to the EMA will lead to less transparent decision-making and less accountability to the Member States.

Focus of discussion: How may the desired administrative simplification and efficiency gains in the working methods of the EMA best be achieved, whilst minimizing the identified risks? What conditions should the Dutch government place on the proposed restructuring to ensure proper safeguards are in place?

Relevant sections of the proposals

- Proposal for a Regulation:
  - Explanatory Memorandum: "Reducing regulatory burden and providing a flexible regulatory framework to support innovation and competitiveness", p.19
  - Art. 64(4)
  - Art. 150 Scientific working parties and scientific advisory groups

[127] The Committee for Herbal Medicinal Products will likewise be replaced by a working party. The work of this committee, however, falls outside the scope of the present study.

C.2 Medicines manufacturing without a marketing and/or manufacturing authorisation

Background: The EU general pharmaceutical legislation is primarily designed to support the development, assessment and use of medicines that are covered by a marketing authorisation and produced according to the GMP standards under a manufacturing authorisation. The legislation, however, also provides a framework for exemptions to the normal authorisation requirements. This includes magistral formulation, hospital exemptions for ATMPs and decentralized manufacturing. The framework lays down the conditions under which these exemptions may apply, though these conditions may be further specified at the Member State level.

Several changes are being proposed:

- Magistral formulation: A clause has been added to specify that magistral formulation may be used also to prepare products in advance "on the basis of the estimated medical prescriptions within that hospital for the following seven days" in "duly justified cases". This would facilitate the production at a somewhat larger scale than before so that the pharmacy may hold a limited amount stock. The proposal maintains the limitation that pharmacies may only prepare medicines for their own patients.
- To obtain better oversight of how, when and where the hospital exemption for ATMPs is being used, and what the experiences with this are, it is proposed to make it mandatory for national competent authorities to inform the EMA of any approvals (and subsequent changes) for use of the exemption. Member States also must ensure that preparation complies with GMP-equivalent requirements. The proposal maintains the current limitation that products produced under a hospital exemption may be used only within the same Member State where they have been produced.
- Recognising that centralised manufacturing is not always possible, particularly for innovative ATMPs, the proposed legislation will allow more space for 'decentralised manufacturing' (DCM). Here, a decentralised site does not require its own manufacturing authorisation. Instead, it falls under the responsibility of a qualified central site. The product must still be covered by a marketing authorisation.
-

Reaction from the field: Various parties are advocating for a broader scope for the magistral formulation and/or hospital exemption, which would enable products to be prepared not only for individual patients or for patients within the own hospital or country setting. ATMPs are considered a class of products with great potential for future impact, yet their preparation can be very complex. Removing the clause that products may only be used in the Member State where they have been produced, could enable preparation of products in the hereto most qualified sites and increase equitable access across the EU.

Concerns have also been raised about potential expansion of the use of magistral formulation and the hospital exemption. These concerns primarily relate to the risk of insufficient quality control, lack of standardization, and insufficient collection of data on effectiveness and safety. There are also concerns that increased production by parties that are not bound by the same very strict criteria for manufacturing as commercial parties will lead to unfair competition and may lead to companies being unwilling to invest in the development and production of such products.

Focus of discussion: To what extent are amendments to the proposals desirable from the perspective of access and affordability of treatment and how may any associated risks best be mitigated by amendments to the legislation? Under what conditions should exemptions be allowed?

Relevant sections of the proposals

- Proposal for a Directive
  - Article 1(5) and 1(6): Magistral formula
  - Article 2: Advanced therapy medicinal products prepared under hospital exemption
  - Article 142: Manufacturing authorisation
  - Article 148: Registration and listing process of decentralised sites

C.3 Drug repurposing

Background: The repurposing of existing medicines for new indications is an important development that can have positive impacts on both the availability of treatments, including for patients with rare diseases, and on the affordability of healthcare as these medicines often are no longer under patent or regulatory protection. With the proposals, the Commission is issuing a signal that it wants to stimulate drug repurposing by offering additional data protection for registration of a new indication. Simultaneously, it wants to promote that drug repurposing is brought 'on-label' by providing the possibility for "an entity not engaged in an economic activity ('not-for-profit entity')" to submit evidence to support the registration to the EMA. If, after evaluation, the EMA issues as positive opinion all marketing authorisation holders of the product concerned must file a submission for variation of the authorisation to register the new indication.

Reaction from the field: Whilst the Commission's efforts to promote drug repurposing and increase registration of new indications is generally welcomed, there are concerns about unintended consequences of the proposals. Filing for a variation of the authorisation – and subsequently maintaining that authorisation – is not without costs to the marketing authorisation holder. As most repurposed medicines concern older, off-patent products for which profit margins may already be small, these additional costs could push the product over the point where it is no longer commercially interesting for the authorisation holder. In response, they may opt to withdraw the authorisation completely rather than submit a variation. Rather than supporting on-label use (and enabling reimbursement), the measure could therefore backfire and make the product unavailable even for off-label use. Some stakeholders have therefore argued that filing for variation of the authorisation should only be mandatory for products that are still under regulatory protection and be optional for all other products.

Focus of discussion: How best may any risks associated with the obligation to submit an application for a variation be mitigated? What other measures might be considered to encourage registration of new indications without jeopardizing product availability?

Relevant sections of the proposals

- Proposal for a Directive
  - Article 48: Scientific opinion on data submitted from not-for-profit entities for repurposing of authorised medicinal products

C.4 Need for clarity and vision on regulatory acceptance of new ways for generating evidence

Background: Innovations are happening not only in types of treatment but also in the way that studies are designed and how data are generated to provide evidence on the safety and effectiveness of those treatments. For instance, the development of organs-on-a-chip could reduce the need for animal testing, whilst re-use of existing data sets, along with use of real-world data and Artificial Intelligence, can enable the generation of synthetic controls. However, such innovations will not find widespread application if they are not accepted by regulators. It is therefore imperative that the regulatory framework provides sufficient space for, on the one hand, experimentation and flexibility but, on the other, also clearly demarcates its 'lines in the sand', i.e. the minimum standard of evidence below which it will not accept applications. This requires, among other things, proper validation of new methods and guidance on how and when these may be applied. Throughout the proposals, there is an awareness of the need for regulatory flexibility to accommodate innovation. For instance, the proposed Regulation specifies that:

- Animal tests should not be performed in cases where scientifically satisfactory non-animal testing methods are available (for products going through the centralized marketing application)
- Regulatory decision-making on the development, authorisation and supervision of medicinal products may be supported by access and analysis of health data, including real world data, where appropriate (Preamble (60))
- Regulatory sandboxes can provide the opportunity for advancing regulation through proactive regulatory learning

Questions remain, however, about how the EMA will operationalize this in its assessment procedures.

Reaction from the field: Among parties there is much uncertainty and confusion about how the EMA intends to take these concepts forward in practice. For instance: when will it consider a method to be "scientifically satisfactory" to accept evidence from non-animal models rather than still require data obtained from animal models? The concept of the regulatory sandbox in particular is understood differently by different parties, most of whom are uncertain as to when and how it may be applied.

Focus of discussion: What clarity is needed from the Commission and EMA about the application of innovative methods and their potential for future regulatory acceptance? What more may be done to encourage uptake of innovations, without compromising on safety and effectiveness?

Relevant sections of the proposals

- Proposal for a Regulation
  - Article 6(5) on Centralised marketing authorisation application
  - Preamble, point 60
  - Chapter IX Regulatory Sandbox

C.5 Support for non-commercial operators

Background: A substantial percentage of all pharmaceutical innovation, in particular early-stage research, is not performed by large pharmaceutical companies but by academia, research institutes, not-for-profit organisations and small start-ups. These parties tend to have less experience with the further clinical development and with the regulatory processes needed to get to a marketing authorisation. As a result, early-stage research is frequently not designed with those next stages in mind and parts of the research may need to be redone. When trials need to be redone, this not only leads to extra costs but also places an unnecessary burden on patients who participate in the research. Although the EMA offers scientific advice to developers, and this advice is considered very valuable, there is a sense that the distance between the EMA and these types of developers remains (too) large.

Whilst not detailed in the proposals for the revision of the EU general pharmaceutical legislation, the EMA is working on creating an 'Academia Office" to support not-for-profit entities by providing them free of charge early scientific advice. Its tasks, analogous to the already existing SME office, will include procedural and administrative assistance to "not-for-profit" entities, including direct assistance and briefing meetings on regulatory strategy, providing fee waivers and reductions to eligible entities, provide free-of-charge translations of the product information in all EU languages for initial EU marketing authorisations, and provide training and education to "not-for-profit" entities. The office must be set up within 6 months of adoption of the Regulation.

Reaction from the field: Parties were not asked specifically to comment on the proposed set up of an 'Academia Office' but discussions about the role of EMA more generally support the relevance of such an office. There is a perceived need for earlier and more informal dialogue between the regulator and developers. Although it is recognized that there should remain a clear separation between regulatory assessors and developers, to protect the independence and integrity of the assessment, it would be welcomed if the EMA could take less of an 'arm's-length' approach with academia than it does with commercial parties.

Focus of discussion: What role can the EMA play in supporting non-commercial operators in the pharmaceutical development process, already from an early stage, to ensure that research is optimally designed to generate relevant and robust data to support regulatory assessment? How can this be done in a way that protects the independence and transparency of the assessment process?

Relevant sections of the proposals:

Not directly covered in the proposals, other than that in the Proposed Regulation (p. 164 and p. 179), the creation of the Academia Office, and its budget and staff requirements, are mentioned.

Appendix D Country Case Study: Singapore

D.1 Description of regulatory approval in Singapore

D.1.1 Pharmaceutical innovation and R&D in Singapore

Table 10 Descriptive statistics on pharmaceutical R&D in Singapore

Characteristic	**Measure for most recent year**
Amount of medical research / number of clinical trials	309 trials registered as collecting data in Singapore in 2022 (up from 43 in 2012) (WHO)[128]; 365 trials registered in Singapore in 2022 (Clinicaltrials.gov)[129]
R&D expenditure	19 billion USD (2020)
Number of patents for pharmaceutical innovation	83.4 pharmaceutical patents registered in 2019[130] 101.8 medical technology patents registered in 2019[131]
Number of (new) products approved 2020 – 2023	60 therapeutic products[132]; 4 Class 2 CTGTPs[133]

Since 2000, the Singapore government has been committed to establishing itself as a biotech hub with an initial US$2 billion invested in the Singapore Biomedical Sciences (BMS) initiative over a five-year period.[134] Between 2006 and 2015, the government further invested approximately US$5.5 billion (7.3 billion Singapore dollars) in the biomedical sector to help develop infrastructure and human capital and build up translational and clinical research capabilities[135]. In 2016, another US$ billion (4 billion Singapore dollars) was invested under the five-year R&D expenditure plan. The latest initiative called the Research, Innovation, and Enterprise 2025 (RIE2025) scheme consists of a record funding of US$19 billion (25 billion Singapore dollars),[136] which includes the Human Health and Potential (HHP) as one of the four

[128] Between 1 January 2022 and 31 December 2022 (most recent complete year). Based on country of recruitment. World Health Organisation. ICTRP Platform Search Portal. Available at: https://trialsearch.who.int/AdvSearch.aspx

[129] Clinicaltrials.gov. Available at: https://www.clinicaltrials.gov/. Searched on 'Singapore' and study start between 01/01/2022 and 31/12/2022.

[130] For pharmaceutical patents registered in at least two of the IP5 patent families (US, EU, China, Japan, and South Korea), based on inventor's country of residence. Most recent complete year. Note: this data uses fractional counting, which divides a patent equally over each listed inventor country / technology field. See: OECD.stat (2023)

[131] For medical technology patents registered in at least two of the IP5 patent families (US, EU, China, Japan, and South Korea), based on inventor's country of residence. Most recent complete year. Note: this data uses fractional counting, which divides a patent equally over each listed inventor country / technology field. See: OECD.stat (2023)

[132] 'HSA | Summary Reports of Benefit-Risk Assessment' <https://www.hsa.gov.sg/therapeutic-products/register/summary-reports-of-benefit-risk-assessment> accessed 28 November 2023.

[133] 'HSA | Register of Class 2 Cell, Tissue or Gene Therapy Products' <https://www.hsa.gov.sg/ctgtp/ctgtp-register> accessed 28 November 2023.

[134] Heather L Van Epps, 'Singapore's Multibillion Dollar Gamble' (2006) 203 The Journal of Experimental Medicine 1139 </pmc/articles/PMC2121196/> accessed 28 November 2023.

[135] 'Written Reply to PQ on the Returns of Investment in Biotechnology Industry' <https://www.mti.gov.sg/Newsroom/Parliamentary-Replies/2018/01/Written-reply-to-PQ-on-the-returns-of-investment-in-biotechnology-industry#> accessed 28 November 2023.

[136] '20 Years in, Singapore Still Searches for Its Biotech Success Story' <https://www.fiercebiotech.com/biotech/20-years-singapore-still-searches-its-biotech-success-story> accessed 28 November 2023.

pillars of focus. Highlighting the ambition for greater emphasis on translational and clinical research to better the country's health and economic outcome[137].

D.1.2 Regulatory agency

- In Singapore, the regulatory body responsible for regulating pharmaceuticals and medical devices is the Health Sciences Authority (HSA)[138]. It was established by the Health Science Authority Act 2001, operating under the Ministry of Health. The HSA manages the implementation of health-related laws and regulates the health products sector. Its primary responsibility is to ensure that drugs, innovative therapeutics, medical devices, and other health-related products are appropriately regulated and comply with established safety, quality, and efficacy standards. Additionally, the HAS plays a role in shaping national drug policies.[139]

The HSA offers services under four professional groups: 1) the Applied Sciences Group, 2) the Blood Services Group, 3) the Health Products Regulations Group, and 4) the Corporate Services Group. The professional groups engage in routine consultations with both the industry and clients, aiming to keep them well-informed about emerging directions and regulations, while also attentively addressing their concerns. The Health Products Regulation Group is responsible for the regulation of health products, facilitating access to safe and efficacious health products, and developing regulations supporting innovation.

D.1.3 Main pharmaceutical legislation or regulation

Medicines are governed as "therapeutic products" under the *Health Products Act 2007***Error! Bookmark not defined.** and are defined by the *Health Products (Therapeutic Products) Regulations 2016*[140]. This classification encompasses other health products, including medical devices and cosmetic products. In 2021, the HSA introduced a new regulation for Cell, Tissue and Gene Therapy Products (CTGTPs) as a novel and innovative class of health products (also known as ATMPs in the EU) and updated the Health Products Act accordingly[141,141].

[137] National Research Foundation (Prime Minister's Office - Singapore), 'Research, Innovation and Enterprise 2025 Plan' (2020).

[138] 'Health Sciences Authority (HSA)' <https://www.hsa.gov.sg/> accessed 28 November 2023.

[139] 'Life Sciences Regulation in Singapore: Overview | Practical Law' <https://uk.practicallaw.thomsonreuters.com/1-525-9055?transitionType=Default&contextData=(sc.Default)&firstPage=true> accessed 17 November 2023.

[140] Health Products (Therapeutic Products) Regulations 2016 - Singapore Statutes Online.

[141] 'Health Products (Cell, Tissue and Gene Therapy Products) Regulations 2021 - Singapore Statutes Online accessed 29 November 2023.

CTGTPs are categorised based on risk into two classes:[142]

- Class 1 (lower risk): must be minimally manipulated,[143] intended for homologous use,[144] and not combined or used in conjunction with therapeutic products or medical devices.
- Class 2 (higher risk): CTGTPs that do not meet the criteria for Class 1 CTGTPs.

Products classified as ATMPs in the EU, such as gene-modified cells, cells grown on a scaffold, culture-expanded cells, and vectors with therapeutic genes, are categorised as Class 2 CTGTPs.[142]

D.1.4 Organisation of regulatory system

The pharmaceutical regulations and registration process in Singapore require obtaining a valid product license through registration for the export or sale of new or generic drugs. To achieve this, one must submit a license application (dossier) to the HSA, adhering to the common technical document (CTD) format established by the International Conference on Harmonization (ICH). In a broader context, all therapeutic products designated for import or sale in Singapore must undergo registration with the Health Products Regulation Group of the HSA, with specific exceptions. The responsibility for product registration rests with a locally registered company, ensuring alignment with the *Health Products Act* and relevant subsidiary legislation. [139]

For new product registrations, companies can choose to submit either a new drug application (NDA) or a generic drug application (GDA). The GDA applies to products essentially identical to a reference product that is currently registered in Singapore. Biosimilar products, however, require submission through an NDA. This ensures a systematic regulatory process aligned with international standards, making it clear for companies aiming to market pharmaceutical products in Singapore.[139]

There are four evaluation routes for registering a therapeutic product with the HSA:

[145]

- Full route: Applies to any new product that has not been approved by any drug regulatory agency at the time of application submission to HSA.
- Abridged route: Applies to any new or generic product that has been evaluated and approved by at least one drug regulatory agency.

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[142] 'HSA | Regulatory Overview of Cell, Tissue or Gene Therapy Products' <https://www.hsa.gov.sg/ctgtp/regulatory-overview> accessed 29 November 2023.

[143] Minimally manipulated refers to any processing of the cell or tissue stated below that does not alter the cell's biological characteristics or functions, or the tissue's structural properties: cutting or sizing, grinding, shaping, centrifugation, soaking in an antibiotic or antimicrobial solution, sterilisation or irradiation, cell separation, concentration or purification, filtration, lyophilisation, freezing, cryopreservation or vitrification.

[144] Homologous use refers to using the CTGTP to repair, reconstruct, replace or supplement the cells or tissues of the recipient to perform the same basic function(s) as the original cells and tissue in the donor in the same anatomical or histological environment.

[145] Guidance on therapeutic product in Singapore 2023.

- Verification route: Applies to any new or generic product that has been evaluated and approved by HSA's reference drug regulatory agencies, which are EMA,[146] US FDA, Health Canada, TGA and UK MHRA[147].
- Verification-CECA route: Applies to any generic product manufactured in India which has been evaluated and approved by HSA's reference drug regulatory agencies, which include EMA,[146] US FDA, Health Canada, TGA and UK MHRA.[147]
- All applications are to be submitted via the online Pharmaceutical Regulatory Information System (PRISM), followed by the submission of the accompanying technical dossier within two working days[145].

D.1.4.1 Expedited MA pathways

There does not appear to be expedited marketing authorisation pathways in Singapore for pharmaceutical products. However, in 2018, the HSA identified the need for facilitating access to medical devices and introduced expedited routes and a Priority Review Scheme for fast-tracking medical device approval[148].

D.1.4.2 Specific pathways for ATMPs or unmet medical need (UMN)

A priority review via the Abridged route for life-saving drugs can be requested under specific conditions. This includes treating a serious life-threatening condition with unmet medical needs, such as the absence of a treatment option or the lack of safe and effective treatments. The drug must demonstrate a significant improvement compared to available marketed products, evidenced by increased effectiveness in treating, preventing, or diagnosing a disease, as well as the elimination or substantial reduction of treatment-limiting adverse reactions. Additionally, diseases of local public health concern, such as cancer and infectious diseases, qualify for priority review. The request, embedded in the introduction document of the application dossier, needs to be accompanied by justifications and evidence, including the seriousness of the disease, mortality rates, local epidemiology data, and the impact of the product on medical practice, substantiated by clinical evidence supporting claims of significant improvement over existing treatments[149].

ATMPs, known in Singapore as CTGTPs, are regulated separately under the CTGTP guidance. Class 1 CTGTPs are exempt from the standard product registration process. Instead, suppliers must notify the HSA about the product and wait for HSA's written acceptance or acknowledgement of the notification before it can be marketed. Additionally, suppliers must guarantee that the product originates from an accredited or licensed facility and is free from infectious agents[150].

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[146] For products approved via the Centralised Procedure.

[147] For products approved via the national procedure or where MHRA acted as the RMS for the MRP or Decentralised Procedures on or prior to 31 January 2020 when the UK has formally left the European Union.

[148] 'QT ANALYSIS: 5 New Motivating Routes to Register Medical Device Products Quickly in ASEAN - January 2022' <https://www.qualtechs.com/en-gb/qt-analysis-5-new-motivating-routes-to-register-medical-device-products-quickly-in-asean--january-2022#> accessed 29 November 2023; 'HSA | Registration Overview of Medical Devices' <https://www.hsa.gov.sg/medical-devices/registration/overview> accessed 29 November 2023.

[149] 'HSA | Abridged Evaluation Route for New Drug Application' <https://www.hsa.gov.sg/therapeutic-products/register/guides/new-drug/abridged-evaluation> accessed 29 November 2023.

[150] Guidance on Cell, Tissue and Gene Therapy Products registration in Singapore 2021.

On the other hand, Class 2 CTGTPs must be registered with HSA before being supplied in Singapore. Applicants need to ensure compliance with specified submission requirements outlined in the guidance document. Any deviations from these requirements must be scientifically justified and discussed with HSA before submission to avoid potential rejection. HSA may request additional information if necessary for assessing safety, efficacy, and quality[150].

D.1.4.3 Other tools

In addition to the four types of evaluation routes for registering a therapeutic product, the HSA has three Special Access Routes (SAR):

- Import a therapeutic product on consignment basis: For importers who are neither the registrants nor authorised by the registrant and intend to import a registered therapeutic product. The imported product must be identical to the one currently registered in Singapore, encompassing matching chemistry, manufacturing, and controls standards, as well as an identical package insert. Additionally, the therapeutic product should not contain any controlled drug specified under the *Misuse of Drugs Act* and its regulations. The applying company must be a registered business entity in Singapore, holding valid licenses as a Therapeutic Product Importer and a Therapeutic Product Wholesaler.
- Import and supply of an unregistered therapeutic product for patient use: To facilitate access to life-saving therapies where there is an unmet medical need, such as in situations where a treatment option is absent, and the patient's health will be clinically compromised without treatment with the unregistered therapeutic product. This route is reserved for situations where there is no alternative registered treatment available.
- Special Consignment Scheme: Intended to ensure continued availability of a registered therapeutic product in the event of a supply disruption caused by the inability of the product registrant to provide stock as registered in Singapore. In these circumstances, product registrants are required to obtain approval from the HSA to import a consignment of a registered therapeutic product intended for another market, addressing potential stock-out situations.

During the COVID-19 pandemic, the HSA saw an increase in demand for medical devices. To facilitate access, the HSA introduced new regulations and guidelines for the use of Artificial Intelligence (AI), *in vitro* diagnostics, and 3D printing, specifically for medical devices (see Table 11).[151]

Table 11 New regulations and guidelines introduced in 2021

Guidelines	Details
Collaboration with the Ministry of Health (MoH) - AI Guideline for Safe Development and Implementation of Artificial Intelligence (AI) in Healthcare	• HSA addressed the risks present in the development and implementation of AI medical devices (AIMDs) in healthcare settings • The purpose of the guideline is to encourage partnership between developers and implementers to ensure patient safety • The guideline is targeted to be launched in the second half of 2021
Guideline on changes relating to the new regulatory frameworks for Medical Devices Regulation (MDR) and In Vitro Diagnostic Regulation (IVDR)	• The European Union (EU) introduced two new regulations — MDR and IVDR, in place of the current Medical Devices Directive (MDD) • As a result of this change, revisions to device labelling and instructions for use on a significant number of medical devices are expected as many devices in Singapore share common labelling with those supplied in EU • This new guideline serves to provide clarity on the changes which would require submissions to HSA

	• The proposed guideline went through a focus group session in July 2020 and was finalised in October 2020
New regulatory guideline for 3D Printed Medical Devices (3DP MDs)	• 3D printing allows for the production of medical devices matched to an individual's specific anatomy • This new guideline for 3DP MDs serves to differentiate mass-produced from custom-made 3DP MDs and explain the regulatory controls involved • The guideline was published in January 2021 for consultation and is expected to be finalised in Q3 2021

Source: Adopted from Health Sciences Authority (HSA), 'Annual Report 2020/2021 - Rising to the Challenge'[151]

D.1.4.4 Scientific advice offered by the HSA

The HSA's Innovation Office is dedicated to supporting developers seeing early scientific and regulatory advice on therapeutic products and CTGTPs development. This includes non-clinical development, clinical development, quality developments, as well as considerations related to manufacturing and GMP. Moreover, it extends support in navigating regulatory submissions[152].

It is unclear how the Innovation Office is set up, and the type of experts within the department. However, it was established in an effort to streamline the efficient development and timely registration of innovative therapeutic products, including chemical and biologic compounds, as well as CTGTPs in Singapore[153].

D.2 System/agency ability to adapt the regulatory assessment of innovation

D.2.1 Level of regulatory flexibility provided by law

During the COVID-19 pandemic, the Government of Singapore introduced the Pandemic Special Access Route (PSAR) for the supply of both emergency therapeutic products and medical devices. This is an interim authorisation put in place to enable regulatory agilities responding to a public health emergency.[154] Furthermore, specific regulations were introduced in 2021 to guide the use of vaccines manufactured outside of Singapore[151].

The HSA does not have dedicated regulations for orphan drugs (i.e., medications used for treating rare diseases that may not be financially viable without government support) since the repeal of the Medicines (Orphan Drugs) (Exemption) Order in 2016. Currently, orphan drugs are subject to governance under the *Health Products Act*, following the same regulations as other therapeutic products[139]. The only potential flexibility is through drug repurposing, which will be further discussed in the following sections.

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[151] Health Sciences Authority (HSA), 'Annual Report 2020/2021 - Rising to the Challenge' (2021) <https://www.hsa.gov.sg/docs/default-source/default-document-library/hsa-ar_web-fa8a739947c357410b9a05adebf44e0b07.pdf> accessed 17 November 2023.

[152] 'HSA | Innovation Office' <https://www.hsa.gov.sg/clinical-trials/innovation-office> accessed 17 November 2023.

[153] 'Singapore HSA Launches Innovation Office to Support Product Development - Pharma To MarketPharma To Market' <https://www.pharmatomarket.com/singapore-hsa-launches-innovation-office-to-support-product-development/> accessed 17 November 2023.

[154] 'HSA | Pandemic Special Access Route (PSAR) for Supply of Emergency Therapeutic Products' <https://www.hsa.gov.sg/therapeutic-products/register/special-access-routes/psar-emergency-therapeutic-product> accessed 29 November 2023.

D.2.2 *Manufacturing without marketing or manufacturing authorisation*

Regulation 58 of the Health Products (Therapeutic Products) Regulation outlines exceptions to the prohibition of supplying unregistered health products[140]. These exceptions include the supply of a therapeutic product formulated at a private hospital, extending to another private hospital or to a patient of a qualified practitioner at any private hospital or medical clinic. Furthermore, exceptions also extend to formulated products at a medical clinic, licensed retail pharmacy, or by a qualified practitioner, all subject to specific conditions and approvals from the HSA. Other exceptions include products intended for use on ships or aircraft, for scientific education or research and development, and for wholesale purposes, provided the product does not contain psychotropic substances or is not a controlled drug. Export-related exceptions are also granted with approval from the HSA[139].

Additionally, unregistered therapeutic products may be brought into Singapore on a named-patient basis, subject to obtaining special approval from the Health Products Regulation Group of the HSA. The application must include details about the product to be imported, information on the importer, the responsible physician, and particulars regarding the patient to be treated[155].

Individuals generally have the authorisation to import therapeutic products into Singapore, without needing an importer's license, as long as the products do not contain psychotropic substances or exceed specified amounts of codeine and dextromethorphan set by the HSA. However, prior approval from the HSA is required[155].

D.2.3 *Drug repurposing*

To repurpose drugs in Singapore, a MAV-1 application must be submitted, covering changes in a registered therapeutic product across various areas, such as approved indication, route of administration, dosing regimen, patient group, and the inclusion of clinical information to expand product usage. Each product registration allows a maximum of three MAV-1 applications simultaneously. For orphan drugs, prior consultation with the HSA is advised before submitting the application. It is essential to demonstrate that the proposed indication for the orphan drug product has been designated as such by at least one reference drug regulatory agency. A note in the eligibility states that the product may not need a more rigorous assessment, considering differences in local disease patterns or medical practices[156].

D.2.4 *COVID-19 pandemic flexibilities*

Under the Pandemic Special Access Route[151], the HSA is able to direct the distribution and supply of emergency therapeutic products, provided there is evidence suggesting that the benefits outweigh the risks. Ongoing data on the product's quality, safety, and efficacy must support a potential transition from interim authorisation to product registration under the *Health Products Act*. The interim authorisation offers regulatory flexibility for swift responses to public health emergencies, such as pandemics, allowing the HSA to prioritise the review of novel therapeutics and vaccines for timely access while maintaining scientific rigour in their

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[155] 'Commercialisation of Healthcare in Singapore: Overview | Practical Law' <https://uk.practicallaw.thomsonreuters.com/2-618-4110?transitionType=Default&contextData=(sc.Default)&firstPage=true> accessed 17 November 2023.

[156] 'HSA | Overview of MAV-1 Application' <https://www.hsa.gov.sg/therapeutic-products/variation-application/mav-1/overview> accessed 17 November 2023.

assessment. Applicants must meet specific prerequisite criteria before submitting an application for interim authorisation[139].

D.2.5 Support to non-commercial operators

In an effort to streamline the efficient development and timely registration of innovative therapeutic products, including chemical and biologic compounds (therapeutic products), as well as CTGTPs, HSA set up an Innovation Office in 2021, as a pilot initiative. This office is designed to cultivate a supportive regulatory environment aimed at enhancing the biomedical sector. Through the pilot, the HSA aims to continuously implement adjustments to further refine process efficiency and better align with stakeholder needs[153].

The Innovation Office serves as a resource for providing scientific and regulatory guidance to researchers, academia, and biotech and pharmaceutical companies involved in early-stage clinical product development with the intention of seeking product registration in Singapore. Collaborating closely with researchers from public sector research agencies and the biotech-pharma industry, the office offers regulatory support to facilitate the transformation of scientific discoveries into clinical treatments beneficial to patients in Singapore[152].

To promote proactive collaboration, the Innovation Office encourages engagement with individuals, researchers, and companies, fostering a collaborative approach with HSA on regulatory requirements. It also provides an avenue for seeking early guidance on technical or scientific matters crucial for consideration during the product development phase. Including non-clinical development, clinical development, quality development such as Chemistry, Manufacturing, and Controls (CMC), as well as considerations related to manufacturing and Good Manufacturing Practice (GMP), along with assistance in regulatory submissions[152].

D.2.6 Structure and organisation of expertise in regulatory agency

Singapore is part of international committees including the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH),[157] the International Medical Device Regulators Forum (IMDRF),[158] and the Pharmaceutical Inspection Co-operation Scheme (PIC/S)[159]. The EU, UK, US and China are all part of these committees.

Singapore participates actively in many international scientific discussions, which helped inform and evolve their policies, and has helped the country manage through COVID-19[151]. These include the 'Access Consortium' a network of regulatory agencies from Australia, Canada, Singapore, Switzerland, and the UK focused on enhancing global collaboration, regulatory alignment, and capacity building,[160] and 'Project Orbis', an initiative aimed at faster approval for promising oncology treatments, bringing together eight regulatory agencies for concurrent

[157] 'ICH Official Web Site : ICH' <https://www.ich.org/> accessed 17 November 2023.

[158] 'International Medical Device Regulators Forum (IMDRF) | International Medical Device Regulators Forum' <https://www.imdrf.org/> accessed 17 November 2023.

[159] 'PIC/S' <https://picscheme.org/en/picscheme> accessed 17 November 2023.

[160] 'Australia-Canada-Singapore-Switzerland-United Kingdom (Access) Consortium | Therapeutic Goods Administration (TGA)' <https://www.tga.gov.au/international-activities/australia-canada-singapore-switzerland-united-kingdom-access-consortium#> accessed 29 November 2023.

submission and review of oncology products. Inclusion is based on the FDA's clinical criteria for priority review[161].

In 2007, the HSA joined with national authorities of Australia, Canada, and Switzerland to form a consortium known as 'ACSS Consortium'[160]. It was renamed to 'Access Consortium' in 2020, after the inclusion of the UK MHRA as a new member. Since then, five ACCESS working groups for therapeutic products have been established:[162]

- *New Active Substance Working Group (NASWG):* Established with the aim of fostering opportunities and regulatory programs for collaborative efforts, it seeks to achieve greater alignment in regulatory approaches and technical requirements for medicines. This initiative has considered the challenges faced by regulatory agencies, particularly the strain on available resources, to ensure timely access to effective new therapies amidst increasing workloads and application complexities. The working group is complemented by an innovative work-sharing model called the New Active Substance Work Sharing Initiative (NASWSI), facilitating the coordinated assessment of applications filed with multiple consortium agencies.
- *Generic Medicines Working Group (GMWG):* Created to address issues related to generic medicines, with a focus on enhancing regulatory programs. Its objectives include fostering alignment in regulatory approaches and technical requirements, optimising resource utilisation through information and work sharing, building an effective network among trusted regulatory authorities, achieving immediate and sustained results in priority areas, and serving as a "proof of concept" for other global regulatory cooperation initiatives. The working group is complemented by an innovative work-sharing model called the Generic Medicines Work Sharing Initiative (GMWSI), facilitating the coordinated assessment of generic applications filed with multiple consortium agencies.
- *Biosimilars Working Group (BSWG):* Formed to enhance collaborative opportunities and regulatory programs by aligning regulatory approaches and technical requirements for biosimilar medicines. This initiative addresses the challenges encountered by regulatory agencies, focusing on the strain on resources amid the growing workload and complexities of applications, with the goal of ensuring timely access to effective alternatives to biologic medicines. The working group is currently looking to establish the Biosimilars Work Sharing Initiative (BSWSI) consisting of at least two consortium agencies, to help facilitate the coordinated assessment of biosimilar applications.
- *Clinical Trials Working Group (CTWG):* The primary aim of this group is to enhance collaboration in the area of clinical trials, focusing on harmonising technical and regulatory requirements. Its objectives include facilitating information exchange on new developments and exploring opportunities for work-sharing among the member agencies.
- *Advanced Therapy Medicinal Products Working Group (ATMG WG):* The most recent working group, formed in 2023, is dedicated to advanced therapy medicinal products (ATMPs). The primary objectives of this group are to facilitate interdisciplinary scientific discussions on emerging therapeutic concepts and technologies, provide a forum for consortium members to address ATMP-specific topics, with a focus on the assessment of

[161] 'Project Orbis | FDA' <https://www.fda.gov/about-fda/oncology-center-excellence/project-orbis> accessed 29 November 2023.

[162] 'HSA | Access Consortium' <https://www.hsa.gov.sg/therapeutic-products/international-collaboration/access> accessed 29 November 2023.

benefits and risks in regulatory decision-making, encourage mutual exchange and harmonisation in the regulatory assessment of ATMPs, explore opportunities for work-sharing and reliance, and issue guidance and recommendations on harmonised approaches in relevant areas.

D.2.7 Current experience in assessing medical innovation

For the past two decades, the Singapore government has been committed to establishing itself as a biotech hub, with the ambition for greater emphasis on translational and clinical research to better the country's health and economic outcome. The HSA has established new regulations and resources to help with the transformation to assist innovation and digitalisation. The introduction of specific guidelines for CTGTPs, streamlining regulatory processes in for both pharmaceuticals and medical devices, and publishing their benefit-risk assessment summary reports, are all outcomes of consultations with stakeholders, working in a collaborative way to the regulations are not preventing innovations but enabling the implementation of fit-for-purpose, risk-based regulations that support product development and commercialisation of innovative therapies. The regulations also facilitate patients' access to novel products that meet the appropriate standards of safety, efficacy and quality[139]. The HSA publishes annual reports to reflect on its work and to communicate new regulations to aid stakeholders in understanding the regulatory system and initiate early discussion through the Innovative Office.

D.2.7.1 Dealing with uncertainty in assessments and new evidence generation techniques

In 2018, the Ministry of Health (MoH) launched the Licensing Experimentation and Adaptation Programme (LEAP), which serves as a regulatory sandbox initiative designed to engage early with industries, particularly those pioneering innovative services. Through the partnerships, LEAP aims to assess the most effective, efficient, and suitable methods to support innovation, prioritising patient safety and welfare in healthcare delivery[163].

The regulatory sandbox was initiated specifically for telemedicine (TM) and mobile medicine (MM), a proactive measure to understand associated risks and collaboratively create risk mitigation strategies with industry stakeholders before the anticipated licensing under the Healthcare Services Act (HCSA) in 2023. As of February 2021, MOH has successfully met its objectives and is concluding the sandbox for TM and MM[163].

In transitioning to licensing, MoH will enlist direct TM service providers who have demonstrated awareness of associated risks and benefits, implemented measures to address these risks and are committed to adhering to safe TM practice guidelines set by the Ministry[164].

The MoH aim to establish regulatory sandboxes for various novel and innovative healthcare services, extending beyond TM and MM. Regular updates on these initiatives will be available on their website to ensure stakeholder engagement[163].[163]

D.2.8 Futureproofing

The HSA has made a few regulatory updates to the therapeutic product registration. These include clarification of the eligibility criteria for the post-approval Minor Variations guidelines

[163] 'MOH | Licensing Experimentation and Adaptation Programme (LEAP) - A MOH Regulatory Sandbox' <https://www.moh.gov.sg/home/our-healthcare-system/licensing-experimentation-and-adaptation-programme-(leap)---a-moh-regulatory-sandbox> accessed 17 November 2023.

[164] 'MOH | News Highlights' <https://www.moh.gov.sg/news-highlights/details/moh-launches-first-regulatory-sandbox-to-support-development-of-telemedicine> accessed 17 November 2023.

and documentary requirements, along with the expansion of the "Do-and-Tell" checklist to help reduce regulatory submission burden and enable timely implementation of administrative as well as minor CMC changes that do not impact the product's safety, efficacy, and quality. They have also extended the verification evaluation route to biological and biosimilar products to enable greater reliance on reference agencies' assessments and to minimise duplication of efforts[139]. The main regulatory transformation in the last few years has been for the regulation of medical devices due to the demand observed during the COVID-19 pandemic[151]. The transformation of the medical device regulations, including the implementation of the expedited pathways, was the result of the successful regulatory sandbox initiative, which allowed the HSA to better understand new innovative services by partnering at an early stage with industry, allowing them to review an effective, efficient and appropriate way to support innovation, while delivering care that prioritises patient safety and welfare. The HSA will continue to introduce new regulatory sandboxes for new and innovative healthcare products and services as a part of their futureproofing solution[163].

Additionally, the HSA is continuously looking for ways to streamline its regulatory processes, through the digitalisation of its workflow, including the implementation of pre-submission consultation mechanisms and automating the application and processing of marketing authorisation certificates for medicinal products that do not require the full assessment, such as Class 1 CTGTPs[139]. As previously mentioned, all therapeutic product applications are submitted online via PRISM to enhance the application process for the stakeholders. Finally, the HSA hope the regular publication of regulatory actions related to the therapeutic product on their website would enhance transparency and accessibility to regulatory updates[139].

Appendix E Country Case Study: United Kingdom

E.1 Description of regulatory approval in the UK

E.1.1 Pharmaceutical innovation and R&D in the UK

Innovation is one of the main health objectives of pharmaceutical policy in the UK, together with access and affordability[165]. The United Kingdom has a large pharmaceutical R&D market, ranking in the top three of R&D activity (EUR millions) by the European Federation of Pharmaceutical Industries and Associations, placing only after Germany and Switzerland[166]. However, the UK spends less on R&D than the OECD average[165]. It is estimated that between 1992 and 2004 more than 10% of new medicines were developed in the UK[165].

Table 12 Descriptive statistics on pharmaceutical R&D in the UK

Characteristic	Measure for most recent year
Amount of medical research / number of clinical trials	2,213 trials registered as collecting data in the UK in 2022 (up from 217 in 2012) (WHO)[167] 2,284 trials registered in the UK in 2022 (Clinicaltrials.gov)[168] Approximately 12% of all ongoing ATMP trials globally are in the UK[169]
R&D expenditure (pharmaceutical industry)	5,639,000,000 EUR (2020) [166,170]
Number of pharmaceutical innovation patents	550.1 pharmaceutical patents registered in 2019[171] 689.8 medical technology patents registered in 2019[172]

[165] Naci, H and Forrest, R. (2023). Pharmaceutical Policy: Balancing Innovation, Access and Affordability Pharmaceutical Policy in the UK. The Health Foundation. Available at: https://www.health.org.uk/sites/default/files/2023-03/report_3_pharmaceutical_policy_in_the_uk_final.pdf

[166] EFPIA (2023a). Pharmaceutical industry research and development in Europe (2020). Available at: https://www.efpia.eu/publications/data-center/the-pharma-industry-in-figures-rd/rd-in-europe/

[167] Between 1 January 2022 and 31 December 2022 (most recent complete year). Based on country of recruitment. World Health Organisation. *ICTRP Platform Search Portal*. Available at: https://trialsearch.who.int/AdvSearch.aspx

[168] Clinicaltrials.gov. Available at: https://www.clinicaltrials.gov/. Searched on 'United Kingdom and study start between 01/01/2022 and 31/12/2022.

[169] Association of the British Pharmaceutical Industry (ABPI) (2023). Advanced Therapy Medicinal Products (ATMPs). Available at: https://www.abpi.org.uk/value-and-access/advanced-therapy-medicinal-products-atmps/

[170] Hofer Matthias P., Criscuolo Paola, Shah Nilay, Wal Anne L. J. ter, Barlow James (2022). Regulatory policy and pharmaceutical innovation in the United Kingdom after Brexit: Initial insights. Frontiers in Medicine, Vol. 9. Available at: https://www.frontiersin.org/articles/10.3389/fmed.2022.1011082

[171] For pharmaceutical patents registered in the IP5 patent families (US, EU, China, Japan, and South Korea), based on inventor's country of residence. Most recent complete year. Note: this data uses fractional counting, which divides a patent equally over each listed inventor country / technology field. Taken from: OECD.stat (2023).

[172] For medical technology patents registered in the IP5 patent families (US, EU, China, Japan, and South Korea), based on inventor's country of residence. Most recent complete year. Note: this data uses fractional counting, which divides a patent equally over each listed inventor country / technology field. Taken from: OECD.stat (2023)

Number of (new) products approved 2018 – 2021	111 products in England[173], which is a rate of availability of 66%[174] 105 in Scotland, which is a rate of availability of 63%

E.1.2 Regulatory agency

The UK regulatory agency for medicines and medical devices is the *Medicines and Healthcare products Regulatory Agency (MHRA)*. The MHRA approves new medicines or devices for sale in the UK, assessing their safety and quality standards and the safety of the supply chain[175]. Prior to Brexit, the MHRA was also responsible for upholding medicines authorised through the European central authorisation procedure of the European Medicines Agency and for authorising medicines not subject to central European authorisation. Now, all applications for regulatory approval of a medicine for England, Scotland, and Wales (Great Britain) must be submitted to the MHRA[176].

The MHRA introduced a new structure in 2021. This structure has three core functions: 1) Science, Research, and Innovation, 2) Healthcare, Quality and Access, and 3) Safety and Surveillance[177]. It is led by an Executive Committee, the highest decision-making body in the MHRA. Further, the MHRA is governed by a board of directors, which advises on the strategic direction of the agency.

The MHRA can receive expert advice from several independent expert advisory committees[178], including the Commission on Human Medicine (CHM). The CHM which operates several independent advisory boards[179], each set up for a short period of time. The boards focus on specific topic areas (e.g. infectious diseases, paediatrics, COVID-19, oncology etc.), aiming to provide advice on the safety, quality, and efficacy of medicines[180]. These committees are meant to provide additional expertise and input to allow the MHRA to ensure they are

[173] Comparted to an EU average of 76 products. See: EFPIA (2023b). EFPIA Patients W.A.I.T. Indicator 2022 Survey. Available at: https://www.efpia.eu/media/s4qf1ego/efpia_patient_wait_indicator_final_report.pdf

[174] The highest rate of availability was seen in Germany. See: EFPIA (2023b). EFPIA Patients W.A.I.T. Indicator 2022 Survey. Available at: https://www.efpia.eu/media/s4qf1ego/efpia_patient_wait_indicator_final_report.pdf

[175] In addition to its function as a licensing agency, the MHRA also carries out a) post-marketing surveillance, b) operates the UK Official Medicines Control Laboratory, c) monitors the safety and quality of imported medicines, d) ensures compliance with UK and European standards through inspection and enforcement, e) management of the British Pharmacopoeia, f) overseeing the UK bodies that audit medical device manufacturers, g) providing scientific, technical, and regulatory advice, h) regulation of clinical trials/investigations, and i) promoting good practice in the safe use of medicines and medical devices. See: MHRA (2022a).

[176] Northern Ireland will continue to apply the EU regulation framework.

[177] MHRA. (2022a). Annual Report and Accounts 2021/2022. Available at: https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/1093177/MHRA_Annual_Report_and_Accounts_2021-22.pdf

[178] The Commission on Human Medicines (CHM); The Herbal Medicines Advisory Committee (HMAC); The Advisory Board for Registration of Homeopathic Products (ABRHP); The British Pharmacopoeia Commission (BPC); The Committee on Medical Devices (CMD); The United Kingdom Stem Cell Bank Steering Committee (UKSCBSC) and The Review Panel (MHRA), which reviews the provisional determinations for the classification of medicines by the MHRA and acts as reviewers in decisions related to the 'grant, renewal, revocation, suspension, refusal or variation of manufacturer's or wholesale dealing licences'.

[179] MHRA. (n.d. (a)). About us. Available at: https://www.gov.uk/government/organisations/medicines-and-healthcare-products-regulatory-agency/about

[180] 'The function and purpose of MHRA advisory Committees: Annex 2'.

delivering the right outcomes for patients[181]. Of the current advisory boards, none is dedicated to ATMPs, though there are boards for COVID-19, real-world data, oncology, and haematology, as well as other topics which may pertain to this study.

E.1.3 Main pharmaceutical legislation or regulation

The legal basis for the MHRA and regulation of medicines is the Medicines Act 1968 (legislation was updated with a new set of regulations, known as the Human Medicines Regulation 2012). Other legislation has been introduced since 1968, such as the Medicines and Medical Devices Act from 2021, which requires a Patient Safety Commissioner for the use of medicines and medical devices[182].

Pharmaceutical products are regulated by the Human Medicines Regulations 2012 (HMRs), which set out requirements for authorisation (Part 4) and the procedures for marketing authorisation (Part 5). The HMRs were amended by the Human Medicines (Amendment etc.) (EU Exit) Regulations 2019 and 2020 to adjust the legislation for use after the UK departure from the EU. ATMPs and biosimilar products will continue to be regulated through the same principles that existed prior to the UK's departure from the EU[183].

The MHRA Corporate Plan for 2023 – 2026 states the MHRA plans to introduce new guidance and legislation by March 2025[184].

E.1.4 Organisation of regulatory system

Marketing authorisation applications are submitted to the MHRA. Marketing authorisation applications for new active substances and biosimilar products will be subject to two phases of assessment[185]. The Human Medicines Regulations set out the conditions that need to be assessed or considered for a UK marketing authorisation to be issued[186]. These Regulations also have specific considerations for applications relating to paediatric medicines, orphan

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[181] MHRA (2022g). Press release: MHRA launches new conflicts of interest code of practice for independent advisors. Available at: https://www.gov.uk/government/news/mhra-launches-new-conflicts-of-interest-code-of-practice-for-independent-advisors#:~:text=The%20Medicines%20and%20Healthcare%20products,interest%20are%20robust%2C%20consistent%20and

[182] Ferner, R.E. and Aronson, J.K. (2022). Medicines legislation and regulation in the United Kingdom 1500-2020. BJCP. Volume 89, Issue 1 January 2023 Pages 80-92

[183] Certara (2023). A Guide to the UK Regulation of Medicines and Medical Devices Post-Brexit. Available at: https://www.certara.com/app/uploads/2023/02/WP_Medicines-and-Medical-Devices-Post-Brexit-final.pdf

[184] MHRA (2023a). NOW 2023c Guidance: Innovative Licensing and Access Pathway. Available at: https://www.gov.uk/guidance/innovative-licensing-and-access-pathway

[185] Assessment phase 1, to be completed within 80 days, followed by a 'clock-off' period of maximum 60 days where the applicant may be asked to provide further information based on the initial assessment in phase 1, and assessment phase 2, to be completed within a further 70 days starting from receipt of responses from the applicant (a total of 150 days for both phases). See: MHRA (2023b). Guidance: 150-day assessment for national applications for medicines. Available at: https://www.gov.uk/guidance/guidance-on-150-day-assessment-for-national-applications-for-medicines#:~:text=Active%20Substances%20Applications-,The%20assessment%20process%20will%20run%20in%20two%20phases%20totalling%20150,80%20days%20after%20clock%20start.

[186] *Human Medicines Regulations 2012. Legislation.gov.uk. Available at: https://www.legislation.gov.uk/uksi/2012/1916/part/5/crossheading/consideration-of-application*. Note: the HMRs 2012 are currently still being edited, and the latest available version may not have all outstanding changes included yet.

medicines, combined advanced therapy medicinal products, conditional marketing authorisations, and medicines containing genetically modified organisms. There is limited public information available on how and by who regulatory applications are assessed within the MHRA.

E.1.5 Expedited MA pathways

Specific expedited pathways for marketing authorisation are presented in the table below[187].

Table 13 Expedited pathways for marketing authorisation in the UK

MHRA pathways	**Comparable pathways in the US and EU[188]**
Accelerated assessment	- Accelerated Assessment, EMA - Priority Review, FDA
Rolling review	- Rolling Review, EMA - Rolling Review, FDA
Innovative licensing and access pathway (ILAP)	- PRIME Designation, EMA - Breakthrough Therapy Designation, FDA
Conditional Marketing Authorisation	- Conditional Marketing Authorisation (EMA) - Accelerated Approval (FDA)

- *Accelerated assessment*. This pathway exists for all 'high-quality' applications for new and existing medicines, and shortens the time taken for regulatory review[188]. This process is similar to the EMA's Accelerated Assessment pathway.
- *Rolling Review*. This procedure for new active substances and/or biologics is intended to enhance the development of innovative medicines, providing ongoing advice throughout the development process, and allowing for the incremental submission of the dossier[189,190]. The MHRA will review data as and when it becomes available, where usually all data is reviewed once all of it is available[188]. The process is made up of a pre-assessment phase[190], where a module (component) of the eCTD dossier application can be submitted for review, after which the manufacturer can update the module for the final marketing authorisation. This repeats for each module submitted. The MHRA may consult with the CHM and/or therapy area experts during the assessment. A pre-submission meeting prior to the

[187] Up until the end of 2023, the MHRA can also take advantage of the European Commission Decision Reliance Procedure (ECDRP), which allows the MHRA to perform a more limited assessment for medicines which have already received a positive recommendation from the EMA.

[188] Naci, H and Forrest, R. (2023). Pharmaceutical Policy: Balancing Innovation, Access and Affordability Pharmaceutical Policy in the UK. The Health Foundation. Available at: https://www.health.org.uk/sites/default/files/2023-03/report_3_pharmaceutical_policy_in_the_uk_final.pdf

[189] Certara (2023). A Guide to the UK Regulation of Medicines and Medical Devices Post-Brexit. Available at: https://www.certara.com/app/uploads/2023/02/WP_Medicines-and-Medical-Devices-Post-Brexit-final.pdf

[190] MHRA (2020e). Guidance: Rolling review for marketing authorisation applications. Available at: https://www.gov.uk/guidance/rolling-review-for-marketing-authorisation-applications

submission of the final marketing authorisation application is recommended. On submission, the application is validated for completeness, and then a final phrase assessment commences. The rolling review pathway is available for any new active substance or biologic based on a 'full dossier' submission. This MHRA pathway was introduced in 2020 and differs from the EMA rolling review, which is an ad hoc procedure used in an emergency context only under the EMA's emerging health threats plan[191].

- *Innovative licensing and access pathway (ILAP)*. The ILAP is a new pathway introduced in 2021 for new chemical entities, biological medicines, new indications, and repurposed medicines, including those for rare diseases and ATMPs. The ILAP aims to accelerate time to market and improve patient access[192]. Entry requirements focus on whether there is a significant public need or life-threatening illness, whether it fulfils a specific area (e.g. innovative new medicines, ATMPs, product for rare disease), and whether there is the potential for benefits to the patient[193] Repurposed medicines are included in the scope of the ILAP[194]. The ILAP pathway provides access to tools designed to help more efficient patient access, many of which are based on learnings from the COVID-19 pandemic. This includes early and frequent interactions with the MHRA and other stakeholders, an 'Innovation Passport' designation and a 'Target Development Profile'[195]. A multi-agency approach allows for flexible support throughout the development cycle[196]. While similar to the EMA PRIME designation[197], the eligibility criteria and benefits accessed through these pathways do differ slightly.

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[191] EMA (2023a). EMA initiatives for acceleration of development support and evaluation procedures for COVID-19 treatments and vaccines (obsolete). Available at: https://www.ema.europa.eu/en/documents/other/ema-initiatives-acceleration-development-support-evaluation-procedures-covid-19-treatments-vaccines_en.pdf

[192] MHRA (2023c) NOW 2023a. Corporate Plan 2023 to 2026. Available at: https://www.gov.uk/government/publications/mhra-corporate-plan-2023-to-2026/medicines-and-healthcare-products-regulatory-agency-corporate-plan-2023-to-2026

[193] Eligibility criteria include:

(1) details of the condition, patient, or public health area (submitting either for a life-threatening or seriously debilitating condition or where there is significant patient or public health need)

(2) the product fulfils one or more specific area (where the areas are a) innovative medicine such as an advanced therapy medicinal product (ATMP) or new chemical or biological entity or novel drug device combination, b) medicines being developed in a clinically significant new indication for an approved medicine, c) medicines for rare disease and/or other special populations such as neonates and children, elderly and pregnant women, or d) development aligning with the objectives for UK public health priorities such as the Chief Medical Officer, Department of Health and Social Care (DHSC) or Life Sciences Sector Deal (including those in Devolved Administrations, where appropriate)

(3) the medicinal product has the potential to offer benefits to patients

[194] LifeArc (2021). Repurposing medicines: the opportunity and the challenges. Available at: https://www.lifearc.org/wp-content/uploads/2021/06/LifeArc-Repurposing-digital_FINAL.pdf

[195] Naci, H and Forrest, R. (2023). Pharmaceutical Policy: Balancing Innovation, Access and Affordability Pharmaceutical Policy in the UK. The Health Foundation. Available at: https://www.health.org.uk/sites/default/files/2023-03/report_3_pharmaceutical_policy_in_the_uk_final.pdf

[196] Hofer Matthias P., Criscuolo Paola, Shah Nilay, Wal Anne L. J. ter, Barlow James (2022). Regulatory policy and pharmaceutical innovation in the United Kingdom after Brexit: Initial insights. Frontiers in Medicine, Vol. 9. Available at: https://www.frontiersin.org/articles/10.3389/fmed.2022.1011082

[197] EMA (2023b). PRIME: Priority Medicines. Available at: https://www.ema.europa.eu/en/human-regulatory/research-development/prime-priority-medicines#:~:text=The%20PRIME%20scheme%20focuses%20on,therapeutic%20advantage%20over%20existing%20treatments

- *Conditional marketing authorisation*[195]. CMA exists for products addressing an unmet medical need with incomplete data for full approval, similar to the eligibility criteria as the EU CMA pathway. This allows the MHRA to grant conditional marketing authorisation for products when comprehensive clinical data is not yet available, and the manufacturer completes a post-approval study to demonstrate the benefits of the medicine[195,198].

E.1.6 Specific pathways for ATMPs or unmet medical need (UMN)

ATMPs: The MHRA updated its guidance on obtaining marketing authorisation for ATMPs[199] (defined as gene therapy medicinal products, somatic cell therapy medicinal products and tissue engineered products) after Brexit. Marketing authorisation applications for ATMPs are regulated by the MHRA for Great Britain[200], assessed according to the general provisions for medicine licensing but taking specific requirements for ATMPs into account[201]. The MHRA Innovation Office handles all regulatory inquiries about regenerative medicines, and is the single point of contact for all relevant regulators in the UK (the Human Tissue Authority, the Human Fertilisation and Embryology Authority, the Health Research Authority, and the MHRA itself).[202] ATMPs are explicitly named in one of the eligibility criteria for the ILAP, and are eligible for inclusion if the product also fulfils the other eligibility requirements.

UMN: products which address an unmet medical need are eligible for CMA and the ILAP if the product also fulfils the other eligibility requirements. See above for more information on these pathways. Products responding to an unmet medical need may also be eligible for the EAMS (see Section 1.4.3.).

E.1.7 Other tools

Innovation or access is promoted by the MHRA through several additional tools:

- A 'promising innovative medicine/Early Access to Medicines Scheme' (EAMS) for seriously debilitating conditions with an unmet medical need. The EAMS provides early access authorisation for products that do not have a marketing authorisation yet but do respond to an unmet medical need[196]. This could be considered similar to the EMA's compassionate use scheme, which allows the use of an unauthorised medicine as a treatment.
- An 'Innovation accelerator', which assists innovators in accessing scientific expertise and regulatory guidance, through means such as queries to the MHRA Innovation Office, an advice service on regenerative medicines, scientific advice from the MHRA, and support to the delivery of the ILAP[203].

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[198] MHRA (2020a). Guidance: Conditional Marketing Authorisations, exceptional circumstances Marketing Authorisations and national scientific advice. Available at: https://www.gov.uk/guidance/conditional-marketing-authorisations-exceptional-circumstances-marketing-authorisations-and-national-scientific-advice

[199] Similar guidance was published for biosimilars and Plasma Master Files (PMF) and Vaccine Antigen Master Files.

[200] Northern Ireland will continue to follow the EMA's conditional marketing authorisation (CMA) route.

[201] MHRA (2020b). Guidance: Guidance on licensing biosimilars, ATMPs, and PMFs. Available at: https://www.gov.uk/guidance/guidance-on-licensing-biosimilars-atmps-and-pmfs

[202] MHRA (2015). Guidance: Advanced therapy medicinal products: regulation and licensing. Available at: https://www.gov.uk/guidance/advanced-therapy-medicinal-products-regulation-and-licensing

[203] MHRA (n.d. (b)). Guidance: Innovation Accelerator. Available at: https://www.gov.uk/government/publications/innovation-accelerator/innovation-accelerator

E.1.8 Scientific advice offered by the MHRA

The MHRA offers advice at any stage of the initial development of a product, prior to the submission of an MA application[204]. Notable assistance routes include[205]:

- Clinical trial protocol advice, supporting the design of studies to assist with meeting licensing requirements.
- Scientific advice, offered to assist organisations at various points in their development pathway.
- The MHRA Innovation Office, as a single point off access to regulatory information and guidance. The MHRA Innovation Accelerator was created in 2022 to assist innovators in accessing guidance or advice from the MHRA.
- 'Broader scope' meetings, which do not need to pertain to a specific product.

The MHRA also offers scientific advice as part of the some of the pathways described in section 1.4.1. Some of the advice offered by the MHRA is not dissimilar to the EMA's offering. A comparison is provided in the table below.

Table 14 Comparison between advice offered by MHRA and by EMA

MHRA	**EMA**
Clinical trial protocol advice (No further detail)	*Protocol assistance* - Available only to those developing treatments for rare diseases - Responding to questions on criteria for authorisation of an orphan medicine
Scientific advice - Available at any stage of a medicine's development - Responding to a broader range of topics/questions on the development of a specific medicine - Ideally prospective and about the future development of a medicinal product - Not legally binding	*Scientific advice* - Available at any stage of a medicine's development - Responding to specific questions206 on the development of a specific medicine - Prospective only, no pre-evaluation of results - Not legally binding
MHRA Innovation office	No similar offering

[204] MHRA (2014)

[205] Association of Medical Research Charities (AMRC) (2017)

[206] Included: quality aspects; non-clinical aspects; clinical aspects; methodological issues; overall development strategy; and significant benefit for maintaining orphan designation, and paediatric developments. Not Compassionate use, advanced therapy medicinal product (ATMP) classification, PRIME eligibility, and accelerated assessment; adequacy of planned paediatric studies or changes to the key elements of Paediatric Investigation Plan (PIP); matters of a purely regulatory nature; adequacy of existing data for assessment of a regulatory application.

'Broader scope' meetings - Not limited to one development programme or product - May include external experts or patient representatives, depending on topic - No written advice, meeting only	No similar offering

E.2 System/agency ability to adapt the regulatory assessment of innovation

E.2.1 Level of regulatory flexibility provided by law

No information was found to clarify whether the legislation or regulations which apply to the MHRA provide for flexibility in its working practice to adjust to assess innovation in medicines.

There are flexibilities in the law for manufacturing without a marketing authorisation and for aspects of marketing authorisation considering public health concerns. These are discussed in the following sections.

E.2.2 Manufacturing without a marketing or manufacturing authorisation

Manufacturing without a marketing authorisation is possible in Great Britain: 'specials' are medicines manufactured by the holder of a 'Specials' Manufacturing Authorisation or for imported medicines with no MHRA marketing authorisation. The preparation and supply of these products is possible under an exemption in the HMR 2012. A 'special' can be prescribed in some cases (e.g. when the medicine has not been commercially manufactured or if it has been discontinued, for example). A pharmacist can either formulate it themselves or has a pharmaceutical specials manufacturer to do so[207]. To manufacture an unlicensed product, a manufacturer must hold a 'specials' license[208]. No evidence was found to clarify whether unlicenced products can be manufactured without a manufacturing authorisation or license.

The MHRA is also introducing a one-of-a-kind framework to allow the manufacture of innovative medicines at the point of care to ensure the supply to patients through clinical trials studies to MA approval[209,210]. This plan will apply to all point-of-care products manufactured in the UK, including ATMPs. The framework will ensure there are no regulatory barriers, while maintaining quality and safety standards. Currently, legislation is being introduced to support this framework. The framework itself has not been released yet.

[207] Association of Pharmaceutical Specials Manufacturers (2022). Pharmaceutical Specials. Available at: https://www.apsm-uk.com/specials

[208] Thomson Reuters (2017). Unlicensed medicinal products in the UK. Available at: https://www.arnoldporter.com/~/media/files/perspectives/publications/2017/02/unlicensed-medicinal-products-in-the-uk.pdf

[209] MHRA (2023d). Press release: UK to introduce first-of-its-kind framework to make it easier to manufacture innovative medicines at the point of care. Available at: https://www.gov.uk/government/news/uk-to-introduce-first-of-its-kind-framework-to-make-it-easier-to-manufacture-innovative-medicines-at-the-point-of-care

[210] MHRA (2023e). Consultation outcome: Consultation on Point of Care manufacturing. Available at: https://www.gov.uk/government/consultations/point-of-care-consultation/consultation-on-point-of-care-manufacturing

E.2.3 Drug repurposing

Adding or amending an indication to the marketing authorisation for that product is considered a 'major variation' by the MHRA, meaning it must be approved prior to being made[211]. Marketing authorisation holders can extend their authorisation for new indications, dosage, or administration methods. If the variation is deemed to have a significant clinical benefit and is submitted in the first eight years, an extension of one year of market protection can be given. The NHS recognises options to establish further market protection as an incentive for variations to include currently off-label uses. For off-patent products, an already approved generic or biosimilar product can be the basis for the variation application[212]. The NHS recognises that a generic manufacturer may not recover costs by applying for a variation, and new incentives are needed which, ideally, do not affect price competition[212].

The Repurposing Medicines Programme was established to identify opportunities to 'strengthen the evidence base, licensing, supply, and cost effectiveness of un-licensed or off label medicines in current (or likely future) common use in the NHS'[212]. The programme has a threefold aim:

- 'identify and develop opportunities to repurpose prioritised medicines to improve outcomes, patient experience and value for money
- support and advance innovative research into medicines that might be repurposed and adopted into the NHS.
- facilitate and encourage the licensing of repurposed medicines to support clinical decision making and improve equity of access'[213]. This can occur through a dedicated working group to assist with applying for a licensing variation or with evidence generation.

The NHS is also considering establishing a fund which can support the licensing process for repurposed products in priority areas. Other actions include holding scientific advice meetings for repurposed medicines and the willingness to explore how the Early Access to Medicines Scheme may be used to collect real-world data to generate further evidence for licensing applications[212].

Candidate medicines can be put forward by voluntary-sector organisations, registered healthcare professionals working in the NHS, and pharmaceutical companies. The programme is supported by the MHRA and other government organisations, such as the Department of Health and Social Care (DHSC), the National Institute for Health and Care Excellence (NICE), the National Institute for Health and Care Research (NIHR) and NHS England.

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[211] MHRA (2014). Guidance. Medicines: apply for a variation to your marketing authorisation. Available at: https://www.gov.uk/guidance/medicines-apply-for-a-variation-to-your-marketing-authorisation#major-variations-type-ii

[212] NHS (2021). Opportunities to Repurpose Medicines in the NHS in England. Available at: https://www.england.nhs.uk/wp-content/uploads/2021/03/B0342-oportunities-to-repurpose-medicines-in-the-nhs-in-england.pdf

[213] NHS (n.d.). Repurposing medicines in the NHS in England. Available at: https://www.england.nhs.uk/medicines-2/medicines-repurposing-programme/

In its guidance on randomised control trials using real-world data, the MHRA recognises this may be very relevant for label changes for already approved products[214]. The MHRA encourages organisations to approach the MHRA if they have any questions.

E.2.4 COVID-19 pandemic flexibilities

The UK government issued several temporary regulatory flexibilities in response to the coronavirus pandemic.

- *Clinical trials*: Good clinical practice guidelines already referenced many relevant flexibilities (e.g. risk-based monitoring, electronic consent etc.), but these were underused prior to the pandemic. Risk adaptation has been embedded since 2011, when guidance on risk-adapted approaches for clinical trials was published by the MHRA. This was followed by a good clinical practice guide in 2012 and examples of real-life risk assessment in 2013. The MHRA issued further guidance on applications for trials and trial management early in the pandemic. The MHRA noted there were challenges in good clinical practice resulting from the pandemic and for their Clinical Trial Unit and inspections[215], as well as deviations from study protocols. The MHRA also provided expediated scientific advice and rapid review of clinical trial applications.
- *Marketing authorisation*: flexibilities related to deadline extensions, flexibilities related to audit declarations (e.g. encouraging off-site auditing, extensions of the audit window), expedited assessment for applications impacting the medicines supply chain, among others[216]. The MHRA also introduced the 'rolling review', through which MHRA staff reviewed data in a staggered process as the data became available[217]. The rolling review was not linked solely to COVID-19 and is still available as a marketing authorisation pathway in Great Britain (see Section 1.4.1.).

The MHRA also issued flexibilities for pharmacovigilance, inspections and good manufacturing practices and published exceptional guidance on good distribution practices flexibilities during the pandemic, relating to supply chains, transportation, 'responsible persons', and facilities and equipment[218].

The UK Parliament reported that the rolling submission of clinical trial results resulted in the UK being the first Western country to approve a COVID-19 vaccine[219]. No further evidence was

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[214] MHRA (2021a). Guidance: MHRA guidance on the use of real-world data in clinical studies to support regulatory decisions. Available at: https://www.gov.uk/government/publications/mhra-guidance-on-the-use-of-real-world-data-in-clinical-studies-to-support-regulatory-decisions

[215] MHRA (2022c). Regulator's experience of clinical trials during the Covid-19 pandemic (Part 2) – what we have learned. Blog: MHRA Inspectorate. Available at: https://mhrainspectorate.blog.gov.uk/2022/02/14/regulators-experience-of-clinical-trials-during-the-covid-19-pandemic-part-2-what-we-have-learned/

[216] MHRA (2020c). Guidance: MHRA regulatory flexibilities resulting from coronavirus (COVID-19). Available at: https://www.gov.uk/guidance/mhra-regulatory-flexibilities-resulting-from-coronavirus-covid-19#:~:text=Safety%20variations%20(published%2016%20April,will%20be%20advised%20of%20timelines

[217] UK House of Commons (2021). Coronavirus: Lessons learned to date. Sixth Report of the Health and Social Care Committee and Third Report of the Science and Technology Committee of Session 2021-22. Health and Social Care and Science and Technology Committees. Available at: https://committees.parliament.uk/publications/7496/documents/78687/default/

[218] MHRA (2020d). Guidance: Exceptional good distribution practice (GDP) flexibilities for medicines during the coronavirus (COVID-19) outbreak. Available at: https://www.gov.uk/guidance/exceptional-good-distribution-practice-gdp-flexibilities-for-medicines-during-the-coronavirus-covid-19-outbreak

[219] The Pfizer/BioNTech vaccine in December 2020. See: UK House of Commons (2021) in footnote 212.

found on the successes or learnings from these temporary flexibilities across marketing authorisation, clinical trials, or distribution practices.

The MHRA also addressed the pandemic through amended practices[220], such as the prioritisation of the review of applications for COVID-19 therapeutics and vaccine trials during the pandemic, assigning dedicated COVID-19 assessors; and the implementation of a process to pre-assess documents related to clinical trials (so issues could be addressed as early as possible, reducing the possibility of a rejection). These practices also contributed to ensuring there was no major impact on the approval process for non-COVID-19 applications.

Learnings from the pandemic will be considered in current efforts towards updating legislation and guidance[221].

E.2.5 Support to non-commercial operators

The MHRA offers payment easements[222] or waivers[223] for MA applications or scientific advice requests for applicants which fulfil requirements as an SME. No non-financial incentives are offered[224].

There are no legal barriers to a medical research charity or an academic group becoming a marketing authorisation holder[225].

E.2.6 Structure and organisation of expertise in regulatory agency

The MHRA's corporate plan for 2023 to 2026 highlights the need to 'enable healthcare access to safe and effective medical products'. Within this, the Agency sets out a vision for improved regulatory pathways, where existing capabilities and expertise will be developed to address highly innovative areas. Notable areas of focus include vaccines and immunotherapies, biotherapeutics, cell and gene therapies, diagnostics and genomics, data science, and AI/software as a medical device[226]. Among other specific actions in this field, the MHRA aims to introduce new guidance and legislation which creates a positive environment for medical innovation (by March 2025).

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[220] MHRA (2022d). Regulator's experience of clinical trials during the Covid-19 pandemic (Part 1) – our initial response. Blog: MHRA Inspectorate. Available at: https://mhrainspectorate.blog.gov.uk/2022/02/08/regulators-experience-of-clinical-trials-during-the-covid-19-pandemic-part-1-our-initial-response/

[221] MHRA (2022e). Regulators' experience of clinical trials during the Covid-19 pandemic (Part 3) – looking forward. Blog: MHRA Inspectorate. Available at: https://mhrainspectorate.blog.gov.uk/2022/02/18/regulators-experience-of-clinical-trials-during-the-covid-19-pandemic-part-3-looking-forward/

[222] Between 25% to 50% required at the time of application, and the remainder payable after a period depending on the type of application. See: Gov.uk (2023f)

[223] Payment waived depending on total value of products sold in a given period. More information at: MHRA (2022f). Collection: MHRA innovation case studies. Available at: https://www.gov.uk/government/collections/mhra-innovation-case-studies

[224] Arriello (2023). SME application and status. Available at: https://arriello.com/regulatory-consulting/sme-application/

[225] Association of Medical Research Charities (AMRC) (2017). Facilitating adoption of off-patent, repurposed medicines into NHS clinical practice. Available at: https://www.amrc.org.uk/Handlers/Download.ashx?IDMF=c1a3904c-78de-47ed-813c-b34b57ca587c

[226] MHRA (2023a). NOW 2023c Guidance: Innovative Licensing and Access Pathway. Available at: https://www.gov.uk/guidance/innovative-licensing-and-access-pathway

There are several independent expert panels (see section 1.4) which provide the MHRA with appropriate expertise to ensure decisions related to the safety, quality and efficacy of medicines reflect on the scientific evidence and related uncertainty and consequences. the While, for example, the CHM or its sub-committees contribute where the CHM finds it appropriate, of if asked to do some by the MHRA, there is limited public information available to indicate with what frequency the MHRA relies on these bodies, or how their input is incorporated into marketing authorisation decision-making.

Since Brexit, the MHRA also participates in international collaborations aimed at encouraging pharmaceutical innovation. These include the 'Access Consortium', a network of regulatory agencies from Australia, Canada, Singapore, Switzerland, and the UK focused on collaboration, regulatory alignment, and capacity building, and 'Project Orbis', an initiative aimed at faster approval for promising oncology treatments[227]. The Access Consortium seeks to leverage the regulatory scientific capacity within the consortium for emerging technologies and innovative products and explore the use of real-world data/evidence in clinical trials and for regulatory decision making, among other aims[228]. The consortium leverages resources and expertise, as well as sharing workloads across three authorisation procedures[229] while retaining sovereignty to take independent decisions[230,231]. Project Orbis brings together eight regulatory agencies[232] for concurrent submission and review of oncology products. Inclusion is based on the FDA's clinical criteria for priority review.

In 2022 and 2023, the MHRA sought to improve how patients are engaged in the decisions the Agency makes. Changes focused on how these insights are collected and used by the MHRA, as well as piloting tools to ensure patient perspectives are embedded in the new pathways, like the ILAP[233]. The MHRA plans to pilot public hearings on safety issues as a tool for patients and stakeholders to share their experiences by March 2025, and ensure patient input both prior to product authorisation and into benefit-risk reviews after authorisation by March 2026[234].

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[227] Hofer Matthias P., Criscuolo Paola, Shah Nilay, Wal Anne L. J. ter, Barlow James (2022). Regulatory policy and pharmaceutical innovation in the United Kingdom after Brexit: Initial insights. Frontiers in Medicine, Vol. 9. Available at: https://www.frontiersin.org/articles/10.3389/fmed.2022.1011082

[228] Access Consortium (n.d.). Access Consortium Strategic Plan 2021-2024. Available at: https://assets.publishing.service.gov.uk/media/60d05812d3bf7f4bd11a240e/Access_Strategic_Plan_2021-2024_Final__with_graphic_.pdf

[229] The New Active Substances, Biosimilar, and Generic Medicine work sharing initiatives.

[230] Access Consortium (2020). Terms of Reference. Available at: https://assets.publishing.service.gov.uk/media/5fd23c22d3bf7f306291b592/Terms_of_Reference_Australia__Canada__Singapore__Switzerland_and_United_Kingdom_Consortium.pdf

[231] Working groups include the New Active Substances Working Group; Generic Medicines Working Group; the Biosimilars Working Group; the Complementary Health Products Working Group; the Collaboration on International Council for Harmonization (ICH) Working Group and the IT Architecture Working Group.

[232] Australia (Therapeutic Goods Administration (TGA)); Brazil (Agência Nacional de Vigilância Sanitária (ANVISA)); Canada (Health Canada); Israel (Ministry of Health); Singapore (Health Sciences Authority (HSA)); Switzerland (Swissmedic); UK (MHRA); US (FDA – coordinator)

[233] MHRA (2023e). Consultation outcome: Consultation on Point of Care manufacturing. Available at: https://www.gov.uk/government/consultations/point-of-care-consultation/consultation-on-point-of-care-manufacturing

[234] MHRA (2023a). NOW 2023c Guidance: Innovative Licensing and Access Pathway. Available at: https://www.gov.uk/guidance/innovative-licensing-and-access-pathway

E.2.7 Current experience in assessing medical innovation

The MHRA has published several case studies showing how it can help companies navigate regulatory processes for innovative medicines[235]. Examples include:

- Use of the scientific and regulatory advice streams offered by the MHRA.
- MHRA flexibility on timing and cooperation because of the nature of a national application.
- MHRA assistance in initiating discussions with academic groups.
- MHRA support in ensuring company compliance.
- Use of the EAMS to ensure access.

Post-Brexit, the MHRA has incurred some regulatory delays, but the reason and importance of these delays are not clear yet[227]. The regulatory mechanisms that have been introduced do seem to offer quicker approval of innovation in oncology and other areas of unmet need, as well as in areas of public interest[227].

E.2.7.1 Dealing with uncertainty in assessments and new evidence generation techniques

Real-world evidence has not been used extensively for regulatory purposes, often limited to products for which RCTs are difficult to conduct. However, companies are increasingly seeking to use RWE for their regulatory submissions. The MHRA held a consultation in 2020 to prepare guidance on randomised control trials and generating RWE which can support regulatory decisions[236]. This resulted in two guidance documents on the use of real-world data in clinical studies, and on RCTs which use real-world data (routinely collected health data), to demonstrate safety and efficacy for marketing authorisation regulatory decisions in 2021[237]. The guidance sets out factors to consider when collecting real-world data.

The MHRA stated "there is nothing barring the use of RWE to gain an initial approval or approval of a new indication – it is not the source of the data that is the critical question, but whether the data quality is robust" and emphasised the importance that the trial is "*designed in a way which allows it to provide the evidence required to answer the regulatory question*"[238].

The MHRA announced their intention to launch AI-Airlock, a regulatory sandbox for AI developers, in October 2023. This sandbox will allow developers to generate evidence for the

[235] MHRA (2023f). Statutory guidance: Payment easements and waivers for Small and Medium Companies. Available at: https://www.gov.uk/government/publications/mhra-fees/payment-easements-and-waivers-for-small-and-medium-companies

[236] MHRA (2021b). Guidance: MHRA guideline on randomised controlled trials using real-world data to support regulatory decisions. Available at: https://www.gov.uk/government/publications/mhra-guidance-on-the-use-of-real-world-data-in-clinical-studies-to-support-regulatory-decisions/mhra-guideline-on-randomised-controlled-trials-using-real-world-data-to-support-regulatory-decisions

[237] MHRA (2021a). Guidance: MHRA guidance on the use of real-world data in clinical studies to support regulatory decisions. Available at: https://www.gov.uk/government/publications/mhra-guidance-on-the-use-of-real-world-data-in-clinical-studies-to-support-regulatory-decisions

[238] BioSlice Blog (2020). UK MHRA consultation on real-world evidence. Available at: https://www.biosliceblog.com/2020/12/uk-mhra-consultation-on-real-world-evidence/

AI-in-healthcare technologies and work together with the MHRA to identifying and managing evidence requirements[239].

E.2.8 Futureproofing

The MHRA is part of legislative reform aimed at improving the attractiveness of the UK as a location to develop and market medicines. As part of this, the MHRA has encourage a refocus of the health technology regulatory framework with the aim of responding to the rapid evolution of the sector[240].

The MHRA's corporate plan for 2023-2026 proposes an approach which recognises the importance of 'creating state-of-the-art specialist expertise in highly innovative areas of medical product development, where risk-proportionate regulation often needs to be established in parallel with the development of innovative products'[241]. Related actions include introducing new guidance and legislation, revising the regulatory framework for compliance, formalising new recognition pathways, optimising timelines etc[242]. The MHRA's corporate plan also aims to enhance access to scientific evidence for decision-making by 'building on existing and forming new partnerships to establish a network of Centres of Excellence in Regulatory Science, made up of academic and key scientific and research bodies nationally and internationally'[241].

Additionally, the MHRA published a roadmap to reform the legislation around the regulation of software and AI in medical devices and announced the Software and AI as a Medical Device Change programme in 2022[243].

[239] MHRA (2023h). Press release. MHRA to launch the AI-Airlock, a new regulatory sandbox for AI developers. Available at: https://www.gov.uk/government/news/mhra-to-launch-the-ai-airlock-a-new-regulatory-sandbox-for-ai-developers

[240] MHRA (2023d). Press release: UK to introduce first-of-its-kind framework to make it easier to manufacture innovative medicines at the point of care. Available at: https://www.gov.uk/government/news/uk-to-introduce-first-of-its-kind-framework-to-make-it-easier-to-manufacture-innovative-medicines-at-the-point-of-care

[241] MHRA (2023a). NOW 2023c Guidance: Innovative Licensing and Access Pathway. Available at: https://www.gov.uk/guidance/innovative-licensing-and-access-pathway

[242] Non-exhaustive list. See footnote 236.

[243] MHRA (2023g). Guidance: Software and AI as a Medical Device Change Programme – Roadmap. Available at: https://www.gov.uk/government/publications/software-and-ai-as-a-medical-device-change-programme/software-and-ai-as-a-medical-device-change-programme-roadmap

Appendix F Country Case Study: United States

F.1 Description of regulatory approval in the United States[244]

F.1.1 Pharmaceutical innovation and R&D in the United States

Table 15 Descriptive statistics on pharmaceutical R&D in the United States

Characteristic	Measure for most recent year
Amount of medical research / number of clinical trials	- 7,071 trials registered as collecting data in the US in 2022 (up from 500 in 2012) (WHO)[245] - 18,517 trials registered in the US in 2022 (Clinicaltrials.gov)[246]
R&D expenditure	- 72,412,000,000 USD (2020)[247]
Number of patents for pharmaceutical innovation	- 11,051.2 pharmaceutical patents registered in 2019[248] - 6,049.9 medical technology patents registered in 2019[249]
Number of (new) products approved in 2022	- 37 novel medicines and 7 biosimilars approved by the FDA's Center for Drug Evaluation and Research in 2022 (average 43 medicines a year)[250]. 65% of 37 novel medicines approved by CDER in 2022 used one or more expedited marketing authorisation programme[250]. - 7 cell and gene therapies approved by the FDA's Center for Biologics Evaluation and Research, plus 2 indication amendments, in 2022[251].

[244] Note: the USA uses the term 'drug' to refer to medicines or medical products. Where the term is essential (e.g. names, phrases) for context, it has been retained. Otherwise, this case study uses the phrasing 'medicine' or 'medical product'.

[245] Between 1 January 2022 and 31 December 2022 (most recent complete year). Based on country of recruitment. World Health Organisation. *ICTRP Platform Search Portal*. Available at: https://trialsearch.who.int/AdvSearch.aspx

[246] Clinicaltrials.gov. Available at: https://www.clinicaltrials.gov/. Searched on 'United States' and study start between 01/01/2022 and 31/12/2022.

[247] EFPIA (2023). Pharmaceutical R&D Expenditure in Europe, USA, Japan, and China (millions of national currency units*), 1990-2020. Available at: https://www.efpia.eu/publications/data-center/the-pharma-industry-in-figures-rd/pharmaceutical-rd-expenditure-in-europe-usa-china-and-japan/

[248] For pharmaceutical patents registered in at least two of the IP5 patent families (US, EU, China, Japan, and South Korea), based on inventor's country of residence. Most recent complete year. Note: this data uses fractional counting, which divides a patent equally over each listed inventor country / technology field. See: OECD.stat (2023)

[249] For medical technology patents registered in at least two of the IP5 patent families (US, EU, China, Japan, and South Korea), based on inventor's country of residence. Most recent complete year. Note: this data uses fractional counting, which divides a patent equally over each listed inventor country / technology field. See: OECD.stat (2023)

[250] FDA.gov (2023m). *New Drug Therapy Approval 2022.* Available at: https://www.fda.gov/drugs/new-drugs-fda-cders-new-molecular-entities-and-new-therapeutic-biological-products/new-drug-therapy-approvals-2022#:~:text=In%202022%2C%20CDER%20approved%2037,Biologics%20License%20Applications%20(BLAs)

[251] A total of 32 cell and gene therapy products have been approved by CBER in total. Source: FDA.gov (2023n). Approved Cellular and Gene Therapy Products. Available at: https://www.fda.gov/vaccines-blood-biologics/cellular-gene-therapy-products/approved-cellular-and-gene-therapy-products

Spending on pharmaceutical R&D has increased in the United States over the past two decades[252]. The US pharmaceutical market has a disproportionately large and influential role in global pharmaceutical R&D trends[253].

F.1.2 Regulatory agency

The American regulatory agency for medicines and medical devices is the *U.S. Federal Drug Administration (FDA)*[254]. The FDA is a federal agency of the US Department of Health and Human Services (HHS).

The FDA's Center for Drug Evaluation and Research (CDER) ensures human medicines are safe and effective for use. The CDER's Office of New Drugs (OND) provides regulatory oversight during drug development, reviews and approves marketing approval applications for new products, and sets guidance for the industry on clinical, scientific, and regulatory matters[255]. CDER evaluates applications for IND, NDA or ANDA applications for OTC, generic, and prescription medicines (including biologics and biosimilars). The OND is made up of eight review offices with 27 review divisions, including offices for infectious diseases, oncology, rare diseases, among others[255,256]. Each division is staffed with scientists, experts, and physicians in these fields, who work with experts in other CDER divisions (e.g. statistics) to review evidence in the marketing authorisation application received within the remit of their Office's division. In 2018, CDER proposed a modernisation strategy which, among other elements, aimed to improve the review process more 'predictable, consistent, and structured'[257].

ATMPs, referred to as cell and gene therapies (CGT) in the US, are regulated as biological products by the FDA[258]. The Center for Biologics Evaluation and Research (CBER) regulates CGT, as well as vaccines, allergenic products, and blood and blood products within the FDA[258].

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[252] Congressional Budget Office (2021). Research and Development in the Pharmaceutical Industry. Available at: https://www.cbo.gov/publication/57126

[253] Naci, H and Forrest, R. (2023a). A primer on pharmaceutical policy and economics. The Health Foundation. Available at: https://www.health.org.uk/sites/default/files/2023-03/report_1_a_primer_on_pharmaceutical_policy_and_economics_final.pdf

[254] The FDA also regulates food, radiation-emitting products, vaccines, blood and biologics, animal and veterinary products, cosmetics and tobacco products.

[255] FDA.gov (2022a). Office of New Drugs. Available at: https://www.fda.gov/about-fda/center-drug-evaluation-and-research-cder/office-new-drugs

[256] The eight offices are: the Office of Cardiology, Hematology, Endocrinology, and Nephrology; the Office of Immunology and Inflammation; the Office of Rare Diseases, Pediatrics, Urology and Reproductive Medicine; the Office of Infectious Diseases; Office of Neuroscience; Office of Nonprescription Drugs; Office of Oncologic Diseases and; Office of Speciality Medicine

[257] Gottlieb, S (2018). FDA's Comprehensive Effort to Advance New Innovations: Initiatives to Modernize for Innovation. FDA.gov. Available at: https://www.fda.gov/patients/fast-track-breakthrough-therapy-accelerated-approval-priority-review/fast-track

[258] Salazar-Fontana, L.I. (2022). A Regulatory Risk-Based Approach to ATMP/CGT Development: Integrating Scientific Challenges With Current Regulatory Expectations. Front. Med., 13 May 2022. Sec. Regulatory Science Volume 9 – 2022. Available at: https://www.frontiersin.org/articles/10.3389/fmed.2022.855100/full?trk=article-ssr-frontend-pulse_x-social-details_comments-action_comment-text

F.1.3 Main pharmaceutical legislation or regulation

The *Federal Food, Drug, and Cosmetic Act 1938 (FD&C Act)* is the basic pharmaceutical law in the US. The pharmaceutical legislation in the US is made up of more than 200 laws and amendments to the FD&C Act. Relevant amendments include the Kefauver-Harris amendment from 1962, which strengthened rules for drug safety and introduced manufacturers to prove the effectiveness of medicines. Pharmaceuticals are regulated primarily at federal level.

The *Code of Federal Regulations* provides regulations for Investigational New Drugs (INDs), New Drug Applications (NDAs), Abbreviated New Drug Applications (ANDAs) and Biologics License Applications (BLAs).

The *Manual of Policies and Procedures* provides official instructions for CDER staff to ensure standardised review practices. The Standard Operating Procedures and Policies provide officials instructions for CBER staff.

F.1.4 Organisation of regulatory system

The FDA has five application pathways: the Investigational New Drug (IND) Application, the New Drug Application (NDA), the Abbreviated New Drug Application (ANDA) and the Therapeutic Biologics Applications (BLA). Marketing authorisation is granted by either the CDER or the CBER if the benefits of the product in question outweigh the risks, through the following steps[259]:

- Analysis of the target condition and currently available treatments.
- Assessments of risks and benefits based on the submitted clinical data (most often from two clinical trials).
- Development of strategies for risk management (e.g. drug label requirements).

CDER can regulate CBER-regulated biologic products through BLAs and INDs/NDAs. It can also provide for expanded access (compassionate use) to experimental biologics[260].

F.1.4.1 Expedited MA pathways

Specific pathways for marketing authorisation are presented in the table below. The sections which follow provide an overview of the specific tools and regulatory pathways for CDER and CBER.

[259] FDA.gov (2022b). Development & Approval Process | Drugs. Available at: https://www.fda.gov/drugs/development-approval-process-drugs

[260] FDA.gov (2019a). Expanded Access to Experimental Biologics. Available at: https://www.fda.gov/vaccines-blood-biologics/development-approval-process-cber/expanded-access-experimental-biologics

Table 16 Expedited pathways for marketing authorisation in the US

FDA pathways[261]	**Comparable pathways in the EU and UK**[262] [263]
Accelerated approval pathway	- Conditional marketing authorisation (EMA) - Conditional marketing authorisation (MHRA)
Priority review	- Accelerated assessment (EMA) - Accelerated assessment (MHRA)
Breakthrough therapy designation	- PRIME designation (EMA) - Innovative Licensing and Access Pathway (MHRA)
Fast track designation	(no comparable designation)
(Rolling review)	- Rolling review (EMA) - Rolling review (MHRA)
Regenerative Medicine Advanced Therapy (RMAT) designation (CBER)	- PRIME designation (EMA) - Innovative Licensing and Access Pathway (MHRA)

- *Accelerated approval*. An accelerated approval pathway exists for therapies which treat a serious or life-threatening illness and have a benefit over currently available therapies. Approval can be granted based on surrogate or intermediate endpoints, with post-marketing trials taking place to confirm the medicine's benefit[264]. Accelerated approval in the US is associated with faster approval than standard review processes but also with more adverse events and post-marketing safety revisions[265].
- *Priority review*. The FDA reviews the application within 6 months, instead of 10, for products where significant improvements in the safety or effectiveness of treatment of serious

[261] In addition to these, there is also an orphan designation. See: Michaeli et al (2023).The orphan pathway is not discussed here due to the scope of this case study.

[262] Naci, H and Forrest, R. (2023b). Pharmaceutical Policy: Balancing Innovation, Access and Affordability Pharmaceutical Policy in the UK. The Health Foundation. Available at: https://www.health.org.uk/sites/default/files/2023-03/report_3_pharmaceutical_policy_in_the_uk_final.pdf

[263] Autolus (2022). FDA Grants Regenerative Medicine Advanced Therapy (RMAT) designation to Autolus' CAR T cell therapy, obe-cel, for the treatment of adult B-ALL. Available at: https://autolus.gcs-web.com/node/8886/pdf

[264] FDA.gov (2023h). Accelerated Approval. Available at: https://www.fda.gov/patients/fast-track-breakthrough-therapy-accelerated-approval-priority-review/accelerated-approval

[265] Michaeli, D.T., Michaeli, T., Albers, S. et al. (2023). Special FDA designations for drug development: orphan, fast track, accelerated approval, priority review, and breakthrough therapy. Eur J Health Econ (2023). https://doi.org/10.1007/s10198-023-01639-x

conditions are possible[266,267]. Priority review is the most common special designation, with on average 55% of products benefitting from it. Evidence shows products approved under priority review are more likely to have a higher therapeutic value than those approved through standard review processes[265]. Shorter review times have been found to have more post-approval safety revisions.

- *'Breakthrough therapy' designation*. This expedites the development and review of the medicine in question if it treats a serious condition provides a substantial improvement over available therapies[268]. Products benefit from all 'fast track' designation features, more intensive guidance on an efficient drug development program, and involvement of senior FDA staff[268].
- *'Fast track' designation*. This process facilitates the development and review of medicines for serious conditions and responding to an unmet medical need, benefitting from more frequent meetings and communication with the FDA, rolling review, and eligibility for accelerated approval or priority review if criteria are met[269]. The 'fast track' designation has been linked to a higher median benefit for QALYs, though also to higher prices[265].
- *Rolling review*. This sees the FDA begin reviewing completed sections of the application without full submission. It does not seem to be a full, separate pathway but rather a component offered in some of the expedited pathways[270].

F.1.4.2 Specific pathways for ATMPs or unmet medical need (UMN)

ATMPs, are regulated as biological products by the FDA and assessed by the CBER[266]. The FDA has issued many guidance documents to assist with the regulation of ATMPs, mostly importantly made up of four key guidance documents for the regulation of regenerative medicine products[271,272]. A Regenerative Medicine Advanced Therapy (RMAT) designation was created in 2016 to include more frequent interactions between developers and regulators. Eligibility criteria include fulfilling 'the definition of regenerative medicine; [if the product] intends to treat, modify, reverse, or cure a serious condition, and preliminary clinical evidence indicates

[266] Salazar-Fontana, L.I. (2022). A Regulatory Risk-Based Approach to ATMP/CGT Development: Integrating Scientific Challenges With Current Regulatory Expectations. Front. Med., 13 May 2022. Sec. Regulatory Science Volume 9 – 2022. Available at: https://www.frontiersin.org/articles/10.3389/fmed.2022.855100/full?trk=article-ssr-frontend-pulse_x-social-details_comments-action_comment-text

[267] FDA.gov (2018b). Priority Review. Available at: https://www.fda.gov/patients/fast-track-breakthrough-therapy-accelerated-approval-priority-review/priority-review

[268] FDA.gov (2018c). Breakthrough therapy. Available at: https://www.fda.gov/patients/fast-track-breakthrough-therapy-accelerated-approval-priority-review/breakthrough-therapy

[269] FDA.gov (2018d). Fast track. Available at: https://www.fda.gov/patients/fast-track-breakthrough-therapy-accelerated-approval-priority-review/fast-track

[270] FDA (2014). Guidance for Industry Expedited Programs for Serious Conditions – Drugs and Biologics. Available at: https://www.fda.gov/media/86377/download

[271] FDA.gov (2023i). Cellular & Gene Therapy Guidances. Available at: https://www.fda.gov/vaccines-blood-biologics/biologics-guidances/cellular-gene-therapy-guidances

[272] FDA.gov (2019b). Framework for the Regulation of Regenerative Medicine Products. Available at: https://www.fda.gov/vaccines-blood-biologics/cellular-gene-therapy-products/framework-regulation-regenerative-medicine-products

its potential to address an unmet medical need'[273]. The RMAT designation provides access to rolling review, early discussions on surrogate or primary endpoints. The RMAT functions similarly to the breakthrough therapy designation (but is not the same), or the EU PRIME scheme. If not eligible for RMAT designation, the product can still be expedited through a BLA. To date, 5 products have been approved through the RMAT designation[274].

A 2021 study[275] concluded that while the EU and US regulatory pathways differ, the main regulatory milestones reached by ATMPs are similar. The main differences the study found were the time for marketing authorisation approval, the number of authorised projects in each jurisdiction, and the type of authorisation used for some products.

Unmet medical need is explicitly mentioned in the 'fast track' designation.

F.1.4.3 Other tools

The OND offers a voluntary Pilot Program for the Review of Innovation and Modernization of Excipients (PRIME). This programme allows for FDA review of inactive ingredients prior to use in medicines[276].

The FDA also offers expanded access (i.e. compassionate use, or early access) for treatment outside of clinical trials when no suitable alternative treatments are available[277].

F.1.4.4 Scientific advice offered by the FDA

The FDA offers four types of scientific advice meetings:278

- type A, to help the development programme of a stalled product.
- type B, such as pre-IND/NDA/BLA meetings, or meetings to discuss overall development for products granted breakthrough therapy designation.
- end of phase type B, which cover certain end of phase 1 meetings, end of phase 2 and pre phase 3 meetings.
- type C, which are meeting regarding development and review of a product not covered by the other categories.

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[273] Salazar-Fontana, L.I. (2022). A Regulatory Risk-Based Approach to ATMP/CGT Development: Integrating Scientific Challenges With Current Regulatory Expectations. Front. Med., 13 May 2022. Sec. Regulatory Science Volume 9 – 2022. Available at: https://www.frontiersin.org/articles/10.3389/fmed.2022.855100/full?trk=article-ssr-frontend-pulse_x-social-details_comments-action_comment-text

[274] FDA.gov (2023b). CBER Regenerative Medicine Advanced Therapy (RMAT) Approvals. Available at: https://www.fda.gov/vaccines-blood-biologics/cellular-gene-therapy-products/cber-regenerative-medicine-advanced-therapy-rmat-approvals

[275] Iglesias-Lopez C, Obach M, Vallano A, Agustí A. (2021) Comparison of regulatory pathways for the approval of advanced therapies in the European Union and the United States. Cytotherapy. 2021 Mar;23(3):261-274. doi: 10.1016/j.jcyt.2020.11.008. Epub 2021 Jan 19. PMID: 33483292. No full-text available.

[276] FDA.gov (2022c). Pilot Program for the Review of Innovation and Modernization of Excipients (PRIME). Available at: https://www.fda.gov/drugs/development-approval-process-drugs/pilot-program-review-innovation-and-modernization-excipients-prime

[277] FDA.gov (2022i). Expanded Access. Available at: https://www.fda.gov/news-events/public-health-focus/expanded-access

[278] FDA (2009). Guidance for Industry Formal Meetings Between the FDA and Sponsors or Applicants. Available at: https://www.fda.gov/media/72253/download

CBER offers an 'Initial Targeted Engagement for Regulatory Advice on CBER Products' (INTERACT) meeting promote science-based discussions between manufacturers and the regulator for initial advice[279].

The FDA also runs a complex innovation designs (CID) meeting programme to assist in the development and use of novel clinical trial designs (piloted from 2018 onward and renewed for 2023-2027)[280]. The CID meeting programme allows product develops to meet with relevant staff from the FDA's CDER and CBER to discuss regulatory approaches to novel trial designs.

F.2 System/agency ability to adapt the regulatory assessment of innovation

F.2.1 Level of regulatory flexibility provided by law

Public health emergencies can be declared under the Public Health Service Act (section 319). Section 564 of the FD&C Act allows the Secretary of HHS to declare emergency use authorisations are appropriate. Under a EUA, the FDA can authorise an unapproved (use of a) product for emergency use with a lesser level of effectiveness evidence than for an NDA or BLA[281]. EUAs are temporary and do not stay in effect indefinitely.

F.2.1.1 Manufacturing without a marketing or manufacturing authorisation

The FDA allows some products to be used without marketing authorisation. Generally, this is limited to where there is no FDA-approved medicine to treat a serious condition, in response to insufficient supply of an FDA-approved medicine, or if the medicine is subject to a drug efficacy study implementation (DESI) proceeding[282]. The Federal Right to Try Act of 2018 created a framework for patients to access investigational medicines and/or biologics outside of the FDA's expanded access programme[283]. In this context, an investigational medicine is defined as a medicine which has completed a phase 1 clinical trial and is in active development but has not been approved by the FDA for use[284].

Use of a medicine through this act is exempt from FDA requirements for authorisation, though the manufacturer does have to be compliant with FDA requirements for investigational

[279] A similar pathway exists in Europe, where informal meetings with country innovation offices or the EMA Innovation Taskforce can be requested. Salazar-Fontana, L.I. (2022). A Regulatory Risk-Based Approach to ATMP/CGT Development: Integrating Scientific Challenges With Current Regulatory Expectations. Front. Med., 13 May 2022. Sec. Regulatory Science Volume 9 – 2022. Available at: https://www.frontiersin.org/articles/10.3389/fmed.2022.855100/full?trk=article-ssr-frontend-pulse_x-social-details_comments-action_comment-text

[280] Gottlieb, S (2018). FDA's Comprehensive Effort to Advance New Innovations: Initiatives to Modernize for Innovation. FDA.gov. Available at: https://www.fda.gov/patients/fast-track-breakthrough-therapy-accelerated-approval-priority-review/fast-track

[281] FDA.gov (2023c). Coronavirus (COVID-19) | Drugs. Available at: https://www.fda.gov/drugs/emergency-preparedness-drugs/coronavirus-covid-19-drugs

[282] FDA.gov (2021b). Unapproved Drugs. Available at: https://www.fda.gov/drugs/enforcement-activities-fda/unapproved-drugs

[283] UCI Office of Research. (2023). Right to Try - Unapproved Drugs or Biologics. Available at: https://research.uci.edu/human-research-protections/clinical-research/drugs-and-biologics-used-in-clinical-research/right-to-try-drugs-biologics/

[284] FDA.gov (2023p). Right to Try. Available at: https://www.fda.gov/patients/learn-about-expanded-access-and-other-treatment-options/right-try#:~:text=The%20Right%20to%20Try%20Act%20permits%2Fallows%20eligible%20patients%20to,life%2Dthreatening%20disease%20or%20condition

medicines. Manufacturers are required to report to the FDA on various aspects of the use of the investigational medicine (e.g. number of doses, adverse events etc.). Patients may be responsible for the cost of the medicine they use under this Act. Eligibility criteria are in place to assess who can receive an investigational medicine or biologic.

Under the Compounding Quality Act of 2013, certain medicinal products may be prepared by pharmacies or product at 'outsourcing facilities' on a per patient basis without FDA market approval[285]. A compounded drug is one where medicine ingredients are combined, mixed, or altered to create a medication tailored to the individual patient[286]. This is only used where there is no appropriate FDA-approved medicine.

F.2.1.2 Drug repurposing

Estimates include that between 30-40% of products approved by the FDA between 1984 and 2009 could be considered repurposed drugs287.

The primary regulatory pathway for a repurposed product which already has FDA-approval is a label extension[288]. For in-patent products, companies may be incentivized to apply for a label extension by being able to market the product to a larger patient population. All applications for repurposed products should be submitted to the FDA through the '505(b)(2)' pathway, which is an NDA which allows the applicant to rely on studies they have not conducted themselves for approval[289]. However, the process for repurposed off-patent products is less clear and often used off-label without FDA approval[288]. The FDA RWE programme seeks to evaluate the potential use of RWE to support labelling changes, including adding or modifying the indication[290].

The Orphan Product Extensions Now Accelerating Cures & Treatments (OPEN) Act provides an additional six months of exclusivity if a repurposed medicine treats a rare disease[291]. The National Center for Advancing Translational Sciences (NCATS) provides financial support

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[285] The FDA does not conduct pre-market approval for compounded medicines. See for more: FDA.gov (2022d). Is It Really 'FDA Approved'? Available at: https://www.fda.gov/consumers/consumer-updates/it-really-fda-approved

And FDA.gov (2020b). Compounding Laws and Policies. Available at: https://www.fda.gov/drugs/human-drug-compounding/compounding-laws-and-policies

[286] FDA.gov (2023o). Human Drug Compounding. Available at: https://www.fda.gov/drugs/guidance-compliance-regulatory-information/human-drug-compounding

[287] Krishnamurthy, N. Alyssa A. Grimshaw, Sydney A. Axson, Sung Hee Choe, and Jennifer E. Miller. Drug repurposing: a systematic review on root causes, barriers and facilitators. BMC Health Serv Res. 2022; 22: 970. Available at: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC9336118/

[288] Duke Margolis Center for Health Policy (2023). Drug Repurposing for Pandemic Innovation: Establishing an Effective and Efficient Ecosystem. Available at: https://healthpolicy.duke.edu/sites/default/files/2023-06/Drug%20Repurposing%20for%20Pandemic%20Innovation.pdf

[289] A similar pathway exists in Europe: Article 10 of Directive 2001/83/EC. See for more: Hernandez JJ, Pryszlak M, Smith L, Yanchus C, Kurji N, Shahani VM, Molinski SV. (2017). Giving Drugs a Second Chance: Overcoming Regulatory and Financial Hurdles in Repurposing Approved Drugs As Cancer Therapeutics. Front Oncol. 2017 Nov 14;7:273. doi: 10.3389/fonc.2017.00273. PMID: 29184849; PMCID: PMC5694537.

[290] FDA (2018). Framework for FDA's Real-World Evidence Program. Available at: https://www.fda.gov/media/120060/download#:~:text=FDA%20will%20explore%20strategies%20for,tools%2C%20wearables%2C%20and%20biosensors

[291] Everylife Foundation for Rare Diseases (2015). Press Release: Senate Introduces the OPEN ACT. Available at: https://everylifefoundation.org/press-release-senate-introduces-the-open-act/

through research grants for various stages of drug repurposing research[292]. There is a public-private partnership, the CURE Drug Repurposing Collaboratory, which seeks to use real-time data shared by clinicians to inform clinical trials and, potentially, labelling of medicines[293]. This includes the use of an app to allow clinical practitioners to report novel uses of existing medicines.

F.2.1.3 COVID-19 pandemic flexibilities

The COVID-19 pandemic caused public health emergency to be declared. Between 2020 and 2022, the FDA issued 84 guidance documents to provide flexibility and transparency in accessing medical products for COVID-19[294]. Regulatory flexibilities enacted include suspending on-site inspections, reducing data requirements for clinical trials, relaxing in-person safety protocols, facilitating importation of PPE, and loosening regulatory restrictions for manufacturing delays or supply shortages[295]. The FDA also issued guidelines for conducting clinical trials while social distancing.

Four emergency use authorisations (EUAs) were employed during this time, as possible under the FD&C Act[296]. Some of these EUAs were medicines repurposed to treat COVID-19. The FDA issued guidance on the generation of data to support a EUA for COVID-19[297].

The FDA also created a Coronavirus Treatment Acceleration Program (CTAP) to facilitate the development of medicines and biologics for COVID-19 and leverage cross-agency scientific advice. This includes a 'ultra-rapid protocol review'[298]. In the three years since its start, CTAP has reviewed several hundred development programmes and clinical trials, and numerous treatments authorised by the FDA for COVID-19, either through the regular pathways or as a EUA[299].

While these flexibilities may improve access or cut costs, there were two instances of risk associated with these flexibilities: 1. Fraudulent diagnostic tests entering the market after states

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[292] Hernandez JJ, Pryszlak M, Smith L, Yanchus C, Kurji N, Shahani VM, Molinski SV. (2017). Giving Drugs a Second Chance: Overcoming Regulatory and Financial Hurdles in Repurposing Approved Drugs As Cancer Therapeutics. Front Oncol. 2017 Nov 14;7:273. doi: 10.3389/fonc.2017.00273. PMID: 29184849; PMCID: PMC5694537.

[293] FDA.gov (2020g). CURE ID App Lets Clinicians Report Novel Uses of Existing Drugs. Available at: https://www.fda.gov/drugs/science-and-research-drugs/cure-id-app-lets-clinicians-report-novel-uses-existing-drugs

[294] FDA.gov (2023l). COVID-19-Related Guidance Documents for Industry, FDA Staff, and Other Stakeholders. Accessed at: https://www.fda.gov/emergency-preparedness-and-response/coronavirus-disease-2019-covid-19/covid-19-related-guidance-documents-industry-fda-staff-and-other-stakeholders . Note: removed by the FDA on 21 November 2023 but available through archived webpages.

[295] Commonwealth Fund (2020). The Cost of Speed: FDA Regulatory Flexibilities During the Coronavirus Pandemic. Available at: https://www.commonwealthfund.org/blog/2020/fda-regulatory-flexibilities-during-coronavirus-pandemic

[296] FDA.gov (2023c). Coronavirus (COVID-19) | Drugs. Available at: https://www.fda.gov/drugs/emergency-preparedness-drugs/coronavirus-covid-19-drugs

[297] FDA.gov (2021a). Development of Monoclonal Antibody Products Targeting SARS-CoV-2, Including Addressing the Impact of Emerging Variants, During the COVID 19 Public Health Emergency. Available at: https://www.fda.gov/regulatory-information/search-fda-guidance-documents/development-monoclonal-antibody-products-targeting-sars-cov-2-including-addressing-impact-emerging

[298] Lynch, H.F., Dickert, N.W. Zettler, P.J., Joffe, S., Largent, E.A. (2020). Regulatory flexibility for COVID-19 research. Journal of Law and the Biosciences, Volume 7, Issue 1, January-June 2020. Available at: https://academic.oup.com/jlb/article/7/1/lsaa057/5868444?login=true

[299] FDA.gov (2023d). Coronavirus Treatment Acceleration Program (CTAP). Available at: https://www.fda.gov/drugs/coronavirus-covid-19-drugs/coronavirus-treatment-acceleration-program-ctap

were allowed to independently authorise tests, and 2. The issuing of EAUs for antimalarial drugs hydroxychloroquine and chloroquine phosphate, later retracted as new studies showed greater risk than benefit to patients[300].

F.2.1.4 Support to non-commercial operators

The Regulatory Flexibility Act 1980 requires agencies to consider the impact of their rules on small entities301. The CDER Small Business and Industry Assistance (SBIA) provides a single channel for technical assistance to small pharmaceutical companies through meetings, workshops, and information materials[302]. A fee waiver for costs exists for small business applicants submitting its first FDA application[303].

F.2.2 Structure and organisation of expertise in regulatory agency

The CDER and CBER both house in-house expertise on specific medical fields.

- CDER: The CDER has an extensive list of offices dedicated to specific medical fields, each of which houses specialists.
- CBER: The CBER has recently established an Office of Therapeutic Products (previously the Office of Tissues and Advanced Therapies), which includes six offices: an Office of Gene Therapy Chemistry, Manufacturing, and Controls (CMC), an Office of Cellular Therapy and Human Tissue CMC, an Office of Plasma Protein Therapeutics CMC, an Office of Clinical Evaluation (for general medicines, oncology, haematology, pharmacology) and an Office of Pharmacology/ Toxicology. The CBER believes this new structure will address the growth in cell and gene therapies, allowing for more flexibility while also enhancing expertise in specialised disciplines[304].

The FDA also relies on advisory committees to provide independent advice from outside expertise on issues relating to its remit[305]. Currently, the FDA has 47 technical and scientific advisory committees, including a Cellular, Tissue, and Gene Therapies Advisory Committee[306]. These committees allow the FDA to obtain advice from external experts and encourage

[300] Commonwealth Fund (2020). The Cost of Speed: FDA Regulatory Flexibilities During the Coronavirus Pandemic. Available at: https://www.commonwealthfund.org/blog/2020/fda-regulatory-flexibilities-during-coronavirus-pandemic

[301] U.S. Equal Employment Opportunity Commission. (n.d.). Regulatory Flexibility Act Procedures. Available at: https://www.eeoc.gov/regulatory-flexibility-act-procedures

[302] FDA.gov (2020c). Small Business Assistance. Available at: https://www.fda.gov/industry/small-business-assistance#:~:text=These%20units%20provide%20technical%20assistance,acquire%20information%20from%20the%20FDA

[303] FDA.gov (2023g). Prescription Drug User Fee Amendments. Available at: https://www.fda.gov/industry/fda-user-fee-programs/prescription-drug-user-fee-amendments

[304] FDA.gov (2023e). Establishment of the Office of Therapeutic Products. Available at: https://www.fda.gov/vaccines-blood-biologics/cellular-gene-therapy-products/establishment-office-therapeutic-products

[305] FDA.gov (2018a). What is an FDA Advisory Committee? Available at: https://www.fda.gov/about-fda/fda-basics/what-fda-advisory-committee

[306] FDA.gov (2020d). Learn About FDA Advisory Committees. Available at: https://www.fda.gov/patients/about-office-patient-affairs/learn-about-fda-advisory-committees

patients, healthcare providers and others to share their views during open public hearings[307]. Their primary role, providing independent advice, sees these committees review and evaluate data on the safety, effectiveness, and use of medicines for human conditions. Meetings can occur at any stage of review of a marketing authorisation application. Most often, these meetings are held to assess the FDA's review division with interpretation around trial data, though the decision to involve an advisory committee is at the discretion of the director of the review division[308]. The recommendations issued by the advisory committees is non-binding. The committees are usually made up of nine committee members are selected for their expertise, often including a consumer and an industry representative[308]. If needed, committees can invite further experts if needed for a specific medical product or topic.

The FDA's Emerging Sciences Working Group performs horizon scanning, which, if needed, may result in a new scientific work group, staff recruitment, funding of in-house or external research projects, and/or training programmes for FDA reviewers[309].

The OND Research Program (OND-RP) fosters regulatory science research, addressing knowledge gaps which arise during review of marketing authorisation applications[310]. The research conducted as part of this programme is meant to reduce uncertainty in regulatory decision-making. The OND also initiates collaboration with SMEs through the Centers for Excellence in Regulatory Science and Innovation programme, which sees a group of selected academic institutions work with the OND to co-design studies. The Oak Ridge Institute for Science and Education fellowship programme supports OND staff in designing and managing regulatory science research projects.

Since 2003, the FDA and EMA have worked together to establish expert groups ('clusters') for scientific collaboration and exchange of information[311]. Some clusters also include regulatory agencies from other countries, including Australia, Canada, Japan, and Switzerland. Example clusters include a specific cluster for advanced therapies and regenerative medicines (ATRM) or for breakthrough therapies/PRIME[312].

[307] FDA.gov (2022f). Advisory Committees Give FDA Critical Advice and the Public a Voice. Available at: https://www.fda.gov/consumers/consumer-updates/advisory-committees-give-fda-critical-advice-and-public-voice

[308] FDA.gov (2020d). Learn About FDA Advisory Committees. Available at: https://www.fda.gov/patients/about-office-patient-affairs/learn-about-fda-advisory-committees

[309] FDA.gov (2022h). Increasing Choice and Competition through Innovation. Available at: https://www.fda.gov/science-research/focus-areas-regulatory-science-report/increasing-choice-and-competition-through-innovation

[310] FDA.gov (2023f). Office of New Drugs Regulatory Science Research. Available at: https://www.fda.gov/about-fda/center-drug-evaluation-and-research-cder/office-new-drugs-regulatory-science-research

[311] Teixeira, T., Kweder, S.L. and Saint-Raymond, A. (2020). Are the European Medicines Agency, US Food and Drug Administration, and Other International Regulators Talking to Each Other? Clin. Pharmacol. Ther., 107: 507-513. https://doi.org/10.1002/cpt.1617

[312] See overview of all clusters at Teixeira et al (2020, see footnote 306

F.2.3 *Current experience in assessing medical innovation*

Regulation has become more flexible in the last three decades, with more regulatory approvals being issue despite not being supported by at least two late-stage clinical trials[313].

Tools: The OND supports a number of medicine development tools (DDT – drug development tool), with DDT programmes for biomarkers, clinical outcome assessment, and animal models.

Flexibilities: The FDA has issued guidance on 'umbrella' trials for cell and gene therapies (ATMPs), which are 'trials designed to evaluate multiple investigational drugs administered as single drugs or as combination drugs in a single disease population'[314]. These trials can reduce the total development and approval time for new medicines, as multiple versions can be studied in parallel.

F.2.3.1 Dealing with uncertainty in assessments and new evidence generation techniques

The FDA has recognised the regulatory challenges around emerging fields for many years. For example, its 2011 Strategic Plan for Regulatory Science[315] sought to, among other things:

- '*Stimulate innovation in clinical evaluations and personalized medicine to improve product development and patient outcomes*'. Proposed actions include developing or refining clinical trial designs or elements and levering clinical data. The FDA also proposes developing a virtual physiologic patient to encourage the development of computer models.
- '*Ensure FDA readiness to evaluate innovative emerging technologies*'. In light of emerging fields, the FDA plans to develop novel assessment tools and methodologies, especially for new therapies, while maintaining standards for safe and effective medicines.
- '*Harness diverse data through information sciences to improve health outcomes*'. The FDA plans to develop its information science capacity and infrastructure to develop and use models for regulatory science uses and analyse large scale (pre-)clinical datasets.

While the FDA prefers RCTs as the evidence submitted through market approval applications, it recognises that these may not be feasible in some cases[316]. The FDA is engaged in seeking to use real-world data and evidence (RWD/E), issuing guidance on RWD/E in clinical trials in August 2023[317]. CDER staff are also conducting research to develop innovative trial designs to address obstacles in clinical evaluation, together with the Clinical Trials Transformation

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[313] Naci, H and Forrest, R. (2023a). A primer on pharmaceutical policy and economics. The Health Foundation. Available at: https://www.health.org.uk/sites/default/files/2023-03/report_1_a_primer_on_pharmaceutical_policy_and_economics_final.pdf

[314] Advarrra (2023). FDA Guidance Offers New Flexibility to Biotechs in Cell and Gene Therapy. Blog: Resource Library. Available at: https://www.advarra.com/blog/fda-guidance-offers-new-flexibility-to-biotechs-in-cell-and-gene-therapy/

[315] FDA (2011). Advancing Regulatory Science at FDA: A Strategic Plan. Available at: https://www.fda.gov/media/81109/download

[316] FDA.gov (2022g). Designing Sound Clinical Trials That Incorporate Real-World Data. Available at: https://www.fda.gov/drugs/regulatory-science-action/designing-sound-clinical-trials-incorporate-real-world-data

[317] FDA.gov (2023j). Considerations for the Use of Real-World Data and Real-World Evidence To Support Regulatory Decision-Making for Drug and Biological Products. Available at: https://www.fda.gov/regulatory-information/search-fda-guidance-documents/considerations-use-real-world-data-and-real-world-evidence-support-regulatory-decision-making-drug

Initiative[318,319]. The CID meeting programme (see Section 1.4.4.) also allows developers to meet with the FDA to discuss novel trial designs.

While the FDA's standard on evidence for effectiveness has not changed since 1998, it did issue more guidance on flexibilities in the amount and type of evidence that can be submitted to meet the evidence standard in light of the changing landscape of medicine development[320]. Similar guidance is available for, for example, oncology clinical trials[321]. The FDA RWE programme seeks to evaluate the potential use of RWE to support labelling changes, including adding or modifying the indication[322].

The FDA has experimented with AI techniques to assist with regulatory decision-making, such as using AI for molecular modelling, virtual humans, and patient-specific models, and simulated clinical trials[323]. For example, the FDA has been assessing the use of computational models for regulatory decision-making[324,325]. AI has also been tested in post-market surveillance and adverse event reporting[323]. The success and appropriateness of these tools are not clear yet, with some calling into question how these are incorporated into the FDA's decision-making[323]. Other examples of FDA action include the creation of PrecisionFDA, a collaborative computing platform to assist experts in the analysis of biological datasets to assist with precision medicine[326].

Some academics have argued that the EUAs used during the COVID-19 pandemic were a type of regulatory sandbox. The EUA process allows the FDA to authorise a product under more relaxed evidence standards, where the benefit-risk analysis framework allows the FDA to tailor EUA requirements to the specific circumstances for its use[327].

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[318] FDA.gov (2022g). Designing Sound Clinical Trials That Incorporate Real-World Data. Available at: https://www.fda.gov/drugs/regulatory-science-action/designing-sound-clinical-trials-incorporate-real-world-data

[319] Gottlieb, S (2018). FDA's Comprehensive Effort to Advance New Innovations: Initiatives to Modernize for Innovation. FDA.gov. Available at: https://www.fda.gov/patients/fast-track-breakthrough-therapy-accelerated-approval-priority-review/fast-track

[320] FDA (2019). Demonstrating Substantial Evidence of Effectiveness for Human Drug and Biological Products Guidance for Industry. Available at: https://www.fda.gov/media/133660/download

[321] FDA.gov (2023k). FDA Issues Draft Guidance Aimed at Improving Oncology Clinical Trials for Accelerated Approval. Available at: https://www.fda.gov/news-events/press-announcements/fda-issues-draft-guidance-aimed-improving-oncology-clinical-trials-accelerated-approval

[322] FDA (2018). Framework for FDA's Real-World Evidence Program. Available at: https://www.fda.gov/media/120060/download#:~:text=FDA%20will%20explore%20strategies%20for,tools%2C%20wearables%2C%20and%20biosensors

[323] Sharkey, C.M., and Fodouop, K.M.K. (2022). AI and the Regulatory Paradigm Shift at the FDA. Duke Law Journal Online, Vol 72. Available at: https://scholarship.law.duke.edu/cgi/viewcontent.cgi?article=1100&context=dlj_online

[324] FDA.gov (2020e). Promoting Innovation in Medical Product Assessment: A Risk-based Framework for Evaluating Computational Models for Regulatory Decision-Making. Available at: https://www.fda.gov/drugs/news-events-human-drugs/promoting-innovation-medical-product-assessment-risk-based-framework-evaluating-computational-models

[325] More examples available here: FDA.gov (2020f). Focus Area: Artificial Intelligence. Available at: https://www.fda.gov/science-research/focus-areas-regulatory-science-report/focus-area-artificial-intelligence

[326] PrecisionFDA (n.d.)

[327] Burd, J. (2021). Regulatory Sandboxes Slowed the Spread of COVID-19. The Regulatory Review. Available at: https://www.theregreview.org/2021/07/27/burd-regulatory-sandboxes-slowed-spread-covid-19/

F.2.4 *Futureproofing*

The FDA reports on its focus areas for regulatory science regularly, to align with scientific advancement and ensure these areas receive targeted investment and are prioritised. In 2022, the FDA listed four strategic initiatives covering 23 focus areas: the table below highlights areas relevant to this study[328].

Table 17 Strategic FDA initiatives with areas relevant to this study

Strategic initiatives	**Focus areas relevant to this case study**
Public health emergency preparedness and response	- Medical Countermeasures and Preparedness for Emerging Infectious Diseases
Increasing choice and competition through innovation	- Individualized Therapies and Precision Medicine - Complex Innovative Trial Design - Regenerative Medicine - Novel Technologies to Improve Predictivity of Non-Clinical Studies and Replace, Reduce, and Refine Reliance on Animal Testing - Model-Informed Product Development
Unleashing the power of data	- Artificial Intelligence - Use of Real-World Evidence to Support Medical Product Development and Regulatory Decision-Making
Empowering patients and consumers	n/a

These are supplemented by cross-cutting priority areas, including minority health and health equity, women's health, paediatric health, oncology, rare diseases, and the one health initiative.

[328] FDA (2022). 2022 Advancing Regulatory Science at FDA: Focus Areas of Regulatory Science (FARS). Available at: https://www.fda.gov/media/161381/download?attachment

Appendix G Country Case Study: China

G.1 Description of regulatory approval in China

G.1.1 Pharmaceutical innovation and R&D in China

Table 18 Descriptive statistics on pharmaceutical R&D in China

Characteristic	Measure for most recent year
Amount of medical research / number of clinical trials	- 6,347 trials registered as collecting data in China in 2022 (up from 43 in 2012) (WHO)[329] - 7,853 trials registered in Singapore in 2022 (Clinicaltrials.gov)[330]
R&D expenditure	- 78,460 million Yuan (2020)[335]
Number of patents for pharmaceutical innovation	- 1,719.4 pharmaceutical patents registered in 2019[331] - 1,674.4 medical technology patents registered in 2019[332]
Number of (new) products approved in 2022	- 61 total approved New Drug Applications (NDA)[333] - 29 innovative chemical drugs - 22 innovative biopharmaceuticals - 10 innovative Traditional Chinese Medicine (TCM)

Over the past decade, China's pharmaceutical industry has prioritised drug innovation due to evolving medical needs, market expansion, and regulatory reforms[334]. The rapid growth of the market and research environment in China, and countries such as Korea, is driving a shift of economic and research activities away from European markets. In 2021, China nearly matched Europe in originating new active substances introduced globally, with 18 and 19 new substances, respectively. However, still far behind the US leading with 35 on a total of 95 new

[329] Between 1 January 2022 and 31 December 2022 (most recent complete year). Based on country of recruitment. World Health Organisation. ICTRP Platform Search Portal. Available at: https://trialsearch.who.int/AdvSearch.aspx

[330] Clinicaltrials.gov. Available at: https://www.clinicaltrials.gov/. Searched on 'China' and study start between 01/01/2022 and 31/12/2022.

[331] For pharmaceutical patents registered in at least two of the IP5 patent families (US, EU, China, Japan, and South Korea), based on inventor's country of residence. Most recent complete year. Note: this data uses fractional counting, which divides a patent equally over each listed inventor country / technology field. See: OECD.stat (2023)

[332] For medical technology patents registered in at least two of the IP5 patent families (US, EU, China, Japan, and South Korea), based on inventor's country of residence. Most recent complete year. Note: this data uses fractional counting, which divides a patent equally over each listed inventor country / technology field. See: OECD.stat (2023)

[333] '2022年度药品审评报告' <https://www.nmpa.gov.cn/xxgk/fgwj/gzwj/gzwjyp/20230906163722146.html> accessed 30 November 2023.

[334] Linghui Kong et al., 'Innovation in the Chinese Pharmaceutical Industry' (Nature Research, 1 January 2023) 12.

pharmaceutical active substances[335]. Despite this, China's drug procurement reform, focusing on patient-centred clinical value, is expected to drive companies to prioritise innovation quality in the coming years[334].

The annual growth rate in pharmaceutical R&D expenditure in China has been decreasing, from 33.3% between 2007 and 2011 to 12.9% between 2017 and 2021. On the other hand, both the US and EU are seeing an increasing trend in the annual growth rate of pharmaceutical R&D expenditure[335].

In December 2021, eight Chinese authorities jointly issued 'The 14th Five-Year Plan for National Drug Safety and High-Quality Development' in China, outlining the guiding ideology, principles, and goals for drug safety and high-quality development during the 14th Five-Year Plan period. Emphasising adherence to comprehensive CPC leadership, reform, innovation, scientific regulation, law-based supervision, and social co-governance, the plan aims to transform China into a pharmaceutical manufacturing power and enhance drug regulatory capacity. It sets ambitious goals for the improvement of drug safety, supply, and regulatory environment, fostering high-quality industry development, and advancing innovation in drugs, medical devices, and traditional Chinese medicine. The plan involves specific tasks, projects, and measures to achieve its objectives, emphasising coordination, leadership, global participation, and local government responsibilities in ensuring drug safety and promoting economic and social development[336].

G.1.2 Regulatory agency

The National Medical Products Administration (NMPA) is the primary regulatory body for pharmaceuticals under the State Administration for Market Regulation (SAMR). The National Health Commission (NHC) oversees public hospitals and healthcare professionals nationally, while SAMR regulates pharmaceutical advertising and promotion. The National Healthcare Security Administration (NHSA) manages pharmaceutical pricing and reimbursement through the Basic Medical Insurance scheme. Local counterparts at provincial, municipal, and county levels have rulemaking and enforcement authority in compliance with People's Republic of China (PRC) laws[337]. NMPA includes technical divisions such as Medicines Registration (standards, guidelines, registration, preclinical and clinical practices, involved in formulation of national essential medicines), Medicines Regulation (covering GMP, GSP, site inspections, and adverse drug reaction monitoring), Medical Device Registration (standard, registration, clinical trial practice, guideline, site-inspection), Medical Device Regulation (GMP, GSP site-inspection, sampling test and adverse reaction monitoring of medical device), and Cosmetics Regulation (standard, guideline, registration, inspection, sampling test, and adverse reaction monitoring)[338].

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[335] Efpia (n.d.), 'Pharmaceutical R&D Expenditure in Europe, USA, Japan and China', https://www.efpia.eu/publications/data-center/the-pharma-industry-in-figures-rd/pharmaceutical-rd-expenditure-in-europe-usa-china-and-japan/ accessed 30 November 2023.

[336] 'Issuance of the 14th Five-Year Plan for National Drug Safety and High-Quality Development' <http://english.nmpa.gov.cn/2021-12/30/c_736377.htm# > accessed 1 December 2023; '"十四五"医药工业发展规划'.

[337] 'Life Sciences Regulation in China: Overview | Practical Law' <https://uk.practicallaw.thomsonreuters.com/4-500-8862?transitionType=Default&contextData=(sc.Default)&firstPage=true> accessed 30 November 2023.

[338] 'National Medical Products Administration' <http://english.nmpa.gov.cn/index.html> accessed 1 December 2023.

In addition to the main organisations under NMPA, there are also affiliated institutions that provide technical support to NMPA, including:[338]

- Centre for Food and Drug Inspection: responsible for formulating and revising normative and technical documents for inspecting drugs, medical devices, and cosmetics. Additionally, it oversees accreditation, conformity inspections, and various types of inspections for drugs, medical devices, and cosmetics, while also handling the evaluation, employment, and administrative tasks related to state-level inspectors, participating in research and academic exchange on inspection theories, and engaging in international cooperation in drug, medical device, and cosmetic inspections.
- Centre for Drug Evaluation (CDE): responsible for reviewing applications for drug clinical trials and marketing authorisation, including the technical review of generic drugs' quality and efficacy consistency evaluation. It also conducts technical reviews for emerging medical products, participates in drafting regulatory documents, coordinates inspection and testing activities, conducts research on drug review theories and technologies, and engages in international cooperation and consulting services related to drug review, in addition to undertaking other assigned tasks by NMPA.
- Centre for Medical Device Evaluation: tasked with accepting and technically reviewing registration applications for domestic Class III medical device products and imported medical device products, as well as handling the filing of imported Class I medical device products. Additionally, it participates in the development of laws, regulations, and normative documents related to medical device registration, coordinates inspection activities, conducts research on medical device review theories and technologies, and provides guidance and technical support for local departments, along with engaging in international cooperation and undertaking other assigned tasks by NMPA.

G.1.3 Main pharmaceutical legislation or regulation

According to the Drug Administration Law (DAL), the term "pharmaceuticals" encompasses substances, such as Chinese medicine, chemical drugs, and biological products. These substances are intended for human use in preventing, treating, or diagnosing diseases, or for the deliberate regulation of human physiological functions, with defined indications, primary functions, usage, and dosage[337].

China has been undergoing regulatory reforms since 2015[339]. In 2016, the Chinese government released the Pharmaceutical Industry Development Planning Guidelines, outlining the nation's strategy for enhancing the pharmaceutical system from 2016 to 2020. Addressing the historical weakness in NMPA standards for drug approval and regulation, a key focus of the plan was to elevate product quality and safety. Recent reforms have been implemented over the past decade to enhance drug approval standards and overall drug quality[340]. **Error! Reference s ource not found.** presents an overview of the drug approval processes in China, and **Error! Reference source not found.** presents the evolution of China's regulatory reform and

[339] 'An Inside Look at China's Regulatory and Drug Approval Processes - Redica Systems' <https://redica.com/pharma-an-inside-look-at-chinas-regulatory-and-drug-approval-processes/> accessed 17 November 2023.

[340] Mackenzie Mills, Anwen Zhang and Panos Kanavos, 'Pharmaceutical Policy in China' <https://doi.org/10.21953/lse.fg2t522b8r1x> accessed 1 December 2023.

comparisons with the US Food and Drug Administration (FDA), the European Medicines Agency (EMA), and the International Conference on Harmonization (ICH).

Table 19 NMPA drug approval processes

NMPA approval processes	Type of product	Evidence requirements	Monitoring period/additional notes
New Drug	New product without overseas authorisation	Local Phase I, II, and III trials	Monitoring period of 5 years
	Modified innovative product without overseas authorisation (e.g. new formulation/new indication)	Local Phase I, II, and III trials	Monitoring period of 3-4 years
Imported Drug	New product approved and manufactured outside China	Local pharmacokinetic and phase III trial	N/A
	Generic product approved and manufactured outside China	Local bioequivalence study	N/A
Generic Drug	Locally manufactured generic product with approval only outside China	Pharmacokinetics and Phase III trial	N/A
	Locally manufactured generic product already approved in China	Bioequivalence study	N/A
Priority Review	Innovative products not approved overseas, innovative products with plans for local manufacturing or global clinical trials in China, innovative drugs for HIV/AIDs, viral hepatitis, rare diseases, malignant tumours or paediatric indications	Local Phase I, II, and III trials	Additional consultation with CDE. Targeted review time of six months
	Newly launched generic products	Bioequivalence study	Additional consultation with CDE. Targeted review time of six months
Conditional Approval	Products indicated for serious life- threatening conditions or for significant unmet medical needs	Early or mid-stage clinical data	Defined risk management plan required and completion of clinical trials
	Orphan drugs	Trials with fewer trial subject numbers	Completion of clinical trials

Source: Adopted from Mackenzie Mills, Anwen Zhang and Panos Kanavos, 'Pharmaceutical Policy in China'[340]

Table 20 Comparison of NMPA pharmaceutical guidance with comparable guidance from FDA, EMA, and ICH

Guidance Document	Year Published	References
Technical Guideline of New Drug Phase I Clinical Study Application	2018	FDA guidance (1995), Questions and Answers (2000), EMA guidance (2017)
Estimating the Maximum Recommended Starting Dose in Initial Clinical Trials for Therapeutics in Adult Healthy Volunteers	2012	FDA guidance (2005)
Technical Guideline of Clinical Pharmacokinetic Study for Chemical Drugs	2005	FDA guidance (2001, updated 2018)
Technical Guideline on Pharmacokinetics and Pharmacodynamics Study in the Development of Antibacterial Drugs	2015	EMA guidance (2016)
Technical Guideline of Pharmacokinetics in Patients with Impaired Hepatic Function	2012	FDA guidance (2003)
Technical Guideline of Pharmacokinetics in Patients with Impaired Renal Function	2012	FDA guidance (2010, updated 2020)
Technical Guideline of Drug Interaction Studies (draft)	2020	FDA guidance (2020), draft guidance on Drug-Drug Interaction Assessment for Therapeutic Proteins (August 2020)
Technical Guideline of Safety Testing of Drug Metabolites	2012	FDA guidance (2008, finalized in 2016)
Technical Guideline of Bioavailability and Bioequivalence Studies	2005	FDA guidance (2003, updated in 2014 and 2019)
Technical Guideline for Human Bioequivalence Studies with Pharmacokinetic Endpoints for Chemical Drug Generics	2015	FDA guidance (2013)
Guideline of Waiver of In Vivo Bioequivalence Studies	2016	FDA draft guidance (2015, finalized in 2017)
Guideline of Statistical Approaches to Establishing Bioequivalence	2016/2018	FDA guidance (2001)
Technical Guideline of Bioequivalence of Highly Variable Drugs	2018	FDA and EMA guidance on Bioavailability and Bioequivalence Studies Submitted in NDAs or INDs (2014)

Source: Weifeng Tang et al. (2021)[341]

G.1.4 Organisation of regulatory system

The regulatory framework for pharmaceuticals in China consists of various key documents, including the Drug Administration Law (DAL), Implementing Regulations of the DAL, Drug Registration Rules (DRR), Measures for the Supervision and Administration of Drug Manufacturing, Measures for the Supervision and Administration of Drug Distribution, Administrative Measures for the Special Review of New Drugs, PRC Pharmaceutical Good

[341] Weifeng Tang and others, 'Evolving Drug Regulatory Landscape in China: A Clinical Pharmacology Perspective' (2021) 14 Clinical and Translational Science 1222 </pmc/articles/PMC8301550/> accessed 1 December 2023.

Laboratory Practice (GLP), Good Clinical Practice (GCP), Good Manufacturing Practice (GMP), Good Supply Practice (GSP), and Good Pharmacovigilance Practice (GVP) standards. Additionally, there are rules and measures addressing adverse drug reaction reporting, the establishment of a trustworthiness evaluation system for drug prices and centralised procurement, the use of drugs under basic medical insurance, and the review of advertisements for drugs, medical devices, health food, and formula food for special medical purposes[337].

In May 2022, the NMPA published a new draft of 'Regulations for the Implementation of the Drug Administration Law of the People's Republic of China', listing a total of 181 regulations[342]. Key proposed changes are presented in Table 21Table .

Table 21 Key regulatory changes in the new draft regulation published in May 2022

Regulatory Change	Details
Removal of definition of new drug	Currently, the definition of "new drug" in Article 77 of the Current Regulations states that it must be new in China. The proposed change in the Draft Regulations is to align with the State Council Opinions, removing the requirement for new drugs to be new in China and recognizing drugs that have not been marketed worldwide.
Data exclusivity	Article 34 of the Current Regulations provides six years of data exclusivity for undisclosed trial data and other data of a drug containing a new chemical entity (NCE). The Draft Regulations propose data exclusivity protection for "undisclosed trial data and other data of a part of drugs approved for marketing authorization," but clarification is needed on the meaning of "a part of drugs."
Paediatric drug exclusivity and orphan drug exclusivity	The Draft Regulations (Articles 28 and 29) introduce market exclusivity for paediatric and orphan drugs. Paediatric drugs may have up to 12 months of exclusivity, while orphan drugs may enjoy up to seven years of market exclusivity, subject to compliance with supply guarantees.
Removal of new drug monitoring period	The proposal is to entirely remove the monitoring period, previously under Article 33 of the Current Regulations, during which the NMPA would not approve the manufacture and importation of the same drug of the same variety. This monitoring period system is being repealed entirely.
Patent protection	Articles 38 and 39 of the Draft Regulations mention the patent linkage mechanism and the 12-month market exclusivity for generic chemical drug manufacturers. Article 121 specifies the mechanism for compulsory licenses for drug patents in the event of a public health event or a national emergency. Marketing Authorisation applications subject to compulsory patent licenses can benefit from priority review.

Source: 'New Draft Implementing Regulations Propose Key Changes for Pharmaceuticals in China - Bird & Bird'[343]

G.1.4.1 Expedited MA pathways

China has four expedited marketing authorisation pathways (called accelerated registration pathways in China):

[342] '国家药监局综合司公开征求《中华人民共和国药品管理法实施条例（修订草案征求意见稿）》意见' <https://www.nmpa.gov.cn/xxgk/zhqyj/zhqyjyp/20220509222233134.html> accessed 1 December 2023.

[343] 'New Draft Implementing Regulations Propose Key Changes for Pharmaceuticals in China - Bird & Bird' <https://www.twobirds.com/en/insights/2022/china/new-draft-implementing-regulations-propose-key-changes-for-pharmaceuticals-in-china> accessed 1 December 2023.

Table 22 Pathways for marketing authorisation in China

NMPA pathways[339]	**Comparable pathways in the US, EU, and UK**[344]
Conditional Approval	• Accelerated approval pathway (US) • Conditional marketing authorisation (EMA) • Conditional marketing authorisation (MHRA)
Priority review	• Priority review (US) • Accelerated assessment (EMA) • Accelerated assessment (MHRA)
Breakthrough therapy designation	• Breakthrough therapy designation (US) • PRIME designation (EMA) • Innovative Licensing and Access Pathway (ILAP)
Special Approval	• Emergency use Authorisations (US) • Temporary emergency marketing authorisation (EMA)

- *Breakthrough Therapy (BT):* To qualify during local clinical trials, a drug must be innovative or a modified new drug. It should aim to prevent or treat serious life-threatening diseases or conditions that significantly impair quality of life, with no effective prevention or treatment available. Additionally, there should be sufficient evidence demonstrating the drug's substantial clinical superiority over existing therapies. This is specific for Phase I and Phase II clinical development stage and the developers benefit from priority review and rolling submission.
- *Conditional Approval (CA):* To qualify during local clinical trials in China, a drug can be considered this pathway if the clinical data can predict its efficacy and clinical benefits. This applies to target indications that involve serious and life-threatening diseases with unmet clinical needs. The drug should address urgent needs for the treatment of rare diseases, be urgently required for public health reasons, or be a vaccine needed in response to major public health emergencies. The latter includes vaccines recognized by the state health administrative department and listed in special approval procedures. This pathway benefits from the priority review and post-approval changes alignment before NDA approval.
- Priority Review (PR): Cover breakthrough drugs with clinical superiority, conditional approval for drugs addressing urgent needs, including rare diseases and major infections, and

[344] 'U.S. Food and Drug Administration' <https://www.fda.gov/> accessed 1 December 2023; 'European Medicines Agency |' <https://www.ema.europa.eu/en> accessed 1 December 2023; 'Medicines and Healthcare Products Regulatory Agency - GOV.UK' <https://www.gov.uk/government/organisations/medicines-and-healthcare-products-regulatory-agency> accessed 1 December 2023.

innovative vaccines for public health emergencies. Additionally, other drugs fall under PR regulation, ensuring expedited assessment and approval processes.

- *Special Approval (SA):* This is decided by NMPA case by case to manage public health crisis.

G.2 System/agency ability to adapt the regulatory assessment of innovation

G.2.1 Level of regulatory flexibility provided by law

China has been going through pharmaceutical regulation reforms and is continuously introducing new regulations that either allow some flexibilities to incentivise innovations, but also some stricter regulations to ensure only products of the utmost quality are approved. The following sections outline some of the flexibilities implemented.

G.2.1.1 Manufacturing without marketing or manufacturing authorisation

In 2022, China's National Healthcare Commission (NHC) introduced the Interim Import Plan, addressing the importation of small quantities of urgently needed overseas-marketed drugs that are not available in China or face immediate production challenges. The plan prioritises drugs falling into categories such as orphan drugs for rare diseases, drugs for severe life-threatening conditions lacking effective treatments, and drugs with evident clinical advantages[345]. While all pharmaceutical products in China typically require approval, the NMPA may grant emergency or conditional marketing approvals in public health emergencies. To enhance patient access to pharmaceutical products that meet unmet clinical needs, Hainan Medical Products Administration (MPA) and Guangdong MPA have been authorised to approve the importation, without marketing authorisation, of eligible pharmaceutical products for designated hospitals in the Lecheng International Medical Tourism Pilot Zone (BMTPZ) and the Greater Bay Area (GBA)[346].

G.2.1.2 Drug repurposing

There are no specific regulations for drug repurposing in China. While not directly related to repurposing, there are considerations regarding regulatory data protection and market exclusivity in China. Since 2002, Implementing Regulations have included data protection measures, granting exclusive rights to the manufacturer or seller of a registered drug containing new chemicals. This exclusivity prohibited unauthorised use of the data, with a six-year period during which the NMPA would not approve others' applications utilising the data. In 2018, the draft Implementing Measures for the Protection of Trial Data of Drugs proposed exclusive periods of six years for new drugs, rare disease drugs, and paediatric drugs, and 12 years for therapeutic biological products. While this draft was not officially adopted, the recent Draft Regulations on Market Authorisation of Pharmaceuticals suggest regulatory data protection for certain marketed drugs, though the scope is undefined. Qualified rare disease and paediatric drugs may have exclusivity periods preventing approval of generic applications. New paediatric drugs could have market exclusivity for up to 12 months, and new rare disease drugs for up to seven years, with the Draft Regulations providing the longest exclusivity periods for

[345] 'Updates on Pharmaceutical Regulations in China | June 2022 - REACH24H' <https://www.reach24h.com/en/news/industry-news/pharma-industry-news/updates-on-pharmaceutical-regulations-in-china-june-2022.html> accessed 17 November 2023.

[346] 'Life Sciences Regulation in China: Overview | Practical Law' (n 5).

these specific types. Notably, the first generic successfully challenging a patented drug could be granted a fixed 12-month market exclusivity period. The definition of "new drug" limited to those "first worldwide" emphasises the importance for pharmaceutical companies to decide whether to launch innovative products in China first[347].

G.2.1.3 COVID-19 pandemic flexibilities

During the COVID-19 pandemic, the NMPA published special technical guidelines and evaluation procedures to ensure the quality and accelerated development of COVID-19 medical products[348].

G.2.1.4 Support to non-commercial operators

China is keen to maintain the promotion of innovative drug development focused on clinical value. Since the publications of the 2019 Implementing Regulations, various policy documents, such as the Guiding Principles for Clinical Research and Development of Antitumor Drugs Based on Clinical Value, have advocated for prioritising first-in-class or best-in-class research and discouraging redundant investments in certain cancer drugs. The Draft Regulations reinforce this approach, signalling the regulator's intention to persist in promoting clinical value-oriented standards for all therapeutic products. Additionally, the Draft Regulations affirm government support for innovative drug discovery, leveraging diverse policy tools in government-backed research projects, financing, procurement, payment standards, and medical insurance. Given the government's assertive approach to volume-based procurement and pricing negotiation, these regulations may offer increased incentives to address concerns of pharmaceutical companies related to investment in the development of innovative therapeutic products[347].

G.2.2 Structure and organisation of expertise in regulatory agency

Since joining the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) in 2017, China has strengthened its integration with the international market, prompting more Chinese companies to pursue global development.[349] The new legislation published in 2022, particularly Article 2 and Article 4, focuses on ensuring the presence of qualified experts within the government to conduct rigorous assessments of medical products and aims to incentivize innovation[342].

G.2.3 Current experience in assessing medical innovation

To qualify for the 'Breakthrough Therapy' pathway, drug must be innovative or a modified new drug, address serious or life-threatening diseases without effective treatment, and demonstrate substantial clinical superiority over existing therapies. This pathway offers priority review and rolling submission. The 'Conditional Approval' pathway, another option, requires clinical data from local trials predicting efficacy and benefits. It applies to serious diseases with unmet needs,

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[347] 'China on the Move: Lesson from China's National Negotiation of Drug Prices in 2022 | Insights | Greenberg Traurig LLP' <https://www.gtlaw.com/en/insights/2023/2/china-on-the-move-lesson-from-chinas-national-negotiation-of-drug-prices-in-2022> accessed 1 December 2023.

[348] 'China Focusing Innovation Through ICH Global Regulatory Vision' <https://globalforum.diaglobal.org/issue/august-2021/china-focusing-innovation-through-ich-global-regulatory-vision/#> accessed 1 December 2023.

[349] ibid; 'China's Innovative Drugs: An Inside Look at Application Boom | PPD Inc' <https://www.ppd.com/blog/chinas-innovative-drugs-applications-inside-look/> accessed 1 December 2023.

drugs for rare diseases, those urgently needed for public health, and vaccines for emergencies. The process involves priority review, PAC alignment, and NDA approval[339].

G.2.4 Futureproofing

The NMPA is aiming to incentivise innovation in the pharmaceutical sector through proposed regulatory changes. Key points include the potential adoption of a stricter definition of "new drug", emphasising clinical value-oriented drug innovation, strengthening regulatory data protection, and integrating past reform documents. The Draft Regulations also introduce measures such as exclusivity periods for certain drugs, regulatory data protection for "some drugs approved for marketing," and additional compliance burdens related to investigational new drug (IND) sponsor changes. Challenges for pharmaceutical companies include compliance obligations for off-shore activities and uncertainties related to cross-border arrangements under the new Marketing Authorisation Holder (MAH) regime. Despite potential challenges, innovation remains a focal point for China's pharmaceutical industry, aligning with the country's broader economic goals outlined in the 14th Five-Year Plan for the bio industry. Foreign companies may benefit from China's emphasis on innovation but should navigate potential hurdles and align with local strategies[347].

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