Bundesministerium
für Gesundheit

The Medical Research Act (*Medizin-forschungsgesetz*) & the EU Pharmaceutical Package

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I. Medical Research Act

1. Starting point and genesis of the National Pharma Strategy

1.1 Starting point/the problem

On the one hand: Importance of **Germany** as a pharmaceutical location

The pharmaceutical industry is Germany's most research-intensive sector (in terms of the share of R&D spending)

Germany is an important biotech location globally, of great importance for growth and employment

Germany is no. 1 in Europe in terms of revenue

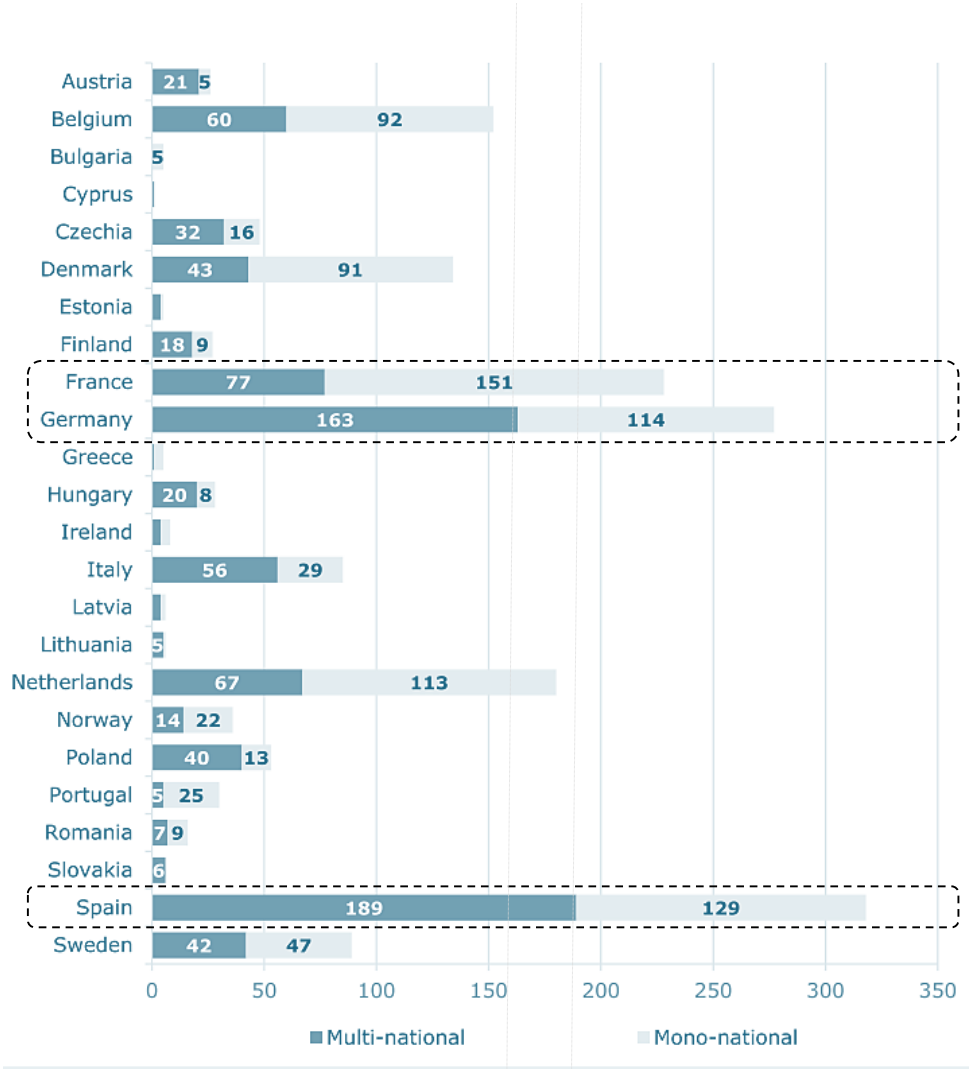
Germany is the fourth-biggest pharmaceuticals market globally (market share of approx. 4%)

On the other hand: Loss of attractiveness

→ In recent years, Germany has become less attractive as a place to do research and development and as a production location (both in an international and a European comparison)

Number of RMS rapporteurships of approved applications for clinical trials on medicinal products

31 January 2022 –
30 November 2023



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1.2 Drafting a National Pharma Strategy

- **July 2023:** Future Council in the Federal Chancellery; following that, Federal Ministry of Health commissioned with drafting a pharma strategy
- **August to November 2023:** Interministerial coordination processes on the pharma strategy
- **Late November 2023:** Industry invited to take part in Pharma Summit
- **13 December 2023:** National Pharma Strategy adopted by Federal Cabinet and published

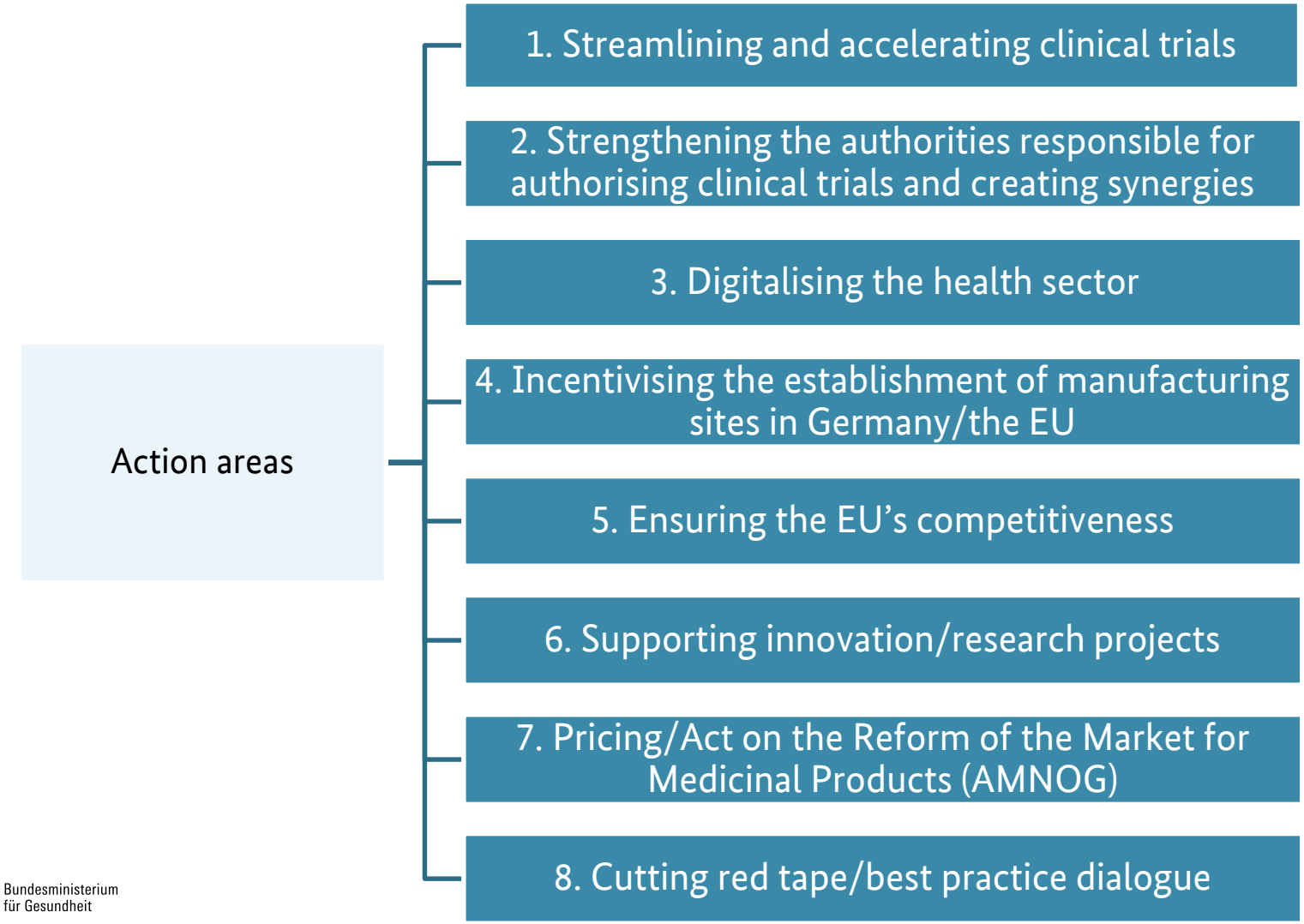
1.3 Goals of the Pharma Strategy

To restore and expand Germany's attractiveness as a pharmaceutical location and to secure a reliable supply of medicinal products

by...

- Improving the conditions for a strong, sustainable and internationally competitive pharmaceutical industry in Germany/the EU
- Creating reliable market conditions as a key locational factor for new investment
- Establishing a good research infrastructure with highly qualified specialists and close cooperation with the relevant research facilities
- Reducing Germany's/the EU's strategic dependencies and securing the supply of medicinal products

1.4 Overview of proposed action areas



2. Implementing the Pharma Strategy in the Medical Research Act

2. Implementing the Pharma Strategy in the Medical Research Act

➢ Objectives

- Improve the conditions for developing, authorising and manufacturing of medicinal products and medical devices
- Boost Germany's attractiveness as a place to do medical research
- Accelerate patients' access to new therapies
- Promote growth and employment

➢ Qualification

The Federation does not have legislative competence for studies beyond the scope of medicinal products and medical devices (see Article 74 (1) no. 19 of the Basic Law (*Grundgesetz*)).

2. Implementing the Pharma Strategy in the Medical Research Act

➢ Measures

- Incorporation of the radiation protection procedure into the procedure for authorising clinical trials of medicinal products under the law on medicinal products
- Specialisation and harmonisation of Ethics Committees
- Acceleration of mononational clinical trials
- Publication of standard contractual clauses for clinical trials
- Regulatory adaptations to enable decentralised clinical trials
- Simplification of labelling of investigational/auxiliary medicinal products
- Strengthening of authorities responsible for authorisation (Federal Institute for Drugs and Medical Devices (BfArM) and Federal Institute for Vaccines and Biomedicines (PEI))
- Harmonisation of manufacturing authorisations for certain classes of medicinal products
- Introduction of confidential rebates

2.1 Radiation protection

2.1 Radiation protection

- Synchronising notification and authorisation procedures under radiation protection law (relating to the use of radioactive substances and ionising radiation in humans for the purposes of medical research) with the procedures for clinical trials on medicinal products and medical devices.

- Most important changes

  - Introduction of a **single gate approach** to notification and authorisation under radiation protection law: Use of the same electronic submissions portals as are used in procedures under the law on medical devices and medicinal products

  - Research projects with low-dose applications in trials on sick minors to be included in the notification procedure

2.1 Radiation protection

- Ethics Committees to assess **notification procedures** under radiation protection law
  - BfArM/PEI formally made lead authorities
  - Advantage: Reduction in duplication of assessments, as the Federal Office for Radiation Protection (BfS) will no longer conduct reviews

- As regards **authorisation procedure** under radiation protection law:
  - BfS still responsible
  - BfS/Ethics Committees both conduct assessments of medicinal products
  - Alignment of deadlines to those in the law on medicinal products

The rules still guarantee that the same high level of radiation protection will be maintained.

2.2 Ethics Committees

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1. Establishment of a Specialist Ethics Committee for Special Procedures

- Responsible for the following clinical trials:
  - Studies dealt with by the EMA's Emergency Task Force
  - Master protocol studies
  - First-in-human studies
  - Advanced therapy medicinal products (ATMP) studies
- Pooling of expertise for such especially urgent or complex procedures

2. Specialisation of some of the registered Ethics Committees in the federal states in regard to certain procedures

- Areas of specialisation are for instance: relevant indicators, population groups, study phases or types
- Registered Ethics Committees are to draw up a special (after consultation of BfArM/PEI) and a general allocation of competences plan

2.2 Ethics Committees

3. Authority to issue guidelines to the Working Group of Medical Ethics Committees (AKEK)

- AKEK to issue guidelines, applicable to all the registered Ethics Committees, concerning the application and interpretation of the requirements set out in Regulation (EU) No 536/2014
- Compliance is precondition for registration
- Further harmonisation as regards the registered Ethics Committees in the federal states

4. Medical devices

- The Specialist Ethics Committee for Special Procedures that will be established and be based in the BfArM will also be responsible for certain medical devices
- New competences in the context of performance studies involving companion diagnostics (CDx): The Ethics Committee responsible for the medicinal product in question will also be asked for an opinion on the companion diagnostic

2.3 Accelerating mononational clinical trials

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- Validated applications assessed within 26 days
- Decision on application within 5 days
- Time saving of up to 19 days is key locational factor for pharmaceutical research
- Time saving equals the number of days required for the EU coordination phase, as this does not apply to mononational clinical trails

  ➢ Number of days for assessing content is not cut

2.4 Standard contractual clauses

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Starting situation:

- Contract negotiations once a clinical trial has been authorised take too long and delay the start of the trial
- Not enough use is made of those model contractual clauses that are already available
- Contracting parties' freedom of will is protected under the Basic Law. Article 2 (1) of the Basic Law protects the freedom to conclude or not conclude a contract and to design private law contracts (freedom of contract) – Article 12 (1) of the Basic Law is *lex specialis* regarding a person's occupation or profession
- The severity of the restriction of fundamental rights must not be disproportionate to the significance of the grounds justifying it following consideration of all the relevant facts

2.4 Standard contractual clauses

Result of consideration of all the relevant facts:

- Legal basis for the publication, by the Federal Ministry of Health, of standard contractual clauses relating to clinical trials
- The affected associations, organisations and authorities in industry and science will be involved in preparing the standard contractual clauses
- This will support current harmonisation activities in this area

2.5 Further streamlining

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- **Decentralised clinical trials**: Investigational and auxiliary medicinal products to be given to trial participants under certain conditions and with the permission of BfArM/PEI

- Simplification of **labelling** of investigational and auxiliary medicinal products: labelling exclusively in English permitted in the case of direct application

- In addition to the written consent to the clinical trial: **Electronic consent in compliance with EU regulations**

- Further harmonisation as regards **manufacturing authorisations** for certain classes of medicinal products, especially ATMP and bacteriophages:
  - BfArM/PEI to publish recommendations for interpreting the principles of and guidelines on good manufacturing practice
  - Federal state authorities can request a statement from BfArM/PEI when questions regarding interpretation of good manufacturing practice arise

2.5 Further streamlining

- **Nuclear medicine facilities to be exempt from the obligation to obtain authorisation** for the manufacture of radioactive medicinal products used as diagnostic investigational medicinal products (exemptions were previously limited to pharmacies)

2.5 Strengthening Competent Authorities

Goal: To ensure that pharmaceutical research and development in Germany benefits from **accelerated** procedures in relation to clinical trials and (marketing) authorisations, whilst **maintaining the high quality** in consultation and assessment (streamlining procedures for innovative medicinal products, e.g. antibody-drug conjugates)

Implementation: Coordination and management of procedures for the authorisation of clinical trials on medicinal products ⇒ Federal Institute for Drugs and Medical Devices (BfArM)

Planned provision:
- The Federal Ministry of Health is to be authorised to issue an Ordinance to adapt the processes of ~~the~~ BfArM and Paul Ehrlich Institute (PEI)
- The Ordinance may provide for the establishment of a coordination office based in the BfArM to coordinate and harmonise cooperation between the federal higher authorities

2.6 Confidential rebates

2.6 Introduction of confidential rebates

- Pharmaceutical companies receive the option to agree confidential rebates on medicinal products containing new active ingredients – confidentiality applies until the expiry of data exclusivity

- Pharmaceutical companies are required to notify the payers and eligible administration of the amount of the confidential rebate and to compensate for the difference to the actual sales price paid

- **Goal**: To ensure that the German medicinal products market remains attractive. Currently, the amount of rebate that contracting parties have negotiated for patent-protected medicinal products is publicly accessible. Since rebates serve as an international reference amount, the room to negotiate these amounts may be limited.

2.7 Outlook

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- **National Pharma Strategy**: Federal Ministry of Health to swiftly implement these measures within its remit

- **Medical Research Act**
  - Currently passing through parliament
  - Planned entry into force: autumn 2024, with some parts to enter into force on 1 July 2025
  - Thereafter: Implementation of the measures

II. EU Pharmaceutical Package

EU Pharmaceutical Package – An Overview

COM proposal of 26 April 2023, draft regulation (COM(2023) 193 final) and draft directive (COM(2023) 192 final)

Key Updates:

- **Extension of scope:** The criterion for medicines produced industrially or through industrial processes is being removed to better accommodate advancements in personalised medicine.
- **Regulatory data protection**: Basic data protection period reduced from 8 to 6 years; 2-year extension for products marketed throughout the EU.
- **Vouchers for innovative antimicrobials**: The voucher extends the regulatory data protection period by 1 year and is transferable.
- **Orphan drugs**: Market protection modified for orphan drugs
- **Shortages**: Measures to increase security of supply introduced, including shortage prevention plans and a Union list of critical medicinal products.

EU Pharmaceutical Package – An Overview

Key Updates:

- **Reducing regulatory complexity:** Initial authorisations no longer come with a time limit (= mandatory market authorisation renewals abolished); mandatory electronic approval procedure; fewer scientific committees
- **Electronic product information:** Member States are to decide whether product information will be supplied in paper format, electronically or in both forms
- **Environmental risk assessment (ERA) and environmental aspects:** Incomplete assessment of potential environmental risks/insufficient risk mitigation will lead to refusal of approval.
- **Extension of the prescription requirement:** Antimicrobials and medicinal products with environmentally hazardous active substances will require a prescription
- **Regulatory sandbox:** A legal framework enabling innovative technologies to be tested in a real-life environment under regulatory supervision

Scope Extended

(Art. 1 of the draft directive)

- Currently, EU pharmaceutical legislation applies only to medicines produced **industrially or through industrial processes**.
- This criterion is now being removed to better incorporate advancements in personalised medicine.
- This would eliminate the **in-pharmacy production** option:
  - Medicines made by pharmacies in advance, in quantities of up to one hundred ready-to-dispense packs per day within normal pharmacy operations, do not require authorisation (extemporaneous medicinal products, as per section 21(2)(1) of the German Medicinal Products Act (AMG)).
  - The ECJ has ruled that the directive does not apply to the production of quantities below this threshold because it does not constitute "commercial" or "industrial" production (C-276/15)

Data and Market Protection

(Art. 80 ff of the Draft Directive)

- The **8+2+1 rule** currently applies: Eight-year data protection, two-year market protection; market protection extended if new indications are added

- COM proposes: Reduce data protection to **six years;** market protection stays as it is.

  → Options to extend the data protection period:

  a) Six months for medicinal products that address an unmet medical need
  b) Two years if the medicinal product is placed on the market in sufficient quantities in all member states within two years
  c) Six months if comparative studies are submitted
  d) One year if a new indication is added

- Total achievable protection period: 12 years

- Aim: All member states have equal access to new medicines

Vouchers for Innovative Medicinal Products

(Art. 40 ff. of the Draft Regulation)

- COM plans to issue up to 10 transferable data protection vouchers in 15 years for priority antimicrobials

- Priority antimicrobials must demonstrate significant clinical benefit and meet certain innovation criteria.

- The voucher extends the data protection of a new medicinal product by one year and can be sold to another company which may use the voucher for its own medicinal products

Differentiated Incentives for Orphan Drugs

(Art. 63 ff of the Draft Regulation)

- Currently: 10 years of market protection for all orphan drugs
- COM proposes:
  - Ten years for high unmet medical need
  - Five years for well-established use orphan products and
  - Nine years for all other orphan drugs

- The new criterion "high unmet medical need" is based, among other things, on significant reduction of disease or mortality rates in the targeted segment of the population.
- EMA is to draw up more specific criteria.
- If the medicinal product receives a new orphan indication at least two years before market protection expires, the market protection period will be extended for an additional year (not more than twice).

Shortages

(Art. 116 ff. of the Draft Regulation)

- COM wants to counteract shortages by extending companies' reporting obligations and introducing an EU list of critical medicines.

- Marketing authorisation holders are required to draft a shortage prevention plan and proactively announce any anticipated shortages. A shortage mitigation plan can be requested if there is a risk of a shortage.

- A Union list of critical medicinal products (= medicinal products whose non-availability poses a risk of serious harm to patients) will be created on the basis of a common methodology defined by the EMA (already published in December 2023). Member states and marketing authorisation holders are subject to information and disclosure obligations with regard to the medicinal products listed there.

- COM will be empowered to issue implementing acts to increase security of supply (including quotas) directed mainly at marketing authorisation holders and wholesalers.

Reducing Regulatory Complexity

- The standard assessment period for regulatory review of marketing authorisation applications in the procedure will be reduced from 210 days to 180 days
- A time-limit will no longer be imposed on initial authorisations (= mandatory market authorisation renewals abolished - some exceptions apply).
- Mandatory electronic marketing authorisation procedure.
- Number of EMA committees for medicinal products for human use reduced from seven to two.
- EU member states can determine whether patient information needs to be provided on paper, electronically, or both ways.

Electronic Package Leaflet

(Art. 63 of the Draft Directive)

- Member States can choose whether package leaflets need to be provided electronically, on paper, or both ways
- Patients can request a printed version free of charge (to be made law by member states)
- 6½ years after the directive becomes effective, COM can make electronic package leaflets mandatory by means of a delegated act (including the right to a printed version)
- COM sets standards for electronic package leaflets by issuing implementing acts
- The technologies used to access electronic package leaflets must protect user anonymity

Environmental risk assessment and environmental aspects (Art. 47 of the draft directive; Art. 15 of the draft regulation)

- Incomplete assessment of potential risks to the environment or public health, including antibiotic resistance, or insufficient risk minimisation may lead to refusal of marketing authorisation.
- ERA will be extended to include environmental hazards in the manufacture of antibiotics.
- EMA will present an environmental risk assessment program for medicinal products approved before October 2005 and classified as potentially harmful to the environment.
- Monograph system detailing the environmental properties of known active substances.

Prescription status

(Art. 50 ff. of the draft directive)

- Antimicrobials and environmentally hazardous medicines will be available by prescription only
- "**Antimicrobial**" is defined as "any medicinal product with a direct action on micro-organisms used for treatment or prevention of infections or infectious diseases, including antibiotics, antivirals and antifungals" (Art. 4(22) of the draft directive)

  → Extension of the prescription requirement to all antimicrobial drugs would also include antiseptics, antifungals and antivirals that are currently approved for over-the-counter self-treatment

- **Environmental criterion**: "A medicinal product shall be subject to medical prescription [...] for which medical prescription is required as risk minimisation measure with regard to the environment, unless the use of the medicinal product and patient safety require otherwise."

→ System change; previously, prescription status was based solely on health aspects

Regulatory sandbox

(Art. 113, draft regulation)

- Definition: a limited legal framework enabling the testing of innovative technologies in a real-life environment under regulatory supervision to facilitate the development and approval of innovative products.
- Purpose: allows companies to accelerate R&D; authorities can gain insights into new developments at an early stage and respond accordingly
- Conditions:
    1. The medicinal product cannot be developed in the current regulatory environment because of specific characteristics
    2. These characteristics significantly contribute to the expected quality, safety and efficacy
- Process:
    - EMA conducts horizon scanning and suggests the establishment of a sandbox to COM
    - EMA drafts a sandbox plan; COM issues a temporary implementing act
    - National authorities oversee the sandbox and can halt its use at any time

Process Status

Council Working Groups:

- Extensive discussions under the Belgian EU Council Presidency on supply shortages, incentives and marketing authorisations (over 20 meetings); the Hungarian Presidency plans a similar number of meetings

European Parliament:

- Draft reports by Tiemo Wölken (S&D) on the draft regulation and Pernille Weiss (EPP) on the draft directive from October 2023
- Compromise texts adopted by the ENVI Committee on 19 March 2024; position approved by the plenary on 10 April 2024
- Material discontinuity principle *does not* apply at EU level

Due to the scope and complexity, negotiations are expected to take several years

European Parliament's position – Highlights

Data protection and EU marketing:

Basic data protection duration: **7.5 years**

- 12-month extension: for medicinal products addressing an unmet medical need
- 6-month extension: for comparative trials
- 6-month extension: if a substantial part of the R&D takes place in the EU and with the collaboration (at least in part) of EU research institutions

- 2 years of market protection
- 12 months extended *market protection* for new indications

→ Total duration of data protection: limited to **8.5 years**
→ Total duration of data/market protection: limited to **11.5 years**

European Parliament's position – Highlights

Medicinal products for rare diseases (orphan drugs):

- Basic duration of market protection: 9 years
- Medicines addressing a high unmet medical need (HUMN): 11 years (COM: 10), bibliographic approvals: 4 years (COM: 5)

Incentives for antimicrobials:

- Introduction of a "transferable data protection voucher" with specific conditions
- Support for innovative antimicrobials through milestone payments
- Subscription models for joint procurement

Electronic package leaflet:

- Proposal for purely electronic patient information for medicinal products administered directly by healthcare professionals

European Parliament's position – Highlights

Pharmacy manufacturing:
Hospital pharmacies can pre-manufacture medicinal products for one or more patients based on the stability of the medicinal product, exceeding the 7-day supply proposed by COM

Scope of prescription status:
Prescription status limited to antibiotics and antimicrobials with identified antimicrobial resistance risks

Environment:
Greater consideration of environmental impacts in manufacturing, including environmental impact assessment

Thank you for your attention.

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