The EU Pharmaceutical Reform

Awareness session for SMEs
EMA

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#HealthUnion

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Overview

Glossary

- MA – marketing autorisation
- MAA – marketing autorisation application
- ERA – environmental risk assessment
- ASMF – active substance master file
- CP – centralised procedure
- MRP – mutual recognition procedure
- DCP - decentralised procedure
- PhV – pharmacovigilance
- EMA – European Medicines Agency
- PRIME – priority medicinal products
- SoHO – substances of human origin

('SoHO' as defined in the 'SoHO Reg')

- ATMP – advanced therapy medicinal products
- GMO – genetically modified organisms
- CMA – conditional marketing authorization
- comp. use – compassionate use
- TEMA – temporary emergency marketing authorisation
- UMN – unmet medical needs
- HUMN – high unmet medical needs
- HTA – health technology assessment
- P&R – pricing and reimbursement
- PIP – paediatric investigation plan
- PUMA – paediatric-use marketing authorisation
- IPCEI – Important Projects of Common European Interest

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57 years of EU pharmaceuticals regulation

SAFETY – EFFICACY - QUALITY

Thalidomide disaster exemplifies the need for EVIDENCE-BASED AUTHORISATION

1965
1st EC legislation: medicines need to be authorised before being placed on the market

1995
Centralised, EU-wide procedure for authorisation – creation of the EMA

2000
Legislation on medicines for rare diseases

2004
Last major revision – extending scope of centralised procedure, simplification

2006
Legislation on medicines for children

2007
Regulation on advanced therapy medicines

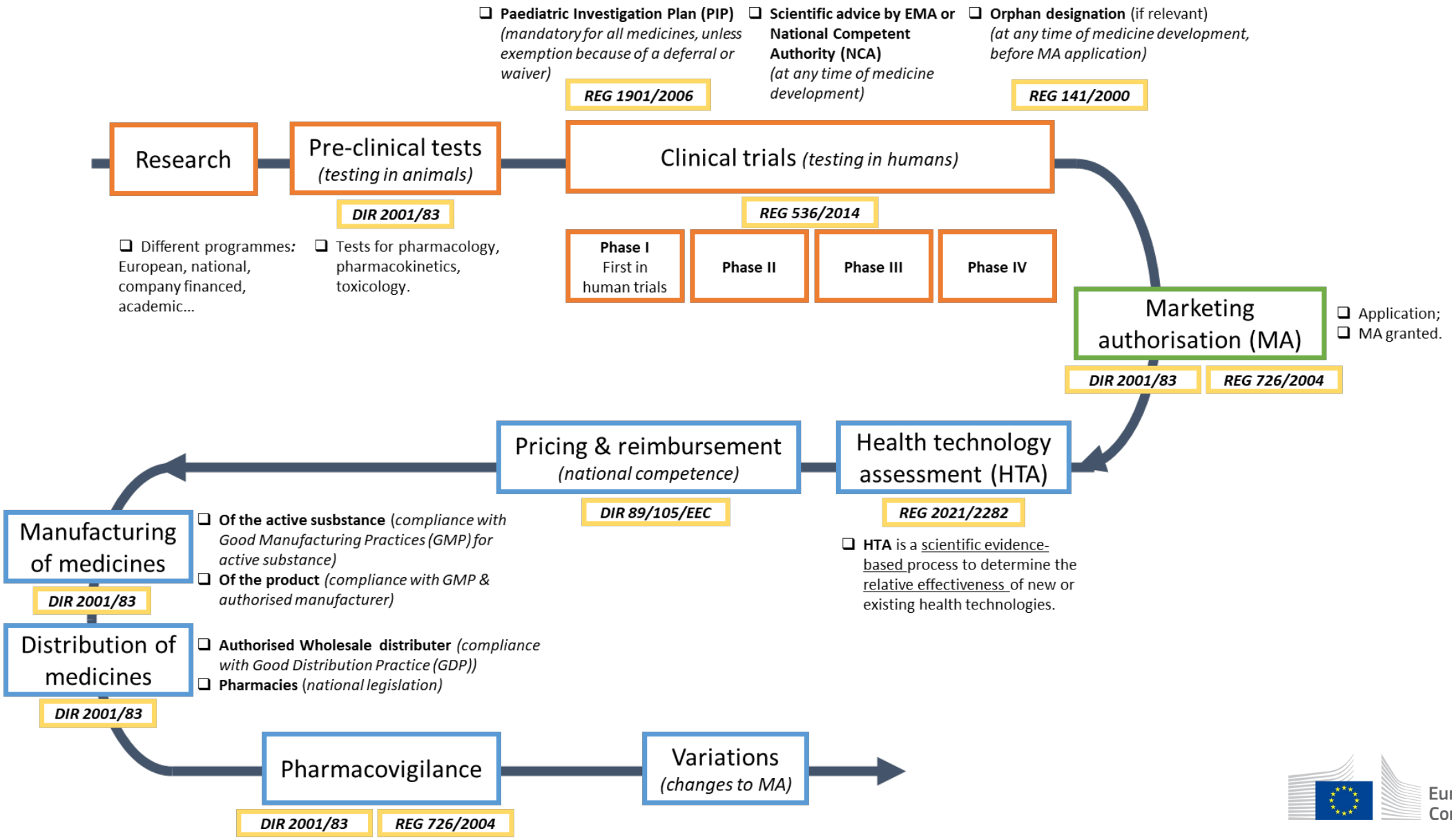
2010
New EU Pharmacovigilance rules: better prevention, detection and assessment of adverse reactions, direct patient reporting of adverse events

2011
Legislation against falsified medicines

2020
Pharmaceutical strategy for Europe: addresses long standing challenges, learnings from COVID-19

2022
Reform of general pharmaceutical acts packaged with revision of the O/P legislation

Lifecycle of a medicinal product



Responsibilities shared between EU and Member States

EU (harmonised) general pharmaceutical legislation

- Centralised authorisation procedure
- Inspections of manufacturing sites
- Pharmacovigilance

Decentralised procedure and mutual recognition procedure to authorise medicines in MS

By EU-level standards

EC and EMA through a network of MS experts and National Competent Authorities

Strictly MS competence outside the scope of the pharmaceutical legislation!

- Organisation and delivery of health services and medical care
- Setting of prices for medicinal products or their inclusion in the scope of national health insurance schemes

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#EUPharmaStrategy

- Adopted in November 2020
- Ambitious long-term agenda in the field of pharmaceutical policy
- Objective: creating a future proof regulatory framework and at supporting industry in promoting research and technologies that actually reach patients in order to fulfil their therapeutic needs

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Impact Assessment

- Commission published two impact assessments supporting the reform:
  - Impact assessment related to changes of the general pharmaceutical legislation
  - Impact assessment related to changes of the orphan/paediatric legislation
- The impacts assessments considered several policy options and include a granular analysis of multiple elements supporting the policy interventions
- The impacts assessments were supported by two independent studies and stakeholder consultations

A 4-part package

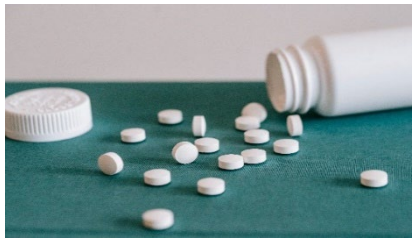
Chapeau communication

New Regulation

- Specific rules for the most innovative medicines such as orphans, antimicrobials
- Rules on shortages and security of supply
- EMA governance

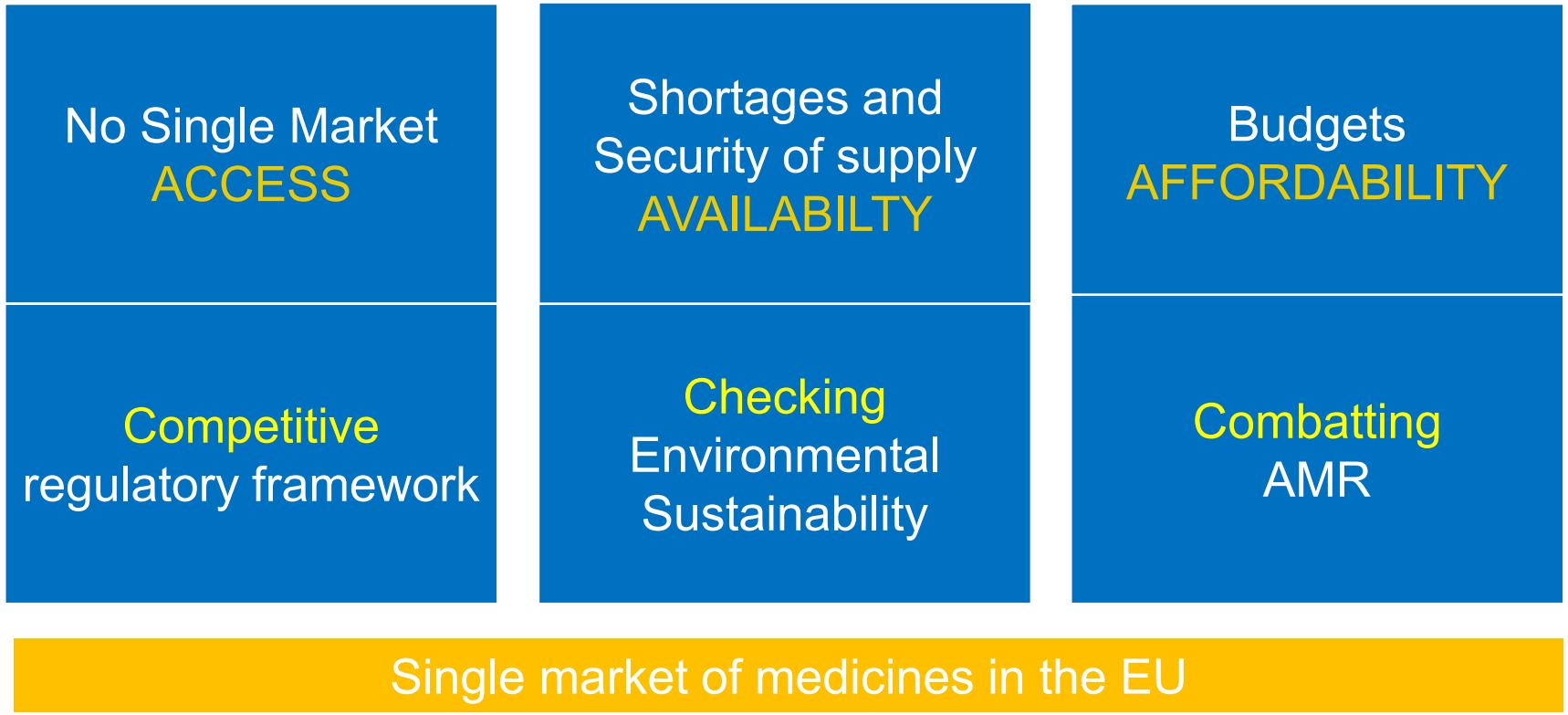
New Directive

- Placing on the market of all medicines
- Authorisation and labelling requirements
- Strong incentives for access



Council Recommendation on AMR

6 Key political objectives



Access to medicines

Current challenges:

Access is not timely and differs across Member States:

90% variance between Northern and Western European countries and Southern and Eastern European countries

Average waiting time across the EU is from 4 months to 29 months

Proposed solutions:

Incentives for innovation and access:

Targeted approach vs current “one-size-fits-all” unconditional data protection and market exclusivity (for orphans)

Earlier market entry of generic and biosimilar medicines

- Faster authorisation
- Pre-authorisation support

Availability – shortages of all MPs and supply

Shortages: Multiple root causes

Quality and manufacturing issues

Commercial reasons, incl. market withdrawals, and unexpected increases in demand

EU dependency on non-EU countries for medicines for supply of certain pharmaceutical ingredients.

Current challenges

Growing concern for **all EU countries**

- **Critical shortages** of medicines; current examples thrombolytics, antibiotics
- Security of supply of **critical medicines**

Ad hoc processes for dealing with **critical shortages**

Proposed solutions

Improved **coordination, monitoring and management** of shortages, in particular critical shortages (MS and EMA); **Earlier** and **harmonised notification** of shortages and withdrawals (industry) (REG Art 116)

Shortage Prevention Plans

Union list of critical medicines

Stronger coordinating role for **EMA &** more powers for **MS** and **Commission**

Outside pharma package

- Other **Commission initiatives**, including the work of **HERA**
- **Joint Action** on shortages
- **IPCEI** in the area of health
- **National measures** e.g. State aid
- **EMA mandate extension** (Regulation (EU) 2022/123)

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Affordability

Current challenges:

- Pricing, reimbursement and procurement of medicines is a **national** competence
- High prices endanger national health systems' sustainability **& restrict patient access**
- Lack of **transparency of public funding** is a growing issue
- Lack **of streamlined coordination** among national authorities

Proposed solutions:

- **Earlier market entry of generics/biosimilars** to increase competition and reduce prices
- Increased **transparency on public contribution** to R&D
- Comparative **Clinical Trials** to support national decisions on pricing
- Further support for **information exchange** between Member States (cooperation on pricing, reimbursement and payment policies)

Streamlined and agile regulatory framework catering for innovation

Current challenge:

Longer approvals times than in other regions
(US 244 days)

Administrative burden and compliance costs for the industry

The clock stop mechanism

Proposed solutions:

Faster autorisation:
a) 180 days standard procedure
b) 150 days accelerated procedure
Regulatory efficiency:
Improved EMA structure, simplified procedures, better use of data and digitisation, regulatory sandboxes

Pre-authorisation support to promising medicines to accelerate development and attract investments

Lower regulatory burden (especially important for SMEs and not-for-profits)

Environmental sustainability

Current challenge:

Pharmaceuticals in environment can **harm environment and human health**

Presence of antimicrobials in the environment exacerbates AMR

Weak enforcement of current rules

Proposed solutions:

Better enforcement of the current rules on **Environmental Risk Assessment** (part of the application)

Extending ERA to **medicines already on the market before 2005**

Stricter environmental rules for AMR, also covering manufacturing

Electronic leaflet and **electronic submission** of applications (less use of paper)

Combatting AMR

Current challenge:

AMR causes **35000 deaths per year** in the EU.

It amounts to +/-1.5 bn EUR per year in healthcare costs

By 2050, **10 million deaths globally each year**

Current market failure/ Lack of effective antimicrobials

Lack of market incentives

0,5 bln EUR cost of a new antibiotic

AMR toolbox

Measures on prudent use of antimicrobials – prescription, restricted quantities, education etc.

Regulatory incentives with transferable exclusivity vouchers under strict conditions

Financial incentives with **procurement mechanisms** (HERA)

5 Targets, incl on the total **EU consumption of antibiotics for humans** (ECDC) → reduction by 20% by 2030

(Council Recommendation)

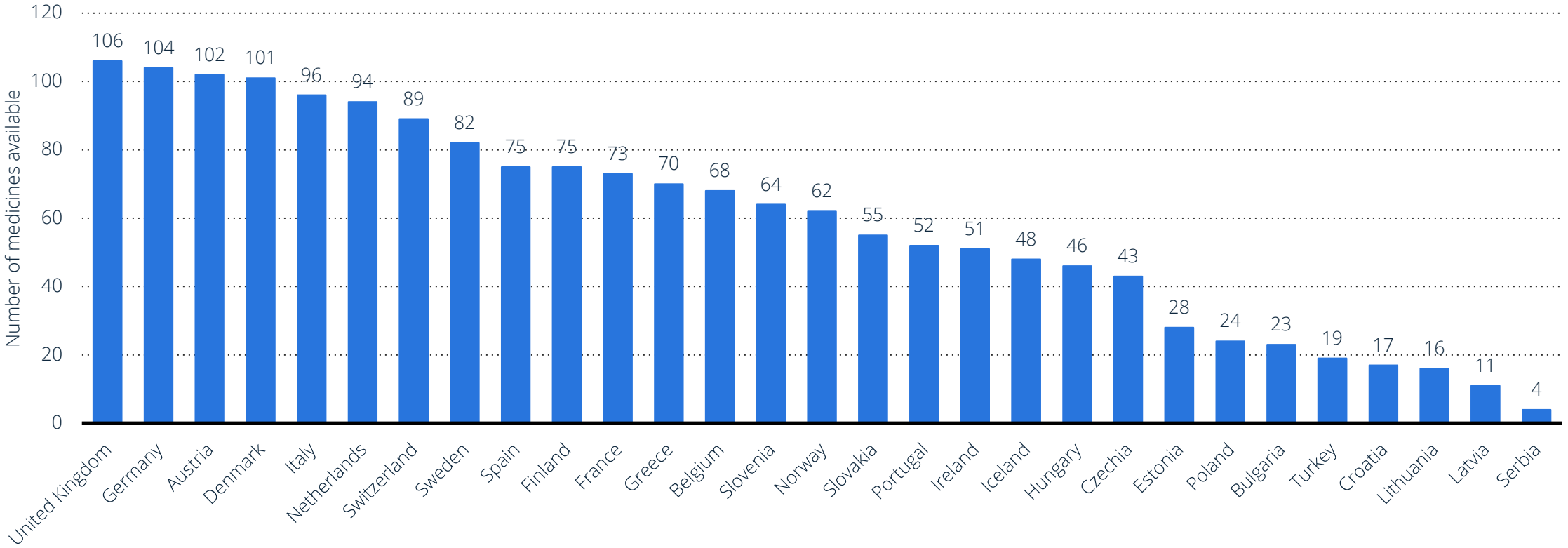
AMR voucher

- Additional year of data protection
- Strict conditions (only novel antimicrobials, full transparency of all funding, obligation of supply, max 10 vouchers in 15 years, review after 15 years, etc.)

Access

Access to medicines

Number of medicines approved by the EMA between 2015-17 available to patients in Europe as of 2018, by country



Note(s): Europe; 2017

Further information regarding this statistic can be found on page 8.

Source(s): IQVIA; ID 1011132

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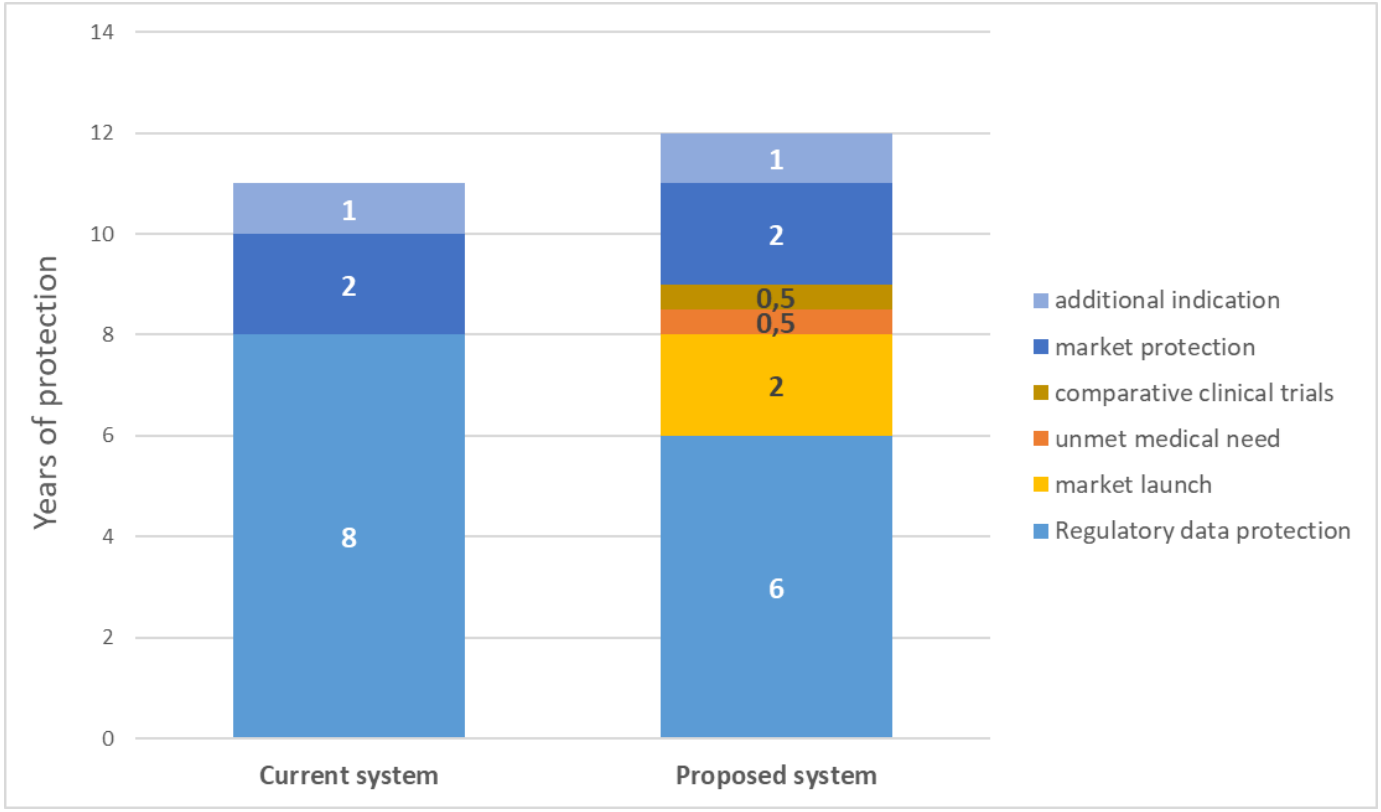
Modulation for the majority of innovative medicines

Regulatory data and market protection today and as proposed



Current system, max 11 years protection

Proposed system, max 12 years protection

Unmet medical needs

All rare diseases-orphan medicines automatically considered UMN

Indication criterion: Therapeutic indication must relate to a *life threatening [*OR] *severely debilitating* condition

Comparison to authorised medicines:

- *No medicine is authorised* in the EU

[OR]

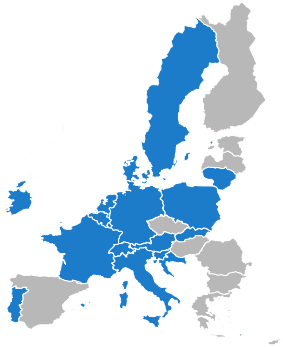
- A medicine *is authorised* in the EU but disease is associated with remaining *high morbidity / mortality*

Effect criterion: Use of the medicine results in *meaningful reduction in disease morbidity / mortality* for the relevant patient population

EMA to set *scientific guidelines* for the application of the article + consultation process of downstream actors and stakeholders (HTA/P&R bodies (possibility to include patients, industry, others).

Market launch conditions

- Launch in all Member States where the marketing authorisation is valid (CP and DCP)

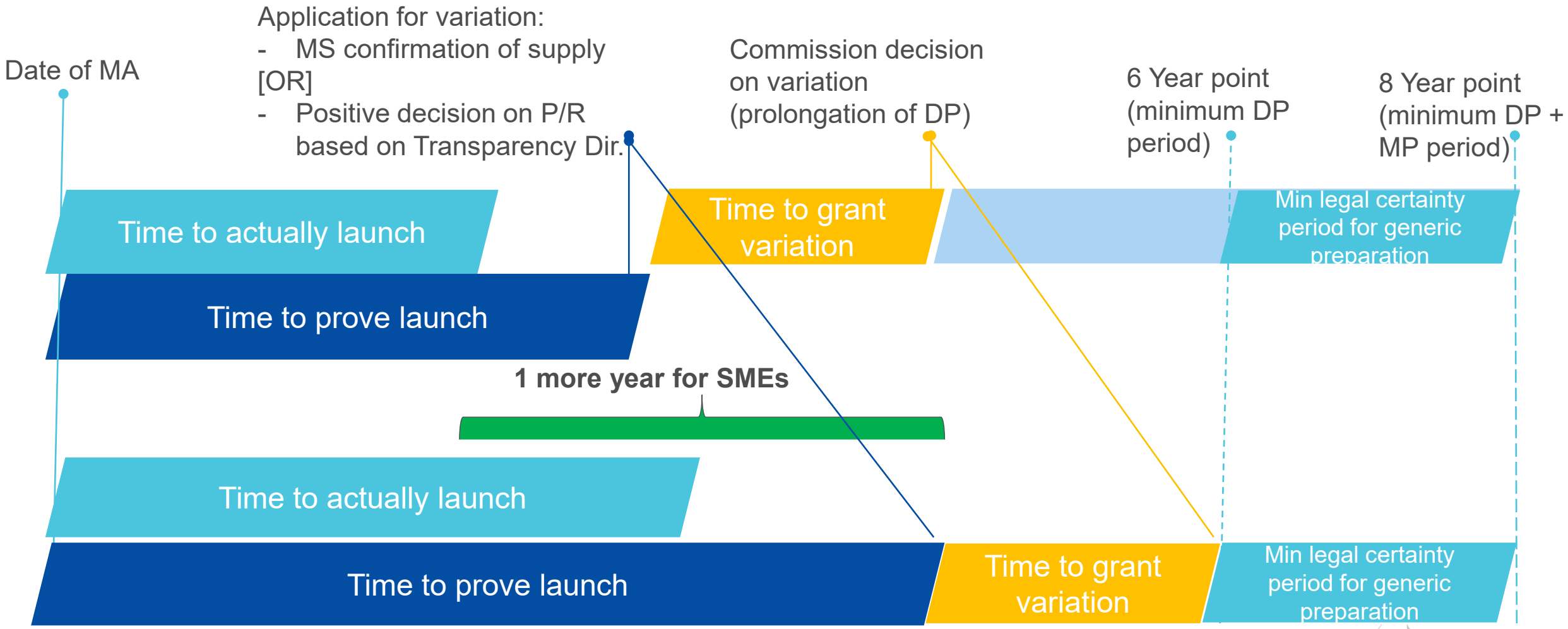


- **Actual placing** on the market and continuous supply for the needs of the patients in each MS (incl. presentations, quantities)
- **MS has 4+1 options**:
  - Positive/negative confirmation of actual supply
  - Waiver
  - Tacit [or]
  - positive pricing and reimbursement decisions (Transparency Directive)

Access

- **Regulatory protection periods and modulation of data protection incentive -** market launch (+24m), unmet medical need (+6m), comparative clinical trials (+6m), additional therapeutic indication (+1yr) (DIR Art 81)
- **Market launch incentive modalities -** Incentive given if product launched in all MS covered by the marketing authorisation (*not necessarily in all 27* in cases of decentralised applications) (DIR Art 82)
- **Unmet Medical Need** criterion based on defined criteria
- **Repurposing incentive:** +4 years DP with respect to additional indication not authorised in Union, off-patent or innovative medicines (DIR Art 84)
- **Broadened BOLAR exemption:** Exemption to cover HTA and P&R activities in addition to studies/trials conducted for a MA (DIR Art 85)
- EMA **consultation process with downstream actors** and stakeholders

ML Decision mechanism



Impact Assessment

Modulation of incentives	Cost/benefit for **public payer and patients**	Cost/benefit for **originators**	Cost/benefit for **generic industry**
2 year conditional protection for **all EU launch in 2 years**	€444 m gain +15% access	-€469m gross profit (5 non-complying MP)	+€63m gross profit
+6 months extension of RP for medicines addressing **UMN**	+ €123m cost + 1 new UMN addressing medicine	+ €141m gross profit (3 incentives)	- €20m gross profit
+6 months extension of RP for conducting **comparative clinical trials**	+ €328m cost + faster access and cost saving thanks to improved reimbursement decisions	+ €378m gross profit +€280m cost (8 medicines)	- €52m gross profit
Total balance	**+ €7m cost** + 1 new UMN medicine +comparative clinical data +15% access	**- €230m gross profit**	**- €9m gross profit**

Simplification measures will bring annually
up to **€204m** savings for authorities and up to **€70m** savings for companies

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Availability

Shortages of all medicines (1)

- Obligation on **MAHs and wholesalers** to ensure **appropriate and continued supplies** (DIR Art 56 and 167)
- **Shortage prevention plans** for **all medicines** (REG Art 117) and **Shortage mitigation plans** for shortages (REG Art 119, Annex IV)
- **Notification of market cessations (decision), withdrawals, suspensions and shortages** (temporary disruptions) (REG Art 116, Annex IV)
- **Shortage monitoring** by both NCAs and EMA based on MAH notifications REG Art 118 (all shortages), Art 124 (critical shortages)
- **MSSG list of critical shortages and recommendations** (REG Art 123)
- **MAH obligations to provide information, based on MSSG recommendations, comply with national and Union level measures and report on measures taken** (REG Art 118, 125, Annex IV)
- **Commission role** in implementing measures, taking MSSG recommendations into account (REG, Art 126)

Shortages of all medicines (2)

- Possibility for **wholesale distributors and other actors to report shortages** can provide any information on shortages requested by NCAs or EMA (REG Art 120)
- **NCA requests for information and information sharing with EMA** and **SPOC working party activities** to allow for **improved coordination and management of critical shortages** (REG Art 121)
- **EMA requests for information, collaboration with SPOC working party and reporting to MSSG and the Commission** to allow for improved coordination and management of critical shortages (REG Art 122,124)
- EMA establishment of **criteria** to adopt and review **critical shortages list**, **specification of tools, methods and criteria** to be used in **monitoring and reporting of critical shortages** and methods for MSSG recommendations and development of guidance on risk assessments (REG Art 122)
- **Publication** of shortages by NCAs and EMA (REG, Art 121,124)

Security of supply of critical medicines

- MS (national competent authority) identification of critical medicines at national level and MS, EMA and Commission preparation for **Union list of Critical Medicinal Products** (REG Art 127)
- **MAHs and other actors** shall **submit information** on critical MPs (REG Art 129,131)
- **MSSG recommendations** on appropriate security of supply measures to MAHs, the Member States, the Commission or other entities (REG Art 132)
- Responsibility of **MAHs** to **take MSSG recommendations into account, comply with measures taken at EU or national level** and **report on measures** they have taken (REG Art 133)
- Role of the Commission, including a provision on **Commission** adoption of an **implementing act to improve security of supply of certain medicines on the Union list of Critical Medicinal Products,** directed towards on MAHs, wholesale distributors or other relevant entities (REG Art 134)

Affordability

Measures to support generics and biosimilars

- **Earlier access** to the market (DIR Art 81)
- **Broaden and harmonise the Bolar exemption** (DIR Art 85)
- **Risk management plan** is not required for generics (DIR Art 21)
- **Active substance master file –** harmonised EU assessment (DIR Art 25)
- Facilitate **the repurposing of off-patent medicines** (DIR Art 84)
- **Simplification** of procedures for all medicines (higher impact on generics and biosimilars): e-PL (DIR Art 63), abolish renewal and sunset clause
- **Recognition of interchangeability of biosimilars** with their biologic counterparts in recitals promotes uptake of biosimilars (DIR Rec 27).

Comparative clinical trials

Additional 6 months of data protection for medicines containing a **new active substance** if the pivotal clinical trials submitted use a **relevant comparator**
(DIR Art 81)

Objectives:

- Support early engagement with EMA on scientific advice (parallel scientific advice)
- Helps to align the design of CTs between regulators and HTA bodies
- Incentivise the compliance with scientific advice
- Provide meaningful clinical trial data to HTA and pricing authorities
- Avoid duplications of clinical trials

Transparency on public funding

Scope (DIR Art 57)

- All direct financial support provided by any **public authority or publicly funded body**
- Received for the **R&D** of the medicinal product
- Irrespective of the legal entity that received that support

Procedure (DIR Art 57, REG Art 138)

- **Electronic report by MAH** listing the amount, date, source & receiving entity
- **Audited** by independent external auditor
- Accessible on **MAH webpage**
- Link shared with EMA/NCA, **published in Union database for medicines for human use**
- Yearly update, as necessary
- **Harmonised** reporting (template → implementing act).

Competitive regulatory framework

Marketing authorisations

Incentivizing innovation by regulatory simplification

- Reduction of assessment and **approval time** from 277 days to 226 days (DIR Art 30, REG Art 6,12,13)
- **Optimising EMA's structure and simplifying regulatory procedures** (REG Cpt XI Sec 2)
- Possibility for regulators to reject **immature applications** to limit clock stops that delay the decision (DIR Art 29(3), REG Art 10(2))
- Strengthening the **early regulatory support** by EMA, part. for promising medicines under development for unmet medical needs (PRIME) (REG, Art 60)
- **Parallel scientific advice** and **advice involving consultations** (REG Art 58 and 59))
- Scientific **recommendation on regulatory status** (REG Art 61, 62)
- **Support for SMEs and non-for-profit entities** (regulatory, procedural and administrative support and reduction, deferral or waivers of fees)

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Incentivizing innovation by regulatory simplification

- Facilitate use of **real-world evidence**, and of **health data** for regulatory purposes (REG Art 6(1), Art. 166+169)
- Simplifying requirements for authorising **generic and biosimilar medicines**
- Promote **use of new methodologies to reduce animal testing** (DIR Art 6 and 44, REG Art 6(5),8,12(4)(m),138)
- Possibility for EMA to review **data in phases**, as they become available (rolling or phased review) (REG Art 6(2))
- **Active substance master file** to avoid duplication of assessment of chemical active substances (and additional quality master file) (DIR Art 25)
- **Pharmacovigilance Risk management plan** not required for off patent medicines (DIR Art 21)
- **Abolishing marketing authorisation renewals** in most cases

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Incentivizing innovation by regulatory simplification

- **Electronic submission** of applications (DIR Art 6, REG Art 5(3),6(1))
- **Facilitate the use of electronic product information and multi-language packages** (Dir Ch. VI)
- **Facilitation of repurposing** through a mandatory variation on the basis of data submitted from not-for-profit entities for repurposing of authorised medicinal products (REG Art 48)
- **Conditional marketing authorisation to** meet an unmet medical need of patients (REG Art. 19)
- **Accelerated assessment** for medicinal products for human which are of major interest from the point of view of public health **(DIR Art. 6(7))**
- Marketing authorisation in **exceptional circumstances** (REG Art. 18/DIR Art. 45)
- **Decentralized manufacturing** to enable novel technologies where manufacturing steps need to be performed very close to the patient **(e.g. separate** manufacturing authorisation –not required)

Incentivizing innovation by future-proofing

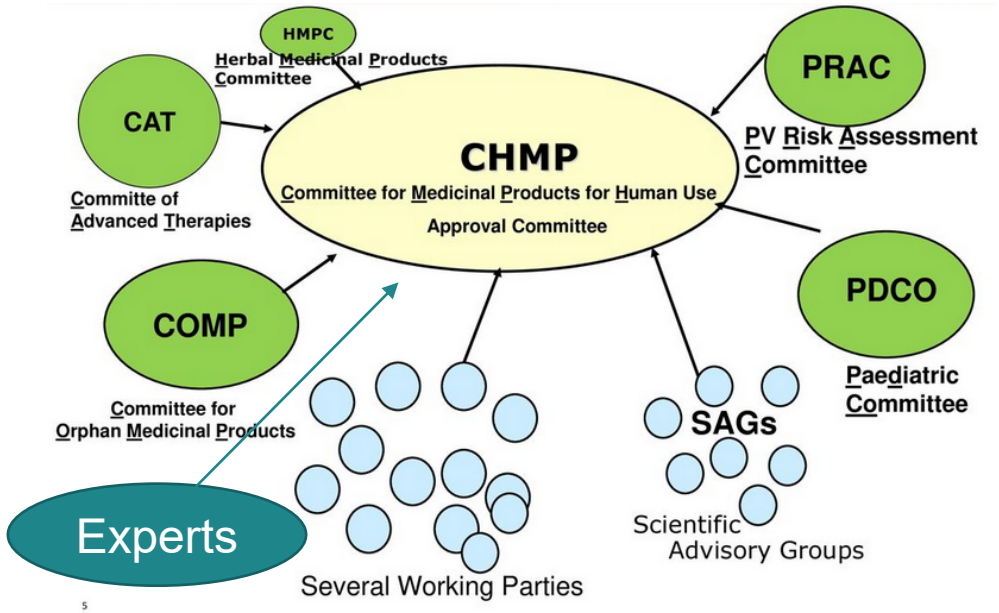
- **Regulatory sandboxes to test new and innovative therapies (**REG Art. 113-115)
- **Adapted frameworks** with specific regulatory requirements tailored to the characteristics of certain novel medicines (DIR Art 28)
- **Improved clarity on the interplay** between EU legislative frameworks for **medicines** and **other health technologies** (e.g. medical devices, substances of human origin) (DIR Art 19,20, 21 and 56(5))
- Introduction of possibility for a scientific recommendation/decision on **regulatory status** of a product under development (REG Art. 61 and 62)
- **Recognising platform technologies** i.e. adjustments to the medicine are made based on the characteristics of the patient or the causing pathogen (DIR Art 15(2))

Learnings from the crisis – Temporary Emergency Marketing Autorisation (TEMA)

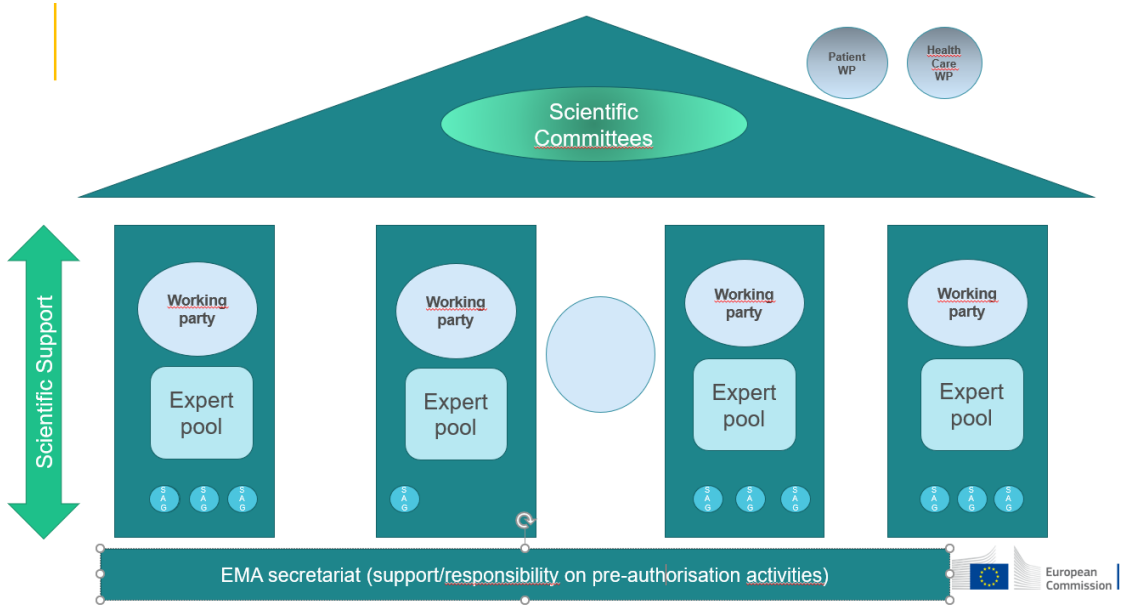
- New type of autorisation during public health emergency (REG Art. 30) - Temporary emergency MA
- Based on scientific opinion of CHMP following recommendation of ETF
- Subject to specific conditions, including batch related
- Granted through a Commission Decision
- Validity linked to duration of public health emergency
- Increased possibilities to vary, suspend or revoke
- May be switched to a CMA or a full marketing authorisation

EMA structure – today and tomorrow

Today



Tomorrow



Principles maintained in the future structure	
Full MS representation in EMA committees	Maintained
Rapporteurship	Maintained (no impact on fees)

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Simplification of DCP&MRP procedures

- Duration of procedure is 180 days (shortened deadline for agreement → 60 days, deadline for evaluation remains) (DIR Art 30)
- Applicant shall inform **all** MSs of its application, MS that are not Member State Concerned, may request to enter ('opt-in') the procedure **on public health grounds** (DIR Art 33(3), 36(4))
- **Simplification** of 'repeat use procedure' → if MSs do not request the update of assessment report, RMS shall provide the AR within 30 days (instead of 90 updated AR) (DIR Art 36(5))
- If the application dossier is not of sufficient quality or maturity for the completion of the examination, it can be terminated within 90 days (DIR Art 34(4)).

Competitive regulatory framework

Supervision, controls and inspections

Reasons to propose these measures (DIR)

SYSTEM OF SUPERVISION AND INSPECTIONS

- System of supervision
  - Built a more efficient and resilient supervision of the sites
  - Improved surveillance capacity through a more efficient and flexible use of inspection resources
  - Lesson learned from the Covid-19 crisis : the asset of remote inspections, reliance, compliance control measures
- **Frequency of inspections at different premises or activities**
  - Ensure a better surveillance based on a risk assessment
  - Apply the same supervision frequency to equivalent sites in the EU or in third countries, based on risk
  - Allow the inspections of specific products and activities whenever there is a public health concern

COOPERATION ON INSPECTIONS

- Better use of resources and creation of synergies between Member States
- Sharing of best practice and fostering exchanges of experience and expertise within the Network
- Allowing more flexibility MS to conduct/delegate an inspection depending on the circumstances.

System of supervision (1)

- NCAs to put in place a system of supervision (SoS) including announced/unannounced on-site inspections, remote inspections, compliance control measures and the effective follow-up (DIR Art 188(1))
- NCAs and EMA to exchange info on the on-site inspections and remote inspections (DIR Art 188(2))
- NCAs to ensure that measures included in the SoS are carried out at an appropriate frequency based on risk; and at premises or activities of certain entities (DIR Art 188(3))
- What to take in account to determine the appropriate frequency based on risk (DIR Art 188(4))
- Under which conditions and at the premises or activities of which entities the measures included in the SoS can be carried out (DIR Art 188(5)).

System of supervision (2)

- Possibility for the Agency to request that activities associated with the SoS are carried out (DIR Art 188(6))
- NCAs to empower its official representatives to carry out certain activities (DIR Art 188(7))
- NCAs to ensure that on-site inspections and remote inspections are carried out in compliance with principles developed by the Commission (DIR Art 188(8))
- How to carry out and conclude inspections and issue inspection report (DIR Art 188(8)-188(11))
- **NCAs - require a manufacturer of a medicinal product or of an active substance established in a third country to submit to an inspection** (DIR Art 188(12))
- NCAs to issue a certificate of compliance or a statement of non-compliance and to enter it in the relevant Union database (DIR Art 188(13)-188(16))
- Pharmacovigilance inspections (DIR Art 188(17)).

Cooperation on Inspections & Inspections guidelines

- NCAs and Agency, under certain conditions, to jointly carry out measures included in the SoS at the premises or activities of certain entities (DIR Art 188(3)-188(5)) (**joint inspections**, DIR Art 189(1)-189(5))
- NCAs, under certain conditions, possibility to request another NCA or the Agency to carry out measures included in the SoS at the premises activities of certain entities (DIR Art 188(3)-188(5), 189(6)-189(8))
- Commission to lay down **principles applicable to SoS**, **joint inspections**, **exchange of information** and **trusted non-EU regulatory authorities** (DIR Art 190(1))
- Commission to establish the form and content of: manufacturing authorisation, wholesale distribution authorisation, compliance report, certificate of compliance (DIR Art 190(2)).

Reasons to propose these measures (REG)

- **Inspection Capacity of the Agency**

Supporting the inspectors' network by adding inspector capacity and capability

  - Improving the resilience of the network and reducing the backlog of inspections
  - Avoiding the MA to be delayed and support of the network in emergency situations, and when specific capacity and expertise is required

- **International Inspections**
  - Foster international cooperation for an optimised supervision of sites which supply globally
  - Save inspectors resources and create trust with international partners by inspecting together
  - Share good practice and expertise with strategic partners

- **Joint Audit Programme**
  - Continuously improve the quality system of the inspectorates
  - Ensure harmonised inspections standards and a harmonised interpretation of GMDP based on EU legislative requirements to support mutual recognition of inspection outcomes across the EU
  - To contribute to the development of a world-class GMP medicines regulatory system based on a network of agencies operating to best practice standards.

Inspection capacity of the Agency

- Participation in inspections or carrying out of **inspections in third countries** by the Agency at the request of an NCA (REG Art 52(1))
- **Decision making** of the Agency following a request from an NCA (REG Art 52(2)-52(5), Annex III))
- Setting up and requisites of the inspection capacity of the Agency (REG Art 52(6))

- **International inspections**

- Agency to coordinate a structured cooperation on inspections in third countries between MSs, the EDQM, WHO and trusted international authorities, by means of **international inspection programmes** (REG Art 53(1))
- Agency to adopt **guidelines** laying down **principles applicable to international inspection programmes** (REG Art 53(2)).

Joint Audit Programme

- The inspection working group of the Agency to establish, develop and supervise the **joint audit programme** (JAP) (REG Art 54(1))
- Requisite for participation of the Member States in the JAP (REG Art 54(2))
- The JAP is an integral part of the quality system of the inspectorates (REG Art 54(3))
- Audit reports and follow-up actions of audits (REG Art 54(4))
- Role of the Agency in the JAP (REG Art 54(5)-54(6))
- Financing of the JAP (REG Art 54(7))
- Establishing the inspection working group (REG Art 142(k)).

Competitive regulatory framework

Manufacturing

MANUFACTURING AND IMPORT OF MEDICINAL PRODUCTS	MANUFACTURING, IMPORT AND DISTRIBUTION OF ACTIVE SUBSTANCES
▪ adapt the legislation to the advent of new therapeutic approaches that have features such as very short shelf-lives and which may be highly personalised and innovative new manufacturing modes and technologies	▪ no major changes made
▪ recognise the need for manufacturing steps to be performed in decentralised locations as close to the patient as appropriate for the quality of the product as well as for the safety of the patients.	▪ manufacturers, importers, and distributors of active substances, registration and requisites (DIR Art 156-159)
▪ adapt the legislation with regards to the responsibilities of the manufacturing authorisation, the duties of the Qualified Person responsible for oversight of the remote site(s) and the request for a registration of the decentralised site.	

PRINCIPLES OF GOOD MANUFACTURING AND GOOD DISTRIBUTION PRACTICES	WHOLESALE DISTRIBUTION AND BROKERING OF MEDICINAL PRODUCTS
▪ no major changes made except the implementing act to be in line with the veterinary legislation and give the same legal status to the veterinary and the human GMDP guidelines.	▪ Adding in the obligations of the wholesale distribution authorisation holder that they can obtain and supply, including by financial transaction, medicinal products only from and to persons who are themselves wholesale distribution authorisation holders. This is necessary to strengthen the legal supply chain by avoiding financial transaction resulting in medicinal products being the propriety of non-authorized entities located in third countries
▪ Rules applicable to medicinal products, active substances and excipients (DIR Art 160-161).	▪ Obligations of the wholesale distribution authorisation holder (Dir, A166) - in particular letter (l)

Relevant measures

Manufacturing and import of medicinal products

- Requisite of manufacturing authorisations for sites manufacturing medicinal products in the EU/EEA **with the exception of decentralised sites** (DIR Art 142)
- Requirements, granting and changes to manufacturing authorisation (DIR Art 143 –146)
- Obligations of the manufacturing authorisation holder (DIR Art 147)
- **Registration and listing process of decentralised sites** (DIR Art 148)
- Conditions related to the safety feature and falsified medicinal products (DIR Art 149-150)
- Availability, qualification, responsibilities and professional code of conduct of qualified person (DIR Art 151-154, Annex III) + obligation for the qualified person of manufacturing sites to be resident in the EU.
- Certificate for export of a medicinal product (DIR Art 155).

Environmental sustainability

Strengthening the ERA in the MA procedure

Include a stand-alone ground of refusal if ERA does not sufficiently substantiate + address risks to the environm. and public health (AMR)

(DIR Art 47, REG Art 15)

Add the risk for AMR selection in the environment due to the manufacturing, use and disposal of antimicrobials into the protection goals of ERA (DIR Art 4(33)

Compliance with EMA scientific guidelines on ERA becomes mandatory

(DIR Art 22)

Update ERA in light of new information (DIR Art 22)

Obligation to conduct post-authorisation ERA studies at the time of MA and after authorisation

(DIR Art 44, 87, REG Art 20)

Grounds for suspension, variation, revocation of MA +prohibition of the supply of medicines in case of environmental concerns

(DIR Art 195, 196)

Relevant measures (1)

- Definition of environmental risk assessment (ERA) for MPs (use and disposal) and for MPs with an antimicrobial mode of action (manufacturing, use and disposal) (DIR Art 4(33))
- Applicant to prepare the ERA + **ERA requirements** (incl. compliance with scientific guidelines) (DIR Art 22(1)-22(4))
- **Agency to draw up scientific guidelines to specify technical details regarding the ERA requirements** (DIR Art 22(5))
- Applicant to submit the ERA (DIR Art 6(2)), **MAH, if new info, to update the ERA + ERA requirements** (DIR Art 22(6))
- Specific provisions for ERA of generic, hybrid, biosimilar, bio-hybrid medicinal products (DIR Art 22(7))
- National MA subject to conditions → to conduct post-authorisation ERA studies (DIR Art 44)
- MA to be refused if the ERA is incomplete or insufficiently substantiated by the applicant or if the risks identified in the ERA have not been sufficiently addressed by the applicant – NCAs (DIR Art 47) or Agency (REG Art 15).

Relevant measures (2)

- **After granting a marketing authorisation, possibility to impose obligation on the holder to conduct a post-authorisation environmental risk assessment study – NCAs** (DIR Art 87) or Agency (REG Art 20)
- Possibility for Commission to amend ERA requirements (DIR Art 22(1)-22(6),213)
- The European public assessment report to include a summary of ERA studies and their results as submitted by the marketing authorisation holder and the assessment of the ERA (REG Art 16)
- Agency to set up and maintain a register of ERA studies conducted for the purpose of supporting an ERA for medicinal products authorised in the Union, unless such information is made public in the Union by different means (REG Art 104)
- The CHMP may establish an ERA working party and other scientific working parties, as necessary (REG Art 150)
- **Suspending, revoking or varying the terms of marketing authorisations (DIR Art 195)**
- **Prohibition of supply or withdrawal of a medicinal product from the market (DIR Art 196).**

Other measures to address environmental issues

Catching-up procedure for MPs before 30 Oct 2005	Monographs
▪ Agency to establish a programme for ERA of medicinal products authorised before 30 October 2005, that have not been subject to any ERA and that the EMA has identified as potentially harmful to the environment (DIR Art 23(1))	▪ NCAs and Agency to set-up an active substance-based review system of ERA data (ERA monographs) (DIR Art 24(1)-24(4))
▪ Agency to set scientific criteria for the identification of the medicinal products as potentially harmful to the environment and for the prioritisation of their ERA, using a risk-based approach (DIR Art 23(2))	▪ Possibility for Commission to specify the content and format of ERA monographs, the procedures for adopting and updating the ERA monographs, the procedure for submission of information, studies and data, the risk-based prioritisation criteria, the use of ERA monographs in the context of new MAA (DIR Art 24(5)).
▪ MAH to submit the ERA of medicinal products identified in the programme (DIR Art 23(3)-23(4))	

GMO authorisation in the context of authorisation of CT

- **Alignment of ERA** requirements in the context of marketing authorisation of medicines and authorisation of clinical trials (REG Art 177)
- **Transfer of the ERA requirements for the GMO-IMP assessment from the GMO framework into the pharma framework** (REG Art 177)
- Transfer of the competence for ERA evaluation from national GMO authorities to CHMP➔ **one single GMO application (CTIS) and assessment (CHMP) process in the context of authorisation of clinical trials** (REG Art 177)
- The expertise of national GMO authorities is retained though their involvement in the drafting of ERA scientific guidelines and in the potential dedicated CHMP working party
- **Environmental risk assessment for medicinal products containing or consisting of genetically modified organisms** (REG Art 7)
- **Content** of the environmental risk assessment for medicinal products containing or consisting of genetically modified organisms (REG Art 8)
- **Procedure** for the environmental risk assessment for medicinal products containing or consisting of genetically modified organisms (REG Art 9).

Combat AMR

Description: transferable data exclusivity voucher

- Transferable **regulatory data protection** voucher allows the developer of a novel antimicrobial product that fights AMR to benefit from additional **data protection (+12 months)** on that product, on another product in their portfolio or sell the voucher to another company to use (REG Cpt III)
- **Selling only permitted once** → powerful incentive that may boost development of new antimicrobials
- **Conditions of granting the voucher** → PRIORITY antimicrobial (not cumulative):

− new class
− new mechanism of action (different from any other authorised in EU)
− new active substance that addresses a multi-drug resistant/serious infection
+ priority antimicrobial must present preclinical and clinical data that underpin a significant clinical benefit with respect to AMR
− MAH has a capacity to supply in sufficient quantities for needs of Union market
− transparency of all (private and public) direct funding received for R&D → information to be made public

Conditions of use and transfer, validity

- Can only be used once in relation to a single medicinal product
- Receiving product: Use only in first 4 years of its data protection → 2 years legal certainty/preparation for generics and biosimilars
- Use possible only if priority antimicrobial is **still on the market** (not withdrawn)
- Transfer possible **only once** → obligation to inform EMA (information will be published on EMA website): (1) who the new bearer is and (2) the value of the transaction
- Voucher ceases to be **valid**:
  a) once it is used
  b) if not used within 5 years of granting
- Commission can **revoke** a voucher [prior to its transfer] if a request for supply or procurement of the priority antimicrobial in the EU is not fulfilled
- In case a priority antimicrobial if is **withdrawn** → immediate access to generics and biosimilars
- Measure only available for **15 years from entry into force** of the Regulation **OR** [whichever is earliest] **10 vouchers** available in total.

Prudent use measures

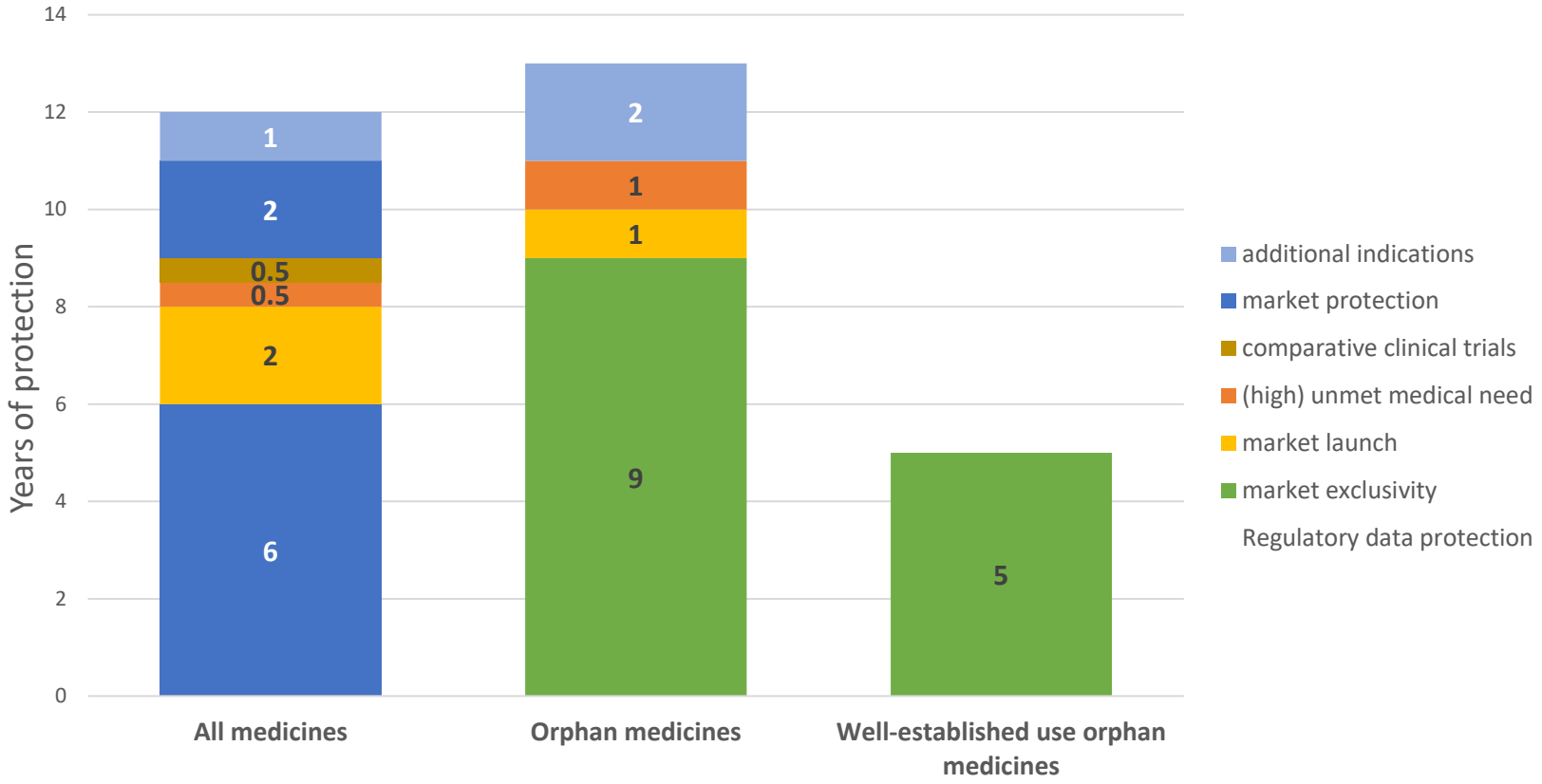
- **Antimicrobial stewardship plan** (risk mitigation measures, monitor and report) (DIR Art 17)
- Special information requirements for antimicrobials (**educational materials** to HCPs, **awareness card**) (DIR Art 69)
- Special **ERA for antimicrobials** (DIR Art 22(4))
- All antimicrobials are subjects to the **medical prescription** (DIR Art 51)
- **Pack size** of the antimicrobial shall correspond to the usual posology and duration of treatment (DIR Art 17)
- **Additional obligations** if the risk mitigation measures contained in the antimicrobial stewardship plan is unsatisfactory (DIR Art 17)

Orphan and paediatric medicines

Modulation of incentives for orphan medicines

Modulation of data protection

Modulation of market exclusivity



List of changes

- Default **market exclusivity** is 9 years (from 10 today)
- MPs addressing **HUMN** get +1 year market exclusivity = 10 years
- Launching in all MS adds +1 year **market exclusivity**
- Well-established use orphan medicines (application based on literature without trials) = 5 years of **market exclusivity** (from 10 today)
- **Data protection (left bar)** applies also to orphans, including modulation, e.g. 6m for comparative clinical trials. However, for market launch orphans benefit from 1 year market exclusivity only.
- To note, well established use products do not benefit from data protection as literature-based applications are not protected by data protection.

max. 12 years protection

max. 13 years protection for orphan medicines

European Commission

High unmet medical needs

only medicines for rare diseases (orphan medicines)

Established use products excluded

Indication criterion: therapeutic indication must relate to a *life threatening [*OR] *chronically debilitating condition –criterion of the definition of the orphan medicinal product*

Comparison to authorised medicines:

- *No medicine is authorised* in the EU

[OR]

- A medicine *is authorised* in the EU but it will bring exceptional therapeutic advancement (more than 'significant benefit')

Effect criterion: Use of the medicine results in *meaningful reduction in disease morbidity / mortality* for the relevant patient population

EMA to set *scientific guidelines* for the application of the article + consultation process of downstream actors and stakeholders (HTA/P&R bodies (possibility to include patients, industry, others).

Orphans – main changes (1)

- **Orphan medicinal products - Chapter IV of REG**
- **Market exclusivity modulation** – *improving access* (REG Art 71 and 72)
- **High unmet medical needs concept** – *innovation* (REG Art 70)
- **Orphans addressing High Unmet Medical Needs** would benefit from 10 year market exclusivity (REG Art 71(2)) and enhanced scientific and regulatory support ((PRIME) REG Art 60(1)(a))
- **Non-accumulation of market exclusivity periods** (for products with the same active substances) – 'global market exclusivity' - and other measures aimed at *faster access of generics* REG Art 71(3),(5),(6)

Orphans – main changes (2)

- **Specific criteria for orphan designation** for scientific reasons by a delegated act when prevalence criterion not appropriate (possibility of **incidence** criterion) - *adjustment to scientific progress* (REG Art 63(2))
- *DELETION:* **No 'insufficient return criterion/ sufficient profitability '** neither as a criterion for designation nor as a reason for reducing the market exclusivity
- **Competence on orphan designation** (and also the Register of designated orphan medicinal products) transferred from the Commission to EMA – *procedural simplification* (REG Art 64 and 67)
- **Validity of orphan designation** – 7 years (or until a MA granted), no validity period in current Orphan Regulation - *procedural simplification* (REG Art 66)
- **Other changes:** distinction between the designated orphan medicinal product and orphan medical products, definitions from implementing acts/guidelines (REG Art 2(2)-2(8))

European Commission

Paediatrics – main changes (1)

- Paediatric provisions **both in Regulation** “Chapter VII” and **in Directive** (Art 4, 6, 48, 49, 59, 60, 86, 94)
- Centralised MA procedure **compulsory for PUMA** medicines, optional for paediatric only MPs (REG Annex 1 & Art 3(2))
- Step-wise PIP, simplified PIP (REG Art 74(2), Art 85(2))
- **Mandatory PIP** on the base of the mechanism of action of a MP (same therapeutic area – REG 75(1))
- **Temporary waiver** from PIP obligation during public health emergencies for medicines relevant for the public health emergency (DIR Art 6(5) & REG Art 83).

Paediatrics – main changes (2)

- Cap to the **length of deferrals** (extendible) (REG Art 75(3))
- EMA responsible for agreeing on PIP, when appropriate CHMP for PIP compliance (REG Art 77, 86 & DIR Art 48)
- **6 months SPC extension** following PIP completion **also for orphan medicines** (DIR Art 86)
- **Increased transparency** on PIP conducted for discontinued medicines - REG Art 88
- Multi-stakeholders discussions about **prioritisation of paediatric R&D** in a pre-competitive environment (REG Art 95)
- Amendment of **Clinical Trials Regulation** to reflect the current timing of publication of summary of results of paediatric CT (6 months after the end of the trial) (REG Art 177)

Measures for SMEs

Special measures for SMEs (1)

- **SMEs and not-for-profit entities** are offered a **support scheme**: regulatory, procedural and administrative support and reduction, deferral or waivers of fees.
- **Scheme covers**: pre-authorisation procedures (and in particular scientific advice), the submission of the marketing authorisation application, and the post-authorisation procedures.
- As regards **regulatory, procedural and administrative support** – to be developed further based on today's system
- As regards **waivers and deferrals** – for SMEs they are laid down in Commission Regulation (EC) No 2049/2005 and [**revised** Council Regulation (EC) No 297/95]

Special measures for SMEs (2)

- **Longer timelines to prove market entry in all Member States for the additional 2 years of regulatory data protection – 3 years** (instead of 2)
- A broad “definition” i.e. SMEs but also companies “unexperienced” with the EU system i.e. not holding more than 5 central MA
  - SMEs within the meaning of Commission Recommendation 2003/361/EC
  - entities not engaged in an economic activity (‘not-for-profit entity’); and
  - undertakings that, by the time of granting of a marketing authorisation, have received not more than five centralised marketing authorisations for the undertaking concerned or, in the case of an undertaking belonging to a group, for the group of which it is part.

Measures with greater impact on SMEs (1)

- SMEs play a fundamental role in the 'EU pharmaceutical ecosystem'
- SMEs involved in the development of medicinal products are **expected to benefit, in particular, from e.g.**:
  - the wider use of **electronic processes** and reduction of administrative burden;
  - **regulatory sandboxes** to support the development of innovative products,
  - **scientific support** from EMA (especially for PRIME),
  - biopharmaceutical SMEs in particular are expected to benefit from the incentives **scheme for unmet medical needs and AMR (vouchers)**
- However, the burden of increased environmental and shortage reporting requirements, as well as the market launch conditionality are likely more challenging for SMEs than big firms (adaptations).

Measures with greater impact on SMEs (2)

- **Regulatory support for promising medicines under development (PRIME)**
  - enhanced scientific and regulatory support,
  - accelerated assessment mechanisms,

  These is for certain medicinal products that, based on preliminary evidence submitted by the developer fulfil the following conditions:

  - are likely to address an **unmet medical need**
  - are **orphan** medicinal products;
  - are expected to be of major interest from the point of view of public health, in particular as regards therapeutic innovation, **or novel** antimicrobials

What next?

Legislative process

- Formal negotiations started after translations were made available
- Technical meetings with Council and EP

European Parliament:

- Rapporteurs: Directive Pernille WEISS (EPP/DK), Regulation Tiemo WÖLKEN •
- Cttes for opinion: BUDG, IMCO, JURI, ITRE, LIBE, CONT, AGRI

Council:

• Preliminary general discussions held on COREPER and EPSCO, SANTE presented package in CWP

• First two WPs on Impact Assessments

• Continuation of WPs on different chapters

Thank you