The revision of the European Pharma Package

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Introduction

A few words before we start

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- I studied chemical technology in the Netherlands.
- I am a global API regulatory specialist leading a small consultancy in the Netherlands. I have 38 years of experience in the API industry, always in the regulatory field. My latest position in industry was with Aspen API in the Netherlands.
- I was for a long time a Board member of APIC (the European API organization) and represented APIC often in meetings and symposia with Health Authorities all around the world (including these events at CPhI Japan in former years)
- I am a trainer for the European Compliance Academy in a large number of API regulatory oriented trainings every year.

Overview

Contents of this presentation

- Background of the revision, some history
- Consequences for the API industry
  - the API certificate
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- Points to consider in Japan

Background of the revision

<u>Why was there a need for change?</u>

The COVID-19 pandemic has, and continues to have, a very serious impact on Europe. Though Europe's response has demonstrated strengths, existing vulnerabilities have been thrown into sharp focus, including those related to data availability, the supply of medicines or the availability of manufacturing capacities to adapt and support the production of medicines.

Background of the revision

In April 2023, the Commission adopted a proposal for a new Directive and a new Regulation, which revise and replace the existing general pharmaceutical legislation.

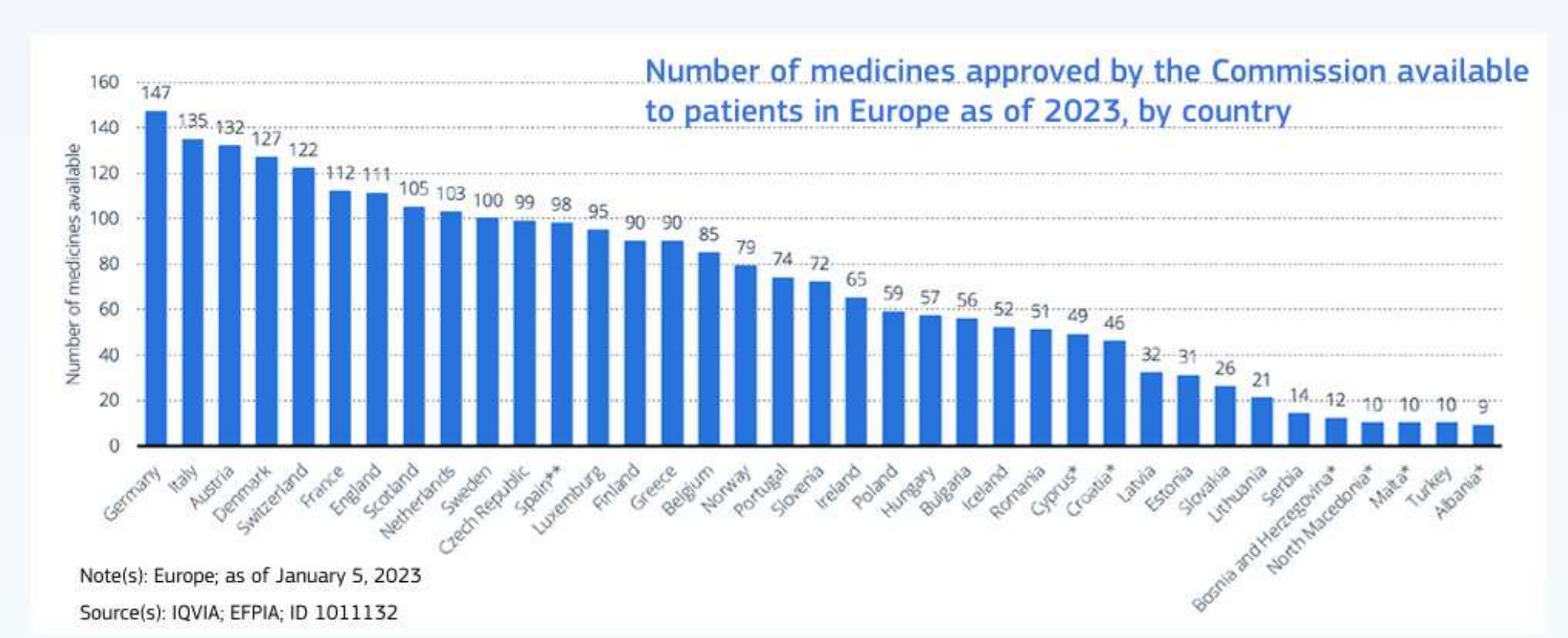
The largest reform in 20 years, putting patients at the center.

Background of the revision

The revision aims to achieve the following main objectives:

- Make sure all patients across the EU have timely and equitable access to safe, effective, and affordable medicines
- Enhance the security of supply and ensure medicines are available to patients, regardless of where they live in the EU
- Continue to offer an attractive and innovation-friendly environment for research, development, and production of medicines in Europe
- Make medicines more environmentally sustainable
- Address antimicrobial resistance (AMR) and the presence of pharmaceuticals in the environment through a One Health approach.

Background of the revision



Background of the revision

<u>Key elements of the proposal</u>

- new incentives will encourage companies to make their medicines available to patients in all EU countries but also to develop products that address unmet medical needs. Furthermore, earlier availability of generic and biosimilar medicines will be facilitated, and market authorization procedures simplified.
- the reform will create an innovation-friendly regulatory environment for the development of new medicines and the repurposing of existing ones. The scientific evaluation and authorization of medicines will be sped up and the regulatory burden will be reduced through simplified procedures (e.g., by introducing simpler procedures for generic medicines).

Background of the revision

Key elements of the proposal (continued)

- Effective incentives for innovation: regulatory protection of up to a maximum of 12 years for innovative medicines, to ensure Europe remains an attractive hub for investment and innovation.
- Addressing shortages of medicines and ensuring security of supply: obligations on companies will be strengthened, including earlier reporting of shortages and withdrawals of medicines and development and maintenance of shortage prevention plans. An EU-wide list of critical medicines will be established, and supply chain vulnerabilities of these medicines will be assessed, with specific recommendations on measures to be taken by companies and other supply chain stakeholders. In addition, the Commission can adopt legally binding measures to strengthen security of supply of specific critical medicines.

Background of the revision

Key elements of the proposal (continued)

- Stronger protection of the environment: better enforcement of current environmental requirements will limit the potential negative consequences of medicines on the environment and public health.
- Tackling antimicrobial resistance (AMR): AMR is considered one of the top three health threats in the EU. The reform offers incentives to companies that invest in novel antimicrobials that can treat resistant pathogens, addressing the current market failure.

Background of the revision

Where do we stand today?

In April 2023, the Commission adopted a proposal for a new Directive and a new Regulation, which revise and replace the existing general pharmaceutical legislation. This reform is currently being negotiated by the European Parliament and Council.

On March 11, 2025 a Regulation to improve the availability of critical medicines in the EU was proposed: the Critical Medicines Act. The proposal aims to protect human health by incentivizing supply chain diversification and boosting pharmaceutical manufacturing in the EU.

Japan is also struggling with this type of issues: a dependency on other regions for APIs and medicinal products.

Consequences for the API industry

The API certificate

One of the concepts mentioned in the proposed new Directive is the so-called API or ASMF-certificate.

Obviously, the API Industry strongly supports the introduction of a centralized procedure for the assessment of European ASMFs. This would take away a lot of the problems with the current ASMF system (mainly repetition of assessments and difficulties when introducing changes).

The API certificate would be used in the same way in Marketing Authorizations as the CEP.

Consequences for the API industry

<u>The API certificate</u>

Such a certificate:

- will allow the active substance manufacturer to take more control over the lifecycle of the active substance
- Reduce the number of variations to be filed by the MAA holder: only for revised ASMF certificate (and it will then be a notification : type IA)
- Prevents blocking of improvements/innovation for active substance by MAA holder
- Reduce number of variations for assessment:
  * Same change only submitted once instead of multiple times (for each MAA holder, using the API from a certain supplier)
- Increased oversight for HA's over ASMF

Consequences for the API industry

The new variations guideline

Another consequence of the revised Directive is the publication of a new guideline on variations.

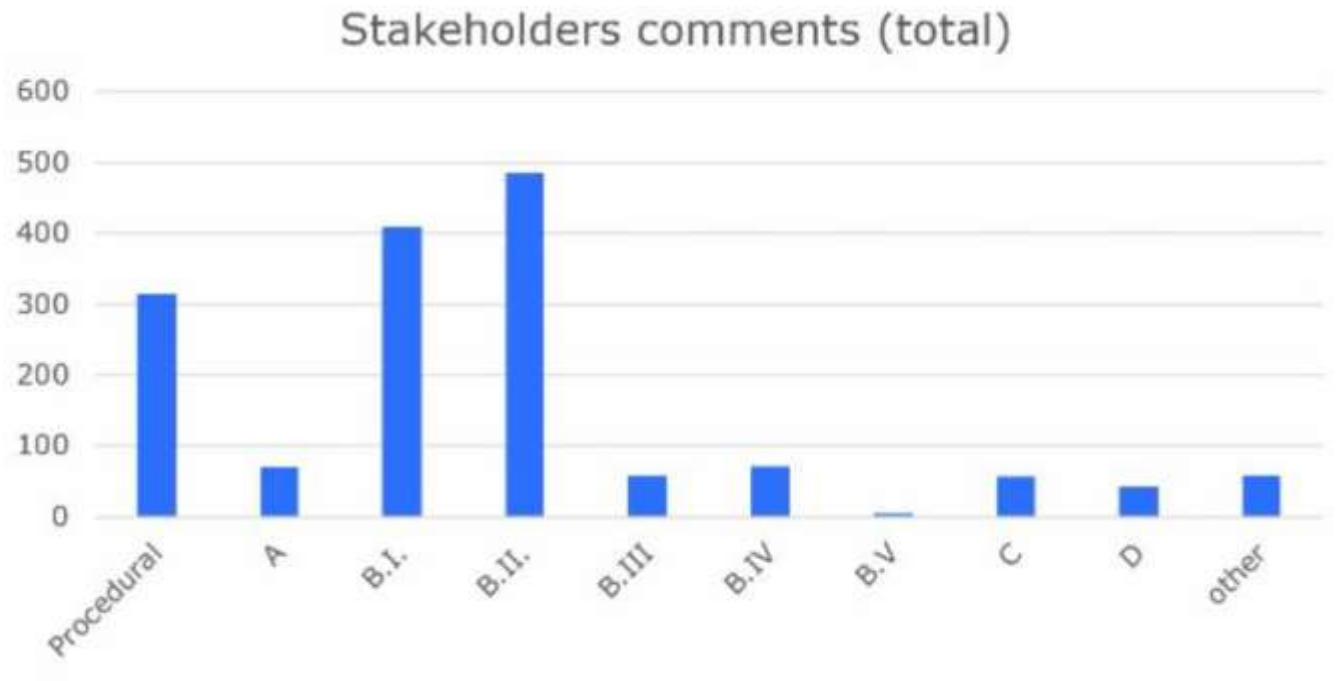
- The final revision of the classification guideline to include the new regulation is expected in 2025.
- The draft can already be found on the EMA website : Guidelines on the details of the various categories of variations 2013-C 223-01 13 June 2024 - proposed revision - clean version

Consequences for the API industry

<u>The new variations guideline</u>

During the consultation period many comments have been submitted to the EMA:

Section	Comments
Procedural	314
A	69
B.I.	409
B.II.	485
B.III	59
B.IV	71
B.V	5
C	57
D	42
other	58
TOTAL	**1569**



Consequences for the API industry

The new variations guideline

B.	**QUALITY CHANGES**
I.	**Active Substance**
	a) Manufacture
	b) Control of active substance
	c) Container closure system
	d) Stability
	e) Additional regulatory tools
II.	**Finished Product**
	a) Description and composition
	b) Manufacture
	c) Control of excipients
	d) Control of finished product
	e) Container closure system
	f) Stability
	g) Additional regulatory tools
	h) Adventitious Agents Safety

Consequences for the API industry

<u>The new variations guideline</u>

It seems a bit odd, that the guideline is officially valid as per January 1, 2025, whereas the final version has not yet been published, moreover so considering the huge amounts of comments submitted.

Obviously, API companies and APIC (the European API organization) have also submitted comments as there are several points that have been changed but need further clarification.

Points to consider in Japan

The problems Europe is facing are obviously partly similar to the problems Japan is facing:

- Dependency on other regions for a stable supply
- Complicated and sometimes lengthy procedures on change control
- the security of supply to ensure medicines are available to patients at all times

Points to consider in Japan

- We are aware that there is a trial phase ongoing in Japan with respect to change control: the PMDA is now collecting cases of moderate changes and the concept of annual reporting is also being implemented on a trial basis.
- Unfortunately, the guidance around these new procedures is not available in the English language.
  It is therefor impossible for non-Japanese companies or organizations to comment on and/or test the newly proposed system.
- There has been a meeting between APIC and the PMDA/MHLW last year in the PMDA offices where we discussed these concepts.

Points to consider in Japan

- Harmonization is what the global industry is looking for: there are too many examples of differences in categorization of changes between the regions, meaning that something that could be considered minor (notification, annual report like) could be considered moderate or even major in other regions.
- As the basis for categorization is the same in all countries (namely the potential to affect the quality of the API /Drug Product and thus the impact the product has on the patient), this should of course not be the case.

Points to consider in Japan

- In general, categorization (based on risk) should lead to three categories:

➢ Minor: do and tell: implement and inform the authorities later (annual report)

➢ Moderate: tell and do: inform the authorities and implement either immediately or after a short, fixed amount of time (e.g. 30 days)

➢ Major: tell, wait and do: inform the authorities and wait for their explicit approval before implementing.

Points to consider in Japan

- We hope that the current trial phase in Japan will lead to the implementation of a system in which the three levels of changes are clearly described and where the categorization is harmonized with the other regions.
- If science is the basis, the outcome of categorizations should, in my view, be similar all around the world.
- Having clear guidance, including categorization of often occurring changes, makes life easier, both for the applicants and the Health Authorities.
  Imagine the amount of time saved, when less consultations on the categorization of changes is needed.

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