Medicines regulation in Europe

Introduction

Medicines regulation is the basis for ensuring that only medicines of a high quality are marketed. Medicines should be effective in treating the intended disease or condition, they should be free of unacceptable side effects and be of high quality.

In Europe, the European Commission proposes high-level legislation in the form of regulations and directives. Proposals are approved and become legislation through joint efforts between the Commission, the Member States (MSs) via the Council of Europe (CoE), CoE working groups, and the European Parliament. Individual MSs contribute to the process via CoE working groups.

Detailed instructions on the best or most appropriate way to fulfil an obligation laid down in the EU pharmaceutical legislation take the form of guidelines. They provide advice to marketing authorisation applicants or holders, competent authorities and/or other interested parties. Guidelines are developed by the European Medicines Agency (EMA) or the European Commission. The EU also collaborates with other parts of the world to prepare harmonised guidelines – for instance with the USA, Japan, Canada, Switzerland and other countries in the International Council on Harmonisation (ICH) – and with the World Health Organisation (WHO). Annual meetings between senior officials from the WHO and the European Commission discuss general problems in the medicines field. These meetings and collaborations all have an impact on EU legislation.

The WHO and EMA also collaborate to build joint regulatory capacity. Additionally, the EMA may assist the WHO in assessment tasks on medicines intended for markets outside the EU.

The European network in medicines regulation

In order to provide concrete and detailed guidance to industry, National Competent Authorities (NCAs, national regulatory agencies) work together with the EMA. An informal network has been established between the heads of the medicines agencies (HMAs) of each of the EU member states. This network meets on a regular basis, with EMA participation.

NCAs participate in the development of medicines legislation at all levels. Formally, an MS's ministry of health – often represented by a staff member from the NCA – participates in directives and regulations development. The EMA coordinates the development of new and revised EU scientific guidelines. This work is done in EMA working groups/parties. Typically, the NCA of each member states may appoint a member to each EMA working party where much of the work on scientific guidelines is done.

Regulatory guidelines are most often developed by the European Commission in the Notice to Applicants (NtA) Working Party. Here, too, NCA delegates participate substantially in the process.

[glossary_exclude]Guideline development in the EU

The development of scientific guidelines for medicines regulation follows a fixed procedure, typically used by all Working Parties (WPs) of the EMA's Committee for Medicinal

Products for Human Use (CHMP):

1. Concept paper on new guideline.
2. Acceptance by CHMP.
3. Appointment of rapporteur.
4. Draft guideline in WP.
5. Draft published for consultation.
6. Comments.
7. Finalisation of guideline in WP.
8. Adoption of guideline in CHMP.
9. Implementation of guideline.

Members of the WPs are appointed by, and come from, the NCAs of member states. Before a working party begins developing a guideline, the proposal for this new guideline must be approved by the CHMP.

A member of the WP is selected to act as the rapporteur. The rapporteur prepares the first draft of the guideline. The WP then discuss and modify the draft during meetings at the EMA. This draft is then published on the EMA web site so that industry, NCAs, and other stakeholders can comment on the draft.

The guideline is then finalised in the WP and sent to the CHMP, who must formally adopt the guideline before it is published on the EMA website https://www.ema.europa.eu/en/human-regulatory-overview/research-and-development/scientific-guidelines. The new guideline typically comes into effect six months after publication.

Guidelines can also be developed within the ICH structure. This work takes place as a collaboration between the EU, USA, Japan, Switzerland, Canada and other regional and national organisations. A final new ICH guideline is agreed on by the parties involved and implemented on a regional basis. In the EU, the CHMP must formally adopt an ICH guideline; it is then published on the EMA website as a CHMP/ICH

guideline.[/glossary_exclude]

[glossary_exclude]The role and implementation of CHMP guidelines

Guidelines are not the same as regulations, directives, or national laws. They simply offer guidance. Industry is recommended to follow the guidelines when preparing documentation for a marketing authorisation application for a new medicine. However, it takes many years to develop a new medicine, and a guideline only applies to development or research that begins after that guideline comes into force (typically six months after the guideline has been adopted by the CHMP).

In some specific situations, it may be inappropriate to follow a guideline when developing a new medicine. If a company wants to deviate from the guideline during development, they must provide sound scientific justification for that deviation. This is considered by the authorities assessing the documentation, who must decide whether the deviation is justified. If they find the justification acceptable, they may even begin the process of updating the guideline accordingly.

If the Marketing Authorisation Application (MAA) is being made directly to the National Competent Authority (NCA) via a national procedure, then the NCA assessment team decides whether or not an application adheres to the guidelines and if any deviations are scientifically justified. However, in cases where the MAAs are submitted via the Centralised Procedure (CP), Mutual Recognition Procedure (MRP), or the Decentralised Procedure (DCP), complications may arise. For instance, even though the primary assessor may deem that all the guidelines have been sufficiently respected or that any deviations have been acceptably justified, assessors from other agencies may look at the situation differently.

Each marketing authorisation procedure has a different way of dealing with these disagreements. In the CP, these disagreements are dealt with by the CHMP. In the DCP and MRP, they are discussed by the Coordination group for Mutual recognition and Decentralised Procedures (human) (CMDh) from the HMA (http://www.hma.eu/cmdh.html). If the CMDh can reach a unanimous decision, the case is closed. If no unanimous decision is reached, then CMDh must refer the case to the CHMP for the final decision.[/glossary_exclude]

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