Analytical methods in regulatory field: requirements to be considered in the assessment of a registration dossier (module 3)

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SSPA 2014 - Advanced Analytical Methodologies in Chemical Drug Manufacturing

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Public Declaration of transparency/interests*

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Interests in pharmaceutical industry	NO	Currently	Last 2 years	More than 2 years but less than 5 years ago	More than 5 years ago (optional)
Direct interests:					
Employment with a company	X				
Consultancy for a company	X				
Strategic advisory role for a company	X				
Financial interests	X				
Ownership of a patent	X				
Indirect interests:					
Principal investigator	X				
Investigator	X				
Individual's Institution/Organisation receives a grant or other funding	X				

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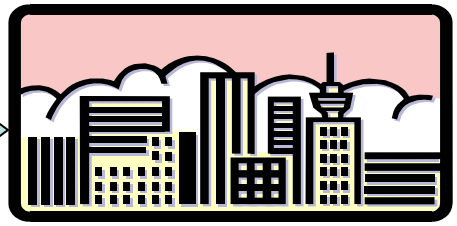
The Assessment Process

Company dossier

Competent authorities



Product

Output

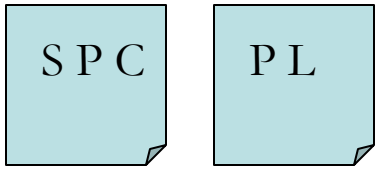
Assessment Report

Resources

Assessors (Experts) – Internal / External

Legislation and Guidelines – Harmonised interpretation

Product information



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Criteria for Authorising Medicines

Benefits Risks

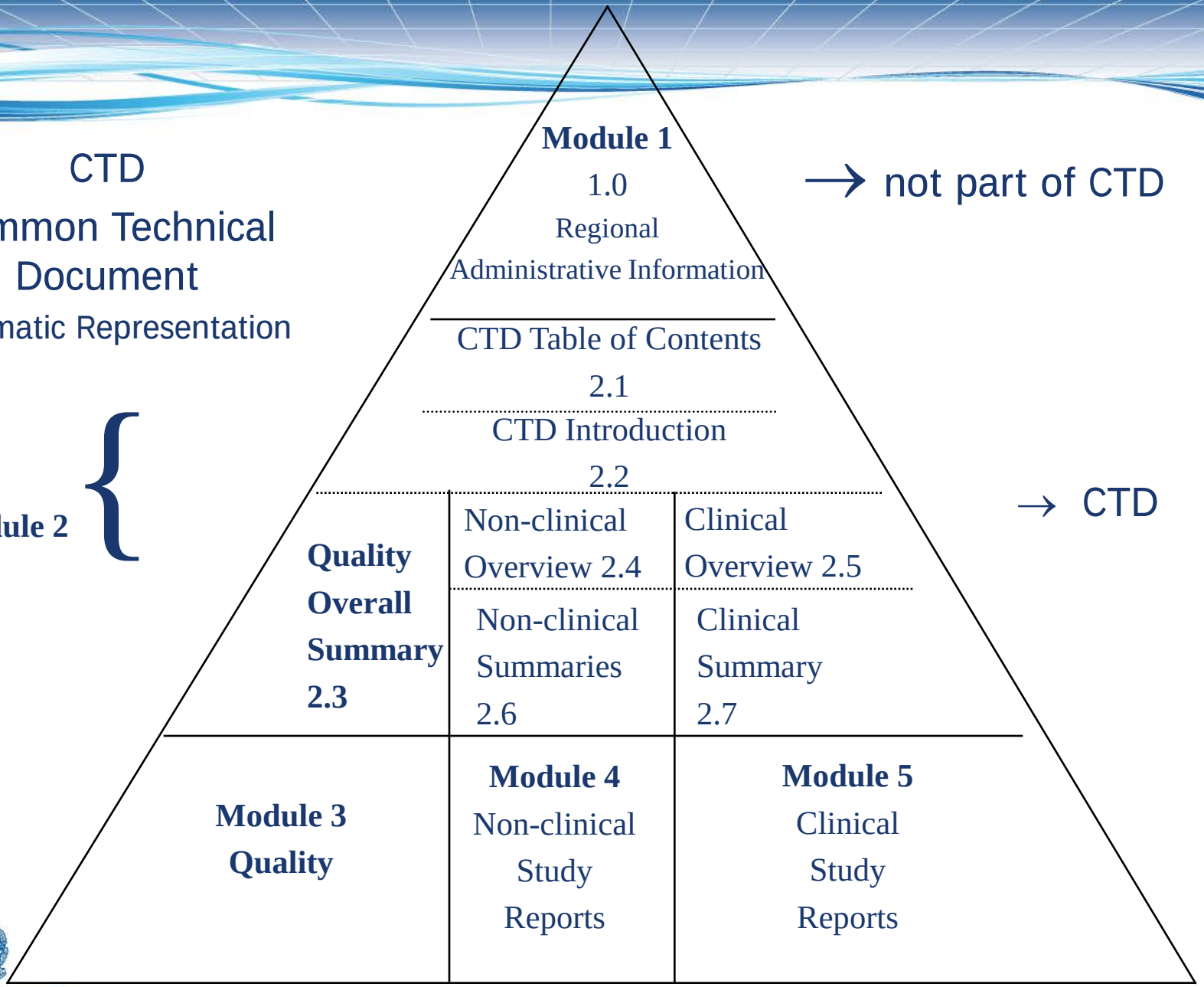
The evaluation of Benefit-Risk balance of a product is based on the assessment of the registration dossier

MA is granted when the Benefit-Risk balance of a product is positive, meaning that benefits from use of this product outweigh risks associated with its use

CTD

Common Technical Document

Diagrammatic Representation



→ not part of CTD

→ CTD

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CTD-Q: two main documents

3.2.S Drug substance	3.2.P Drug Product
3.2.S.1 General Information	3.2.P.1 Description and Composition
3.2.S.2 Manufacture	3.2.P.2 Pharmaceutical Development
3.2.S.3 Characterisation	3.2.P.3 Manufacture
3.2.S.4 Control of Drug substance	3.2.P.4 Control of Excipients
3.2.S.5 Reference Standards or Materials	3.2.P.5 Control of Drug Product
3.2.S.6 Container Closure System	3.2.P.6 Reference Standards or Materials
3.2.S.7 Stability	3.2.P.7 Container Closure System
	3.2.P.8 Stability

Main aspects to be considered

Drug substance	Drug product
Compliance to ➢ European Pharmacopoeia, if applicable ➢ EU quality guidelines Focus on: ➢ Manufacturing process (synthesis) (GMP, QP declaration, starting materials) ➢ Chemical-physical characteristics with potential impact on efficacy (particle size, polymorphism) and safety (impurity profile, residual solvents, catalysts..) ➢ Control test and specifications with focus on analytical methods validation	Compliance to ➢European Pharmacopoeia ➢EU quality guidelines Focus on: ➢Pharmaceutical development (e.g. justification for the choice of excipients, compatibility studies ...) ➢Manufacturing process (adequate validation) ➢Control test and specifications with focus on analytical methods validation ➢Stability sudies To set "safe" shelf-life (expiry date) and storage conditions

Analytical methods

- The chemical and pharmaceutical dossier must include the analytical procedures necessary to ensure the identity, purity and content of the active ingredient and finished medicinal product, including bioavailability.
- Data must be available to establish that that analytical procedures used in testing meet proper standards of accuracy and reliability.
- All analytical test procedures described in the various sections of the chemical-pharmaceutical documentation are expected to be described in sufficient detail to enable the procedure to be repeated if necessary (e.g. by an official laboratory).
- All procedures need to be validated and the results of the validation studies must be provided.

Analytical methods information: which sections? (1)

3.2.S Drug Substance	3.2.P Drug Product
3.2.S.4 Control of Drug Substance 3.2.S.4.1 Specification(s) ➢3.2.S.4.2 Analytical Procedures ➢3.2.S.4.3 Validation of Analytical Procedures 3.2.S.4.4 Batch Analysis 3.2.S.4.5 Justification of Specification 3.2.S.7 Stability Is it confirmed that the analytical methods are stability-indicating?	3.2.P.4 Control of Excipients 3.2.P.4.1 Specifications ➢3.2.P.4.2 Analytical Procedure ➢3.2.P.4.3 Validation of Analytical Procedures 3.2.P.4.4 Justification of Specifications 3.2.P.4.5 Excipients of Human or Animal Origin 3.2.P.4.6 Novel Excipients

...Analytical methods information: which sections ? (2)

3.2.P.5 Control of Drug Product	3.2.P.8 Stability
3.2.P.5.1 Specification(s) ➢3.2.P.5.2 Analytical Procedures ➢3.2.P.5.3 Validation of Analytical Procedures 3.2.P.5.4 Batch Analysis 3.2.P.5.5 Characterisation of Impurities 3.2.P.5.6 Justification of Specification	Are the methods used the same as or different to those described in P.5? If different are they well-validated?

Rules governing Medicinal Products in the European Union

The '*Introduction and general principles' of Annex I of Directive 2001/83/EC1, as amended, defines* the principles governing the assurance of quality of medicinal products:

(4) In assembling the dossier for application for marketing authorisation, applicants shall also take into account the scientific guidelines relating to the quality, safety and efficacy of medicinal products for human use as adopted by the Committee for Proprietary Medicinal Products (CPMP) and published by the European Medicine Evaluation Agency (EMEA) and the other pharmaceutical Community guidelines published by the Commission in the different volumes of The rules governing medicinal products in the European Community.

(5) With respect to the quality part (chemical, pharmaceutical and biological) of the dossier, all monographs including general monographs and general chapters of the European Pharmacopoeia are applicable.

How to assess analytical methods?

The quality assessors should refer to:

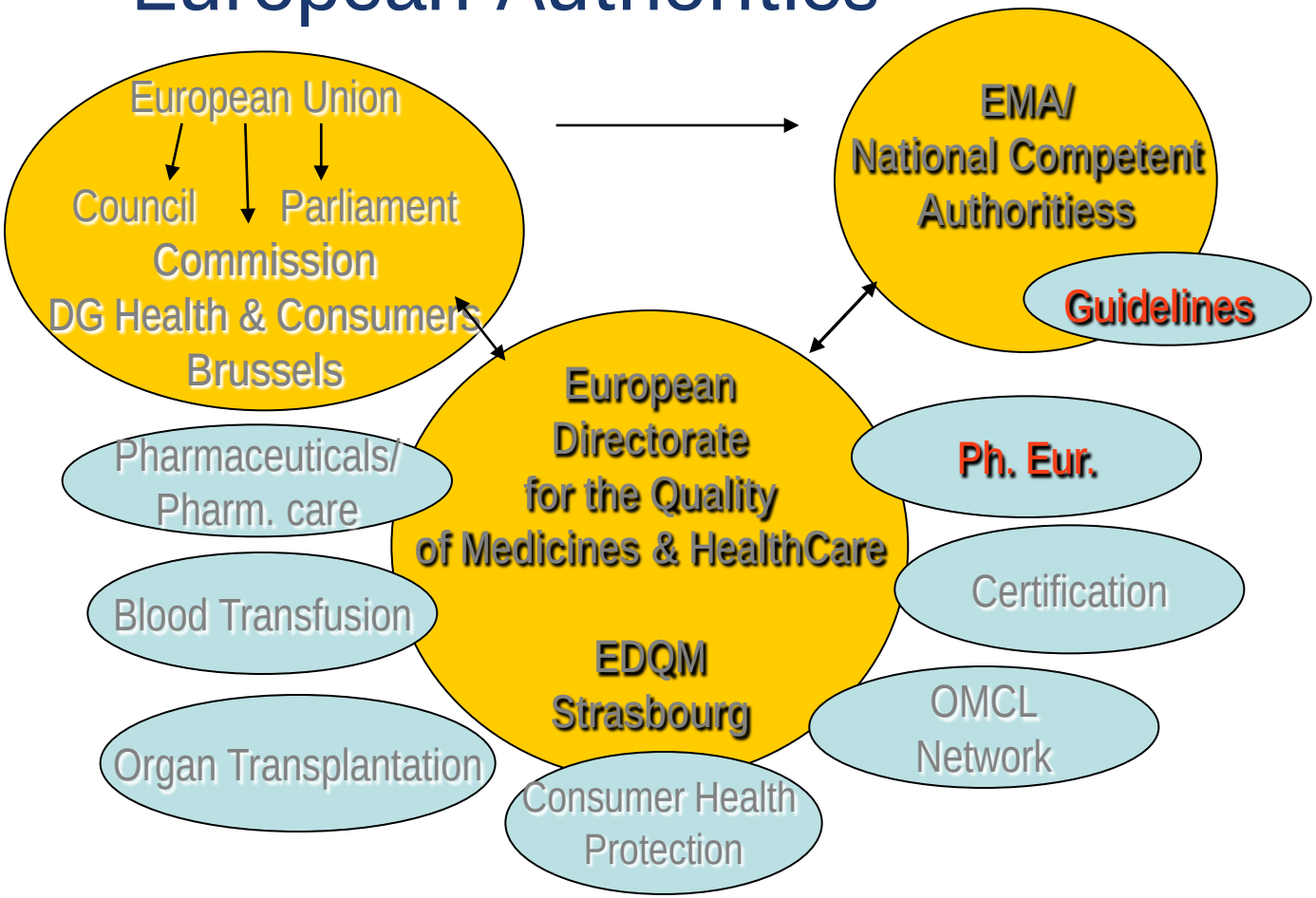
- Quality guidelines
- European Pharmacopoeia

EMA scientific guidelines and European Pharmacopoeia monographs and chapters are complementary

European Regulatory Network
European Authorities

European Union

Council of Europe



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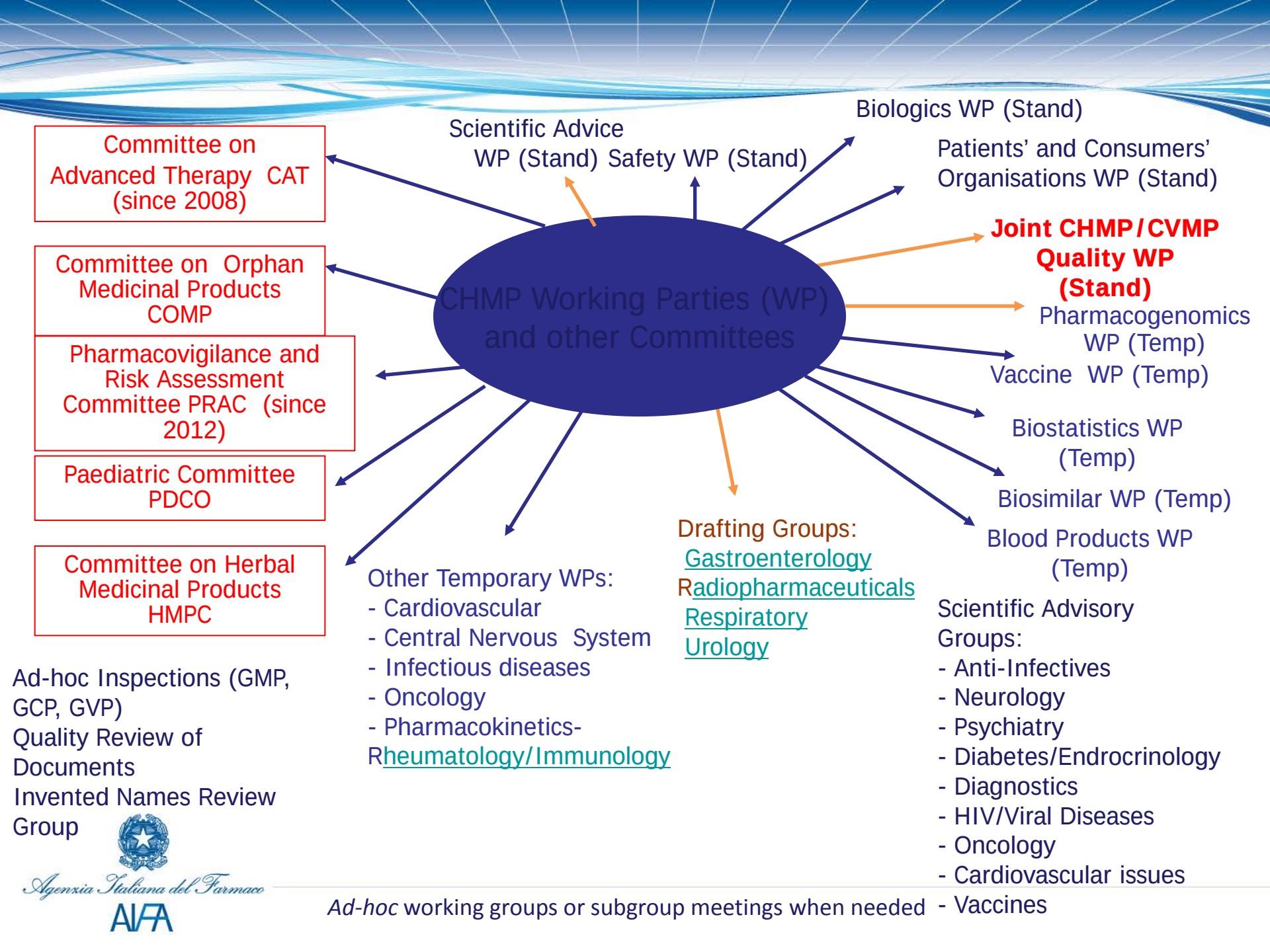
European Medicines Agency (EMA)

- The European Medicines Agency is a decentralised agency of the European Union, located in London. The Agency is responsible for the scientific evaluation of medicines developed by pharmaceutical companies for use in the European Union.
- Scientific evaluation on applications from pharmaceutical companies is carried out by Scientific Committees. These Committees normally meet on a monthly basis and are comprised of members nominated by the Member States.
- Assessments are based on purely scientific criteria and determine whether or not the medicines concerned meet the necessary quality, safety and efficacy requirements (in accordance with EU legislation, particularly Directive 2001/83/EC).
- These processes ensure that medicines have a positive risk-benefit balance in favour of patients/users of these products once they reach the marketplace.



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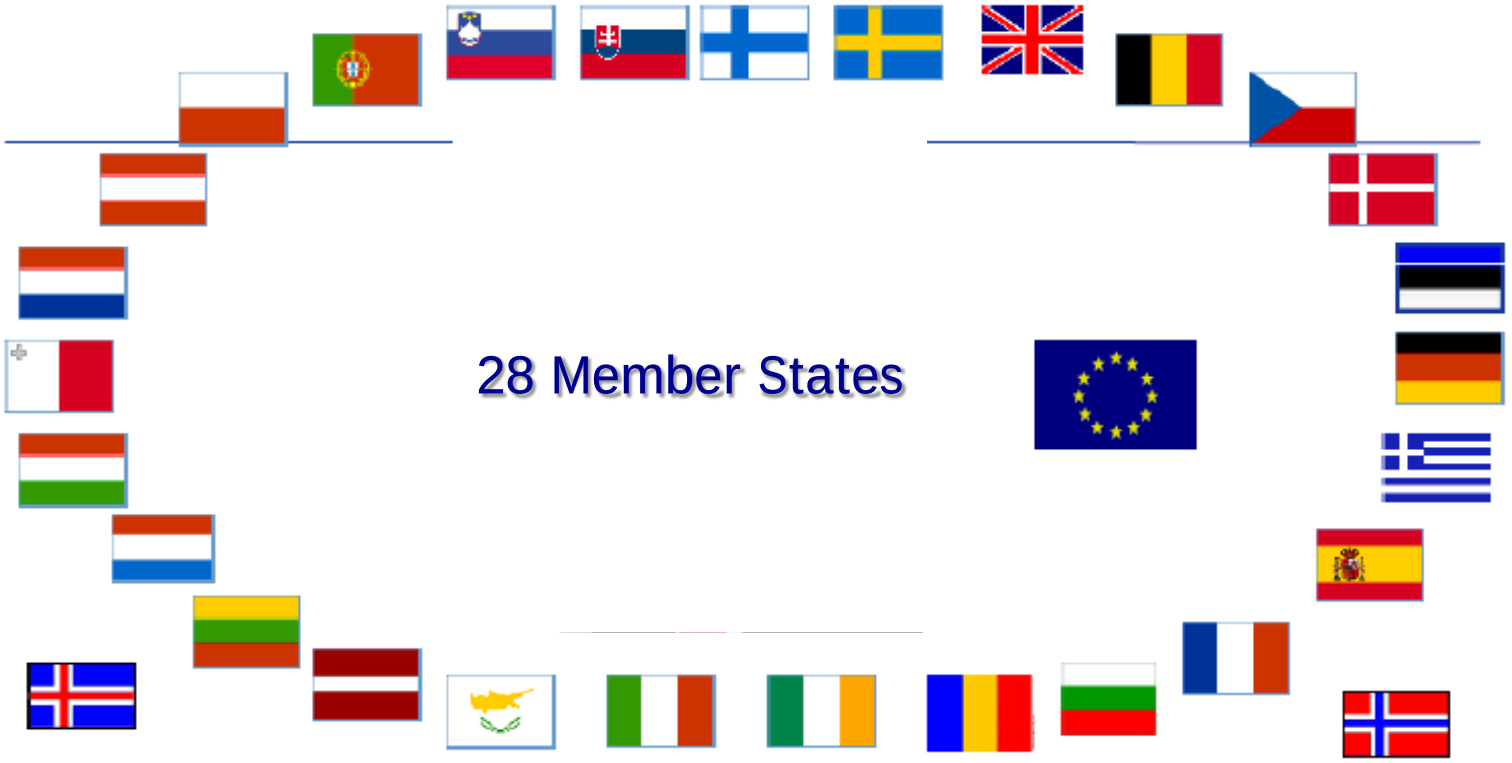
CHMP - Human Medicines



1 scientific expert member nominated by each MS and 1 alternate
1 scientific expert member from NO and IS and 1 alternate (observers)
5 co-opted members as appointed by Management Board

Scientific guidelines

- Aim: guidance to industry and regulators providing a basis for practical harmonisation of assessment of scientific data in the dossier and facilitate the preparation of dossiers for MA by the Pharmaceutical industry
- Guidelines referred to in the legislation are applicable throughout the EU, irrespective of the procedure used (national, mutual recognition, decentralised, centralised)
- Guidelines are not legally binding (they are not legislation). Their purpose is to set out principles and general requirements that should be followed
- Important is the spirit of a Guideline: derogations can be acceptable provided that they are adequately justified
- Main tool used by regulators for assessment of applications
- Quality GLs are complementary to chapters and monographs of the Ph. Eur.

...Scientific guidelines and QWP

The GL are adopted by the relevant EMA committees (CHMP/CVMP, HMPC, PDCO...)

EMA scientific GLs related to quality are mainly developed by

CHMP/CVMP Quality Working Party (QWP)

The general objective of the QWP is to provide a forum for dialogue and understanding between pharmaceutical experts/assessors in the human and veterinary area to reach a harmonised approach to quality issues and to avoid national divergences in assessing quality problems and interpreting quality guidelines

Quality Working Party (QWP)

- The Joint CHMP/CVMP Quality Working Party (QWP) is established to provide recommendations to the Committees (CHMP and CVMP) on matters relating directly or indirectly to the quality of medicinal products

- The QWP is composed of experts selected from the European expert list according to their specific expertise in the area of quality assessment

- CVMP and CHMP members are invited to nominate one expert per Member State for products for human use and, where there is a separate agency for veterinary medicinal products, one expert per Member State for products for veterinary use

- The European Directorate for the Quality of Medicines (EDQM) nominate an observer to participate in the work of the QWP

Publication of guidelines

All scientific guidelines on quality, safety and efficacy are published together on the EMA website, divided in categories to make their use easier, following the structure of the dossier

Quality guidelines on the EMA website:

From the EMA Homepage http://www.ema.europa.eu/

Regulatory>Human Medicines>Scientific Guidelines>Quality

Quality guidelines

Quality GLs are provided for:

- Active Substance
- Manufacturing
- Impurities
- **Specifications, analytical procedures and analytical validation**
- Excipients
- Packaging
- Stability
- Pharmaceutical development
- Specific types of products
- Post approval change management protocols
- Herbal medicinal products

GL on validation of analytical procedures

Reference Guideline:

ICH Q2(R1) Validation of Analytical Procedures: Text and Methodology

- Combines former ICH Q2A (Definitions and Terminology) and ICH Q2B (Methodology) guidelines

- To be considered during the validation of the analytical procedures included as part of registration applications submitted within the EU, Japan and USA.

The International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) is unique in bringing together the regulatory authorities and pharmaceutical industry of Europe, Japan and the US to discuss scientific and technical aspects of drug registration

...GL on validation of analytical procedures (2)

- The GL provides an indication of the data which should be presented in an application for marketing authorisation.
- All relevant data collected during validation and formulae used for calculating validation characteristics should be submitted and discussed as appropriate.
- Approaches other than those set forth in the GL may be applicable and acceptable. It is the responsibility of the applicant to choose the validation procedure and protocol most suitable for the product.

To remember: the main objective of validation of an analytical procedure is to demonstrate that the procedure is suitable for its intended purpose, namely to produce results allowing a reliable comparison with the product specifications (acceptance criteria)

Types of analytical procedures to be validated (1)

In the GL ICH Q2(R1) the discussion of the validation of analytical procedures is directed to the four most common types of analytical procedures:

- Identification tests
- Quantitative tests for impurities' content
- Limit tests for the control of impurities
- Quantitative tests of the active moiety in samples of drug substance or drug product or other selected component(s) in the drug product.

... Types of analytical procedures to be validated (2)

• Identification tests: are intended to ensure the identity of an analyte in a sample. This is normally achieved by comparison of a property of the sample (e.g., spectrum, chromatographic behavior, chemical reactivity, etc) to that of a reference standard.

• Testing for impurities can be either a quantitative test or a limit test for the impurity in a sample. Either test is intended to accurately reflect the purity characteristics of the sample. Different validation characteristics are required for a quantitative test than for a limit test.

• Assay procedures are intended to measure the analyte present in a given sample. the assay represents a quantitative measurement of the major component(s) in the drug substance or drug product, or other selected component(s).

Analytical procedure description and validation

- The analytical procedure should be described an validated in module 3.

- The analytical procedure refers to the way of performing the analysis. It should describe in detail the steps necessary to perform each analytical test. This may include but is not limited to: the sample, the reference standard and the reagents preparations, use of the apparatus, generation of the calibration curve, use of the formulae for the calculation, etc...

- The following validation characteristics should be considered:

  Accuracy, Precision, Repeatability, Intermediate Precision, Specificity, Detection Limit, Quantitation Limit, Linearity, Range

Validation parameters-table

Type of analytical Procedure Characteristics	Identification	Testing for impurities		Assay
		Test quantitat	Test limit	-Dissolution (measurement only) - content/potency
Accuracy	–	+	–	+
Precision				
Repeatability	–	+	–	+
Interm Precision	–	+	–	+
Specificity	+	+	+	+
Detection limit	–	–	+	–
Quantitation limit	–	+	–	–
Linearity	–	+	–	+
Range	–	+	–	+

- signifies that this characteristic is not normally evaluated
+ signifies that this characteristic is normally evaluated

European Directorate for the Quality of Medicines & HealthCare (EDQM)

A Council of Europe Directorate, based on the Convention on the Elaboration of a European Pharmacopoeia (PA, 1964)

The preparation of the Pharmacopoeia is the responsibility of the European Pharmacopoeia Commission ('the Commission'), appointed in accordance with Article 5 of the above-mentioned Convention

Mission: to contribute to a basic human right: access to good quality medicines and healthcare

European Pharmacopoeia Commission

One delegation per member state or observer

36 Member States plus a delegation from the EU (a representative from DG Health & Consumer and the EMA); 22 Observers countries and World Health Organization (WHO).

Persons come from health ministries, health authorities, pharmacopoeias, universities, or industry and are appointed by the national authorities on the basis of their expertise.

Three sessions a year; texts are adopted by unanimous vote.

20 Permanent Groups of Experts & 46 Working Parties - experts appointed by Ph. Eur. Commission

One Secretariat: EDQM

European Pharmacopoeia purpose

To promote public health by the provision of recognised common standards for use by healthcare professionals and others concerned with the quality of medicines. Such standards are to be appropriate as a basis for the safe use of medicines by patients. Their existence:

- facilitates the free movement of medicinal products in Europe

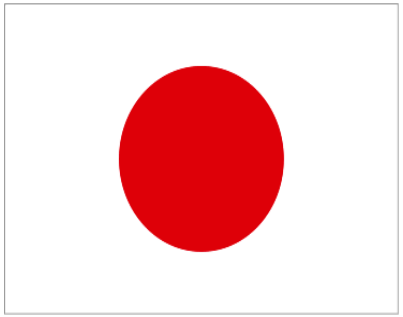
- ensures the quality of medicinal products and their components imported into or exported from Europe.

Ph. Eur. designed for ...

European Pharmacopoeia monographs and other texts are designed to be appropriate to the needs of:

- regulatory authorities
- those engaged in the quality control of medicinal products and their constituents
- manufacturers of starting materials and medicinal products

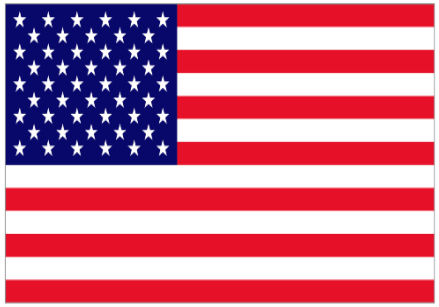
Three major Pharmacopoeias



Japanese Pharmacopeia

Ph. Eur.

EDQM, Council of Europe



US Pharmacopoeia

Priority of pharmacopoeias according to EU legislation Ph. Eur. > national pharmacopoeia > third country pharmacopoeias, e.g. USP, JP

European Pharmacopoeia

- The texts of the European Pharmacopoeia (Ph. Eur.) concern the tests to be carried out on medicines, on the raw materials used in the production of medicines and on the intermediates of synthesis

- It contains texts covering substances, excipients as well as dosage forms and containers

...European Pharmacopoeia (2)

- General Notices (Address general issues and provide the basic information to the user. Apply to all texts. Rules to understand texts, conventional expressions).
- General chapters (e.g. Analytical methods, containers, reagents...)
- General monographs (two types):
  - ✓ General monographs on classes of substances (es. vaccines, radiopharmaceuticals, homeopathic preparations, etc...)
  - ✓ General monographs on dosage forms (es. ear preparations, capsules, tablets etc...)
- Individual monographs

Eur. Ph. general chapters

Analytical methods:

- Editorial convenience: avoid repeating standard methods in each monograph
- Provide standard methods that can be used for substances not covered by monographs
- Not mandatory “per se”
- When referred to in a monograph, they become part of the standard

Individual monographs

Test to detect: organic impurities, inorganic impurities, volatiles

Methods:

- Physical and physico-chemical
- Chemical
- Chromatographic

➢ Robust, validated analytical methods based on collaborative laboratory testing

Validation of Pharmacopoeial methods

"The test methods given in monographs and general chapters have been validated in accordance with accepted scientific practice and current recommendations on analytical validation. Unless otherwise stated in the monograph or general chapter, validation of the test methods by the analyst is not required."

General Notices, 8th edition

Alternative methods

"*The tests and assays described are the official methods upon which the standards of the Pharmacopoeia are based. With the agreement of the competent authority, alternative methods of analysis may be used for control purposes, provided that the methods used enable an unequivocal decision to be made as to whether compliance with the standards of the monographs would be achieved if the official methods were used. In the event of doubt or dispute, the methods of analysis of the Pharmacopoeia are alone authoritative.*"

General Notices, 8th edition

Flexibility in the Ph.Eur.-Alternative methods

- Ph. Eur. tests are reference methods, essential in cases of dispute.
- Compliance is required, but alternative methods may be used as long as they lead to the same pass/fail result. It is the responsibility of the user to demonstrate their suitability.
- Approval of the competent authority is necessary

Scientific guidelines *vs* Ph. Eur. Legal status

- Ph. Eur: Mandatory, legally binding quality standard

- GLs: No legal force, do not have the force of law, but represent the agreed views of regulators on certain topic. They represent:

•Alternative approaches may be taken – provided appropriate justification

•Facilitate assessment approval and control

•Harmonised community position

Concluding Remarks

- The chemical and pharmaceutical dossier must include the analytical procedures necessary to ensure the identity, potency and purity of the drug substance and finished medicinal product
- Data must be available to establish that that analytical procedures used in testing are adequately validated to meet proper standards of accuracy and reliability
- To evaluate the analytical methods the quality assessor should refer to Eur. Ph. and quality guidelines
- Compliance to Eur. Ph. methods is required, but alternative methods may be used if validated and approved by Competent Authorities
- GLs have no legal force, Alternative approaches may be taken – provided appropriate justification

Useful addresses

EUROPEAN COMMISSION

http://ec.europa.eu/health/index_en.htm

EMA home page

http://www.ema.europa.eu/

EDQM Home page

http://www.edqm.eu/en/Homepage-628.html

Contact details

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