Analytical procedures under regulatory perspective: requirements to be considered in the assessment of the registration dossier

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WORKSHOP: Modern analytical techniques in Pharmaceutical Industry
A tool to support pharmaceutical quality and to ease regulatory process
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AIFA
Agenzia Italiana del Farmaco

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Public Declaration of transparency/interests*

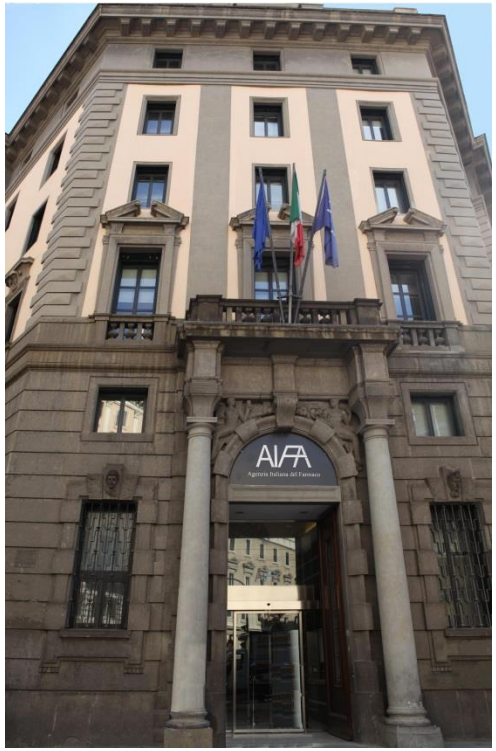
The view and opinions expressed are those of the individual presenter and should not be attributed to AIFA

Interests in pharmaceutical industry	NO	Current	From 0 to 3 previous years	Over 3 preavious years
DIRECT INTERESTS:				
1.1 Employment with a company: pharmaceutical company in an executive role	X	☐	☐	☐ mandatory
1.2 Employment with a company: in a lead role in the development of a medicinal product	X	☐	☐	☐ mandatory
1.3 Employment with a company: other activities	X	☐	☐	☐ optional
2. Consultancy for a company	X	☐	☐	☐ optional
3. Strategic advisory role for a company	X	☐	☐	☐ optional
4. Financial interests	X	☐	☐	☐ optional
5. Ownership of a patent	X	☐	☐	☐ optional
INDIRECT INTERESTS:				
6. Principal investigator	X	☐	☐	☐ optional
7. Investigator	X	☐	☐	☐ optional
8. Grant or other funding	X	☐	☐	☐ optional
9. Family members interests	X	☐	☐	☐ optional

*Eugenia Cogliandro, in accordance with the Conflict of Interest Regulations approved by AIFA Board of Directors (25.03.2015) and published on the Official Journal of 15.05.2015 according to EMA policy /626261/2014 on the handling of the conflicts of interest for scientific committee members and experts.

N.B. I am not receiving any compensation

Italian Medicines Agency (AIFA)

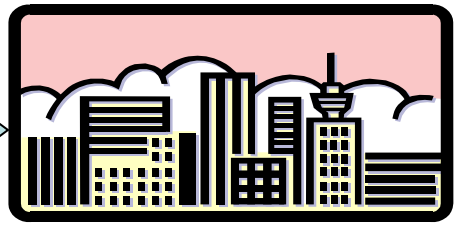


- The Italian Medicines Agency (AIFA) is the only national authority responsible for drugs (human) regulation in Italy
- AIFA is a public body operating autonomously, transparently and according to cost-effectiveness criteria, under the direction of the Ministry of Health and under the vigilance of the Ministry of Health and the Ministry of Economy
- AIFA cooperates with the Regional Authorities, the National Institute of Health (ISS), Research Institutes, Patients' Associations, Health Professionals, Scientific Associations the Pharmaceutical Industry, Drug Distributors and with all Regulatory Authorities Worldwide

The Assessment Process

Company dossier

Competent authorities



Product

Output

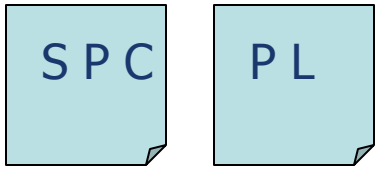
Assessment Report

Resources

Assessors (Experts) – Internal / External

Legislation and Guidelines – Harmonised interpretation

Product information



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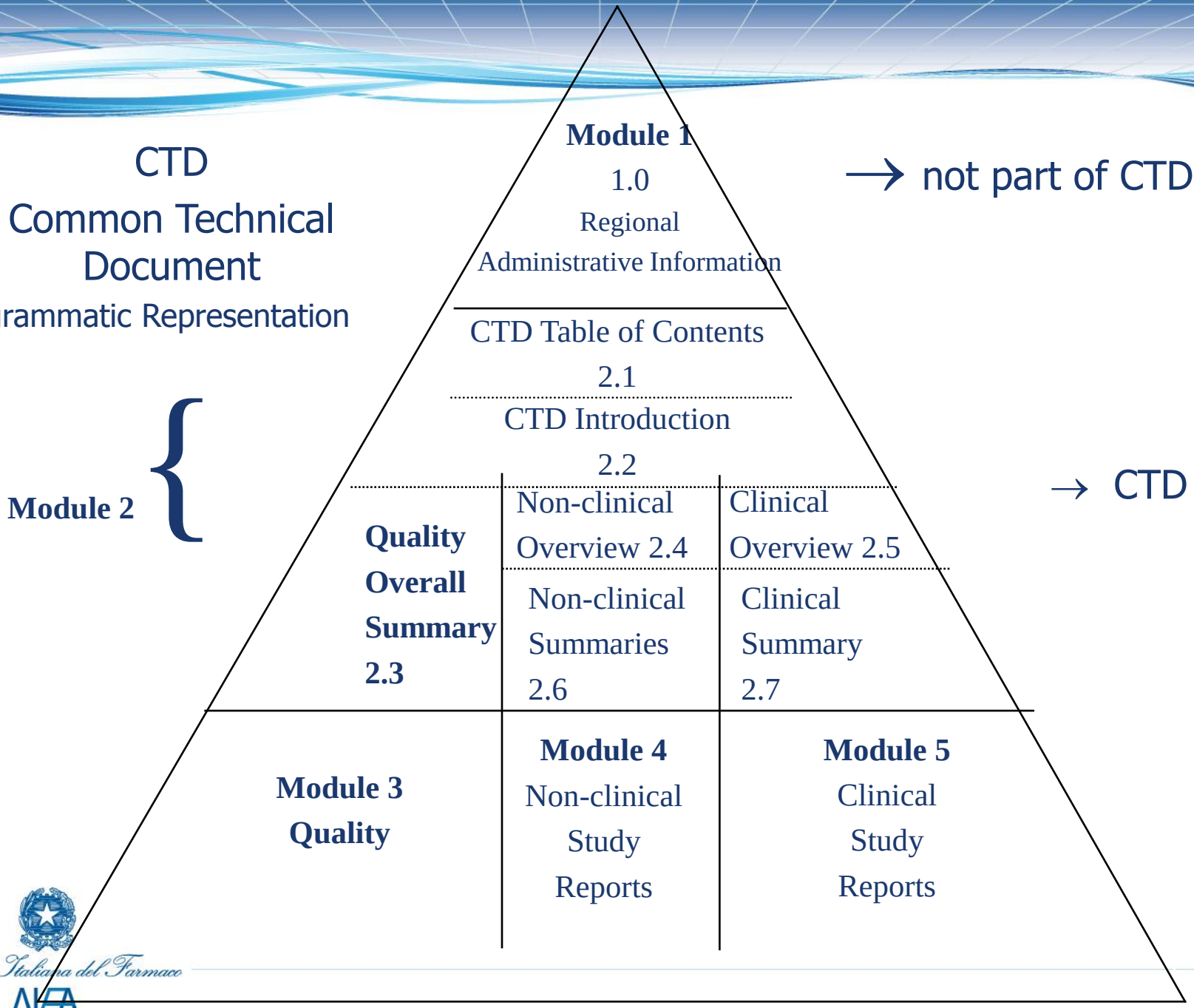
Criteria for Authorising Medicines

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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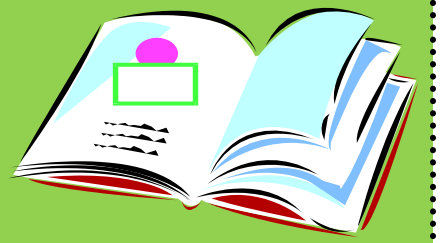
Quality information

Main review document

Summarized

Module 2 (QOS)



Module 3

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.

Responsibility and control

Responsibility!

CONTROL

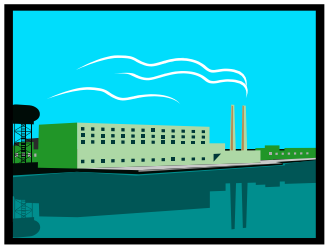
MAH

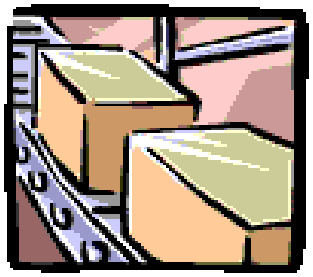
NCA

Review and inspections

- **Supervise and manage the manufacturers**
- **Ensure proper release to market**

Manufacturer A drug substance → **Manufacturer B drug product** → **Manufacturer C packaging, label** → **Market Release**





External Testing laboratory

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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**	**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?

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

Rules governing Medicinal Products in the European Union

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

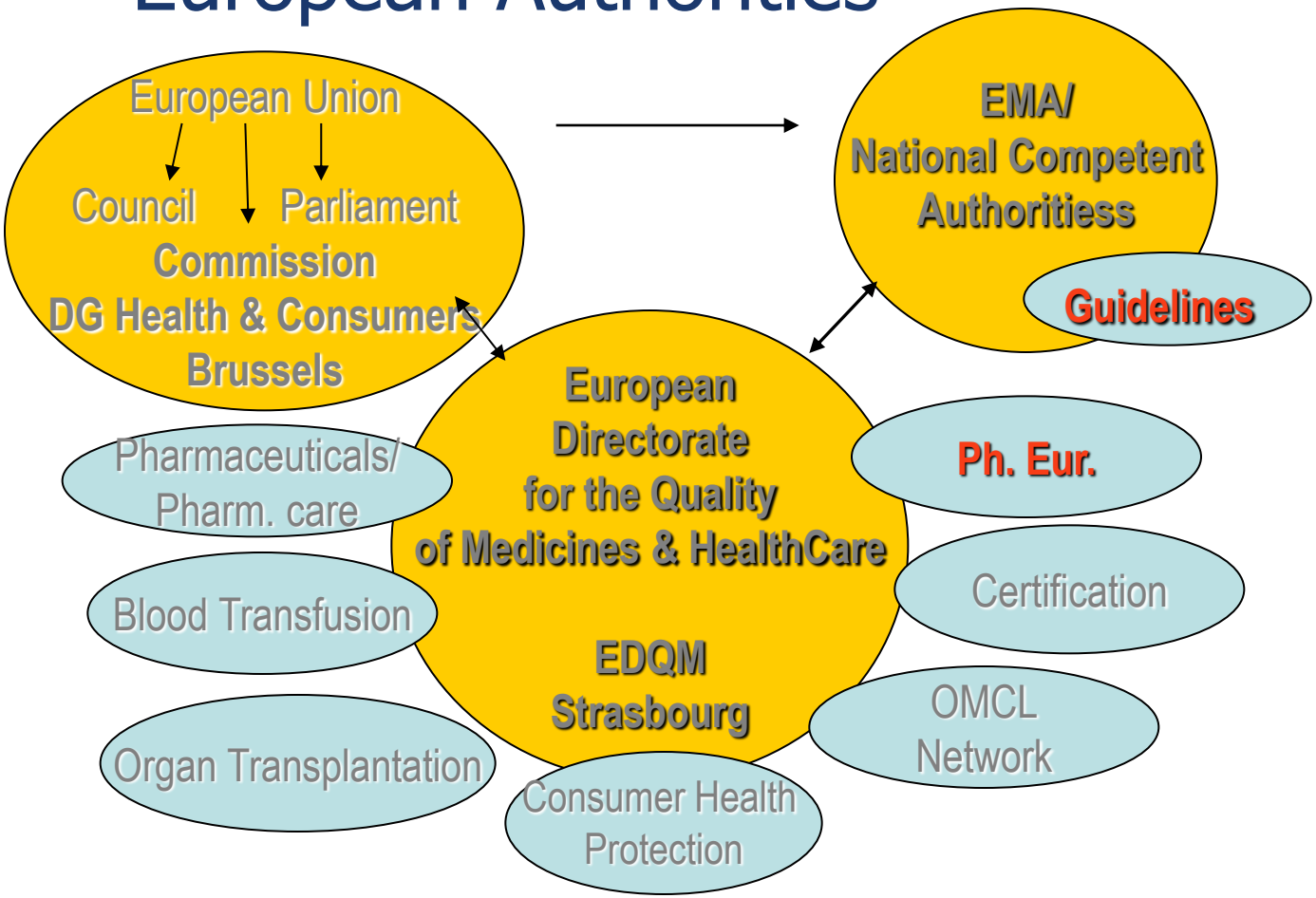
(4) In assembling the dossier for application for marketing authorisation, applicants shall also take into account the scientific guidelines relating to the quality, safety and efficacy of medicinal products for human use as adopted by the Committee for Proprietary Medicinal Products (CPMP) and published 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.

European Regulatory Network
European Authorities

European Union

Council of Europe



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.

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 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-Structure

- 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:

Test to detect: organic impurities, inorganic impurities, volatiles

Methods: physical and physico-chemical, chemical, chromatographic

Robust, validated analytical methods based on collaborative laboratory testing

Individual monographs example from Paracetamol

- **TESTS**
- **Related substances**. Liquid chromatography (2.2.29). *Prepare the solutions immediately before use.*
- *Test solution*. …Dissolve 0.200 g of the substance to be examined in 2.5 mL of methanol R containing 4.6 g/L of a 400 g/L solution of tetrabutylammonium hydroxide R and dilute to 10.0 mL with a mixture of equal volumes of a 17.9 g/L solution of disodium hydrogen phosphate R and of a 7.8 g/L solution of sodium dihydrogen phosphate R.
- *Reference solution (a)*. Dilute 1.0 mL of the test solution to 50.0 mL with the mobile phase. Dilute 5.0 mL of this solution to 100.0 mL with the mobile phase.
- *Reference solution (b)*. Dilute 1.0 mL of reference solution (a) to 10.0 mL with the mobile phase.
- *Reference solution (c)*. Dissolve 5.0 mg of 4-aminophenol R, 5 mg of paracetamol CRS and 5.0 mg of chloroacetanilide R in methanol R and dilute to 20.0 mL with the same solvent. Dilute 1.0 mL to 250.0 mL with the mobile phase.
- *Reference solution (d)*. Dissolve 20.0 mg of 4-nitrophenol R in methanol R and dilute to 50.0 mL with the same solvent. Dilute 1.0 mL to 20.0 mL with the mobile phase.
- *Column*:
- — *size*: *l* = 0.25 m, Ø = 4.6 mm,
- — *stationary phase*: octylsilyl silica gel for chromatography R (5 µm),
- — *temperature*: 35 ° C.
- *Mobile phase*: mix 375 volumes of a 17.9 g/L solution of disodium hydrogen phosphate R, 375 volumes of a 7.8 g/L solution of sodium dihydrogen phosphate R and 250 volumes of methanol R containing 4.6 g/L of a 400 g/L solution of tetrabutylammonium hydroxide R.
- *Flow rate*: 1.5 mL/min.
- *Detection*: spectrophotometer at 245 nm.
- *Injection*: 20 µL.
- *Run time*: 12 times the retention time of paracetamol.
- *Relative retentions* with reference to paracetamol (retention time = about 4 min): impurity K = about 0.8; impurity F = about 3; impurity J = about 7.
- *System suitability*: reference solution (c):
- — *resolution*: minimum 4.0 between the peaks due to impurity K and to paracetamol,
- — *signal-to-noise ratio*: minimum 50 for the peak due to impurity J.
- *Limits*:
- — *impurity J*: not more than 0.2 times the area of the corresponding peak in the chromatogram obtained with reference solution (c) (10 ppm),
- — *impurity K*: not more than the area of the corresponding peak in the chromatogram obtained with reference solution (c) (50 ppm),
- — *impurity F*: not more than half the area of the corresponding peak in the chromatogram obtained with reference solution (d) (0.05 per cent),
- — *any other impurity*: not more than half the area of the principal peak in the chromatogram obtained with reference solution (a) (0.05 per cent),
- — *total of other impurities*: not more than the area of the principal peak in the chromatogram obtained with reference solution (a) (0.1 per cent),
- — *disregard limit* for the calculation of the total of other impurities: the area of the principal peak in the chromatogram obtained with reference solution (b) (0.01 per cent).

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

Flexibility in the Ph.Eur.- 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

- 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

Example table of specifications

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 harmonised community position
  - Alternative approaches may be taken – provided appropriate justification
  - Facilitate assessment approval and control

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

Useful addresses

EUROPEAN COMMISSION

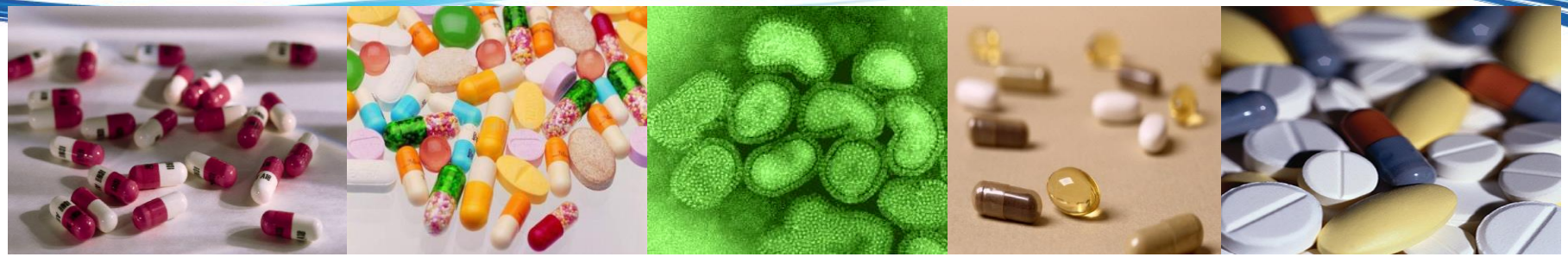
http://ec.europa.eu/health/index_en.htm

EMA home page

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

EDQM Home page

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



Thanks

Any questions?
….but not too many!

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