

**From the Assessor's Perspective
Key Requirements for the Evaluation
of
the Quality Dossier**

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- Introduction
- Presentation of the application dossier
- Good Regulatory Practices
- Key Requirements for the Evaluation of the Quality Dossier from the Assessor's Perspective
- Take Home Message

Introduction

(2) The essential aim of any rules governing the **production**, **distribution** and **use** of medicinal products must be to **safeguard public health**.

(3) However, this objective must be attained by means which will not hinder the **development** of the **pharmaceutical industry** or **trade** in **medicinal products** within the **Community**.

No medicinal product may be placed on the market of a Member State unless a **marketing authorization** has been issued by the **competent authorities** of that **Member State** in accordance authorization has been granted in accordance with this Directive or an authorization has been granted in accordance with Regulation (EEC) No 2309/93.

Article 6 (1), Directive 2001/83/EC, as amended

In order to obtain an authorization to place a medicinal product on the market regardless of the procedure established by Regulation (EC) No 2309, an **application** shall be made to the **competent authority** of the Member State concerned.

Article 8 (1), Directive 2001/83/EC, as amended

Presentation of the application dossier

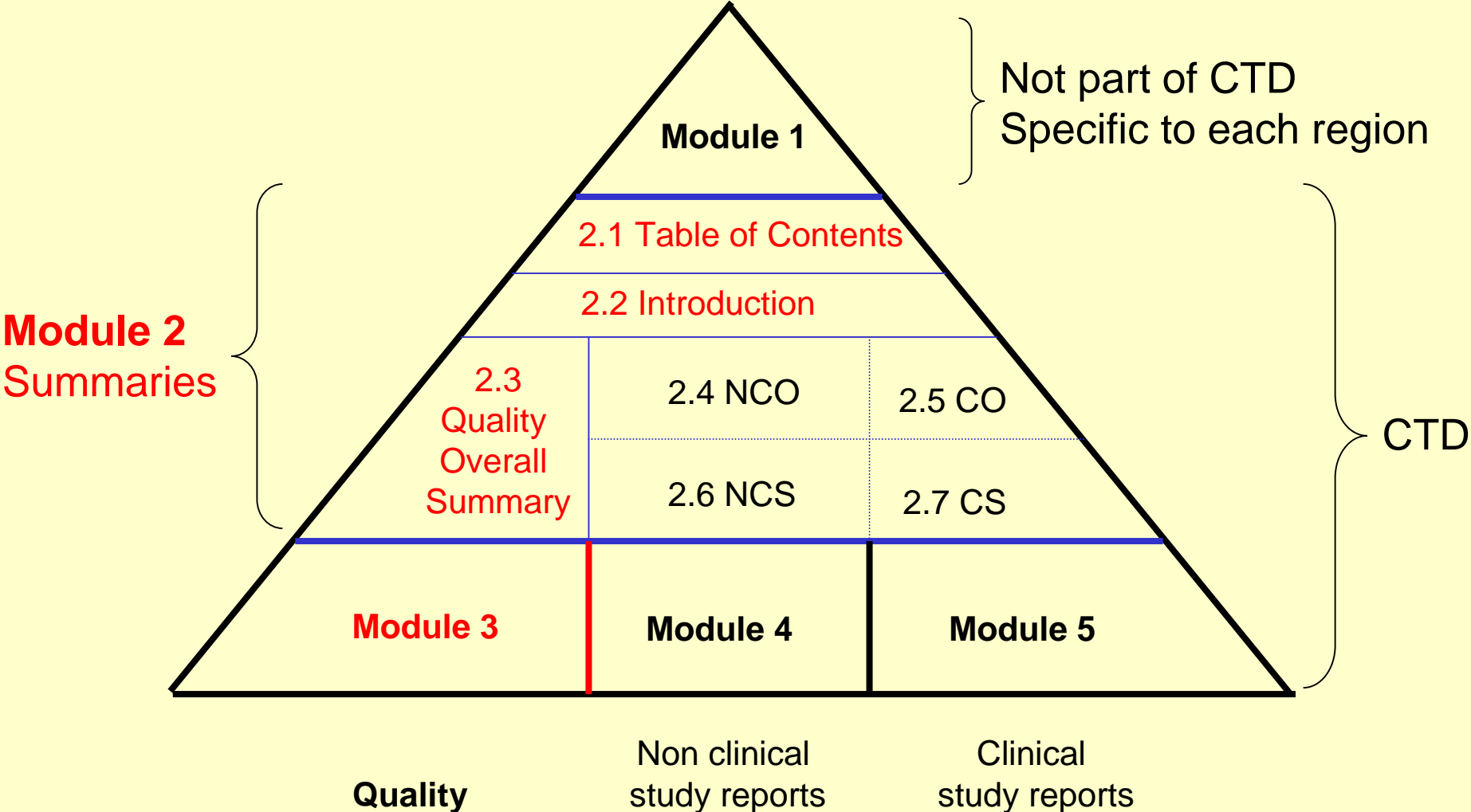
Dossier
for
the Marketing Authorisation Application

Quality

Safety

Efficacy

The CTD Pyramid



Introduction and general principles, (2), Directive 2003/63/EC

Module 1: **Specific to each region (= Country)**

- 1B1: Application form
- 1B2: SPC labelling leaflet
- 1B3: Experts form
- 1B4: Additional requirements

Module 2: **Summaries**

- A: Table of contents
- B: Introduction (1 pp)
- C: Quality overall summary (30 pp)
- D: Non clinical overview (30 pp)
- E: Clinical overview (30 pp)
- F: Non clinical summary
(written summary & tabulated summary)
(100 – 150 pp)
- G: Non clinical summary
(written summary & tabulated summary)
(100 – 150 pp)

Module 3:

Quality

- A: Table of contents
- B: Body of data
- C: References

Module 4:

Non clinical study reports

- A: Table of contents
- B: Study reports
- C: References

Module 5:

Clinical study reports

- A: Table of contents
- B: Tabular listing studies
- C: Study reports
- D: References

In assembling the dossier for application for marketing authorisation, applicant shall also take into account the **scientific guidelines** relating to the **quality**, safety and efficacy of medicinal products for human use as adopted by **CPMP** ...

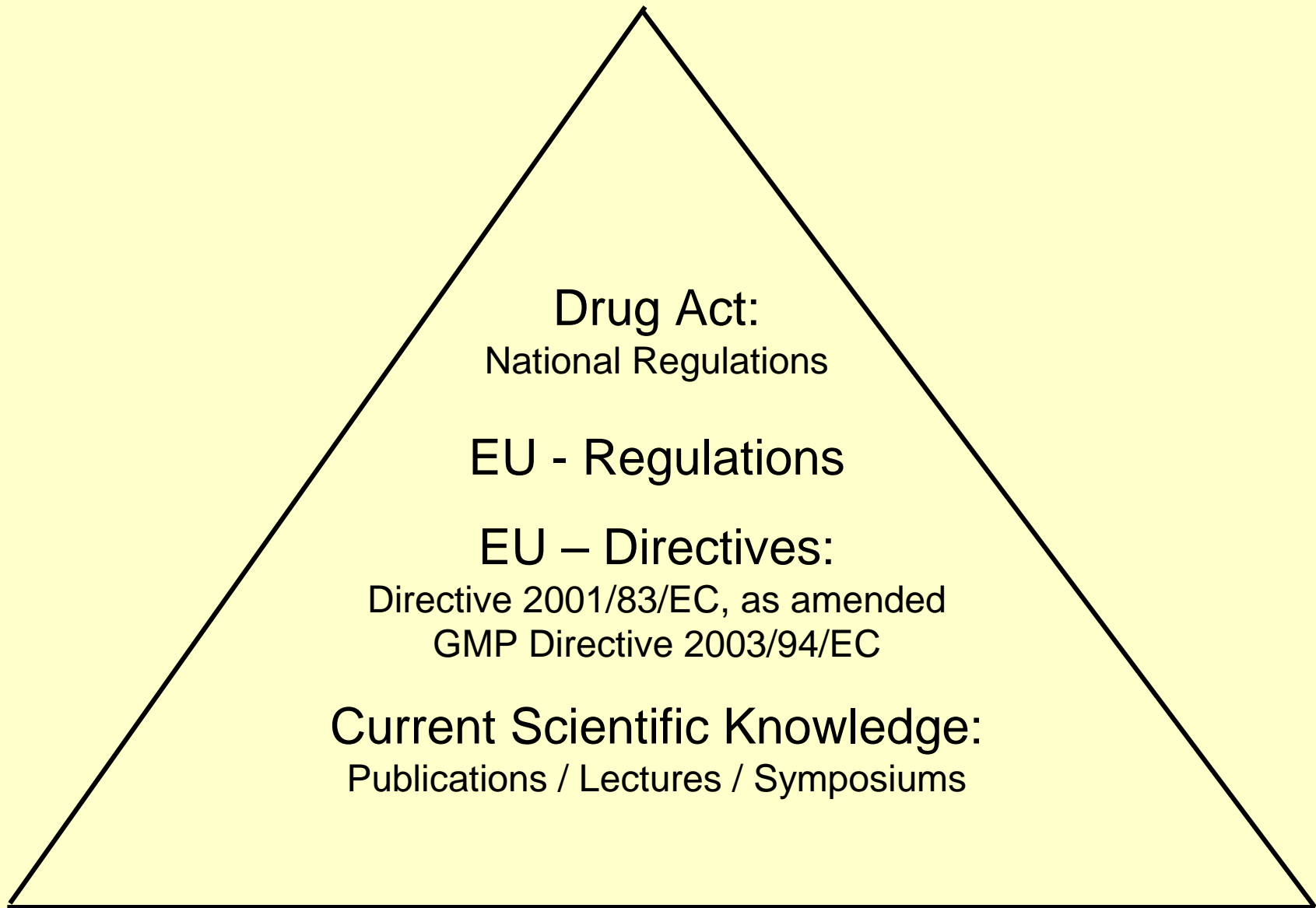
Introduction and general principles, (4), Directive 2003/63/EC

All information, which is relevant to the evaluation of the medicinal product concerned, **should be included** in the application, **whether favourable** or **unfavourable** to the product. In particular, all relevant details should be given of any incomplete or abandoned pharmacotoxicological or clinical test or trial relating to the medicinal product and/or completed trials concerning therapeutic indications not covered by the application.

The adoption of the **same standards** and protocols by all the Member States will enable the competent authorities to arrive all their **decisions** on the basis of **uniform tests** and by reference to **uniform criteria** and will therefore help **avoid differences** in **evaluation**.

Preamble, (11), Directive 2001/83/EC

Good Regulatory Practice (GRP)



GLP:	GOOD	LABORATORY	PRACTICE
GCP:	GOOD	CLINICAL	PRACTICE
GMP:	GOOD	MANUFACTURING	PRACTICE
GSP:	GOOD	STORAGE	PRACTICE

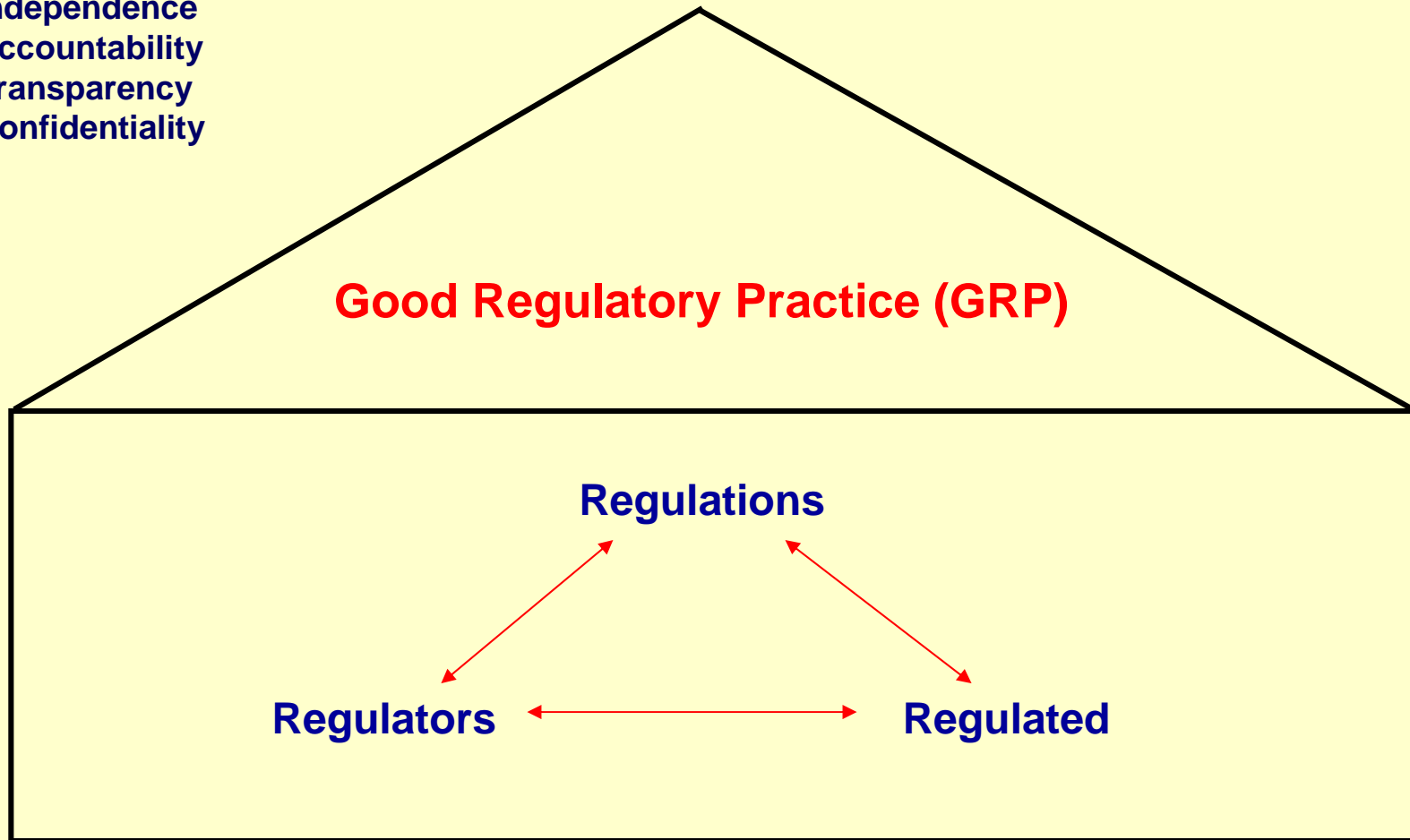
G "X" P:	GOOD	"X"	PRACTICE
GRP:	GOOD	REGULATORY	PRACTICE

Principles of GRP

1. Independence
2. Accountability
3. Transparency
4. Confidentiality

Good Common Sense

Good Regulatory Practice (GRP)



Principles of GRP

1. Independence
2. Accountability
3. Transparency
4. Confidentiality

Good Common Sense

Good Regulatory Practice (GRP)

Good Documentation Practice

Good Guidance Practice

Good Review Practice

Key Requirements for the Evaluation of the Quality Dossier from the Assessor's Perspective

Key Requirements

Assessor's Perspective

I.
Active
Substance

II.
Pharmaceutical
Development

III.
Stability
Testing

I. Active substance

Definition of a new substance / a known active substance / a stable active substance

New Substance (NCE)	According to Part B of the Annex to Council Regulation 2309/93, a new active substance is defined as a substance not authorised by any Member State on 1.1.95 for use in a finished product intended for human use. Ref.: [CPMP/ICH/2736/99 (Revision 2) or ICH Q1A (R2)]
Known Active Substance (Generic)	An existing active substance is one that has been authorised previously through a finished product within the European Community. Ref.: (CPMP/QWP/122/02, Rev. 1)
Stable Active Substance (“Old” generic)	An active substance is considered as stable if it is within the defined/regulatory specifications when stored at 25°C / 60 % RH (2 years) and 40°C / 75 % RH (6 months). Ref.: (Annex 1 to CPMP/QWP/122/02, Rev. 1)

- NfG: Stability Testing of New Drug Substances and Products (Revision 2) - Revision of CPMP/ICH/380/95 – (CPMP/ICH/2736/99) or [ICH Q 1 A (R2)]
- NfG on Stability Testing of Existing Active Substances and Related Finished Products (CPMP/QWQP/122/02 Rev. 1)

Dossier for the drug substance

- **Complete part 3.2.S for a new drug substance (NCE)**
- **EDMF for NCE or existing active substance**
- **Certificate of Suitability of the European Directorate for the Quality of Medicines (EDQM)**



Definition:
Impurities in the drug substance / product

- a) Any component of the new drug substance which is not the chemical entity defined as the new drug substance.
- b) Any component of the drug product which is not the chemical entity defined as the drug substance or an excipient in the drug product.

- NfG: Specifications: Test procedure and acceptance criteria for new drug substance and new products: Chemical substances - (CPMP/ICH/367/96 corr or ICH Q 6)

3.2. S 3.2 Impurities

- Discussion of *potential impurities* most likely to arise during synthesis, statement on their formation
- Statement whether potential impurities have been synthesised, information on structural analysis and methods of analysis to determine these impurities
- Discussion of *potential degradation products*
- Information on methods of analysis (**L**imit **O**f **D**etection (LOD) and **L**imit **O**f **Q**uantitation (LOQ) for the determination of likely impurities and related substances

Dossier for the active ingredients (e.g. NCE)

- Copies of chromatograms
- Summary of nature and amount of actual impurities found in the batches tested
- Justification of specification based on safety and toxicology aspects, test method and actually found values

3.2. S 7.3 Stability Data

- Results of stress testing as an integral part of the dossier, to generate degradation products and elucidate the mechanism of degradation, e.g., hydrolysis, photolysis, sensitivity to higher temperatures, oxidation....
- Information on analytical procedures and their validation

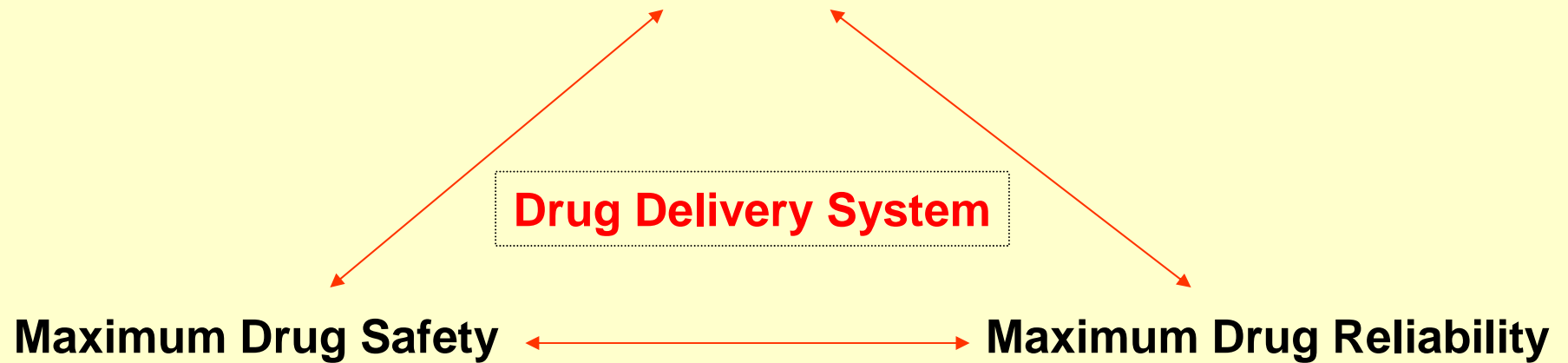
Specifications for Impurities in the Active Ingredients

- Impurities Testing Guideline: Impurities in New Drug Substances (ICH Q3A*)
- Pharmacopoeial monograph and general monograph “Substances for pharmaceutical use“

*No. of the Guideline of the International Conference of Harmonisation

II. Pharmaceutical Development

Optimum Drug Effectiveness



Factors Affecting Drug Product **Reliability**

- Chemical stability
- Physical stability
- Microbiological stability
- Unit-dose precision
- Bioavailability
 - High percentage
 - Uniformity
 - Stability
- Patient acceptance
 - Convenience**
 - Pharmaceutical elegance**

II. Pharmaceutical Development

P 2.1 Components of the finished drug

P 2.1.2 Excipients

P 2.2 Finished drug

P 2.2.1 Formulation development

P 2.2.2 Overages

P 2.2.3 Physical and biological properties

P 2.3 Manufacturing process development

P 2.4 Container/Closure system

P 2.5 Microbiological attributes

P 2.6 Compatibility

Note for Guidance on Development Pharmaceuticals

1. Introduction
2. Components of the product
3. Formulated products
4. Packaging materials
5. Manufacturing process
6. Conclusion

II. Development of pharmaceuticals

Conclusion:

Properly conducted development studies should ensure that relevant release and shelf-life specifications are applied in order that the desired product characteristics can consistently be met at release and through out shelf-life.

III. Stability Testing

The **purpose** of stability testing is to **provide evidence** on how the **quality of a drug/an active substance** or drug/finished product **varies with time** under the **influence** of a variety of environmental factors such as **temperature, humidity and light**, and to **establish** a **re-test period for the drug/active substance** or a shelf life for the finished product and recommended storage conditions.

- NfG: Stability Testing of New Drug Substances and Products (Revision 2) - Revision of CPMP/ICH/380/95 – (CPMP/ICH/2736/99) [ICH Q 1 A (R2)]
- NfG on Stability Testing of Existing Active Substances and Related Finished Products (CPMP/QWQP/122/02 Rev.1.)

Information on the stability of the active substance is an integral part of the systematic approach to stability evaluation.

- NfG: Stability Testing of New Drug Substances and Products (Revision 2) - Revision of CPMP/ICH/380/95 – (CPMP/ICH/2736/99) [ICH Q 1 A (R2)]
- NfG on Stability Testing of Existing Active Substances and Related Finished Products (CPMP/QWQP/122/02 Rev1.)

Stability studies

Pharmaceutical Development	<ul style="list-style-type: none">• Stress testing• Photo -Stability• Studies to support process and product development• Clinical trial stability• Shipping and In-use stability• Intermediates
Submission and Approval	<ul style="list-style-type: none">• Formal studies for the application• Stability commitment
Post-approval	<ul style="list-style-type: none">• On-going stability testing• Commitment batches• Stability studies initiated by:<ul style="list-style-type: none">- Changes- Deviations

Contents of Stability Testing Guidelines

1. General
2. Stress Testing
3. Selection of Batches
4. Container Closure System
5. Specification
6. Testing Frequency
7. Storage Conditions
8. Stability Commitment
9. Evaluation
10. Statements/Labelling

Stability Testing Guidelines

CPMP/ICH/2736/99 (Revision 2)	CPMP/QWP/122/02, Rev. 1
<p data-bbox="304 512 427 560">Scope</p> <ul data-bbox="304 580 949 1254" style="list-style-type: none"><li data-bbox="304 580 949 735">• Information to be submitted in registration application for new molecular entities<li data-bbox="304 767 949 1254">• Does not cover<ul data-bbox="344 836 927 1254" style="list-style-type: none"><li data-bbox="344 836 927 943">- abbreviated or abridged applications<li data-bbox="344 963 927 1007">- variations<li data-bbox="344 1027 927 1070">- clinical trial applications<li data-bbox="344 1091 927 1254">- Specific details on sampling and testing for particular dosage forms	<p data-bbox="1135 512 1258 560">Scope</p> <ul data-bbox="1135 580 1760 735" style="list-style-type: none"><li data-bbox="1135 580 1760 735">• Information to be submitted in registration application for existing active substances

Definition of Storage Conditions

Testing conditions where stability has been shown	Required label	Additional label, where relevant
25°C/60 % r.F. (Lt) 40°C/75% r.F. (acc) or 30°C/65% r.F. (Lt) 40°C/75% r.F. (acc)	None ***	Do not refrigerate or freeze
25°C/60% r.F. (Lt) 30°C/60% r.F. (int) or 30°C/65% r.F. (LT)	Do not store above 30°C Or Store below 30°C	Do not refrigerate or freeze
25°C/60% r.F. (It)	Do not store above 25°C Or Store below 25°C	Do not refrigerate or freeze
5°C (It)	Store refrigerated OR Store and transport refrigerated	Do not freeze
Below zero	Store in a freezer OR Store and transport in a freezer	

***** SPC: The product does not require any special storage conditions within Europe**

Definition "significant change" for a finished Drug

- $\geq 5\%$ potency loss
- OOS* for degradation product(s)
- OOS for pH-value
- OOS in in vitro dissolution
12 capsules or tablets
- OOS in appearance, physical properties

*OOS = Out Of Specification

Stability Tests – Frequent Deficiencies

Storage conditions

- not defined
- no stress testing or testing under acc. conditions

Selection of batches

- too small batches
- initial value OOS
- different synthesis/manufacturing process
- different container/closure system

Test results

- Test method not stability indicating
- degradation products not identified or qualified
- no mass balance
- insufficient data basis to define re-test period/shelf-life and
- storage conditions

Take Home Message

3.2.S.2 Control of a finished Drug

Pharmacopoeial Monograph

...

It must be kept in mind, that, even when a monograph has been in force for many years it will not necessarily be sufficient in relation to a new route of synthesis.

...

NfG: Summary of Requirements for Active Substances in Part II of the Dossier
(CPMP/QWP/297/96)

[4. Other evidence of suitability of the Pharmacopoeial monograph]

3.2.P.2 Control of a finished Drug

3.2.P.3.3 Description of the Manufacturing Process and Process Controls

...

It is in the interest of both the applicant and the regulatory authority to avoid unnecessary applications for variations.

Therefore: Very detailed description of the manufacturing process, apparatus and in-process controls should be avoided.

...

NfG: Manufacture of the Finished Dosage Form (CPMP/QWP/486/95) Re-issued in April 1996, [4. Description of the manufacturing process]

3.2.P.3.5 Control of a finished Drug

...

- Release limits of $\pm 5\%$ are acceptable without further justification.
- Release limits wider than $\pm 5\%$ would need to be justified in the part "Development Pharmaceuticals" with experimental results which are normally based on a confidence level of 95%. The wider limits also include both, the variation of production and of the test procedure for assay.

...

Specifications and Control Tests on the Finished Product
EudraLex, 3AQ11a, 1998

[1.5.2 Maximum acceptable deviation in the contents of active substance]

3.2.P.5 Control of a finished Drug

3.2.P.5.3 Validation

Remember

a) Validation is not

- an exercise to create as much paper as possible
- another unnecessarily burdensome regulatory requirement.

b) Validation provides

- documented evidence of consistency from batch to batch.

3.2.P.5 Control of a finished Drug

3.2.P.5.3 Validation

The 4 R's:

- **Repeatability**
 - precision within short time-frame, same conditions
 - intra-assay
- **Reproducibility** - intermediate precision
 - precision over longer time-frame, some conditions altered: different analyst, different system
 - inter-assay
- **Ruggedness** (Reproducibility of)
 - precision with major conditions altered: different laboratory; collaborative studies
- **Robustness**
 - reliability

3.2.P.7 Container Closure System

...

In principle, medicinal products should be packed in containers that ensure stability and protect from deterioration.

A label statement can not be used to compensate for inadequate or inferior packaging.

...

NfG : ... Declaration of Storage Conditions for Medicinal Products in the Product Particulars (CPMP/QWP/609/96 Rev.1)
[5. General storage statements]

It should be emphasized that no guidance can cover all eventualities, and **common sense** and a **clear focus on the needs** of the regulatory authority assessor are the **best guides** to constructing a document.

Module 2 F, Nonclinical Summary, NTA, Vol. 2 B, Edition 2001

Thank you for
your kind attention