


Welcome

Common Technical Document (CTD)


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Promoting the Quality of Medicines

CTD Dossier and PQM experiences


- WHO's CTD requirements
- Common Deficiencies observed by PQM

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Assessment of data on
safety, efficacy and quality

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Inspection for compliance
with GMP

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Inspection for compliance
with GCPs and GLPs

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Reliance on information supplied
by SRAs



Prequalification



Essential Medicines and Health Products: Prequalification of medicines

Information for



Quality Assessment
Safety & Efficacy Assessment
Product Labeling

**PREQUALIFYING FINISHED
PHARMACEUTICAL PRODUCTS,
ACTIVE PHARMACEUTICAL
INGREDIENTS AND QUALITY
CONTROL LABORATORIES**

HIV/AIDS
Tuberculosis
Malaria
Hepatitis B&C
Neglected Tropical Diseases
Diarrhea
Influenza
Reproductive Health

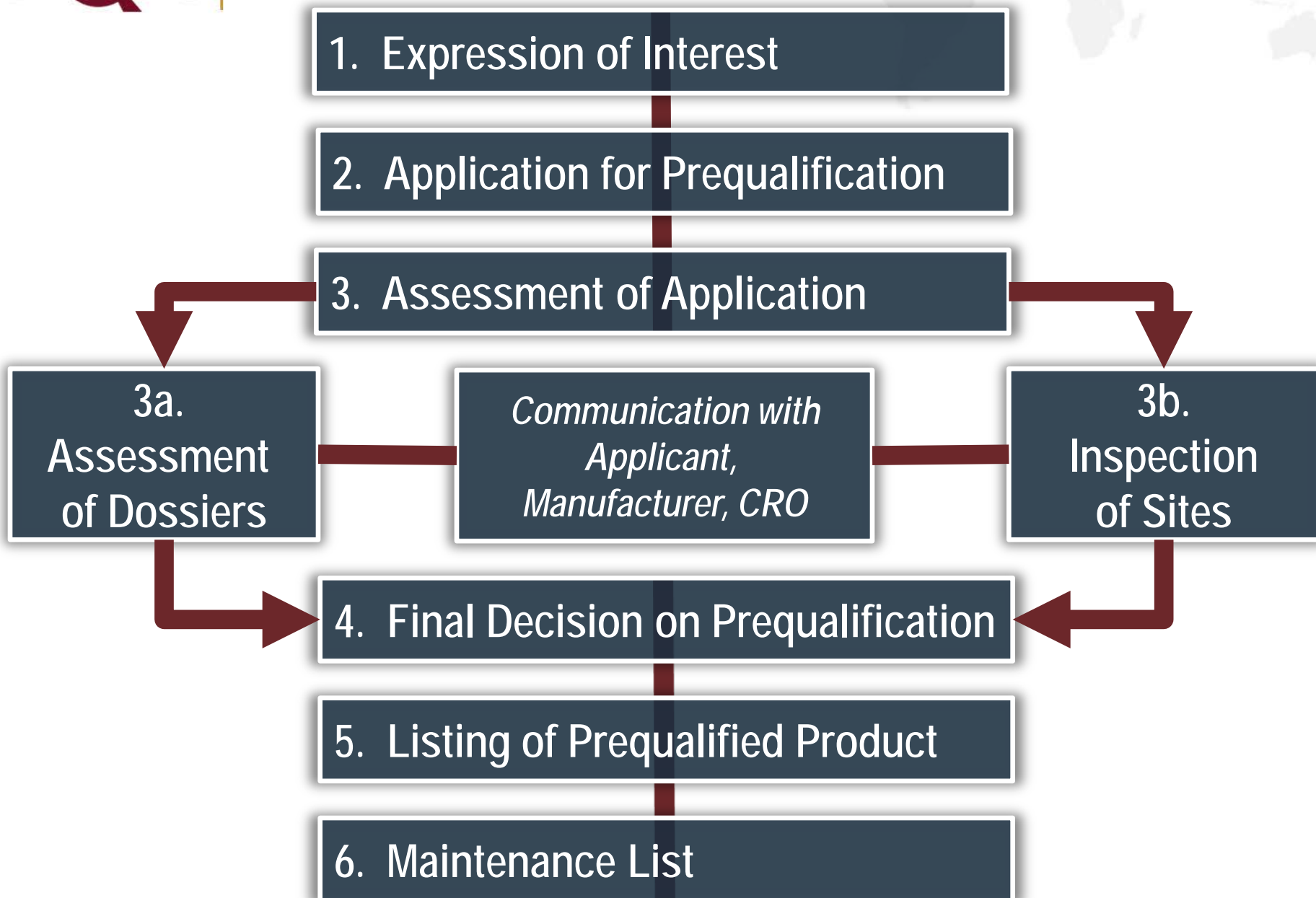


1. Cover letter
2. Product Dossier
3. Product Samples
4. Site Master file for each manufacturing site
5. Contract Research Organization master file (CROMF) for each clinical site.

Submit all documentation in English

1. Submission of application
2. Screening by WHO (Accepted, queried, rejected)
3. Reference number issued
4. Dossier assessment (Quality, Efficacy/ BE, Labeling and printed information)
5. Site inspection- based on risk management principles
6. Reporting and communication of results- Timelines for responses
7. Final decision on Prequalification
8. Listing of Prequalified Product
9. Maintenance of Prequalification status – changes or variations to be communicated to WHO

Prequalification Process

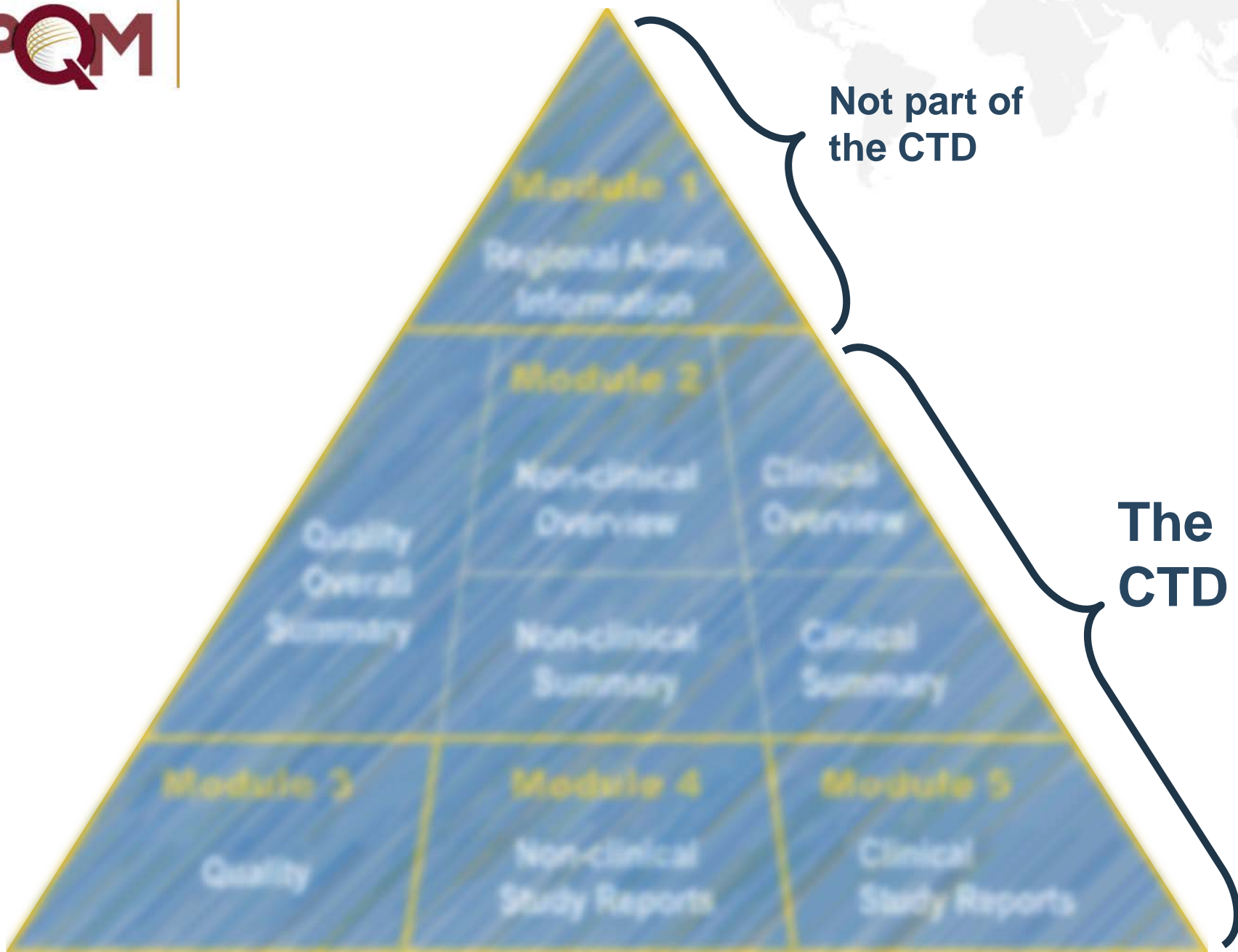


Common Technical Document (CTD)

Background: International Council for Harmonisation (ICH)



Joint regulatory-industry initiative
Harmonize regulatory requirements
Common Technical Document (CTD)



Makes life difficult!

Difficult to access!

Too complicated!

Too many requirements!



- ▶ Provides a logical way for dossier data organization - a single dossier can be submitted to multiple Authorities
 - *Dossier in CTD format* significantly improves the quality of dossiers and efficiency of assessment process
- ▶ **General Guidance for the preparation of Dossier:**
 - Provides general guidance for **preparation** and **organisation** of dossiers; and,
- ▶ **Describes and adopts** the modular format of the CTD
- ▶ Provides guidance on the location of **regional** information and other general data requirements

- Guideline on submission of documentation for a multisource (generic) Finished Pharmaceutical Product for the WHO Prequalification of Medicines programme: quality part [TRS 970, annex 4—published in 2012]
 - Guidelines on submission of documentation for a multisource (generic) finished product. General format: preparation of product dossiers in common technical document format.[TRS 961, annex 15- published in 2011]
-
- Quality overall summary (QOS)
 - Quality information summary (QIS)
 - Bioequivalence trial information form (BTIF), if BE is required
 - Other WHO TRS



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Module 1

Administrative and Prescribing Information


Documents specific to WHO and each region with content and format specified by WHO and relevant regulatory authorities

Summary of bioequivalence/bioavailability information according to WHO's Bioequivalence Trial Information Form (BTIF)


Quality information summary (QIS) per WHO's Guideline on submission of documentation for a multisource (generic) finished pharmaceutical product (FPP)




Module 1




- 1.0 Cover Letter**
- 1.1 TOC**
- 1.2 Application Information**
- 1.3 Product information**
- 1.4 Regional summaries**
- 1.5 Electronic Review**
- 1.6 Samples**



- 1.2.1 EOI**
- 1.2.2 MA**
- 1.2.3 CEP and LOA**
- 1.2.4 LOA**
- 1.2.5 GMP Cert.**
- 1.2.6 Biowaiver request**



- 1.3.1 SMPC**
- 1.3.2 Labelling**
- 1.3.3. PIL**



- 1.4.1 BTIF**
- 1.4.2 QIS_JULY 2017**



The QOS Template

Summary of the quality information- WHO's quality overall summary-product dossier (QOS-PD)

Summary of the quality information presented in modules 3, 4, and 5
Completed in electronic word format by applicant as part of a PD

The QIS Template

Filled out by applicant as part of summary of QOS
Basis of the quality assessment approval summary

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Module 2



2.1 TOC
2.2 CTD Introduction
2.3 QOS



QOS_PD_Mar 2017



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Module 3

Quality

Information on quality should be presented in the structured format described in ICH M4Q and WHO's Guideline on submission of documentation for a multisource (generic) finished pharmaceutical product (FPP): quality part (8).

Module 3

3. Quality Body of Data

3.2 Regional Information



3.2.R1 Production documentation
3.2.R2 Analytical procedure and validation

3.2 S



S.1 General information
S.2 Manufacture
S.3 Characterization
S.4 Control of the API
S.5 Reference Standard
S.6 Container Closure system
S.7 Stability

3.2 P



P.1 Description of Composition
P.2 Pharmaceutical Development
P.3 Manufacture
P.4 Control of excipients
P.5 Control of FPP
P.6 Reference Standard
P.7 Container Closure system
P.8 Stability



API Data Submission

API data for an FPP dossier

- APIMF procedure
- Reference to prequalified and/or API accepted with WHO/PQ
 - Prequalified, accepted in prequalified FPP or pending FPP PDs without concern of API section
- CEP: certificate of suitability (EDQM)
- Full API data in FPP PD by FPP manufacturer

Module 3

3.2 S



S.1 General information
S.2 Manufacture
S.3 Characterization
S.4 Control of the API
S.5 Reference Standard
S.6 Container Closure system
S.7 Stability

3.2 P



P.1 Description of Composition
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P.5 Control of FPP
P.6 Reference Standard
P.7 Container Closure system
P.8 Stability



P.2.1 Components
P.2.2 FPP
P.2.3 Manufacturing Process Dev
P.2.4 Container Closure System
P.2.5 Microbiological attributes
P.2.6 Compatibility



P.3.1 Manufacturer(s)
P.3.2 Batch formula
P.3.3 Description of manuf.proces
P.3.4 Control of critical steps and intermediate
P.3.5 Process validation and evaluation



P.4.1 Specifications
P.4.2 Analytical procedure
P.4.3 Validation of analytical procedure
P.4.4 Justification of specification
P.4.5 Excipients of human or animal origin
P.4.6 Novel excipients



P.5.1 Specification
P.5.2 Analytical procedure
P.5.3 Validation of analytical procedure
P.5.4 Batch analysis
P.5.5 Characterization of impurities
P.5.6 Justification of specifications



P.8.1 Stability Summary and conclusion
P.8.2 Stability protocol and commitment
P.8.3 Stability data

A purple binder with a silver ring on the left side. A white label on the right side of the binder reads 'Module 4' in a bold, dark blue font.

Module 4


**NOT
APPLICABLE**

Nonclinical study reports

Generally not applicable for multisource products

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Module 5

A circular orange icon with a silver border, containing a white folder symbol.

Clinical study reports

Generic drugs requiring bioequivalence

Generic eligible for biowaiver based on BCS



PQM Experiences



Common Technical document format not followed

Cover letter does not state that the information and data submitted is “true, complete and correct”

Product types and strength not invited in the EOI: Type of product, Strength should be included. If score is stated, this should be included.

Critical documents are not signed, dated, or version controlled.



QOS-PD and QIS not submitted as word documents.

QOS-PD not completed in an acceptable way including references to dossier pages: Information should be summarized in the respective sections.

Failure to include adequate summary of the dossier information in the QOS/ QIS/ BTIF. Only page references are provided under each of the sections.

A large white oval with a thin black border. Inside the oval, the text 'I ♥ FIXING PROBLEMS' is centered. 'I' is in a large, black, serif font. '♥' is a solid red heart. 'FIXING PROBLEMS' is in a smaller, black, serif font, stacked on two lines.

**I ♥
FIXING
PROBLEMS**

The option used for the submission of API data not indicated: Clearly indicate option used- APIMF, API prequalification(PQ-API), CEP or full data

Name and address of the API and FPP manufacturing sites do not indicate the block/ unit numbers: indicate the building/ block/ unit used for the manufacture of the API/ FPP.

Confirmation of API Prequalification, letters of access nor EDQM CEP not provided: valid versions should be submitted.

Failure to discuss polymorphism and PSD when relevant; both affect intrinsic solubility

- Future API batches may have different properties than the batches used in the bio-batch
- Check dose solubility and presence of known polymorphs

Control of the API

- Failure to provide signed and dated specifications used by the FPP manufacturer
- Failure to provide COAs for Exhibit API batches (including biolot API batch) as tested by the FPP site

Reference Standards

- Failure to provide information on the source and qualification of RS used at the FPP site

Manufacturing process:

- Failure to include appropriate limits (as a range) for moisture content of final blend
- Failure to provide supporting hold time data
- Failure to include in Process Validation the need for dissolution profile testing of process validation batches and similarity determination to the bio batch profile

Only one set of specifications provided

Assay limit at release is too wide (90-110%)

Description is given in a separate document

Failure to include specific identity test (or combination of tests)

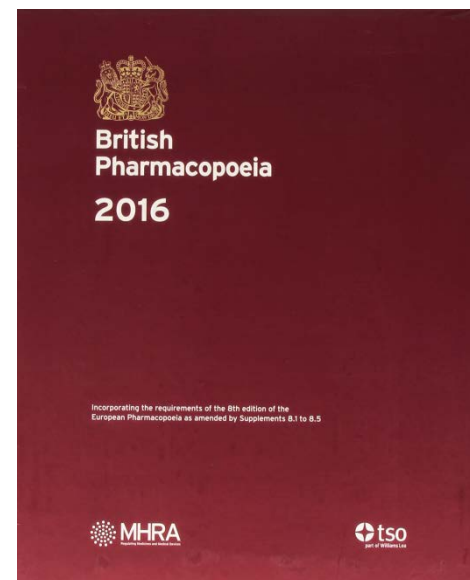
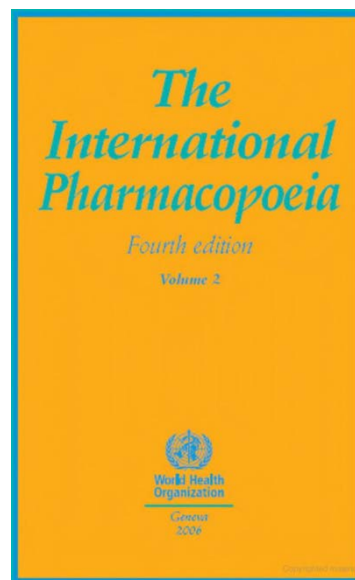
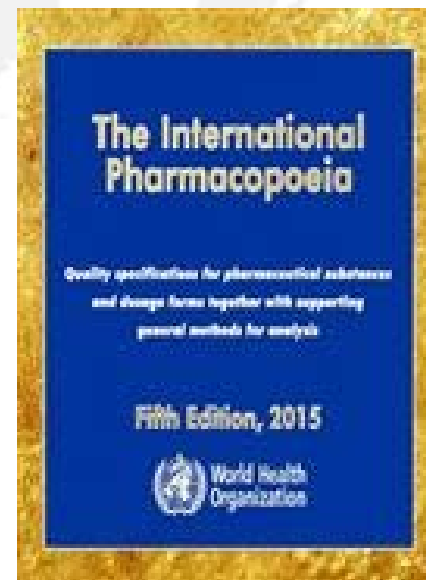
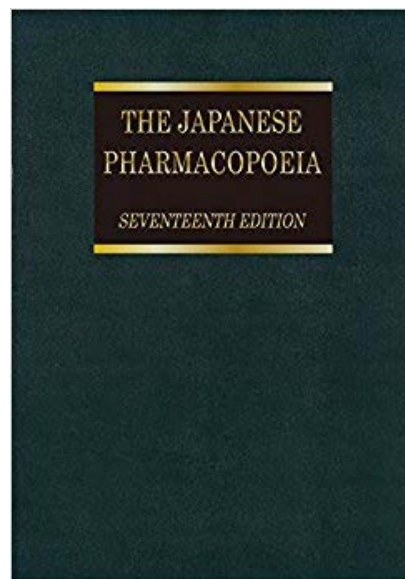
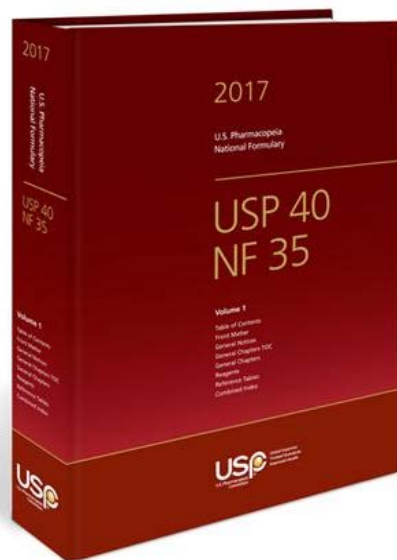
Premature skip testing proposals

- Two sets of specifications (dated, signed, and version-controlled) should be provided
- Assay limit at release should be $100 \pm 5\%$ unless otherwise justified
- The FPP description should be fully defined in the release and shelf life specifications
- Skip testing is only acceptable under defined conditions

Compendial references

1. Confirm up-to-date (i.e., “most recent” column)
2. Reference to available monographs is an important part of quality assessment; monograph standards are considered the **minimum** requirements for an API/FPP

Recognized Pharmacopoeias



1. In case of oral liquids, failure to include dose measuring device
 - a. Doses as low as 0.6 ml may be withdrawn
2. Missing ID tests from specifications for primary containers
 1. Failure to provide stability protocol and commitments for future stability programs:
 - a. Primary stability batches
 - b. Commitment batches: *not less than three production batches in each container closure system*
 - c. Ongoing stability batches: *at least one production batch per year (unless none is produced that year) in each container closure system*

Section 3.2.R.1.2: Master Production Records

1. Failure to submit blank master production records for the intended commercial batch size(s)
2. Include a comparison of the formulation and process (equipment, parameters, and controls) of the proposed production batches versus the executed records of the bio-lot
3. Granulation should be characterized by a set of parameters (mixing mechanism, mixing time, mixing speed, fluid and its addition rate)

WHO PQP website: <http://apps.who.int/prequal/>

- ▶ WHO: Multisource (generic) pharmaceutical products: guidelines on registration requirements to establish interchangeability. WHO Technical Report Series 992, Annex 7 (2015). *MA: Guideline on the Investigation of Bioequivalence* (London, 20 January 2010). [Doc. Ref.: CPMP/EWP/QWP/1401198 Rev.I/Corr**]
- ▶ *USFDA: Guidance for Industry, Bioavailability and Bioequivalence Studies for Orally Administered Drug Products - General Considerations*. U.S. Department of Health and Human Services, Food and Drug Administration, Centre for Drug Evaluation and Research (CDER) (March 2003; Revision 1).
- ▶ Canada: Guidance Document- *Conduct and Analysis of Comparative Bioavailability Studies* (2012) and Guidance Document - *Comparative Bioavailability Standards: Formulations Used for Systemic Effects* (2012).

Good Clinical Practice (GCP) & BE Requirements

Gabriel Kaddu, Senior GMP Specialist
Promoting the Quality of Medicines Program (PQM)
U.S. Pharmacopeial Convention (USP)

A standard for the design, conduct, performance, monitoring, auditing, recording, analysis and reporting of clinical trials that provides assurance that the data and reported results are credible and accurate, and that the rights, integrity and confidentiality of trial subjects are protected. (ICH GCP)

A standard for clinical studies which encompasses the design, conduct, monitoring, termination, audit, analyses, reporting and documentation of the studies and which ensures that the studies are scientifically and ethically sound and that the clinical properties of the pharmaceutical product (diagnostic, therapeutic or prophylactic) under investigation are properly documented. (WHO GCP)

- Declaration of Helsinki: Adopted by the 18th WMA General Assembly, Helsinki, Finland, June 1964 and amended at subsequent WMA General Assemblies 1975 – 2013

Preamble

The World Medical Association (WMA) has developed the Declaration of Helsinki as a statement of ethical principles for medical research involving human subjects, including research on identifiable human material and data. The Declaration is intended to be read as a whole and each of its constituent paragraphs should be applied with consideration of all other relevant paragraphs.

- CIOMS International Ethical Guidelines for Biomedical Research Involving Human Subjects
- GCP (ICH, WHO or other)
- Local laws and regulations
 - Clinical trial
 - Ethics
 - Medical care and records
 - Secrecy and confidentiality



WMA Declaration of Helsinki - Ethical Principles for Medical Research Involving Human Subjects

Adopted by the 18th WMA General Assembly, Helsinki, Finland, June 1964
and amended by the:

- 29th WMA General Assembly, Tokyo, Japan, October 1975
- 35th WMA General Assembly, Venice, Italy, October 1983
- 41st WMA General Assembly, Hong Kong, September 1989
- 48th WMA General Assembly, Somerset West, Republic of South Africa, October 1996
- 52nd WMA General Assembly, Edinburgh, Scotland, October 2000
- 53rd WMA General Assembly, Washington DC, USA, October 2002 (Note of Clarification added)
- 55th WMA General Assembly, Tokyo, Japan, October 2004 (Note of Clarification added)
- 59th WMA General Assembly, Seoul, Republic of Korea, October 2008
- 64th WMA General Assembly, Fortaleza, Brazil, October 2013

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The Declaration is intended to be read as a whole and each of its constituent paragraphs should be applied with consideration of all other relevant paragraphs.

2. Consistent with the mandate of the WMA, the Declaration is addressed primarily to physicians. The WMA encourages others who are involved in medical research involving human subjects to adopt these principles.

General Principles

3. The Declaration of Geneva of the WMA binds the physician with the words,

Oversight of Clinical Trials Responsibilities

- Institutional Review Board/Independent Ethics Committee /(IRB/IEC)
- Investigator responsibility
 - Patient well-being - Safety, Health, Rights
 - Protocol adherence
- Sponsor responsibility
 - Protocol
 - Background information
 - Monitoring & data management
- Monitor verifies
 - Background information
 - Protocol adherence
- Competent Authority
 - Regulatory Agency approval
 - Ethics Committee approval
 - Inspections
 - Training and education



Investigational Products

Drug Handling:

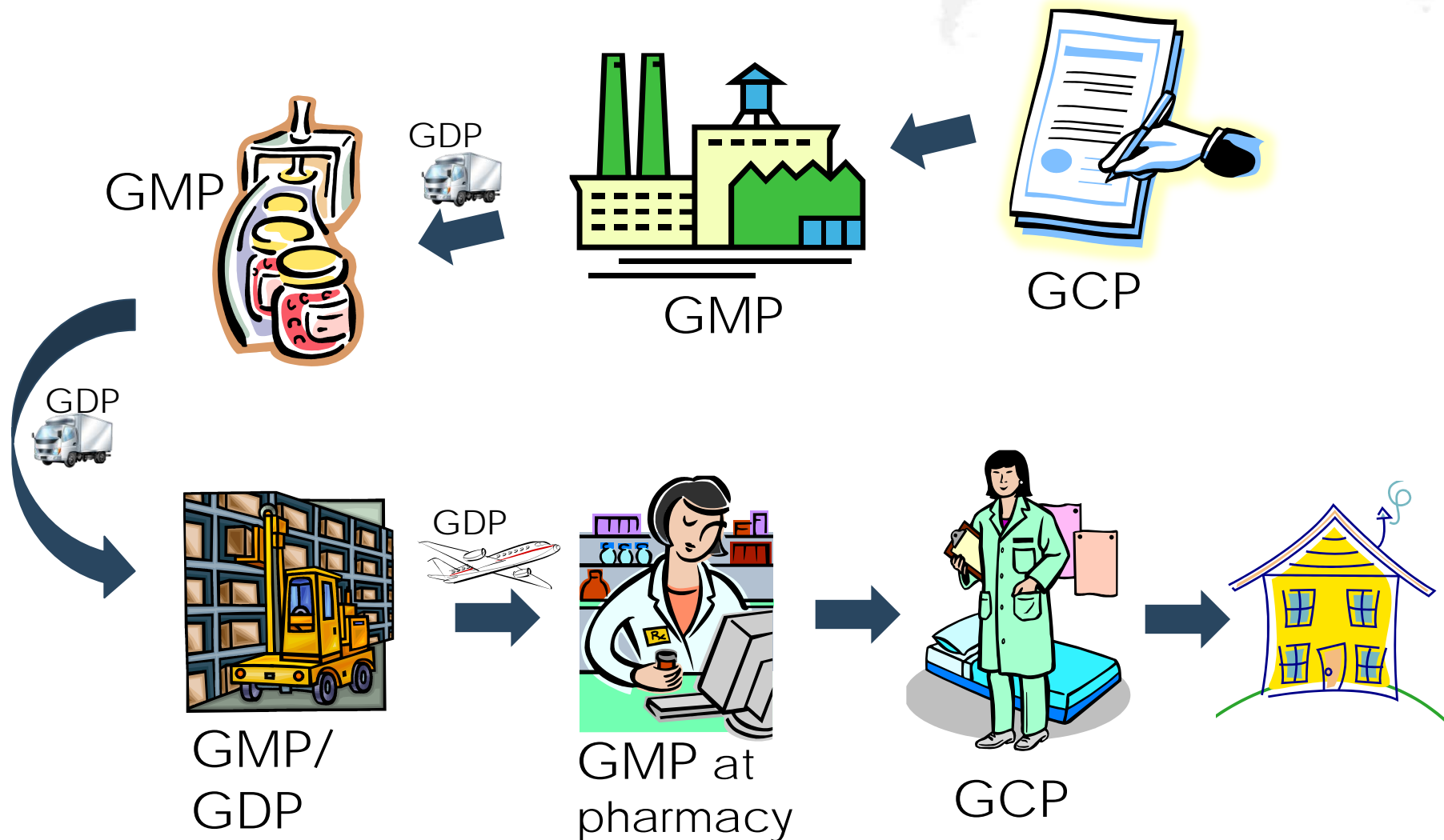
- Investigator responsibility
 - Drug handling
- Sponsor responsibility
 - Study drug
 - Manufacture
 - Storage and instructions
 - Labelling
- Monitor verifies
 - Drug accountability
 - Drug handling
 - Code envelopes



Trial workflow

- IRB/IEC approval,
- Regulatory approval,
- Inform consent,
- Enrollment (**Physical examination**, Screening)
- Dose administration,
- Monitoring,
- Sampling,
- Bioanalysis,
- PK/Statistics,
- Documentation,
- Reporting
- Investigational Products Management

Actors and Interfaces on the Way to the Patient



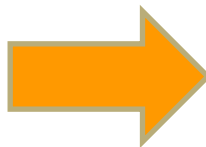
Bioequivalence Requirements

- **BE trial is a clinical trial**
 - GCP
 - Independent Ethics Committee opinion
 - Informed consent
 - Personnel, qualification, delegation of tasks
 - QC, QA
 - Facilities
 - Safety aspects (emergency care)
 - Computerised systems validation

Brand Drugs

1. Labeling
2. Pharm/Tox
3. Chemistry
4. Manufacturing
5. Controls
6. Microbiology
7. Inspection
8. Testing
9. Animal Studies
10. Clinical Studies
11. Bioavailability

Versus



Generic Drugs

1. Labeling
2. Pharm/Tox
3. Chemistry
4. Manufacturing
5. Controls
6. Microbiology
7. Inspection
8. Testing
9. Bioequivalence
(in vitro, in vivo)



What is a Bioequivalence Trial?

- **A BE trial is:**
 - Comparison of PK parameters
 - Extent of absorption: AUC
 - Rate of absorption: C_{max}, t_{max}...
 - Based on drug concentrations in plasma/serum/blood/urine
- **A BE trial is NOT:**
 - Intended to evaluate activity/tolerability
 - Limited number of healthy volunteers

- **Key points of a BE trial**
 - Investigational medicinal products
 - Identity of test and reference product used
 - Clinical part
 - Existence of healthy subjects, participation in trial
 - Product received by each subject at each period (compliance with randomisation list)
 - Conditions of administration: fed, fasted
 - Blood samples
 - Processing
 - Storage

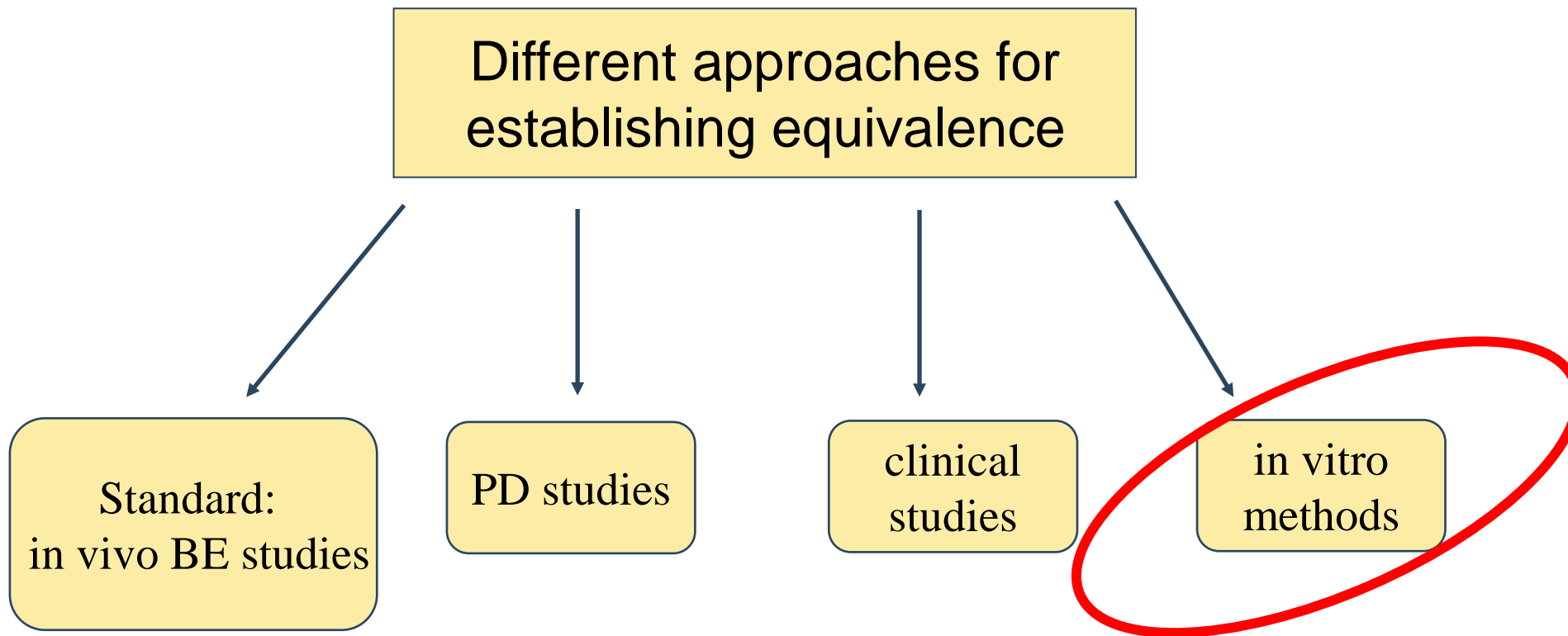
- **Design of BE trial**
 - > 90 % : 2x2 cross-over design, randomized, open-label
 - Usually single-dose
 - Also multiple-dose, steady-state for prolonged release product, or in patients
 - Usually fasted; may be fed depending on prescription recommendations; fasted + fed required for modified release
 - Number of subjects: depends on intra-subject variability, minimum 12
 - Complicated BE designs possible – parallel and highly variable drugs

- Most FPPs submitted are multisource (generic) products
 - Abbreviated clinical component
 - Safety & efficacy (S&E) based on comparison to a FPP with established S&E
- Establishing Equivalence
 - Comparative pharmacokinetic studies
 - *In vivo* comparative bioavailability studies
 - Comparison of performance of FPPs based rate and extent of absorption of API from each formulation
 - Comparative *in vitro* methods
 - Biopharmaceutics Classification System (BCS)-based biowaivers
 - Additional strengths biowaivers



Products that Require Studies to Determine Equivalence

- Solid oral FPPs
 - Immediate- and modified-release FPPs
- Complex topical formulations
 - Emulsions, suspension, ointments, pastes, foams, gels, sprays, and medical adhesive systems
- Complex parenteral formulations
 - Depot injections, nasal/inhalational suspension etc.



Rationale

- Requirement for *in vivo* bioequivalence testing may be waived under certain conditions
 - Solubility of API
 - Permeability of API
 - Uncomplicated API
 - Not narrow therapeutic range
 - No known bioavailability problems
 - Immediate-release FPP
 - Acceptable dissolution characteristics of FPP

Biopharmaceutics Classification System

- BCS originally explored with the aim of granting biowaivers for scale-up and post-approval changes (SUPAC)
- Biowaiver
 - An *in vivo* bioavailability and/or bioequivalence is considered not necessary for FPP approval
 - *In vivo* studies can be expensive and time consuming
 - Under certain circumstances, a dissolution test could be used as a basis for the decision on equivalent product performance

Current Situation

- WHO Prequalification Programme has reviewed existing information on the solubility, bioavailability, and dissolution data of the invited medicines and has identified APIs eligible for a BCS-based biowaiver application as either monocomponent or fixed-dose combination (FDC) products.
- Monocomponent or FDC FPPs containing other APIs must be supported with *in vivo* BE data

BCS-based Biowaiver Guidance

- WHO – Technical Report Series No. 937, May 2006

Annex 7: Multisource (generic) pharmaceutical products: guidelines on registration requirements to establish interchangeability

Annex 8: Proposal to waive in vivo bioequivalence requirements for WHO Model List of Essential Medicines immediate release, solid oral dosage forms

High solubility:

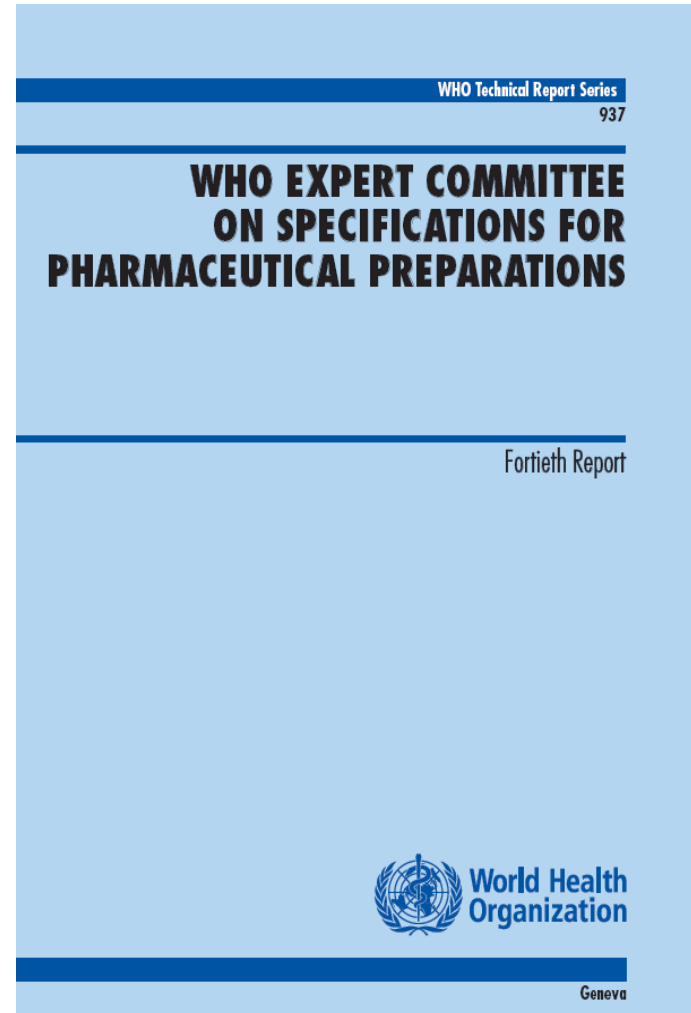
The highest dose is completely soluble in 250 ml or less of aqueous solution at pH 1.2, 4.5 and 6.8 (37° C)



250 ml: derived from typical BE study protocols that prescribe the administration of a FPP to fasting human volunteers with a glass (approximately 250 ml) water

Guidance

“Multisource (generic) pharmaceutical products: guidelines on registration requirements to establish interchangeability”. In: *Fortieth report of the WHO Expert Committee on Specifications for Pharmaceutical Preparations*. Geneva, World Health Organization. WHO Technical Report Series, No. 937, 2006, Annex 7



Comparator (Reference) Products

- Comparator products should be obtained from a well regulated market with stringent regulatory authority *i.e.*, from countries participating in the International Conference on Harmonization (ICH)
- Countries officially participating in ICH
 - ICH members: European Union, Japan and USA
 - ICH observers: Canada and EFTA as represented by Switzerland
 - Other countries associated with ICH (through legally binding mutual recognition agreements) include Australia, Norway, Iceland and Liechtenstein

Comparator Lists

- List of acceptable comparator products for each treatment area on WHO PQP website
- http://apps.who.int/prequal/info_applicants/info_for_applicants_BE_comparator.htm

Comparator (Reference) Products

Information Requirements

Within the submitted dossier, the country of origin of the comparator product should be reported together with lot number and expiry date, as well as results of pharmaceutical analysis to prove pharmaceutical equivalence. Further, in order to prove the origin of the comparator product the applicant must present all of the following documents:

1. Copy of the comparator product labelling. The name of the product, name and address of the manufacturer, batch number, and expiry date should be clearly visible on the labelling.
2. Copy of the invoice from the distributor or company from which the comparator product was purchased. The address of the distributor must be clearly visible on the invoice.
3. Documentation verifying the method of shipment and storage conditions of the comparator product from the time of purchase to the time of study initiation.
4. A signed statement certifying the authenticity of the above documents and that the comparator product was purchased from the specified national market. The certification should be signed by the company executive or equivalent responsible for the application to the Prequalification Programme

Experience

1. Comparator product and manufacturer selected not acceptable: Only recommended comparators from acceptable sources should be used.
2. Lack of documentation verifying method of shipment and storage conditions (use of a data logger recommended) of the comparator product from the time of purchase to the time of study initiation.
3. Applicant does not submit the bioequivalence trial information form (BTIF) where BE study is required.
4. For biowaver, submission of the request for a biowaver and the appropriate biowaver application form as a word document.

References

WHO PQP website: <http://apps.who.int/prequal/>

- ▶ WHO: Multisource (generic) pharmaceutical products: guidelines on registration requirements to establish interchangeability. WHO Technical Report Series 992, Annex 7 (2015).
- ▶ *EMA: Guideline on the Investigation of Bioequivalence* (London, 20 January 2010). [Doc. Ref.: CPMP/EWP/QWP/1401198 Rev.I/Corr**]
- ▶ *USFDA: Guidance for Industry, Bioavailability and Bioequivalence Studies for Orally Administered Drug Products - General Considerations*. U.S. Department of Health and Human Services, Food and Drug Administration, Centre for Drug Evaluation and Research (CDER) (March 2003; Revision 1).
- ▶ Canada: Guidance Document- *Conduct and Analysis of Comparative Bioavailability Studies* (2012) and Guidance Document - *Comparative Bioavailability Standards: Formulations Used for Systemic Effects* (2012).



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