Pharmaceutical Standards for Artemisinin and its derivatives
Requirements for Prequalification of ACTs

Artemisinin Forum 2008
Guilin, China

Maryam MEHMANDOUST, PhD
Prequalification of Medicines Programme
QSM / EMP / HSS
<table>
<thead>
<tr>
<th>Acronym</th>
<th>Definition</th>
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<tr>
<td>API</td>
<td>Active Pharmaceutical Ingredient (interchangeable with drug substance or active substance)</td>
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<tr>
<td>APIMF</td>
<td>Active Pharmaceutical Ingredient Master File</td>
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<tr>
<td>ARV</td>
<td>Antiretroviral</td>
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<tr>
<td>CoS (CEP)</td>
<td>Certificate of Suitability</td>
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<tr>
<td>CRO</td>
<td>Contract Research Organisation</td>
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<td>EDQM</td>
<td>European Directorate for Quality of Medicines and HealthCare</td>
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<tr>
<td>EoI</td>
<td>Expression of Interest</td>
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<tr>
<td>FPP</td>
<td>Finished Pharmaceutical Product</td>
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<tr>
<td>GCP</td>
<td>Good Clinical Practices</td>
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<tr>
<td>GLP</td>
<td>Good Laboratory practices</td>
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<tr>
<td>GMP</td>
<td>Good Manufacturing Practices</td>
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<tr>
<td>ICH</td>
<td>International Conference on Harmonization</td>
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<tr>
<td>Ph. Int.</td>
<td>International Pharmacopoeia</td>
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<tr>
<td>JP</td>
<td>Japanese Pharmacopoeia</td>
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<td>Ph. Eur.</td>
<td>European Pharmacopoeia</td>
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<td>PQ</td>
<td>Prequalification</td>
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<td>RH</td>
<td>Reproductive Health</td>
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<tr>
<td>SM of the API</td>
<td>Starting material of the API</td>
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<tr>
<td>SPC</td>
<td>Summary of Product Characteristics</td>
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<tr>
<td>TB</td>
<td>Tuberculosis</td>
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<tr>
<td>USP</td>
<td>United States Pharmacopoeia</td>
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</table>
UN / WHO Prequalification Programme for Medicines

Action plan of UN since 2001 aiming to facilitate access to priority medicinal products

Revision of the procedure in October 2008

– Categories: HIV/AIDS, Malaria, Tuberculosis, Reproductive Health, Influenza
– Potentially other categories of products possible, if there is the need

– To ensure quality, efficacy and safety of medicines procured using international funds (e.g. GFTAM, UNITAID)

– Products meeting WHO recommended Quality Standards to be included in the list of Prequalified products

– Inclusion in the list does imply any approval by WHO of the products and manufacturing sites - this is the sole prerogative of National Authorities
Prequalification Programme for Medicines
Principles of Quality assessment procedure

- General understanding of the production and quality control activities of the manufacturer
- Assessment of product data and information on safety, efficacy and quality
- Assessment of manufacturing sites for consistency in production, quality control of starting materials and FPPS through compliance with GMP
- Assessment of clinical testing units or CROs for compliance with GCP and GLP
- Reliance on the information supplied by national DRAs
- Random sampling and testing
- Handling of complaints and recalls
- Monitoring of complaints from agencies and countries
Prequalification Programme for Medicines

How does it work?

Expression of Interest

Product dossier
SMF

Prequalification Listing

Assessment

Response to questions

Compliance

Inspections

Corrective actions

Compliance

Maintenance and monitoring

SMF

Expression of Interest

Product dossier

Prequalification Listing

Assessment

Response to questions

Compliance

Inspections

Corrective actions

Compliance

Maintenance and monitoring

World Health Organization
Several Components

✓ Reporting of variations
  • To demonstrate that intended or implemented changes have no negative impact on safety and efficacy of the Prequalified product

✓ Random sampling and testing of prequalified products, investigation if failure to meet the approved criteria
  • Random sampling and testing of prequalified products, investigation if failure to meet the approved criteria

✓ Investigation of complaints on prequalified products communicated to WHO
  • Report of the investigation available to the applicant/manufacturer and the concerned DRA

✓ Re-evaluation of the products and manufacturing sites including re-inspection of Mfg sites and clinical testing units at least once every 5 years
  • Re-evaluation of the products and manufacturing sites including re-inspection of Mfg sites and clinical testing units at least once every 5 years

Risk-based approach e.g. information received from the stringent authorities
Prequalification Programme for Medicines

Characteristics of the prequalified products to be made available for public access at the WHO website

1. Product WHO reference number
2. International Nonproprietary Name (INN) of active ingredient(s)
3. Dosage form and strength
4. Trade name(s) of the product (if applicable)
5. Name of applicant and official address
6. Name of manufacturer of finished product, physical address of manufacturing site(s) (and unit, if applicable)
7. Name of API manufacturer, physical address of manufacturing site(s) (and unit, if applicable)
8. Product description (as in finished product specifications, i.e. coated, scored, etc.)
9. Pack size(s), primary and secondary packaging material(s)
10. Storage conditions
11. Shelf-life (provisional, if applicable)
12. Summary of product characteristics
13. Package leaflet
14. Labelling
Prequalification Programme for Medicines

ACTs in the latest (6th) Expression of Interest

1. Artemisinin-based fixed dose oral combination formulations
   - Artemether + Lumefantrine, tablet 20 mg + 120 mg; tablet 40 mg + 240 mg
     tablet 60 mg + 360 mg; tablet 80 mg + 480 mg

2. Artemisinin-based fixed dose combination or co-blistered oral formulations
   - Artesunate + Amodiaquine, tablet 25 mg + 76.5 mg; tablet 50 mg + 153 mg
     tablet 100 mg + 306 mg
   - Artesunate + Mefloquine, tablet 25 mg + 250 mg; tablet 50 mg + 250 mg
     tablet 100 mg + 250 mg
   - Artesunate + Sulfadoxine + Pyrimethamine, tablet 25 mg + 500 mg + 25 mg
     tablet 50 mg + 500 mg + 25 mg; tablet 100 mg + 500 mg + 25 mg

3. Artemisinin-based fixed dose combination or co-blistered oral paediatric formulations, preferably dispersible
   - Artemether + Lumefantrine
   - Artesunate + Amodiaquine
   - Artesunate + Mefloquine
   - Artesunate + Sulfadoxine + Pyrimethamine
Prequalification Programme for Medicines
Guidelines for the assessment of product dossiers/quality

- Guideline on submission of documentation for prequalification of multi-source (Generic)-Finished Pharmaceutical Products (FPPs) used in treatment of HIV/AIDS, Malaria and Tuberculosis (Main Generic guide with 8 annexes) [under revision]

- Innovators Under revision-

- Supplement 1 : Dissolution testing -

- Supplement 2 : Extension of the WHO list of stable APIs (not easily degradable)

- Guidelines for registration of fixed-dose combination medicinal products

- Guideline on Active Pharmaceutical Ingredient Master File (APIMF) Procedure

- Guidance on variations to a prequalified dossier- will be revised in 2009-2010-

When PQ guidelines are silent, ICH requirements will apply-
Active Pharmaceutical Ingredient (API)

A substance or compound that is intended to be used in the manufacture of a pharmaceutical product as a therapeutically active compound (ingredient).

Artemisinin is not currently listed in PQ EoI as an API.
- Artemether (listed in PQ EoI)

- Artemisinin described as an API in the Ph. Int., monographs of related capsules and tablets available

- Artemotil (arteether)

- Artenimol (Dihydroartemisinin)

- Artesunate (listed in PQ EoI)
Prequalification Programme for Medicines

Difficulties in PQ dossiers/quality

- Information on method of preparation/extraction of artemisinin and its quality controls is lacking

- Manufacturing process is fragmented and what is presented in dossiers is usually very short, e.g. one step

- Monographs of the Ph. Int. on artemether and artesunate should be further clarified e.g. addition of list of impurities

Acknowledgment in working document QSM/EC/08.30 of the EC of October 2008 to revise and improve the monographs but first the FPP ones.
Scientific data on the API can be submitted to PQ using following ways and order of preference:

- A valid Certificate of Suitability (CoS) or CEP, issued by EDQM (not applicable to artemisinin derivatives as not described in the Ph. Eur.)

- An APIMF (Active Pharmaceutical Ingredient Master File) submitted by the API manufacturer, containing the whole information requested in section 2 and presented in CTD format (see APIMF guideline and separate presentation)

- Complete submission of data requested in Section 2 of PQ product dossier
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<td>- General Properties</td>
<td>2.2 Properties of API (s)</td>
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<td>S.2 Manufacture</td>
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<td>- Manufacturer</td>
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<td>- Control of materials</td>
<td>2.4 Route(s) of synthesis</td>
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<tr>
<td>- Process validation</td>
<td>- API not described in pharmacopoeia</td>
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<tr>
<td>- Manufacturing process development</td>
<td>- Specifications of raw materials and intermediates used in synthesis</td>
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<tr>
<td></td>
<td>- API described in a pharmacopoeia</td>
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<td>S.3 Characterisation</td>
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<td>- Elucidation of structure</td>
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<td>S.6 Container Closure System</td>
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<td>S.7 Stability testing</td>
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3.2.S.1. General Information

Nomenclature

- INN or modified INN,
- Pharmacopoeial reference if relevant (Ph. Int., USP, Ph. Eur.),
- Chemical name (CAS or IUPAC), other chemical names such as USAN or BAN,
- CAS (Chemical Abstracts Service) registry number.

Chemical structure

- Structural formula including relative and absolute stereochemistry,
- Molecular formula and relative molecular mass
- Indication if the API is a racemate or an enantiomerically pure substance or a specific isomer.

E.g. artemether is obtained only as alpha-epimer (10S) or artemether is predominantly the beta-epimer
3.2.S.1. General Information

General properties

List properties of the API such as below (relevant for manufacturability and performance of the FPP):

- physical forms (crystalline, amorphous,…),
- partition coefficient (oil/water),
- hygroscopicity (water uptake at specified ambient temperature),
- pH and pKa values,
- solubility characteristics (solubility in water at different pH 1.2 to 6.8),
- particle size,
- polymorphism.

Artemisinin derivatives are either insoluble or slightly insoluble in water, therefore need to address issues of particle size and polymorphism.
3.2.S.2. Manufacture / Manufacturer(s)

Name, address and responsibility of each manufacturer, including contractors, and each proposed manufacturing site or facility involved in the manufacturing chain including specific steps such as milling or micronization.

Actual manufacturing sites with indication of unit, plot, block (if any)
Same information as above for alternative sites

GMP compliance certificate for each site of production of API (if available), A valid manufacturing authorization for the production of APIs (PQ requirement)

Manufacturing process should be performed according to the GMP for APIs according to ICH Q7A: Good manufacturing practice for active pharmaceutical ingredients, Adopted by WHO EC.
3.2.S.2. Manufacture
Description of manufacturing process and process controls
- A flow diagram of the process and a scheme of synthesis
- Description of the synthesis should go sufficiently back to well-characterized starting materials
- Detailed description of the synthesis step-by-step indicating materials, reagents and solvents used and critical steps identified by the manufacturer
- Scale of manufacture: typical batch size and the maximum batch size (the range)
- Last step of purification/crystallisation and solvents used should be described

Alternate processes (if any), description with the same level of details than the main process. Attention if change in the impurity profile

Reprocessing and reworking steps should be clearly described (if any) with justification, attention to different impurity profile resulting from reworking
3.2. S. 2. Manufacture, Description of manufacturing process and process controls

Artemisinin

DHA

β-artemether

α-artesunate

configuration at 10 should be inversed
3.2.S.2. Manufacture
Control of Materials/ Starting material of the API

Definition as per ICH Q7A: a raw material, intermediate, or an API that is used in production of an API and that is incorporated as a significant structural fragment into the structure of the API. It can be an article of commerce, purchased from another supplier or manufactured in-house.

Starting material
$\text{C}_{15}\text{H}_{24}\text{O}_{5} (M_w=284.4)$

Expected product
$\text{C}_{16}\text{H}_{26}\text{O}_{5} (M_w=298.4)$
3.2.S.2. Manufacture
Control of Materials/ Starting material of the API

Definition of API starting material as per ICH Q7A should be distinct from the concept of "Starting material for synthesis" used in assessment. It defines the starting point of the synthetic process of an API to be submitted in the dossier.

Starting material for synthesis in the dossier **may precede** the ICH Q7A "API starting material" by several steps in the synthetic process.

In general, the starting material for synthesis should be a synthetic precursor one or more-synthetic steps **prior to the final API intermediate**.

*Pharmaceutical sciences- Questions and answers*
*Therapeutic Products Directorate, Health Canada*
3.2.S.2. Manufacture
Control of Materials/ Starting material of the API

Provide brief outline of the preparation of the starting material of the API beginning from simpler molecules including solvents and reagents in order to enable assessors to judge of the appropriateness of specifications of the starting material of the API.

CPMP/QWP/130/96, Rev 1 (December 2003)
3.2.S.2. Manufacture

Control of Materials/ **Starting material of the API should be qualified**

- Name and address (manufacturing site) of the starting material manufacturer(s)
- If several sources, indication of differences in the mode of preparation
- If differences, then specifications should cover the quality of material sourced from all suppliers

Starting material of the API should be **well characterized**, structure well defined. Specifications proposed for the starting material as a minimum: identification, related substances, assay and sometimes residual solvent and catalysts

For artemisinin as SM of atemether or artesunate, it is not obligatory that it complies with the limits of the Ph. Int. but the specifications should be appropriate for the intended use.

If the route of synthesis **too short i.e. 1 step** and the starting material is pharmacopoeial, full compliance with its monograph should be shown by evaluation of its quality.
3.2.S.2. Manufacture
Control of Materials

Specifications for solvents and reagents

ICH class I solvents such as benzene should be avoided

- Solvents used in final stages require greater purity and control
- Control of residual benzene in solvents such as toluene

Recovered solvents: specifications and use
Quantitative and qualitative composition of denatured solvents

Recovered materials: description of recovery, specifications and use

Any material used in the process which may be of biological origin, viral and/or TSE safety aspects should be addressed. Declaration on use/non use of material of biological origin.
3.2.S.2. Manufacture
Controls of critical steps and Intermediates

- Specifications for isolated intermediates: as a minimum identification, related substances and assay testing.

- In-process controls

Identification of critical steps (examples)-
- Where significant impurities are introduced or removed
- Where an essential structural element is introduced e.g. a chiral center
- Where a major chemical transformation is performed
- Step having an impact on solid state properties or homogenity of the API
3.2.S.2. Manufacture

Process validation and/or evaluation
- Validation of critical steps identified
- Validation of aseptic processing and/or sterilization

Manufacturing Process Development
- Significant changes made to the manufacturing process and/or site during development of the process and scale-up
3.2.S.3. Characterisation
Elucidation of structure and other characteristics

**Confirmation of structure based on synthetic route and spectral analyses**

**Pharmacopoeial APIs:** comparison of spectral data between the pharmacopoeial reference standard and the test product

- Non pharmacopoeial API: evidence of structure should be brought by elemental analysis, IR, NMR (proton and carbon), UV, mass with interpretation of spectra, X-ray and so on.
- Unequivocal proof of configuration of chiral centres (if applicable) and geometric isomerism (if applicable) e.g. by single X-ray crystal
3.2.S.3. Characterisation/ Impurities
Discussion on potential and actual impurities
Impurities are to be considered not only for their chemical aspects but also for their safety aspects (qualification)

- **Organic impurities**
  By-products
  Starting materials and/or intermediates not reacted
  Impurities contained in starting materials
  Degradation products of the API
  Reagents, catalysts

- **Residual solvents** *(PQ refers to ICH Q3C)*
- **Inorganic impurities** *(reagents, heavy metals, inorganic salts, metal catalysts)*
3.2.S.3. Characterisation/ Impurities

Impurities contained in the starting material - Artemisinin
Biosynthetic by-products: Starting materials from vegetable origin should be fully characterized and a contaminant profile should be established and submitted.
Arteannuin, Artemisinic acid, 
Cultivation reagents
Pesticide residues (Ph. Eur. 2.8.13.), fumigants, mycotoxins
Solvents from the extraction process
Hexane, benzene, acetonitrile, ether, pentane, chloroform, etc….
In any case ICH Q3C (R) will apply.
3.2.S.3. Characterisation/Impurities

By-products, starting materials or intermediates not reacted
- Artemisinin
- Dihydroartemisinin (starting material for derivatives)
- $\alpha$-Arthemether, $\alpha$-Artheether
- $\beta$-Artesunate.

Reagents, catalysts, residual solvents from the chemical transformation
Methanol, acetonitrile, chloroforme, acetone …
Boron residues, succinic acid/anhydride, triethylamine, dimethylaminopyridine, other bases

Degradants
- Product obtained by opening of the endoperoxide leading to loss of antimalarial activity,
- Product after loss of succinic moiety known as glycan
3.2.S.3. Characterisation/ Impurities

Artemether related substances example

No impurity more than 0.5%, only one impurity between 0.25% and 0.5%, any other impurity NMT 0.25%, total of impurities NMT 1%.

No list of impurities at the end of monograph

Some manufacturers only report one figure between 0.25% and 0.5% and one figure below 0.25%. Not at all clear what is there: artemisinin, DHA, alpha artemether or other impurities which can be unknown?
3.2.S.3. Characterisation/ Impurities

- It should be clarified each time what impurities are known such as artemisinin, DHA, ...

- All the results are to be provided from the disregard limit of the monograph (usually 0.05%)

It should be clarified if there are unknown recurrent impurities -

If important levels are found, attempts should be made to characterise them or to reduce them

Absolute need for more collaboration between manufacturers of artemisinin-derivatives and Ph. Int. to improve these monographs
Prequalification Programme for Medicines

API section

3.2.S.3. Characterisation/ Impurities

For non pharmacopoeial APIs, impurities should be either identified and qualified

IF NOT

ICH Q3A thresholds of identification and qualification apply

<table>
<thead>
<tr>
<th>Maximum Daily Dose</th>
<th>Reporting Threshold</th>
<th>Identification Threshold</th>
<th>Qualification Threshold</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤ 2g/day</td>
<td>0.05%</td>
<td>0.10% or 1mg per day intake (whichever is lower)</td>
<td>0.15% or 1mg per day intake (whichever is lower)</td>
</tr>
<tr>
<td>≥ 2g/day</td>
<td>0.03%</td>
<td>0.05%</td>
<td>0.05%</td>
</tr>
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</table>
3.2.S.4. Control of the API
Specifications for NON Pharmacopoeial substances
ICH Q6A apply

Specifications for Pharmacopoeial substances
Recognised Pharmacopoeias by Prequalification: Ph. Int., USP, Ph. Eur., BP

The claimed pharmacopoeia by the applicant should be specified

The current monograph in force in the claimed pharmacopoeia always applicable BUT use of in-house method acceptable provided to be superior

Complete by additional specifications not included in the monograph
- Residual solvents (specific to each process)
- Polymorph and particle size (where applicable e.g. poorly soluble drugs)
- Sterility or microbial contamination,…(where applicable)
3.2.S.4. Control of the API
Analytical procedures/ Pharmacopoeial APIs

Any non pharmacopoeial method should be described in detail to be replicated by a Control Laboratory

Validation of analytical procedures
For pharmacopoeial methods, the applicability of the method to the manufacturer's equipment should be shown: SST, specificity, ...

The pharmacopoeial related substances method should be always shown suitable to determine impurities related to the manufacturer's specific route of synthesis

If monograph available but in-house method chosen, it should be shown that the in-house methods is superior or at least equivalent to that of the monograph
Non pharmacopoeial methods should be fully validated
Prequalification Programme for Medicines

API Section

3.2.S.4. Control of the API

Batch analyses

Description of the batches: batch number, size, site and date of manufacturing, use of the batch e.g.

Results of at least 2 primary batches from each source of API and each site
Primary batches should be at least of pilot size

For quantitative tests, actual numerical results should be given.
Statements such as "complies" are not acceptable.

Justification of specifications
- inclusion OR omission of certain main/ critical tests and acceptance criteria,
- any modification of pharmacopoeial tests.

- Specifications of non pharmacopoeial APIs justified as per ICH Q6
3.2.S.5. Reference Standard or Materials

For pharmacopoeial APIs: use an official Reference Standard. Working standard should be qualified against the official RS.

For non-pharmacopoeial APIs
A primary and/or a working standard are to be established with description of how it has been set in terms of identity and assay.

3.2.S.6. Container Closure system
- Description of the bulk storage container / primary packaging
- Identification of materials and their specifications
- Choice of material to be justified: compatibility of the API with materials of the container
  - by stability results obtained
  - protection from moisture and light (if applicable)
  - sorption, leaching to be studied mainly in case of liquid APIs
3.2.S.7. Stability testing

- Help to know about the intrinsic stability of the API

- Help to know about the degradation pathways and degradation products formed

- Help to know whether the analytical method is suitable to determine degradation products and whether it is stability-indicating

For an existing API, it is possible not to perform stress testing if the information can be found in literature or included in transparency list of Ph. Monograph, not possible for artemisinin derivatives because of lack of list of impurities
3.2.S.7. Stability testing

Regulatory stability testing serves to define a re-test period for the API to recommend a storage condition.

Definition of re-test period

Period of time during which the API is expected to remain within its specifications and can be used in the manufacture of a given product (without control prior to manufacture of Drug Product) in condition that the API has been stored under defined conditions.

If the re-test period not defined, The API is to be tested before manufacture of each lot of drug product.
3.2.S.7. Stability testing
Re-test period of the API

- Selection of batches (at least 3 pilot)
- Same packaging than that proposed for commerce/distribution
- Parameters to be tested

Those susceptible to change during storage and affecting quality and safety: assay, impurities, isomeric nature…

Analytical methods (should be the same at release OR if different validated-and demonstrated to be stability indicative)
3.2.S.7. Stability testing
Re-test period of the API

Storage conditions (ICH general case): long term, intermediate, accelerated

The long term storage condition should go with real climatic conditions
- e.g. Zone IVb: long term is 30°C / 75% RH
- Zone IVa: long term is 30°C / 65% RH

NEW WHO guideline on stability adopted by the EC in October 2008

Extrapolation: possible either according to PQ supplement 2 (not applicable to artemisinin derivatives) or according to ICH Q1E

Stability study should be continued to cover the re-test period accorded
Prequalification Programme for Medicines

FPP Section

- Manufacturing and marketing authorization
- Pharmaceutical development
- Formulation
- Sites of manufacture
- Manufacturing process
- Manufacturing process controls of Critical steps and intermediates
- Process validation and Evaluation
- Specifications for excipients
- Control of the FPP
- Container/closure system (s) and other packaging
- Stability testing
- Labelling
- SPC
- PIL
Thank you for your attention