The WHO Biowaiver Project
Dr Valeria Gigante - WHO, Technical Officer MQA
Congrès international du laboratoire national du contrôle des medicaments, Tunis 5-6 April 2019
Agenda
The WHO Biowaiver Project: towards a BCS-based classification of APIs on the EML

01 The WHO and the 2030 Agenda: the SDGs
02 The WHO experience in the BCS-based biowaiver & interchangeability
03 The Biowaiver Project
04 Operational aspects
05 Case study and wrap-up
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The WHO and the 2030 Agenda: the SDGs

The WHO experience in the BCS-based biowaiver & interchangeability

The Biowaiver Project

Operational aspects

Case study and wrap-up
The World Health Organization working within countries and for countries

1 Global HQ
6 Regional offices
149 Country offices
7000 WHO staff working across the world
194 WHO Member States
Partnership to achieve health goals
The WHO has six core functions: setting Norms & Standards is one of them

**Leadership & partnership**
- Providing leadership on matters crucial to health
- Engaging in partnerships where joint action is needed

**Research**
- Shaping the research agenda
- Stimulating the generation, translation and dissemination of valuable knowledge

**Norms and standards**
- Setting norms and standards
- Promoting and monitoring their implementation

**Policy options**
- Articulating ethical and evidenced-based policy option

**Technical support**
- Providing technical support, catalyzing change
- Building sustainable institutional capacity

**Monitoring**
- Monitoring the health situation
- Assessing health trends
Norms and standards settings in MQA
Among the 17 SDGs, indicator #3 focuses on good health and well-being

https://sustainabledevelopment.un.org/
A specific sub-indicator highlights the importance for safe, effective, quality and affordable essential medicines

SDG 3 – Target 3.8
Achieve universal health coverage, including financial risk protection, access to quality essential health-care services and access to safe, effective, quality and affordable essential medicines and vaccines for all
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WHO has built almost **30 years** of experience in the field of biowaiver and bioequivalence.
The WHO experience with BCS-based biowaiver

Two basic documents were released in 2006 including the first BCS-based biowaiver list

- **1992** - 33rd ECSPP recognized the need for global guidelines with respect to multisource products. WHO TRS No. 834, 1993.


The WHO experience with BCS-based biowaiver

Two basic documents were released in 2006 including the first BCS-based biowaiver list

- In 2006 the WHO published:
  - As part of this guidance, WHO had provided with the assistance of its WHO collaborating Centre at that time a provisional list of APIs eligible for biowaiver mostly based on literature data

- In the same year revision of the 1996 publication of:
The WHO experience with BCS-based biowaiver

The criteria to establish biowaiver were tightened-up excluding BCS Class II products

- The criteria to grant biowaiver were revised: BCS Class II APIs were excluded from a BCS-based biowaiver

- The WHO guidelines on registration requirements to establish interchangeability was thus republished as “Multisource (generic) pharmaceutical products: guidelines on registration requirements to establish interchangeability” (WHO TRS 992, Annex 7, 2015)

The WHO experience with BCS-based biowaiver

The ECSPP recommended to revise the 2006 BCS-based biowaiver list

- The **Expert Committee on Specifications for Pharmaceutical Preparations (ECSPP)** recommended the WHO Secretariat to revise the “WHO Biowaiver list” (2006) with robust laboratory data to promote access to quality multisource (generic) essential medicines
### The WHO experience with BCS-based biowaiver

The WHO basic document was enriched with a new Appendix & the WHO Biowaiver Project was launched.

<table>
<thead>
<tr>
<th>Year</th>
<th>Event</th>
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<tbody>
<tr>
<td>1990’s</td>
<td>General and high level recommendations for conducting solubility experiments were provided in the document “Equilibrium solubility experiments for the purpose of classification of active pharmaceutical ingredients according to the BCS.”</td>
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<td>2006</td>
<td>This was published as Appendix 2 to the basic document: “Multisource (generic) pharmaceutical products: guidelines on registration requirements to establish interchangeability” republished as WHO TRS 1003, Annex 6, 2017</td>
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<td>2015</td>
<td>Following the ECSPP’s 2016 directions, the WHO Secretariat started a multi-centric project: the WHO Biowaiver Pilot Project</td>
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<td>2018</td>
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<td>2019</td>
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Source: Annex 2 WHO TRS 1003, Annex 6, 2017
The WHO experience with BCS-based biowaiver

The Appendix 2 evolved in a self-standing Protocol and the first set of API was classified accordingly

- **The WHO Biowaiver Pilot Project** run throughout 2018
- The original Appendix 2 was reshuffled to be fit for purpose and become the formal *“Protocol to conduct equilibrium solubility experiments for the purpose of Biopharmaceutics Classification System-based classification of Active Pharmaceutical Ingredients for biowaiver”* (QAS/17.699/Rev.2)
- The **first set of APIs** prioritized from the EML were classified according to the newly developed Protocol as “Revised WHO biowaiver list based on the WHO model list of essential medicines” (QAS/18.777/Rev.1)
- The **53rd ECSPP** in October 2018 endorsed the Protocol, the classification of the **first set of APIs** and the **second set of APIs** prioritized from the EML for characterization in **2019**
The WHO experience with BCS-based biowaiver

In 2019 we have the opportunity to scale up the Biowaiver project

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<td>• WHO BP Project phase II - scale up of the pilot phase</td>
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The WHO Biowaiver project focus is on the BCS-based classification of APIs in the EML

Potential application of the BCS-based biowaiver

- Comparative BA/BE studies (e.g. multisource)
- Pre-approval changes requiring BE studies
- Post-approval changes requiring BE studies

API level: classification

BCS-based classification of API from the EML

- Class II/IV: Data from in vivo BE study required
- Class I/III: Biowaiver in principle possible

FPP level: evaluation

Confirm eligibility at the FPP level, considering:

- Excipients (type & content)
- Dissolution profile
- NTIDs (not eligible)
- Stability
- Formulation (IR, oral, solid dosage forms)
- Risk of an incorrect decision
Such BCS-based classification of APIs promotes access to essential medicines on multiple levels

**Regulators**
- Optimize regulatory procedures
- Decrease the regulatory burden, diff. regulat. capacity
- Optimize the use of HR, focus on higher-risk products

**Ethics**
- Reduce human exposure in clinical trials
- Lower burden for Ethic Committees

**Patients**
- Quicker access to multisource products
- Potential impact on final costs

**Payers**
- Potential impact on final cost of multisource products
- Optimization of financial resources

**Manufacturers**
- Reduce time to develop multisource products
- Reduce costs to develop multisource products
- Support pre/post approval changes

**Procurement (UN/GOV/NGO)**
- Facilitate international procurement
- Increase the use of harmonized regulatory tools
- Replace the WHO list published in 2006
The WHO 52nd ECSPP recommended to develop a new WHO Biowaiver list based on verified laboratories data and using the revised criteria (2017) for BCS-based biowaiver with the aim of promoting access to quality medicines by reducing the number of unnecessary in vivo BE studies.

Start Pilot: 3 APIs measured experimentally for the solubilities + Protocol to perform equilibrium solubility studies for BCS-based classification of APIs
Scale-up: 15 APIs to be characterized in 2019
Objective: build a revised WHO biowaiver list

Involving Universities and State laboratories spread worldwide with the support of pharmaceutical manufacturers
In collaboration with the PQ Team supporting the APIs prioritization exercise from the EML
Biowaiver project: overview II

Phase I - Pilot

Phase II - scale up

1. aciclovir (antiviral)
2. amoxicillin trihydrate (antibacterial)
3. azithromycin (antibacterial)
4. codeine phosphate (central nervous system)
5. bedaquiline (multidrug-resistant TB)
6. cefixime (antibacterial)
7. daclatasvir (hepatitis C)
8. darunavir (HIV)
9. efavirenz (HIV)
10. furosemide (cardiovascular)
11. methyldopa (pregnancy-induced hypertension)
12. primaquine (malaria)
13. pyrimethamine (malaria)
14. rifampicin (TB)
15. raltegravir potassium (HIV)
A protocol to conduct equilibrium solubility experiments was drafted and fit for purpose

Protocol to conduct equilibrium solubility experiments for the purpose of BCS-based classification of APIs for biowaiver

PROTOCOL TO CONDUCT EQUILIBRIUM SOLUBILITY EXPERIMENTS FOR THE PURPOSE OF BIOPHARMACEUTICS CLASSIFICATION SYSTEM-BASED CLASSIFICATION OF ACTIVE PHARMACEUTICAL INGREDIENTS FOR BIOWAIVER

(July 2018)

TAKEN FROM DRAFT NOTES ON THE CONDUCT OF SOLUBILITY STUDIES (AUGUST 2017)

REVISED DRAFT FOR DISCUSSION

[Notes on protocol]

Should you have any comments on the attached text, please send these to Dr Valeria Gianatte, Technical Officer, Medicines Quality Assurance, Technologies Standards and Norms (gianatte@who.int) with a copy to Ms Xenia Finanery (finanery@who.int) by 30 September 2018.

Working documents are sent out electronically and they will also be placed on the Medicines website (http://www.who.int/medicines/patients/safety/quality_assurance_guidelines/en/) for comments under the “Current projects” link. If you have not already received our draft guidelines, please send your e-mail address to jones@who.int and we will add you to our electronic mailing list.
Limitations of the BCS-based biowaiver

- Solid, oral, IR, pharmaceutical dosage forms
- Parent drug vs active metabolites: dissolution and pH-solubility data on both parent drug and active metabolites can be relevant
- NTIDs excluded
- Solubility/permeability data not generated in this phase
- FDC: lack of comparators for dissolution studies
- Stability issues
- Different regulatory framework (MSs w/o biowaiver among their legal provisions)
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THE WHO BIOWAIVER PROJECT OPERATION

From the original footprint with 4 laboratories in the pilot phase ...
THE WHO BIOWAIVER PROJECT OPERATION II

... we are shaping a global network of laboratories to achieve a global goal

- University of Cincinnati, USA
- University M. H., Spain
- University of Valencia, Spain
- F.S. University of Jena, Germany
- NIFDC, China
- Ajou University, South Korea
- Indian Pharmacopoeia Commission, India
- North West University, South Africa
- Monash University, Australia
- University of Goja, Brazil
- University of Goja, Brazil
Manufacturers supporting the project with the API samples for the tests

- Pfizer, USA
- Sanofi, France
- ACS Dobfar, Italy
- Egis, Hungary
- Sandoz, India
- Lupin, India
- Apicore, India
- Laurus, India
- Ipca Lab., India
- Shenyang Antib., India
- Mylan, India
- Mangalam, India
- Shanghai Desano, India
- Aurobindo, India
- Zhejiang Jiangbei P., China
- Aurobindo, India
- Lupin, India
- Apicore, India
- Laurus, India
- Ipca Lab., India
- Shenyang Antib., India
- Mylan, India
- Mangalam, India
- Shanghai Desano, India
- Aurobindo, India
- Zhejiang Jiangbei P., China
WHO BIOWAIVER PROJECT OPERATION IV

APIs are analysed in parallel at multiple laboratories to allow comparisons in results according to the 2- 3- 4- 6 matrix

1. Controlled substances are measured in parallel at 2 facilities
2. Each API is measured in parallel at 3 facilities
3. Very high soluble compounds are measured in parallel at 4 facilities
4. Unknown & expected borderline solubility compounds measured in parallel at 6 facilities
WORKPLAN

Tests phase
- Training for laboratories
- Shipment of APIs
- Experiments

Public consultation
Provisional classification posted on WHO website for comments from stakeholders

54th ECSPP
- Presentation of results.
- Prioritization of APIs for WHO BP cycle 3

Planning phase
- Sourcing APIs
- Consolidate network of labs
- Criteria 4 measurements
- APIs voluntary/assignment

Consolidation phase
- Global TC to present and discuss results obtained at each laboratory and potential issue
- May 2019, presentation of preliminary results

Wrap up phase
Global TC to discuss the outcome of the public consultation
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CASE STUDY: ETHIONAMIDE

Why we want to achieve a solid Biopharmaceutic Classification System of APIs?

Ethionamide represents an extraordinary case study.

This API was previously (in 2006) classified by WHO as highly soluble compound and considered eligible for biowaiver. However during the WHO BP pilot phase:

we had turned upside down the previous outcome

indeed the new tests revealed that ethionamide is not highly soluble suggesting a BCS Class II/IV and the need for BE studies to support the development of new generics.

- A sound and robust WHO BCS-based classification is crucial for patients, regulators, payers, manufacturers, ethic committee, international procurement

- The biowaiver project is a useful and meaningful exercise allowing the generation of robust experimental data underpinning the revised WHO BCS-based List.