Etudes in vitro en bioéquivalence et les exemptions de biodisponibilité

The WHO Biowaiver Project

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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 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

World Health Organization

Leadership & partnership

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

Policy options

- Articulating ethical and evidenced-based policy option

Research

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

Technical support

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

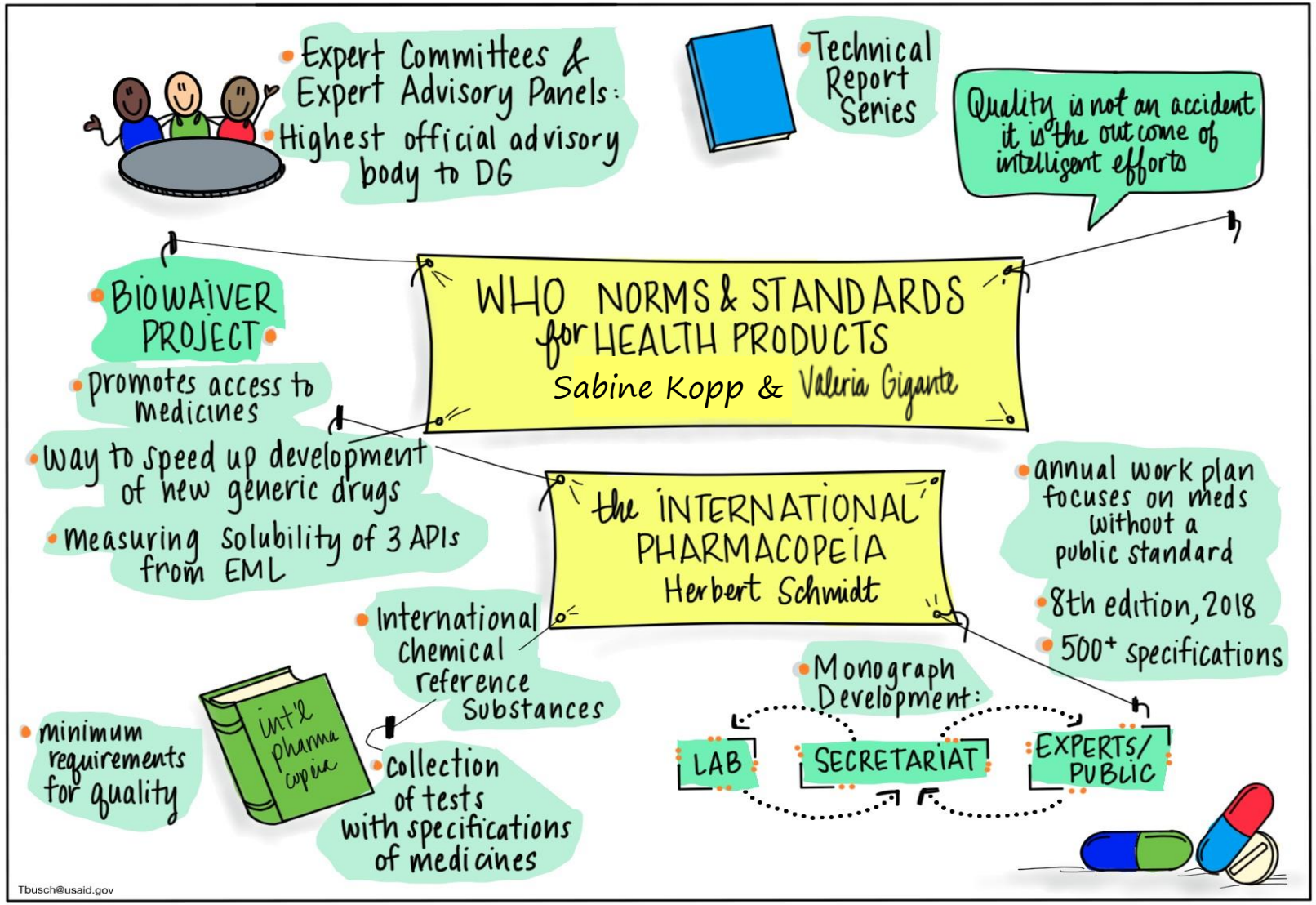
Norms and standards

- Setting norms and standards
- Promoting and monitoring their implementation

Monitoring

- Monitoring the health situation
- Assessing health trends

Norms and standards settings in MQA



courtesy of @ T. Bush 2018

Among the 17 SDGs, indicator #3 focuses on good health and well-being

World Health Organization

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**

https://sustainabledevelopment.un.org/

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Milestones

WHO has built almost **30 years** of experience in the field of biowaiver and bioequivalence

1990's

2006

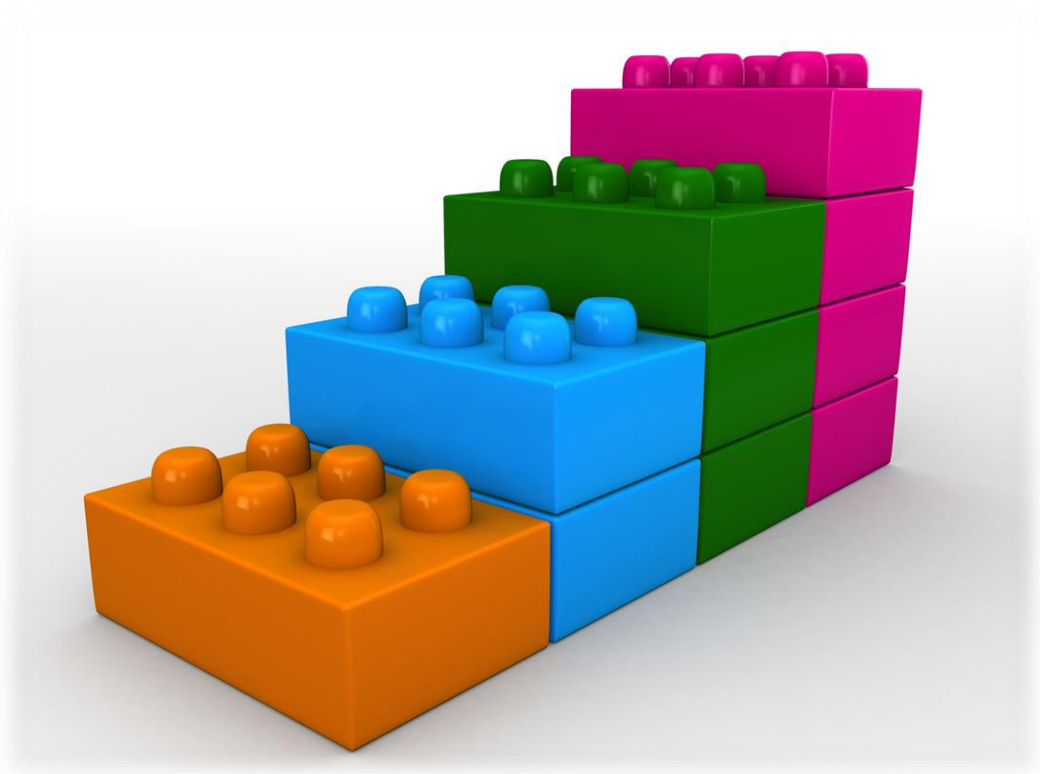
2015

2016

2017

2018

2019



The WHO experience with BCS-based biowaiver

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

1990's

2006

2015

2016

2017

2018

2019

- **1992** - 33rd ECSPP recognized the need for global guidelines with respect to multisource products. WHO TRS No. 834, 1993.
- **1994** - 34th ECSPP report: *Multisource (generic) pharmaceutical products: guidelines on registration requirements to establish interchangeability*. WHO TRS No. 863, Annex 9, 1996.
- **1999** - 35th ECSPP report: *Guidance on the selection of comparator pharmaceutical products for equivalence assessment of interchangeable multisource (generic) product*. WHO TRS No. 902, Annex 11, 2002.

The WHO experience with BCS-based biowaiver

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

1990's
2006
2015
2016
2017
2018
2019

- In 2006 the WHO published:
  - "*Proposal to waive in vivo bioequivalence requirements for WHO Model List of Essential Medicines immediate-release, solid oral dosage forms*" (WHO Technical Report Series No. 937, Annex 8, 2006)
    - 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:
  - "*Multisource (generic) pharmaceutical products: guidelines on registration requirements to establish interchangeability*" (WHO Technical Report Series No. 937, Annex 7, 2006)

The WHO experience with BCS-based biowaiver

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

1990's

2006

2015

2016

2017

2018

2019

- 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)
- "Guidance on the selection of comparator pharmaceutical products for equivalence assessment of interchangeable multisource (generic) products" republished form 2002 (WHO TRS Annex 8 No. 992, 2015)

The WHO experience with BCS-based biowaiver

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

1990's
2006
2015
2016
2017
2018
2019

- 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

1990's
2006
2015
2016
2017
2018
2019

- 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"*
- 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
- Following the ECSPP's 2016 directions, the WHO Secretariat started a multi-centric project: the **WHO Biowaiver Pilot Project**

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

1990's

2006

2015

2016

2017

2018

2019

- 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

1990's

2006

2015

2016

2017

2018

2019

- **WHO BP Project phase II -** scale up of the pilot phase

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The WHO Biowaiver project focus is on the BCS-based classification of APIs in the EML

World Health Organization

Focus of the project

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

World Health Organization

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 Biowaiver project: overview

Why

- The **WHO 52nd ECSPP** recommended to develop a new WHO Biowiaver 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

What

- 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**

How

- 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

World Health Organization

Phase I - Pilot

FIRST SET OF ACTIVE PHARMACEUTICAL INGREDIENTS

WHO Biopharmaceutics Classification System (BCS)-based classification of prioritized active pharmaceutical ingredients (APIs from the Model List of Essential Medicines (EML)

API contained in medicines on the EML	Therapeutic Area	Indication	Highest therapeutic dose [mg]	BCS Class[a]	Eligible for biowaiver	PQ EOI[b] /PQ
Tenofovir disoproxil fumarate	Anti-infectives	HIV	300 mg	I/III	Yes	Yes[c]
Dolutegravir	Anti-infectives	HIV	50 mg	II/IV	No	Yes[d]
Ethionamide	Anti-infectives	TB	15-20 mg/kg	II/IV	No	Yes[e]

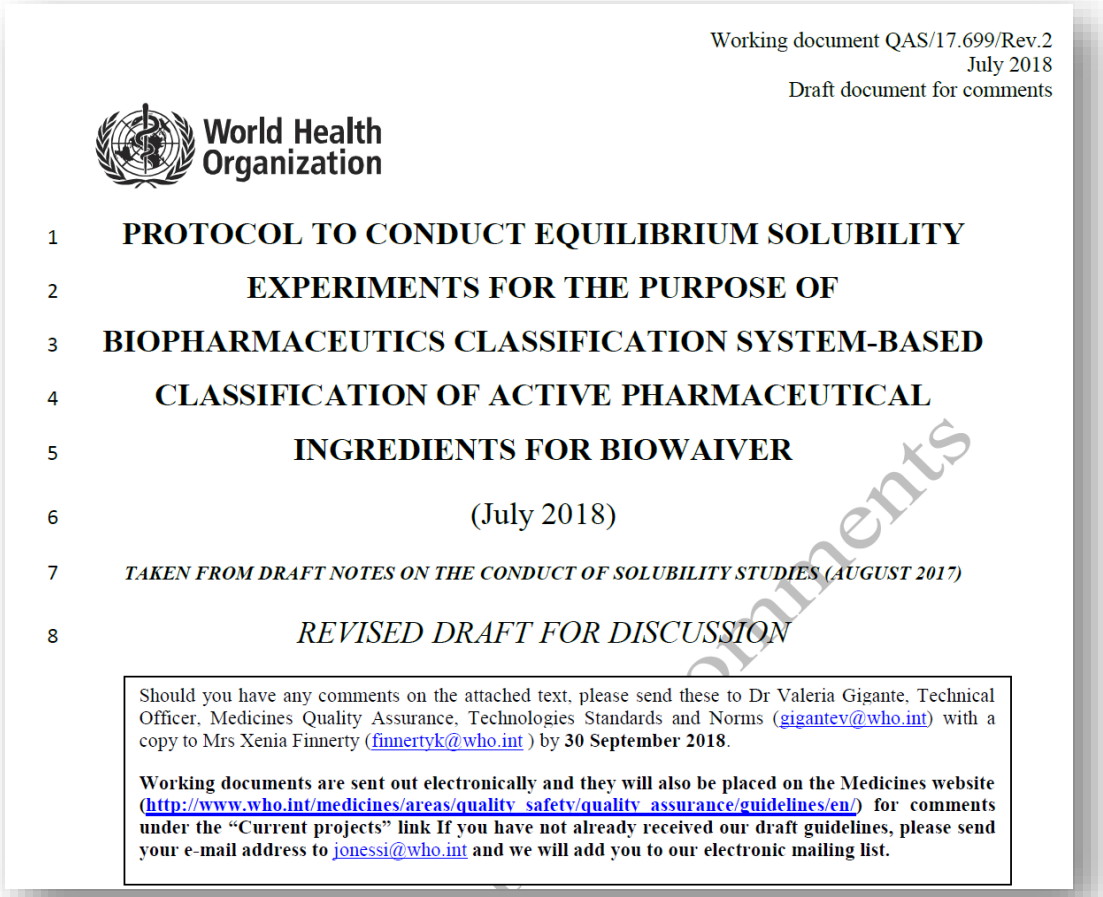
[a] According to the WHO guidelines, *Multisource (Generic) Pharmaceutical Products: Guidelines on Registration Requirements to establish Interchangeability* (WHO Technical Report Series, No. 1003, Annex 6 2017), APIs belonging to Class I and III are eligible for biowaiver. Once experimental permeability data will be available, the exact class attribution will be possible (i.e. either class I or class III). The present solubility characterization is already sufficient to provide an indication on whether an API is eligible for biowaiver or not.

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



Working document QAS/17.699/Rev.2
July 2018
Draft document for comments

World Health Organization

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

Should you have any comments on the attached text, please send these to Dr Valeria Gigante, Technical Officer, Medicines Quality Assurance, Technologies Standards and Norms (gigantev@who.int) with a copy to Mrs Xenia Finnerty (finnertyk@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/areas/quality_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 jonessi@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

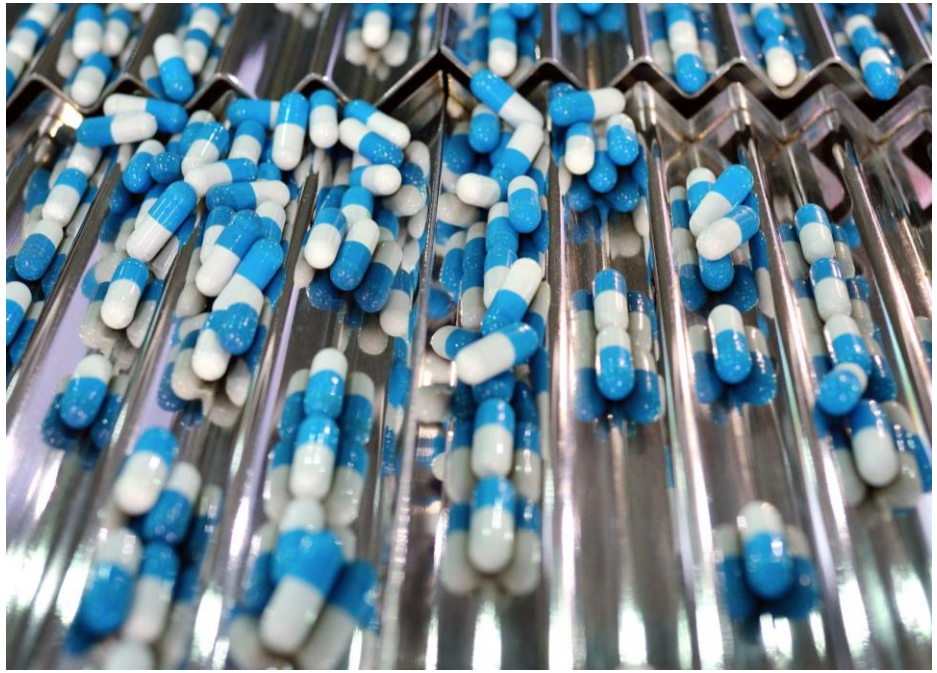
… we are shaping a global network of laboratories to achieve a global goal

THE WHO BIOWAIVER PROJECT OPERATION III

Manufacturers supporting the project with the API samples for the tests

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



2 **Controlled** substances are measured in parallel at **2 facilities**

3 **Each API** is **measured in parallel** at **3 facilities**

4 **Very high soluble** compounds are measured in parallel at **4 facilities**

6 **Unknown & expected borderline solubility** compounds measured in parallel at **6 facilities**

WORKPLAN

Tests phase

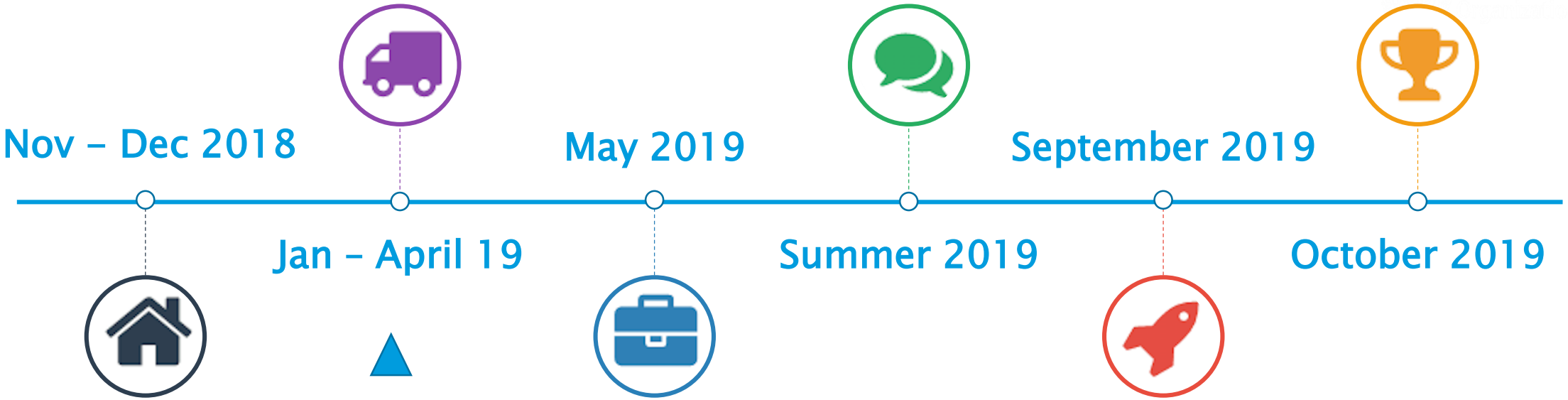
- Training for laboratories
- Shipment of APIs
- Experiments

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?

CASE STUDY: ETHIONAMIDE

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.

IMPORTANCE OF THE PROJET

- 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.

Thank you

WHO

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