



## Overview of comments on the guideline received so far and a summary of major areas that require attention.

Eva Gil Berglund

PKWP, Medical Products Agency, Sweden

EMA workshop on qualification and reporting of physiologically-based pharmacokinetic (PBPK) modelling and simulation, EMA 2016-11-21

# Please provide written comments!

- **Deadline for comments Jan 31st, 2017**
- **Use specific form and be as clear and constructive as possible**

[http://www.ema.europa.eu/ema/index.jsp?curl=pages/news\\_and\\_events/events/2016/10/event\\_detail\\_001331.jsp&mxxxid=WC0b01ac058004d5c3](http://www.ema.europa.eu/ema/index.jsp?curl=pages/news_and_events/events/2016/10/event_detail_001331.jsp&mxxxid=WC0b01ac058004d5c3)

- **We provide a response to each comment in a tabular format**



EUROPEAN MEDICINES AGENCY  
SCIENCE MEDICINES HEALTH

17 November 2016

<Name of committee (Committee abbreviation)>

## Overview of comments received on '<document title>' (EMA/.../...)

Interested parties (organisations or individuals) that commented on the draft document as released for consultation.

Stakeholder no.	Name of organisation or individual
1	
2	
3	

Comments recieved:

## **IQ Consortium**

International Consortium for Innovation and Quality in  
Pharmaceutical Development

# Selection of General comments from IQ

- **Include other areas than DDI**, such as mechanistic absorption issues (PPI DDIs, food-effect), hepatic and renal impairment, multiple-dose pharmacokinetics, induction, etc

Qualification needed before  
this may be accepted

# Backup slide: Translating qualification dataset requirements

**Renal impairment:**  
Predict large number of renally excreted drugs

## Restrictions

RI range

Transporters

fe

fu

**Hepatic impairment:**  
Predict large number of metabolised drugs

HI range

Transporters

fm

fu

Solubility

Enzymes

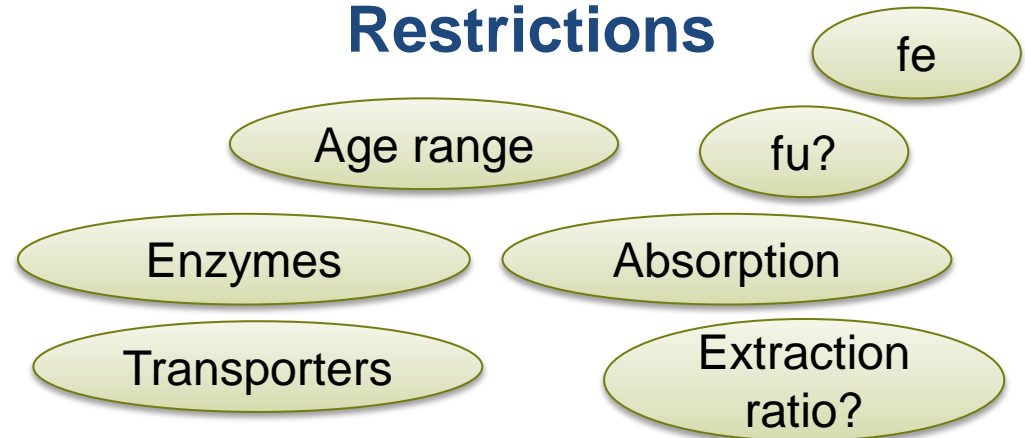
Non-linear  
elimination

Extraction  
ratio

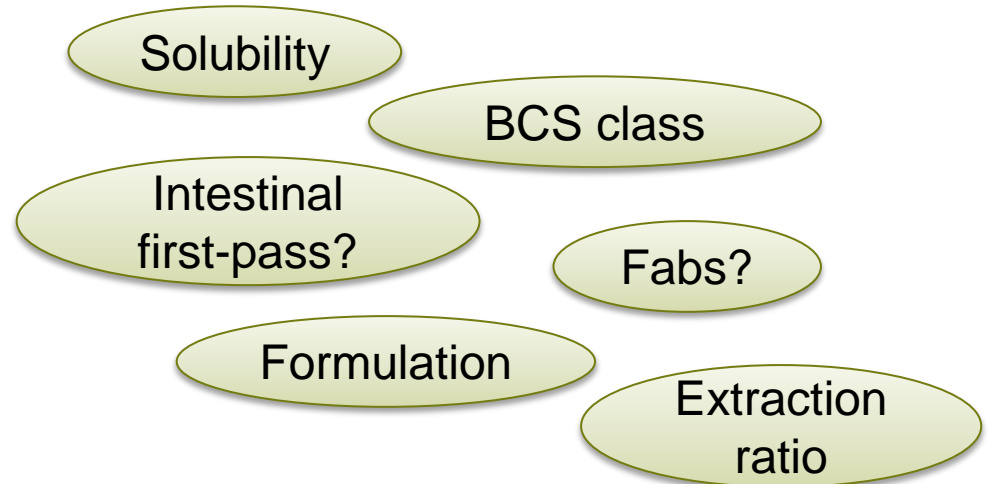
# Backup slide: Translating qualification dataset requirements

## Restrictions

**Paediatrics:**  
Predict large number of drugs



**Food interaction:**  
Predict large number of drugs food interaction



# General comments

- **Is i.v. data mandatory? (indicated by the GL text)**
- **Clearer separation between drug and system**
- **Need to re-perform all submitted PBPK simulations using the latest (qualified) version?**

The version used needs to be qualified.  
If old but qualified - discuss consequences.



## Specific comments

- **How will the CHMP qualifications be listed at the Ema web? Can this be a source to what components are qualified?**
- **Are all papers included in peer reviewed journals considered qualified as long as enough detail is provided?**
- **Version control: Full qualification or bridging dataset?**

Depends on alterations.  
Full dataset is default.

# Specific comments

- **Qualification dataset: clarify selection criteria with regards to PK characteristics. Give examples for perpetrator and victim.**
- **What does qualified "scenario" mean? Could mass-balance data or DDI with perpetrator be a limiting condition?**
- **Requirements for in-house vs commercial platform? What differences? (encouraged to seek central advice)**
- **Concentration at site of enzyme – how?**
- **Guidance on sensitivity analysis**

# Examples of questions to take home

- **How do we streamline the qualification process to allow for it to be as fast as possible?**
- **For the qualification – what is adequate precision?**
- **When we apply a qualification having a certain precision, how do we take the uncertainty into account?**
- **Clarify qualification requirement for low impact and possible consider high ethical impact (supporting study design paediatrics)**
- **Clarify how to select parameters which should be subject to SA**
- **Which qualification requirements should be set for situations where parts of the platform behaviour has been qualified before through the CHMP procedure.**

# further

- **Learned societies qualification: details**
- **Possibility to retract qualifications?**

Please remember to comment in writing also when you have commented orally in this meeting!



The secret of getting ahead is  
getting started

-Mark Twain