EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

# FRAMEWORK OF SETTING CLINICALLY RELEVANT SPECIFICATIONS: APPROACH, INFORMATION NEEDED, AND CRITERIA

DISSOLUTION AND TRANSLATIONAL MODELING STRATEGIES
ENABLING PATIENT-CENTRIC PRODUCT DEVELOPMENT

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*The views expressed in this presentation are the personal views of the speaker and may not be understood or quoted as being made on behalf of or reflecting the position of the EMA or any of its committees or working parties.*

# Outline

- **Some definitions and background**
  - **EMA Reflection paper on setting dissolution specifications**
  - **EMA expectations regarding discriminatory methods**
- Clinically relevant drug product specifications (CRDPS)
- EMA and M&S
- Conclusions

# What are we looking for?

The role of specifications should be to assure that products meet clinical performance and that processes are performing as expected.

The ultimate goal is to assure consistent in vivo product performance (safety and efficacy) for the marketed product relative to the clinical trial formulation.

# What are we looking for? How?

Traditionally dissolution specifications driven by regulatory and compendial expectations, aiming primarily at quality control and ensuring batch-to-batch consistency.

Mainly based on evaluation of developmental, process validation and failure batches.

# What are we looking for? How?

Consistent product quality comes from design and control of the manufacturing processes - QbD principles

And consistent product quality leads to:

Consistent in vivo product performance (safety and efficacy profiles) for the marketed product relative to the clinical trial formulation

**This order cannot be reversed**

# Setting Specifications for Dissolution Reflection Paper on dissolution specifications of generics

- Prerequisite for extrapolation of the results of the bioequivalence study to the drug product administered to the patient is a similar dissolution compared to the biobatch.
- Similar dissolution of two batches requires differences of less than 10% in their mean results.

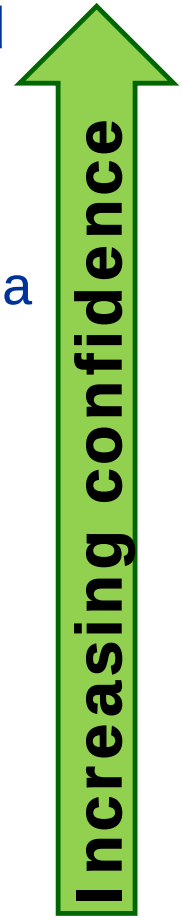
# How to demonstrate discriminatory power (in order of priority)

1. Inclusion of **batches** shown to be **bioequivalent** and **batches bioINequivalent** .

2. **"Side batch" approach-** inclusion of a range of bioequivalent batches and by comparison of dissolution data to average PK parameters (matching rank order)

3. **Inclusion of batches with deliberate but meaningful variations of attributes:**

- Attributes of API and/or excipients (e.g. particle size)
- formulation (excipients)
- Manufacturing process (e.g. compression force)



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# Can we do more?
# Clinically relevant specifications

Need to establish a link (qualitative or quantitative)
from in vitro dissolution data
through in vivo drug release
to pharmacokinetic parameters
and therefore consistent therapeutic performance of routine production batches.

(*http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2014/07/WC500170465.pdf* )

**The stronger the link, the bigger the confidence, larger potential flexibility**

# Can we do more? Clinically relevant specifications?

if only available:

- ✓ A small number of clinical phase III batches,
- ✓ No (in vivo) data linking material attributes and process parameters,

Then assuming a well developed discriminating method,

- ➢ Specifications around those limited batches based on dissolution similarity (f2 criteria)

**Narrow? No, based on the available data!**

# Can we do more? Clinically relevant specifications

- ✓ in vivo PK data available from a number of batches with different in vivo profiles – all bioequivalent (i.e., fastest and slowest "side batch")

Then assuming a well developed discriminating method,

- ➢ Specification based on the "side-batch" with the slowest dissolution

**Narrow? No, based on the available data!**

See: Reflection Paper on dissolution specifications

# Can we do even more? How?

Meaningful in vitro tests, discriminating with regard to changes in critical process parameters and /or critical material attributes which may have an impact on the bioavailability.

Ideally all non-bioequivalent batches should be detected by the *in vitro* dissolution test.

**IVIVC golden standard?**

# Can we do even more? How?

A strategy for setting specification by:

Using methods that can predict the impact that changes in the manufacturing processes or formulation may have in vivo.

Establishing systematic proces… development phases to sp…

Aiming at establishing a predictive …d robust in vivo in vitro relation **-> Model**

pivotal value in decision making

**Specification based on the available data!**

# Qualification of the PBPK platform for the intended use- What do we mean?

Qualification is related to the PBPK platform

Is there enough scientific support for a certain use for that particular platform?

**Extrapolation of PK data in young children**

**DDI**

**Prediction of Food effect**

**IVIVC**

**Prediction of PK in Special populations**

**Formulations changes**

**Biowaivers**

# Qualification of the PBPK platform for the intended use- What do we mean?

The Applicant should be able to answer the question :

- Has the platform including the specific version been shown to adequately predict the same kind of situations?

This should be evaluated using external data.

# Framework for M&S in Regulatory Review

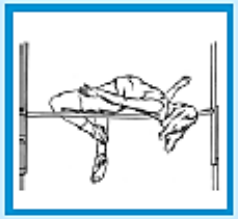
## According to the impact on regulatory decision

**High impact**

Scientific Advice, Supporting Documentation, Regulatory Scrutiny } +++

**Medium impact**

Scientific Advice, Supporting Documentation, Regulatory Scrutiny } ++



**Low impact**

Scientific Advice, Supporting Documentation, Regulatory Scrutiny } +

Impact on regulatory decision

http://www.emea.europa.eu/docs/en_GB/document_library/Presentation/2011/11/WC500118262.pdf

# High regulatory impact decisions

- **High regulatory impact decisions**

**Examples:**

  - All changes to SmPC
  - Such as waiving for a study
  - Non studied scenarios
  - Extrapolation of pk-information in to younger age groups

- **Medium regulatory impact decisions**
  - Such as paediatric dose setting that will be confirmed by a clinical study

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# The Role of Modelling and Simulation in Development and Registration of Medicinal Products

- appropriate use of M&S is an indicator of a more rational drug development
- supports robust outcomes of clinical trial authorisation, scientific advice, pediatric investigation plans, and benefit/risk decisions.
- To date these have comprised mainly DDI applications and have been included in a number of SmPCs and/or EPARs (e.g. Halavan, Jakavi, Olysio).

➢ **early discussions with regulators encouraged**

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## Modelling and Simulation Working Group (MSWG):

http://www.ema.europa.eu/ema/index.jsp?curl=pages/contacts/PDCO/people_listing_000123.jsp&mid=WC0b01ac058063f485

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## Experts from regulatory agencies and academia

*Chair: Ine Skottheim (NOMA)*

*Vice Chair: Flora Musuamba (FAMHP, UCL)*

## 10 TC/per year + 1 F2F meeting

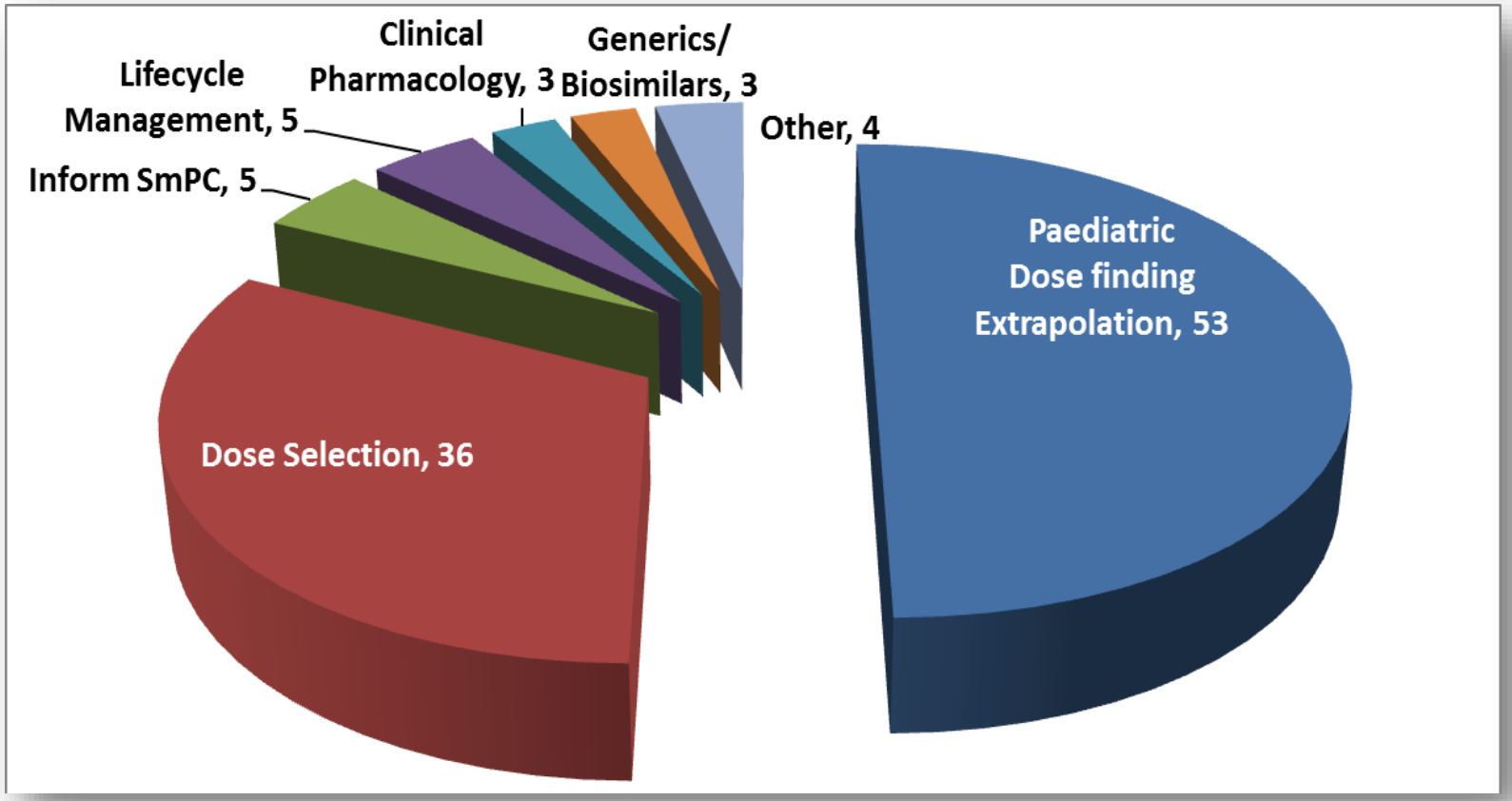
## Product related work and guidelines

## 2016 Activity report of the MSWG:

http://www.ema.europa.eu/docs/en_GB/document_library/Report/2017/03/WC500222778.pdf

# Use of M&S in 2016

105 product related procedures were referred to the MSWG with 41 from PDCO, 62 from SAWP, 2 from CHMP.




**A breakdown of the scope of questions addressed by M&S WG- Scope of M&S in regulatory submissions.**

# MSWG 2016 Activity Report

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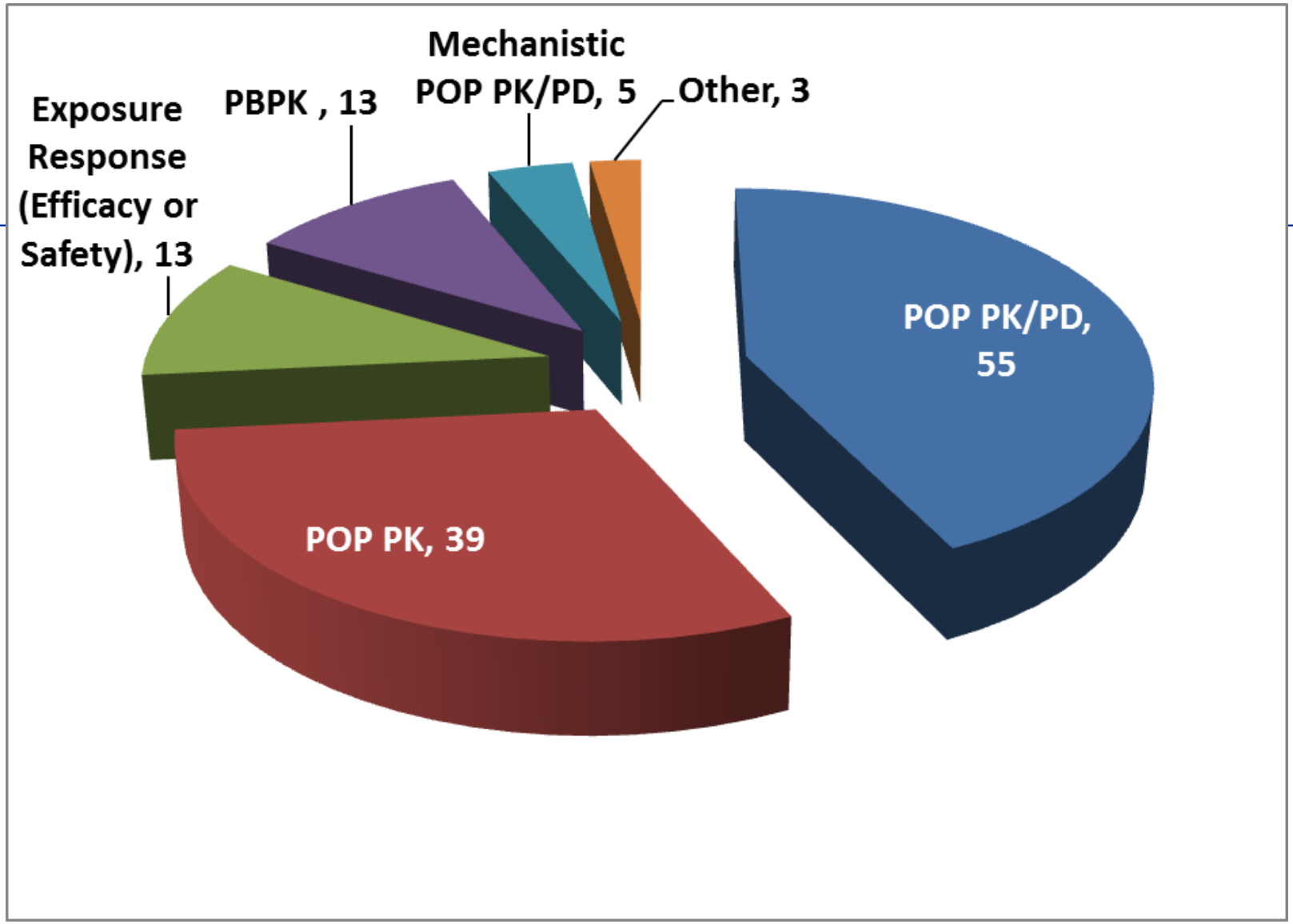


**A breakdown of the type of models seen by M&S WG**

# Conclusions

- ✓ CRDPS not new! Depends on the available data.
- ✓ M&S is a powerful tool for building strong scientific rationale and guidance for setting CRDPS.
- ✓ M&S should be more integrated in drug development and regulatory assessment.
- ✓ Model scrutiny will depend on the impact of the exercise on the regulatory decision and product labelling.
- ✓ Early dialogue with regulators encouraged- Qualification of novel methodologies

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# Thank you