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EMA EFPIA Workshop on the importance of dose finding and dose selection for the successful development, licensing and lifecycle management of medicinal products

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Disclaimer: 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 one of its committees or working parties.

Outline

- **Regulatory Background: ICH E4, E8, E9**
- **Experience in MSWG**
- **Experience in Scientific Advice**
- **Experience in CHMP**
- **Key Questions/Expectations**

ICH E8 General Considerations for Clinical Trials

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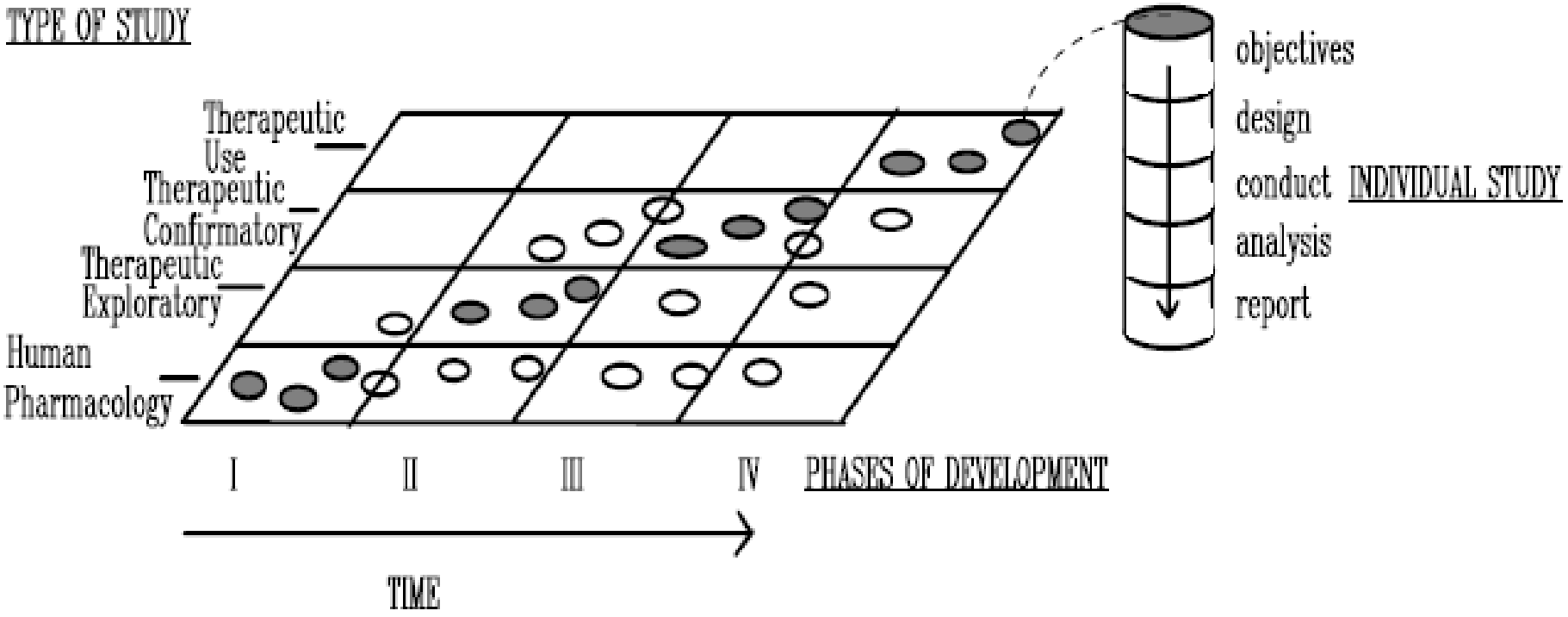
Type of Study	Objective of Study	Study Examples
Human Pharmacology	• Assess tolerance • Define/describe PK[1] and PD[2] • Explore drug metabolism and drug interactions • Estimate activity	• Dose-tolerance studies • Single and multiple dose PK and/or PD studies • Drug interaction studies
Therapeutic Exploratory	• Explore use for the targeted indication • Estimate dosage for subsequent studies • Provide basis for confirmatory study design, endpoints, methodologies	• Earliest trials of relatively short duration in well- defined narrow patient populations, using surrogate or pharmacological endpoints or clinical measures • Dose-response exploration studies
Therapeutic Confirmatory	• Demonstrate/confirm efficacy • Establish safety profile • Provide an adequate basis for assessing the benefit/risk relationship to support licensing • Establish dose-response relationship	• Adequate, and well controlled studies to establish efficacy • Randomised parallel dose-response studies • Clinical safety studies • Studies of mortality/ morbidity outcomes • Large simple trials • Comparative studies
Therapeutic Use	• Refine understanding of benefit/risk relationship in general or special populations and/or environments • Identify less common adverse reactions • Refine dosing recommendation	• Comparative effectiveness studies • Studies of mortality/morbidity outcomes • Studies of additional endpoints • Large simple trials • Pharmacoeconomic studies

Correlation between Development Phases and Types of Study



European Medicines Agency

November 1994
CPMP/ICH/378/95

ICH Topic E 4
Dose Response Information to Support Drug Registration

Step 5

NOTE FOR GUIDANCE ON DOSE RESPONSE INFORMATION TO SUPPORT DRUG REGISTRATION
(CPMP/ICH/378/95)

APPROVAL BY CPMP	May 1994
DATE FOR COMING INTO OPERATION	November 1994

ICH E4 Methodological considerations

- **D-E-R integral Part of Drug Development**
- **Wide range of doses**
- **Several dose levels**
- **Dose-response function, not individual pairwise comparisons**
- **Importance of PK**
- The **entire database** should be examined intensively for possible dose-response effects
- Focus in good **surrogate markers**
- Focus in **informative study designs**
- **Open to new approaches**
- **No loss of time and minimal extra effort compared** to development plans that ignore dose-response

ICH E4 Regulatory Impact

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- Approval decisions are based on a consideration of the **totality of information on a drug**
- Although dose-response information should be available, **depending on the kind and degree of effectiveness shown, imperfections in the database may be acceptable** with the expectation that **further studies will be carried out after approval**

Dose-Response trials may serve a number of objectives

- **The confirmation of efficacy**
- The investigation of the shape and location of the dose-response curve
- The estimation of an appropriate starting dose
- The identification of optimal strategies for individual dose adjustments
- The determination of a maximal dose beyond which additional benefit would be unlikely to occur
- The estimation of the relationship between dose and response, including the construction of confidence intervals and the use of graphical methods, is as important as the use of statistical tests
- The hypothesis tests that are used may need to be tailored to the natural ordering of doses or to particular questions regarding the **shape of the dose-response curve**

During the last 20 years since ICH E4

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- 1995 Opening EU agency in London
- 2004 SAWP was established
- 2009 Qualification of novel methodologies
- 2009 BSWP was established
- 2011 EMA-EFPIA Modelling Workshop
- 2013 MSWG was established

EMA Website

http://www.ema.europa.eu/ema/index.jsp?curl=pages/news_and_events/events/2011/07/event_detail_000440.jsp&mid=WC0b01ac058004d5c3

Editorial
Regulatory Modeling and Simulation Moves Into the Next Gear in Europe
P H van der Graaf
CPT Pharmacometrics Syst. Pharmacol. 2: e32; doi:10.1038/psp.2013.8
Full Text | PDF

Perspective
The Role of Modeling and Simulation in Development and Registration of Medicinal Products: Output From the EFPIA/EMA Modeling and Simulation Workshop
E Manolis, S Rohou, R Hemmings, T Salmonson, M Karlsson and P A Milligan
CPT Pharmacometrics Syst. Pharmacol. 2: e31; doi:10.1038/psp.2013.7
Abstract | Full Text | PDF | Supplementary information

Perspective
Modeling and Simulation at the Interface of Nonclinical and Early Clinical Drug Development
S A G Visser, E Manolis, M Danhof and T Kerbusch
CPT Pharmacometrics Syst. Pharmacol. 2: e30; doi:10.1038/psp.2013.3
Full Text | PDF | Supplementary information

Perspective
Modeling and Simulation in Clinical Pharmacology and Dose Finding
A Staab, E Rook, M Maliepaard, L Aarons and C Benson
CPT Pharmacometrics Syst. Pharmacol. 2: e29; doi:10.1038/psp.2013.5
Abstract | Full Text | PDF

Perspective
Modeling and Simulation as a Tool to Bridge Efficacy and Safety Data in Special Populations
L Harnisch, T Shepard, G Pons and O Della Pasqua
CPT Pharmacometrics Syst. Pharmacol. 2: e28; doi:10.1038/psp.2013.6
Abstract | Full Text | PDF

Perspective
Modeling and Simulation to Optimize the Design and Analysis of Confirmatory Trials, Characterize Risk–Benefit, and Support Label Claims
S F Marshall, R Hemmings, F Josephson, M O Karlsson, M Posch and J-L Steimer
CPT Pharmacometrics Syst. Pharmacol. 2: e27; doi:10.1038/psp.2013.4
Full Text | PDF

2011 EFPIA-EMA M&S Workshop

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Supplementary Table: Opportunities, Challenges and Actions arising from plenary discussion

Opportunities with M&S	Challenges with M&S	Actions / Next Steps
Increase efficiency of drug development by integrative data analysis and design optimisation	Communication gap between modelling scientists and other disciplines both within Industry and between Industry and Regulators	Establish a more standardised and quantitative framework for extrapolation
Integration of new technologies (e.g. Omics) in the development and evaluation of medicinal products	Mis-perception that dose-response characterization and dose regimen selection are determined solely at the company's risk	Strengthen model and data sharing initiatives
Support extrapolation of clinical data across different populations	Lack of standardisation of methods for data generation, analysis and reporting	Debate an update to the current regulatory guidance on dose ranging/finding
Increase the robustness of both Regulatory and Industry decision-making	Heterogeneity and inconsistency in practice of M&S approaches within Industry	Agree on common good practices, standardisation of methods and reporting
Better use of resources by prioritising more promising drug	Use of model based approaches to make inferential statements around efficacy and safety	Development of standards on when and how longitudinal analysis can be used for inference in a similar way to landmark analysis
Better informed benefit risk decisions and labelling of medicinal products	Difficulties in sharing data in a competitive environment	Establish communication strategy utilizing existing regulatory pathways
	Variable readiness and capacity of the regulatory system to evaluate M&S approaches	Organise further workshops to continue to share experiences
	eCTD structure does not lend itself to detailed reporting of MBDD activities	To integrate and expand the influence of M&S competence in the EU regulatory network

Extrapolation CP ICH E11

MID3

SAWP Qualification

MSWG

MSWG experience on Dose Finding & D-E-R

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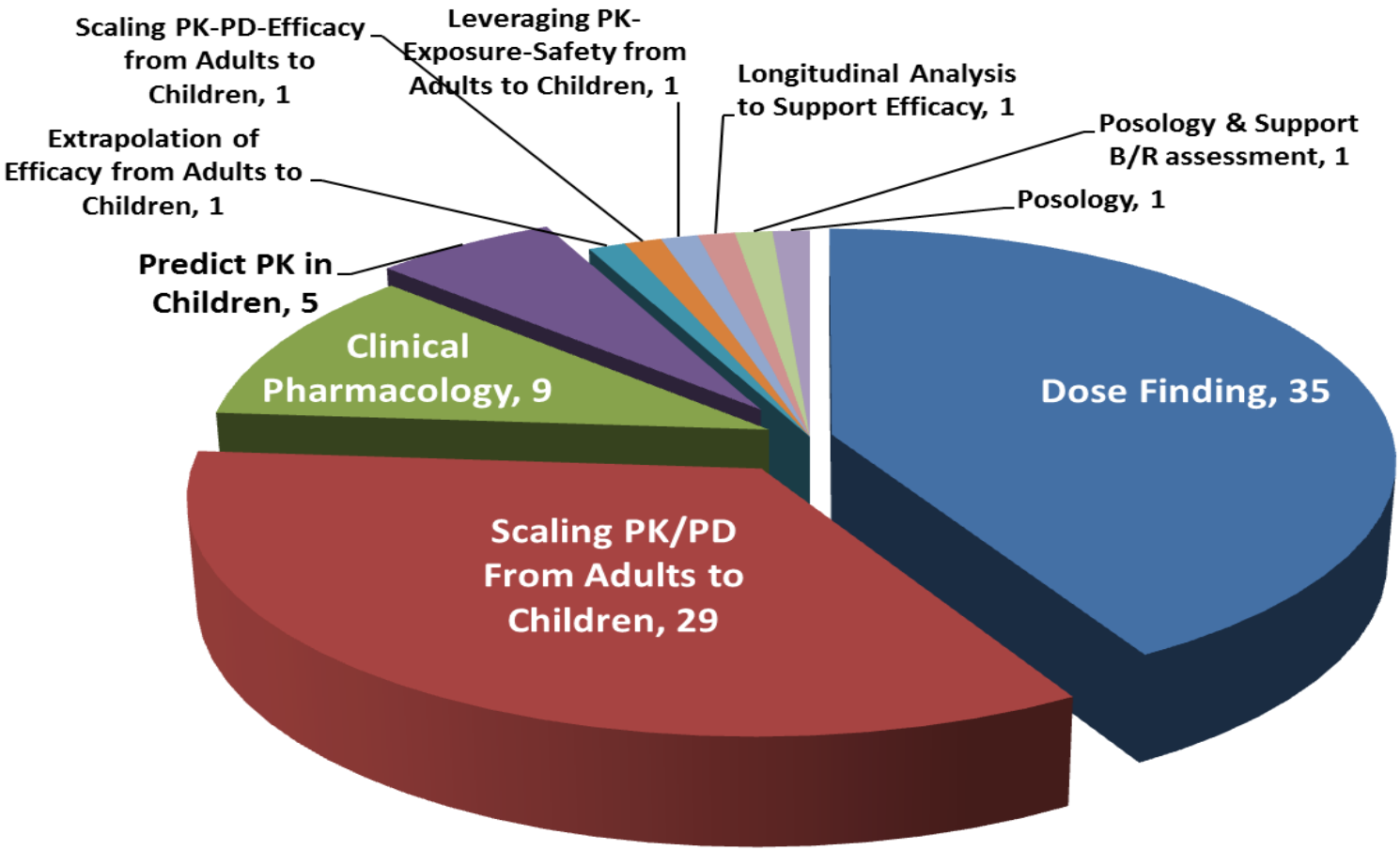

Number of referrals to MSWG in **2014** categorised according to **scope**

- *85 Referrals in 2014*

MSWG experience on Dose Finding & D-E-R

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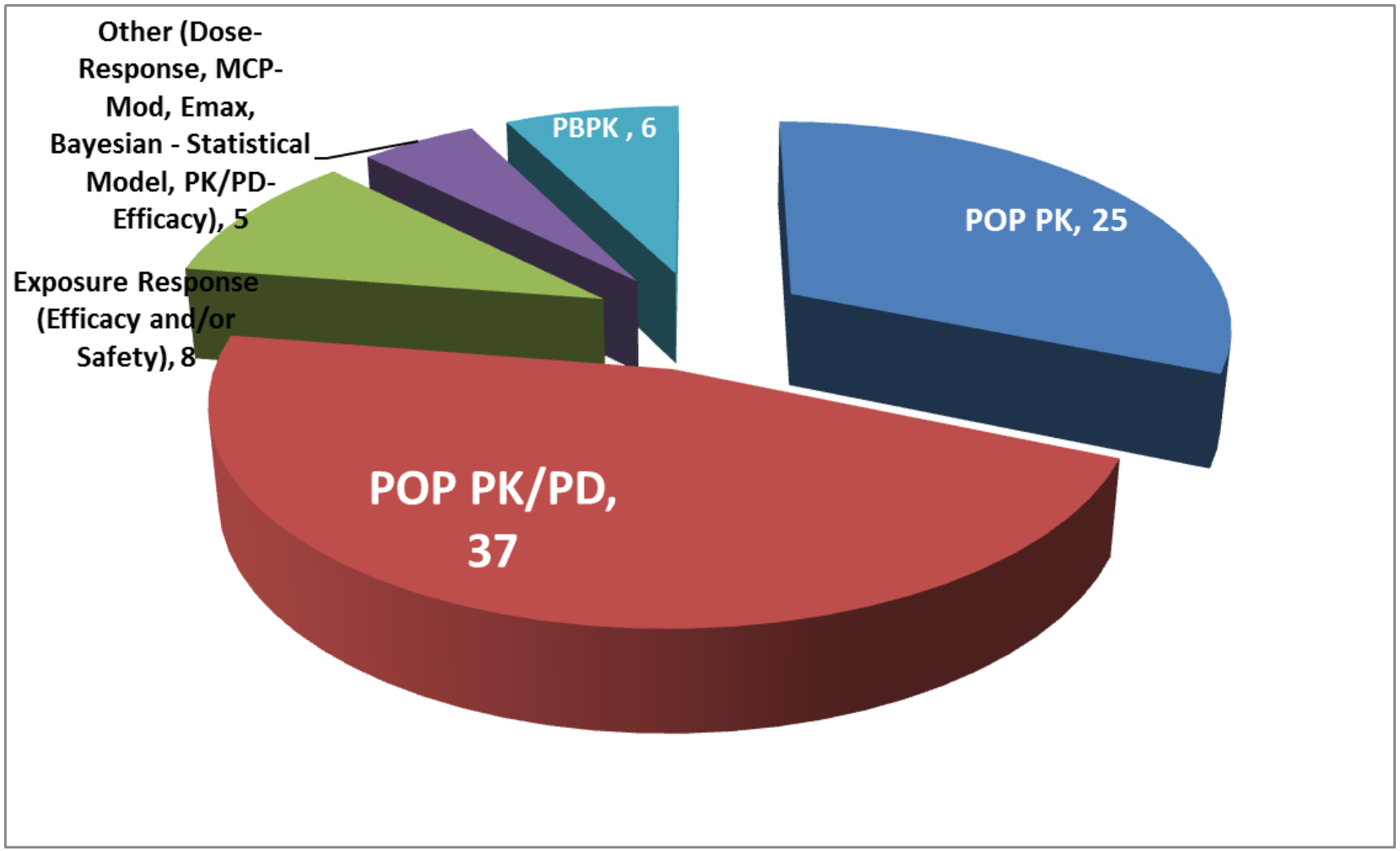
- Methods discussed by MSWG in 2014



SAWP experience on Dose Finding & D-E-R

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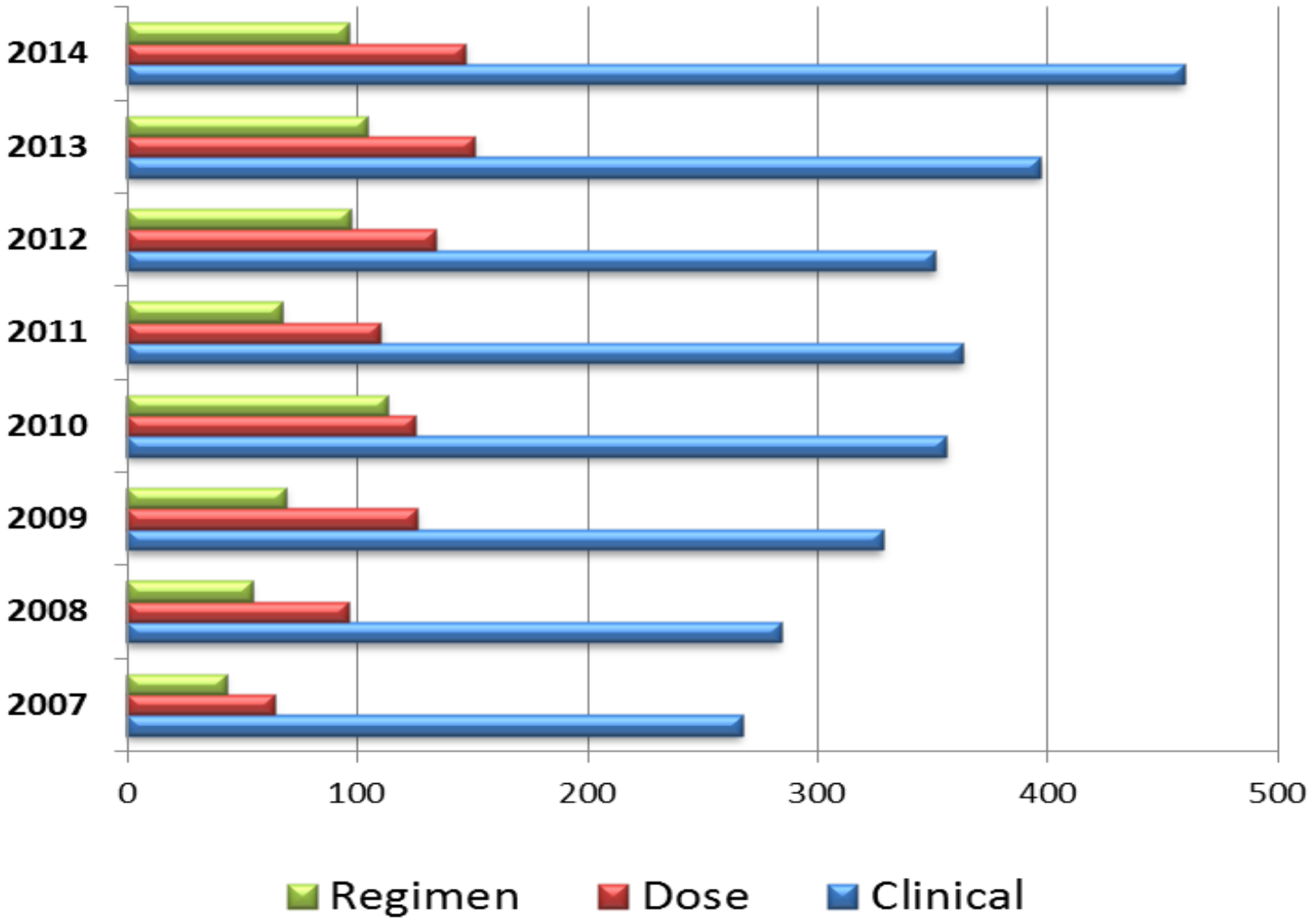

Number of requests to SAWP discussing Clinical development (Clinical), Dose, or Regimen based on the Scientific Advice database (from 2007-2014)

Qualification Opinions on Dose Finding

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5 November 2014
EMA/CHMP/SAWP/381716/2014
Committee for Medicinal Products for Human Use (CHMP)

Draft qualification opinion

In-vitro hollow fiber system model of tuberculosis (HFS-TB)

Draft agreed by scientific advice working party	5 June 2014
Adopted by CHMP for release for consultation	26 June 2014[1]
Start of public consultation	18 November 2014[2]
End of consultation (deadline for comments)	9 January 2014[3]

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r Human Use (CHMP)

Qualification Opinion of MCP-Mod as an efficient statistical methodology for model-based design and analysis of Phase II dose finding studies under model uncertainty

Draft agreed by Scientific Advice Working Party	5 September 2013
Adopted by CHMP for release for consultation	19 September 2013[1]
Start of public consultation	15 October 2013[2]
End of consultation (deadline for comments)	24 November 2013[3]
Adoption by CHMP	23 January 2014

SAWP experience on Dose Finding & D-E-R

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Broad range of designs and analysis methods - Slide 8 "Dose-Response trials may serve a number of objectives":

- Parallel group fixed doses designs with multiple doses well informed by previous preclinical experiments and HV PK and safety data
- Systems pharmacology approaches
- Regression methods
- ANOVA methods
- Pharmacometrics (PK/PD analyses)
- Stand-alone or adaptive designs, with a variety of methods in Stage I
- ***All acceptable if fit for purpose***

However we often see:

- Rushed exploratory phase; fewest regulatory demands?
- Incomplete (or no) dose/exposure response characterisation (few doses, inadequate endpoints, analysis)
- Therapeutic exploratory trials designed as a mini Phase 3 with the objectives to waive a second phase 3 pivotal trial
- ***CHMP/SAWP challenge weak exploratory developments, but to what end?***

SAWP experience on Dose Finding & D-E-R

Dose finding/selection was referred to as “the sponsor’s risk”.

This is unfortunate wording and should be avoided.

It was never meant to abrogate responsibility or show a lack of scientific or regulatory interest, it is poor shorthand for “… conducting a weak exploratory development, D-E-R investigation or rushing D-F represents a risk to the possibility for successful development…”

Scientific challenges

- Not only which design for which question?
- Relevance of the endpoints/BMs selected
- >1 dose in Phase III
- Usual 'external validity' of exploratory trials
- What precision is 'acceptable'?
- Type I error control is not debated by regulators for dose selection, however if many doses/regimens are tested with few patients and no clear plan to utilise this information concerns are expressed that the study might be misleading and sub-optimal
- As for B/R evaluation dose selection is based on the totality of data. Sometimes the wisdom of adaptive Ph2/3 designs are challenged on the basis that they don't leave the gap between Ph2 and 3 needed to evaluate the totality of Ph2 data before progressing
- Scenarios where dose-finding, dose-response not possible?
- Safety

SAWP experience on Impact

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Good dose finding and D-E-R

- Provides evidence of efficacy
  - The example of antibiotics: Dose exposure response information could be used as primary evidence of efficacy if this justified by unmet medical need (Ref. PK/PD of antibiotics session 3)
- Could support a single pivotal trial; ***EMA points to consider on one pivotal trial.*** **"**The extent of confirmatory phase III data needed will depend upon what is established for the product in earlier phases...**", *but is this the strongest incentive…?***
- Facilitates informed decisions when planning the pivotal development for both sponsors (scenario planning) and regulatory bodies increasing the chances of success.
- Can provide a strong database to support extrapolation to different age/organ impairment/ethnic groups
  - *(Ref. Sessions 4 & 5)*

European Directive 2001/83/EC

MHRA

- **Legislation** requires that marketing authorisation for a medicinal product shall be **refused** if:

(a) the **risk-benefit** balance is not considered to be favourable; or

(b) its **therapeutic efficacy** is insufficiently substantiated by the applicant; or

(c) its qualitative and quantitative composition is not as declared.

- **"therapeutic efficacy"** is considered in terms of the clinical relevance as well as statistical significance

CHMP experience

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Well characterised and reported D-E-R relationships

- Evidence of a good development programme; support for a coherent development
- Provide a strong data base Provides a basis to address limitations of data and uncertainties at the stage of MAA, e.g. a basis to discuss different age groups /organ impairment/ethnic groups etc. *(Ref. Sessions 4 & 5)*
- SmPC more informative for patients and prescribers, fewer restrictions, post-authorisation obligations
- Burden of poor dose finding in post approval studies and post approval SmpC modifications could be expected *(Ref. Falk Ehmann's Presentation, session 5)*

Key Questions / Expectations

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- Why do sponsors not see value in strong exploratory development?
- Why pairwise comparisons for dose selection prevail?
- Phase II trials serve multiple purposes in addition to dose selection, D-E-R characterisation (i.e. understand the population, the clinical endpoint and estimate an effect size, prepare clinical trial logistics, safety), can these competing objectives be combined in the same study design?
- What is the toolkit for the well informed drug developer and regulator (session 2)
- Can we define some rules of thumb on how to use the different tools? (sessions 2, 3, 4)
- How does this toolkit/rules apply in practice, i.e. in different therapeutic areas? (session 3)
- How can regulators incentivise sponsors to invest in dose selection and better characterise and report D-E-R information? Is there a room to move away from 2 pivotal trials if there is good D-E-R (sessions 5,6)