

Update: Validation of New Technology for Use in Drug Discovery in Europe

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Disclaimer

The views and opinions expressed in the following presentation are personal and should not be attributed to the Belgian Federal Agency for Medicines and Health Products or to the European Medicines Agency



Outline

3R's: setting the scene in the EU

Regulatory background

Regulatory acceptance of 3R methods

Conclusions



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3R's: setting the scene in the EU

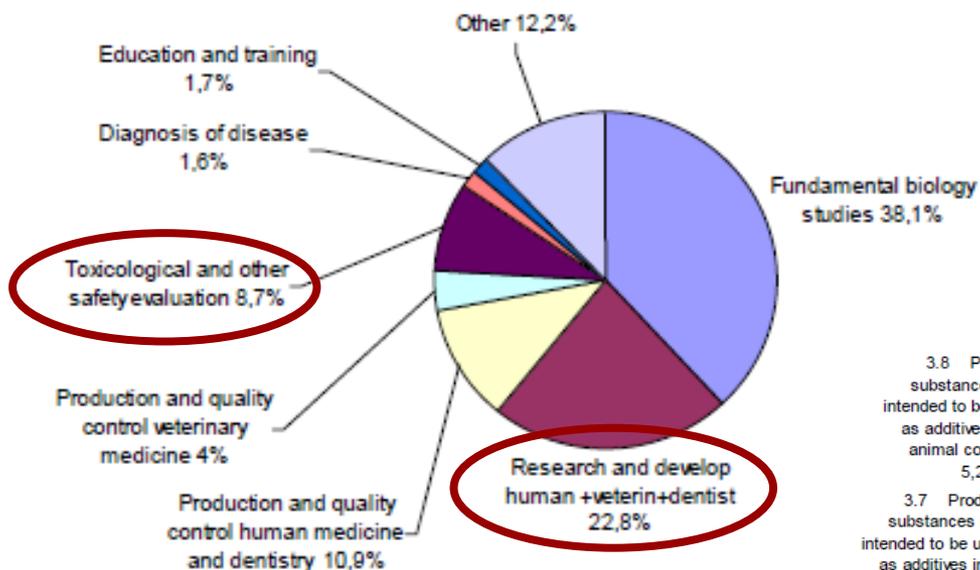
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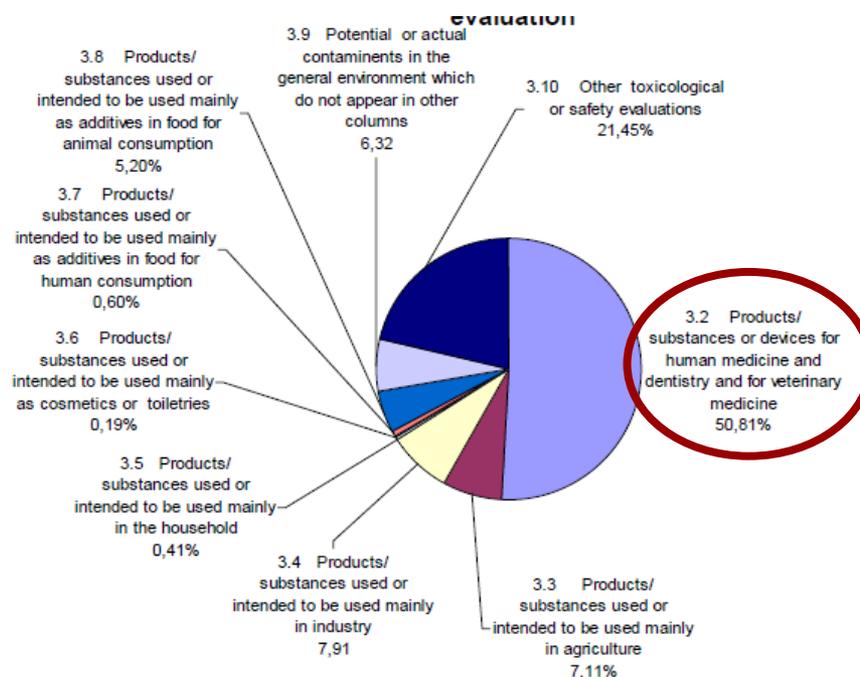
Purposes of animal experiments



2008:

12 million of animals/year in 27 Member States

Animals used in toxicological or other safety experiments



Directive 2010/63/EU of the European Parliament and of the Council

of 22 September 2010 on the protection of animals used for scientific purposes

Different articles relate to the application of the 3R's.

Article 4 clearly states that:

Member States shall ensure that, wherever possible, a scientifically satisfactory method or testing strategy, not entailing the use of live animals, shall be used instead of a procedure .

Member States shall ensure that the number of animals used in projects is reduced to a minimum without compromising the objectives of the project.

Member States shall ensure refinement of breeding, accommodation and care, and of methods used in procedures, eliminating or reducing to the minimum any possible pain, suffering, distress or lasting harm to the animals.



Directive 2010/63/EU of the European Parliament and of the Council

of 22 September 2010 on the protection of animals used for scientific purposes

Article 13 states that:

1. *Without prejudice to national legislation prohibiting certain types of methods, Member States shall ensure that a procedure is not carried out if another method or testing strategy for obtaining the result sought, not entailing the use of a live animal, is recognised under the legislation of the Union.*
2. *In choosing between procedures, those which to the greatest extent meet the following requirements shall be selected:*
 - (a) *use the minimum number of animals;*
 - (b) *involve animals with the lowest capacity to experience pain, suffering, distress or lasting harm;*
 - (c) *cause the least pain, suffering, distress or lasting harm; and are most likely to provide satisfactory results.*



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Non-clinical guidelines, recommendations by:



EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

Safety Working Party (SWP) of the Committee on Human Medicinal Products (CHMP)

Tasks include:

- Support dossier evaluation
- Scientific advice - general and product specific
- Contribution to the Scientific Advice Working Party (SAWP) of the CHMP
- Assessment of non clinical safety findings raised post authorisation
- **Preparation, review and update of guidelines**
- Training
- On request, advice, to the CHMP, other WPs, CMDh, HMPC, EC
- Liaison with interested parties (e.g. EFPIA, ECVAM, ABPI, ILSI)



The global context



EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

EU: EMA (European Medicines Agency;
www.ema.europa.eu)



ICH: International Conference on Harmonisation
(www.ich.org)



WHO: World Health Organisation (www.who.int)



EU: EDQM (European Directorate for the Quality
of Medicines and Healthcare;
www.edqm.eu)



Joint *ad hoc* Expert Group on the Application of the 3Rs in Regulatory Testing of Medicinal Products - JEG 3Rs

A **joint CHMP/CVMP expert group** set up to provide advice to the Committees on 3Rs topics relevant to the testing of medicines for regulatory purposes

Made up of experts from CHMP/CVMP and all EMA working parties for which testing in animals is relevant, plus observers from ECVAM and EDQM

Chair: Sonja Beken (SWP)

Vice chair: Ellen-Margrethe Vestergaard (CVMP)

Meets twice a year



Joint Expert Group on the Application of the 3Rs in Regulatory Testing of Medicinal Products - JEG 3Rs

Tasks include:

- Identification of opportunities for implementation of 3Rs in regulatory testing
- Coordinating, facilitating and prioritising EMA activities within the 3Rs arena
- Establishing strong ties with EDQM and ECVAM
- Training on 3Rs for experts working within the field medicinal products regulation
- Contribute to development of guidelines in which 3Rs issues are applicable in collaboration with relevant Working Parties
- Provide information and advice on 3Rs to stakeholders
- Consider how progress on 3Rs issues can most usefully be used to influence development of regulatory guidance at an international level through ICH, VICH etc





What we do

Who we are

How we work

Committees

Working parties and other groups

CHMP

CVMP

Efficacy Working Party

Environmental Risk Assessment Working Party

Immunologicals Working Party

[Home](#) [About Us](#) [Working parties and other groups](#) [CVMP](#) [Expert Group on 3Rs](#)

Expert Group on the Application of the 3Rs in Regulatory Testing of Medicinal Products

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The **Joint Committee for Medicinal Products for Veterinary Use/Committee for Medicinal Products for Human Use Ad-hoc Expert Group on the Application of the 3Rs in Regulatory Testing of Medicinal Products** (JEG 3Rs) provides advice and recommendations to the [Committee for Medicinal Products for Veterinary Use](#) (CVMP) and [Committee for Medicinal Products for Human Use](#) (CHMP) on all matters relating to the **use of animals** and the application of the **'3 R' principles** (replacement, reduction and refinement) in the testing of medicines for regulatory purposes.

Mandate, rules of procedure and work programme

- [Mandate](#)
- [Work plan](#)

Statement of the European Medicines Agency's position on the application of the 3Rs

- [Agency position on the application of the 3Rs](#)

Composition

The JEG 3Rs consists of a **core group** of one or two [European experts](#) from each of the existing CVMP and CHMP Working Parties for which animal testing is relevant:

http://www.ema.europa.eu/ema/index.jsp?curl=pages/contacts/CVMP/people_listing_00094.jsp&mid=WC0b01ac05803a9d6d



JEG 3Rs: current achievements and tasks

- 3Rs statement for publication on EMA website
- Review of animal testing requirements (CXMP and international guidance)
- Concept paper on the need for revision of the position on the replacement of animal studies by *in vitro* models (EMA/CHMP/SWP/169839/2011)
- Review of final product batch testing requirements (collaboration with EDQM)
- Consistency of manufacturing approach for quality control of vaccines (→ EPAA Technical Committee)
- Preliminary analysis of regulatory relevance of new alternative methods (PARERE) (coordinating body of EMA responses)
- Communication with stakeholders
- Develop strategies to encourage implementation of 3Rs

approaches





23 September 2011
EMA/470807/2011
Veterinary Medicines and Product Data Management

Statement of the EMA position on the application of the 3Rs (replacement, reduction and refinement) in the regulatory testing of human and veterinary medicinal products

The European Medicines Agency (EMA) commits to the application of replacement, reduction and refinement (the 3Rs) of animal testing as detailed in Directive 2010/63/EU¹. To this end, a Joint ad hoc Expert Group (the JEG 3Rs) has been created in order to promote best practice in the implementation of the 3Rs in regulatory testing of medicinal products and to facilitate full and active cooperation with other European groups working in the 3Rs area.

While significant progress has been made in relation to regulatory testing involving animals it remains the case that certain types of data can only be generated by means of animal studies. Where such studies are needed they should be selected and conducted in strict adherence to the 3Rs principles.

As a European body with responsibility for developing harmonised European regulatory requirements for human and veterinary medicinal products the EMA has and will continue to play a key role in eliminating repetitious and unnecessary animal testing in the European Economic Area (EEA), in collaboration with other European organisations such as EDQM. Through its active participation and collaboration in the work of other multinational organisations such as the ICH and the VICH, the EMA contributes to the application of the 3Rs in the development of globally harmonised requirements, the implementation of which contributes to the elimination of unnecessary animal testing.



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3R's: setting the scene in the EU

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Regulatory acceptance of 3R methods: current situation

Early tox / compound screening:

in-house validation by companies, NO regulatory involvement

Exploratory/mechanistic studies for regulatory decision-making:

based upon demonstrated scientific validity

Pivotal (guideline-driven) studies:

different routes of formal (?) validation

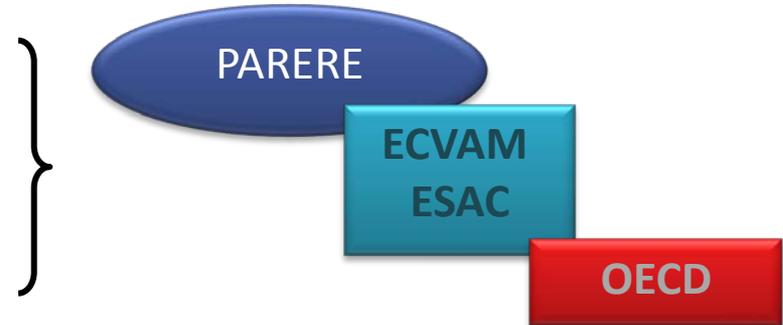
- o *historically introduced in vitro models*
- o *transition from exploratory/mechanistic screening models to pivotal studies based on accumulating experiences (review of data bases)*
- o *targeted replacement of established animal study by in silico or in vitro model(s) requires formal validation*



What is considered a validated test for regulatory acceptance?

validated

- reliability
- reproducibility
- predictivity



valid

- scientific data
- reliability is proven



What constitutes a good *in vitro* model?

- Robust, technically reliable across laboratories
- Ideally directly usable for human risk assessment
- Very good understanding of translation to human situation
- Good understanding of false negatives/positives vs. animal or human
- Scientifically sound assessments of human risk



Development of 3R methods: current situation

Various initiatives/institutions are today involved with developing 'Alternatives' or improved translational testing paradigms

→ IMI, EPAA, VAM's, C-Path, ILSI, CAAT,

BUT

- Little or no coordination
- No driver to introduce results into regulatory environment
- No unique process for introduction into regulatory testing
- No guarantee for optimal performance within pharmaceutical regulatory environment when implementing technically validated assays or assays with a long history of use



Towards a single pathway of regulatory acceptance of 3R methods EU and worldwide

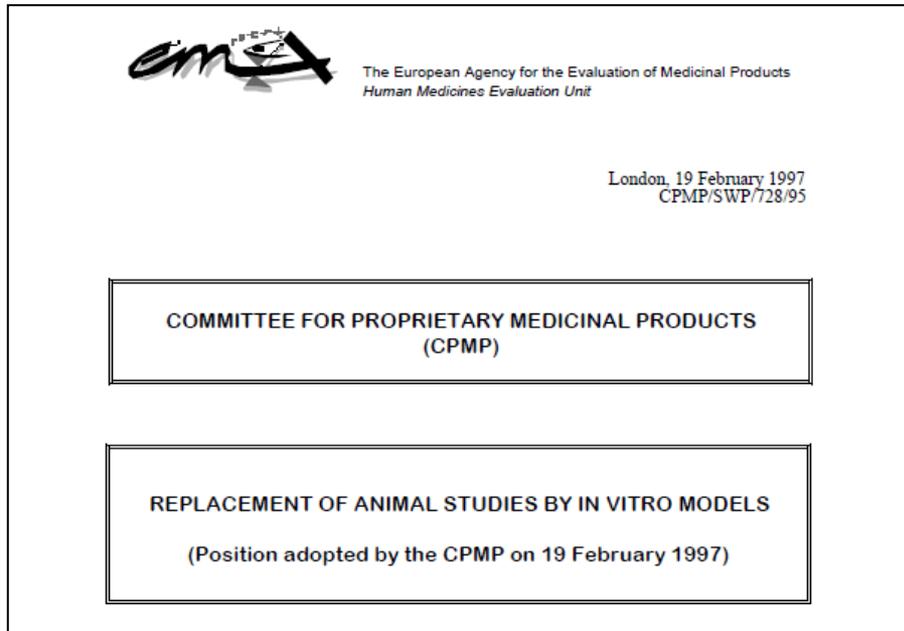
Set of minimal criteria is needed!

Regulatory acceptance process should be harmonised both at EMA and at ICH level through:

1. EMA Guideline on regulatory acceptance of 3R methods & Qualification of novel methodologies for drug development (EMA/CHMP/SAWP/72894/2008 Corr1) via EMA Scientific Advice Working Party (SAWP)
2. ICH Safety Topic Recommendation Working Group (STRWG)



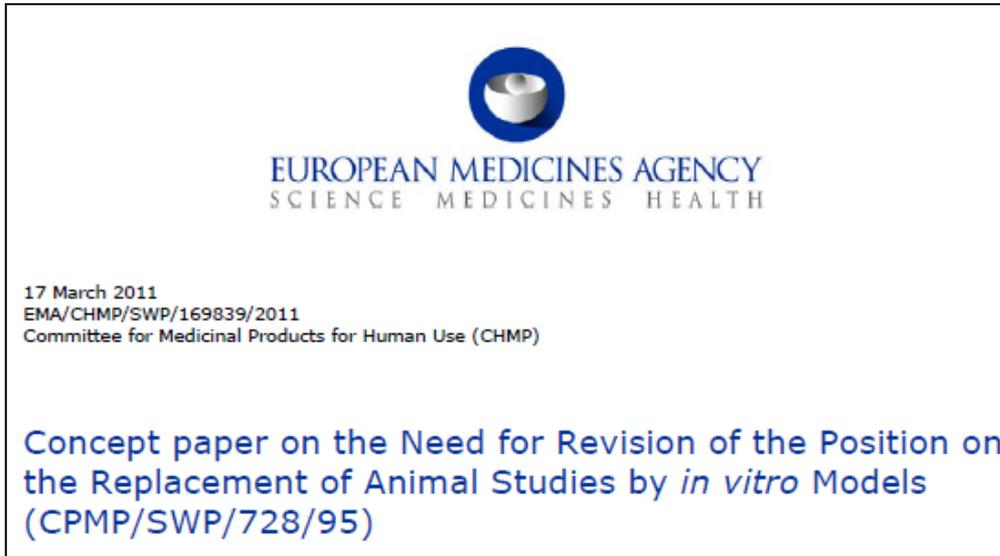
EMA Guideline on regulatory acceptance of 3R methods



- Feasibility of replacing *in vivo* animal studies
- Procedure for validating *in vitro* tests
- Procedure for incorporating *in vitro* tests into the regulatory requirements
- Areas for which the acceptance of *in vitro* tests can be considered



EMA Guideline on regulatory acceptance of 3R methods



- extended focus: replacement, reduction and refinement
- clear process for regulatory acceptance of all 3R alternatives
- discussion on the need for formal validation studies versus proof of scientific validity
- if applicable, updating of formal validation requirements update as per Directive 2010/63/EC



EMA Guideline on regulatory acceptance of 3R methods

- Multidisciplinary drafting group under the JEG 3Rs
- Guideline applies only to testing paradigms that are subjected to regulatory guidance for human and veterinary medicinal products which are used to support regulatory applications
- Definition of regulatory acceptance
- 3R testing paradigms: form related vs scientifically valid, modification of existing paradigms vs new testing paradigms
- Criteria for regulatory acceptance (e.g. method validation, predictivity of endpoints, use in risk assessment, real life data, etc.)
- Data collection period under safe harbour principle
- Procedure follows Guideline on Qualification of Novel methodologies for Drug Development (EMA/CHMP/SAWP/72894/2008_Corr1)



Qualification of novel methodologies for drug development (EMA/CHMP/SAWP/72894/2008 Corr1)

Scientific Advice Working Party (SAWP)

- The only Working Party established in the legislation and the first Working Party in the EMA history to be put together by expertise, not by Member State
- The SAWP is a Multidisciplinary Expert Group and includes the Chairperson and 27 Members, who are experts from National Authorities or from University Clinics and other Institutions
- The SAWP is supported by the SA Section of the EMA secretariat: 10 medical doctors and pharmacists and 7 secretaries and administrative assistants
- Extensive list of external experts with no conflicts of interests



Qualification of novel methodologies for drug development (EMA/CHMP/SAWP/72894/2008 Corr1)

CHMP Qualification Advice on future protocols and methods for further method development towards qualification, based on the evaluation of the scientific rationale and on preliminary data submitted

CHMP Qualification Opinion on the acceptability of a specific use of the proposed method (e.g. use of a biomarker) in a research and development (R&D) context (non-clinical or clinical studies), based on the assessment of submitted data



Qualification of novel methodologies for drug development (EMA/CHMP/SAWP/72894/2008 Corr1)

Early involvement in the design of the strategy towards qualification of novel methodologies (Qualification Advice – confidential)

Commitment to evaluate the data obtained from the agreed studies and to provide a Qualification Opinion regarding the use of the method in R&D

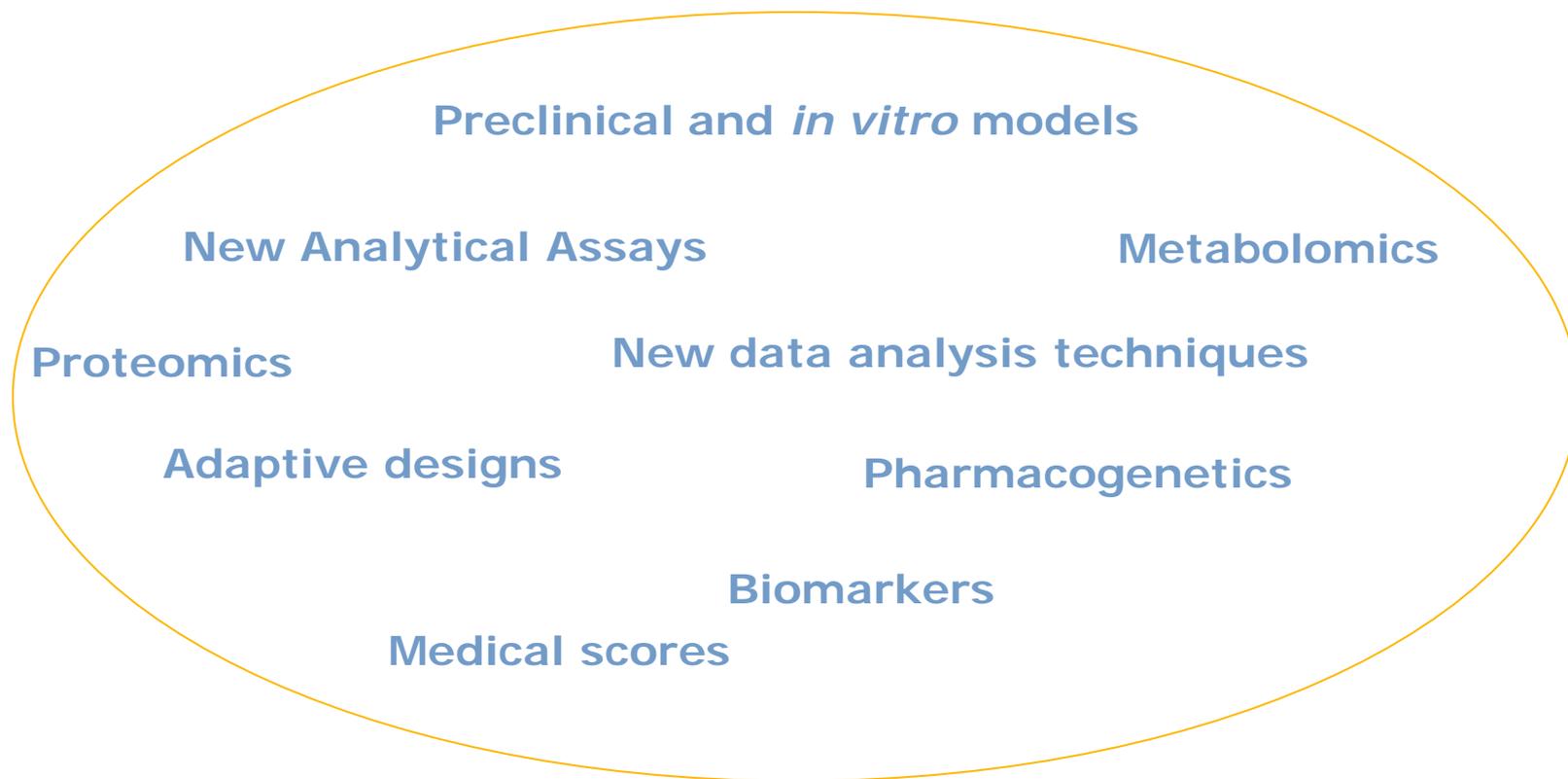
Goal: speed up/optimize drug development, contribute to public health

Data driven process!



Qualification of novel methodologies for drug development (EMA/CHMP/SAWP/72894/2008 Corr1)

Novel methodologies



Qualification of novel methodologies for drug development (EMA/CHMP/SAWP/72894/2008 Corr1)

Qualification Context

Preclinical development

- pharmacological screening
- mechanism of action
- predict activity/safety
- toxicogenomics

Clinical development

- verify mechanism
- dose-response
- proof of concept
- design optimisation
- surrogate endpoint

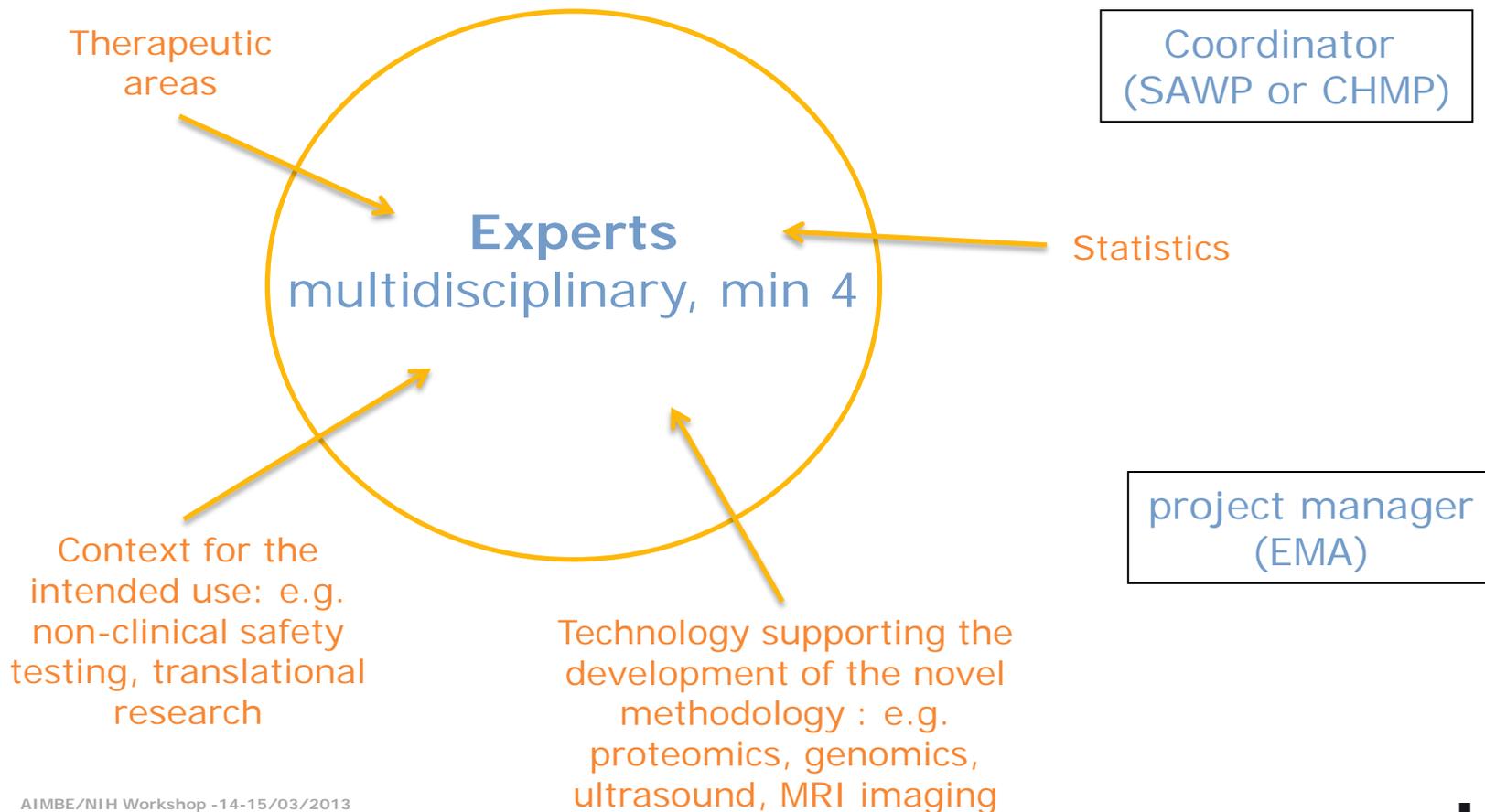
Drug utilisation

- optimise target population
- guide treatment regimen



Qualification of novel methodologies for drug development (EMA/CHMP/SAWP/72894/2008 Corr1)

Qualification Team



Qualification of novel methodologies for drug development (EMA/CHMP/SAWP/72894/2008 Corr1)

Qualification procedure (1/2)

Optional

Applicants: Consortia, Networks, Public/private partnerships, Learned societies, Pharmaceutical industry, Academia

Input: Protocols, study reports, raw data etc to establish the use of a defined methodology for a specific purpose in drug development

Fee related activity:

- Same fee reductions as in scientific advice for paediatric, orphan conditions and SMEs
- Ad-hoc fee reduction (90%) granted by the EMA executive director on the basis of the public health benefit



Qualification of novel methodologies for drug development (EMA/CHMP/SAWP/72894/2008 Corr1)

Qualification procedure (2/2)

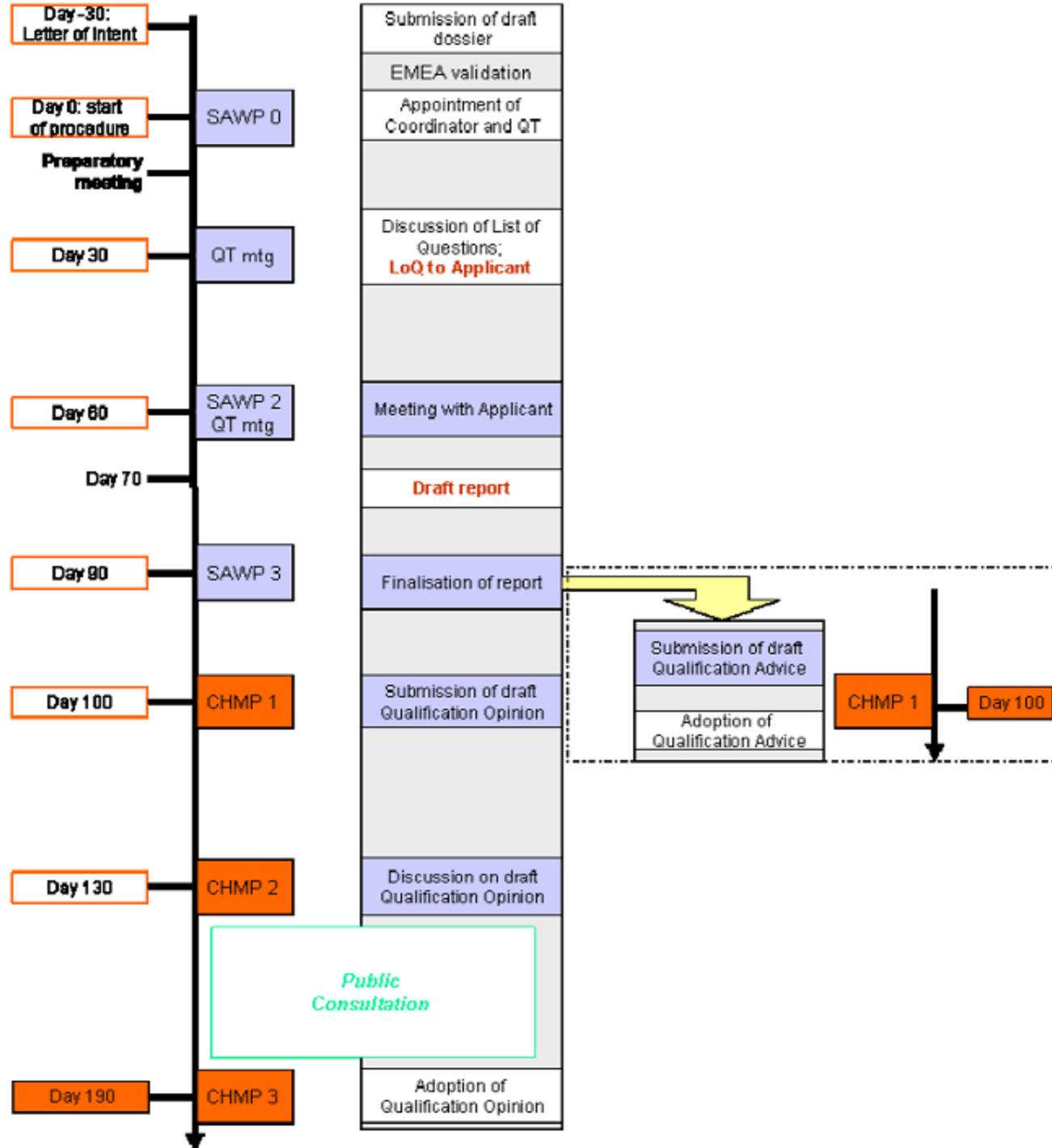
Assessment of the data (focuses on methodology)

Flexible timelines

Forum for discussions

- Qualification Team to meet with the Applicant face-to-face on one or more occasions
- Public consultation & Workshop (Advice always confidential, qualification opinion is made public after consultation with the applicant)
- FDA and other regulatory authorities can be involved





Qualification of novel methodologies for drug development (EMA/CHMP/SWP/72894/2008 Corr1)

Dossier content –

statement on the need for and impact of the novel method

- Intended use
 - Integration in drug development and regulatory review
 - Limitations
 - Impact on regulatory guidelines
 - Relevance and adequacy to extrapolate to the clinical setting
- Experimental setting
- Currently available tools
- Characteristics of the novel method (e.g. scientific rationale, validation, qualification)



Qualification of novel methodologies for drug development (EMA/CHMP/SAWP/72894/2008 Corr1)

Dossier content –
methodology (very basic principles)

- Experimental approach:
 - Design of studies,
 - selection of (animal) model,
 - definition of reference standard,
 - positive and negative controls
- Analytical/technological platform used for novel method quantification
- Statistical plan for analytical/technological assay validation and biological qualification
 - Biological (e.g. intra- and inter-animal variability, difference between species/strain)
 - Analytical/technological Assay Validation (e.g. repeatability, intermediate precision, reproducibility)



Qualification of novel methodologies for drug development (EMA/CHMP/SAWP/72894/2008 Corr1)

HESI Nephrotoxicity Biomarkers



EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

30 April 2010
EMA/283298/2010
Committee for Medicinal Products for Human Use

Consultation on the Qualification Opinion ILSI/HESI Submission of Novel Renal Biomarkers for Toxicity

Agreed by Scientific Advice Working Party	February 2010
Adoption by CHMP for release for consultation	18 March 2010
End of consultation (deadline for comments)	31 July 2010

Comments should be provided using this [template](#). The completed comments form should be sent to SAWPsecretariat@ema.europa.eu

Keywords *Non-clinical, renal biomarkers, nephrotoxicity⁴*

http://www.emea.europa.eu/docs/en_GB/document_library/Regulatory_and_procedural_guideline/2010/05/WC500090466.pdf



ICH Safety Topic Recommendation Working Group (STRWG)

The role of ICH

- A regional implementation of new 3R methods is mostly not feasible taking into account existing ICH S-regulations
- ICH mission includes commitment to take 3R aspects into consideration, but no formal criteria are defined

→ Implementation of new 3R methods should preferably proceed via ICH process



ICH Safety Topic Recommendation Working Group (STRWG)

History

- ICH SC Meeting – Fukuoka – June 2012: EFPIA proposal for a Pre-S Procedure → request by the SC to draft a formal Concept Paper
- ICH SC Meeting – San Diego – November 2012: Presentation of concept paper, renamed into Safety Brainstorming Group
- Endorsement of the group, with another name change by the ICH SC on 1 February 2013:

**Safety Topic Recommendation Working Group
STRWG**



ICH Safety Topic Recommendation Working Group (STRWG)

Objectives

- Monitoring and evaluating scientific and technological developments on an ongoing basis
- Improve predictivity of non-clinical safety testing by the implementation of innovative approaches into regulatory requirements
- Formalisation of the current *ad hoc* process to identify safety topics within ICH and thus to create a clear contact/entry point for institutions/initiatives that are involved with developing new testing paradigms.



ICH Safety Topic Recommendation Working Group (STRWG)

Who/What/How?

- One member (non-clinical expert) nominated by each of the 6 parties of the ICH, and one member nominated by each of the ICH observers
- STRWG to work on a permanent basis, meetings will be virtual (TC/webconference). Based on a need and on an *ad hoc* basis and subject to ICH SC approval F2F meetings may be held during regular planned ICH meetings
- STRWG will be on occasion supplemented by appropriate experts from interested parties depending on the subject.



ICH Safety Topic Recommendation Working Group (STRWG)

Who/What/How? (cont')

- STRWG will interact and partner with external parties (e.g. VAMs, IMI, ILSI, EPAA, C-CAAT, NC3Rs) to evaluate the status of emerging science/technology with regards to its applicability and possible implementation
- STRWG will provide recommendations to the ICH SC on how implementation of identified and relevant new testing paradigms can be facilitated.



ICH Safety Topic Recommendation Working Group (STRWG)

Process –

Stage 1: Identification of new testing paradigms

- STRWG proactively identifies or receives proposals for potential new testing paradigms*
- Based on a review of summary information provided, the WG decides whether or not a proposed testing paradigm warrants an in-depth evaluation in Stage 2

* Excluding proposals by commercial vendors



ICH Safety Topic Recommendation Working Group (STRWG)

Process –

Stage 2: Evaluation

- STRWG in collaboration with the testing paradigm developer(s) and other invited experts (optional) performs an in-depth evaluation of the proposed new testing paradigm
- Points of consideration:
 - Is there a well-defined test methodology/standard protocol with clear defined/scientifically sound endpoints?
 - Known test characteristics: reproducibility, false negative & false positive rate?
 - What reference chemicals were used for validation?
 - Does it fill a potential gap?
 - Will it improve predictive value of existing paradigms by being added to or replacing these?
 - Is there a contribution to the 3Rs or a reduction in drug development timelines?



ICH Safety Topic Recommendation Working Group (STRWG)

Process –

Stage 2: Evaluation

- o Although invited test developers/technical experts may advise, recommendations resulting from this evaluation stage are the responsibility of the regular ICH party's WG members



ICH Safety Topic Recommendation Working Group (STRWG)

Process –

Stage 3: Recommendations

- The STRWG, based on stage 2 in-depth evaluation will provide recommendations to the ICH SC
- Proposal on scope, ie where would this testing paradigm fit (in an existing or new guidance)
- Proposal regarding approach on how to get to final implementation, possible option, for instance:
 - Advice for immediate implementation in an existing or new guidance since sufficient data is available
 - Advice to gather more data including details on how this can be achieved before deciding to implement
- Proposal, based on above considerations, to create an Informal Working Group or an Expert Working Group or to have a next phase addressed by STRWG.



ICH Safety Topic Recommendation Working Group (STRWG)

Next steps

- Awaiting formal nomination of ICH party representatives
- Kick-off: working out details of process to be followed
- First topics to be addressed:
 - Toxicokinetics: alternative methodologies (incl. microsampling/TKtD modelling) within the context of ICH S3(A/B)): a new proposal that will be the first topic to be addressed by the STRWG with the aim to deliver an advice/Concept Paper to the ICH SC at earliest opportunity (topic identified by EFPIA/EPAA, NC3Rs workshop to be organised in May 2013)
 - Reproductive toxicity: data gathering to evaluate *in vitro* methods to replace one test species for developmental toxicity testing (already ongoing activity to be addressed by STRWG)



Past activities at the level of ICH

- **ICH Expert Working Group Meeting, Brussels, May 2007:**

- 1st ICH meeting with ICCVAM, ECVAM & JaCVAM:

- possibility of future collaboration
 - input of CVAMs when drafting new or revising existing guidelines
 - input of CVAMs on defining acceptance criteria

- **recent ICH topics in relation to 3Rs:**

- M3 (R2), Non-clinical safety studies for the conduct of human clinical trials and marketing Authorisation for pharmaceuticals
 - S2 (R1), Guidance on Genotoxicity Testing and Data Interpretation for Pharmaceuticals Intended for Human Use
 - S9, Nonclinical Evaluation for Anticancer Pharmaceuticals
 - S6 (R1), Addendum to ICH S6: Preclinical Safety Evaluation of Biotechnology-Derived Pharmaceuticals
 - S10, Photosafety evaluation of pharmaceuticals



Past activities at the level of ICH

ICH Workshop, Tallinn, June 2010:

In Vitro Models for Reproduction Toxicity Workshop – Use?

The workshop was held as part of an assessment of whether the S5(R2) Guideline on Detection of Toxicity to Reproduction for Medicinal Products and Toxicity to Male Fertility needed to be revised.

It was agreed that no further work needed to be undertaken on the topic at the current time at the ICH level

More work needed on: validation of EST (IMI, C-Path?), rat vs rabbit comparison (FDA?).



Follow-up on reproductive toxicity testing

DART Testing Strategies for Human Pharmaceuticals: Animal Models vs In-Vitro Approaches

Event #11116
10-11 October 2011
Hotel Holiday Inn, Leiden, The Netherlands



U.S. Food and Drug Administration

Protecting and Promoting *Your* Health

Public Workshop on Reproductive and Developmental Toxicology: From In Vivo to In Vitro, April 16, 2012, White Oak Campus, Silver Spring US

discussion on:

- Value of rodent versus non-rodent species (rat or rabbit) in the evaluation human pharmaceuticals for their effects on embryo-foetal developmental
- Value of 3R methods (especially mouse embryonic stem cells) to detect crucial developmental effects? What type of data is available? Can recommendations be given for further evaluation of these *in vitro* methods?

Objectives:

- to bring scientific information about new *in vitro* technologies for reproductive and developmental toxicology testing to FDA,
- to provide a forum for scientists from FDA, academia, and industry to discuss how these new technologies could eventually be integrated into FDA's regulatory paradigm."



Follow-up on reproductive toxicity testing



2011- 2013:

HESI Developmental and Reproductive Toxicology (DART) Technical Committee (US) will conduct a cross pharma survey to collect data regarding the relative value of non-rodent vs rodent in signal detection of developmental toxicity and the influence on human risk assessment

→ ILSI HESI DART 2nd species working group: database compilation and analysis



Progress report presented at November 2012 ICH Meeting, 10-15 November 2012, San Diego, US.



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Validation of New Technology for Use in Drug Discovery in Europe: Conclusions

Although methods used in drug discovery are not subject to regulatory acceptance they need to comply with minimal acceptable criteria for qualification/validation

The use of the SAWP method qualification process in collaboration with JEG 3Rs is recommended at EU level

Several initiatives underway to clearly define a process for regulatory acceptance of 3R methods used for regulatory decision making, both at the EMA and ICH level.

A global approach (ie ICH STRWG) is the preferred option, if applicable



Contact



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A large, stylized graphic of an eye is centered on the page. The eye is composed of several concentric, semi-transparent shapes: a light grey outer arc, a medium blue middle ring, and a white inner circle. The text is centered within the blue ring.

Your medicines and health products,
our concern