FDA, ICH, and the 3Rs

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FDA, ICH, and the 3Rs

Objectives of this presentation:

- Explain what ICH is
- Describe how ICH contributes to the 3Rs
  - How harmonizing contributes to the 3Rs
  - Use of alternative methods in guidances
    - Generally
    - Specifically
- Impact of guidances

ICH
International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use

- Unique harmonization initiative for regulators and pharmaceutical industry
- Originally founded in 1990
- Reformed as a non-profit legal entity under Swiss Law on October 23, 2015

Purpose of ICH

Promotion of public health through international harmonization that contributes to:

- Prevention of unnecessary duplication of clinical trials and post market clinical evaluations
- Development and manufacturing of new medicines
- Registration and supervision of new medicines
- Reduction of unnecessary animal testing without compromising safety and effectiveness

- Accomplished through Technical Guidelines that are implemented by the regulatory authorities. (*FDA calls these documents Guidances once implemented*.)

ICH Members

Members:

Founding Regulatory:

EC, Europe; MHLW/PMDA, Japan; FDA, US

Founding Industry:

EFPIA; JPMA; PhRMA

Standing Regulatory:

Swissmedic, Switzerland; Health Canada, Canada

Regulatory:

ANVISA, Brazil; HAS, Singapore; NMPA, China; MFDS, Republic of Korea; TITCK, Turkey; TFDA, Chinese Taipei

Industry:

BIO, Global Self-Care Federation, IGBA

ICH Observers

Standing Observers:

WHO

International Federation of Pharmaceutical Manufacturers & Associations

Observers (currently around 30):

Regulatory authorities

Regional harmonization initiatives

International industry pharmaceutical organizations

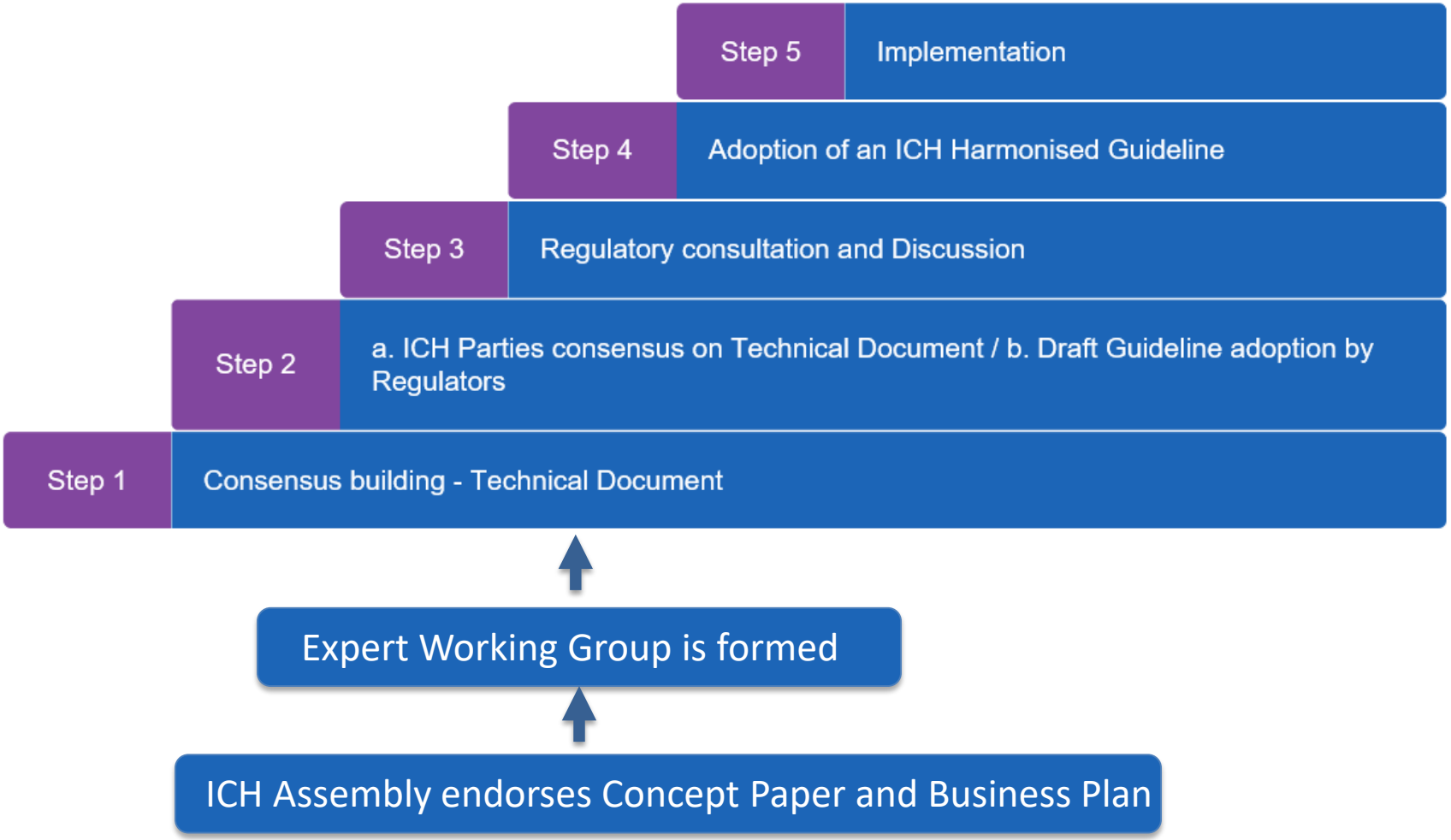
International organizations with an interest in pharmaceuticals

ICH Products (as of Aug 2020)

Over 100 Guidelines or related documents on technical requirements

Other products:
Electronic Standards for the Transfer of Regulatory Information (ESTRI, E2B)
Consideration documents (e.g. participation of women in clinical trials)

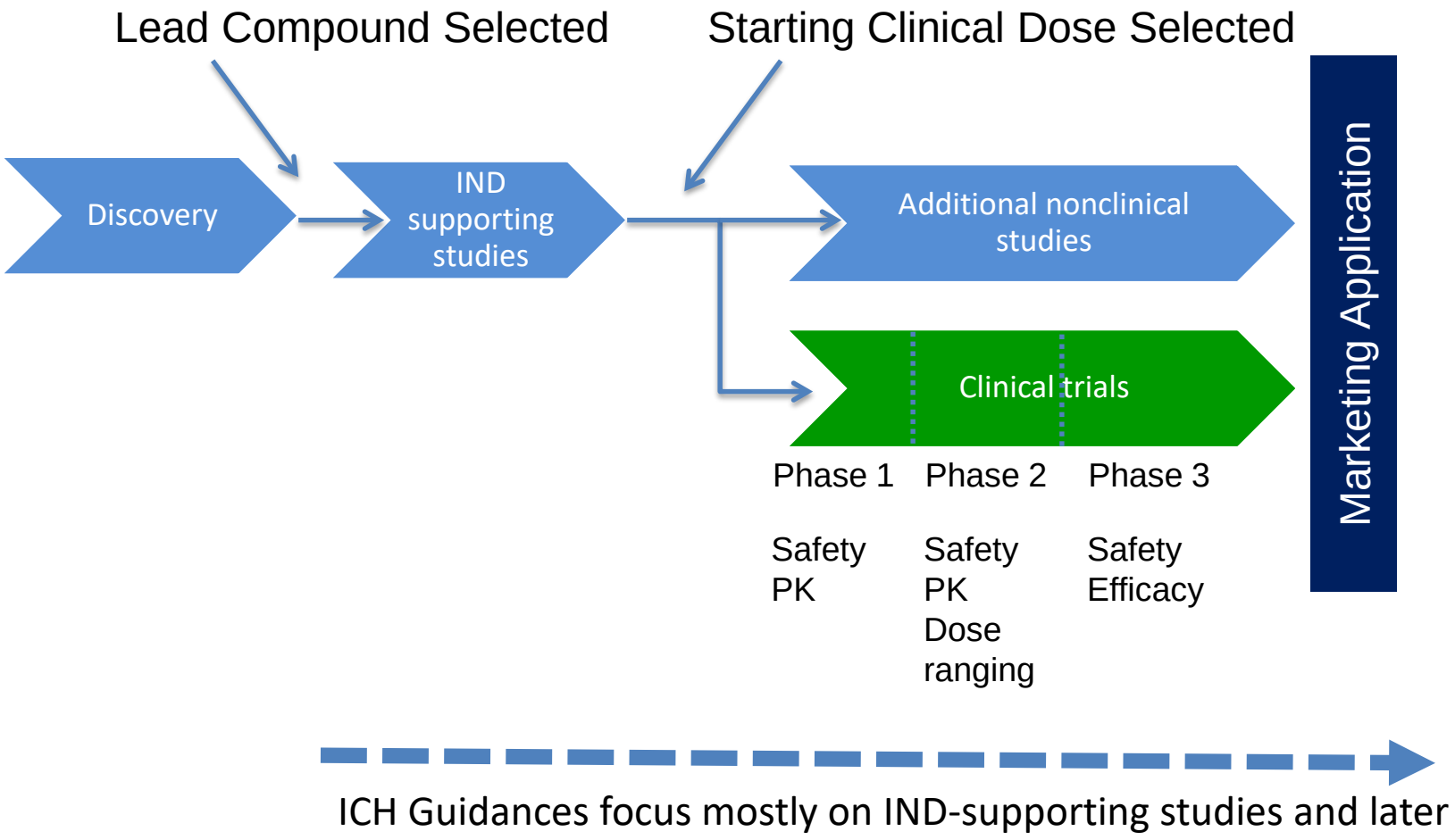
Formal ICH Procedure



Keys to ICH Success

- Involves expertise from both regulatory authorities and regulated industry
- Science-based, consensus driven
- Clear and effectively managed process
- Close collaboration of parties with comparable regulatory and technical capability
- Commitment of regulators to implement products of harmonization
- Common global platform and tools

Use of nonclinical data in drug development



Design of clinical trials and intended marketed use determines what nonclinical data are needed

Primary ICH Guidances for what is recommended nonclinically:

- ICH M3(R2) Nonclinical Safety Studies for the Conduct of Human Clinical Trials and Marketing Authorization for Pharmaceuticals
- ICH S6(R1) Preclinical Safety Evaluation of Biotechnology-derived Pharmaceuticals
- ICH S9 Nonclinical Evaluation for Anticancer Pharmaceuticals

ICH M3(R2)

Objectives of the Guidance

- The purpose of this document is to recommend international standards for, and promote harmonisation of, the nonclinical safety studies recommended to support human clinical trials of a given scope and duration as well as marketing authorization for pharmaceuticals.
- Harmonisation of the guidance for nonclinical safety studies will help to define the current recommendations and reduce the likelihood that substantial differences will exist among regions.
- This guidance should facilitate the timely conduct of clinical trials, reduce the use of animals in accordance with the 3R (reduce/refine/replace) principles and reduce the use of other drug development resources. Although not discussed in this guidance, consideration should be given to use of new *in vitro* alternative methods for safety evaluation. These methods, if validated and accepted by all ICH regulatory authorities, can be used to replace current standard methods.

ICH M3(R2)

Background

- The guidance represents the consensus regarding the type and duration of nonclinical safety studies and their timing to support the conduct of human clinical trials and marketing authorization for pharmaceuticals.

Scope

- The need for nonclinical safety studies and their relation to the conduct of human clinical trials is delineated in the guidance.

ICH M3(R2)

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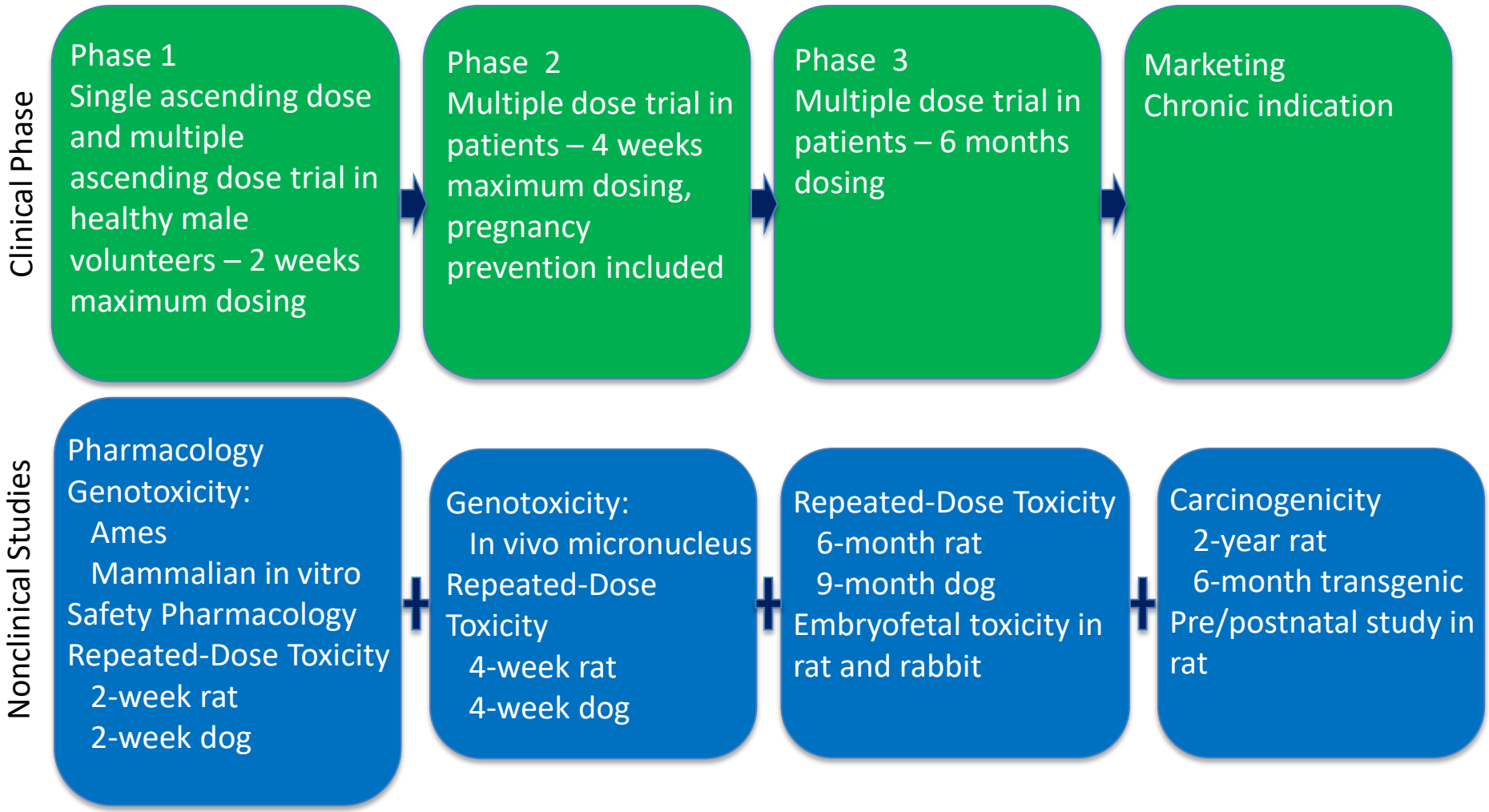
ICH M3(R2)

Table 1 Recommended Duration of Repeated-Dose Toxicity Studies to Support the Conduct of Clinical Trials

Maximum Duration of Clinical Trial	Recommended Minimum Duration of Repeated-Dose Toxicity Studies to Support Clinical Trials	
	Rodents	**Non-rodents**
Up to 2 weeks	2 weeks[a]	2 weeks[a]
Between 2 weeks and 6 months	Same as clinical trial[b]	Same as clinical trial[b]
> 6 months	6 months[b, c]	9 months [b, c, d]

Hypothetical nonclinical drug development timeline



If development is stopped, studies only needed at later stages need not be conducted.

Other ICH Guidances and their impact on 3Rs or use of alternatives

ICH S1A Guideline on the Need for Carcinogenicity Studies of Pharmaceuticals and ICH S1B Testing for Carcinogenicity of Pharmaceuticals

- Carcinogenicity studies generally not needed for
  - Non-chronic use (< 6-months)
  - Populations with short life expectancy
- Alternative models allowed (e.g., transgenic mice)
  - Shorter studies
  - Fewer animals
- Project underway exploring whether in some cases outcome of rat carcinogenicity study could be predicted with sufficient confidence such that the study would not be needed

ICH S3 Toxicokinetics: The Assessment of Systemic Exposure in Toxicity Studies Note: Focus on Microsampling

Microsampling

- A method to collect a very small amount of blood (typically ≤50 µL) to measure TK parameters of the drug and/or its metabolites
- Matrices: blood, plasma or serum, in liquid or dried form
- Can minimize pain and distress in animals (improvement of the animal welfare: refinement)
- Can reduce or eliminate the number of required animals in a TK satellite group for rodents (reduction), particularly for mice

ICH S5(R3) Detection of Toxicity to Reproduction for Human Pharmaceuticals

- Purpose of ICH S5 Guidance
  - Provide harmonized guidance on approaches that can be used for assessing the reproductive and embryofetal development risk associated with exposure to a given drug, biologic or vaccine.
- Some objectives of recent revision include
  - Provide guidance on regulatory use of alternative assays:
    - Necessary performance criteria
    - Scenarios where alternative assays could be appropriate
    - Integration in risk assessment
  - Reduce unnecessary animal use

ICH S5(R3) Section 4.2.2 Alternative Approaches for Addressing EFD Risk

- If properly qualified, alternative assays have the potential to defer or replace (in certain circumstances) conventional in vivo studies.
- Alternative assays should provide a level of confidence for human safety assurance at least equivalent to that provided by the current testing paradigms
- It is expected that for regulatory purposes multiple alternative assays will be used within a tiered or battery approach

Deferral of Definitive EFD Studies (4.2.3) (Outside of USA)

1) A qualified alternative assay that predicts the outcome in one species can be combined with a pEFD study from a second species to enable the limited inclusion of WOCBP (up to 150 WOCBP for up to 3 months).

2) A modified GLP pEFD/DRF study (increased group size + fetal skeletal examinations) in a pharmacologically relevant species, when combined with a pEFD study in a 2nd species, allows for enrolment of an unlimited number of WOCBP in clinical trials through Phase 2.

Why "Outside of USA"

From ICH M3(R2) Section 11.3 – Women of Childbearing Potential

In the United States, assessment of embryo-fetal development can be deferred until before phase 3 for WOCBP using precautions to prevent pregnancy in clinical trials (see above). In the EU and Japan, other than the situations described in the above paragraphs, definitive nonclinical developmental toxicity studies should be completed before exposure of WOCBP.

In all ICH regions, WOCBP can be included in repeated-dose phase 1 and 2 trials before conduct of the female fertility study since an evaluation of the female reproductive organs is performed in the repeated-dose toxicity studies (Note 2). Nonclinical studies that specifically address female fertility (Ref. 3) should be completed to support inclusion of WOCBP in large-scale or long-duration clinical trials (e.g., phase 3 trials).

ICH S5(R3) Annex 2: EFD Alternative Assays 1 of 4

Under limited circumstances qualified alternative assays can be utilized to support hazard identification and risk assessment:

- Circumstances where there is evidence indicating an adverse effect on EFD is likely (e.g., MOA, class effects)
- Toxicity in animal species precludes attaining systemic exposures relevant to the human exposures under conditions of use
- As support for a weight of evidence assessment when there are equivocal findings in animal studies
- As partial support for clinical trials including up to 150 WOCBP for up to 3 months duration (ex-USA)
- Pharmaceuticals being developed for certain severely debilitating or life-threatening diseases or late-life onset diseases

Annex 2: EFD Alternative Assays
2 of 4

- No specific assays are recommended, rather basic scientific principles are included to assist in assay qualification for regulatory use

- Acceptance of an assay by one regulatory authority does not bind other health authorities to accept the assay

- Subject to a maintenance procedure, so that it can be updated as the state of the science and regulatory experience with AAs evolves, without re-opening the entire guidance

Annex 2: EFD Alternative Assays
3 of 4

Qualification of AAs for Prediction of Malformations or Embryo-Fetal Lethality (MEFL)

Should include:

- A thorough description and justification of the predictive model
- An evaluation of the biological plausibility of the model
- An assessment of the accuracy and ability for the alternative assay to detect MEFL
- Definition and justification of the threshold for molecular and metabolic markers predicting MEFL
- The details of the algorithm employed for determining positive and negative outcomes in vivo
- Details of algorithm used to relate in vitro concentrations to in vivo exposure

Annex 2: EFD Alternative Assays
4 of 4

Reference Compound List

- Contains data for 29 compounds that have been shown to induce MEFL in nonclinical studies (rats or rabbits) and/or humans
  - Define NOAEL and LOAEL exposures for MEFL
  - Doses/exposures resulting in embryofetal death or structural malformations
- Negative controls are also required to assess assay specificity
  - Reference Compound List contains data from 3 compounds that were clearly negative in animals at >25-fold human exposure.
- The compounds in this list as well as others (with justification) can be used to support qualification of an alternative assay or battery of assays.

ICH S6(R1) Preclinical Safety Evaluation of Biotechnology-derived Pharmaceuticals

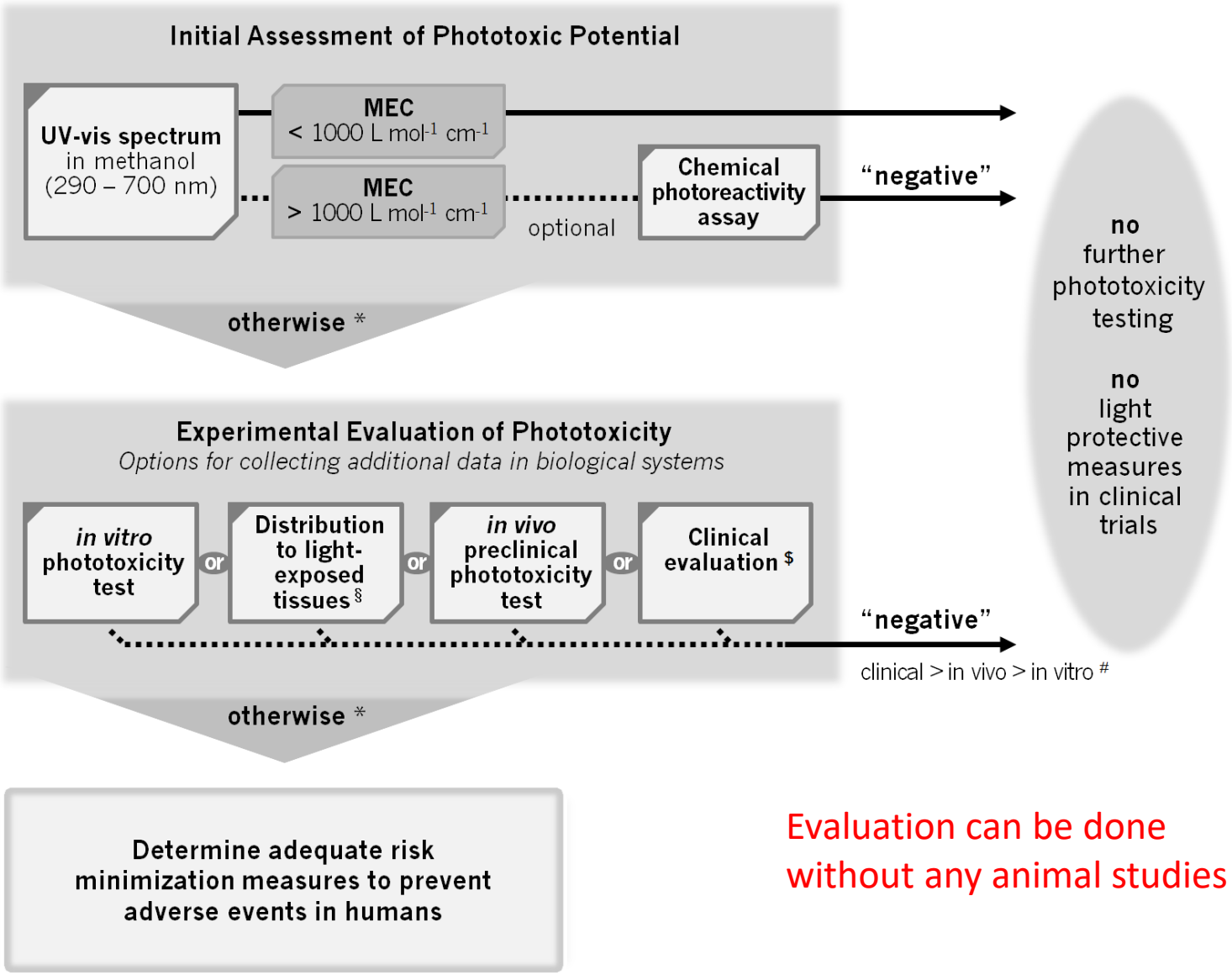
- Genotoxicity not needed (in vitro or in vivo)
- Carcinogenicity studies seldom recommended. A carcinogenicity assessment based on available information usually sufficient.
- Safety pharmacology can be incorporated into toxicity studies
- One species for toxicity studies can be acceptable when
  - only one relevant species can be identified
  - where the biological activity of the biopharmaceutical is well understood or,
  - for chronic studies, when toxicity is comparable in two species in short term studies.

- These approaches are considered acceptable for biotechnology-derived products in part because of high specificity for target and general lack of off-target effects.

ICH S9 Nonclinical Evaluation for Anticancer Pharmaceuticals

- Scope is for pharmaceuticals that are intended to treat cancer in patients with serious and life threatening malignancies
- Safety pharmacology can be incorporated into toxicity studies
- 3-month duration generally sufficient for toxicity studies to support marketing of a pharmaceutical for advanced cancer
- Carcinogenicity studies not warranted for drugs for advanced cancer
- Juvenile animal studies usually not conducted to support inclusion of pediatric population

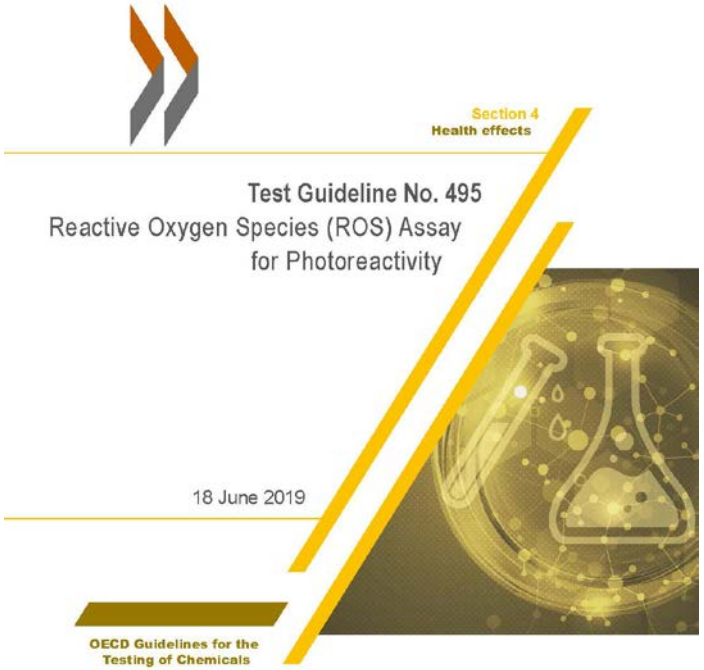
ICH S10 Photosafety Evaluation of Pharmaceuticals

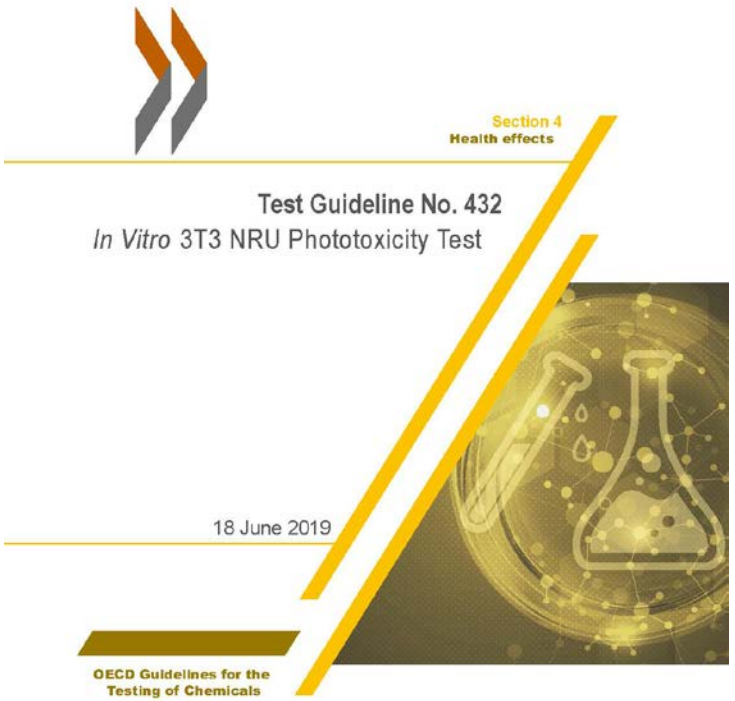


Evaluation can be done without any animal studies

ICH S10 Photosafety Evaluation of Pharmaceuticals

- Chemical photoreactivity can be a reactive oxygen species (ROS) assay such as OECD TG 495
- In vitro phototoxicity test can be 3T3 Neutral Red uptake assay such as OECD TG 432





ICH M7(R1) Assessment and Control of DNA Reactive (Mutagenic) Impurities in Pharmaceuticals to Limit Potential Carcinogenic Risk

- Quantitative Structure Activity Relationship (QSAR) predictions accepted by FDA/CDER in place of conventional testing for drug impurities
- Threshold of Toxicological Concern established
- Impurities exceeding threshold can be assessed by two QSAR methodologies
  - Expert Rule-based
  - Statistical-based
- Absence of structural alerts is sufficient to conclude that the impurity is of no mutagenic concern

FDA, ICH and the 3Rs

Key Take-away points

- Worldwide harmonization promotes reduced animal use by preventing different regions from recommending different studies.
- Stepwise guidance approach and deferral of studies to later stages can reduce the number of studies required overall.
- Guidance recommendations for particular in vivo models or study designs, use of pharmacologically relevant animals and qualified alternative methods can replace, reduce and refine animal use.