Detection of Toxicity to Reproduction for Human Pharmaceuticals

Paving the Way for Alternative Assays in the 3rd Revision of ICH S5

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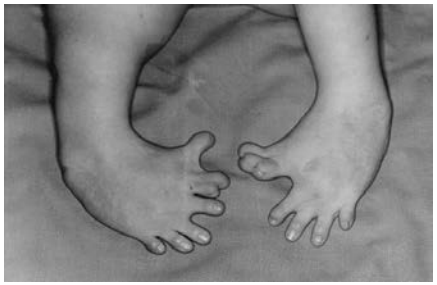
Outline

- Introduction
- Alternative assays in reprotox testing?
- 3rd Revision of ICH S5
- Conclusions

Introduction

Two species EFD testing since Thalidomide



https://commons.wikimedia.org/wiki/File%3ANCP14053.jpg

https://commons.wikimedia.org/wiki/File%3Artificial_limbs_for_a_thalidomide_child%2C_1961-1965._(9660575567).jpg

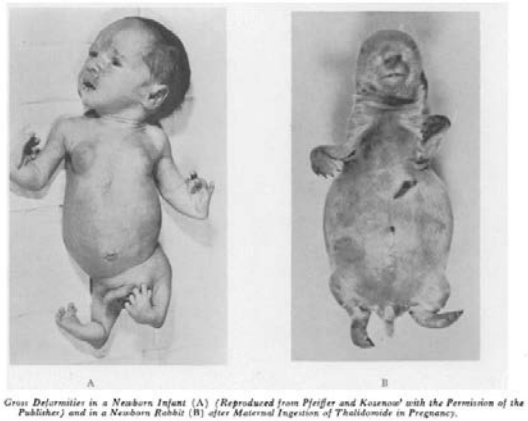


FIGURE 1. Gross Deformities in a Newborn Infant (A) (Reproduced from Pfeiffer and Kosenow¹ with the Permission of the Publisher) and in a Newborn Rabbit (B) after Maternal Ingestion of Thalidomide in Pregnancy.

Thalidomide Embryopathy in Hybrid Rabbits
Theodore H. Ingalls, M.D.†, Francis J. Curley‡, and Peter Zappasodi§
N Engl J Med 1964; 271:441-444

- Rat & rabbit testing became gold standard for EFD studies
- ☞ Single case driven? *Two proper species*

Introduction

Unique Aspects of Reproductive Toxicity

- EFDT studies in rat/rabbit have added value over single studies

see Theunissen et al. 2016

Comparing rat and rabbit embryo-fetal developmental toxicity data for 379 pharmaceuticals: on systemic dose and developmental effects

Critical Reviews in Toxicology , 2016

Comparison of rat and rabbit embryo–fetal developmental toxicity data for 379 pharmaceuticals: on the nature and severity of developmental effects

Critical Reviews in Toxicology , 2016

  - ☞ Even the design of alternative tests need to cover this aspect
  - ☞ Maternal toxicity/exaggerated pharmacology complicate data interpretation of *in vivo* studies
- Data on human teratogenicity are scarce
  - ☞ If the aim is to replace rat/rabbit EFD testing the alternative assays need to predict rat/rabbit teratogenicity/fetal lethality
- 3R considerations:
  - ☞ Segment I-III studies, incl DRF studies: 6792 total animal use *Chapman et al. 2013*

Assay	Developmental period	Test accuracy %	Animal use	Limitations	ECVAM validation	Lit.
Rat/rabbit whole embryo culture	Early to mid organogenesis (ltd period of embryogenesis)	80% for 20 tested cmpds	Yes	No metab., (experimental *ex vivo* approaches) -interlab variation(subjectivity), -costly, time consuming	Yes (Rat)	Piersma et al. 2004
Zebrafish	cleavage, segmentation, majority of organogenesis to skeletogenesis	31 test compounds; 87%, 75-92%	Yes (non-mammalian)	Nonmammalian metabolisation, Chorion may hamper compound uptake (DMSO)	No (Zebrafish embryo acute toxicity test for acute aquatic toxicity testing, 2014)	Brannen 2010 Van den Bulck 2011
Embryonic stem cell test „Hanging drop"	Cardiomyocyte differentiation	78% 81%	No	Metab., less predictive for drugs (ReProTect)	Yes	Genschow 2002 Whitlow 2007 Genschow 2004 Marx-Stölting 2009
Micromass assay (limb bud)	Chondrocyte differentiation	70%	Yes	No metabolic competence	Yes	Genschow 2002 Spielmann 2004

Alternative assays in reprotox testing?

General Features and Performance

- Alternative tests are
  reductionistic, show poor specificity (true negative rate)
  highly sensitive: highly predictive for positive results

- Validation efforts failed (by ECVAM, ICCVAM,...)
  ☞ challenge of regulatory acceptance

ILSI Health and Environmental Sciences Institute

www. RePro Tect .eu

Current *Step 4* version
Parent Guideline dated 24 June 1993
(Addendum dated 9 November 2000 incorporated in November 2005)

Alternative assays in reprotox testing?

Use of Alternative Assays

ICH S5(R2) already highlights the **value of "other test systems"**

also states that *"other test systems **cannot provide assurance** of the **absence of effect** nor provide perspective in respect of **risk/exposure**".*

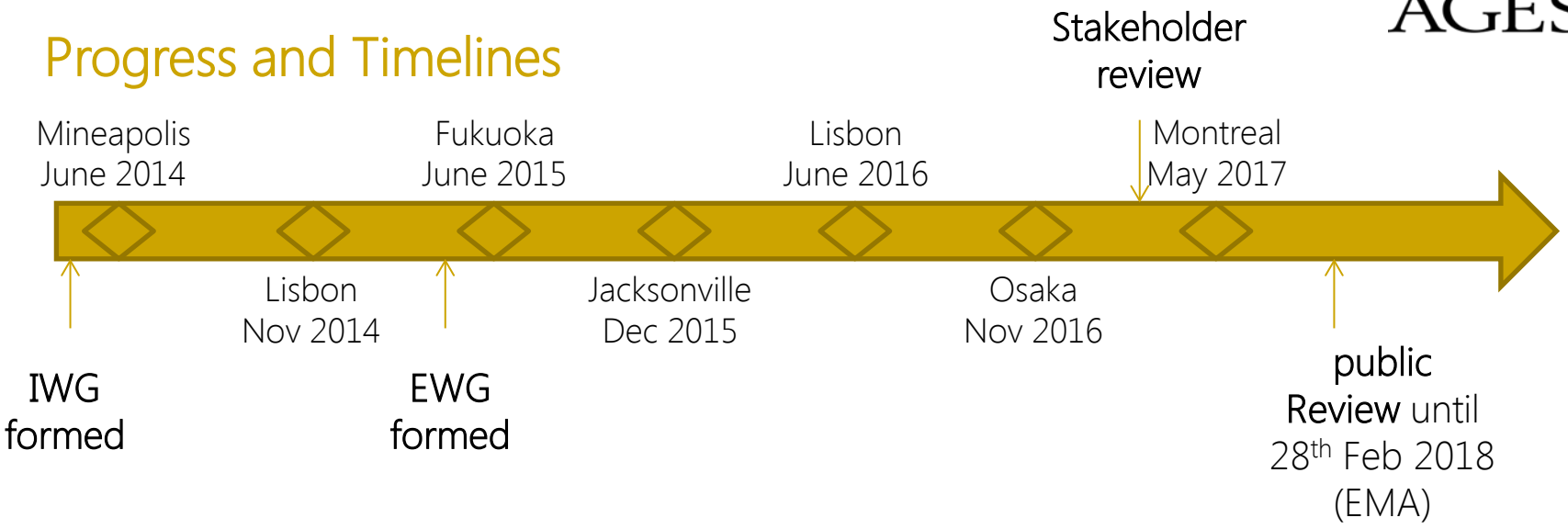
- Nonetheless, after two decades of scientific progress, a number of *in-vitro*, *ex-vivo* and non-mammalian *in-vivo* assays are being used as **discovery screens for EFD**.
- In addition, some of these assays are being examined for **use for regulatory purposes under defined scenarios**.

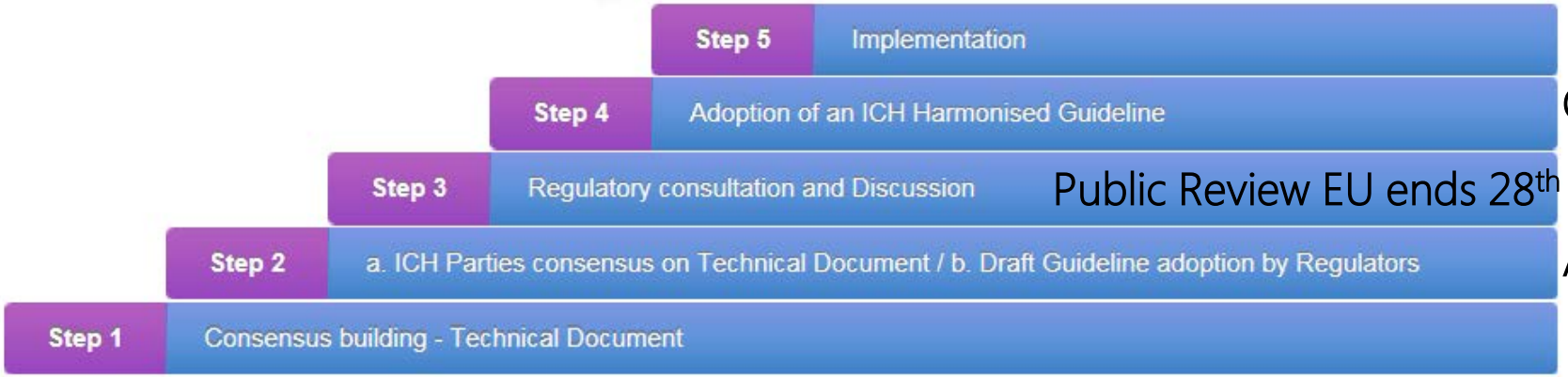
Concept paper ICH S5(R3)

☞ *in-vitro*, *ex-vivo* or non-mammalian *in-vivo* assay(s) intended to evaluate a developmental endpoint = alternative assay(s)

3rd Revision of ICH S5

Progress and Timelines





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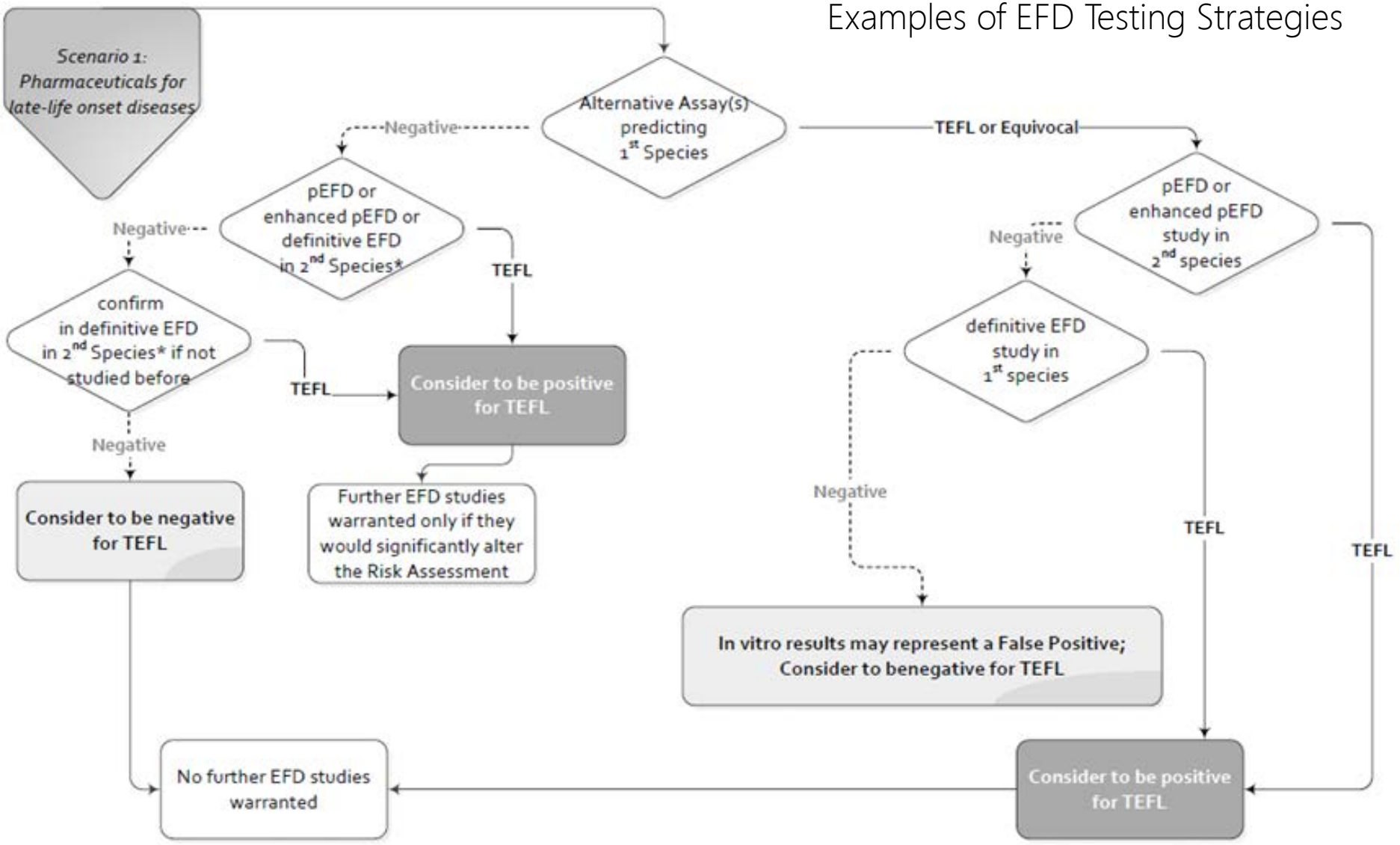
Use of Alternative Assays

Alternative assays should be **GLP** compliant and **qualified** for its intended **context of use** (e.g.):

- As part of an integrated testing strategy (ITS) for EFD endpoints (Scenarios)
- Deferral of definitive studies
- Complete replacement of one species when used in conjunction with an EFD study in limited circumstances
- Contributing to the weight of evidence in case of equivocal animal data
- Toxicity precludes attaining a relevant exposure
- Low systemic exposure in humans (ophthalmics)

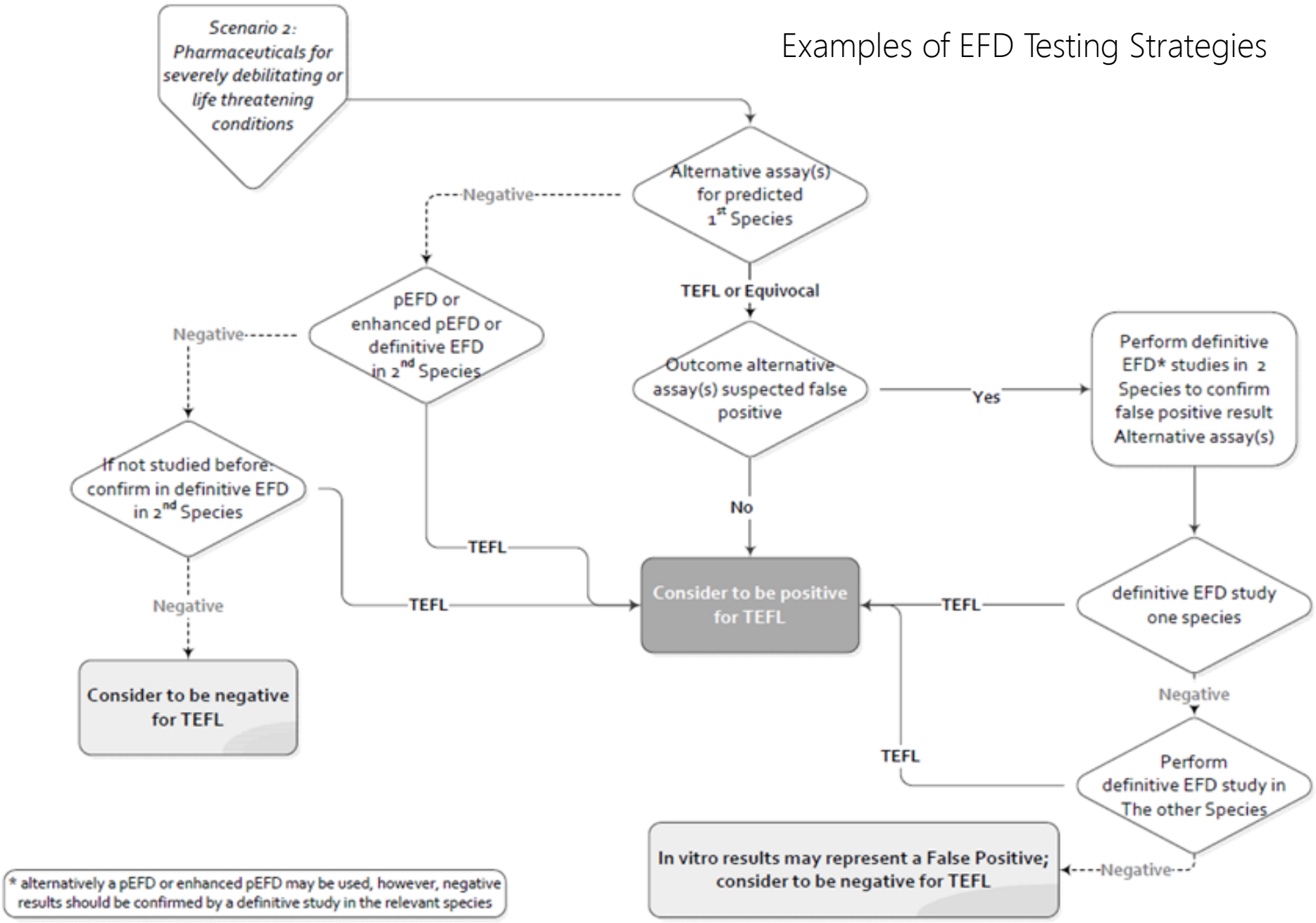
Context of use: applies to regulatory conditions under which the results of an assay can be relied upon.

Examples of EFD Testing Strategies



TEFL: Teratogenic and/or embryofetal lethal
Teratogenicity: term is in reference to malformation

Examples of EFD Testing Strategies



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Rules of the Exemplified Testing Scenarios

Scenarios applicable **when there are at least 2 relevant mammalian species** (crf. Species selection)

- IF a qualified alternative test plus a negative definitive EFD study in another species are NEGATIVE – label negative
- IF a single preliminary or definitive EFD study at clinically relevant exposures is POSITIVE – no further animal testing
- IF an alternative test is POSITIVE, it may be over-ruled if a definitive EFD study in a rodent and non-rodent is NEGATIVE

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Proposed Basic Principles for Possible Regulatory Acceptance

Qualification of Alternative Test Systems for Regulatory Acceptance

Provides a framework including ICH Reference Compound List (RCL): EFD data, organized by overarching categories

RCL is intended to be periodically updated.

This list is generated recognizing that the context of use will inform on acceptability of particular alternative assessments.

Category	Positive Controls	Negative Controls
Channel Modulator	Sotalol	Hydrochlorothiazide
	Almokalant	Chlorthalidone
	Diltiazem	
	Topiramate	
	Trimethadione	
	Phenytoin (Diphenylhydantoin)	
	Carbamazepine	
DNA Modifiers	Cyclophosphamide	
	Busulfan	
	Cisplatin	
	Thiotepa	
Enzyme Modulator	Aspirin	
	Captopril	Saxagliptin
	Enalapril	Vildagliptin
	Methimazole (Thiamazole)	
Hormone/Steroid	Dexamethasone	Progesterone
	Fluticasone	
Kinase Modulator	Afatinib	
	Ceritinib	
	Dabrafenib	
	Dasatinib	
	Ibrutinib	
	Pazopanib	
	Tacrolimus	
	Imatinib	
Nucleoside Modulator/ Central metabolite inhibitor	Cytarabine	
	5-Fluorouracil	
	Hydroxyurea	
	Methotrexate	
	Ribavirin	
	Teriflunomide	
	Warfarin	
Other	Artesunate / amodiaquine	Amoxicillin
	Clarithromycin	Clindamycin
	Doxycycline	Cyclobenzaprine
	Fluconazole	Erythromycin
	Pomalidomide	Sulfasalazine
	Tafamidis	
	Telavancin	
	Thalidomide	
	Valproic acid	
Receptor Modulator		Cetirizine
	Bosentan	Cyproheptadine
	Clobazam	Doxylamine
	Fingolimod	Maraviroc
	Plerixafor	Metoclopramide
	Sumatriptan	Nizatidine
Second Messenger Modulator	Theophylline	
Transcription Modulator	Acitretin	
	Isotretinoin (13-*cis*-retinoic acid)	
	Vismodegib	

ICH List of Reference Compounds - Proposed Selection Factors

AGES

-compounds known for their TEFL (teratogenic and/or embryofetal lethal) effects in animals or humans

-from different chemical/pharmacologic classes

-with overlap with both negative and positive compounds (coverage of diverse chemical structures and mode of action)

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Proposed Selection factors for ICH List of Reference Compounds ctd.

- Availability of PK and TK data in the test species
- Pharmaceuticals are preferred, chemicals considered, no biotech cmpds
- Favours compounds with direct effects on the fetus, a few depending on metabolic activation, cytotoxic/genotoxic cmpds to a limited extent
- Negative cmpds included to assess assay specificity: should be negative at all doses, or positive at high exposures (provided transition predicted)
- Evaluate performance to detect species-specific differences; Commercial availability;…

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Proposed Performance Factors

- At least **45 compounds** in total: substitution of RCL cmpds with other compounds possible, but their use should be justified
- Multiple classes (**at least 2 or 3 from each class**)
- An **approx. ratio 2:1** of positive to negative cmpds to ensure selectivity
- **Sensitivity** to detect a positive signal in an assay should be **at least 80%,** with evidence of selectivity
- Evaluation should identify **applicability domain** and any limitations of the assay(s), include assessments of **accuracy**, and **reproducibility** over time
- Inter-lab reproducibility and transferability
- Individual assays or combinations

physical properties or specific types of substances for which the assay is appropriate. …**applicable chemical space**.

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Proposed Assay Qualification Information to be Provided to Health Authorities

Detailed description of the predictive model:

what species trying to predict, **what reproductive endpoint** it assesses.

Details of the algorithm for determining pos and neg outcomes correlate concentrations to *in vivo* exposure (**exposure-based risk assessment**)

Training Set: nmt 15% compounds from the RCL

Performance of Training and **Test Set**: *sensitivity, specificity, positive predictive value, and negative predictive value*;

Define the category of compounds that can and cannot be predicted

Human teratogens not detected *in vivo* by rat/rabbit: present data separately

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Proposed Assay Qualification Information to be Provided to Health Authorities ctd.

Assay reproducibility: at least one pos ctrl and one neg ctrl in each run or interspersed over time bw test compound runs

Periodic reassessment of several compounds from the RCL

Source of reagents, biologic materials, cmpds tested

Source/reference of all *in vivo* exposure data used for compounds in the qualification data set (except for those in the RCL)

Expectation that regulatory studies should generally be conducted in compliance with **GLP**

State if the alternative assay has been **previously submitted to any health authority**

3rd Revision of ICH S5

Proposed Qualification of Alternative Test Systems for Regulatory Acceptance - Summarized

- Assays qualified based on performance (reliability and predictivity) with known developmental toxicants

- The ICH Reference Compound List **is not complete**.
  - We are soliciting data for additional reference compounds for potential inclusion into the list, including relevant information.
  - Template with examples is provided.

- No centralized approval process for regulatory acceptance of qualified alternative assays is proposed – remains agency specific.

3rd Revision of ICH S5

Summary of Proposed Guidance Revision

- Focus on application of human risk assessment
- Additional dose selection endpoints
- Emphasizes the use of existing data
- Integrated testing strategies for assessing reproductive toxicity, including for biologics
- Guidance on alternative assays: requirement of use & possible integration in risk assessment
- Focus of EFD risk assessment on teratogenicity or embryo/fetal lethality

Conclusions

Are we getting ready for alternative assays?

DEAD LINE FOR COMMENTS - 13 SEPTEMBER 2017

› Draft Guidance Document on Good in Vitro Method 2 Practices (GIVIMP)

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INTERNATIONAL COUNCIL FOR HARMONISATION OF TECHNICAL REQUIREMENTS FOR PHARMACEUTICALS FOR HUMAN USE

DRAFT ICH HARMONISED GUIDELINE

DETECTION OF TOXICITY TO REPRODUCTION FOR HUMAN PHARMACEUTICALS

S5(R3)

15 December 2016
EMA/CHMP/CVMP/JEG-3Rs/450091/2012
Committee for Medicinal Products for Human Use (CHMP)
Committee for Medicinal Products for Veterinary Use (CVMP)

Guideline on the principles of regulatory acceptance of 3Rs (replacement, reduction, refinement) testing approaches

Current *Step 2* draft version
dated 5 July 2017

Questions?

http://www.ich.org/products/guidelines/safety/article/safety-guidelines.html