Human relevance of developmental animal toxicity data of pharmaceuticals from the perspective of the European Teratology Society

7th Workshop on the Terminology in Developmental Toxicology

May 04 to 06th, 2011

Berlin

S. Barbellion

sanofi aventis

L'essentiel c'est la santé.

- "any drug administered at the proper dosage, and at the proper stage of development to embryos of the proper species-and these include both vertebrates and invertebrates-will be effective in causing disturbances in embryonic development“

Karnofsky, 1964

Introduction

- Concordance (=agreement)
  - Thalidomide tragedy
    - Regulatory testing
      - ICH guidelines for pharmaceuticals
      - 2 species
    - General principles of Teratology (Wilson)
- Relevance (=pertinence)
  - Toxicology testing
  - Risk assessment
  - Regulatory aspects
    - Integrative Assessment
- Significance (=importance, meaning)
  - Terminology and classification
  - Teratology findings

Introduction

- Four manifestations of developmental toxicity
  - Structural malformations
    - 3 to 6% of birth defects (Nelson, Holmes 1989)

      28% genetic causes

      23% multifactorial inheritance

      3% uterine factors

      3% toxicants

      43% unknown
  - Deaths

    (miscarriage)
  - Growth retardation
    - Low birth weights (5% of babies); predictor of susceptibility to certain chronic disease
  - Functional deficits
    - Mental retardation (lead, alcohol)

Principles of Developmental Toxicology

- Incidence and severity dependent on dose (and route of administration)
  - Dose-related effect (threshold)
    - Inorganic arsenic (route of administration)
  - More than one manifestations can occur (or one can hide the other)
- Mechanism of action
  - Safer drugs can be designed, safer use
  - Predictive toxicology
- Genetic background and interaction with environment
  - Mother and embryo
  - Difference is metabolism or pharmacokinetics
    - alcohol
- Stage of development at the time of exposure
  - Critical period of development (Wilson, 1973)
    - Thalidomide limb defects between Days 24 to 34 post-fertilization

Concordance

- Animal-to-human
  - Human experience through epidemiology in needed
    - 70-80% concordance with either rodents or rabbits
      - Responses between animals and humans can be different; but evidence of developmental toxicity that would have elicited regulatory action
    - Rodent studies are the most concordant, but also the most non concordant responses (Shardein, 1985)
      - Mycophenolic acid
      - Oral Isotretinoin
  - Olson et al. (1998, 2000)
    - Animal Toxicity vs. Human toxicity (HT) of pharmaceuticals during clinical trials
      - 71% positive HT concordance with rodent and non rodent species
- Human teratogens found positive in at least one animal species
  - 40-50 environmental factors (agents and pathogens, about 25 drugs)
  - Discrepancies between number of chemicals that have DevTox and number of known human developmental toxicants
    - Regulatory system
  - Shepard's catalog, reprotox database

Table 1 Comparison of developmental toxicity detection in rodents and rabbits with human response

Chemical	*Rodent*	*Rabbit*	*Human*
Cyclophosphamide	+	+	+
Diazepam	+		+
Diethylstilbestrol	+	+	+
Phenytoin/trimethadione	+	+	+
Ethanol	+		+
Lithium	+/–		+
Methylmercury	+		+
13-*cis*-Retinoic acid	+	+	+
Testosterone	+	+	+
Thalidomide	–	+	+
Valproic acid	+	+	+
Warfarin	+		+
Fumonisin B_1	+	–	+
Methimazole	+/–		+
Busulfan	+		+
Enalapril/captopril	+		+
Polychlorinated biphenyls	+/–		+
Cocaine	+/–		+
Misoprostol	+	–	+
Penicillamine	+		+
Tetracycline	–		+
Toluene	+		+

+ indicates developmental toxicity in that species; – indicates lack of response; +/– indicates an equivocal response, or a response that might not have been interpreted as indicative of a specific response. Note that a + ranking does not necessarily mean that the same response was elicited in all species, but that some significant, unequivocal manifestation of developmental toxicity was observed.

Daston et al., 2010

Animal-to-human concordance (Schardein, 1985)

Table 4. Predictability of animal models to concordant human malformations.

Teratogen	Reference malformation	Concordant	Nonconcordant
Alcohol	Craniofacial, limb, CV	Mouse, dog	Rat, guinea pig, pig
Androgenic/progestogenic hormones	Pseudohermaphroditism (♀)	Mouse, rat, guinea pig, hamster, rabbit, dog, pig, primate	
Anticancer antimetabolites			
Aminopterin	Skeletal	Rat	Dog, pig
Fluorouracil	Multiple visceral	Mouse, rat, guinea pig	Rabbit, primate
Methotrexate	Skeletal	Rabbit, cat	Mouse, rat, primate
Cytarabine	Limb, ear	Rat	Mouse
Anticancer alkylating agents			
Busulfan	Multiple visceral		Mouse, rat
Chlorambucil	Urogenital		Mouse, rat
Cyclophosphamide	Digits	Mouse, rat	Rabbit, primate
Mechlorethamine	Renal, limb, ear	Rat, rabbit, ferret	Mouse
Anticonvulsants			
Hydantoins	Facial, mental	Mouse	Rat, rabbit, primate
Diones	Facial, mental		Mouse, primate
Valproate	CNS		Mouse, rat, rabbit
Antithyroid agents	Hypothyroidism	Mouse, rat, guinea pig, rabbit	
DES	Uterine lesions	Mouse, rat, primate, ferret	
Methylmercury	Microcephaly, mental	Mouse, rat, cat	Hamster
Thalidomide	Limb	Rabbit, primate	Mouse, rat, hamster, dog, cat, pig, ferret
Lithium	CV		Mouse
D-Penicillamine	Skin lesion	Rat	Hamster
Streptomycin antibiotics	Inner ear	Rat	
Vitamin A analogs	CV, ear, brain	Rat, mouse, hamster, dog, primate	Rabbit, guinea pig, pig

Concordance

- Concordance animal-to-animal
  - Hurt et al. (2003) - teratogenicity
    - 61 % of (a series of) Veterinary drugs showed teratogenecity in any one of the species.

      100% in rats and rabbits together
  - Janer et al. (2008) – developmental toxicity
    - Assessed the added value of a second species (rabbit) when rat data are available

      ICH S9 (oncologic compounds), S6 (biologics)
    - Overall same sensitivity across species with regards to developmental toxicity
    - Direct vs. indirect maternally-mediated effects was problematic in the interpretation

Predictivity of developmental toxicity

- Nonanimal models
  - Rodent embryos in culture
  - Mouse embryonic stem cells and hES
  - Free-living embryos (xenopus, zebra fish)
  - Primary cultures of embryonic tissues
- Teratogenicity Screening Strategy
  - Prerequisites, high throughput
  - Level of concern
  - Warning for subsequent testing (in vivo screening)

Relevance

- Animal testing is considered to be relevant for predicting human toxicity
  - Assume humans are more sensitive
  - NOEL values can be used to predict safe levels in humans
    - Concern when effects within 20-fold the therapeutic blood level ?
    - 100x margin is sufficient ?
  - Mechanistic study to demonstrate that a finding in DART studies is not relevant to humans
  - Hierarchization (and extrapolation) of animal teratology findings ?

Suggested recommendation to clinicians based on experimental data

	Compound-related animal malformations	Compound-related animal embryo–fetal toxicity (excluding malformations)
Animal exposure level similar to human therapeutic dose exposure	High human risk expected	Human risk cannot be excluded
Animal exposure level several-fold higher than human therapeutic dose exposure	Human risk cannot be excluded	No human risk expected

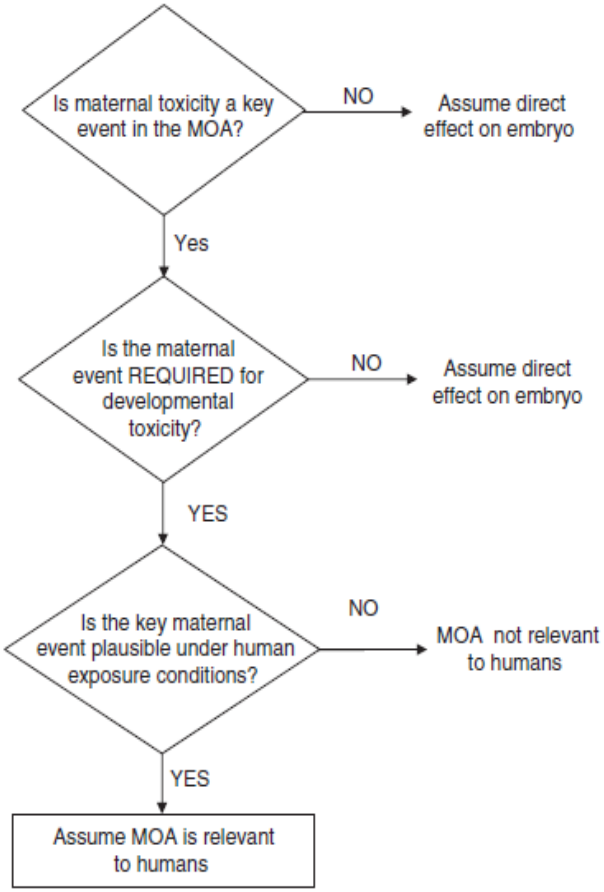
Guittin et al., 2000

Relevance

- Importance of rigorous and relevant testing
  - Quality of the data, relevance of findings
    - Good dose selection for definitive DART studies (avoid marked maternal toxicity)
    - Adequate study design and number of animals
  - Differences in sensitivity between species required attention
    - Relevance of the effects (mechanistic study)
    - Metabolism differences, pharmacokinetics
  - Placental differences (Carney et al. 2004)
    - Inverted yolk sac (histiotropchic nutrition, trypan blue in rats)

Relevance

- Importance of rigorous and relevant testing
  - Maternally-mediated toxic effects
    - Finding that occur in the absence of MatTox are most relevant to the clinical situation where MatTox is unlikely at therapeutic doses (FDA)
    - Sponsors should be able to support claims that DevTox is due to MatTox (EMA)
      - Presence of maternal and developmental toxicity does not change the level of concern for human risk
      - Demonstrate that the developmental toxicity is not relevant to humans not simply that is due to maternal toxicity
    - Assess human relevance of a maternally mediated MOA
      - Diflunisal-induced matenal anemia (Clark, 1984)
      - Potent hERG channel blockers produced fetal death in conventional studies, stage-specific malformations in single administration (Danielsson, ILSI/HESI WS 2010)
    - Weight-of-evidence evaluation of data
      - Plausibility if a causal link e.g. decrease maternal food consumption and BW gain: decrease fetal BW (plausible); fetal malformations (not plausible)
      - Temporal correspondence
      - Individual animal correspondence (association of maternal and litter effects)
      - Potential interactions
      - MOA
  - Historical control data
    - Genetic background and drift



Decision logic for assessing the human relevance of a maternally mediated mode of action (MOA) (Carney, 2010)

Relevance and significance of findings

- Primary concern has been the terminology used to describe structural changes in the offspring
  - Misclassification or inconsistencies in the use of terms
  - Comparative atlas of malformation, images database
    - Guittin et al.
    - DevTox website
  - Classification
    - Malformation and Variation, Chahoud et al., 1999
    - Berlin WS
  - Terminology
    - Wise et al., 1997
    - Makris et al., 2009
  - Grading, severity and adversity
    - Paumgartten et al., 2009
- Integrative Assessment of nonclinical and clinical findings
  - EMA guideline, 2008
  - FDA guidance, 2001

EMA Integrative Assessment

- Nonclinical Assessment
  - Reproductive Tox studies and all pharmacological and toxicological studies
    - Choice of species (2 species for EFD, at least one responsive to the PD effect)
    - Pharmokinetics (relevance of the species)
      - Placental transfer and Milk excretion study is of value for the assessment
    - Route of administration
    - Toxicokinetics in pregnant animals
      - Metabolite
      - Comparison of toxic and PD effective dosage, animal to human exposure ratio
    - Dose Levels
      - Minimal maternal toxicity (magnitude and nature to be considered for relevance)
      - NOAEL
    - Mechanism (desirable when reproductive toxicity identified)
    - Class alert
- Evaluation process
  - Identified lack of data
  - No effect detected
  - Effects detected
    - Recognition of an effect
      - Incidence, rarity, dose-response relationship
    - Cross-species concordance
      - Increase the concern
    - Type of effects
    - Multiplicity of effects
- Clinical Assessment

European Medicines Agency
Evaluation of Medicines for Human Use

London, 24 July 2008
EMEA/CHMP/203927/2005

COMMITTEE FOR MEDICINAL PRODUCTS FOR HUMAN USE

(CHMP)

GUIDELINE ON RISK ASSESSMENT OF MEDICINAL PRODUCTS ON HUMAN REPRODUCTION AND LACTATION: FROM DATA TO LABELLING

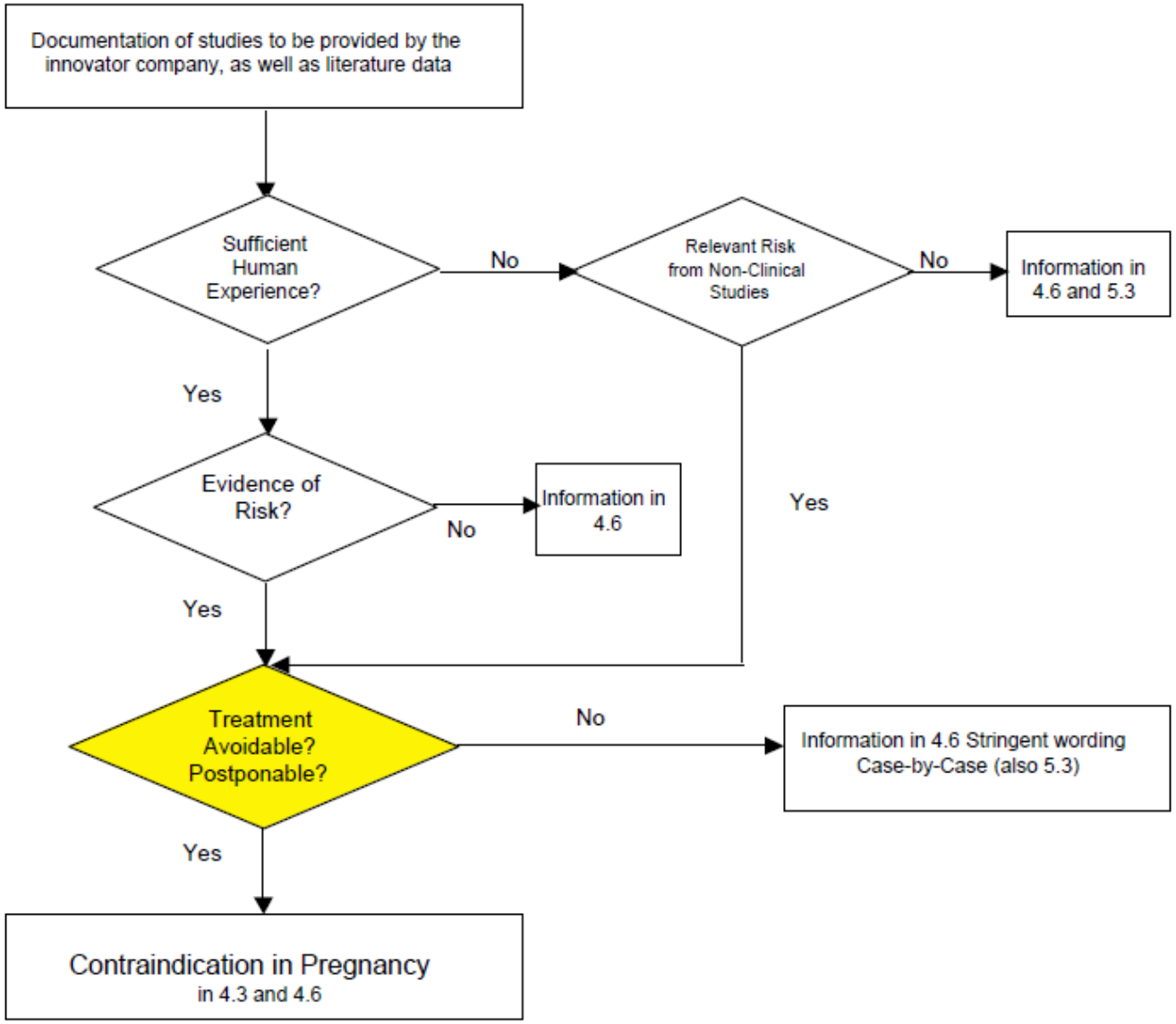
EMA Integrative Assessment - Pregnancy

	Non clinical data	
	Effects detected *	**No effects detected**
Human data	Conclusion from integration *Labelling* *(see appendix 3)*	Conclusion from integration *Labelling* *(see appendix 3)*
Demonstrated human teratogenicity (or fetotoxicity)	Proven risk in humans *Labelling [1]* *See also decision scheme on Contraindication*	Proven risk in humans *Labelling [1]* *See also decision scheme on Contraindication*
Supposed or suspected human teratogenicity (or fetotoxicity)	Strong suspicion of risk in humans *Labelling [2]*	Risk is possible in humans *Labelling [3]*
None or less than 300 prospective exposed pregnancies with known outcome in the 1st trimester and no increased rate of malformation identified	Risk is possible in humans, not confirmed *Labelling [4]*	Malformative risk unlikely in humans, but low evidence *Labelling [5]*
At least 300 prospective exposed pregnancies with known outcome in the 1st trimester and no increased rate of malformation identified	Malformative risk unlikely in humans. but low evidence *Labelling[6]*	Malformative risk unlikely in humans with moderate to substantial evidence *Labelling[7]*
At least 1000 prospective exposed pregnancies with known outcome in the 1st trimester and no increased rate of malformation identified	Malformative risk unlikely in humans with strong evidence *Labelling [8]*	Malformative risk unlikely in humans with strong evidence *Labelling [8]*

Contraception

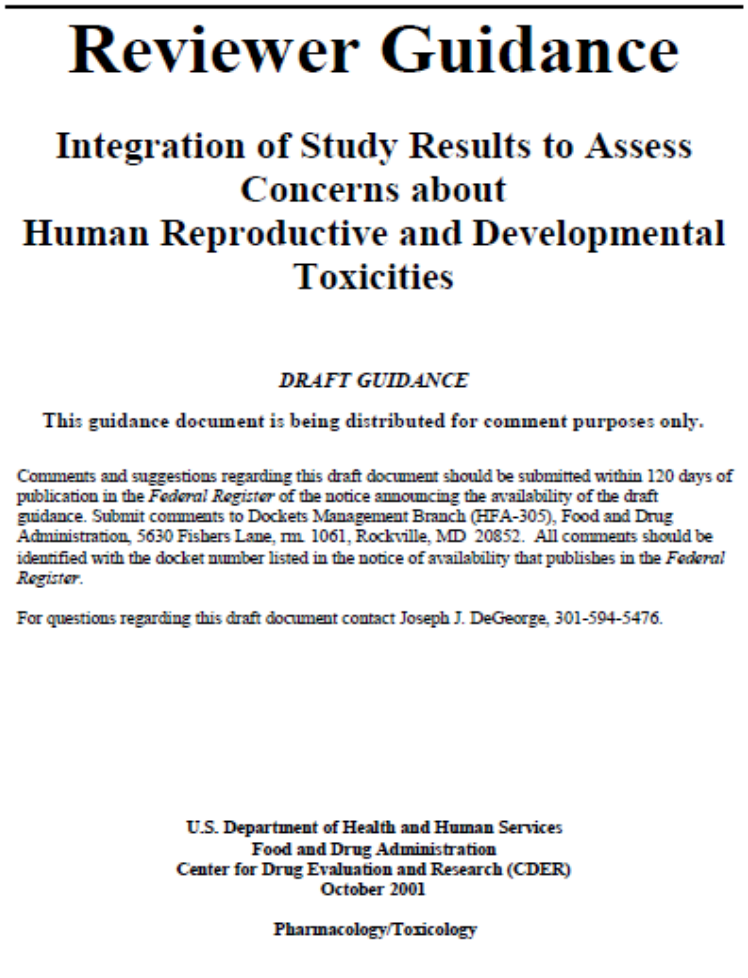
* Insufficient data are considered as effects detected

Contraindication in pregnancy



Integrative Assessment tool

- Integrative Assessment (IA) for Evaluating Data for Potential Human Developmental and Reproductive Toxicology (DART) Risk
- A process for evaluating potential human developmental and reproductive toxicology (DART) risk of a compound using available nonclinical and clinical data.
  - Based on procedures proposed by US FDA and EMEA
  - Uses a weight-of-evidence approach



Reviewer Guidance

Integration of Study Results to Assess Concerns about Human Reproductive and Developmental Toxicities

DRAFT GUIDANCE

This guidance document is being distributed for comment purposes only.

Comments and suggestions regarding this draft document should be submitted within 120 days of publication in the *Federal Register* of the notice announcing the availability of the draft guidance. Submit comments to Dockets Management Branch (HFA-305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852. All comments should be identified with the docket number listed in the notice of availability that publishes in the *Federal Register*.

For questions regarding this draft document contact Joseph J. DeGeorge, 301-594-5476.

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
October 2001

Pharmacology/Toxicology

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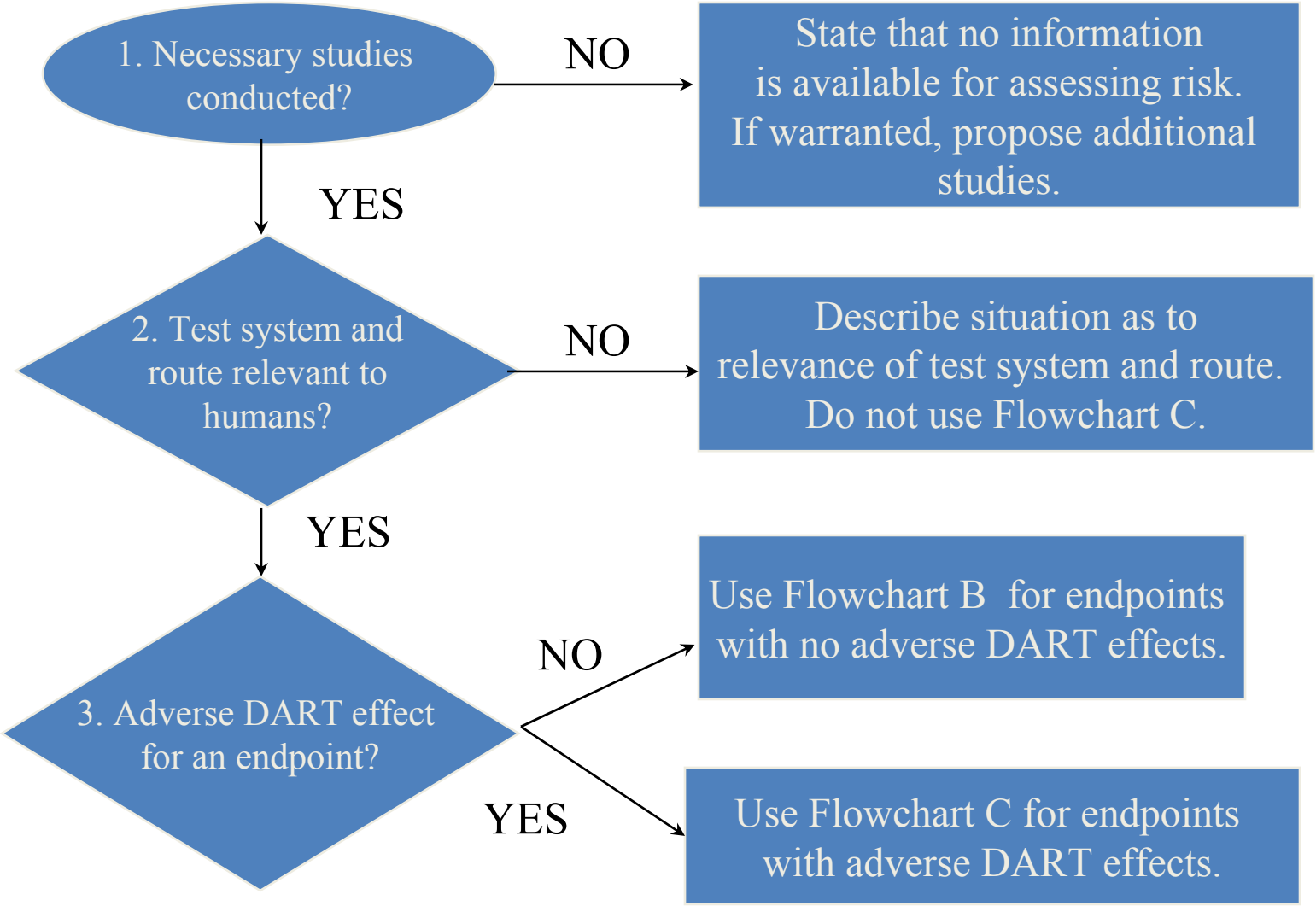
IA: Data Categorization

- Reproductive Endpoints (F0)
  - Fertility and Fecundity
  - Parturition
  - Lactation
- Developmental Endpoints (F1)
  - Mortality
  - Dysmorphogenesis
  - Alterations in growth
  - Functional toxicity
- Additional Data Sources
  - Class alerts
  - Other in-house compounds
  - Human and animal exposure data
  - Published literature
  - Position papers
  - Additional nonclinical safety studies
  - Etc.

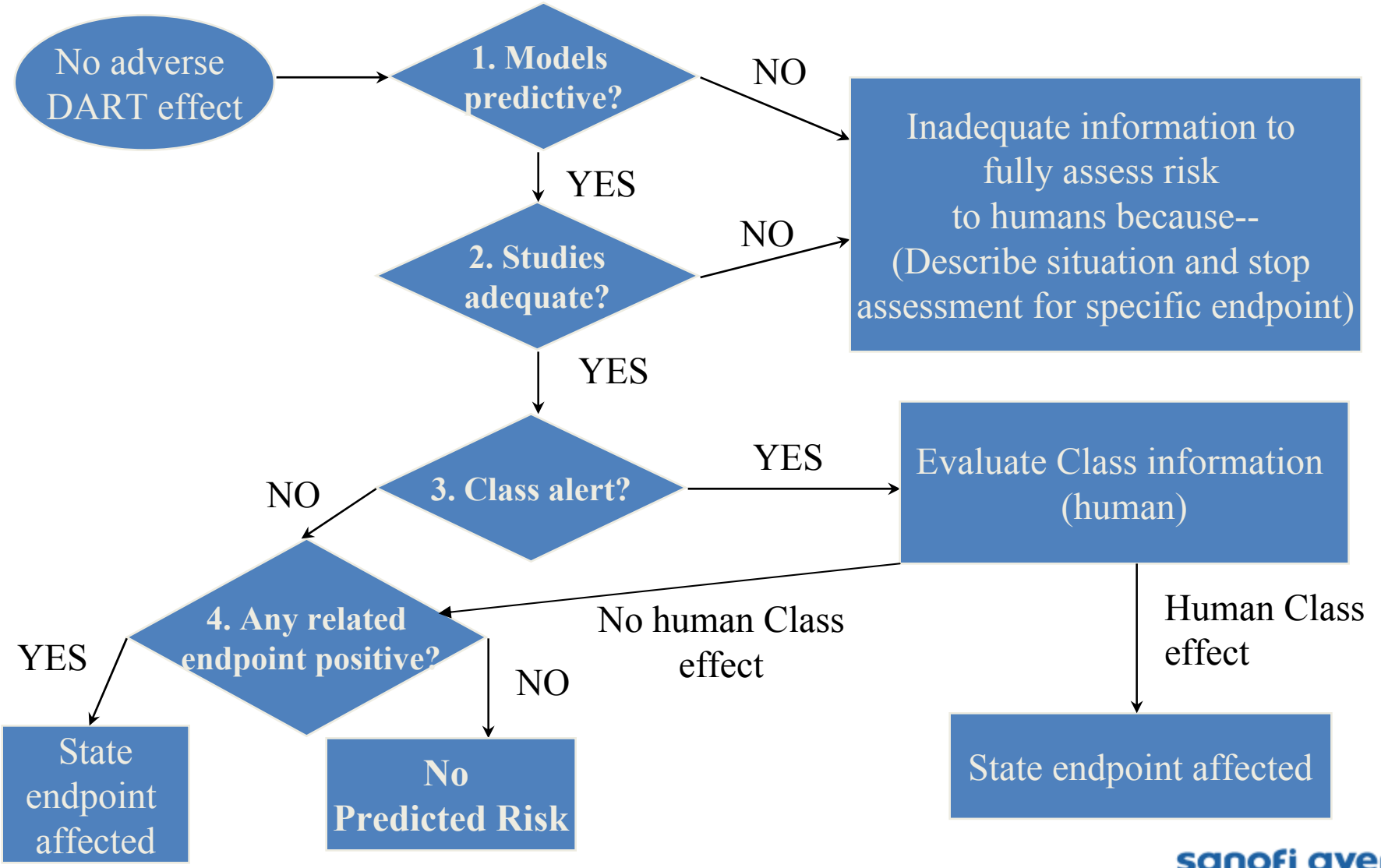
Components of the IA

- Populate templates for each endpoint assessed as appropriate:
  - Template A: Data adequacy
  - Template B: Decision process for endpoints with no adverse effects
  - Template C: Decision process for endpoints with DART effects

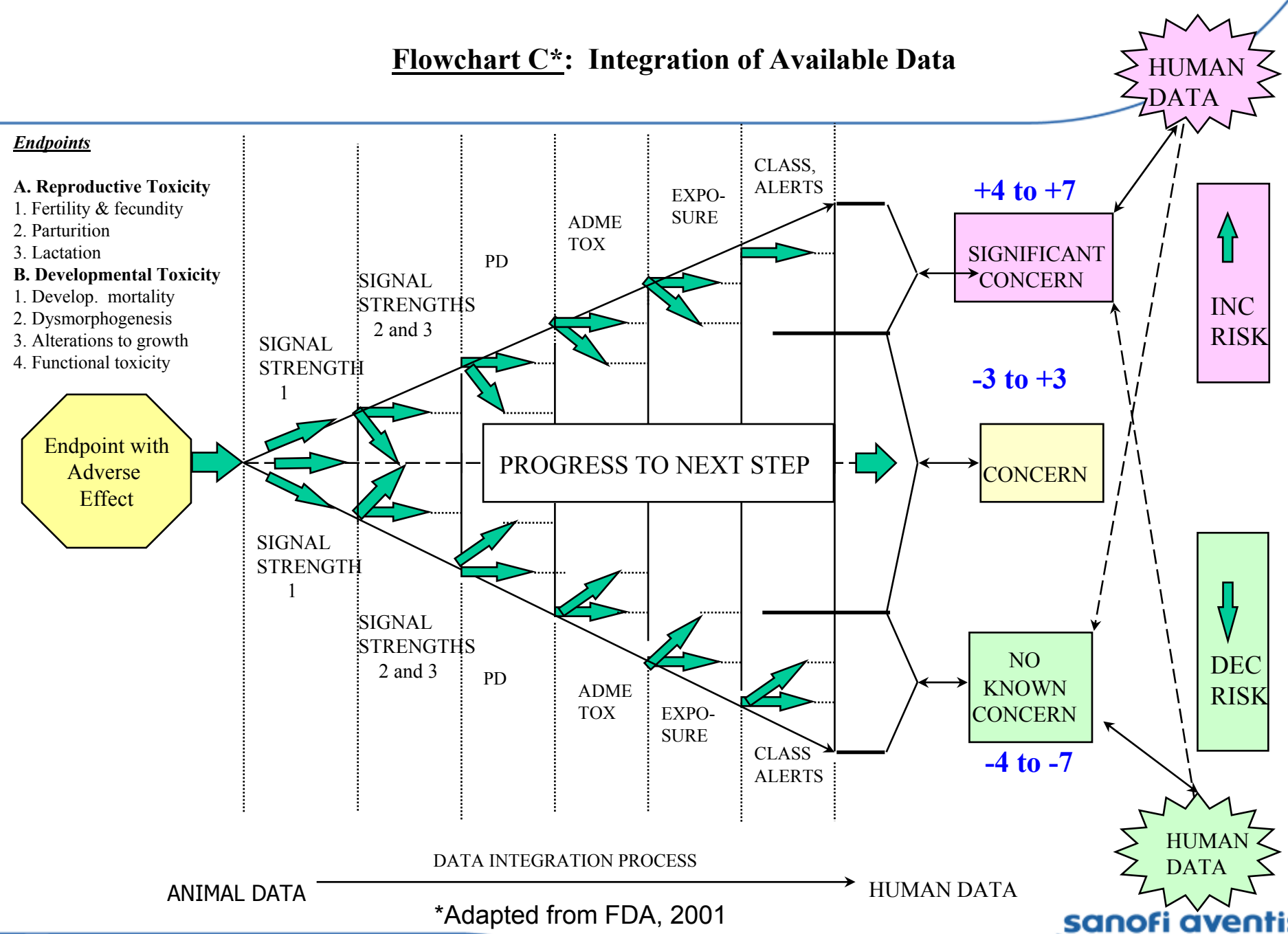
Flowchart A: Data Adequacy



Flowchart B: For Endpoints with No DART Effects



Flowchart C*: Integration of Available Data



*Adapted from FDA, 2001

Template C: Adverse Effects Overview

- Assess each endpoint for which an adverse effect was observed according to 7 factors.
  - Signal Strength 1 (Multiplicity of effects, Adverse effects as a function of time)
  - Signal Strength 2 (Cross-species concordance, Parental toxicity)
  - Signal Strength 3 (Dose-response relationships, Rare events)
  - Pharmacodynamics
  - Species-Human Concordance
  - Animal:Human Relevant Exposure
  - Class Alerts
- Definitive studies carry more weight-of-evidence than range-finding studies. However, if the definitive study is conducted at lower doses than the range-finder, the range-finding study may still carry weight and may be included in the assessment.

Template C: Adverse Effects Overview (cont.)

- Determine level of concern for each of the 7 factors and assign score:
  - +1 for increased concern
  - 0 for no change in concern
  - -1 for decreased concern
- Note:
  - It is important to use a weight-of-evidence approach when assessing the level of concern for a particular factor, since some of the factors contain multiple points of consideration.
  - After all 7 factors for a given endpoint have been determined, add the scores from all factors together to arrive at an overall risk value for the endpoint in question.

Template C: Adverse Effects Overview (cont.)

- Sum factors scores for each endpoint to determine concern for humans:
  - +4 to +7 = Significant concern for human risk
  - -3 to +3 = Concern for human risk
  - -4 to -7 = No known concern for human risk

Discussion

- Assessment relies mainly on nonclinical data until submission
  - Continuum and interactive process
  - Integrative analysis based on (full) evaluation of study reports
  - Fetal findings not reviewed
- Clinicians use the data as indicators of potential outcomes in patients, while the scientist groups use the data as signal indicators of disrupted development
- Clinicians are not aware of the principles of the conduct of regulatory studies (dose selection, or use of effect doses in risk assessment estimate)
- RMP (risk management plan)
  - Rare events should be mentioned