An Integrated Approach to the Evaluation of Non-Clinical Reproductive Toxicity Data

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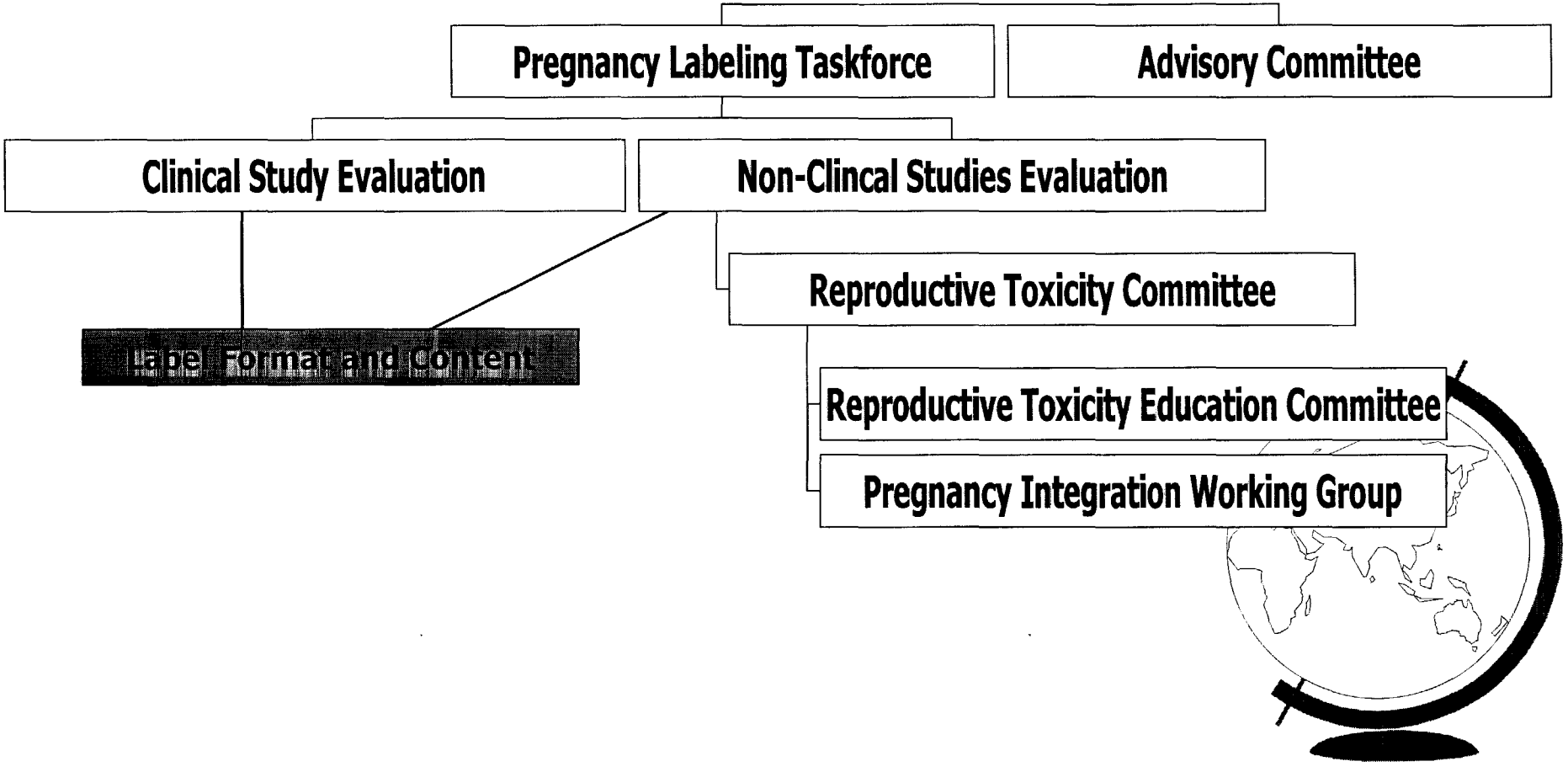
Chairman, Reproductive Toxicity Committee, CDER

Reproductive Toxicity Initiatives



Non-Clinical Studies Evaluation

- Reproductive Toxicity Committee (CDER)
- Reproductive Toxicity Education Committee
- Pregnancy Integration Working Group

Reproductive Toxicity Committee

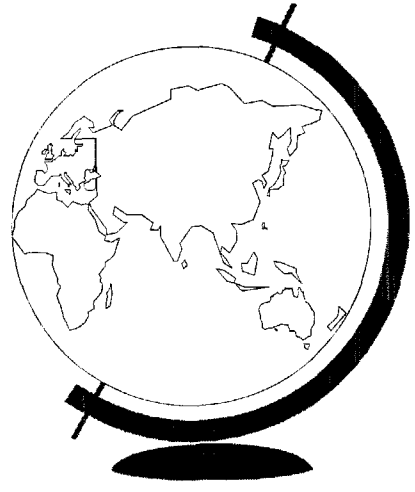
Functions and Initiatives

- Consultation service for Review Divisions
- Forum for discussion and resolution of disparate interpretations of study data
- Promote consistency in study data interpretation and applicable rules and regulations
- Develop a reviewer "Handbook" on Reproductive Toxicity testing

Reproductive Toxicity Education Committee

Functions

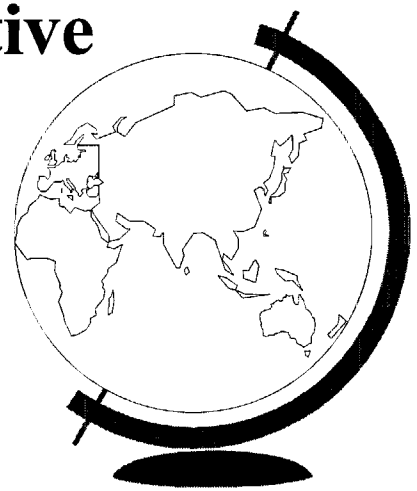
- Define "Core Curriculum" for education in Reproductive Toxicity
- Develop specific course curricula
- Promote Dissemination of Information
  - Seminars and Meeting Presentations
  - Presentation of Staff College courses
  - Publications



Pregnancy Integration Working Group

Specific Objectives

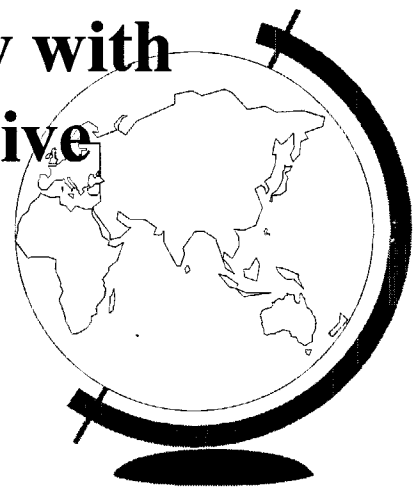
- To develop an evaluative method to judge the adequacy of non-clinical reproductive toxicity study data
- To organize study findings for effective communication to others



Pregnancy Integration Working Group

Goals for the Integration Process

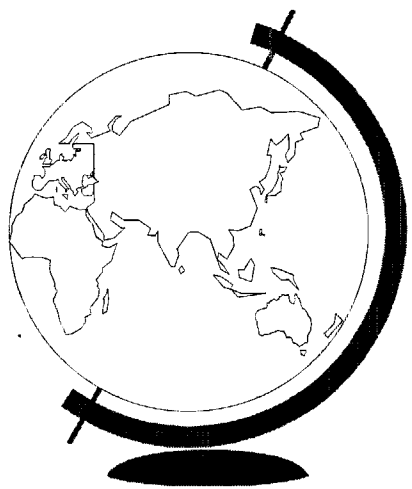
- To effectively integrate non-clinical study data from developmental and reproductive toxicity studies with all other available pharmacologic and toxicologic data
- To enhance the scientific consistency with which developmental and reproductive toxicity studies are evaluated



Pregnancy Integration Working Group

Approach Taken

To enumerate and codify the thought processes of experts in reproductive toxicity and regulatory sciences in assessing drug-induced reproductive risks



Pregnancy Integration Working Group

Defining the Process

- Developed a "tool" which reflects conventional thought processes applied to the interpretation of findings from studies of reproductive and developmental toxicity

INTEGRATION TOOL FOR POSITIVE REPRODUCTIVE TOXICITY RESULTS

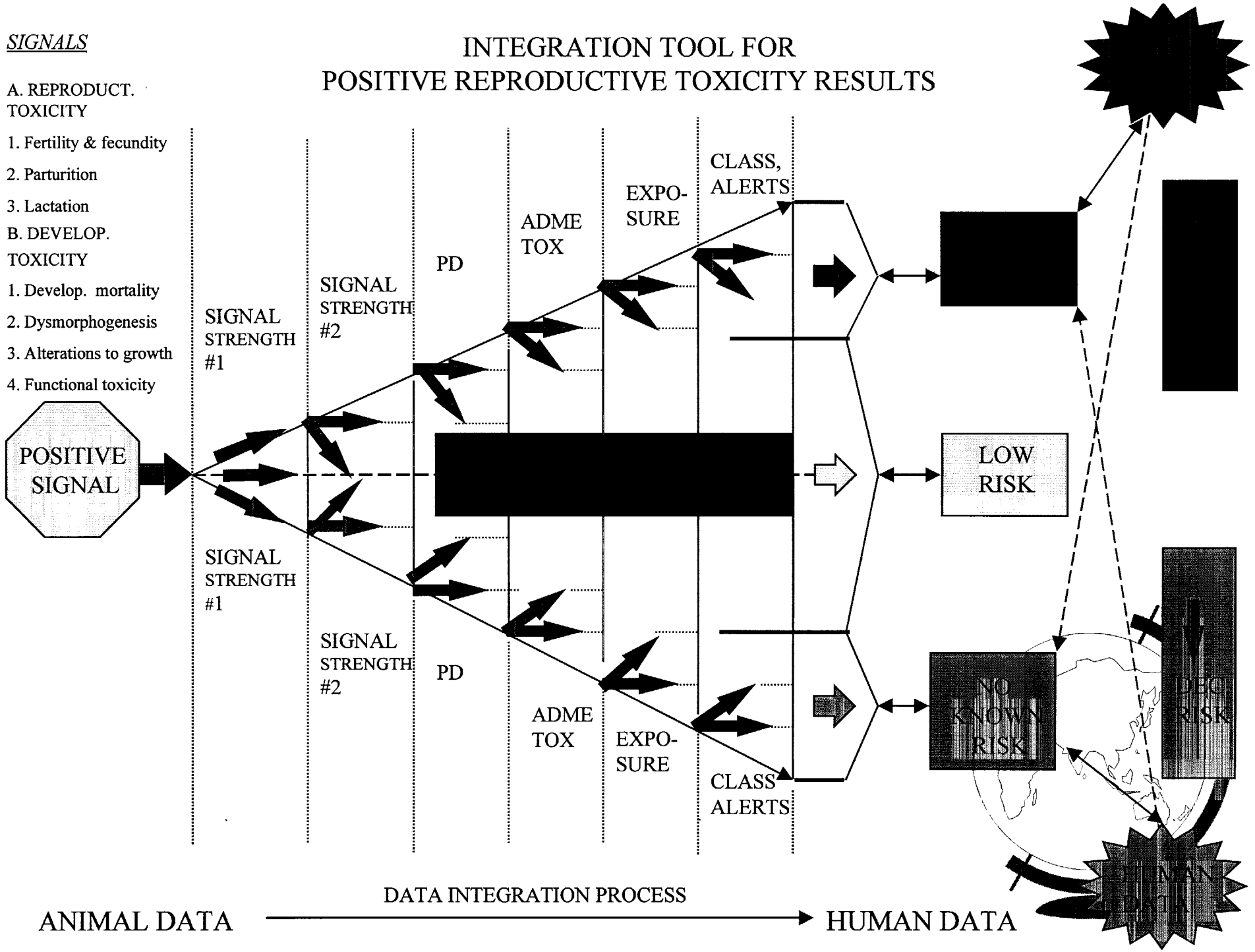
SIGNALS

A. REPRODUCT. TOXICITY

1. Fertility & fecundity
2. Parturition
3. Lactation

B. DEVELOP. TOXICITY

1. Develop. mortality
2. Dysmorphogenesis
3. Alterations to growth
4. Functional toxicity

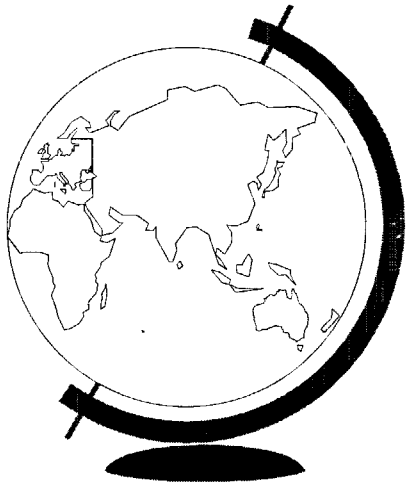


DATA INTEGRATION PROCESS

ANIMAL DATA → HUMAN DATA

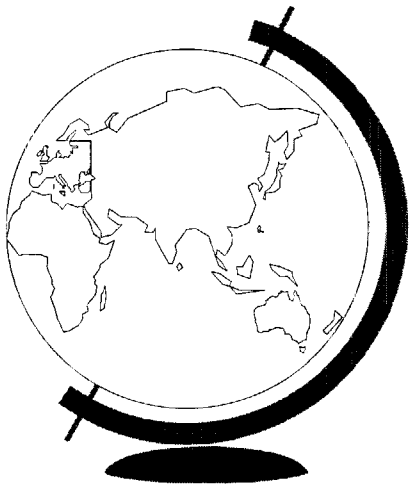
Integration Tool - General Considerations

- A step-wise or hierarchical process
- Begins with animal findings and progresses to findings in humans
- A weight-of-evidence approach based on the nature and quality of the applicable toxicity data
- Hazard or Risk identification



Integration Tool - General Considerations

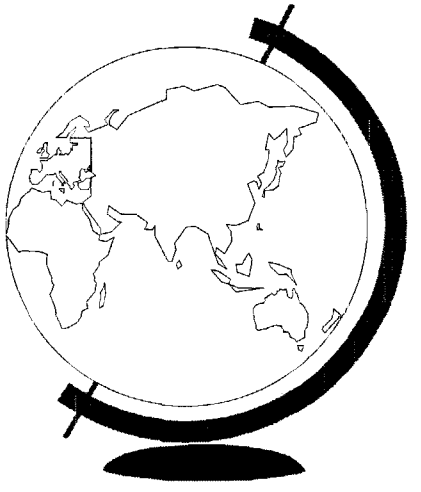
- A series of questions asked of every endpoint
- Adequate quality human data takes precedent over non-clinical study results
- Different questions for positive and negative endpoints



Integration Tool

Process begins with a positive signal for any one of seven defined endpoints

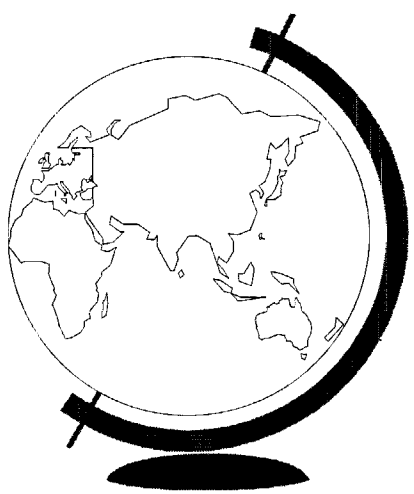
- **Reproductive Toxicity Endpoints**
  - **Fertility and Fecundity**
  - **Parturition**
  - **Lactation**
- **Developmental Toxicity**
  - **Developmental Mortality**
  - **Dysmorphogenesis**
  - **Alterations to Growth**
  - **Functional Toxicity**



Integration Tool

Six Factors may alter the level of concern for a positive signal:

- **Signal Strength, A & B**
- **Pharmacodynamics**
- **Human/Test Species concordance of Toxicity Profiles and Drug Metabolism**
- **Relative Drug Exposure**
- **Class Alerts**



Integration Tool - Conclusions

Why do we need this process?

- To assist in the interpretation and integration of reproductive toxicity study findings
- To promote consistency in the interpretation of reproductive toxicity study findings
- To provide a common framework for the review, interpretation and discussion of findings

Pregnancy Integration Working Group

Current Members

Paul Andrews

Joseph J. DeGeorge

James G. Farrelly

Edward Fisher

Abby Jacobs

David E. Morse

Mark Vogel

Former Members

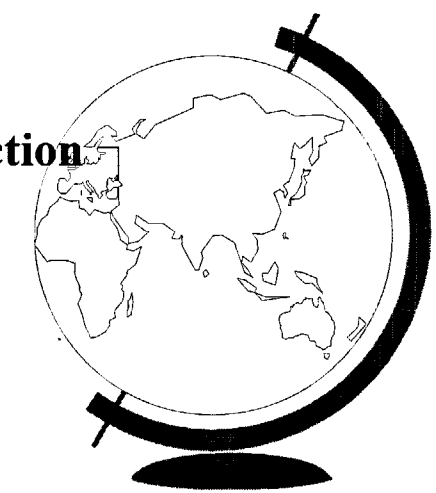
Mary Ellen McNerney

Hilary Sheevers

ICH Guidelines on Scientific Flexibility

"These guidelines are not mandatory rules, they are a starting point rather than an endpoint. They provide a basis from which an investigator can devise a strategy for testing according to available knowledge of the test material and the state-of-the-art…In devising a strategy, the primary objective should be to detect and bring to light any indication of toxicity to reproduction."

Guideline on Detection of Toxicity to Reproduction for Medicinal Products



Pregnancy Labeling Evaluation
Physician Focus Groups

Kathryn Aikin, Ph.D.
Division of Drug Marketing, Advertising, and Communications
Food and Drug Administration

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Introduction

Two focus groups were conducted to provide feedback on proposed changes to the pregnancy section of drug labeling.

Participants

- Fifteen MD's were recruited in advance from the 15th Annual Clinical Update in Obstetrics and Gynecology Conference, February 9-12, 1999.

- 11 OB-GYNs, 3 Family Practitioners, 1 Reproductive Endrocrinologist

Sample Labeling

DRUG X
(Current Format)

Carcinogenesis, Mutagenesis, Impairment of Fertility
xxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxx

Carcinogenicity
xxxxxxxxxxxxxxxxxxxxxxxxx

Mutagenicity
xxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxx
xxxxxxxxxxxxxxx

Pregnancy
Pregnancy Category C
xxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxx
xxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxx
xxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxx

Labor and Delivery
xxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxx
xxxxxxxxxxxxxxxxxxxxxxxxxxxx

Nursing Mothers
xxxxxxxxxxxxxxxxxxxxxxxxxxxxxxx

DRUG Y
(Proposed Format)

Fertility

Clinical Management
xxxxxxxxxxxxxxxxxxxxxxxxxxx

Summary Risk Assessment
xxxxxxxxxxxxxxxxxxxxxxxxxxxx

Description and Discussion of Data
xxxxxxxxxxxxxxxxxxxxxxxxxxxx

Pregnancy

Clinical Management
xxxxxxxxxxxxxxxxxxxxxxxxxxxx

Summary Risk Assessment
xxxxxxxxxxxxxxxxxxxxxxxxxxxx

Description and Discussion of Data
xxxxxxxxxxxxxxxxxxxxxxxxxxxx

Lactation

Clinical Management
xxxxxxxxxxxxxxxxxxxxxxxxxxxxxx

Summary Risk Assessment
xxxxxxxxxxxxxxxxxxxxxxxxxxxxxx

Description and Discussion of Data
xxxxxxxxxxxxxxxxxxxxxxxxxxxxxx

Topics of Interest

- Current thinking: factors taken into account when prescribing during pregnancy
- Availability of information: animal and human data
- Sample labeling: overall impressions, clinical management section, format
- Wish list

Current Thinking

- Reliance on categories
  - "It's an easy reference."
- Reliance on colleagues
  - "The tendency is to use things that have been around. [N]obody wants to be out there on the forefront finding 15 years later that they made a mistake."

Availability of Information

- **Human data is very important**
  - **"We definitely want to see human data."**
- **Explain other animal data in terms of human dosage**
  - **"They just tell you they gave X amount, and you have to go back a couple of pages, look at the regular dose we give our pregnant patients, and what does that mean in a rat compared to humans."**

Format

- **Recommendations up front, details following**
  - **"I'd like to see someone make the summary statements that are in this, for quick reference, right at the top. I hate to read in a couple of pages if I don't have to."**
  - **"It gives you the reference if you want to look up the study and make your own conclusion."**

Format, con't.

- **Uniform format across drugs**
  - **"A lot of inconsistency from drug to drug. Sometimes you don't find what you're looking for. A more standardized format would be very useful."**

Clinical Management Section

- **Participants were generally favorable toward the clinical management statement.**
  - **"The first paragraph tells you how to manage. You don't have to read past clinical management if you don't want to."**
  - **"It's like a newspaper article. The important information is up front."**

Clinical Management Section Examples

Example 1

Pregnancy

Clinical Management
The clinical management of patients who are in early pregnancy and taking or considering taking Roselens should not be affected. Women in the third trimester should be evaluated for the need for continued therapy and monitored for appropriate fetal growth.

Example 2

Pregnancy

Clinical Management
Women who are taking Leural and become pregnant should be advised to consider discontinuing the drug and may warrant evaluation for fetal effects by sonography. Women who are considering pregnancy should be advised to consider alternative treatments for asthma maintenance.

Clinical Management Section, con't.

- **OB-GYNs disliked directive language**
  - **"The statement 'evaluation for fetal effects by sonography' is saying they should all get ultrasounds. Think of the lawsuits."**
- **Family practitioners wanted to be told up front what to do.**
  - **"What is the bottom line- red light, green light or yellow light?"**

Wish List

- Uniform format
- Provide human data
- Order information by species
- Divide information by trimesters
- More information is better
- Provide the "bottom line" - most important information up front, preferably under Clinical Management

Rachel E. Behrman, Deputy Director

Office of Medical Policy

CDER.FDA

t body of data that must be consolidated

osophy

aximally informative

ot necessarily comprehensive

void speculation in absence of information

es complicating the pregnancy subsection

ucity of data

creased reliance on preclinical data

verse audience

ommendations

- lace Categories
- vide more specific, clinically relevant
  ce
- vide a concise summary of risks
- vide more discussion of data
  erlying risk assessment
- ge Fertility, Pregnancy, and Lactation

- tidisciplinary group
- l: Provide structure and organization
  would remain sufficiently adaptable to
  ely varying bodies of data applied to
  ly differing disease states
- ciples
  - stinguish clinical advice from risk
    formation
  - ovide different levels of information for
    fferent needs

ical Management Statement

nmary Risk Assessment

cussion of Data

l is to provide the most specific, ically relevant advice possible

cution is difficult

ew easy cases (never use v. never orry)

hallenges include:

- How to tackle therapeutic alternatives
- How to address inadvertent exposure
- How much advice, and how specific, to provide on monitoring during pregnancy

Pregnancy Category C. . . . . Roselens should be used in pregnancy only if the potential benefit justifies the potential risk to the fetus."

Use of Roselens should not effect the
bstetric or psychiatric management of
atients who are in early pregnancy or
onsidering becoming pregnant.
Women in the latter months of
regnancy should be evaluated for the
eed to continue Roselens therapy, and
continued, monitored for appropriate
tal growth."

cise overview of risk information

ges Discussion of Data and
agement advice that results

lems include:

w to provide needed context

Background risk (if known)

Extent and applicability of animal data

w to quantify or quantitate risk (and which)

Based on studies in animals and
mited human data, there is no known
oncern for malformations or abnormal
eurobehavioral function in infants born
mothers treated with Roselens.
here is some concern, based on
himal studies, for an increased risk of
paired fetal growth and late fetal and
eonatal mortality when Roselens is
dministered during the third trimester
f pregnancy."

nprehensive presentation of
mal and human data

ubheadings for Dysmorphogenesis,
mbryo-fetal death, Growth Retardation,
unctional Toxicity, Maternal Toxicity,
nd Labor & Delivery

escription of data source

onditions under which hazard occurs

blem - how comprehensive?

- ee subsections (Fertility, gnancy and Lactation) of single eling section
- ly same internal format to each section
- linical Management Statement
- ummary Risk Assessment
- iscussion of Data

- ls are clear
- ptimally informative
- elatively reproducible
- dequate structure and adequate exibility
- v best to implement is more nplicated
- atever is developed will need to biloted and refined

Perils and Pitfalls in Talking About Medical Risks

Eric S. Holmboe
National Naval Medical Center
Uniformed Services University

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What is "Risk"?

Webster's Dictionary:

- **"A dangerous element or factor"**
- **"Possibility of loss or injury"**
- **"The degree of probability of such loss"**

SH

What is "Risk"?

Concept of risk embodies at least 2 distinct notions:

- **An unwanted outcome**
- **Uncertainty about occurrence ("probability")**

Understanding Risk

A complex task that must combine:

- **Objective information**

with

- **Subjective interpretation**

Key Elements of Risk

- **Identification**
- **Permanence**
- **Timing**
- **Probability**
- **Value (subjective "badness")**

Elements of Risk: Identification

Identification of the unwanted outcome is the first task of the physician.

<u>Challenges</u>:

- **Are all of the risks known?**
- **Is it a risk, benefit, or both?**
- **Is discussion of risk part of the medical encounter? (identify risk *to the patient*)**

Elements of Risk: Identification

Physician-patient communication:

- **Kalet (1994): Audiotaped 160 patient visits among 19 community-based physicians:**
  - **Risk NOT discussed routinely**
  - **When discussed, risk rarely given in quantitative terms**

Elements of Risk: Identification

- **Patients scheduled for elective angioplasty interviewed day before procedure:**
  - **Only 46% of patients could recall even a single possible risk**
  - **25% offered spontaneously they did not have any discussion of the risks with their doctor**
  - **Most patients (67%) wanted a major role in determining the acceptability of risk**

Elements of Risk: Permanence

- **Is the risk only temporary or permanent?**

<u>Challenge</u>:

- **Not always clear-cut:**
  - **Low birth weight a "temporary" state**
  - **Incontinence and/or impotence after radical prostatectomy**

Elements of Risk: Timing

When will the unwanted outcome occur?

- **<u>Challenge</u> - Now versus later:**
  - **Infarction, bleeding versus re-stenosis after coronary angioplasty**
  - **Immediate versus delayed effects of drugs taken during pregnancy**

Elements of Risk: Probability

How likely is the unwanted outcome?

<u>Challenges</u>:

- **Probability known with varying degrees of certainty**
- **Application of population derived numbers to the individual patient**

Elements of Risk: Value

How much does the unwanted outcome matter to the patient?

<u>Challenge</u>:

- **Patients will differ on how they rate adverse outcomes:**
  - **Tooth discoloration after tetracycline tx**
  - **Impotence after treatment for localized prostate cancer**

Discussion of Risk

Two major components:

- **Which risks should be discussed?**
- **How should risk be communicated?**

Which Risks ?

- **Global versus patient-centered**
- **Professional standard:**
  - **Information that would be generally disclosed by a community of medical peers**
- **Reasonable person standard:**
  - **Information that a reasonable person would want to be told**

How to Communicate Risk

Challenges:

- **The framing effect**
- **Qualitative vs. quantitative expressions**
- **Which quantitative expression to use?**
- **Common errors in risk interpretation**

The Framing Effect

How risk and benefit is presented can influence patient decision making:

- **McNeil (NEJM, 1982)**
  - **Patients more likely to choose surgery over radiation for lung cancer when surgery outcomes framed as probability of survival versus death**

Qualitative Vs. Quantitative

How should outcomes be presented?

- **Qualitative expressions perhaps more "accessible" to patients, but they have no accepted anchoring at specific quantitative levels of frequency.**

Nakao and Axelrod (Am J Med, 1983)

	Percentages		
Expression	Mean	Median	Range
Rare	5	5	0 – 10
	5	5	0 - 10
Sometimes	20	20	10 – 35
	22	20	5 - 40
Frequent	68	70	50 – 85
	66	70	40 - 85
Invariably	88	95	80 – 100
	85	95	40 – 100

Quantitative Expressions

Which expression should you use?

- **Percentage vs. proportion**
- **Relative risk reduction (RRR)**
- **Absolute risk reduction (ARR)**
- **Number needed to treat (NNT)**

Quantitative Expressions: Patients

Malenka, et al (J Gen Intern Med, 1993)

- **Majority of patients (57%) chose medication with outcomes expressed in relative risk terms.**
- **Only 28% of patients were able to convert relative risk to absolute risk correctly**

Quantitative Expressions: Patients

How do patients want information presented?

- **Mazur (J Gen Intern Med, 1991)**

Numerical only	**32%**
Words only	**35%**
Either numbers/words	**22%**
Both numbers/words	**8%**

Quantitative Expressions: Physicians

Forrow, et al. (Am J Med, 1992)

- **Almost half (49%) of physicians were more likely to treat hypercholesterolemia when outcomes expressed as relative reduction vs. absolute reduction**

Quantitative Expressions

Number-needed-to-treat (NNT) or harm (NNH)

- **1 / absolute risk reduction (1 /ARR)**
- **David Sackett and others strong proponents**
- **Effect on patient and physician decision making not clear**

Errors in Risk Interpretation

- Anchoring bias
- Availability bias
- Compression
- Miscalibration

Errors in Risk Interpretation

Anchoring bias:

- **Estimation of risk based on the risk of other related events or procedures familiar to patient**

Availability bias:

- **Patient overestimates risk that receives substantial notoriety**

Errors in Risk Interpretation

Compression:

- **Overestimation of small risks and underestimation of large risks**

Miscalibration:

- **Overconfidence about extent and accuracy of one's knowledge**

Perception of Risk

Slovic (Science, 1987)

- **Two main factors:**
  - **"Dread" risk: lack of control, dread, catastrophic potential, fatal consequences, and inequitable distribution**
  - **"Unknown" risk: unobservable, unknown, new, and delayed in manifestation of harm.**

Summary

- Determination and communication of risk highly complex task
- Does not appear to be "one best" method for risk communication
- Perception critical to understanding impact of risk on population
- Errors common

Relevance to Drug Labeling

Challenges:

- **How to provide information that effectively communicates the nature, degree, and probability of the potential dangers from drugs in a concise, understandable, and accessible format**
- **Large degree of uncertainty**
- **Substantial dread over possible outcomes**

Labeling Products for Use in Pregnancy: Past, Present & New Directions

Sandra L. Kweder, M.D.

Acting Director

Office of Drug Evaluation IV

June 3, 1999

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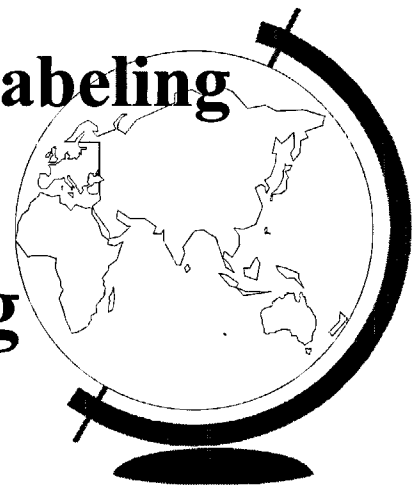
Topics to be Covered

- Introduction to Labeling
- Current regulations ("Categories")
  - Historical
  - FDA's 20 year experience
- Pregnancy Labeling Taskforce
  - Part 15 Hearing on pregnancy labeling
  - Other relevant activities
- Objectives for today's meeting



Glossary

Category System:

Present system of assigning pregnancy labeling letter categories to drugs and biologics, established by law in 1979

Label:

Official FDA approved package insert of a drug or biologic

Guidance Documents:

Official communication mode which FDA makes known its current thinking on a topic. Not binding

Part 15 Hearing:

Special public meeting that allows FDA to hear views of the public

I. Introduction to Labeling

- **FDA regulates drugs and biologic products**
  - **Investigation and development**
  - **Marketing approval or licensing**
- **FDA reviews data provided by sponsors**
  - **We do NOT conduct primary clinical research**
  - **Final vetting ensures quality and integrity**

Introduction to Labeling (continued)

- **Final Printed Label (FPL) represents exactly what is approved/licensed for marketing**
  - **Key data for medical professionals**
- **Commercial sponsor "owns" the label**
  - **Legal document**
  - **Intricate link to product promotion**
  - **Indications and Usage; Safety information**

Introduction to Labeling (continued)

- Once marketed, commercial sponsors
  - periodically report safety data to FDA
  - propose label changes to reflect new data
- FDA may acquire data that it believes warrants label change
  - Resource constraints make this uncommon

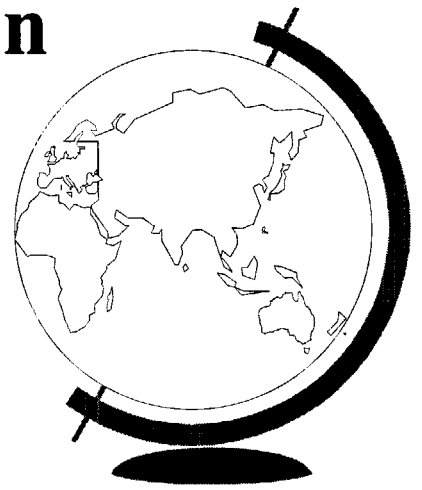
Introduction to Labeling

Important Corollaries

- **FDA does not regulate practice of medicine**
  - **Products are approved for treatment of conditions listed under "Indications"**
  - **Pregnancy section adds information**
  - **Similar to Geriatrics or Pediatrics**
- **Products are not "indicated" or "not indicated" in pregnancy per labeling (except Category X)**

II. Pregnancy Section of Label

- First addressed in regulations in 1979
- To assist physicians prescribing for pregnant women
  - Inadvertent/retrospective issues not addressed
- Simplified risk/benefit information

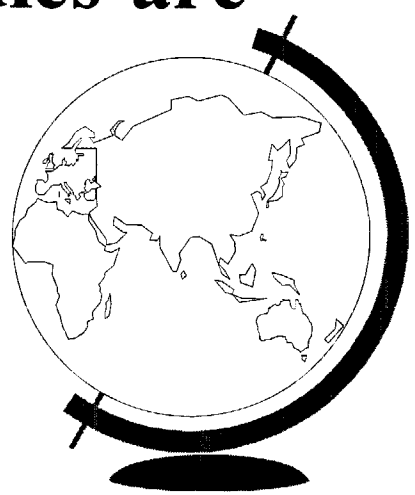


"Pregnancy Categories"

A Controlled studies in pregnancy- no risk

B Animal studies show no evidence of risk, or if positive, human data are reassuring (18%)

C Human data lacking; animal studies are positive OR not done (66%)



40% in Category C have no animal studies

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"Pregnancy Categories"

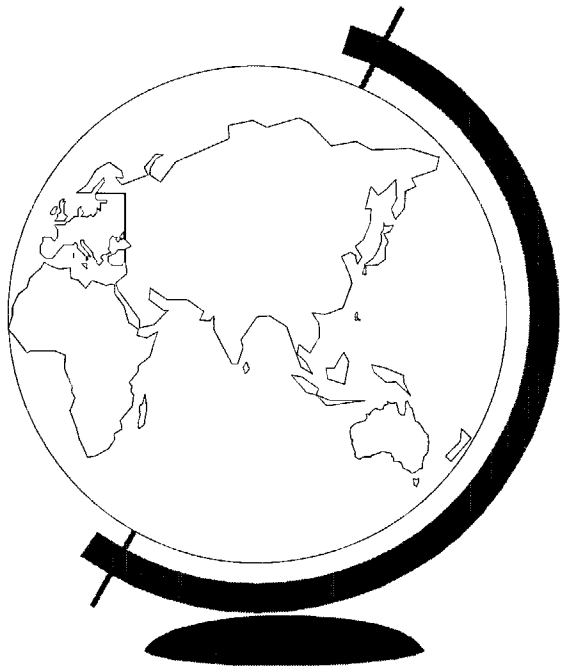
D **Human data suggest risk, but benefit may outweigh risk**

Most assigned "D" on basis of animal data

X **Animal or human data positive and potential benefit does not outweigh risk**

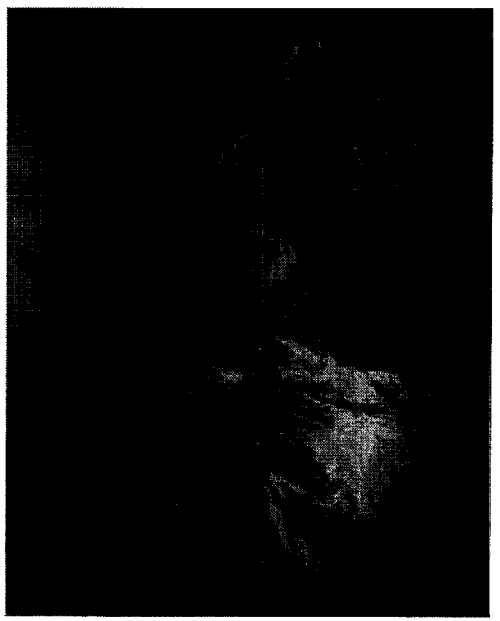
Experience Applying the Categories

- Most products have only animal data
  - Nature of animal studies
  - Positive findings (Category C)
  - Uncertain predictive value
- No requirements to update
- Perception of "warning" language as optimal
- Difficult to change a D to C, or C to A or B
- Criticism from external sources

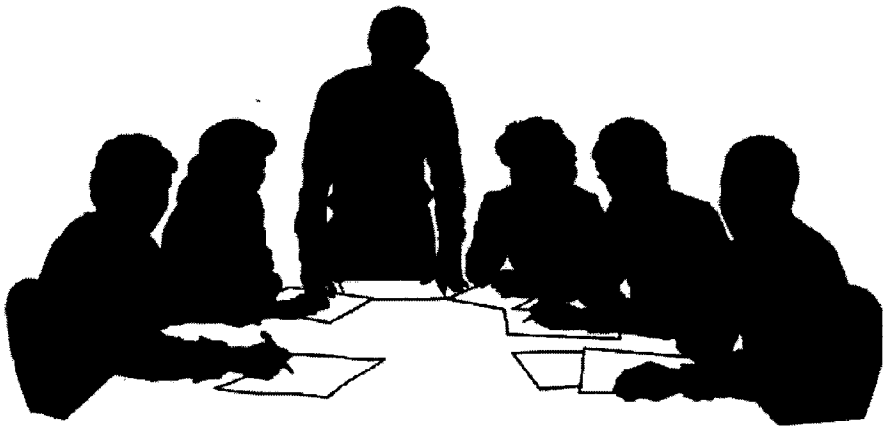


Greatest Challenge

Area of medicine where the most certainty is desired, but there is the least data.



III. Pregnancy Labeling Taskforce



Three Major Tasks

1. Examine current regulations
2. Recommend changes
3. Consider bigger picture of related needs

Task A: Examine Current Regulations: Part 15 Public Hearing

- **September, 1997: Public input on current system of pregnancy labeling**
  - ***Is it relied on by practicing providers?***
  - ***Is it useful? How?***
  - ***What is good and bad about it?***
  - ***If, overall, it is not informative or excessively problematic, what can be done to improve it?***

Public Hearing Participants

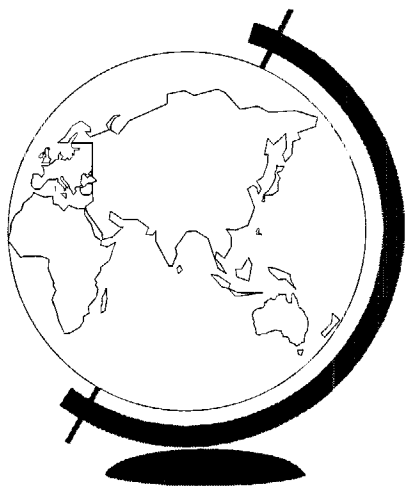
- Teratology Society
- Am Psychiatric Association
- Am College of Dermatology
- Am College of Obs & Gyns
- Pharmaceutical firms
- Org of Teratology Info Services (OTIS)
- Reproductive toxicologists
- Women's health groups
- Society OB Medicine

Part 15 Hearing Feedback on Current System

Positive Aspects

Criticisms

Recommendations



1. Current System: Positive Aspects

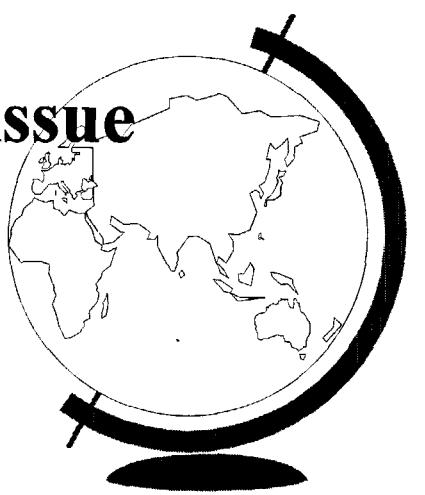
- **Information <u>is</u> relied upon by practitioners**
- **Simplicity is attractive**
  - **Condense down to single, ordered letters**
  - **Fit nicely in tables for pocket handbooks**
  - **Clinician doesn't have to interpret complex data**
  - **Familiar**

2. Current System: Criticisms

- **Overly simplistic (many examples)**
  - **A > B > C > D >>>>>>>>>>>>>>>>X**
  - **Appears risk graded**
  - **Fosters passive approach to complex clinical judgements**
  - **Group unlike risks together**

Criticisms (continued)

- **Heavy focus on teratogenesis**
  - **Often excludes other important fetal endpoints**
  - **Relevance of animal dosing not taken into account**
  - **Rarely addresses maternal toxicity issue (animal or human)**



Criticisms (continued)

- "Risk/benefit" considerations often incomplete
  - Individual maternal and fetal risks of no treatment
  - Context of population risks of adverse outcomes
  - Risks to fetus posed by maternal condition itself, independent of treatment

Criticisms (continued)

- **Do not facilitate "retrospective" considerations of risk**

  "*Deciding what to prescribe is not the same as deciding what to advise patients once exposure has occurred*"

  - **60% of pregnancies are unplanned**
  - **Lack of discrimination between suggested effects from preliminary animal data vs. known effects in humans (e.g. Category C)**

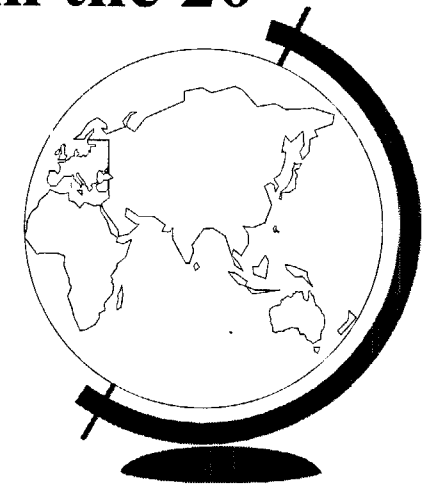
Criticisms (continued)

- **Data underlying categories not well described**
  - **Not informative, even to interested and educated readers**
  - **Human data rarely presented, even when in medical literature (credibility)**
  - **Rarely indicate whether there are degrees of risk posed by timing, extent of exposure, etc.**

Additional "Take Home Messages"

The current system is uninformative and needs to be replaced not revised

Risk communication has increased in sophistication and public attention in the 20 years since the regulations were promulgated



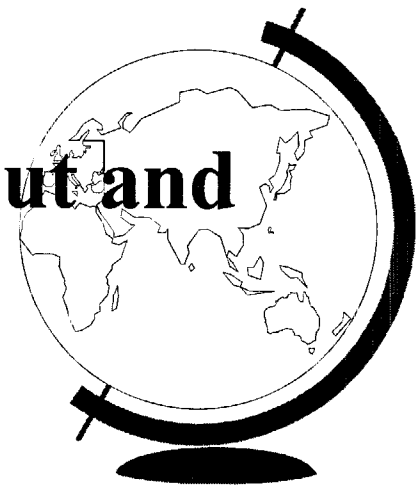
We must do better

3. Current System: Part 15 Recommendations

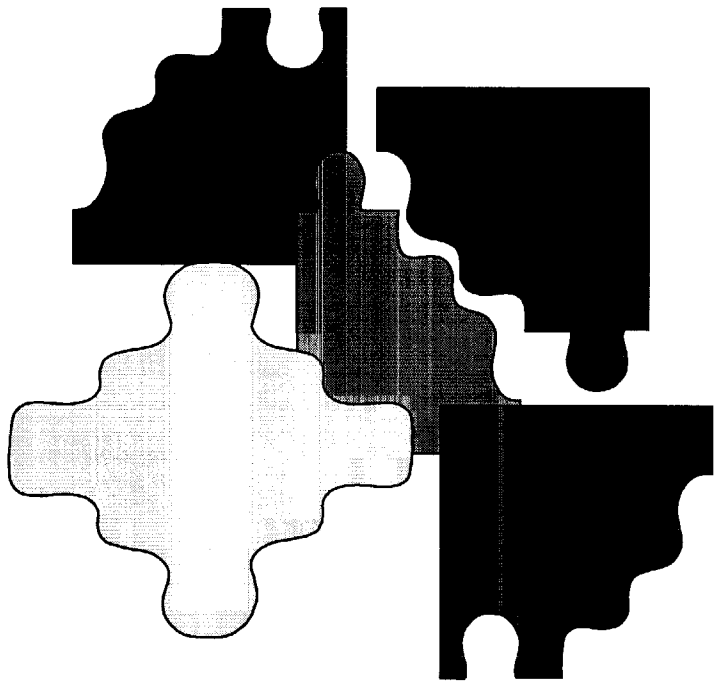
- Replace categories with narrative
- Consider varied readership needs
- Distinguish clinical advice from risk information
  - Important distinction
  - Advice in labels carries different weight
- Provide underlying data
- We must do a better job with language

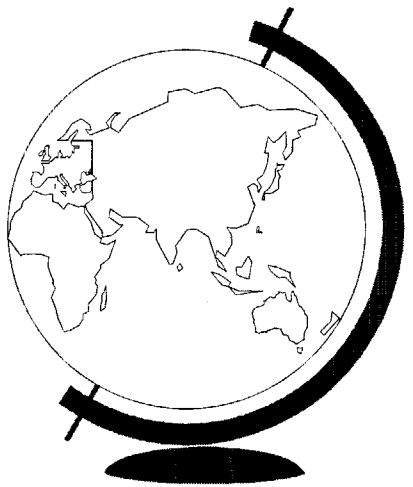
Task B: Make Recommendations for Changes in Labeling

- Began process with Part 15 input and our own experience
- Have developed draft model that incorporates all of this
- Will present model for further input and direction later today



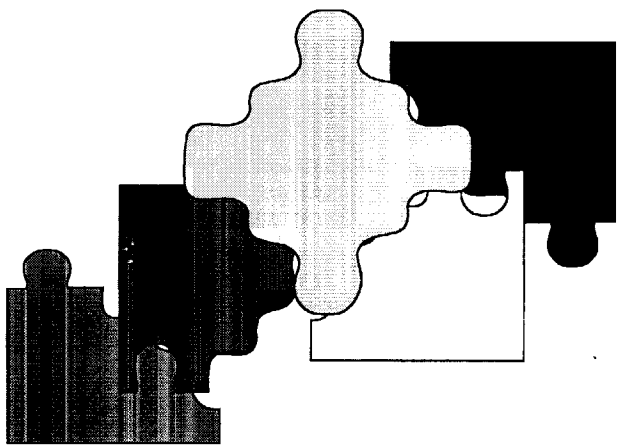
Task C: Consider Broader Needs of Pregnancy Labeling

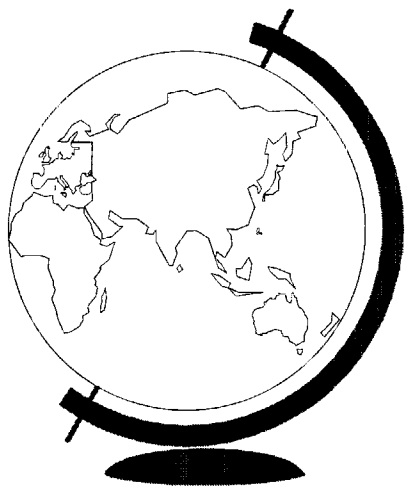




Other Taskforce Activities

- Many pieces of a complex puzzle
  - FDA Expertise
  - Data: collection; generation; quality
- Science must drive process





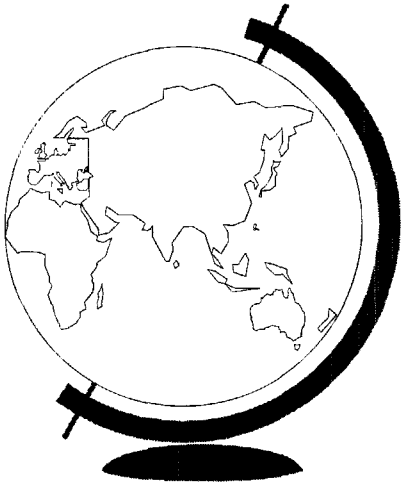
1. FDA Expertise

- **Clinical Expertise**
  - **Reviewer's Guidance Document: Human Pregnancy Outcomes (draft)**
  - **Training for FDA clinical reviewers**
- **Preclinical expertise**
  - **Integrated approach to review of repro tox data**
  - **Dr. Morse to give overview**

2. Improving Data

- <u>Collection</u> - New safety reporting regulation under International Conference on Harmonization (ICH)
  - Pregnant women as special population of interest

- <u>Generation and Quality</u> - Industry Guidance: Establishing Pregnancy Registries
  - First of its kind; no other source
  - Sets standard for data quality



3. Other Possibilities

- **Simplification of pregnancy registry development?**
- **Better use of FDA web site to provide more comprehensive information about pregnancy risks?**
- **Partnerships within and outside government?**

IV. Objectives for Today

1. **Seek your input and general guidance regarding our progress to date with development of a new label model***
   - **Not to add to Part 15 hearing database**
   - **Are we going in the right direction?**
   - **Your suggestions; practical aspects on format and content**

Concept Paper

Objectives (continued)

2. **Seek your input on how best to use language to communicate risk information and management advice**
   - **Challenging**
   - **Critical aspect of labeling given little attention**
   - **Broad spectrum of label user needs and "access" to information**

Helpful Hints

- If this seems difficult, it is because it is
- We seek general guidance
- Consensus helps, but is not a requirement.
- Where you do not reach consensus, it is important to understand why
- FDA's responsibility is to write the new regulation, not the Committee