National Institute of Neurological Disorders and Stroke

Using preclinical data to inform human trials

The safety perspective

Dietrich Haubenberger

Clinical Trials Unit
NINDS Intramural Research Program

Disclosures

- Nothing to disclose

Why non-clinical safety testing?

- As often – it started with a disaster.

Figure 1. An original 1-gallon bottle of Elixir Sulfanilamide.

The 1937 ***Elixir Sulfanilamide*** Disaster

- Formulated and marketed as antimicrobial drug by a small pharmaceutical company, using *diethylene glycol* as solvent, blended with raspberry flavor
- First reports of DEG‘s nephrotoxicity in the 1930s, but not known to the company‘s chemist.
- No required pre-clinical testing at that time
- Over 100 people in 15 states died as a consequence of exposure

JAMA, Sept. 3, 1938

During the months of September and October 1937 at least seventy-six [1] human beings in various localities died as a result of poisoning by Elixir of Sulfanilamide-Massengill.[2] By analysis,[3] the A. M. A. Chemical Laboratory found this preparation to be essentially a 10 per cent solution of sulfanilamide in about 72 per cent diethylene glycol, together with some coloring and flavoring agents. There were no contaminants such as mercury, the effects of which might have resembled the clinical symptoms produced by the elixir. Apparently the makers of this product were unaware of its possible toxicity and distributed it freely without having tested

amide by mouth, 0.2 Gm. per kilogram three times a day. The kidney is essentially normal so far as hematoxylin and eosin staining is a criterion. As a matter

4. Careful and frequent observations of the animals are necessary, so that a composite picture of the clinical course is available. The data on many drugs are very deficient in this respect.

5. Careful pathologic examination of the tissues with appropriate stains is necessary.

6. Effects of the drug on animals with experimental lesions of various important excretory or detoxifying organs, especially of the kidneys and liver, should be studied.

7. The rate of absorption and elimination of the drug, its path and manner of excretion, and the concentration levels in the blood and tissues at varying times after administration must be determined.

8. The possible influence of the presence of certain foodstuffs or drugs should be noted. For example, magnesium sulfate should not be administered to a patient undergoing treatment with sulfanilamide.

9. Careful examinations for idiosyncrasies or untoward reactions should be made.

It is recognized that some will consider these safeguards to be too rigid and that they may simply be considered an ideal. It can correctly be charged, in fact, that some of the pharmacopeial drugs have not been studied along such lines. Admitting this, it is nevertheless regrettably true that many human lives have been sacrificed by the failure to meet the standards of these preliminary tests and that many more lives will be sacrificed if such standards are not put into effect

-> Food, Drug and Cosmetic Act of 1938

Introducing the mandate of pre-clinical safety testing and FDA‘s authority to review

IND: FDA Form 1571

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12. **CONTENTS OF APPLICATION**

This application contains the following items: *(Check all that apply)*

- ☐ 1. Form FDA 1571 *[21 CFR 312.23(a)(1)]*
- ☐ 2. Table of Contents *[21 CFR 312.23(a)(2)]*
- ☐ 3. Introductory statement *[21 CFR 312.23(a)(3)]*
- ☐ 4. General Investigational plan *[21 CFR 312.23(a)(3)]*
- ☐ 5. Investigator's brochure *[21 CFR 312.23(a)(5)]*
- ☐ 6. Protocol(s) *[21 CFR 312.23(a)(6)]*
  - ☐ a. Study protocol(s) *[21 CFR 312.23(a)(6)]*
  - ☐ b. Investigator data *[21 CFR 312.23(a)(6)(iii)(b)]* or completed Form(s) FDA 1572
  - ☐ c. Facilities data *[21 CFR 312.23(a)(6)(iii)(b)]* or completed Form(s) FDA 1572
  - ☐ d. Institutional Review Board data *[21 CFR 312.23(a)(6)(iii)(b)]* or completed Form(s) FDA 1572
- ☐ 7. Chemistry, manufacturing, and control data *[21 CFR 312.23(a)(7)]*
  - ☐ Environmental assessment or claim for exclusion *[21 CFR 312.23(a)(7)(iv)(e)]*
- ☐ 8. Pharmacology and toxicology data *[21 CFR 312.23(a)(8)]*
- ☐ 9. Previous human experience *[21 CFR 312.23(a)(9)]*
- ☐ 10. Additional information *[21 CFR 312.23(a)(10)]*

What should I know about my drug:

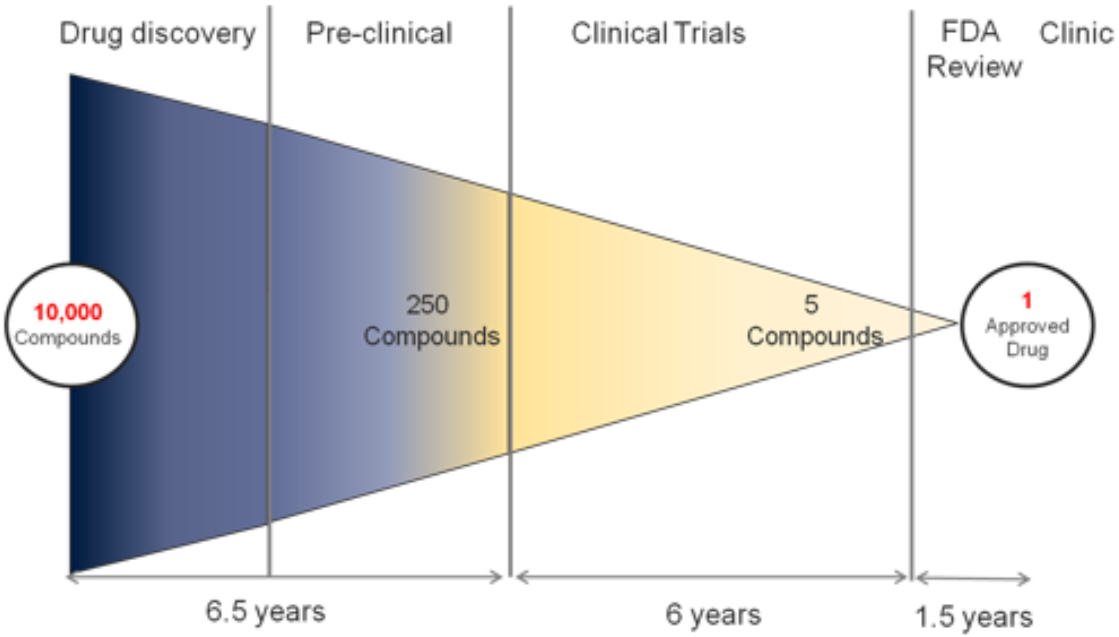
- CMC: Chemistry, Manufacturing, and Control
  - A drug product is composed of
    - Drug substance (API)
    - Excipients
    - Impurities
    - Container
  - Data on ***Identity***, ***Strength***, ***Purity***, and ***Quality*** of drug
  - Additional Information:
    - Manufacturer, Storage, Stability, etc.

What should I know about my drug:

- Pharmacology & Toxicology
  - Pharmacological effect and mechanism in animals
  - **A**bsorption, **D**istribution, **M**etabolism, **E**xcretion
  - Toxicology (acute/subacute/chronic)
  - Safety pharmacology per systems:
    - Cardiovascular, CNS, pulmonary, etc.
  - Special toxicology tests related to mode of administration
    - e.g., dermal toxicology
  - Genetic toxicology (often in vitro)

Pre-Clinical and beyond

non-clinical development



CMC for Phase 1
Pharmacology
Acute Toxicology

CMC: Alternate formulations, lots, etc.
Chronic Toxicology
Pharmacology of alternate formulations
Reproductive toxicology
Addtl. safety pharmacology
...

Why „post-clinical“ matters:

News Room

(/news/)

Investor Announcement, Clinical Trials (/news/category/Investor Announcement, Clinical Trials)

FDA End of Phase 2 Status Update

FEBRUARY 13, 2015

MELBOURNE, Friday, February 13th, 2015: Prana Biotechnology (ASX: PBT/NASDAQ:PRAN) has today announced the status of its End of Phase 2 discussions with the US Food and Drug Administration (FDA).

At the End of Phase 2 meeting for its Reach2HD clinical trial, and following subsequent correspondence, Prana presented its plans and information package to initiate a Phase 3 trial in Huntington Disease.

Upon review, the FDA has issued a Partial Clinical Hold letter based on non-clinical (animal) findings which currently limits the dose of PBT2 that can be given to patients with Huntington disease. Under Prana's open Investigational New Drug application, Prana is able to continue clinical trials but at a dose that is not considered clinically relevant by the Company.

The FDA has provided Prana with options to remove the Partial Clinical Hold. To support moving forward with clinical trials of PBT2 at a clinically relevant dosage in humans, Prana would conduct additional animal neurotoxicity studies or identify a strategy for safely using a clinically relevant dosage in humans in the planned Phase 3 trial in Huntington disease. The FDA has not raised any concerns about PBT2 safety data in human trials conducted to date.

The company is continuing discussions with the FDA in addressing these issues.

Why do we need non-clinical data?

- Is it safe to put drug candidate into humans?
- What is an safe dose for human clinical trials?
  - Starting dose
  - End dose
- What are dose-limiting toxicities?
  - Therefore: what should be monitored in clinical trials?
- What could be potential toxicities that cannot be identified in clinical trials?

Non-Clinical Safety for IND – the regulatory view

- Off the shelf FDA-approved drug:
  - Assume that the drug product meets animal toxicology standards for maximum approved dose and length of exposure per label.
  - If higher dose, longer duration, different formulation, or different route of administration is planned than what is approved in the label, additional non-clinical studies might be necessary.
  - Different patient population: different risk/benefit ratio and propensity for safety events
  - If combination of more than one approved drugs are given: evidence on potential interactions might be necessary
  - CMC: if used exactly as marketed: label sufficient

Non-Clinical Safety for IND – the regulatory view

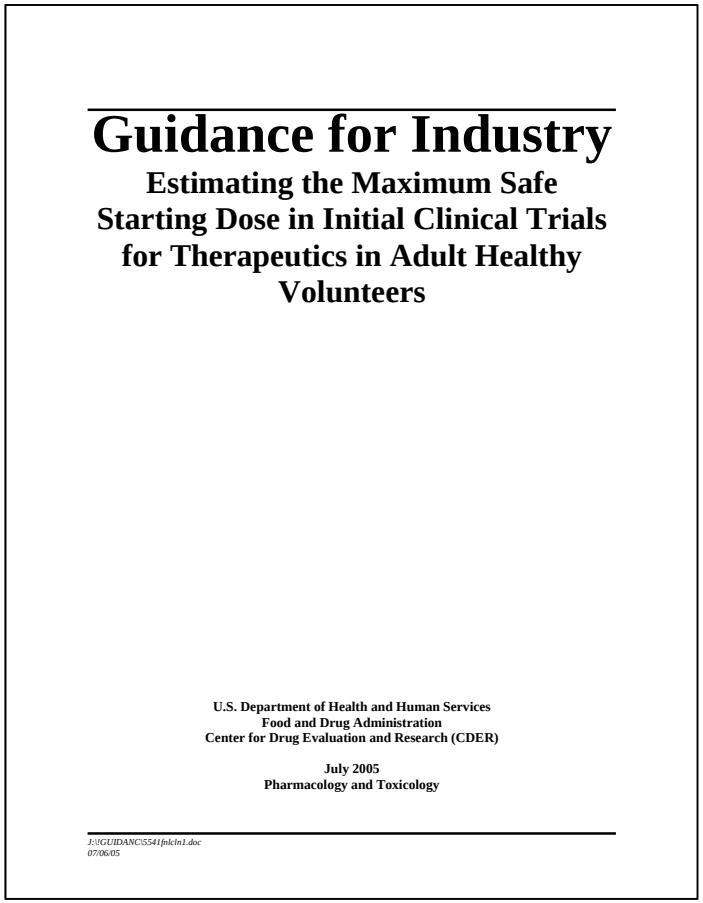
- Investigational drug supplied by another sponsor
  - Obtain a letter allowing reference to another IND.
  - Must support the planned dose and route of administration.
- Dietary supplement
  - Typically not an approved drug without approved safe dose.
  - No non-clinical toxicology can be assumed.
  - If used as drug in a clinical trial: no difference in requirements to “regular” pharmaceuticals
- Investigational drug you make yourself
  - Generally must provide full set of non-clinical pharmacology and toxicology data using you own product.

How to pick a starting dose

- You might not need additional non-clinical information if …
  - There is a FDA-approved dosing range is available (see label)
  - Data in the literature, or any other study that is available to you supports dose range, duration of exposure, and mode of administration
    - Animal studies
    - Human experience
    - *CAVEAT*: Reports/publications should be specific regarding safety information
      - N of exposed animals, humans
      - Doses, duration of exposure, mode of administration
      - Ideally: obtain data sets!

From animal to human …

- If no previous human experience, estimate safe starting dose using 5 steps:



Guidance for Industry

Estimating the Maximum Safe Starting Dose in Initial Clinical Trials for Therapeutics in Adult Healthy Volunteers

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

July 2005
Pharmacology and Toxicology

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07/06/05

http://www.fda.gov/downloads/Drugs/Guidances/UCM078932.pdf

Step 1: NOAEL

- *No Observed Adverse Effect Level*
- Definition
  - "The highest dose level that does not produce a significant increase in adverse effects in comparison to the control group."
  - AEs that are *biologically significant* should be considered for determination of NOAEL
- Benchmark for safety when derived from *appropriate* animal studies
- Can serve as the starting point for determining a reasonably safe starting dose of a new therapeutic in humans

Step 2: Human Equivalent Dose (HED)

- Toxic endpoints (e.g., MTD) are assumed to scale well between species when normalized to body surface area

- HED can be also calculated using body surface area (mg/m²) converted into mg/kg using standardized species-specific scaling factors

Table 1: Conversion of Animal Doses to Human Equivalent Doses Based on Body Surface Area

Species	To Convert Animal Dose in mg/kg to Dose in mg/m², Multiply by k_m	To Convert Animal Dose in mg/kg to HED[a] in mg/kg, Either:	
		Divide Animal Dose By	Multiply Animal Dose By
Human	37	---	---
Child (20 kg)[b]	25	---	---
Mouse	3	12.3	0.08
Hamster	5	7.4	0.13
Rat	6	6.2	0.16
Ferret	7	5.3	0.19
Guinea pig	8	4.6	0.22
Rabbit	12	3.1	0.32
Dog	20	1.8	0.54
Primates:			
Monkeys[c]	12	3.1	0.32
Marmoset	6	6.2	0.16
Squirrel monkey	7	5.3	0.19
Baboon	20	1.8	0.54
Micro-pig	27	1.4	0.73
Mini-pig	35	1.1	0.95

[a] Assumes 60 kg human. For species not listed or for weights outside the standard ranges, HED can be calculated from the following formula:

HED = animal dose in mg/kg x (animal weight in kg/human weight in kg)$^{0.33}$.

[b] This k_m value is provided for reference only since healthy children will rarely be volunteers for phase 1 trials.

[c] For example, cynomolgus, rhesus, and stumptail.

http://www.fda.gov/downloads/Drugs/Guidances/UCM078932.pdf

Step 3: Species selection

- If more > 1 species were studied, which HED to pick?
- Factors to consider
  - Differences in absorption, distribution, metabolism, excretion (ADME)
  - Animal model most predictive of human toxicity
  - For Biologics: does model express relevant receptors/epitopes?
- In absence of data on species relevance: choose species with *lowest* HED

Step 4: Safety Factor

- Goal: providing a margin of safety for protection of human subjects receiving the initial clinical dose
- Allows for variability in extrapolating from animal tox studies resulting
- Default safety factor: **10**
  - Practically: divide appropriate HED by 10
  - Reasons for *increasing* the safety factor: steep dose response curve, severe/irreversible toxicities, non-monitorable toxicities, toxicities without premonitory signs, animal model with limited utility, etc.
  - Reasons for *decreasing* the safety factor: therapeutic is member of well-characterized class, easily monitorable toxicities, etc.

Step 5: Pharmacologically active dose

- Definition:
  - *The PAD is the lowest dose tested in an animal species with the intended pharmacological activity*
- Typically derived from appropriate pharmacodynamic models
- Once the MRSD is determined, compare it to the HED of the PAD.
- If needed, adjust MRSD if *pharmacologic* HED is lower
- PAD might also be a more sensitive indicator of potential toxicity (e.g., vasodilators, anticoagulants, etc.)

Example

- Non-clinical toxicology studies determined a NOAEL of 15 mg/kg in dogs, 50 mg/kg in rats, and 50 mg/kg in monkeys.

- Conversion to HED
  - Division method:
    15 mg/kg (dog) / 1.8 = 8 mg/kg
    50 mg/kg (rat) / 6.2 = 8 mg/kg
    50 mg/kg (monkey) / 3.1 = 16 mg/kg

- Appropriate HED: 8 mg/kg

- Safety factor 10:
  - ***Max. recommended starting dose: 0.8 mg/kg***

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Limitations of the NOAEL/MRSD approach

- Algorithm can be too „mechanical“
- Toxicity focused, less pharmacology-based
- Does not address dose escalation
- Does not apply to locally administered drugs
- Not fully applicable to biologics
  - Often no real NOAEL measureable
  - Alternative approach using Minimum Anticipated Biological Effect Level (MABEL)

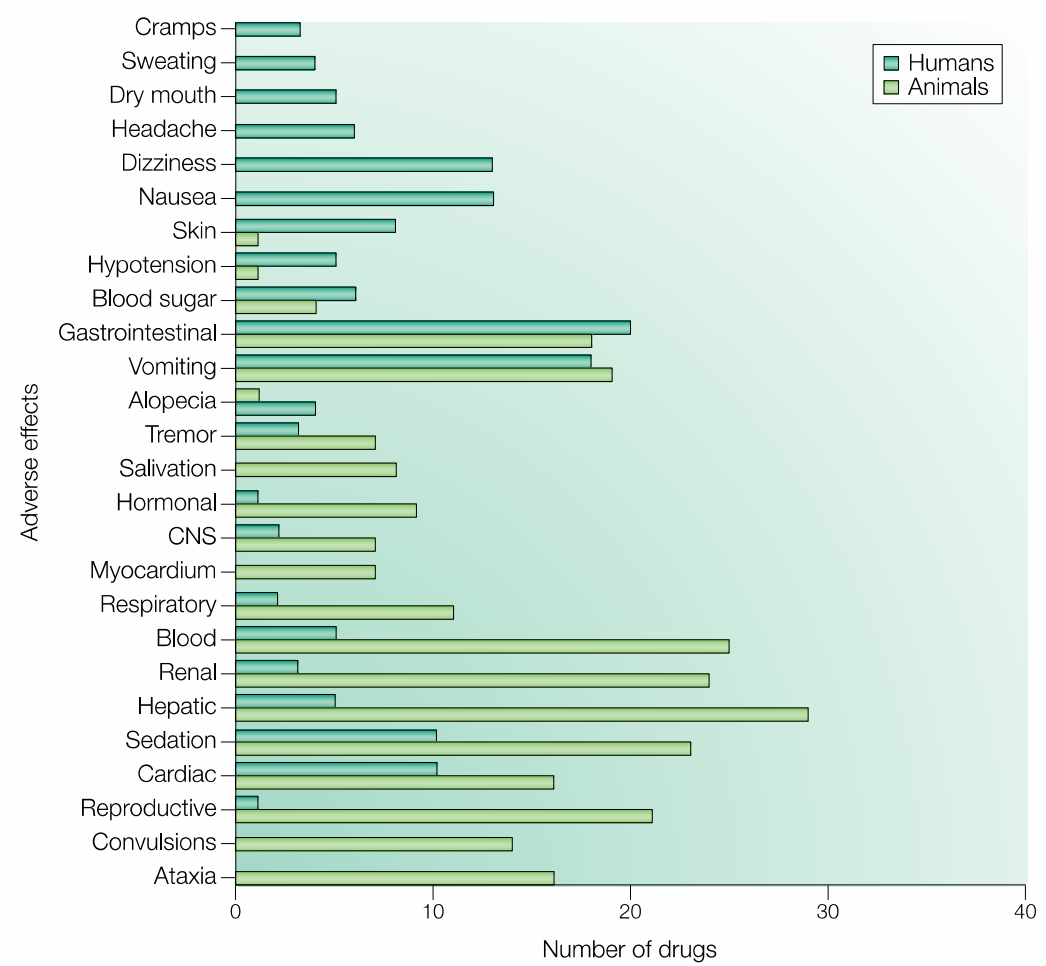
Clinical safety monitoring

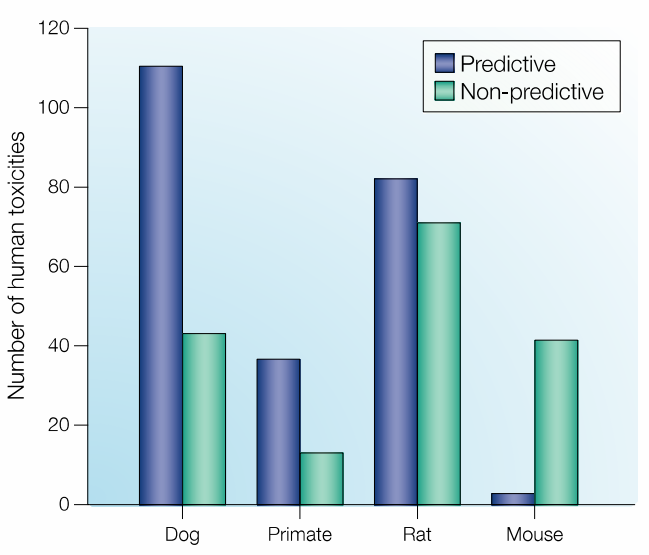
- Any safety signal observed in non-clinical studies should be monitored for clinically

- Be vigilent about the unknown!
  - Review from 150 compounds:
    - positive concordance rate (sensitivity) between observed animal and human toxicities is 70%
    - Therefore, 30% of human toxicities are not predicted.

Olson H, et al. Concordance of the toxicity of pharmaceuticals in humans and in animals. Regul Toxicol Pharmacol. 2000 Aug;32(1):56-67.

Toxicity prediction





Greaves P, Williams A, Eve M. First dose of potential new medicines to humans: how animals help. Nat Rev Drug Discov. 2004 Mar;3(3):226-36.

Summary

- If human data is lacking, non-clinical safety data crucial for
  - Dose selection
  - Safety monitoring
  - Meeting regulatory requirements
- Human data may be more valuable than non-clinical data
- Non-clinical experiments are usually expensive
- Usually no need to worry if compound is FDA approved and used within the limitations of the label

Thank you

clinicaltrials@ninds.nih.gov