Regulation of Impurities in Drug Substances and Products: Risk Assessment

Impurities in Drugs:
Monitoring, Safety and Regulation
The Israel Chapter of PDA

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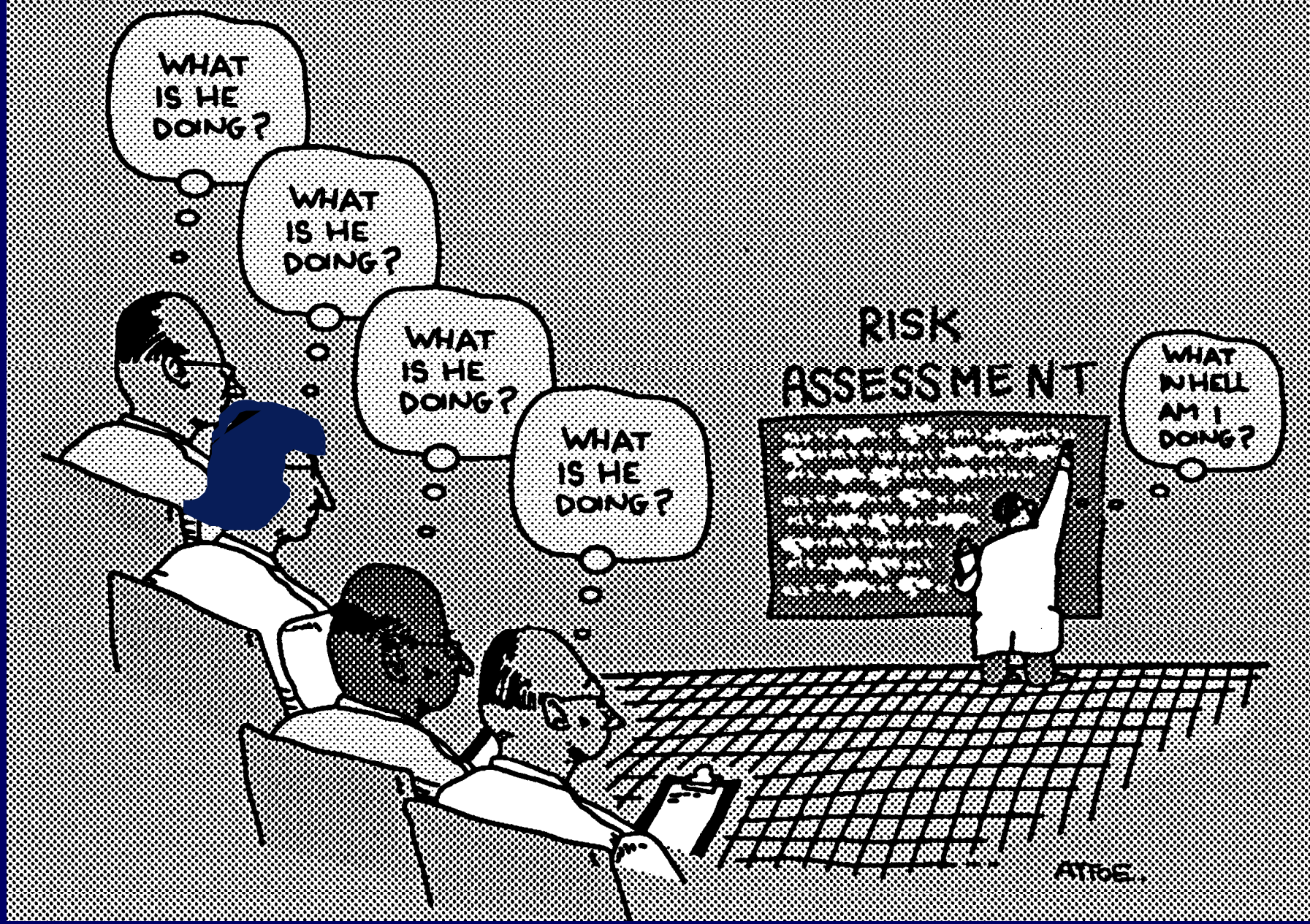
Food and Drug Administration


WHAT IS HE DOING?
WHAT IS HE DOING?
WHAT IS HE DOING?
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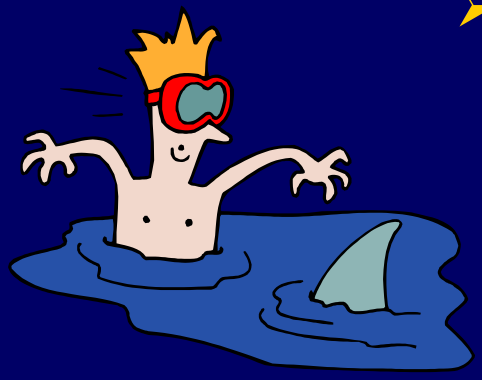
RISK ASSESSMENT
WHAT IN HELL AM I DOING?

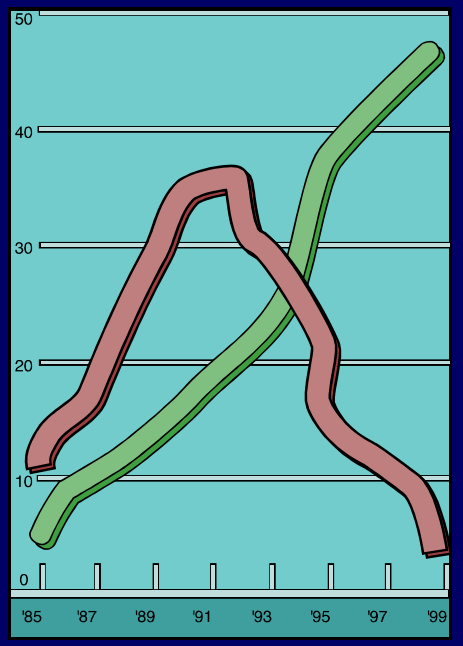
Steps in any Risk Assessment



- Hazard Identification
  - does the impurity have the inherent capacity to induce an adverse health effect at any dose?
  - e.g.. is it carcinogenic, teratogenic neurotoxic etc?

Steps in any Risk Assessment

- Dose-Response Assessment
  - how does the frequency of the adverse event change with exposure?



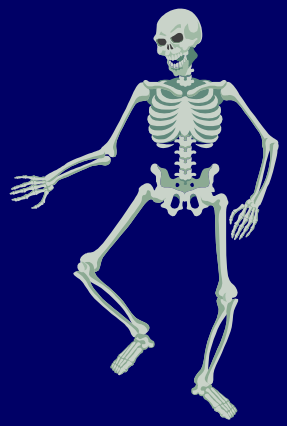
Steps in any Risk Assessment

- Exposure Assessment

  - how much of the material is the person exposed to; much easier for drugs than for environmental or occupational exposures.

Steps in any Risk Assessment

- Risk Characterization
  - how many new cases of the adverse health effect will arise from the expected exposures?



Relevant guidelines, publications and promises on impurities

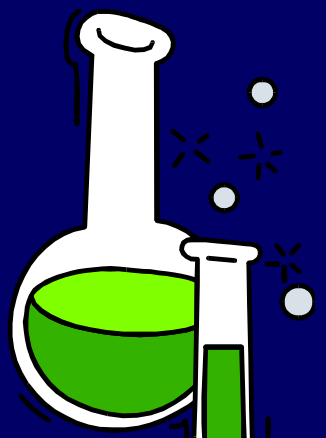
- ICH Q3A(R) Impurities in New Drug Substances, 2002
- ICH Q3B(R) Impurities in New Drug Products, 2003
- ICH Q3C Impurities: Guideline for Residual Solvents, 1997
- EMEA, Guideline on the Limits of Genotoxic Impurities, 2006
- EMEA, Questions and Answers on the CHMP Guideline on the limits of genotoxic impurities, 2008
- Establishment of Allowable Concentrations of Genotoxic Impurities in Drug Substance and Product, 2005, PhRMA position paper.
- FDA draft: Genotoxic and Carcinogenic Impurities in Drug Substances and Products: Recommended Approaches and Acceptable Limits

Impurities in New Drug Substances (Q3A)

- **Organic**-usually a by-product of synthesis or storage of drug substance,
- **Inorganic** from manufacturing process,
- **Residual solvents** from manufacturing process,
- **Extraneous contaminants** such as pesticides, other drugs, etc. GMP issue!

Q3A(R), Impurities in New Drug Substances

Maximum Daily Dose	Reporting Threshold	Identification Threshold	Qualification Threshold
≤ 2g/day	0.05%	0.1% or 1.0 mg/day intake (whichever is lower)	0.15% or 1.0 mg/day (whichever is lower)
> 2 g/day	0.03%	0.05%	0.05%



Tests for qualifying impurities in drug substance

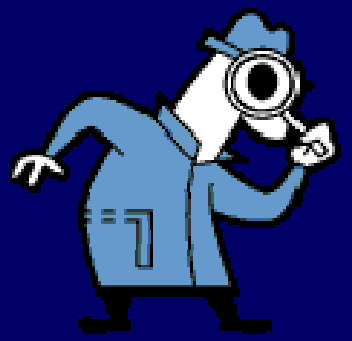
- Genotoxicity studies (point mutation, chromosomal aberration-- Ames assay, *in vitro* cytogenetics or mouse lymphoma assay)
- General toxicity studies (one species usually 14 to 90 days)
- Other specific toxicity endpoints as appropriate

Qualification of impurities in a new drug substance

- "Such studies can be conducted on the new drug substance containing the impurities to be controlled, although studies using isolated impurities can sometimes be appropriate."
- Studies of the drug substance containing the impurity preclude traditional risk assessment.

Are qualification assays sufficiently sensitive to detect an impurity when the test employs the new drug substance (DS) containing the impurity?

- Typical positive controls and doses tested in the Ames assay
  - 2-aminoanthracene 1.0 µg/plate
  - sodium azide 1.0 µg/plate
  - 2-nitrofluorene 10 µg/plate
  - 9-aminoacridine 75 µg/plate
  - methyl methanesulfonate 1,000 µg/plate



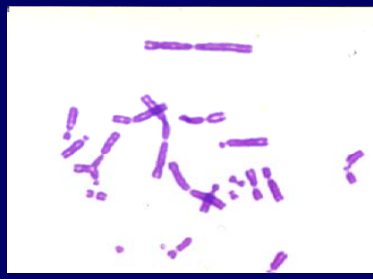
Are qualification assays sufficiently sensitive to detect an impurity when the test employs the new drug substance (DS) containing the impurity?

- Assuming impurity present at 0.15%, (minimum for qualification) and drug is nontoxic, DS tested to 5 mg/plate, 7.5 µg/plate of impurity:
  - 2-aminoanthracene **detected**
  - sodium azide **detected**
  - 2-nitrofluorene **probably detected**
  - 9-aminoacridine **not detected**
  - methyl methanesulfonate **not detected**

- However, toxicity of DS would limit detection of impurity

Are qualification assays sufficiently sensitive to detect an impurity when the test employs the new drug substance (DS) containing the impurity?

- Typical positive controls and doses tested in an *in vitro* chromosomal aberration assay:
  - mitomycin C, 0.1 µg/ml
  - cyclophosphamide 10 µg/ml



- If non toxic, 5 mg/ml of DS or 7.5 µg/ml of impurity tested
- Both materials would detected if parent drug is nontoxic.
- Toxicity of DS would limit detection of impurity

Are qualification assays sufficiently sensitive to detect an impurity when the test employs the new drug substance (DS) containing the impurity?

- In general, endpoints examined in animal toxicology studies, especially of short duration (2 - 4 weeks) are insensitive.
- If the DS was nontoxic and tested up to 2 g/kg, 3 mg/kg of the contaminant would be tested. Even generally toxic chemicals such as cyclophosphamide and dimethylnitrosamine would probably not be detected.
- Toxicity of the DS further limits detectability of impurity.

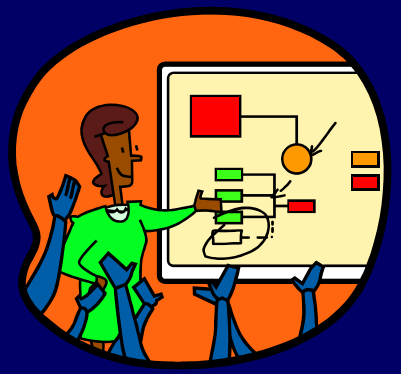
Q3B(R) Impurities in new drug products (DP)

- Guideline only addresses impurities in new DP classified as
  - degradation products of the DS
  - reaction products of the DS with an excipient and/or immediate container closure system.

Q3B(R) Impurities in new drug products-
Thresholds for Degradation Products in New Drug Products

Reporting Threshold

Maximum Daily Dose	Threshold
≤ 1 g	0.1%
> 1g	0.05%



Q3B(R) Impurities in new drug products

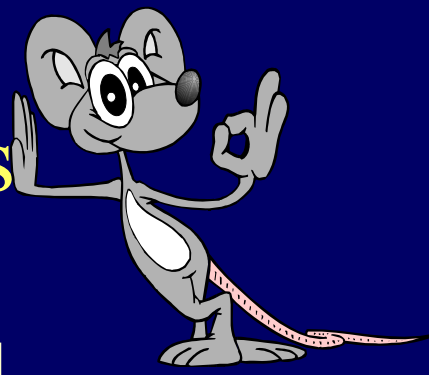
Thresholds for Degradation Products in New Drug Products

Identification Threshold

Maximum Daily Dose	Threshold
< 1 mg	1.0% or 5 µg TDI, whichever is lower
1 mg - 10 mg	0.5% or 20 µg TDI, whichever is lower
> 10 mg - 2 g	0.2% or 2 mg TDI, whichever is lower
> 2 g	0.1%

Q3B(R) Impurities in new drug products

Thresholds for Degradation Products in New Drug Products



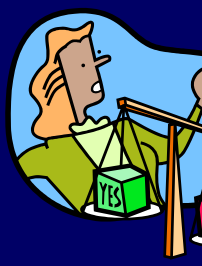
Qualification Thresholds

Maximum Daily Dose	Threshold
< 10 mg	1.0% or 50 µg TDI, whichever is lower
10 mg - 100 mg	0.5% or 200 µg TDI, whichever is lowe
> 100 mg - 2 g	0.2% or 3 mg TDI, whichever is lower
> 2 g	0.15%

Q3B(R) Impurities in new drug products (DP): Qualification

- The level of any degradation product present in a new DP that has been adequately tested in safety and/or clinical studies would be considered qualified.
- Degradation products that are also significant metabolites present in animal and/or human studies are qualified.

Q3B(R) Impurities in new drug products (DP): Qualification, continued



- "Degradation products could be considered qualified at levels higher than those administered in safety studies based on a comparison between actual doses given in safety studies and the intended dose of the new DP." --total dose of impurity given in safety study is high compared to total dose given clinically.

Q3B(R) Impurities in new drug products (DP): Qualification, continued

- Tests for qualifying a degradation product in a DP are the same as those for qualifying impurities in drug substances:
  - bacterial mutation assay
  - *in vitro* assay for chromosomal aberrations
  - toxicology study in one species-- 14 to 90 day duration

Detection of genotoxic impurities

- ICH Q3A(R2) and ICH Q3B(R2): identification of an impurity when it achieves a level of 0.1 percent or 1 mg per day (whichever is lower) at a daily dose of less than or equal to 2 grams for the drug substance or 0.15 percent to 1 percent for the drug product.

- A genotoxic or carcinogenic impurity could be present in a drug product at a level resulting in exposures up to 3,000 µg per day without needing identification!

Q3C, Impurities: Guideline for Residual Solvents

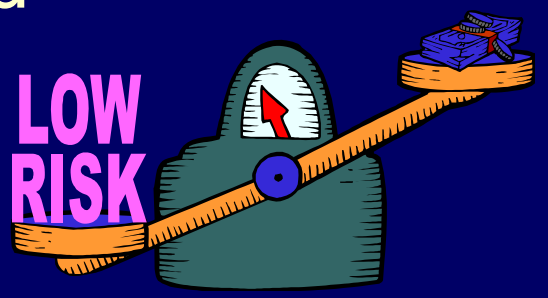
- Q3C is the only guideline that uses traditional risk assessments methods
- Risk assessment methods can be applied to solvents because these chemicals have been tested as neat materials.
- Solvents are grouped by class depending on the hazards associated with exposure.

Q3C, Impurities: Guideline for Residual Solvents, Classification

- Class 1: known or suspected human carcinogens or environmental hazards, e.g. benzene, carbon tetrachloride
- Class 2: non-genotoxic animal carcinogens or inducers of irreversible toxicity such as neurotoxicity or teratogenicity e.g. acetonitrile, dichloromethane
- Class 3: low toxic potential, ethanol, DMSO

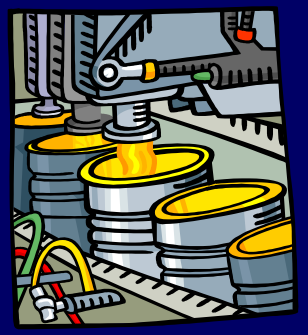
Risk assessment for effects that are thought to have thresholds

- "…..there is some dose below which the probability of an individual responding is zero". *Casarett and Doull.*
- Thresholds have traditionally been assumed for all toxicities with the exception of mutagenicity and carcinogenicity.



Q3C, Impurities: Guideline for Residual Solvents, Risk Assessment fo Class 2 Solvents, Calculating PDEs

$$PDE = \frac{NOEL \times Weight\ Adjustment}{F1 \times F2 \times F3 \times F4 \times F5}$$



F1 = extrapolation between species

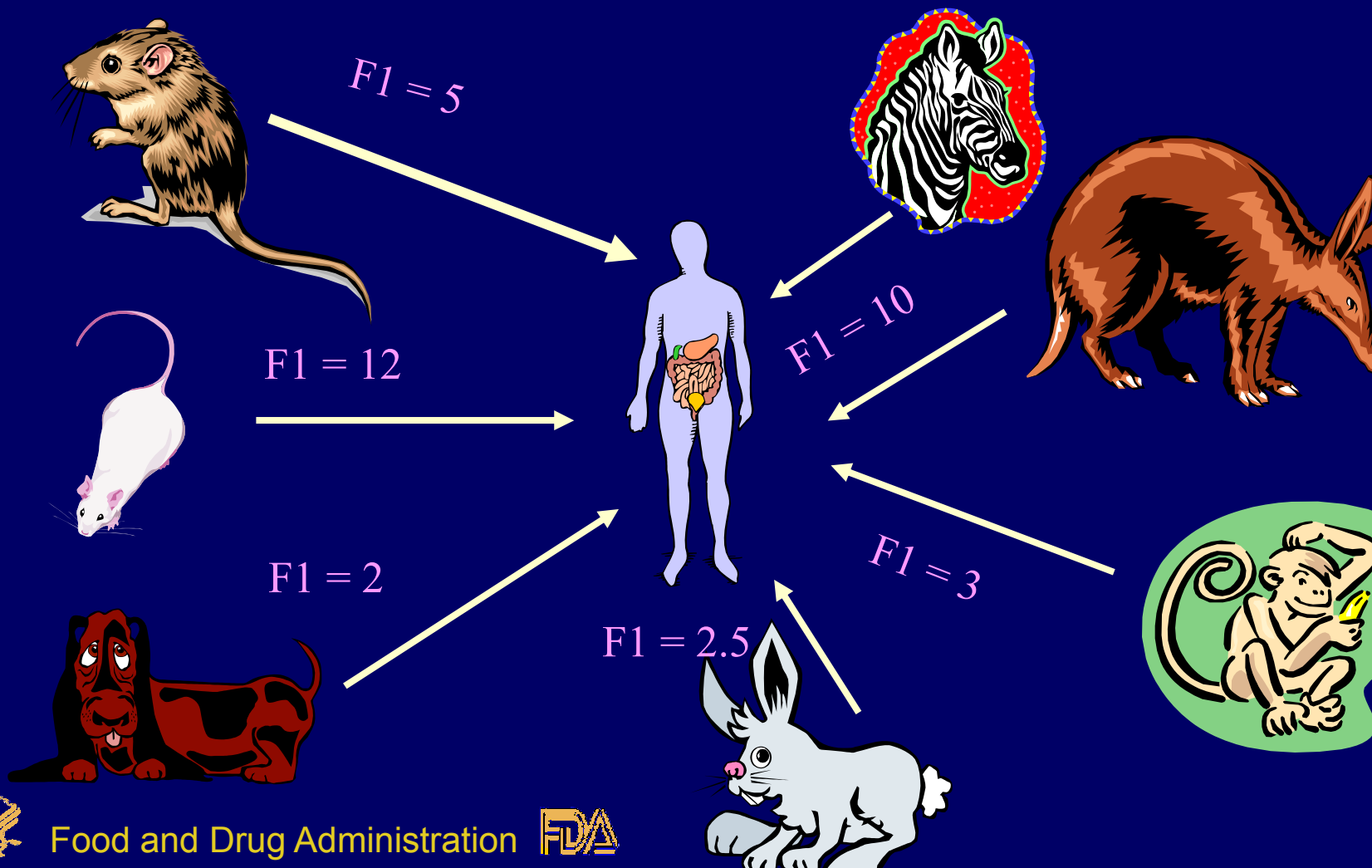
F2 = variability between individuals

F3 = extrapolation from short to long term studies

F4 = for severe toxicities

F5 = lack of NOEL

Q3C, Impurities: Guideline for Residual Solvents, Risk Assessment for Class 2 Solvents, F1: extrapolation between species: Phylogenetic kinship? No, surface area!



Q3C, Impurities: Guideline for Residual Solvents, Risk Assessment fo Class 2 Solvents

F2 = variability between people

F2 = 10

Q3C, Impurities: Guideline for Residual Solvents, Risk Assessment fo Class 2 Solvents

F3 = accounts for toxicity studies of short-term exposure

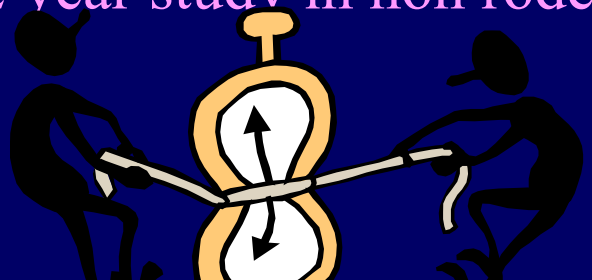
F3 = 1 for studies that last at least one-half lifetime (1 year for rodents or rabbits; 7 years for cats, dogs and monkeys)

F3 = 1 for reproductive studies covering all of organogenesis

F3 = 2 for 6-month study in rodents or 3.5 year study in non rodents

F3 = 5 for a 3-month study in rodents or 2 year study in non rodents

F3 = 10 for studies of a shorter duration



Q3C, Impurities: Guideline for Residual Solvents, Risk Assessment fo Class 2 Solvents

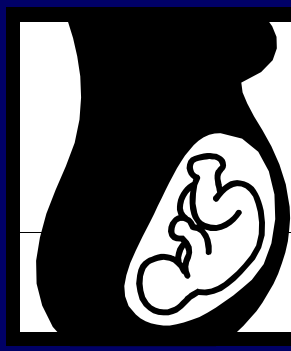
F4 = a factor applied in cases of severe toxicity, non-genotoxic carcinogenicity or teratogenicity

F4 = 1 for fetal toxicity associated with maternal toxicity

F4 = 5 for fetal toxicity without maternal toxicity

F4 = 5 for teratogenic effect with maternal toxicity

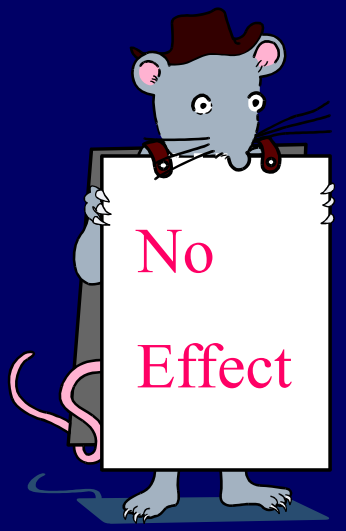
F4 = 10 for teratogenic effect without maternal toxicity



Q3C, Impurities: Guideline for Residual Solvents, Risk Assessment fo Class 2 Solvents

F5 = a factor applied if the no-effect level was not established

F5 = 10 when only a LOEL is available, and depending on the severity of the toxicity.



Q3C, Impurities: Guideline for Residual Solvents, Risk Assessment for Class 2 Solvents: xylene

- The PDE for xylene is 21.7 mg/day
- This implied precision goes far beyond the precision of the science used to calculate it!

Q3C, Impurities: Guideline for Residual Solvents--Options for Describing Limits of Class 2 Solvents

- Option 1:
  Concentration (ppm) = $\frac{1000 \times PDE}{dose}$
  - if all excipients and DSs in a formulation meet limits given in Option 1, components can be used in any proportion
- Option 2: add amounts of residual solvent present in each component

Q3C, Impurities: Guideline for Residual Solvents--Options for Describing Limits of Class 2 Solvents

- Under “option 2” the DS and/or one or more excipients can exceed the concentration limit of a solvent but the overall formulated DP can still conform if the “permitted daily exposure” (PDE) is not exceeded.
- Contrary to EPA philosophy: “dilution is not the solution to pollution.”

What if impurity is found to be genotoxic and cannot be completely removed?

- ICH guidelines are not explicit in this regard
- Quantitative risk assessments for cancer are based on lifetime exposures of animals. What about drugs in clinical trials for relatively short periods? Should permissible levels of genotoxic impurities be higher?

Do we have a science-based approach to setting impurity specifications? Is this risk assessment?