Drug Impurities: The Good, Bad and Ugly

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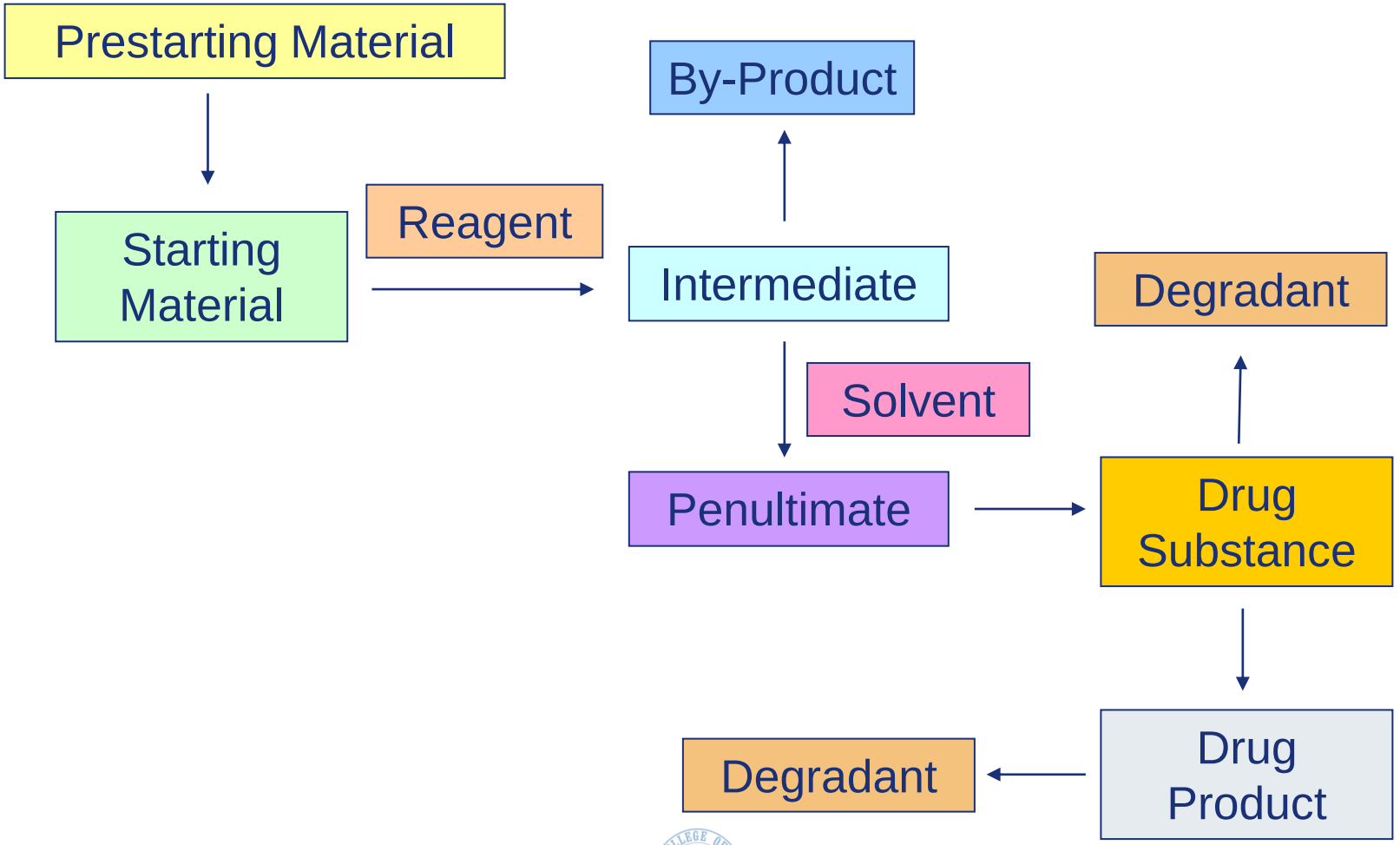
Medicines Impurities

ICH Guidance Documents for Drug Impurities

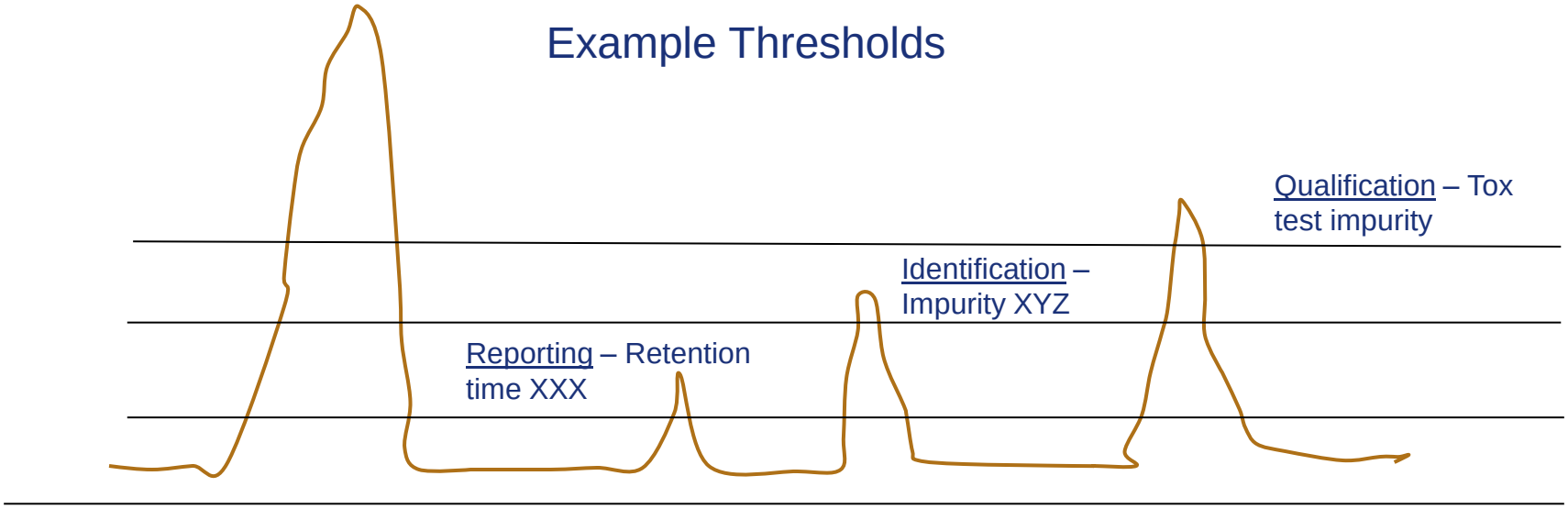
ICH Document	Title	Last Revised
Q3A(R2)	Impurities in New Drug Substances	2006
Q3B(R2)	Impurities in New Drug Products	2006
Q3C(R5)	Guideline for Residual Solvents	2011
Q3D	Guideline for Elemental Impurities	2014
M7	Assessment and Control of DNA Reactive (Mutagenic) Impurities in Pharmaceuticals to Limit Potential Carcinogenic Risk	2014
Q6B	Specifications: Test Procedures and Acceptance Criteria for Biotechnological/Biological Products	1999

Sources of impurities for “small molecules”



Q3A and Q3B Thresholds

Threshold	Definition
Reporting	A limit above (>) which an impurity should be reported.
Identification	A limit above (>) which an impurity should be identified.
Qualification	A limit above (>) which an impurity should be qualified (acquiring data to determine the biological safety).



Qualification Process per Q3A and Q3B

- Tests for genotoxic potential – point mutations and chromosomal aberrations
- Test in animals
  - Tested with active substance (“spiked” or “dirty” material) or test the impurity “neat”
  - Duration depends on data available, 14 – 90 days
  - Performed in species to maximize the potential to detect the toxicity of an impurity
  - Adjust for animal to human surface area correction[1]

1. This is not in ICH guidance but based on regulatory feedback. Guidance on surface area corrections in FDA, 2005 - Estimating the Maximum Safe Starting Dose in Initial Clinical Trials for Therapeutics in Adult Healthy Volunteers

Example Qualification Study with Animals

- Rat API NOAEL = 100 mg/kg/day
- Impurity conc. = 2%
- Surface Area Correction for a Rat = 6.2
- Impurity NOAEL = 0.3 mg/kg/day

- Human API Dose = 100 mg/day
- Impurity conc. = 1%
- Impurity Exposure = 1 mg/day

Impurity NOAEL of **15 mg/day** (50 kg person) > Human API Exposure **1 mg/day**

OR

Up to **15% qualified** in a 100 mg/day API dose

Toxicologist's tips and tricks on general qualification

- ICH qualification thresholds do not cover clinical development
  - Higher thresholds have been suggested during early phase clinical development[1]
  - Surface area animal to human corrections not often done in early phase clinical development
- Low NOAELs in tox studies lead to very low qualification limits if testing as impurity with API
- Patients with advanced cancer – impurity qualifications can be exceeded

1. O'Connor et al. 2012. Early Development GMPs for SmallMolecule Specifications: An Industry Perspective (Part V). Pharma Tech. 36(10).
2. ICH S9. 1999. Nonclinical Evaluation for Anticancer Pharmaceuticals.

ICH Q3C Residual Solvents

Why are solvent limits important?

Highlights of the ICH Q3C document

- Provides the methodology for generating a permitted daily exposure (PDE)
- Generates PDEs for common solvents
- Develops classes for residual solvents

Class	Description
I	Solvents to be avoided
II	Solvents to be limited
III	Solvents with low toxic potential

PDE Equation

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

Modifying Factor	Description
F1	Extrapolation between species
F2	Variability between humans
F3	Short-term to chronic extrapolation
F4	Severe toxicity
F5	LOEL to NOEL extrapolation

PDE intended for all routes of administration

Toxicologist's tips and tricks on solvents

- There may be times where is a solvent is not on the Q3C list
  - There still may be data to generate a PDE
    - Public literature
    - REACH databases
    - TSCA submissions
    - Regulatory limits such as drinking water, etc.
  - The Q3C guidance has handy assumptions used to generate the PDE
- Solvents can cause carcinogenicity, reproductive/ developmental toxicity, or neurotoxicity
- Sometimes there is limited data for a solvent
  - May want to use Q3A limits or conservative assumptions for these situations

ICH Q3D Elemental Impurities

How do elemental impurities enter pharmaceutical development?

- Intentionally added (e.g., catalysts)
- Not intentionally added but exist in the drug substance, water, or excipients
- Manufacturing equipment
- Container closure systems

Highlights of ICH Q3D Document

- Describes a risk assessment process
  - Identify the known and potential sources
  - Compare observed or predicted level with PDE
  - Summarize and document risk. Develop a control strategy to limit exposure.
- Describes a method for developing the PDE
  - Similar to solvents but includes bioavailability adjustments
- Develops PDEs for common elements in pharmaceuticals
  - Oral, Parenteral, Inhalation
  - Speciation – different toxicities for different valence states, the most relevant for pharmaceuticals was selected

Classes of elements

Class	Description
I	Human toxicants that have limited or no use in the manufacture of pharmaceuticals
II	Route-dependent human toxicants • IIA – high probability of occurrence in drug product • IIB – reduced probability of occurrence in drug product
III	Low toxicities via the oral administration

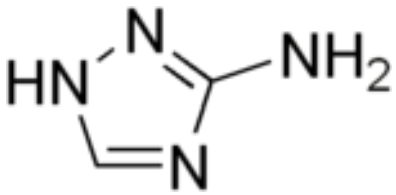
Toxicologist's tips and tricks on elements

- You may be asked to set limits on elements not on the ICH Q3D list
  - Other regulatory guidances may have the limit (e.g., USP, EMA)
  - There can be a lot of summary data on metals in sources such as ATSDR, USEPA, ECHA, WHO, etc.
- There may not be a limit do to regional differences
  - Example – Aluminum
- Route of administration is very important for setting elemental limits
  - Low oral bioavailability for some elements
  - Toxicities specific to a route of administration

Mutagenic Impurities

History of Mutagens / Carcinogens

- Trace levels of a weed killer amitrole, which is carcinogenic in animals, was found in cranberries
- Led to Amendment of the Food, Drug, and Cosmetic Act of 1938 “Delaney Clause (1958)”
- “…no additive shall be deemed to be safe if it is found to induce cancer when ingested by man or animal….”



The problem with the Delaney Clause is

There are carcinogens everywhere, it depends on analytical technology

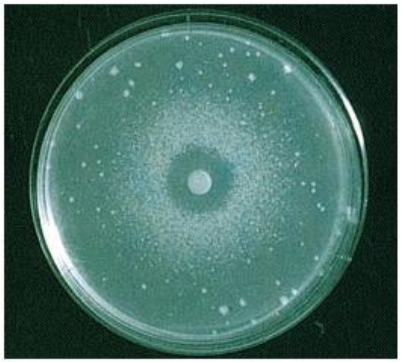
De minimis exposure concept

- Monsanto v Kennedy
  - Monsanto Co – Leaching of an acrylonitrile copolymer in beverage containers
- De minimis non curat lex
  - Latin “the law does not concern itself with trifles”
  - Indicated there is a negligible exposure to carcinogens
- Result – No such thing as zero carcinogens, you just need to control to negligible

ICH M7 Purpose

- Potentially Mutagenic Impurities (PMIs)
  - Impurities that have mutagenic potential far below the qualification thresholds described in ICH Q3A/B.
- ICH M7 was implemented to provide a practical, harmonized framework for the identification, categorization, qualification, and control of mutagenic impurities to limit potential carcinogenic risk.

Hazard evaluation for mutagenicity



Impurity Categorization and Controls

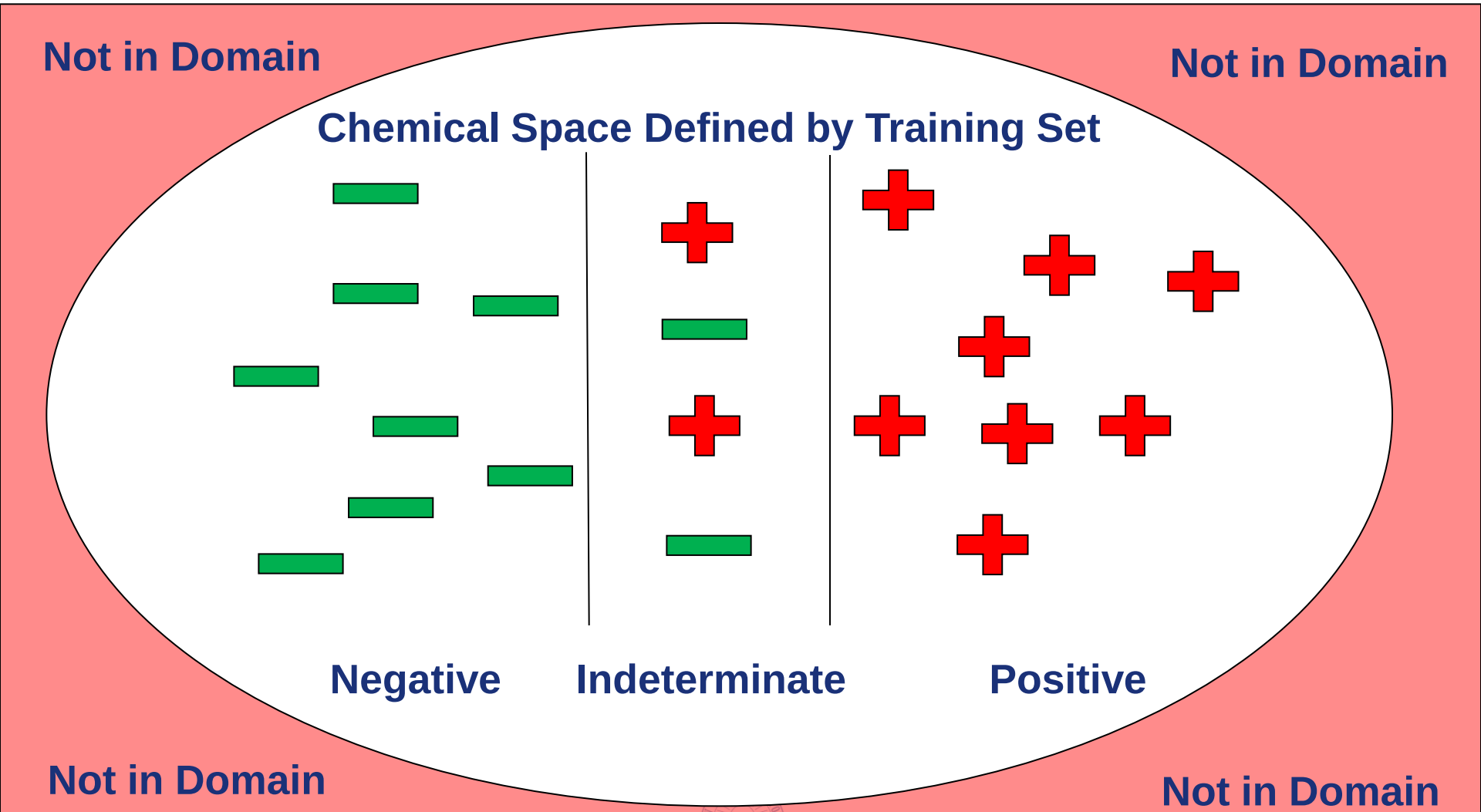
ICH M7 Class	Description
Class 1	Known mutagenic carcinogen
Class 2	Known bacterial mutagen
Class 3	Structural alert No Ames test data
Class 4	Alerting structure; similarity to Ames negative compound (e.g., drug substance or intermediate)
Class 5	No structural alert or alerting structure with negative Ames test

ICH M7 (Q)SAR[1] Evaluation for Bacterial Mutagenicity

- To classify an impurity as non-mutagenic, negative results in two complementary (Q)SAR predictions are required (rules-based and statistical-based)
  - Rules-based software
    - Structure evaluated for presence of alerting features found consistently in Ames positive compounds
  - Statistical-based software
    - Mathematical model calculating the contribution of substructures present in a compound to potential mutagenicity based on a large training set of compounds with Ames data available
- Expert evaluation of any positive, negative, conflicting or inconclusive results (out of domain and indeterminate)
  - Guidance on expert evaluation provide by Powley, 2015 and Sutter et al., 2013

1. (Quantitative) Structure Activity Relationship

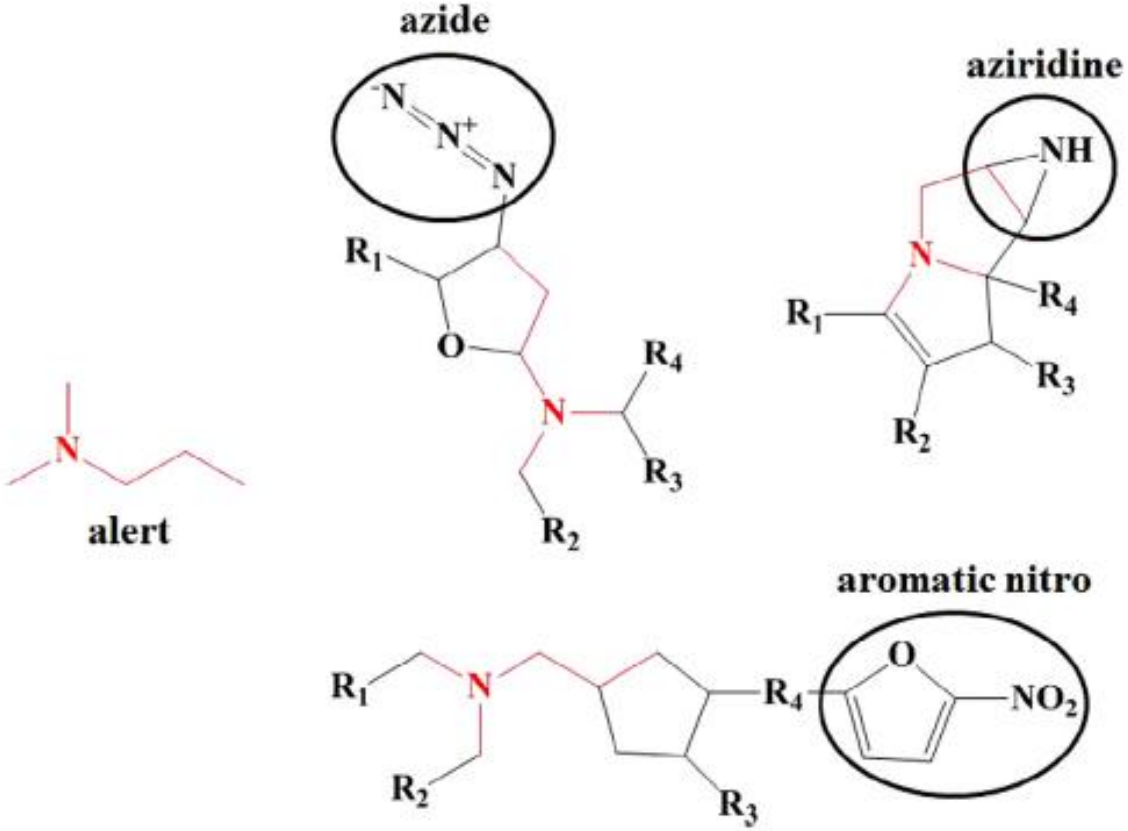
Possible Results of Statistical Model



Expert review with different (Q)SAR results

(Q)SAR Prediction	Why?
Positive in one or both models	To decrease the number of false positives. A review of the training set or structural analogues sometimes show mitigating factors that can be used for a scientific argument.
Indeterminate / Out of Domain Predictions	This can be a frequent occurrence. These predictions are **not negative** predictions to regulatory agencies.
Both are negative	Visually you see a structural alert and want to follow-up based on literature.

Example of refuting a positive prediction



Powley et al., Regul Toxicol Pharmacol. 2015 Mar;71(2):295-300.

Mutagenicity Evaluation

- Can be based on literature data or testing in the bacterial reverse mutation assay
  - OECD 471
  - GLP compliant – may contain GLP deviations such as test article characterization
- Result of assay overrules QSAR result
- In vivo mutagenicity assessment can be used to further investigate a bacterial positive mutagen

What is the limit for a carcinogenic impurity?

- Compound-specific limit
  - Acceptable Intake – Linear model for genotoxic carcinogens with no threshold
  - PDE – Non-linear, mutagenic carcinogen exhibits a threshold
  - This limit may be adjusted for the treatment duration, but the final limit should not be more than 0.5%
- Example of compound-specific limits
  - ICH M7 Draft Addendum

Limits for potential impurities with mutagenicity but not carcinogenicity data (Class 2 & 3)

Based on Threshold of Toxicological Concern TTC (i.e., default limits)

Duration of Treatment	≤ 1month	1-12 months	>1-10 years	>10 years to lifetime
Single impurity (mcg/day)	120	20	10	1.5
Multiple impurities (mcg/day)	120	60	30	5

Or a Class Specific Limit

- A limit for chemically similar compounds
- Example – monofunctional alkyl-chlorides (Brigo and Muller, 2011)

Control Strategies for Mutagenic Impurities

Option	Description
1	Drug substance specification
2	Specification in raw material, starting material or intermediate
3	Specification in raw material, starting material or intermediate above limit but fate and purge used to show below limit
4	Using fate and purge knowledge instead of analytical data

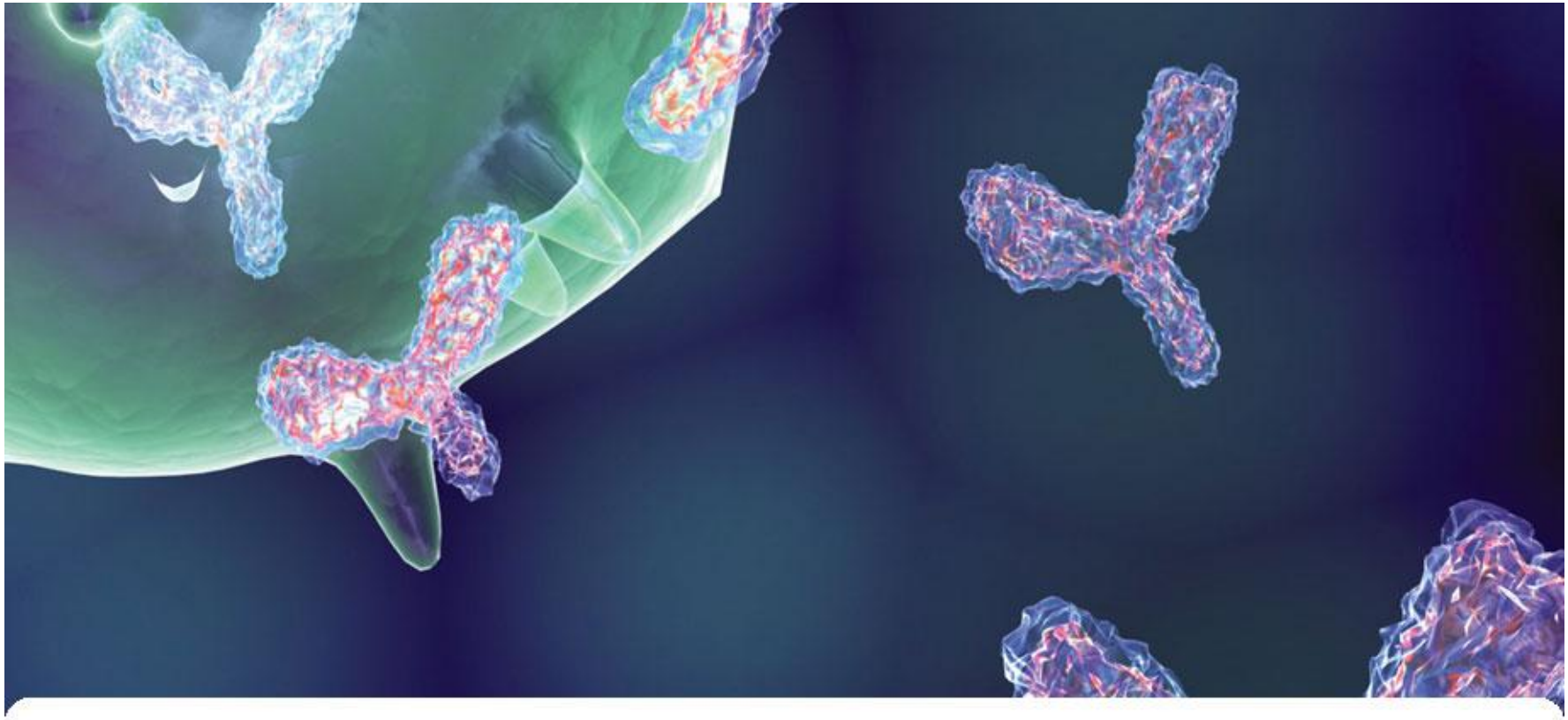
ICH M7 versus Q3A/Q3B

- Note 1 of ICH M7 was used to update differences between Q3A and Q3B
  - Q3A/B recommends a point mutation assay and chromosomal aberrations test for qualification
  - ICH M7 recommends a (Q)SAR and/or bacterial mutagenicity (i.e., point mutation) assay
- Bottom line – If the impurity dose ≤ 1mg/day follow M7 approach, >1 mg/day follow Q3A/B

Toxicologist's tips and tricks for mutagenic impurities

- For QSAR, there are off-the-shelf software by companies such as Lhasa, Leadscope, MultiCase, etc.
- When available, use the carcinogenicity data to set the limit
- If the carcinogenicity data is not adequate to derive a compound-specific limit it is ok to default to the TTC
- Information about the drug (e.g. duration of dosing, metabolites, its mutagenicity, indication) are important for limit setting.
- Multiple impurity limits only apply if you are setting a final drug substance specification.

Biotechnological/Biological Products



ICH Q6B (Specifications) description impurities

- Process-related impurities - derived from the manufacturing process
  - Cell substrate-derived impurities
  - Cell culture-derived impurities
  - Down-stream-derived impurities
- Product-related impurities – variants of the desired drug
  - Truncated forms
  - Modified forms
  - Aggregates

Toxicologist's tips and tricks for Biotechnological/ Biological impurities

- There are established regulatory limits on certain impurities such as endotoxin, etc.
- The limit setting process is not specified in a guidance
  - There is no "ICH process" for toxicological evaluation
  - Established processes for "small molecules" (i.e., Q3A, Q3C, Q3D) can be adapted for "large molecules"

Questions

Thank you for your participation in the American College of Toxicology Webinar!

We hope to see you at the 37th Annual Meeting of the American College of Toxicology.

Presenter Bios

- Joel Bercu
  - Associate Director Environmental and Occupational Toxicology Gilead Sciences, Foster City, CA

Dr. Joel Bercu is an Associate Director in the Drug Substance Evaluation (DSE) group at Gilead Sciences and has 15 years of public health / toxicology experience in pharmaceuticals. His mission while at these positions is to protect the safety of staff, patients, and the environment. He provides expert toxicological documentation for Occupational Health Categorization, Permissible / Acceptable Daily Exposures for cleaning validation, environmental risk assessments, impurities (including mutagenic / carcinogenic impurities) and excipients. He has had several external collaborations to influence regulatory guidances such as chairing the Risk Assessment sub-section for ICH M7 and developing its corresponding Addendum. He received his BS from Texas A&M University, MPH from University of Texas – Houston School of Public Health, PhD from Indiana University, and is a Diplomate of the American Board of Toxicology (DABT). He continues to publish and present at national meetings in the field of toxicology with a focus on public health and risk assessment.