

Derivation and Justification of Safety Thresholds

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Agenda

- Basic Definitions
- Current Regulatory Landscape
 - FDA Guidance Documents
 - ICH Guidance
 - EMEA Guidance
 - Threshold for Toxicological Concern (TTC)
- IPAC-RS
 - Points to Consider Response to FDA Draft Guidance
- PQRI
 - Threshold Approach to Qualify Leachables in OINDP

Definitions

- ***Container Closure System:*** Refers to the sum of the packaging components that together contain and protect the dosage form. This includes both primary and secondary packaging components.
 - *packaging system = container closure system*
- ***Container Closure Component:*** Any single part of a container closure system (metered dose valve, rubber gasket, etc.)
- ***Container Closure Material:*** typically refers to the material of construction (e.g. TPE, PP, rubber, etc.)

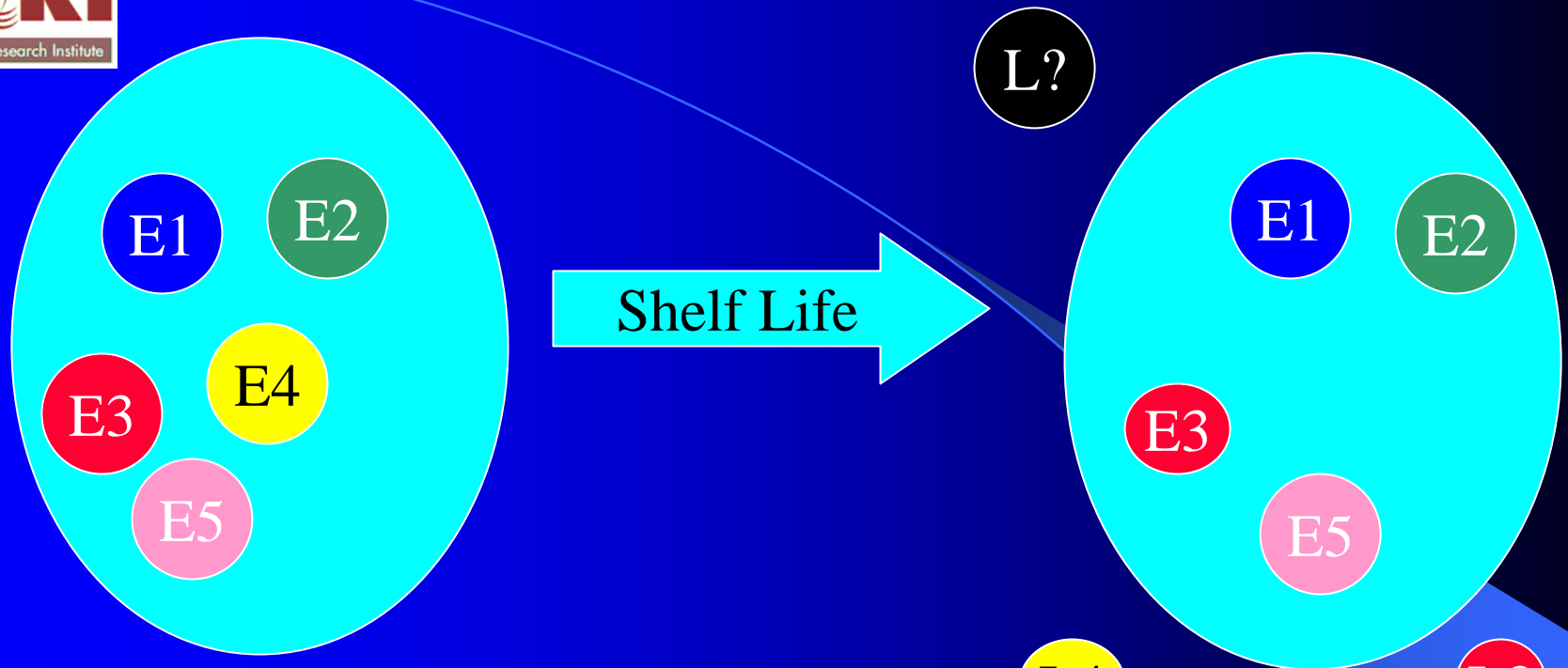
Definitions

- *Extractable*

- Any chemical species that can be removed from a packaging component under laboratory conditions (e.g., component is cut in pieces and incubated with solvent).

- *Leachable*

- An extractable that actually migrates into a drug product under storage conditions.



Container Component
Time (0)

Container Component
Time (n)

- **Not all Extractables are Leachables**
- **Not all Leachables correlate to Extractables**

Laws

- *Food, Drug and Cosmetic Act Section 501(a)(3)*
 - a drug is deemed to be adulterated if its container is composed, in whole or part, of any poisonous or deleterious substance which may render the contents injurious to health...
 - **Section 502:** a drug is considered misbranded if there are packaging omissions.
- *21 CFR Part 211.94 (a)*
 - Drug product containers and closures shall not be reactive, additive, or absorptive so as to alter the safety, identity, strength, quality or purity beyond the official or established requirements.

Guidance

- *FDA Guidance for Industry - Container Closure Systems for Packaging Human Drugs and Biologics (1999)*
 - CDER and CBER approve a container closure system to be used in the packaging of a human drug or biologic as part of the application for the drug or biologic.
 - Each application should contain enough information to show each proposed container closure system and components are suitable for its intended use.
 - The type and extent of information that should be provided in an application will depend on the dosage form and the route of administration.

Container Closure Guidance

Packaging Concerns for Common Drug Product Classes			
Degree of Concern	Likelihood of Packaging-Dosage Form Interaction		
	High	Medium	Low
Highest	Inhalation Aerosols Inhalation Solutions Injections Injectable Suspensions	Sterile Powders Powders for Injection Inhalation Powders	
High	Ophthalmic Solutions Ophthalmic Suspensions Transdermal Ointments Transdermal Patches Nasal Aerosols and Sprays		
Low	Topical Solutions Topical Suspensions Topical & Lingual Aerosols Oral Solutions Oral Suspensions	Topical Powders Oral powders	Oral Tablets Oral Capsules

Container Closure Guidance

Safety Characterization of Extractables for Various Routes/Dosage Forms		
Route / Dosage Form	Safety Category	Typical Safety Data Provided
Inhalation Aerosol Inhalation Solution Nasal Spray	Case 1s	USP Biological Reactivity Test data, Extraction/toxicological evaluation, Limits on extractables, batch-to-batch monitoring
Injection Suspension/Powder for Injection Sterile Powders Ophthalmic Solution/Suspension	Case 2s	USP Biological Reactivity Test data; Possibly extraction/toxicological evaluation
Topical Delivery System Topical Solution/Suspension Topical & Lingual Aerosols Oral Solutions/Suspensions	Case 3s	<u>Aqueous-based solvents:</u> Reference to indirect food additive regulations <u>Non-aqueous solvents & co-solvents:</u> Reference to indirect food additive regulations "Additional suitability information"
Topical Powders Oral Tablets & Capsules	Case 4s	Reference to indirect food additive regulations
Inhalation Powders	Case 5s	Reference to indirect food additive regulations, USP Biological Reactivity testing for mouthpiece

- *Metered Dose Inhaler (MDI) and Dry Powder Inhaler (DPI) Drug Products Chemistry, Manufacturing, and Controls Documentation (1999)*
- *Guidance for Industry Nasal Spray and Inhalation Solution, Suspension, and Spray Drug Products - Chemistry, Manufacturing, and Controls Documentation (2002)*

- The profile of each critical component extract should be evaluated both analytically and toxicologically
- The toxicological evaluation should include appropriate in vitro and in vivo tests
- A rationale, based on available toxicological information, should be provided to support acceptance criteria for components in terms of the extractable profile(s).
- Safety concerns will usually be satisfied if the components that contact either the patient or the formulation meet food additive regulations and the mouthpiece meets the USP Biological Reactivity Test criteria (USP <87> and <88>)
- If the components are not recognized as safe for food contact under appropriate regulations, additional safety data may be needed

- A toxicological evaluation should be made of the extractables from the container, closure, and critical pump components, and the results submitted in the application
- The appraisal should include appropriate in vitro and in vivo tests
- Can also be supported by applicable citations and additional safety data.
- The results of USP Biological Reactivity Tests (USP <87> and <88>) should be submitted.
- A rationale, based on available toxicological information, should be provided to support acceptance criteria for components in terms of the extractable profiles

Impurities in New Drug Products (ICH)

- Q3B
 - unclear on applicability to extractables or leachables
 - Qualification Thresholds based on % API
 - Not rational for container/closure related impurities
- Q3B(r)
 - Impurities arising from excipients present in a new drug product or extracted or leached from the container closure system are not covered by this guidance

Genotoxic Impurity Guideline (EMEA)

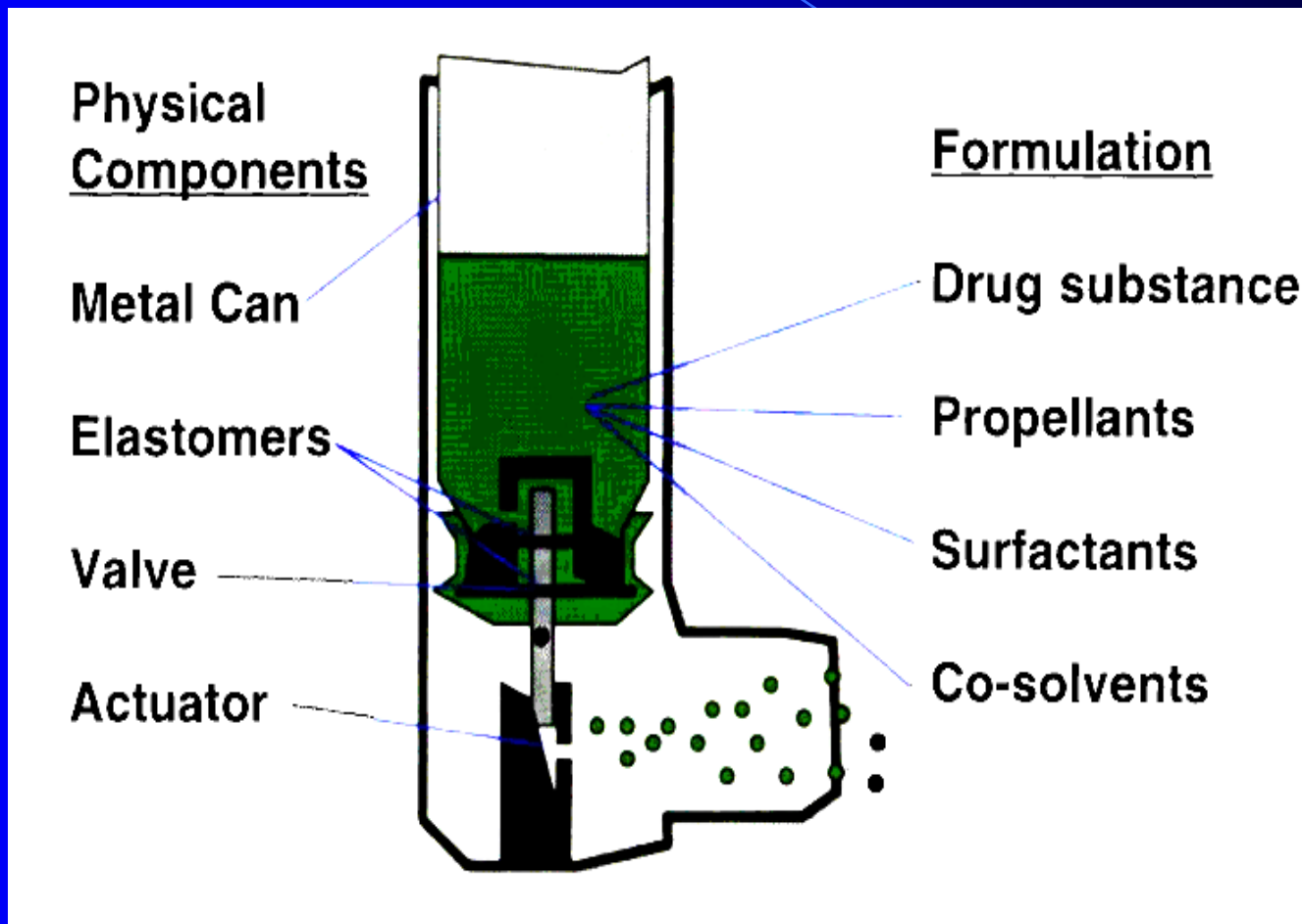
- Provides a rationale for determining acceptable levels of genotoxic impurities in DP
- Genotoxic Impurities divided into 2 classes
 - Those with experimental evidence for a threshold-related mechanism
 - Those w/o experimental evidence for a threshold-related mechanism
 - Threshold for Toxicological Concern (TTC) approach

Threshold of Toxicological Concern (TTC)

- **The TTC is a common exposure level for any unstudied chemical that will not pose a risk of significant carcinogenicity or other toxic effects**
 - TTC estimated to be 1.5 $\mu\text{g}/\text{person}/\text{day}$
 - Corresponds to a 10^{-5} lifetime risk
 - TTC for high potency carcinogens 0.15 $\mu\text{g}/\text{person}/\text{day}$
 - Corresponds to a 10^{-6} lifetime risk
- **TTC value can be higher under certain conditions**
 - Short-term exposure
 - Life-threatening conditions with no safer alternatives
- **TTC should not be used**
 - Carcinogenic impurities where adequate data exist and allow for a compound specific risk assessment

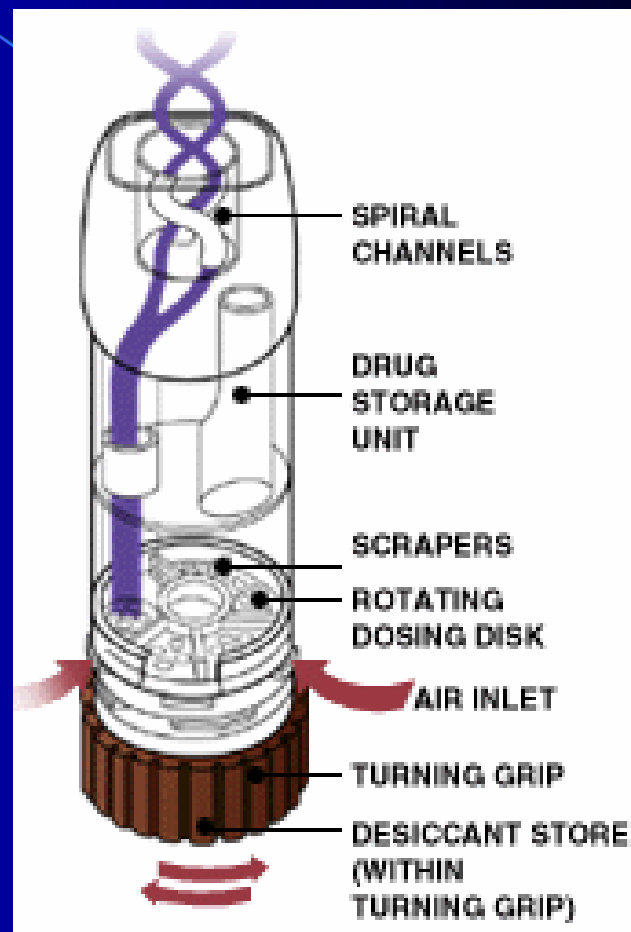
Threshold Approach to Qualify Leachables for OINDP

Metered Dose Inhaler – A Model for Extractable/Leachable Evaluation



Dry Powder Inhalers

- DPIs have similar elastomeric and polymeric components found in MDIs
 - fewer leachables due to lack of solvents in DPI formulation



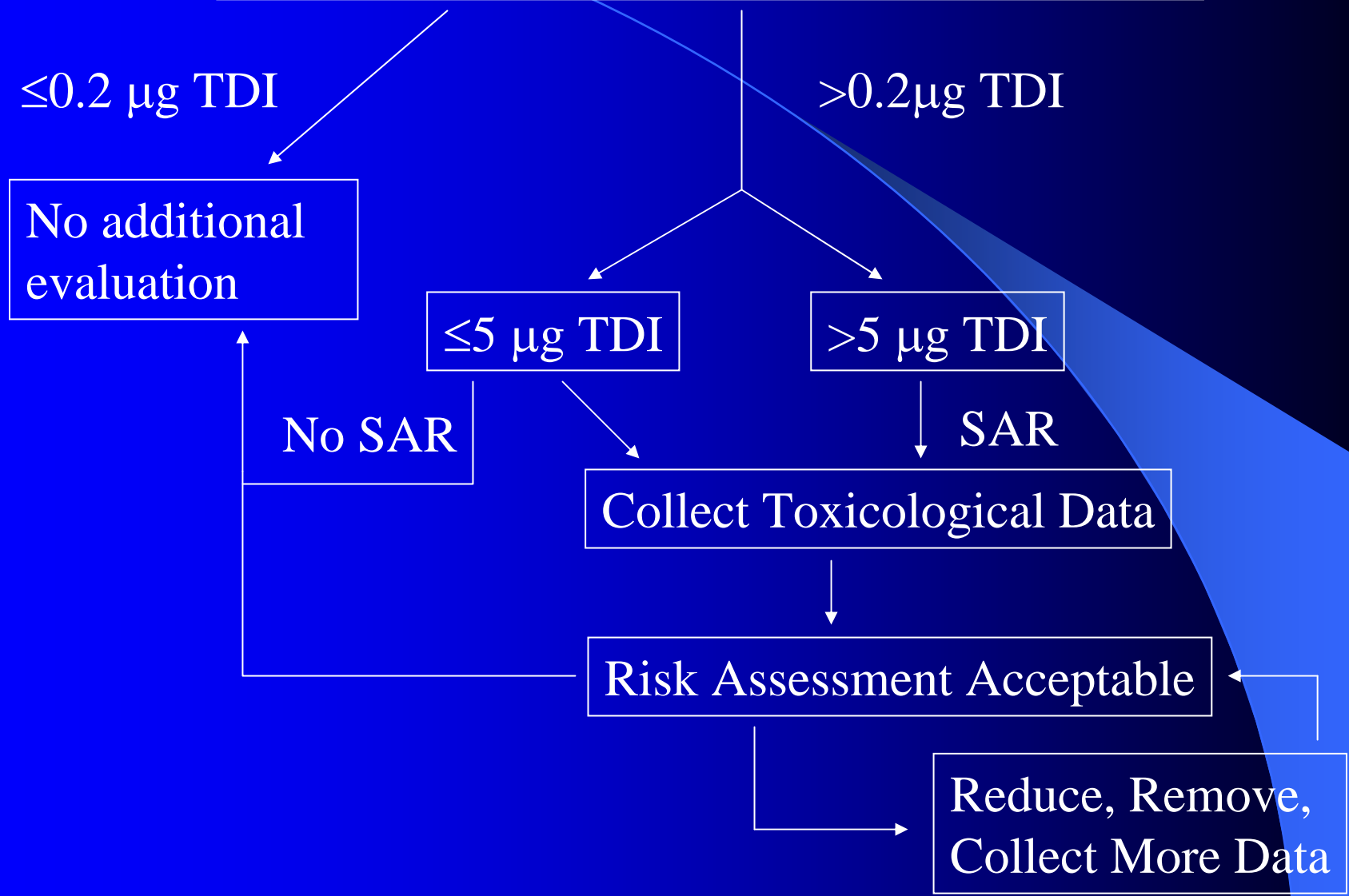
- 2000: Formed a team to respond to FDA MDI/DPI Guidance
 - Issue with toxicological evaluation of all extractables
 - Should focus on qualification of leachables
 - Introduced concept of a qualification threshold
 - Based on Total Daily Intake (TDI), not % API

- Qualification should be performed only on leachables
 - conducted only on those leachables that occur above data-supported thresholds
- Qualification of a product-related leachable composite mixture is sufficient to qualify those leachables for registration
- For qualification, product samples should be qualitatively representative of the end-of-shelf life leachable profiles

Risk Assessment (IPAC-RS)

- Risk assessment of leachables may come from one or more of the following data sources:
 - in-silico, structure-activity relationships (SAR)
 - literature
 - in-vitro or in-vivo testing
- For component suppliers, United States Pharmacopoeia (USP) <87> and <88> may have utility for extractable testing
 - Acceptance criteria for components should be based on extractable profiles and (possibly) USP test results
- USP <87> and <88> are not necessary when a more comprehensive toxicological evaluation is available

Individual leachable above reporting threshold



PQRI Leachable and Extractable Working Group

- Formed in 2001, based on Points to Consider response presented by IPAC-RS
- Comprised of toxicologists and chemists representing:
 - Industry (Pharma, CROs, Material Suppliers)
 - FDA
 - Academia

L&E Work Plan (1)

- Develop Hypothesis
- Develop process to investigate hypothesis
- Implementation of Process
 - Chemists and Toxicologists work in parallel
 - Development of toxicological qualification and safety concern thresholds
 - Development of analytical qualification and evaluation thresholds
 - Development of recommendations for extractables and leachables testing

L&E Work Plan (2)

- Harmonization and Consensus
 - Develop consensus recommendations
 - Develop report for review by PQRI and FDA, containing recommendations for regulatory guidance
 - Publications and presentations

L&E Recommendations

- Recommendations on safety qualification of extractables and leachables, including safety thresholds
- Recommendations on best practices for extractables and leachables testing in the OINDP pharmaceutical development process

Process for Development of Safety Qualification Thresholds

- PQRI working group formed toxicology sub-group to develop safety thresholds and justification of thresholds
- Derived a Qualification Threshold (QT) and a Safety Concern Threshold (SCT)
 - Analyzed information in public databases and literature data
 - Applied risk assessment approaches to data
- Although thresholds similar to IPAC-RS thresholds, derivation is different, and justification more extensive

Safety Qualification

- Derive and justify a Safety Concern Threshold (SCT)
 - 0.15 μg Total Daily Intake (TDI)
 - **The threshold below which a leachable would have a dose so low as to present negligible safety concerns from carcinogenic and noncarcinogenic toxic effects**
- Derive and justify a Qualification Threshold (QT)
 - 5 μg TDI
 - **The threshold below which a given non-carcinogenic leachable is not considered for safety qualification (toxicological assessments) unless the leachable presents structure-activity relationship (SAR) concerns**
- Proposes a safety qualification process incorporating these thresholds

Questions (?)

References

- *FDA Guidance for Industry - Container Closure Systems for Packaging Human Drugs and Biologics (1999)*
 - <http://www.fda.gov/cder/guidance/1714fnl.pdf>
- *Metered Dose Inhaler (MDI) and Dry Powder Inhaler (DPI) Drug Products Chemistry, Manufacturing, and Controls Documentation (1999)*
 - <http://www.fda.gov/cder/guidance/2180dft.pdf>
- *Guidance for Industry Nasal Spray and Inhalation Solution, Suspension, and Spray Drug Products - Chemistry, Manufacturing, and Controls Documentation (2002)*
 - <http://www.fda.gov/cder/guidance/4234fnl.pdf>

ICH Guidance

- <http://www.fda.gov/cder/guidance/4164fnl.pdf>
- <http://www.fda.gov/cder/guidance/5528fnl.pdf>
- <http://www.fda.gov/cder/guidance/Q3Cfnl.pdf>

EMEA CHMP Guideline for Genotoxic Impurities

- <http://www.emea.eu.int/pdfs/human/swp/519902en.pdf>

IPAC-RS/PQRI

- http://www.ipacrs.com/PDFs/Points_to_Consider_FINAL.PDF
- <http://pqri.org/index.htm>