Safety Qualification Process and Application of Thresholds

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Outline

- Safety qualification process
  - What to do when leachables exceed:
    - Safety concern threshold (SCT)
    - Qualification threshold (QT)
  - Decision tree
- Roles for risk assessment in OINDP development
- Application of risk assessment and thresholds

Leachable Safety Qualification Process

- Based on ICH Q3A and Q3B for impurities
- When leachable ≤ SCT, then qualified
- If leachable > SCT but ≤ QT, then options are:
  - Reduce leachable ≤ SCT or
  - Conduct risk assessment, then
  - Qualify leachable via assessment and/or testing, or
  - Propose higher acceptable level for leachable to FDA
- If leachable > QT, then options are:
  - Reduce leachable ≤ QT or
  - Conduct risk assessment, then
  - Qualify leachable via assessment and/or testing, or
  - Propose higher acceptable level for leachable to FDA

Leachable Safety Qualification Process (2)

- Using a higher or lower acceptable level for a leachable is an option based on scientific rationale, potency, and level of concern
  - Alternate acceptable levels may be proposed to FDA and treated on a case-by-case basis.
- Lower acceptable levels are needed for compounds with special safety concerns, such as:
  - Nitrosamines
  - Polynuclear aromatics (PNA's)
  - Mercaptobenzothiazole
  - Such leachables considered on case-by-case basis

Qualification of Leachables

- Qualification steps considered “appropriate” depend on:
  - Patient population
  - Total daily intake (TDI)
  - Duration of drug administration
- Qualification steps
  - Risk assessment
    - Structure-activity relationship (SAR) analysis
    - Literature review
  - Safety studies
    - Genotoxicity
    - General toxicity
    - Other, as needed

Qualification of Leachables (2)

- Safety studies can be conducted on:
  - OINDP containing the leachables to be controlled
  - Isolated leachables may be appropriate
- Genotoxicity – minimum of two in vitro tests
  - Point mutation
  - Chromosomal aberration

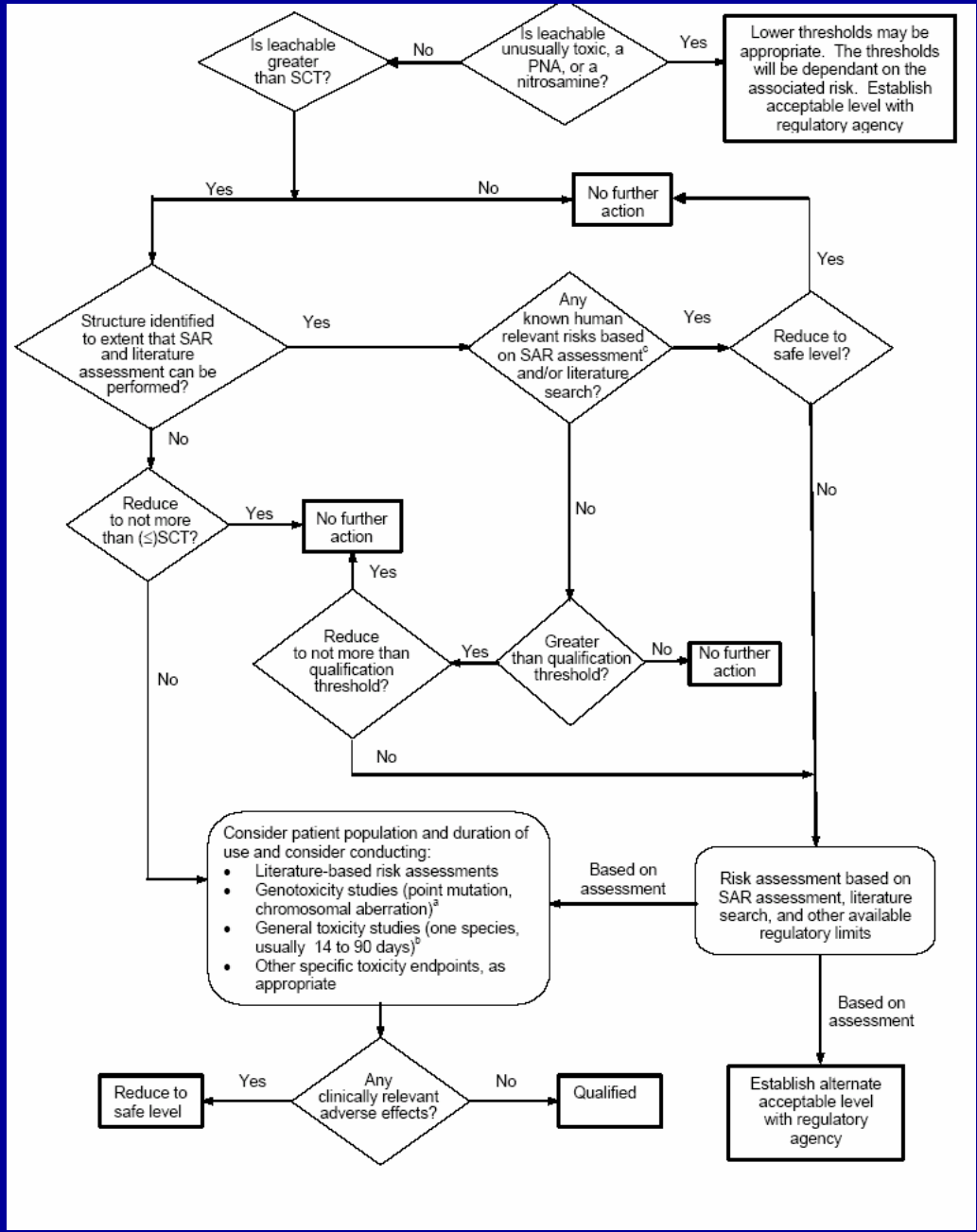
Qualification of Leachables (3)

- General toxicity studies
  - Compare unqualified to qualified material
  - One relevant species
  - Duration
    - Usually 14 to 90 days
    - Single dose appropriate for single-dose drugs
- Other specific toxicity endpoints, as appropriate
  - Carcinogenicity studies may be needed for compounds with SAR alerts for carcinogenicity

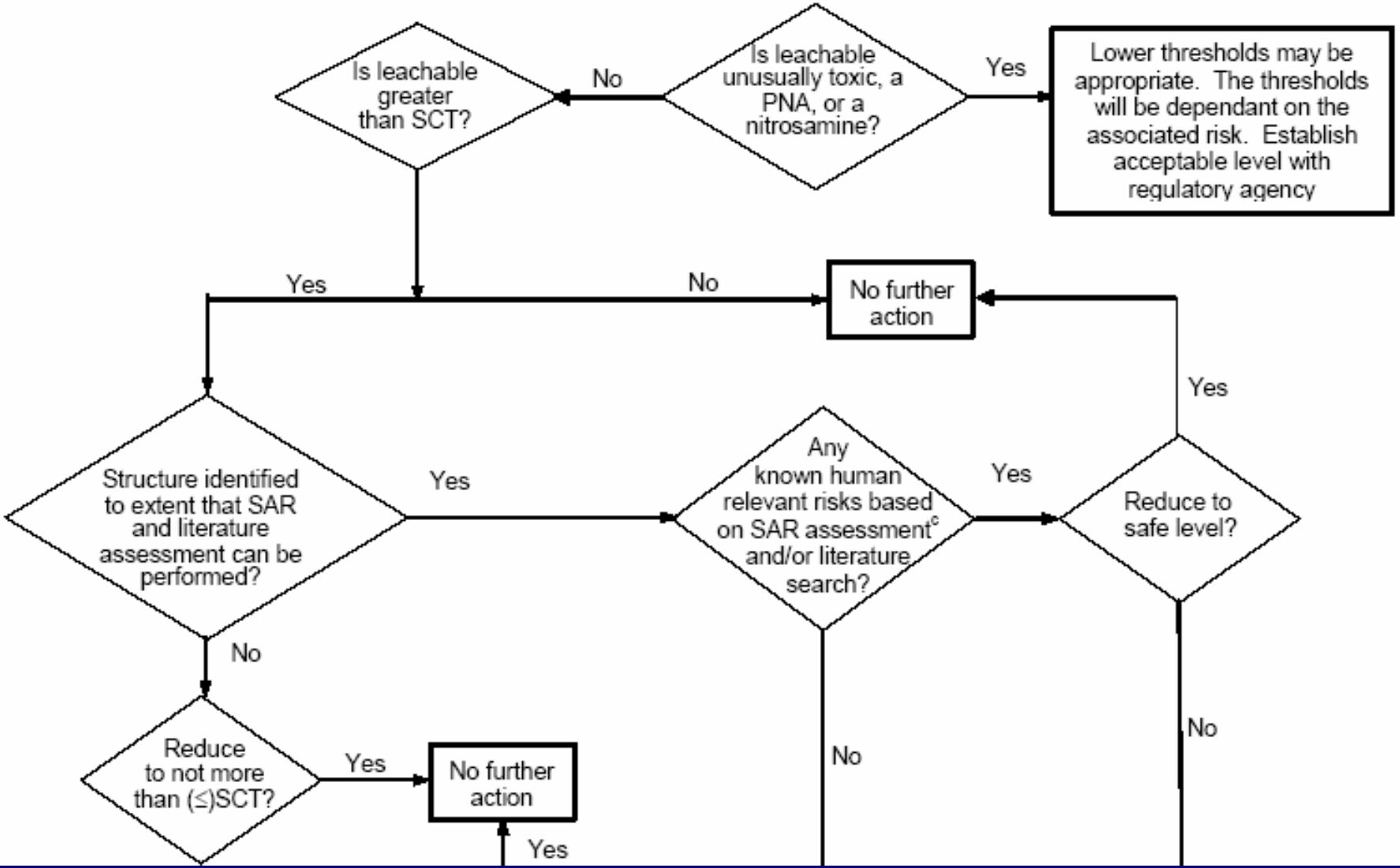
Qualification of Leachables (4)

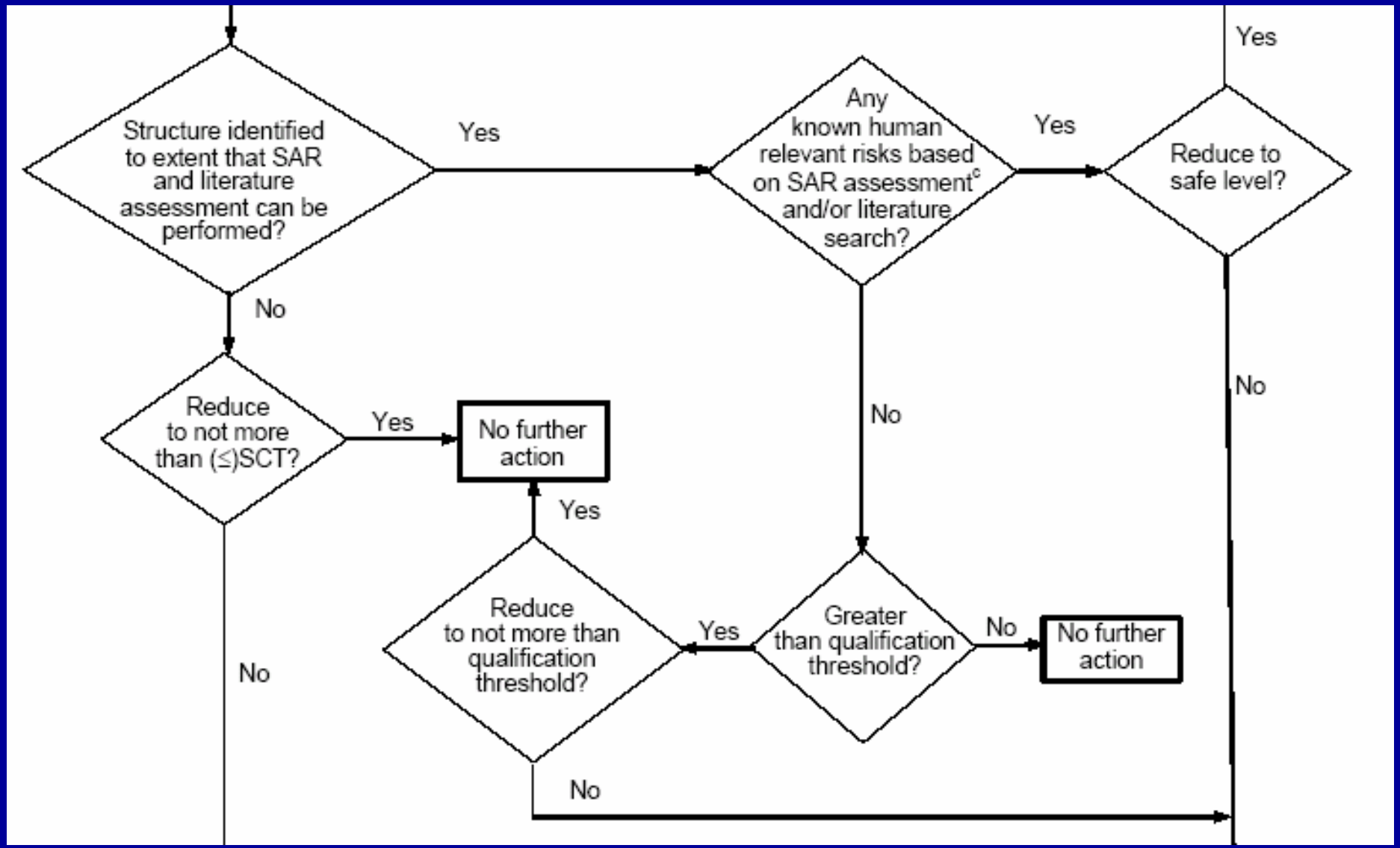
- Role for USP and ISO Biocompatibility Tests
  - United States Pharmacopoeia: USP <87> and <88>
  - International Standards Organization: ISO 10993
  - Propose these tests may be appropriate for suppliers of OINDP device components
  - Drug product manufacturers need not perform these tests when a more comprehensive in-vivo toxicological evaluation is available.

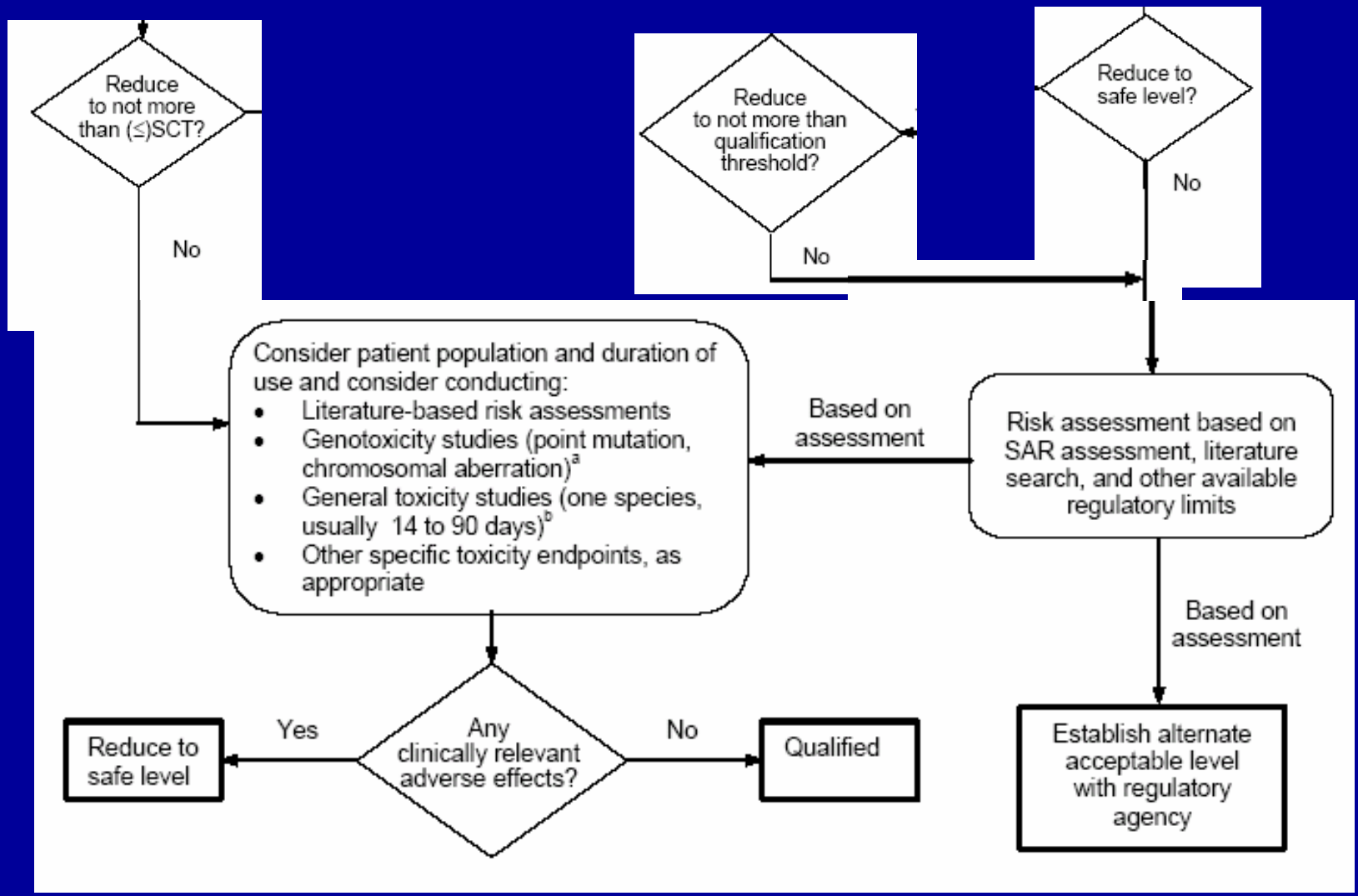
Decision Tree



A. Decision Tree for Identification and Qualification




Structure identified to extent that SAR and literature assessment can be performed?
Yes
Any known human relevant risks based on SAR assessment[c] and/or literature search?
Yes
Reduce to safe level?
Yes
No
No
Reduce to not more than (≤)SCT?
Yes
No further action
Yes
No
Reduce to not more than qualification threshold?
Yes
Greater than qualification threshold?
No
No further action
No
No


Reduce to not more than (≤)SCT?
No
Reduce to not more than qualification threshold?
No
Reduce to safe level?
No
Consider patient population and duration of use and consider conducting:
• Literature-based risk assessments
• Genotoxicity studies (point mutation, chromosomal aberration)[a]
• General toxicity studies (one species, usually 14 to 90 days)[b]
• Other specific toxicity endpoints, as appropriate
Based on assessment
Risk assessment based on SAR assessment, literature search, and other available regulatory limits
Based on assessment
Establish alternate acceptable level with regulatory agency
Any clinically relevant adverse effects?
Yes
Reduce to safe level
No
Qualified

Roles of Risk Assessment in OINDP Development

- Risk assessment tools
  - SAR analysis
  - Literature review
- Risk assessment to evaluate safety of:
  - Components for container/closure system
  - Extractables from initial studies on components
  - Leachables with total daily intake (TDI) > SCT or QT

Risk Assessment: Component Selection

- Preliminary risk assessment done on component formulations provided by suppliers
  - Evaluate in terms of potential extractables and leachables
- Allows for informed component selection early in development
  - Allows for early identification compounds of potential concern, thereby saving time and resources.
- Involves collaboration among toxicologists, material scientists, and chemists

Risk Assessment: Extractables

- Preliminary risk assessment done on extractables from components
- Confirms component selection
- Involves collaboration between toxicologists and chemists

Risk Assessment: Leachables

- Risk assessment on leachables with TDI > SCT or QT
- Involves collaboration between toxicologists and chemists

Risk Assessment: Extractables/Leachables

- Three steps:
  1. Extractable/leachable identification information provided by chemist to toxicologist
  2. Preliminary risk assessment done by toxicologist
  3. If more rigorous risk assessment needed, then more detailed identification and dosage information should be requested by toxicologist from chemist

Application of Risk Assessment & Thresholds (1)

- PQRI L&E Working Group undertook mock safety qualification to assess process
- Performed risk assessment on extractables > AET
  - Extractables from elastomer
  - No leachable data were available
- Risk assessment consisted of only SAR
  - Identified compounds with and without alerts
- Assumed different TDIs for compounds
- Using decision tree, applied thresholds to compounds with different toxicity profiles

Application of Risk Assessment & Thresholds (2)

- Extractable dataset
  - Sulfur-cured elastomer extracted with methylene chloride
    - 66 total extractables > AET identified by GC/MS
  - 29 compounds with confirmed or confident structures
    - Confirmed: matched with reference standards
    - Confident: precluded all but most closely related compounds

Application of Risk Assessment & Thresholds (3)

- SAR Analysis
  - Software
    - DEREK (Pfizer) on 29 compounds
    - Multicase (FDA) on 26 compounds
  - Compared DEREK and Multicase results for 26 compounds, based on:
    - Carcinogenicity
    - Mutagenicity
    - Skin sensitization

Application of Risk Assessment & Thresholds (4)

SAR Results:

Alert	No Alert Both	Alert Both	Alert DEREK Only	Alert Multicase Only
Carcinogen	17	3	5	1
Mutagen	25	1	0	0
Skin Sensitizer	18	0	4	4

Application of Risk Assessment & Thresholds (5)

1. Risk assessment of leachables > SCT
    1. SAR
    2. Literature review of compounds with alerts
2. Based on risk assessment, decide which compounds need further risk assessment
3. Questions for chemist about compounds for further risk assessment:
    1. Is level of structural information sufficient?
    2. What is TDI of leachable?

Application of Risk Assessment & Thresholds (6)

1. Is level of structural information sufficient?
   - Ideally leachables have “confirmed” structures
     - Based on comparison with reference standards
   - If only “confident” or “tentative” structures, then ask chemist for best identification information possible
   - If new information provides new structure, then rerun SAR analysis and literature review

Application of Risk Assessment & Thresholds (7)

2. What is the total daily intake (TDI) of leachable?
    - Request information from chemist on:
        - Concentration of the leachable in drug product
        - Drug product dosage
        - Drug product potency

Application of Risk Assessment & Thresholds (7)

- Further safety assessment is based on application of SCT and QT in decision tree

- The proposed specification for leachable in drug product, the risk assessment and other supporting data should be submitted to FDA, which may:
  - Accept proposed specification for leachable
  - Ask for further qualification
  - Establish alternate acceptable level for leachable

Application of Risk Assessment & Thresholds (8)

- Example #1: 2-chloro-methyl- thiobenzothiazole
  - Potential carcinogen based on SAR alert and literature
  - Patient TDI between SCT and QT
- Options are:
  - Reduce leachable ≤ SCT or
  - Conduct risk assessment and submit to FDA, then
  - Propose higher acceptable level for leachable to FDA, or
  - Qualify leachable via:
    - Risk assessment
    - Safety studies of carcinogenicity in addition to genotoxicity and general toxicity
    - Submit risk assessment and supporting data to FDA for concurrence or a request for further qualification

Application of Risk Assessment & Thresholds (9)

- Example #2: Ethyl-4-ter-butyl phenyl ether
  - No SAR alert for carcinogenicity, mutagenicity, or sensitization
  - Patient TDI > QT
- Options are:
  - Reduce leachable ≤ QT or
  - Conduct risk assessment and submit to FDA, then
  - Propose higher acceptable level for leachable to FDA or
  - Qualify leachable via:
    - Risk assessment
    - Safety studies of genotoxicity and general toxicity
    - Submit risk assessment and supporting data to FDA for concurrence or a request for further qualification

Summary

- Safety qualification process provides clear guidelines and options for leachables based on:
  - Leachable toxicity properties
  - Patient total daily intake (TDI)
- Risk assessment is needed for:
  - Component selection
  - Assessment of extractables
  - Assessment of leachables
- Toxicologists, chemists, and material scientists should collaborate from the start of development
  - Allows for early identification of compounds of potential concern, thereby saving time and resources.