Safety Recommendations: Science and Process

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Disclaimer

This discussion conveys the speaker's experience as a supervisor and reviewer in the FDA's Office of New Drugs.

This talk is not intended to convey official FDA policy and the comments are not binding on the FDA or on the regulated industry.

Objectives

Discuss

- Perspectives on PQRI recommended thresholds
- Recommended approaches for qualification of leachables and extractables
- Qualification examples
- Recommendations for process improvements

Extractables & Leachables

- Can present significant safety issues for
  - Inhalation formulations
  - Others (parenteral, ophthalmic)
- Issues can affect approval of drug product
- No formal guidance on safety evaluation is currently available

PQRI Working Group

- Collaborative effort of industry, academia and government
  - Chemistry
  - Toxicology
- Toxicology: development of safety qualification thresholds
  - Qualification threshold (QT)
  - Safety concern threshold (SCT)

Use of safety thresholds

- Considered an acceptable approach when adequate data is available to support
- Appropriate application of thresholds has potential advantages
  - reduction in unnecessary expenditure of animals, time, effort and money
  - allows resources to be applied to more significant safety concerns

Qualification threshold

- PQRI working group recommended QT of 5 mcg/day (100 ng/kg/day, 50 kg person)
  - No further toxicity data needed when maximum expected daily exposure is below TH
  - Approach assumes no known potential or structural alerts for carcinogenicity/genotoxicity, local irritant effects or hypersensitivity
  - Approach is in agreement with current Div. of Pulmonary and Allergy Products (DPAP) practice

Qualification threshold (2)

- DPAP threshold based on evaluation of EPA database for chemicals with inhalation data
  - RfC's from database ≥ 100 ng/kg
  - 3 exceptions with "safe" doses of 80 ng/kg
  - Large safety factors (1000 - 10000) incorporated
- PQRI expanded the database evaluation to include ATSDR and CAL EPA
  - Concluded that a QT of 5 µg/day presented a negligible safety concern for non-carcinogenic effects

Safety concern threshold

- PQRI working group recommended SCT of 0.15 mcg/day
  - derived from calculated risk-specific doses of genotoxic (SAL-positive) carcinogens from CPDB database
  - dose below which a leachable would present negligible concern for adverse carcinogenic and noncarcinogenic effects
    - < 10% of all compounds would present > 10^{-6} increased cancer risk

Safety concern threshold (2)

- Proposed SCT for negligible carcinogenic effects expands on DPAP's previous use of thresholds
  - past threshold use focused primarily of general toxicological effects
- Proposal is similar in nature to that used previously by FDA (CFSAN) for safety assessment of food contact materials
- Similar proposals have been made to support safety thresholds for genotoxic impurities

Safety concern threshold (3)

- Proposed approach is generally considered acceptable
  - based on robust database
  - applied cancer risk of 10-6 appropriate
    - nature of compounds - industrial
    - lack of derived benefit
- This assessment is considered in DPAP's safety evaluation of suspected carcinogenic leachables and extractables

Exceptions to threshold approaches

- Irritants
- Sensitizers
- High potency carcinogens (nitrosamines, PAHs)

- In the presence of adequate data, compound-specific risk assessment may be supported
  - generally support higher specifications

General qualification approach

- “Identify” the compound
- Conduct SAR assessment for genotoxic/ carcinogenic potential
- Consider the maximum daily human exposure
- Review the available toxicology/safety data
- Conduct toxicology studies as deemed necessary (i.e., 14-90 day toxicology, genetic toxicology)

- Conduct safety assessment based on
  - maximum expected daily human exposure
  - patient population and duration of use

IH products - General process

- Safety assessment has 3 primary components
  - General toxicity
  - Route-specific toxicity (IH irritancy)
  - Mutagenic/carcinogenic potential
- As part of the risk assessment, determine that sensitivity (LOD) is sufficient to identify levels associated with risk

Qualification - Systemic Toxicity

- For exposures > 5 mcg/day, qualify based on
  - Published toxicity data
  - Relevant accepted regulatory exposure limits
  - Structural similarity to chemicals with known toxicity profiles, or
  - Toxicology studies (at least 90 days duration for chronic indications)

Qualification - Systemic Toxicity (2)

- When toxicology data used to support proposed specifications:
  - Most relevant data should be considered
  - Safety margins calculated based upon NOAEL dose
    - Generally 10-fold SM incorporated for cross-species extrapolation
    - 100-fold SM used for data from alternate routes of administration
      - Apply 1000-fold SM if using oral animal data to support human IH use

Local Toxicity

- Determine if any chemical structures are associated with irritancy or sensitization
- Especially important to consider indicated population
- Primary examples
  - Isocyanates
  - Aldehydes
  - Organic acids
  - Strained heterocyclics

Local Toxicity (2)

- If yes, assess risk based on specific compound
  - Reduce potential exposure to as low as possible
  - Evaluate clinical experience with drug product for evidence of any adverse experiences
- If no, threshold exposure = 5 mcg/day
- Exposure > 5 mcg/day, qualify as described for systemic toxicity

Carcinogenic Potential

- Chemicals are qualified in presence of
  - negative genotoxicity and/or carcinogenicity data
  - no genotoxicity or carcinogenicity data but lack of structural alerts
  - qualification threshold of 5 mcg/day is appropriate
- If known genotoxins/suspected carcinogens
  - conduct appropriate tests to alleviate concern
  - reduce specification in consideration of relevant carcinogenicity databases
- If known carcinogen, specification should be set to correlate with carcinogenicity risk of $< 10^{-6}$

Qualification examples

Bis-2-ethyl-hexyl sebacate

- Proposed specification corresponding to daily human exposure of 182 ng/kg/d
- NOEL of 200 mg/kg from published chronic rat dietary study
  - Corresponds to acceptable human IH exposure of 0.2 mg/kg
- > 1,000-fold safety margin

Qualification examples (2)

4-toluenesulfonamide

- Proposed specification corresponding to daily human exposure of 1.2 mcg/kg/d
- Sponsor provided no supporting rationale for proposed specification
- Only acute toxicity data available
- Sponsor was requested to lower specification to correlate with qualification TH (5 mcg/day) or provide adequate toxicology data to support proposal

Qualification examples (3)

Acenaphthene

- Proposed specification corresponding to daily human exposure of 1.33 ng/kg/d
- Only acute toxicity data available
- Drinking water standard: 400 mcg/L
  - Corresponds to acceptable daily IH exposure of 160 ng/kg (assumed intake of 2 L/day, 50 kg BW)
- > 100-fold SM

Qualification examples (4)

Nitrosamines

- Extract from rubber components
- Carcinogenic
- 6 species ID’d at various levels
- Risk assessment based on total nitrosamine exposure using slope factor for NMDA
- Carcinogenic risk estimates up to 1:100,000 accepted based on public health, risk:benefit and technological considerations

Agency process & timing

- Division alerts sponsors to potential issues as early as pre-IND meetings
- Once data is submitted (usually with NDA), CMC group generates a consult to the Pharm/Tox group for safety assessment

Agency process & timing (2)

- Pharm/Tox group reviews safety data and coordinates with CMC to relate acceptable exposure level to a drug product specification
- Review often occurs late in review cycle; can affect drug approval

Process Improvements

- Select materials to limit the number and level of potential leachables.
- Use pre-extraction methods to lower potential exposures.
- Submit clear rationale to support safety of proposed product specifications
  - Thresholds
  - Toxicology data
  - Relevant and accepted exposure limits

Process improvements (2)

- Generate data and initiate communication with relevant division earlier in the development process
  - Data often not available until NDA submission or during review cycle

Process improvements (3)

- Some qualification can be incorporated into standard toxicity testing with active drug
  - Analyze drug batches for leachable levels
- For toxicity tests
  - use aged product
  - store the product in an orientation that maximizes contact with device components

Conclusions

- Safety qualification of extractables and leachables are often required for inhalation drug products
- Relevant toxicology/safety data should be considered to support product specifications
- In the absence of compound-specific data, thresholds may be supported that support negligible risk of toxicity and/or carcinogenicity
- Early communication and clear supporting rationale may assist in more efficient resolution of issues

Thank you.