Safety Thresholds and Best Practices for PODP
Highlights of Day 1 & Day 2

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Session I, Opening Remarks

- **Reggie Saraceno (Boehringer Ingelheim)**
  - PQRI: background of organization, mission and history
  - Workshop objective - participation in the process

- **Prasad Peri (US FDA)**
  - Extractables proactive approach while leachables reactive
  - Consideration based upon patient population, administration and quality control of materials
  - Consideration of sources from N (end user) to back N-4
  - Risk base vs. conservative approach for extractable assessment
  - QbD approach – risk, process control [going to proactive (Q8, Q9, Q10)]
    - Risk: I.D., evaluation and reduction
    - Control: design space (CQA), strategy for process and Life cycle management

**Questions**

1. Will regulators set expectations on which mathematical DOE models should be used?
2. Will best practices in testing lead to regulatory preferred drug product/delivery-material combinations?
3. Material library approaches such as ELSIE can be used as part of a filing. How best to include at initial filing and subsequent actions such as annual reports, etc?
Session I, History

- Dennis Jenke (Baxter)
  - History Lesson (Before Chromatography [BC])
  - Regulatory guidance [movie analogy] to OINDP
  - OINDP Tox. threshold of SCT, QT and AET
  - Chem. procedures extractions, technologies, special compounds, etc.
  - PODP applied to case of c/c systems for the appropriate application
  - Differences between the two in dosage, materials of construction, formulation, etc.
  - PODP status Tox. threshold and classification
  - Chem. classification, threshold and best practices

Questions
1. Can we extend PODP primary packaging concepts to delivery and irrigation sets?
Session II, Toxicological Thresholds Rationale

• Doug Ball (Pfizer)
  – Staged Toxicological Threshold Approach

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<th>Class I</th>
<th>Class II</th>
<th>Class III</th>
<th>Class IV Sensitizer</th>
<th>Class IV Irritant</th>
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Questions

1. What percentage of the 606 were leachables and not just extractables? Can we limit concern to those that really reach the patient?
2. Is threshold approach same or different for leachables or extractables?
3. Is *in silico* sufficient to limit any further literature or *in vitro* testing?
4. If genotoxic alert and if there are so many, how much work to look at actual literature to confirm? What *in vitro* tests beyond *in silico*/literature should be considered?
5. Can WG provide a finite list of genotoxicants for screening? WG recognizes that this will not be exhaustive.
6. Can we propose a second dimension of “Dosing Regimen” to the Staged Toxicological Threshold approach? Where is the dosing regimen as a second dimension on the staged toxicological threshold?
Session II, Tox/Chem Integration

- Dan Norwood (Boehringer Ingelheim)
  - AET is not an identification threshold such as ICH impurity threshold
  - MDIs are unusual in that all extractables are leachables
  - OINDP example shows that AETs are in the parts-per-million range and include analytical uncertainty
  - Introduced “The Dilemma”
  - Recognized by OINDP with Inhalation Solutions in the parts-per-billion range, similar to LVPs
  - If can show no safety concern extractables in aqueous CES extracts and no migration then so further experiments are needed
  - Purpose of a CES is to systematically identify all potential leachables (i.e. extractables)

Questions

1. What are considerations for multiple exposures and/or doses?
2. How to identify whether extractables in aqueous extracts are artifacts of solvent reaction or actual extractables?
Session II, Chemistry Studies  
Design and Results

• Thomas Egert (Boehringer Ingelheim)
  – Comprehensive protocol included multiple variables (materials, solvents, extraction techniques, analysis techniques, and variability)
  – Identification to an extent practicable (OINDP Best Practices)

• Alan Hendricker (Catalent Pharma Solutions)
  – Profiles were complex prior to application of threshold (AET)
  – Residual solvents and metals results were low and generally innocuous
  – Not all additives were detected and not all detected species were additives (degradation chemistry)
  – Typically achieved 0.1 – 100 ug/g identification limit

• Christopher Houston (Bausch & Lomb)
  – Low energy aqueous extracts do not show leachables except for amides
  – An aqueous extraction profile does not provide any material information
  – Control of pH is impactful
  – No such thing as a uniformly strong solvent
  – Use careful sample preparation techniques, good chemistry practice
  – Use right detection tool, but do not remove overlap is good
  – Revisit supplier information but cannot solely rely on those information
Session III, Characteristics and Requirements for LVPs

- Gregory Sacha (Baxter)
  - LVPs have a wide range of volumes ranging from 100 mL to greater than 2 L
  - Product must be sterile, pyrogen-free, particulate matter free, no anti-microbials, isotonic
  - Multiple routes of administration to peripheral or central (subclavian) veins and peritoneal dialysis
  - Solutions are ready-to-use or prepared in pharmacy (24 hour expiration)
  - Some drugs are ready-to-use such as propofol, ciprofloxacin, lidocaine HCl
  - TPN are custom mixed for each patient in US, but are multi-chamber bags used in EU and expose materials to 3 different polarity solvents
  - Must be collapsible, transparent, compatible, low permeation, low sorption, low leachables, little yellowing following gamma radiation sterilization, environmental impact at disposal
  - No polymer has all quality properties needed for LVPs
Session III, Challenges with LVP E&L Safety Assessments

- Dennis Jenke (Baxter)
  - Three Analytical Approaches, Analytical Action Limit, Impurity Limits and the Safety Assessment Triad
  - The question of how low do you go is a question that relates to the identification of a compound not its concentration estimate

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**Material Characterization**
(Controlled Extraction Study);
Screening and Selection
Extractables as *tentative* leachables

**Simulation Study**
(Simulated Extraction Study)
Worst-Case Safety Assessment
Extractables as *probable* leachables

**Migration Study**
(Target Leachables Study)
Actual Case Safety Assessment
Confirmed leachables
Session III, Toxicology of LVPs

- Jackie Kunzler (Baxter)
  - Benefits of therapy outweigh risks associated with the product and data exists to provide justification, “Dose makes the poison”
  - Guidances provide science-based, data-driven approach for problem-solving
  - Opportunities for toxicological contribution occur at all phases: Design, Development and Material Changes
  - What makes LVPs unique from a toxicological perspective? Large, complex, short-term use, low risk/high benefit
  - May need to rely on Analytical Action Limit due to low level

Questions
1. Is it only for LVPs that simulation studies are recommended?
2. Will there be any recommendations on how to set up simulation studies?
3. If simulation study shows no risk, would the leachables/migration study be necessary? PQRI cannot make such regulatory determinations
4. What is proposed timeline for PODP recommendations to be published?
5. Are there best practices on extractables evaluation of post-sterilized materials? Would there be expected changes in profiles after sterilization?
6. Will Safety Assessment Triad answer the question of what to do with peaks below AAL but potentially above AET? Can a study be performed in the final recommendation?
Session III, SVP Case Study and Regulatory Considerations

- Desmond Hunt (U.S. Pharmacopeia)
  - Case Study of Megavac Bio site/material changes
  - Supply chain issues
  - CCS compatibility
  - Label adhesives/inks migration
  - Migration of wooden pallet fungicide byproducts

- Frank Holcombe (US FDA)
  - Packaging must protect from environment, be compatible with product, and add no additional risk to the patient
  - Change from glass to COC expect permeability (environmental), compatibility and safety changes
  - Change from chlorobutyl/NR blend to bromobutyl elastomer expect compatibility and safety changes
  - Need justification to include: description & characterization
  - Safety reflects extractables and leachables identification, quantitation, and toxicological evaluation
Session III, Biological Safety Considerations for SVPs

- Ingrid Markovic (US FDA)
  - Biologics are different
  - Stability studies are not geared to detect leachables
  - No worst-case scenario risk assessment on edges of manufacturing capability while monitoring clinical outcomes
  - Leachables as adjuvant and/or immunomodulatory factors (literature)
    - Silicone oil, DEHP, MEHP, PAHs, soluble Fe, Cd, Ni, Alkyl phenols
  - Animal models are much less sensitive than humans (1000x less for LPS)
  - Routine analytical will not detect finite changes in potency but may affect immunogenicity
  - Case Studies-EPREX, Fe catalyzed oxidation of preservative triggering formation of protein-preservative adducts, divalent cations inactivation, W causes unfolding and protein aggregation, alkali oxide delamination, aluminum phosphate particulates, barium sulfate particulates, silicone oil

Questions

1. Synergistic, additive effects for negative toxicity endpoints should be considered for thresholds?
2. Can ICH, PQRI thresholds be applied to biologics?
3. How to extend to disposable systems?
Session III, SVP Chemistry and Toxicological Impact

- **Ed Smith (Packaging Science Resources)**
  - CES were performed on COC using 5 solvents, but no simulation study
  - Used GC/FID, GC/MS, HPLC/DAD, LC/MS and ICP/MS
  - Higher levels of metals from bromobutyl rubber
  - More organic extractables from bromobutyl rubber than COC
  - Issues include sampling, change controls, migration and permeation
  - Not all additives were detected
  - Analytical limits are challenged at reasonable limits of detection, i.e. many scenarios show that the AETs are below those reasonable analytical LODs

- **Bill Beierschmitt (Pfizer)**
  - No universally accepted regulatory guidelines for E&L
  - Consider the “Big Five”
    - Genetic Toxicology
    - Carcinogenicity
    - Reproductive Toxicology
    - Sensitization
    - Irritation
  - DEREK then literature review was sufficient for RA
Session III, SVP Case Study

Questions

1. What might be the underlying cause of the recent delamination issue? These are all old products.
2. Are there any aluminum specifications for SVP? Are there any safety limits? What literature might be shared?
3. For products that are sensitive to metallic cations, can we suggest that product is lyophilized?
4. Will health authorities consider toxicological threshold approach? How to facilitate this agreement?
5. Is there any literature showing immunogenic response for intraocular injections? Subcutaneous was presented as more problematic than intramuscular.
6. Are we doing too much toxicological risk assessment? Why look at any of the materials characterization data? Can we consider the simulation study as the starting point for the risk assessment?
7. Can the targets for subsequent leachables studies be honed down to just those compounds that are found to raise toxicological concern during simulation studies?
8. How can we convert all of these data to product specifications?
9. What is current FDA position on single-use disposables?
10. Consider the public consensus standards approach (e.g. ASTM) to gain regulatory agreement.
11. Consider how to present studies to evaluate administration sets and processing aids.
Session IV, PFS Case Study

- Reggie Saraceno (Boehringer Ingelheim)
  - Acknowledgement of work and collaboration of regulatory colleagues
  - Keep focus on Science

- Douglas Ball (Pfizer)
  - Opening Remarks

- Kumudini Nicholas (Health Canada)
  - Case Study Presentation, sANDA proposal
  - Change from glass vial/stopper to PFS
  - Injectable coarse suspension, ER, intra-muscular injection
  - Sterilized by radiation, Mfg in Non-MRA country, Transport study, stability study
  - Same analytical methods for previous presentation used and showed no change
  - QbD Enhanced Approach-Determine CQAs
    - Materials of Construction
    - Determination of correct solvents for extractables
    - Final specifications based on what patient sees, i.e. leachables and sterility
  - Compatibility issues, particulates, leachables, irradiated components, transit effects on leachables
  - Supply chain issues, quality variability, dimensions, sterility, change management
  - Justify use of analytical method after change in presentation
Session IV, Chemistry
Considerations of PFS Case Study

- Michael Ruberto (Material Needs Consulting)
  - Polymers more prone to leachables due to additives (active chemistry)
  - Polymers have a deep supply chain
  - Migration (transport) is thermodynamically and (importantly) kinetically constrained
  - Design experiments for extractables testing
    - drug product formulation, processing, and storage
    - materials of construction
  - Use range of solvents to match material and formulation
  - Match extraction technique to solvent
  - Analyze for all possible compounds and consider Safety Assessment Triad
  - Consider unknowns and provide all chemical data to toxicologists
  - Consider leachables and perform correlations both direct and indirect
  - Look for trends
  - Mock leachables shows identified leachables above AET
    - transformation and degradation compounds of additives (indirect)
  - Mock leachables shows an unknown leachable above AET
Session IV, Toxicology Assessment of PFS Case Study

• Stephen Barat (Forest Research)
  – Only actual leachables will undergo toxicological evaluation
  – Based on estimated daily dose
  – Compare identification to proposed toxicological thresholds
  – Any leachable below 0.15 ug, requires no further evaluation
  – 2,4 di t-butyl phenol
    • Genotoxicity alert via DEREK (benzene ring), check literature, evaluate experimentally or reduce and control to appropriate levels
  – Erucamide
    • No alerts, Class III and Class IV
  – Unknown
    • Less than Class III and Class IV, but exceeds Class V
    • Elucidate structure to allow further screening
Session IV, Panel Discussion PFS Case Study

Questions
1. How to determine oxidation state of additive in material when all you have is identity in an extract?
2. Does the degradation/oxidation state of additive affect toxicological risk?
3. How to provide estimated daily dose for unknown without authentic standards?
4. For barrier-lined, e.g. teflon, components, do you need extractables on full composition?
5. If above 0.15 ug/day, but below ICH is it still necessary to elucidate?
6. Are diffusion coefficients useful for prediction of leachables or extraction studies?
7. What is most relevant to predict leachables? Do you need exhaustive extraction? Do you need to get to asymptotic levels?
Session IV, Current Regulatory Recommendations for Ophthalmic Products

Linda Ng (US FDA)

- Ophthalmics are solution or suspension in LDPE bottles/tips or B/F/S sealed vials
- Material must be squeezable, but this necessitates semi-permeable materials
- Could originate from both primary, labels and secondary packaging
- Information on composition often not available to developer or present in Type II DMF
- Potential solution if supplier could supply low molecular weight components to developer and confirmed by reviewer in DMF
- One-time study until next change
- One batch leachables stability test, appropriate technique to pick up leachables, report in parts-per-million
- Report above 1 ppm, identify at 10 ppm, qualify at 20 ppm
- Not included in specification if detected 1000-fold lower than toxicological risk

Questions

1. For leachables, is this only evaluated with exhibit batches or with annual stability testing? Answer: One time until material change

2. Will FDA be open to changing to total daily intake as recommended by PQRI from parts-per-million action levels? Answer: Currently not familiar, but are open to sound science.

3. Are screening methods used for leachables? Would these be validated analytical methods? Answer: some level of validation/qualification is necessary for all methods. Base on science.
Session IV, Chemistry Considerations of Semi-Permeable Packaging

Christopher Houston (Bausch & Lomb)

- Focus only on solutions and suspensions in LDPE bottles/tips or B/F/S sealed vials
- Review PODP experiments on LDPE, just aqueous extractions did not show known additives except for erucamide
- Comparison of PODP thresholds proposal show relative agreement (up to 6 fold) with current FDA regulatory practice
- Generally LDPE contains minimal additives, while harder plastic components have little intimate contact therefore semi-permeability has great leachables effect (labels, inks, etc.)
- Migration through the packaging is on different time-scales
  - Acrylate esters were quick, PEG was slow, o-phenyl phenol quickly outgas from cartons, diethyl phthalate on carton tab seal (tape)
- Without intimate contact can still see many targets, check headspace GC
- QbD for any change

Questions
1. What are the relative merits of 1 ppm vs the PQRI-PODP threshold approach?
2. How to get controls at all aspects of procurement and manufacturing to inform R&D of all changes? Commodity components are riskiest.
3. Do you register ink/label or refer to DMF?
4. Can foil overwrap control external migration compounds?
5. Can lack of additives change permeability of LDPE to migration compounds?
Session IV, Industry Perspective on Regulation of Ophthalmic Drug Products

Michael Lynch (Pfizer)

- Greater focus on the role of packaging-drug product interactions
- Leachables issues falls outside of ICH and genotoxics
- History with FDA starting in 1999, followed by EMA and Health Canada (draft)
- Divergent views on L&E, US strong leachables focus, EU applies genotoxic limits, scrutiny from ROW, veterinary and biologics
- Leachables were treated as quality issues with specified impurity limit of 1 ppm
- Control based on batch data and specific testing beyond other impurities allows science-based risk argument
- Dialogue with health authorities will produce better, safer products

Questions
1. FDA has requested limits 1000-fold lower than PODP threshold proposal, what assurance that this will no longer be necessary?
Session IV, Potential Application of Toxicological Qualification Thresholds

Mary Richardson (Bausch & Lomb)

- Small dose volume can result in high leachables concentrations
- Risk assessment is composed of local, topical and system endpoints with local and topical being of highest concern
- Literature on ocular irritation is limited
- Introduction of OQT, Ocular Qualification Threshold with Verification Protocol

Questions
1. Is OQT reasonable approach for toxicologist/chemist/regulator?
2. Do ICH approaches apply?
3. Is verification testing sufficient for setting threshold?
4. Should we include skin sensitization be included as separate threshold?
5. Can the proposal compare TDI, total daily exposure, and expected concentrations for all 606 extractables to facilitate comparison by regulators?
Session V, Workshop Summary

Gordon Hansen (Boehringer Ingelheim)

– Industry & Regulatory history
  • Performance & price factor on use, resulted in “horror stories”, e.g. PNAs, nitrosoamines, 2-MBT
  • Delivery to diseased organ
– Industry/Supplier uncertainty
  • Leachables & CFC replacement process, IPAC formed
  • Analytical, supply modifications and alternative delivery
– Regulatory guidances generated
  • Packaging, MDI/DPI and Nasal Sprays
  • IPAC-RS formed to support science behind guidances
– Research questions posited and PQRI involvement
  • Reporting/identification/qualification levels
  • Points to Consider (2001)
  • PQRI L&E WG formed (2001)
  • Driven by hypotheses and research plan, published 2006
– Future Improvements
  • QbD at the supplier level, ELSIE database
Acknowledgements

• James F. Castner, Ph.D.

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