Selection and Qualification of Materials - Approaches to Consider

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Agenda

- Current Regulatory Landscape
- Selection of Materials
  - Integrated Approach
- Qualification of Materials
  - Supplier information needed to qualify materials
- Toxicologist Perspective & Case Examples
  - Dr. Beierschmitt

Definitions, Laws, Regulations and Guidances

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 recommended storage conditions.

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 Documents

- *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

Guidance Documents

- *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 drug product should be evaluated for compounds that leach from elastomeric or plastic components of the container closure system.

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	Aqueous-based solvents: Reference to indirect food additive regulations Non-aqueous solvents & co-solvents: 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

Compendial Tests for Biological Reactivity

Compendial Summary for Biological Testing

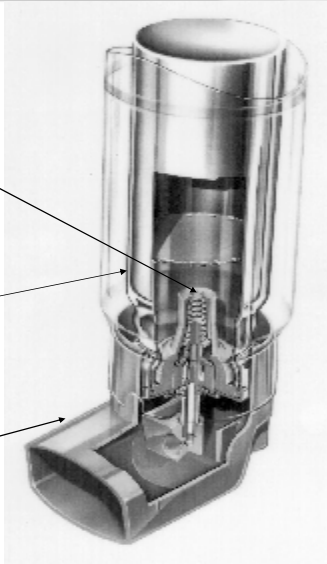
	USP	EP	JP	ISO 10993	ISO 8871-4*
In-Vitro					
Agar Diffusion (cytotoxicity)	+	-	-	-	+
Hemolysis	-	-	+	-	-
Endotoxins (LAL)	-	-	-	-	+
In-Vivo					
Systemic Injection	+	-	+	-	+
Intracutaneous Test	+	-	-	-	+
Pyrogens	-	-	+	-	-

*Elastomeric parts for parenterals and for devices for pharmaceutical use -- Part 4: Biological requirements and test methods (published standard June 06)

OINDP Material Selection

MDI "Critical Components"

- Dose metering valve
  - Metering chamber
  - Stem(s)
  - Seals/gaskets
  - Sealing rings
- Canister
  - Coated?
- Mouthpiece/actuator



MDI Schematic Provided by Bespak Europe

Integrated Approach to Developing a Container Closure System

Current Landscape

- Materials purchased from supplier
  - Materials chosen by cost, not necessarily quality
  - Materials chosen with little (no) input from chemists & toxicologists
  - Formed into container closure components
  - Container Closure System (CCS) manufactured for DP
- Total extract profiling conducted
  - Limited information on material formulation
  - Sensitive analytical methods developed to obtain total extract profile
    - Extract profile established to lowest limits of detection
    - Leachable profile of DP determined
      - Correlate to total extract profile
- Toxicologist evaluates extractable/leachable profile
  - Usually asked late in the process, typically to support NDA
  - Qualifies each material independent of thresholds
  - **Potential Safety Issues Delay NDA Submission**

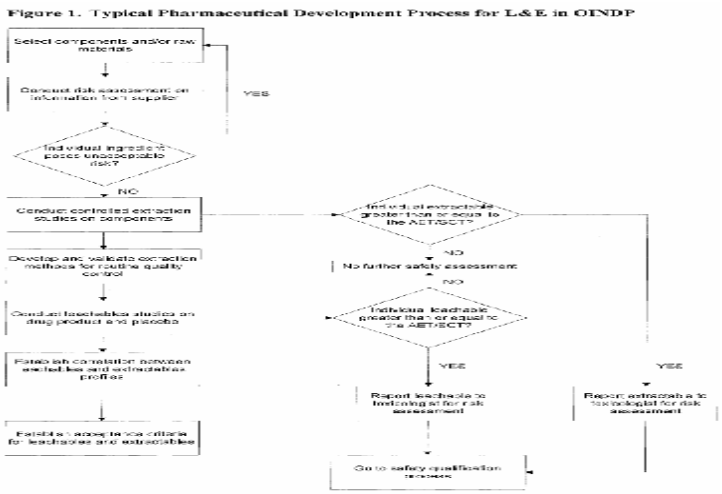
Integrated Approach (1)

- Materials purchased from supplier
  - Container Closure Team (CCT) formed
    - Comprised of chemists, toxicologists, packaging, procurement
  - Quality materials chosen by the CCT
    - Suppliers provide formulation and general extract information
    - Cost a secondary factor
- Toxicologist evaluates material extract profile
  - Initial evaluation made early in the container closure development process
    - Safety information from the supplier (e.g., USP results)
    - In silico evaluation
  - Preliminary qualification of each material based on accepted safety thresholds and anticipated TDI

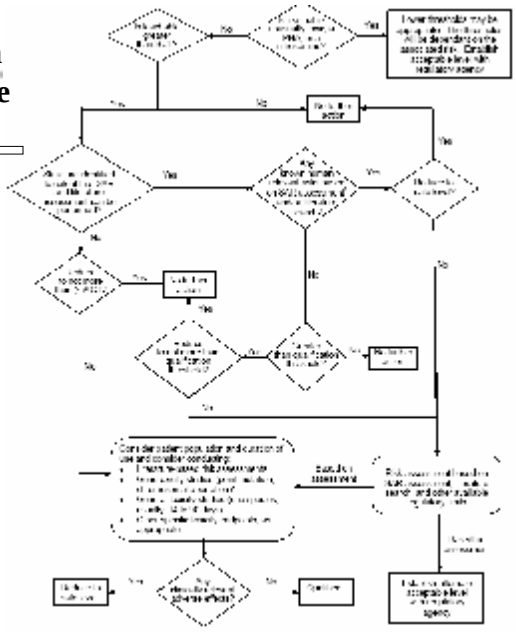
Integrated Approach (2)

- Container Closure developed for DP
  - Total extract profiling conducted by chemists
    - Analytical methods based on material formulation and general extract profile obtained from supplier
    - Analytical LOD based on qualification thresholds
- Toxicological Qualification of CCS
  - Based on leachable profile of DP
  - Leachables below SCT considered qualified
  - Leachables greater than the SCT and less than the QT
    - Qualify with in silico data and published data
    - Additional in vitro, in vivo testing on a case-by-case basis
  - Leachables above the QT can be qualified on a case-by-case basis
    - Develop qualification strategy and work with regulators to establish qualification of leachables above the QT
- Acceptable risk assessment of leachable profile
  - **No registration delay due to safety issues related to CCS**

Integrated Approach Flow Chart



Safety Qualification Decision Tree



Conclusions

- Current regulatory guidance is “high level” in scope
  - Does not provide threshold rationale to evaluate CCS leachables in DP
  - Qualification of all extracts required
- USP <87> <88> and other tests (ISO 10993) have little value in qualifying leachables from CCS
  - However, they are of value when making early assessments of materials
  - Are required for registration or obtaining CE stamp
- Integrated approach will improve CCS early in the DP lifecycle
  - Open dialogue with Suppliers essential in developing a quality CCS (i.e., Quality by Design)
- Scientifically-based thresholds can be used to qualify leachables from CCS in DP
  - Analytical LOD should be based on qualification threshold
  - No need to ID everything

Questions
(?)