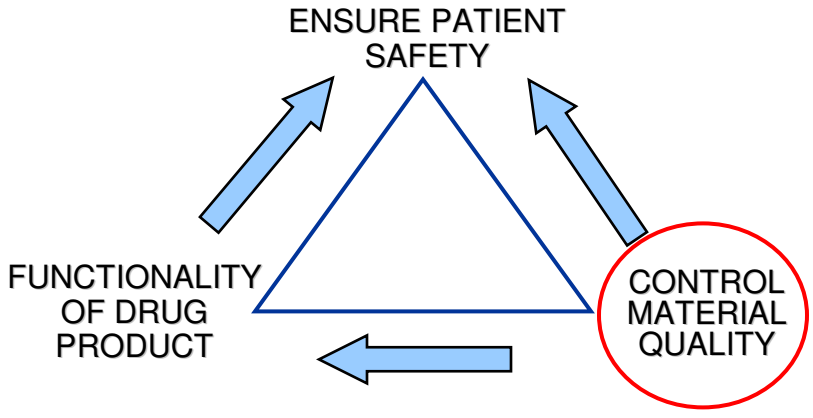
Focused Testing – Is it Possible??

Presented by: Mike D. Hodgson

Authored by: IPAC-RS Materials Working Group

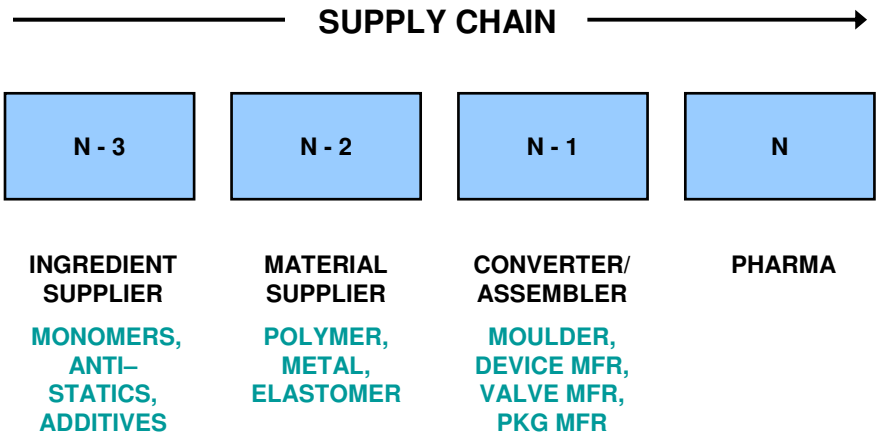
IPAC-RS

Why Test Container Closure/Device Materials?



IPAC-RS

Who is Responsible For This Testing?



Material Testing – Regulatory Guidance

Key Regulatory Guidance

- PQRI – Safety Thresholds & Best Practices For Extractables & Leachables in OINDP (Extractables/Leachables)
- Health Canada/EMEA Guidance – Pharmaceutical Quality of Inhalation and Nasal Products (Extractables/Leachables)
- FDA - MDI/DPI Draft Guidance (Inhalation Product Performance & Characterizaton)
- FDA – Guidance on Inhalation solution, suspension, spray and nasal spray products
- CDRH - Reviewer Guidance for Nebulizers, Metered Dose Inhalers, Spacers and Actuators, (Product Characterization including Leachables)
- FDA - Guidance for Industry: Container Closure Systems for Packaging Human Drugs and Biologics (Packaging Characterization)
- CHMP, CVMP - Guideline for Plastic Immediate Packaging Materials (Packaging Characterization)
- EP 3, USP <381>, <661> (Physicochemical)
- ISO10993, USP<87>, USP<88> (Biocompatibility)

Material Testing – Regulatory Expectations

Items to Specify

- Category of device (Biocompatibility Testing)
- Class of plastic, grade of metal, additives etc
- Critical components (drug contact/mucosal contact)

Testing Expectations

- Controlled Extractions Studies – Material selection, predict likely leachables
- Leachable Registration Studies – Assess patient Total Daily Intake (TDI)
- Routine Control of Materials – ID, Extractables & performance of materials
- Physicochemical – depends on type of material
- Biocompatibility – depends on category of device and may include:
  - Cytotoxicity, (in-vitro)
  - Systemic, Intracutaneous, Sensitisation & Irritation (in-vivo)

Controlled Extraction Studies

What are they…..

Detailed extraction studies incorporating multiple solvent systems, extraction techniques & analytical instrumentation to determine the “worst case” extractable profile, i.e. “worst-case” scenario from a leachables perspective

Extraction Study Variables….

- Sample preparation
- Extraction solvent, temperature and duration
- Extraction technique
- Analytical instrumentation (LC-UV/MS, GC-FID/MS, ICP-MS etc)

Testing & The Drug Product Development Process

MATERIAL SELECTION

Qualify Material (Ext & Bio)

CLINICAL TRIALS (PH2/3)

Evaluate Leachables

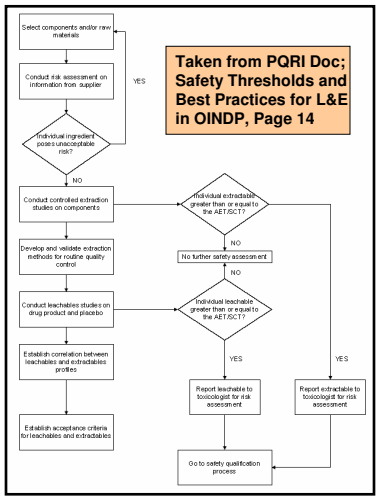
REGISTRATION STABILITY

Confirm Routine Control Strategy

PRODUCTION

Change Management

Risk Assessment & Info Gathering Exercise



Taken from PQRI Doc; Safety Thresholds and Best Practices for L&E in OINDP, Page 14

IPAC-RS

OINDP Supplier & MFR Communication

Technical Communication Early and Often

Business Communication Early and Often

OINDP SUPPLIERS

OINDP MANUFACTURERS

Regulations Discussed Early And Often

Design Quality Into the Product

GMP Guideline for Suppliers Of OINDP

IPAC-RS

Discussion Point – What Does Pharma Need and Why?

What….

Materials that meet functional/mechanical requirements

Materials that are safe for patients

Why….

Understanding of compounds in materials that may reach the patient and may have consequences

Material that is used in production is the same chemically as that which was used in the clinic so that there is assurance that the drug/pkg/patient interaction remains unchanged

Discussion Point – Extent & Type of Testing Throughout Supply Chain

Raw Material Suppliers

- Typically testing is functional/mechanical or biocompatibility
- Certifications may be given for compliance to food regulations
- Certificates of analysis or conformance accepted from ingredient suppliers without confirmation testing
- Several concerns regarding chemical testing:
  - Risk of giving customers false impression of the level of potential leachables
  - Concerns around extractables methodology – can a generic method be developed & applied (e.g. what should the supplier test, and what kind of data should the supplier provide)
  - Testing not representative of final component – useful as an initial indication of risk

Discussion Point – Extent & Type of Testing Throughout Supply Chain

Moulders

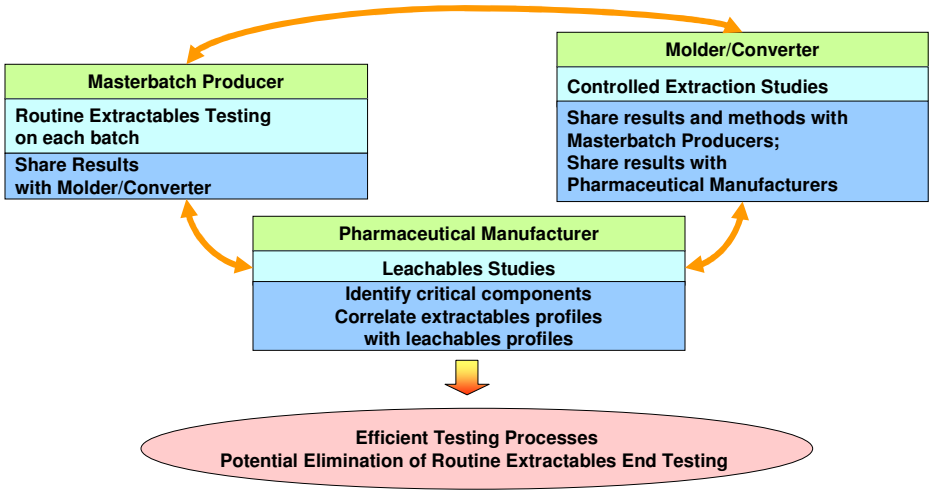
- Perform ID testing at incoming
- Accept certificates of analysis/conformance without confirmation testing
- May perform extractables testing, but have the following concerns:
  - Test can only monitor raw material but not really control it's change or variability
  - Test may be specific to customer so that one material may have six different extractables methods performed on it
  - Molded parts may only be tested, so that several components that are molded under similar conditions are tested individually but have essentially the same extractables profile

Discussion Point – Extent & Type of Testing Throughout Supply Chain

Pharma

- Extent of testing done in accordance with diverse regulatory expectations/guidance
- Testing may be confirmation of supplier's results (e.g. biocompatibility)
- Each dosage form/pkg/device combination requires individual treatment due to different compatibilities
- Leachables testing & Tox Safety Assessment
- Controlled extraction and routine extraction are performed and may generate the following concerns:
  - Implications for the Pharma companies of material changes post-approval: discontinuation of materials may force stockpiling to allow time for replacement materials testing that may take several years
  - Compounds may be detected that are above the AET but pose no toxicological concern but will certainly delay production

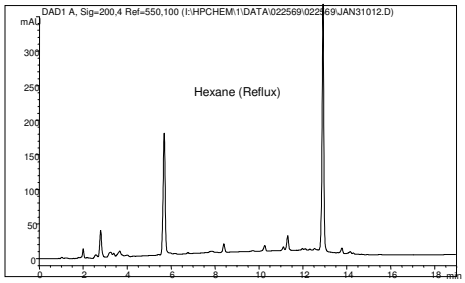
Can a Common Approach To Testing Be Developed between Suppliers and Pharma?



Discussion Points

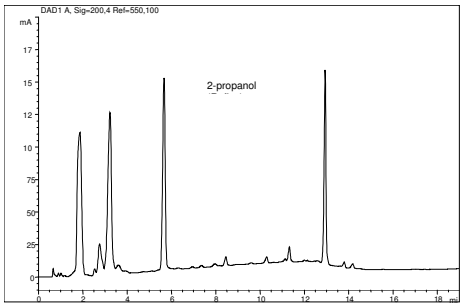
- **Extent & type of testing throughout the supply chain**
  - Can a generic extractables method be developed & applied to raw material/molded components across drug products
- **What information is shared between suppliers & customers?**
- **What would it take to get to a focussed testing approach?**
  - What don't we have that we need?
  - What do we have that we don't need?
  - Is it possible to do a test at only one place, the right place/time, in the supply chain?
  - Can safety/extractable profiles be made available for materials that have been in use for a long time?
  - Can tiered testing approaches for materials be done?
  - Does testing upstream eliminate the impact of change downstream?
- **Life cycle management & legacy products**
  - What do the regulatory authorities want to see
  - Does demonstrating equivalency do enough

Back-Up Slides – Polypropylene CES

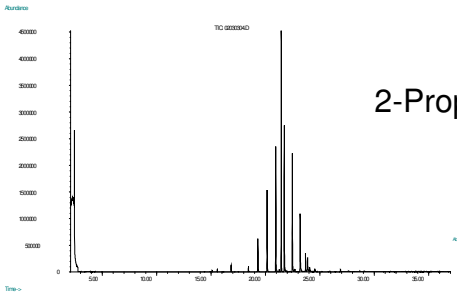


Hexane Reflux

2-Propanol Reflux

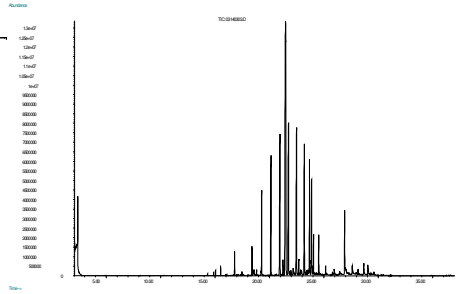


Back-Up Slides – Elastomer CES

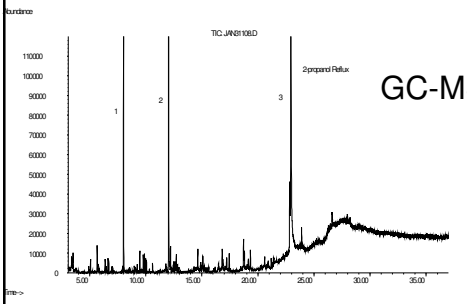


2-Propanol Sonication

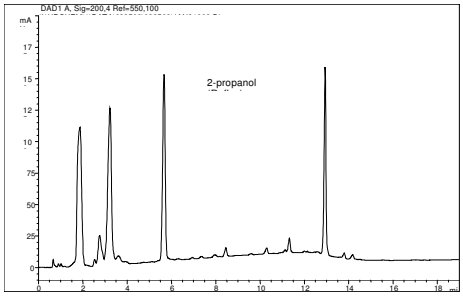
2-Propanol Soxhlet



Back-Up Slides – Polypropylene CES



GC-MS 2-Propanol Reflux



HPLC-DAD 2-Propanol Reflux