Risk Assessment for Pharmaceutical Packaging Material

- Shivkumar Vishwanathan
... should **never** contribute harmful components to the drug

... should **never** impact drug quality

... should **never** impact drug efficacy
Drug – Package Interactions - How to tackle the problem?

We need to characterize the packaging material

• The polymer structure of package and its composition is usually not known by the user.

We need to assess the stability of packaging material

• Although the polymer is classified as food grade, it may not be sufficiently protected against degradation.

We need to understand the possibilities of interaction

• The additives package used to impart specific properties, (e.g. antistatic, MVTR) cannot be fully considered as “inert” and immobile. They may leach into the drug thereby contaminating the contents.

We need to review and optimize the quality control

• The quality control of the drug does not apply after storage or long interaction periods, i.e. it is not able to detect issues happening after sealing. This part of product lifetime cannot be left out of control.
Challenges - Non-technical

Complexity of supply chain – lack of information – source of surprises!

- Monomer Manufacturing
- Polymer Manufacturing
  - Synthesis
  - Extrusion
- Masterbatchers
- Converting
- End Products
- Polymer Recycling
- Processing additives
- Cleaning processes
- Printing inks
- Labels

- Process Chemicals
- Polymerization Regulators
- Storage Stabilizers
- Antioxidants
- Processing Stabilizers (Light stabilizers)
- Light Stabilizers (AO/Proc. stabilizers)
- Colorants
- Additives for Plastics
- Recycling
Potential consequences of interactions between materials and drugs/APIs:

- Decrease of activity due to adsorption of active substance on the material.
- Degradation or modification of active ingredient due to released substances.
- Content precipitation, e.g. proteins.
- Changes in pH due to leaching of material components.
- Change of appearance (color) due to leaching of material components.
- Analytical interferences during determination of active ingredient or impurities.

Impact on safety of the drug due to leaching of toxic material components.
## Definitions

- **Extractables & Leachables Studies:** Qualitative and quantitative investigations which ensure that a pharmaceutical packaging or contact material is safe with regard to chemical components and which does not negatively influence the drug.

- **Extractables:** Any chemical species that can be extracted from components of a material under exaggerated laboratory conditions (solvent, temperature, pH, contact time, etc.).

- **Leachables:** Chemical species that leach from product-contact and/or non-product contact surfaces into a process stream, bulk drug substance, product intermediate and/or final drug product under specified conditions of production, storage and use.
Additives provide properties or effects in addition to stabilization which are additional sources of potential Extractables and Leachables.
There is an increasing set of Regulations and Guidelines:

EU-Pharmacopeia Chapter 3, incl Supplement 5.1, 5.2 & 5.3
USP e.g. <381> for elastomers, <661> for polymer characteristion
FDA Guidance for Industry: Container Closure Systems for Packing Human Drugs and Biologics.
FDA Guidance for Industry: Metered Dose Inhaler (MDI) and Dry Powder Inhaler (DPI) Drug Products.
FDA Guidance for Industry: Nasal Spray and Inhalation Solution, Suspension and Spray Drug Products.
EMEA CPMP/QWP/4359/03, Guideline on Immediate Packing Materials.
EMEA CPMP/QWP/2845/00, Note for Guidance for … Metered Dose Inhalation Products Packing Materials.

The concepts behind these regulatory requirements are more or less similar in the US and EU
### Risk Assessment

#### Potential Interaction of Packaging with Drug

<table>
<thead>
<tr>
<th>Degree of Concern</th>
<th>High</th>
<th>Medium</th>
<th>Low</th>
</tr>
</thead>
<tbody>
<tr>
<td>High</td>
<td>Inhalation aerosols and solutions</td>
<td>Sterile powders and powders for injection</td>
<td>Low</td>
</tr>
<tr>
<td></td>
<td>Injectables</td>
<td>Inhalation powders</td>
<td></td>
</tr>
<tr>
<td>Medium</td>
<td>Ophthalmic solutions</td>
<td>Transdermal ointments / patches</td>
<td>Nasal spays</td>
</tr>
<tr>
<td>Low</td>
<td>Topical Solutions</td>
<td>Topical Powders</td>
<td>Oral Tablets and Capsules</td>
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<tr>
<td></td>
<td>Topical and Lingal aerosols</td>
<td>Oral Powders</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Oral solutions</td>
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For Bulk Packaging

• No dedicated guidelines for doing these studies.

• This risk can be assessed within the scope of process validation procedure.

• Degree of freedom in designing experiments much more than unit containers.

• Relatively lower risk of contaminants from Packaging material affecting the drug.

• Care to be taken if containers are re-used which may then lead to cross contamination and increased release of contaminants.
**Steps in Risk Assessment…**

1. **WHAT?**

   Polymer analysis & characterization  
   Identification of the Additives used.  
   Identification of unknown substances/impurities.

2. **HOW MUCH?**

   Organic Trace Impurities. (up to ppb levels)  
   Additives in Plastics  
   Residual Solvents, Odor Components.  
   Stability Testing.  
   Extractable & Leachable Studies

3. **WHY?**

   Failure Analysis  
   Complaint Investigations  
   Determine the role of each additive in polymer formulations.  
   Make recommendations for alternative stabilizers for greater Compatibility with the package to achieve lower leachability.