Surrogate Selection

There is no perfect surrogate material, but there are standardized materials – the best choice will depend upon the particular manufacturing process and the situational priority of a variety of variables.
Surrogate Selection Variables

Meets Requirements for the Manufacturing Process
Flowability (bulk powder movement)
Compactability and adhesion (tableting)
Solubility (emulsion vs. solution)
Surrogate Selection Variables

Relative Hazard or Toxicity of Test (surrogate) Material
OEL or other health limit
Process safety concerns
Surrogate Selection Variables

Quality Concerns
API vs. non-API
Cleanability
Established cleaning procedures
Surrogate Selection Variables

Test Material Availability and Cost

How much test material is needed?

Cost of bulk material

“Off the shelf” vs. Custom manufacture (micronization)
Surrogate Selection Variables

“Containment Challenge” Similar to Target Material

“Dustiness” - defined as the propensity of a material to emit dust during manufacturing: may be considered analogous to vapor pressure on a molecular scale.

Determined by a complex interrelationship of factors. Can not be predicted reliably by theory and must be measured empirically.

A standardized measure of “dustiness” has not been established.

A variety of individual particle characteristics effect relative dustiness – particle size provides the best correlation.
Material Characteristics Relative to Dustiness

Particle Size and Size Distribution

Characteristic with the greatest impact on powder dustiness

Generally, decrease in particle size results in increase in dustiness

Powders blended to contain only a portion of small particles were found to be nearly as dusty as powders comprised entirely of small particles

For most materials, as the proportion of small particles in a blend diminishes, the faction of small particles in the generated dust increases.
Common Process Surrogates

The most commonly used process surrogates in the Pharmaceutical and Containment Industry

Lactose
Naproxen Sodium
Mannitol
Acetaminophen
Riboflavin
Sucrose
Arizona Road Dust
Insulin
# Surrogate Selection Criteria – Analytical Method

<table>
<thead>
<tr>
<th>Surrogate</th>
<th>Maxxam LOQ Mass/Sample</th>
<th>Method Selectivity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lactose</td>
<td>2.5 ng</td>
<td>► Good</td>
</tr>
<tr>
<td>Naproxen Sodium</td>
<td>0.05 to 0.2 ng</td>
<td>► Very Good</td>
</tr>
<tr>
<td>Mannitol</td>
<td>1.0 ng</td>
<td>► Good</td>
</tr>
<tr>
<td>Acetaminophen</td>
<td>0.5 ng</td>
<td>► Exceptional</td>
</tr>
<tr>
<td>Riboflavin</td>
<td>5 ng</td>
<td>► Good</td>
</tr>
<tr>
<td>Sucrose</td>
<td>5 ng</td>
<td>► Good</td>
</tr>
<tr>
<td>Arizona Road Dust</td>
<td>10,000 ng</td>
<td>► Poor</td>
</tr>
<tr>
<td>Insulin</td>
<td>NA</td>
<td>► Exceptional</td>
</tr>
</tbody>
</table>
## Surrogate Selection Criteria – Quality Concerns

<table>
<thead>
<tr>
<th>Surrogate</th>
<th>Type</th>
<th>Cleanability</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lactose</td>
<td>Excipient</td>
<td>![Highly Soluble]</td>
</tr>
<tr>
<td>Naproxen Sodium</td>
<td>API</td>
<td>![Highly Soluble]</td>
</tr>
<tr>
<td>Mannitol</td>
<td>Excipient</td>
<td>![Highly Soluble]</td>
</tr>
<tr>
<td>Acetaminophen</td>
<td>API</td>
<td>![Modestly Soluble]</td>
</tr>
<tr>
<td>Riboflavin</td>
<td>API</td>
<td>![Sparingly Soluble]</td>
</tr>
<tr>
<td>Sucrose</td>
<td>Excipient</td>
<td>![Highly Soluble]</td>
</tr>
<tr>
<td>Arizona Road Dust</td>
<td>Dirt</td>
<td>![Insoluble]</td>
</tr>
<tr>
<td>Insulin</td>
<td>API</td>
<td>![Poorly Soluble]</td>
</tr>
</tbody>
</table>
## Surrogate Selection Criteria – Availability & Cost

<table>
<thead>
<tr>
<th>Surrogate</th>
<th>Relative Cost</th>
<th>Multiple Specification</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lactose</td>
<td>1</td>
<td>Yes – wide variety</td>
</tr>
<tr>
<td>Naproxen Sodium</td>
<td>100-1000</td>
<td>Custom</td>
</tr>
<tr>
<td>Mannitol</td>
<td>5</td>
<td>Yes – variety</td>
</tr>
<tr>
<td>Acetaminophen</td>
<td>5-10</td>
<td>Custom</td>
</tr>
<tr>
<td>Riboflavin</td>
<td>15</td>
<td>Custom</td>
</tr>
<tr>
<td>Sucrose</td>
<td>5</td>
<td>Yes – variety</td>
</tr>
<tr>
<td>Arizona Road Dust</td>
<td>10-20</td>
<td>Yes – variety</td>
</tr>
<tr>
<td>Insulin</td>
<td>Very high</td>
<td>NA</td>
</tr>
</tbody>
</table>
Surrogate Selection Criteria – Summing it up…

Selection of the best surrogate material for your application depends upon…

• which criteria are your drivers
• particular surrogate characteristics that may also drive the selection process…
Lactose

Selection Drivers

Least expensive in bulk, wide variety of specifications (particle size distribution) available “off the shelf”

Low hazard

Minimal quality concerns, easily cleanable

Sensitive and specific method available (2.5 ng/sample)

Specified surrogate in ISPE guidance document

Dustiness independent of humidity and moisture content

Potential Concerns

Common excipient – may be used in the test formulation or facility may have background levels.

International shipments can be complicated by bovine product import concerns

May lose specification upon storage of micronized material (agglomeration)

Complicated analytical method limits options for analysis
Naproxen Sodium

Selection Drivers

Highest sensitivity (0.05 to 0.2 ng/sample)

Easily cleanable

Uncomplicated analysis increases availability of method

Widely accepted surrogate, first alternative in ISPE Guidance Document

Good containment challenge (high dustiness index)

Potential Concerns

High relative material cost if handling in bulk

API introduction may cause quality concerns

Custom sieving or micronization needed for specific size distribution
Mannitol and Sucrose

Selection Drivers

Low cost in bulk, variety of specifications (particle size distribution) available

Low hazard

Minimal quality concerns, easily cleanable

Sensitive and specific method available (Mannitol is 1.0 ng/sample)

Good alternative if Lactose is present in formulation or facility

Potential Concerns

Common excipients – may be used in the test formulation or facility may have background levels.

Complicated analytical method limits options for analysis
Acetaminophen (Paracetamol)

**Selection Drivers**

- Relatively low cost API in bulk
- Highly sensitive and specific method available (0.5 ng/sample)
- Good surrogate for tableting or tablet handling activities.
- Was one of the first commonly used surrogate materials (EU)

**Potential Concerns**

- API introduction may cause quality concerns
- More difficult to clean
- Custom sieving or micronization needed for specific size distribution
- Unusual elongation ratio for crystals
- High cost and limited options for analysis (LC/MS/MS)
Riboflavin (Sodium Acetate)

Selection Drivers

Common use for CIP coverage testing may eliminate quality concerns

Surface contamination can be visualized by black light

Potential Concerns

API introduction may cause quality concerns

More difficult to clean

Custom sieving or micronization needed for specific size distribution

Low level environmental background common
The Next Step – Ongoing Containment Verification

FAT and SAT testing is performed in order to predict with some degree of certainty, that CPTs and worker exposures are not exceeding limits.

FAT and SAT testing is performed on newly installed equipment, in optimal working conditions.

Performance of containment equipment can degrade or fail over time.

Ongoing evaluations of containment and employee exposures during routine operations is the only means to be confident that containment is maintained, and potent materials are handled safely!
THANK YOU.

PROCESS SURROGATES & DUSTING TESTING

Matt Meiners, CIH
Division Manager, Laboratory Services