Contained processes and equipment

Gordon Farquharson, July 2016
Agenda

• Understanding the hazards and risks of an adverse event.
• Industry developed safety bands or levels (OELs & OEBs).
• Containment principles
  • Closed processes and equipment.
  • Open processes in containment systems.
• Example solutions.
Understanding the hazards
• Toxic effect likely to be dose related.
• Ability to metabolise varies.
• Can be very difficult to render safe. May have to rely on cleaning.
• Broad occupational health and cross-contamination rules apply.
• Industry defines OELs & OEBs, and develops hazard risk mitigation measures.
• GMPs express cross-contamination ADE principles.

• Approach to risk management:
  • Risk assessment.
  • Define mitigation measures.
  • PPE a last resort.
  • Prove performance of equipment & systems.
  • Document rationale.
  • Explain and GMP/SHE conflicts.
• Harmful effect sometimes dose related.
• One bacteria could proliferate and kill/injure you.
• Severity of harm organism related.
• Can be inactivated by sterilisation or alternative bio-decontamination.
• There are bio-safety rules and guidance classifying levels of risk (BSL 1-4), and associated risk mitigation measures.

• Approach to risk management:
  • Risk assessment.
  • Define mitigation measures.
  • PPE a last resort. May not be acceptable in some markets.
  • Prove performance of equipment & systems.
  • Document rationale.
  • Explain and GMP/SHE conflicts.
• Harmful effect dose related.
• Ability to metabolise varies.
• Can be very difficult to render safe. May have to rely on cleaning.
• Can penetrate barriers.
• Often long half-life.
• Broad occupational health and cross-contamination rules apply.
• Industry defines safe limits & develops hazard risk mitigation measures.

• Approach to risk management:
  • Risk assessment.
  • Define mitigation measures.
  • PPE a last resort. Prove performance of equipment & systems.
  • Document rationale.
  • Explain and GMP/SHE conflicts.
Containment principles
Principles of handling hazardous materials – an escalating approach.

- Use an alternative less hazardous material.
- Dilute the hazardous agent.
- Work in a less hazardous material phase – liquid vs gas or solid/powder.
- Handle materials in closed systems.
- Place open systems in primary containment enclosures with secondary containment and PPE as appropriate.
- Place open process in containment room with reliance on PPE for operator protection.
**Principles**

- Closed process
- Open process in isolator
- Open process Operator PPE
Conflict:

*Containing hazardous aseptic manipulations*
Open aseptic process in an isolator

- Which way would you go?
  - -ve or +ve pressure isolator
  - Leakage integrity of isolator
  - Cleanliness Grade of the surrounding room

- Depends on the RISK of an adverse event:
  - Operator exposure vs Sterility assurance.

Grade C/D Room +ve

Grade A Isolator
+ve or -ve
Setting an Occupational Exposure Limit (OEL)

Ultimate goal is to determine the containment necessary for the safe handling of the material by establishing a “protective” airborne limit (OEL).

After assembling the data, the next step is to role up data into a quantitative risk assessment, however...

If data are insufficient for establishing an OEL, or you want a more practical hazardous compound management tool, assign an OEB (Occupational exposure band) (Performance Based-OEL)

- Early in development
- Low volume of production
- Helps to avoid multiple hazard mitigation measures in a business.
**Occupational Exposure Band (OEB)**

Assign chemicals into a few categories based on their inherent properties

Allows listing of unit operations and pre-assignment of safe handling procedures based on exposure potential

Categorizes chemical into an exposure band that can be easily recognized

Helps put hazards in perspective!
<table>
<thead>
<tr>
<th></th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Low</td>
</tr>
<tr>
<td>2</td>
<td>Moderate</td>
</tr>
<tr>
<td>3</td>
<td>Moderate-high</td>
</tr>
<tr>
<td>4</td>
<td>High (default)</td>
</tr>
<tr>
<td>5</td>
<td>Extremely High</td>
</tr>
</tbody>
</table>

*Concept analogous to biosafety levels BSL 1-4*
Typical mitigation measures deployed for the OEBs

1 - Good manufacturing practices
2 - Good manufacturing practices
   (with more stringent controls)
3 - Essentially no open handling
   (closed systems should be used)
4 - No open handling
   (closed systems must be used)
5 - No direct human intervention
Factors Determining OEBs

Evaluate based on qualitative matrix
(use professional judgment)

Assign based on total number of points from a ranked toxicological profile assessment

Assign based on 8hr TWA OEL (ranges):

- 1 - 10 mg/m$^3$ ➔ 1
- 0.1 - 1 mg/m$^3$ ➔ 2
- 10 - 100 mcg/m$^3$ ➔ 3
- 1 - 10 mcg/m$^3$ ➔ 4
- <1 mcg/m$^3$ ➔ 5
Characteristic Traits of OEBs

Band 1
- Relatively non-toxic
- Non-potent
- No systemic effects

Band 2
- Low potency
- Little systemic effect
- First aid / simple med treatment

Band 3
- Reversible or slowly reversible effects
- Not life-threatening or incapacitating
- Satisfactory medical treatment

Band 4 or 5
- Life-threatening
- Short / long term irreversible effects
- Disabling or incapacitating
- Immediate medical treatment
Examples of medicinal compounds in OEBs

<table>
<thead>
<tr>
<th>Band 1</th>
<th>Band 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acetaminophen</td>
<td>Amphetamine</td>
</tr>
<tr>
<td>Aspartame</td>
<td>Phenobarbital</td>
</tr>
<tr>
<td>Mannitol</td>
<td>Diazepam</td>
</tr>
<tr>
<td>Aspirin</td>
<td>Chlorpheniramine</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Band 2</th>
<th>Band 4 or 5</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diphenhydramine</td>
<td>Cytotoxic Anticancer drugs</td>
</tr>
<tr>
<td>Carbamazepine</td>
<td>Beclamethasone</td>
</tr>
<tr>
<td>Codeine</td>
<td>Oral contraceptives</td>
</tr>
<tr>
<td>Hydrochlorothiazide</td>
<td>Fentanyl</td>
</tr>
</tbody>
</table>

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Choosing the right process & equipment
Closed systems

- Closed bioreactor.
- Closed bio-waste system.
- Closed chemical reactor.
Roller compaction vs Wet Granulation & Fluid Bed drying

• Easier to contain.
• Low extract airflow can ensure -ve pressure to process enclosure.
• Possible to inert gas blanket.
• CIP reasonably straight forward.
• Powder feed and granule discharge easily contained.
• Lowe explosion risk.
Roller compaction vs **Wet Granulation & Fluid Bed drying**

- More difficult to contain.
- High air volume on FBD process requires large areas of safety HEPA filtration.
- Not practical to inert gas blanket.
- CIP possible by complex surfaces – filter a big challenge.
- Powder feed and granule discharge easily contained.
- Explosion risk high.
Closed wet milling
GEA “Consigma”™ integrated continuous concept
WIP Contained Tablet Compression
Split butterfly valve

- Connections between containers & process equipment.
- Engineering alignment & maintenance critical.
- Add annular LEV extract systems for lower OEB materials.
- Examples courtesy of:
  - GEA “Buck” ® Valve
  - Hanningfield ™ Valve
The disposable approach

- Single use materials and devices. Can avoid cleaning and decontamination.
- Need to consider the waste handling.
- Transfer chutes.
- Containers.
- Closing and sealing systems.
- Single use.
- Examples courtesy of ICL Dover™
The disposable approach – Glove-bags
Weighing/Dispensing Isolator
Vessel charging Isolator
Reactor charging Isolator

Open handling within a closed isolator
Filter dryer pack-off Isolator
Decontamination techniques
Remember - Isolator Cleaning

- Often forgotten – just as important as the process and process containment.
- Manual Cleaning closed, using the manipulation system.
- Manual Cleaning open, followed by a surface decontamination process.
  - Does this influence the surrounding environment quality requirement?
- CIP potential
  - Process design has to be bespoke.
  - Drainage and cleanability
  - Corrosion
Bio-decontamination methods

- Sterilisation – closed systems only.
  - Moist heat 121 or 134 degC.
- Environments – small or large enclosures.
  - Gaseous methods.
    - \( \text{H}_2\text{O}_2 \)
    - \( \text{ClO}_2 \)
    - \( \text{O}_3 \)
    - \( \text{NO}_2 \)
  - Aerosols – e.g. \( \text{H}_2\text{O}_2 \) & Peracetic acid.
  - Safety & efficacy of the process itself must be proved.
Chemical-decontamination methods

- Degradation and denaturing – converting hazardous compound to a benign one.
- Cleaning – removal of residue of compound to a safe level. Cleaning acceptance criteria based on ADE or %age of active dose.
  - Remember that the waste is likely to have to be considered as contaminated waste for effluent treatment.
Proving the integrity of closed systems

- -ve or +ve pressure process system.
- Pressure test prior to operation.
- Pressure monitoring in service.
- Challenge test or surrogate material testing.

ISPE developed a methodology – “Assessing the particulate containment performance of equipment.”
Assessing Pharmaceutical Equipment Containment performance using surrogate challenge
Simple explanation of surrogate testing

- Handling or processing lactose or another surrogate material in containment equipment such as an isolator, material transfer valve or other equipment intended to contain active pharmaceutical ingredients (APIs).

- Conducting air sampling and surface sampling to determine how much dust escapes from the containment.

- The sampling results provide a means of estimating how effectively the equipment will contain the API under similar conditions of use.
Define a known source challenge of airborne particles inside.

Determine what percentage gets out! This is a measure...
Applied to small enclosures
Applied to bespoke isolators
Applied to contained dust collection

Dust Collection System designed for bag-in/bag-out filter
Changing and collection drum liner removal
Purpose and benefits

- Evaluate containment performance without potential exposures to potent Active Pharmaceutical Ingredients (APIs)
- Evaluate containment performance in situations where an analytical method has not been developed for the API of interest
- Evaluate equipment/devices before purchase
- Obtain baseline data to compare equipment models from different suppliers
- Obtain baseline data to compare different technologies
- Evaluate performance of new equipment before initial production begins using potent API
- Retest to determine if performance of existing equipment has degraded over time versus the baseline
Some limitations of surrogate testing

• Does not evaluate exposures to gases or vapours which may escape the containment
• Results not directly comparable to materials with different physical properties
• Results do not guarantee compliance with OELs established for specific APIs
Surrogate materials

- Lactose
  - Flow characteristics
  - Analytical limit of detection
  - Low toxicity
  - Availability
  - Low cost of surrogate
  - Cost of sample analysis
  - Solubility

- Other surrogates to consider
  - Naproxen Sodium
  - Riboflavin (vitamin B2)
  - Mannitol
  - Sucrose
  - Acetaminophen (paracetamol)
Standard filter sampler

Standard 25 mm filter cassette Respirable Dust Monitor
Surface wipe & Swab Samples
Sampling strategy

• Prevent ingress of any contamination likely to bling the study.
• Background air and surface samples should be taken.
• Take human breathing zone samples.
  • Long term, and
  • Short term (event or task based).
• Take general air samples.
  • Long and short term.
  • At critical points of actual or potential leakage.
• Surface wipe or swab samples at critical locations.
Example of general air samples

Sample location around a split butterfly valve
Surface samples

- Collect after individual process cycles or steps
- Collect at end of overall operation
Surface test results

- Pharmaceutical companies may or may not have established limit for surface contamination for specific APIs.
- Often detect contamination where air samples were below detection.
- May show need for additional cleaning before removing objects from containment or to other areas (e.g. clean contaminated RTP seal when container is undocked).
Test room

Consider permanent room or temporary enclosure
Summary

• Surrogate monitoring evaluates the effectiveness of containment equipment using materials having low toxicity.
• Lactose is the recommended surrogate material, but others may also be used.
• The sampling strategy includes both air samples and surface samples.
• The results can be helpful in selecting containment equipment that will be appropriate for specific applications.
• There are limitations. Therefore, employee exposures to the actual API should also be evaluated once the containment becomes operational in the lab or production setting.
Containment test Class II MBSC

• EN 12469 specifies a method.
• Called KI-Discus.
• Acceptance is 5 log reduction of an internally generated aerosol source.
Thanks for your attention
Questions???
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