Cross Contamination in Pharmaceutical Manufacturing

“Prevention or Cure - What are the Risks?”

Presented By
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Introduction

• Contamination control has long been one of the main challenges in pharmaceutical production as nothing is a greater liability to the safety of patients

• “There shall be separate or defined areas or such other control systems for the firm’s operations as are necessary to prevent contamination or mix-ups” (FDA, GMP Regulations 1978)

• “In order to minimize the risk of a serious medical hazard due to cross-contamination, dedicated and self contained facilities must be available for the production of particular medicinal products” (EMA, GMP Regulations)
Principles of Pharmacology and Toxicology

“Poison is in everything, and no thing is without poison. The dosage makes it either a poison or a remedy” Paracelsus 1493-1541

[Diagram showing a scale with three sections: No Effect, Therapeutic Effect, Toxic Effect]
What is Contamination and Cross Contamination?

• Dirt in the wrong place!!!
• “The act of contaminating or polluting, including (either intentionally or accidentally) unwanted particles, substances or factors”
• “Make something impure by exposure to or addition of poisonous or polluting particles or substances”
• Anything affecting the integrity of a substance
WHO – GMP Definitions for Pharmaceutical Products

- **Clean Area:** an area with defined environmental control of particulate and microbial contamination, constructed and used in such a way as to reduce the introduction, generation, and retention of contaminants within the area.

- **Contamination:** the undesired introduction of impurities of a chemical or microbial nature, or of foreign matter, into or on to a starting material or intermediate during production, sampling, packaging or repackaging, storage or transport.

- **Cross-Contamination:** contamination of a starting material, intermediate product or finished product with another starting material or product during production.
What is Contamination and Where does it come from?

- Particles can be viable or non-viable
- They come in different shapes and sizes
- The most common are less than 10 microns and invisible to the naked eye
- People are the major source of contamination through body regenerative processes, behaviour and work habits
- Particles which fall to floors with gravity or air pressure will break down into smaller ones that will move with air turbulence
Sources of Contamination

- Removing existing environmental contaminants without adding new ones

- Volatile Organic Contaminants
- Airborne Molecular Contaminants
- Nonvolatile Residue
- Absorbed Molecules
- Microorganisms
- Ions
- Visible Particles
- Submicron Particles
- Fibers

ESD
Likely Contaminants

- As well as the last slide and more particularly:
  - Active Pharmaceutical Ingredients (API’s)
  - Cleaning Agents
  - Decomposition products and materials
  - Synthetic intermediaries
  - Excipients
  - Other residues
Effective Contamination Control in Pharmaceutical Facilities

Sources of Contamination
- People
- Processes
- Objects

Critical Manufacturing Environments
- Classic cleanroom
- Controlled areas

Effective Contamination Control
- Product selection
- Spec of material
- Cleaning procedure
Particulate Matter

• Particles are defined as bodies with definite physical boundaries in all directions; diameters ranging from 0.001 micron to 100 microns; they may be liquid or solid or both
• One micron equals one-millionth of a metre
• 25 mm = 25,400 microns
• Eye of a needle = 749 microns
• The dot of an (i) = 397 microns
• Depending upon light intensity/quality, most eyes cannot see below 10 microns
Particle Visibility

• The ability to see individual particles depends on the eye itself, the intensity, the quality of light, the background and the type of particle
• Particles seen on furniture or floating in rays of sunshine are 50 microns or larger
• The majority of invisible particles are 3 microns in diameter and smaller
• In ambient air, 99% of airborne particles by count are less than 1 micron
Motion of Particles is Affected by:

- The Velocity field of the fluid (air!)
- The inertia of the particle
- External forces acting on the particle – gravitational, electrical, magnetic
- The viscous drag (always opposite to direction of movement)
- Collisions with molecules, other particles or surfaces (forming agglomerates)
‘Brownian Motion’

• Particles less than 1 micron have settling velocities so low that they are affected by air movement from hot machinery/plant.

• This makes them subject to erratic movement in a fluid (in this case air).

• ‘Brownian’ effects become dominant on particles less than 0.3 micron in size, where their random motion keeps them almost indefinitely suspended in the air.
Vectors

- Can be defined as anything that carries or transfers particles from one place to another
  - Air and other gases
  - Water and other liquids
  - Physical objects
  - People
- Can be environmental (source to another location) or product
Who Generates these Particles?

- In short, everything generates particles
- 97% of these particles are not visible to us
- All particles represent a threat/danger to the integrity and quality of Pharmaceutical Manufacturing Facilities
- 80% generated by personnel
- 15% generated by equipment
- 5% generated by environment
Sources of Contamination

Micro-organisms are found by the millions in or on:
- The environment around us
- Water
- Raw Materials
- Containers and Closures
- People

GOLDEN RULE

“Always be on the look out for possible contamination and guard against it”
Problem Statement

- At present there is no defined approach in order to outline a method of deriving acceptable exposure limits for cross contamination between products manufactured in shared facilities.
- Concern arises because in the absence of any guidance and with a plethora of toxicological tools a lack of harmonised interpretation could occur both in pharmaceutical industry and National Competent Authorities.
- Currently toxicological data are not always used in establishing limits for cross contamination.
- Commonly limits such as $1/1000^{th}$ of lowest clinical dose or 10ppm are used as limits for cleaning validation.
Common Particulates in Pharmaceutical Manufacturing

- Human/Animal Hairs
- Synthetic Fibres
- Glass
- Paint
- Closures (stoppers)
- Insects
- Metals
- Skin Flakes
- The Environment
- Natural Fibres
- Stainless Steel
- Teflon
- Labels
- Paper Products
- Silicone
- Plastics
- Cardboard
Why is Particulate Matter so common?

- Product constantly in contact with process
- Manufacturing has so many stages
- Chemical breakdown, aging and interaction with other chemicals/materials
- Process precipitation
- Contamination of raw materials
- Originating from containers, packaging, equipment and other materials
- Cleaning and storage
- Contamination from us!!
- Environmental Contamination
How and Where does Contamination Enter?
Cross-Contamination in Production

Prevention of cross-contamination in production

- 5.18 “contamination of a starting material or of a product by another material or product must be avoided. This risk of accidental cross-contamination arises from the uncontrolled release of dust, gases, vapours, sprays or organisms from materials and products in process, from residues on equipment, and from operators’ clothing. The significance of this risk varies with the type of contaminant and of product being contaminated. Amongst the most hazardous contaminants are highly sensitising materials, biological preparations containing living organisms, certain hormones, cytotoxics, and other highly active materials. Products in which contamination is likely to be most significant are those administered by injection, those given in large doses and/or over a long time”

- (EU-GMP; Medicinal Products of human and veterinary use; Ch 5)
Dedicated Facilities (GMP Guide)

No Change

• “GMP/GDP Inspectors Working Group has agreed that the use of dedicated facilities should normally be required when beta-lactam antibiotics are produced. In addition dedicated facilities should be used when live pathogens are handled” (EMA/INS/GMP/809387/2009)

• Going Forward

• “for other products, manufacturers introducing a product into shared facilities should carry out an assessment of all relevant product and process characteristics to evaluate whether it is suitable for production in shared facilities. This assessment should include input from a toxicologist. Where the product has known sensitizing potential, or is highly potent or toxic, the Supervisory Authority should be consulted to discuss the manufacturer’s risk management measures” (EMA/INS/GMP/809387/2009)
The Opportunity to Contaminate

- Toxicity
- Quantity of active ingredient used per batch
- Process train used in product manufacture
- Level of containment and energies used in processing
- Proximity to other products and the use of shared equipment
- Opportunity to contaminate
- Dosing regime of the product and in particular the number of daily doses contained in a batch
- Frequency of the ingredients or product’s manufacture
- Any other products manufactured that might be contraindicated for users of the target drug
The 5 “P’s” of Risk Assessment and Risk Management

- Pathogens
- Procedures (experimental)
- Personnel
- Protective Equipment
- Place
Risk analysis: The ADE equation

- ADE (Acceptable daily exposure) is the daily dose of a substance, below which no adverse effects are anticipated by any route, even if exposure occurs for a lifetime.
- Number is derived from information on the toxicity of the product to the patient. It is based on regulatory information such as NDAs and is used in occupational toxicology to set occupational exposure limits (OELs).
- The use of ADE as a basis of risk management is a scientific approach.

\[
\text{ADE (mg/day)} = \frac{\text{NOAEL (mg/kg/day) x BW}}{\text{UFc x MF}}
\]

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**NOAEL** = No observed adverse effect level  
**BW** = Body weight  
**UFc** = Uncertainty Factor  
**MF** = Modifying Factor

**Rule of thumb for calculation:**  
ADE ≤ 10 OEL
Risk Assessment Elements

- Pathogenicity
- Virulence
- Route of exposure (faecal-oral, through mucous membranes, inhalation etc)
- Transmission
- Infectious dose
- Availability of pre- and post exposure prophylaxis (preventative treatment against a disease)
- Environmental stability
- Hazards associated with the animal species
Risk Management
Risk Identification

Identify

Analyze

Monitor & Control

Plan
### Risk Analysis

<table>
<thead>
<tr>
<th>Likelihood</th>
<th>Consequences</th>
<th>Insufficient</th>
<th>Minor</th>
<th>Moderate</th>
<th>Major</th>
<th>Severe</th>
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<tbody>
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<td>Almost certain</td>
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<td>Unlikely</td>
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</tbody>
</table>
Risk Evaluation

Increasing vulnerability

Increasing probability

Negligible

Low

Moderate

High

Extreme
Risk Control

Elements of Risk Control

- Mitigate Risks
- Plan for Emergencies
- Measure and Control

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Risk Reduction
Risk Review

- Establish the Context
- Identify Risks
- Analyze Risks
- Evaluate Risks
- Treat Risks

Communicate and Consult

The ALS Group Risk Assessment
Quality Risk Management in ICH Q9

Initiate Quality Risk Management Process

Risk Assessment
- Risk Identification
- Risk Analysis
- Risk Evaluation

Risk Control
- Risk Reduction
- Risk Acceptance

Output/Result of the Quality Risk Management process

Risk Review
- Review Events

Risk Communication

Risk Management tools

Unacceptable
Risk Communication
Understanding Particulate Contamination Risk

- Particulate contaminants are a very important factor in the pharmaceutical industry and understanding their sources and behaviour is critical to controlling their infiltration of clean/critical/production areas.
- One way of reducing contamination risk from airborne particles is to reduce the particle source through filters.
- Filters however can produce vortices, air disturbance, and turbulence.
- The Science relating to vortices, disturbance and turbulence is complex and not fully understood but results in uncontrolled particle dispersions.
- It is further affected by gravitational deposition, electrostatic forces or thermal fluctuations.
- As a back-up most facilities implement some barrier technology to augment the filtration.
Risk Management Methodology/Tools

- Basic Risk Management – flow charts/check sheets etc
- Failure Mode Effects Analysis (FMEA)
- Failure Mode, Effects and Criticality Analysis (FMECA)
- Fault Tree Analysis (FTA)
- Hazard Analysis and Critical Control Points (HACCP)
- Hazard Operability Analysis (HAZOP)
- Preliminary Hazard Analysis (PHA)
- Risk Ranking and filtering
- Risk Management planning (RMP) and supporting tools
- Risk-MaPPing
Risk Management Plans (RMP)

- The following questions should be asked at each stage of the product’s life-cycle:
  - What are the safety risks?
  - Who is at the highest risk?
  - What populations are at risk?
  - Are the risks predictable?
  - Are the risks preventable?
  - The last question is important as it forms the basis for any intervention plan.
A Comparison of Approaches (1)

<table>
<thead>
<tr>
<th>FDA – REMS</th>
<th>EMA – RMPs</th>
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<tbody>
<tr>
<td>Medication guides</td>
<td>Patient alert cards</td>
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<tr>
<td>Patient information sheet</td>
<td>Patient information leaflet</td>
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<tr>
<td>Container labels</td>
<td>Summary of Product Characteristic (SPC) contraindications SPC special warnings</td>
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<td>and precautions for use</td>
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<td>Provider communication plan</td>
<td>Summary of Product Characteristic (SPC) contraindications</td>
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<td>Provider information sheet</td>
<td>Educational programmes</td>
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<td>Highlighted information for prescribers</td>
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<td>Training of healthcare professionals</td>
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<td>Monitoring of patients receiving medication</td>
<td>Specific adverse event and pharmacovigilance surveillance reporting requirements</td>
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<td>Prospective observational studies</td>
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<td>Prescriber and patient database</td>
<td>Additional trial and study data</td>
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<td>Post marketing studies Registry</td>
<td>Specific adverse event and pharmacovigilance surveillance reporting requirements</td>
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<td>Registry</td>
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</table>
## Table 2. Requirements not shared between Food and Drug Administration’s (FDA) Risk Evaluation and Mitigation Strategies (REMS) and European Medicines Agency (EMA) Risk Management Plans (RMPs)

<table>
<thead>
<tr>
<th>FDA – REMS</th>
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<tbody>
<tr>
<td>Monitoring of patients receiving medication</td>
<td>SPC undesirable effects</td>
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<tr>
<td>Specification of distribution or dispensing locations</td>
<td>Development of diagnostic tests for adverse event</td>
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<tr>
<td>Monitoring of distribution</td>
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<tr>
<td>Patient or physician survey to evaluate understanding of risk</td>
<td></td>
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<tr>
<td>REMS print advertisement</td>
<td></td>
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<tr>
<td>Audit of communication plan</td>
<td></td>
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<tr>
<td>Audit of pharmacies</td>
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**Prevention of Contamination**

- 70% to 80% of all contamination entering a room is carried in on wheels or feet *(UK Department of the Environment)*

- Contamination on unprotected floors will rise to shoulder level and above on air particle movement created by vortices

- Installation of a contamination control system at floor level is the most cost effective solution to the removal of the majority of contamination

- By removing 80% for small cost compared with the expense of trying to cope with the 20% (air handling systems, gowns, hats, gloves, physical barriers, clean, controlled, critical facility costs!!)
Preventative Measures

- Filters
- Specialist Cleaning
- Containment
- Implementation of Barrier Technology
- Controlling Personnel Habits
- Restricting foreign materials (Cardboard, Packaging, Feed etc)
- Contamination Control Flooring/Mats
Benefits of contamination prevention

- Reduced chance of Animal study failure costing considerable sums and even threatening the viability of the facility
- The animals have a degree of protection which can counter premature death
- Staff and other stakeholders see you are serious about the running of the facility and the importance of controls
- Increased confidence of all using the facility
- Staff not needing time away through preventable illness/allergies
- Less time and money spent in trying to identify rogue organisms and sources of contamination
The Cure...
Solutions: Dust Mats

Made from various materials like coconut, jute and synthetic substances. They can trap and hold dirt and dust, but they can also be a source of contamination. They are not designed to hold particles for any significant length of time. It is possible to transfer off the dirt and dust. They are usually cleaned by washing them.
Solutions: Tacky Mats

Multiple Layers of Polyethylene film coated with an acrylic adhesive
Adhesive strength alone collects contamination
Performance deteriorates after several footsteps/overstrikes
Appropriate for confined spaces, with low personnel traffic volumes
Low efficiency in particulate removal for smaller particle sizes of less than 10µmicrons
When peeled, tens of thousands of viable and non-viable particulates are released into the environment
Cannot be recycled
High costs when analyzed on an annual basis
Solutions: Polymeric flooring

- Polymeric Composition
- Optically smooth, flexible surface enabling maximum contact between shoe and wheels
- High surface energy (Van de Waals forces) allows maximum collection and retention of all particulate sizes
- Ability to collect/retain contamination over a wide range of particle sizes, with effective removal in the 2 to 10 µmicron range
- Simple and regular cleaning regime guarantees effective contamination control over several years
- Picks up contamination over a full floor coverage
- Particulates removed are contained within the controlled medium thereby preventing their release into the environment
- Flooring can be recycled at the end of its life
Polymeric Nano-contamination
Summary

- Contamination can cause any number of problems, including study failure, premature animal death and illness of staff.
- These problems can be prevented by using and implementing an effective Risk Management policy.
- The amount of potential contamination will depend upon a number of factors, particularly the amount of traffic, the location and the design/construction of the Animal facility.
Conclusion

- Numerous studies and independent papers have concluded that contamination in Animal facilities needs to be controlled to protect all the stakeholders and the business itself.
- The environment is the main source of this contamination.
- 80% of all dirt and dust (particles) is brought into areas on the soles of feet and/or wheels at floor level.
- Unless addressed, this contamination can cause untold damage and affects the viability of the work being undertaken.
- For a relatively small investment, this contamination can be controlled, trapped, and removed.
- By keeping the contamination out of the facility, the cost and consequences of dealing with it are considerably reduced.
The End

Any Questions?