School of Pharmacy & Pharmaceutical Sciences QP Forum – Thursday 16th April
Parallel Session - Sterile

Facilitator –
Ms Ann McGee
Query Topics

• Contamination Control Strategy
• Problems virtually managing CMOs
• PUPS FIT
• Visual Inspection (3 queries)
• Growth promotion failures in media fills
• Validated filtration time exceeded- options?
• Use of sporocides in aseptic compounding?
• Rapid Micro Methods- current status & qualification
Query No. 1

**Inspection of Contamination Control strategies**

- HPRA expectations?
EU GMP Guide Ch. 3 – Premise & Equipment

Published on 13 August 2014; Effective 01 March 2015

- Minimal risk of causing contamination
- Contamination Control Strategy expected to be in place

Production Area

Storage Area

QC Areas

Ancillary Areas

Equipment

Premises Production Area – Update:
- QRM principles should be used to assess & control the risks of cross contamination
- Risk Assessment should include among other parameters a toxicological evaluation of the products being manufactured as per the EMA Guideline on setting health based exposure limits for use in risk identification in the manufacture of different medicinal product in shared facilities – Effective date 01 June 2015
- Dedicated facilities are required when a risk cannot be adequately controlled by operational &/or technical measures, when scientific data does not support threshold values or when threshold values are below the levels of detection
Chapter 5 – Production Updates

“A QRM process, which includes a potency & tox evaluation, should be used to assess & control the cross-contamination risks presented by the products manufactured.”
Specific attention to design of the premises and equipment (link to Chapter 3, previous slide)

“The outcome of the QRM process should be the basis for determining the necessity for & extent to which premises & equipment should be dedicated to a particular product or product family. This may include dedicating specific product contact parts or dedication of the entire manufacturing facility.”

“The outcome of the QRM process should be the basis for determining the extent of technical & organisational measures required to control risks for cross-contamination.”

Annex 1- The manufacture of sterile products is subject to special requirements in order to minimise risk of microbiological contamination, and of particulate and pyrogren contamination
Contamination Control Strategy

Technical & Organisational Measures

- Facility design eg one way flow; airlocks; wash/ dry areas
- Dedicated vs multi-product facility or processing areas
- Product type
- Design of HVAC- single pass vs recirculation
- Dust extraction close to point of generation
- Flows of materials, equipment, people & waste
- Gowning regimes & controls
- Process characteristics

- Dedicated vs multi-use manufacturing equipment
- Equipment design- closed vs open; physical barrier systems (eg isolators); ease of cleaning; disposable technology
- Campaign manufacture
- Waste management
- Cleaning validation vs campaign verification & analytical capabilities relevant to established limits
- Cleaning processes – automated vs manual; (operator) qualification
- Micro controls…….
Cleaning Validation – Toxicological Approach

EMA Guideline on setting health based exposure limits for use in risk identification in manufacture of different medicinal product in shared facilities

Outlines a recommended approach for deriving a scientifically based threshold value for individual active substances to be applied for risk identification.

• Basis - is the expectation that a toxicological evaluation should be used to determine the residue limits of pharmaceutical products e.g. permitted daily exposure (PDE) limit.

Companies need to

• Review current Cleaning Validation approach in line with EU requirements to identify the most appropriate strategy to take to implementing the revised requirements
• Determine the toxicological based acceptable residue limits for each products as per the revised requirements of EU GMP
Contamination Control Strategy

Your experiences of Regulatory expectations?
Query No. 2

Virtually managing contract manufacturing organisation (CMO) problems

• Management of Outsourced Activities is a challenging area!
Multiple Relationships to Consider

Multiple reasons for outsourcing:
Cost, Flexibility, Contingency, Expertise……

Outsourcing is a Risky Business!!
All or some can be Virtual
Managing Third Parties

Identify activities to be outsourced
QRM
Quality criteria

Vendor selection
QRM
Pre-selection audit
QTA

Ongoing monitoring
Periodic audit
KPI evaluation

Quality Risk Management Approach – Key Tool; incl. Key Performance Indicator [KPI] evaluation

Quality Technical Agreement (QTA)

Audit

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Outsourced Partners

Challenges:

• Many Contract Acceptors (CAs) means many QTAs
• CAs may not be familiar with GxP standards
• CAs may be reluctant to engage to the level required
• Big challenge for contractors who resist or are not familiar with new expectations

Opportunities:

• CAs with initiative on QTAs will lead the way
• More control on management of contractors – remote & on-site
• Greater control by CG; fewer deviations?
Common Inspection Pitfalls - Outsourced Activities

Lack of clarity of responsibility in QTAs: areas of responsibility not defined, lack of clarity as to who is managing the structure

QTAs not in place or not sufficiently detailed

Failure to review QTAs on an annual basis
Failure to formally & appropriately document reviews

Failure to have interfaces covered (e.g. product quality complaints)

Vendor Management - Suppliers not adequately qualified!
EU GMP Guide Chapter 7 – Mgmt of Problems

Ensure robust Communication process between CG & CA

- Responsibilities should be defined for each activity
- Technical aspects of the contract to be drawn up by SME’s knowledgeable in GxP

Ensure QTA outlines R & R - GxP document – manage it as such

The expectation is that a QTA should be in place for any activity/service that impacts GxP!

Appropriate KPIs; active management process
Outsourced Activities

List of potential Outsourced Activities:

• Qualification & validation work (new premises)
• Maintenance & calibration of equipment / premises
• Assessment & sourcing of starting / packaging materials
• QP & other services such as GxP audits of suppliers
• Washing / depyrogenation / sterilisation of packaging materials used in manufacture
• Document archiving / storage
• Investigational Medicinal Products - Third Parties
• Sales & Marketing
• Hosting of IT functions
• Storage & distribution
• Artwork generation / print ready material
Query No. 3

Filter Integrity Testing post sterilisation and pre-use (PUPS): do the risks outweigh the advantages and is there an option for risk assessment to justify not doing FIT?

Your Experience?
PUPS FIT - MPI Experience

• Annex 1 requirement:
  o “The integrity of the sterilised filter should be verified before use and should be confirmed immediately after use by an appropriate method such as a bubble point, diffusive flow or pressure hold test”

• Is potential to perform RA on current process & to demonstrate by doing the PUPS FIT, that you are increasing the risk of product contamination

• Also need to demonstrate that a change to the design of your manufacturing line cannot be achieved to incorporate the PUPS FIT

• Obtain approval from your GMP Inspectorate in advance of implementation
Query No. 4

Visual Inspection of sterile preparations - management of defects and OOT investigations

- How does industry investigate OOS/Defects?
- How does industry investigate OOTs?
- What kind of AQLs are done on visually inspected product?
- How are defects classified particularly for companies using automated systems?

Whatever the system of inspection – when a defect trend is detected the production process and the inspection process (where necessary) must be investigated re-assessed

(D. Coakley, HPRA Information Day Nov 2014)
Regulatory Requirements:

**EU GMP Guide:** "Quality Control is that part of Good Manufacturing Practice which is concerned with sampling, specifications and testing, and with the organisation, documentation and release procedures which ensure that the necessary and relevant tests are actually carried out and that materials are not released for use, nor products released for sale or supply, until their quality has been judged to be satisfactory."

**EP:** "Solutions for injection, and powders for injection (freeze dried products) examined under suitable conditions of visibility, are clear and practically free from particles".

**USP:** "All particles intended for parenteral administration: Each final container of all parenteral preparations shall be inspected to the extent possible for the presence of observable foreign matter in its contents. The process shall be designed and qualified to ensure that every lot is essentially free from visible particulates. The inspection may take place when inspecting for other critical defects".
## Visual Inspection for Particulates – General

### Hot topic

**Approach** - Define expected particle types (intrinsic and extrinsic); perform a risk assessment with reference to the manufacturing & VI processes; define the Acceptance Criteria

**AQL Approach** – Acceptance criteria for QA AQL can be tighter than line Acceptance Criteria

**Key Challenge** – limited capability of the machines (Vs human eye)

**Trending of Acceptance Criteria** over time; re-evaluate your Acceptance Criteria with reference to process capability

**Requalification of the VI process** at regular intervals - automated & manual

### Discussion points –

- *How does industry investigate OOS/Defects?*
- *How does industry investigate OOTs?*
- *What kind of AQLs are done on visually inspected product?*
- *How are defects classified particularly for companies using automated systems?*
**Industry Best Practice**

Visible particles: 100 % Inspection typically achieved in 1 of 3 ways: Manual inspection, Semi automatic inspection or fully automatic inspection

Followed by acceptance sampling

Recommend that you perform a risk assessment to achieve an efficient inspection process and to establish acceptance/rejection criteria
Best practice for 100% inspection

Define risk to patient to determine particulate size/frequency that can be accepted

If a particulate is not detected during inspection consider using QRM to assess the Severity x Probability x Detectability of the Risk alongside current controls

In defining contaminants in SOP and subsequent training, 2 definitions apply:

• Particulate matter is intrinsic and arises from the product
• Foreign matter is extrinsic and come from the environment

In defining ‘visible’ in the SOP and subsequent training, state the conditions upon which the particle can be detected: e.g. background and magnification & control the environment accordingly
Best practice for 100% inspection

Ensure controlled GMP SOPs are in place & all operators are trained & qualified

- Critical to set defect or action limits
- Overall defect limit for all rejected units:
  - the limit should be set taken into account the batch size, process capability and historical performance
  - limit should be as tight as possible to minimise the number of potential defects that will be accepted
- Be specific - defect limits for each category of defect

Defect categorisation: Procedure should define defects with a sample picture of each: cosmetic, minor, major, critical and action required for each event
Recommendations for OOS/Defects

Confirm presence of Contaminant

Identify affected batches, including those already filled & potentially affected

Identify the contaminant - identify if it is foreign to the process or has the drug precipitated in solution (extrinsic vs intrinsic)

Once contamination confirmed, it is critical to determine what batches or other product lines could potentially be affected, & justify those that are argued to be unaffected by this defect; common regulatory pitfall

If contaminant cannot be identified then product should be rejected
Recommendations for OOS/Defects – contd.,

If contaminant is identified as being intrinsic & can be rectified by reworking, then process for reworking should be validated & justified for each batch

Assess toxicological & other applicable impacts on patient (a medical assessment required)

Determine (potential) root cause: potential root causes (RCs) may not be identified - critical to continue investigation until all avenues are exhausted - common regulatory pitfall; search for systematic higher level RC should be sought

Determine CAPAs

Approve the completed investigation & assess/confirm disposition of affected batch/s
Query No. 5

Regarding 100% visual inspection of medicinal products for particulates – where the product container is opaque i.e. unable to see particles, is a risk assessment to justify not doing VI based on additional checks and controls an option?

• In Summary – not acceptable not do VI due to opaque containers
• Must develop a robust VI method to reflect the limitations posed by the product
Query No. 5 Contd..

Proposed Approach

• Establish the unavailability of suitable equipment that can enable VI of opaque containers
  • consider a dark room with white light
• Validate the manufacturing process with non-opaque containers i.e., conduct qualification studies
• Identify the range of likely particles - intrinsic & extrinsic
• Perform re-qualification periodically (e.g. annually) using non-opaque containers
  • Will need to do media fills in any case
• Sample opaque containers on a batch basis for VI (destructive test)
• If ability to conduct VI is limited, perform a Risk Assessment, define controls and checks & ensure these are applied during manufacture
Query 6

How can quality problems such as fibre-like particles associated with syringe, syringe plunger and cannula be addressed?
Query 7 - Growth Promotion to Support Media Fills

"What do companies do as regards best CAPA practice when they sporadically find that they generate, based on turbidometric inspection, zero growth/ partial failures of growth in growth promotion studies?"

"Have any companies experience of contract/in house non-turbidometric i.e. rapid detect growth technologies not dependant on subjective human visual inspection?"
Query 7 - Growth Promotion to Support Media Fills

Requirement - confirm that the broth used in media fill controls (for a positive control) capable of promoting growth with a variety of representative inoculated organisms

- The inoculating organism - at 10-100 CFU concentration

Qualify the test

Qualify the analyst

Perform RCA on the failure - Analyst or Media?

Invalidate the media fill if root cause is not determined
Query 8

Where the validated filtration time between filter wetting and filtration completion is exceeded for a sterile drug product batch, what options are available?
A hospital trust in the NHS make several sterile products for our patients such as; ward stock prefilled syringes for injection, TPN bags, IV enzyme therapy. Our current sterile process is three stages, alcohol spray and wipe as the components move from each room D<C<B. The MHRA are pushing for the use of a sporicidal step. We are currently evaluating our options.

We are concerned about:

1) Operator health and safety, some sporicides are quite hazardous and have a tendency to dissolve through clean room garments over time

2) Dwell time. Many sporicides require a long dwell time 15-30 mins this is not suitable for our process.

Have you dealt with similar issues??
Query 9 - Use of Sporicides in Aseptic Compounding

Annex 1 requirements - Sanitation

• “The sanitation of clean areas is particularly important. They should be cleaned thoroughly in accordance with a written programme. Where disinfectants are used, more than one type should be employed. Monitoring should be undertaken regularly in order to detect the development of resistant strains”.

• “Disinfectants and detergents should be monitored for microbial contamination; dilutions should be kept in previously cleaned containers and should only be stored for defined periods unless sterilised. Disinfectants and detergents used in Grades A and B areas should be sterile prior to use”

• “Fumigation of clean areas may be useful for reducing microbiological contamination in inaccessible places”
Guidelines for Aseptic Compounding

• National Guidelines for Aseptic Compounding in Irish Hospital Pharmacy Practice, V 1.0, Nov 2013
• FDA Guidance for Industry – cGMP – Interim Guidance for human Drug Compounding Outsourced facility under Section 503B of FD&C Act
Query 9 contd..

Starting point:

• Review the typical environmental isolates expected as surface contaminants
• Determine the worst case
• Assess the required Dwell Time in order for the agent to be efficacious
• Dwell Time is an issue – needs to be moist in order to be effective
  • Options include for e.g., Klericide B
  • New generation Sporicides – low residue; however data may not be available for all types of spores formers
Query 9 contd..

One approach we have seen:

- Deboxing going from unclassified to Grade D – and alcohol wipe down
- Assemble the required components from stock - apply Sporocidal agent from a wipe
  - Allowed to dwell for the validated contact time
  - Validated contact time defined on basis of the expected isolates & the dwell time that was required to be efficacious
- Alcohol spray & wipe into transfer hatch (D-C)
- Alcohol spray & wipe into Grade C room into Grade B transfer hatch

Consideration:

- What are you trying to demonstrate?
  - Bioburden reduction from the transfer process (with an additional degassing step after) or maintenance of the aseptic environment throughout?
Aseptic Compounding - Sporocide Usage

Your experiences?
Query 10a - Rapid Micro Methods

Rapid microbiology testing in general; current status & qualification?

Main types of RMM:

• Quantitative
• Qualitative
• Identification

Regulatory Authorities (HPRA) are encouraging industry to move to using rapid micro testing

HPRA open to discussions with Manufacturers of rapid micro methods

Are industry convinced of the technology & has evolved sufficiently to be robust?
Rapid Micro Methods

Main concern: expense of technology (libraries) & equipment; & level of qualification effort and if any issues – no backup result available

Key Q – is there the appetite from industry for this type of technology?

Validation Guidance:

• PDA Technical Report #33, Evaluation, Validation and Implementation of New Microbiological Testing Methods
• USP <1223>, Validation of alternative microbiological methods
• Ph. Eur. 5.1.6, Alternative methods for control of microbiological quality
PDA Technical Report #33, Evaluation, Validation and Implementation of New Microbiological Testing Methods

Table 5.2-1 Validation Deliverables and Responsibilities

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<td>Design Qualification (DQ)</td>
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<td>Functional Design Specification (FDS)</td>
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<td>Requirements Traceability Matrix (RTM)</td>
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<td>SOPs and Technology Training</td>
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<td>Operational Qualification(1)</td>
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<td>Suitability Testing</td>
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<td>On-going Maintenance and Periodic Reviews(3)</td>
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Query 10b

What are the validation requirements / acceptability for early phase trials of, for example, mycoplasma, endotoxin, rapid micro kits etc?

If being used in any clinical trial with human subjects – requirements are not any less stringent
Questions
MPI’s services cover all product types across the entire product lifecycle

- Large and small molecules/biotech and non-biotech
- Steriles and non-steriles
- Active Pharmaceutical Ingredients (API)
- All dosage forms
- Medical device and device combinations
- Traditional Herbal Medicines
- Cosmetics
# MPI’s Lifecycle Services

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<td>• New Product Development and Introduction (NPDI)</td>
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