MHRA Experience on ‘Early Adopter’ Continuous Manufacturing Inspections

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## Presentation Outline

- MHRA Inspection Process
- Inspection Approach to Continuous Manufacturing (CM)
- MHRA Novel Manufacturing Process Experience
- Issues Encountered on CM Inspections
- Questions
MHRA Inspection Process

• Inspection frequency & duration based on factors including;
  • site history
  • activities carried out
  • size of site,
  • number of personnel
  • risk rating relative to other companies

• Any deficiencies are referenced back to EU guidelines
  • drives consistency between inspectors
  • Interestingly, don’t need to wait for it to go wrong to be able to cite a deficiency.
MHRA Inspection Process

- Assessors review the applications and confirm that the science is sound and supported by the data submitted.
- If questions remain, can ask the inspector to check while on site.

- Inspectors consider your Quality System and level of compliance:
  - What you are *actually doing*, what you are *planning to do* and is it *written down* somewhere.
  - Look for what *could go wrong*, what *has gone wrong* and how you propose to *stop it happening again*.
MHRA Inspection Process

- Approximately equal times spent on documentation and on plant
MHRA Inspection Process

- Sometimes an inspection can feel like a bit of a *rough ride*…

But there are ways to make it smoother…
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Inspection Approach to CM
Inspection Approach to CM

Spot the Difference:
Inspection Approach to CM

Spot the Difference:

- Risk rating not influenced by Continuous vs Batch
- Inspection duration typically the same for both
- Physical time on plant during inspection not impacted by the type of process operated
- Still look at deviations to see what has gone wrong and what CAPA were implemented
- Assessor(s) may come with us on inspections
  - this will be the ‘norm’ until we (and you) have appropriate experience of potential pitfalls
Inspection Approach to CM

- Approaches to cleaning
- Equipment Set Up
- Computerised Systems
- Process Consistency
- Control of Changes
- Deviations & CAPA
- Rejection Mechanisms
- Residence Time Distribution
- Calibration & Maintenance
- Training of Operators

Diagram of a process chamber with components like the Discharger, Granules, Classifier, and Liquid spray system.
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MHRA Novel Manufacturing Process Experience

- The MHRA has an ‘**Innovation Office**’
- Access to expert regulatory information, advice and guidance that helps the development of innovative medicines, medical devices or *novel manufacturing processes*
- Formed in 2012 in response to calls from academia, government and industry
- **Free** expert regulatory information, advice and guidance
- For organisations of all backgrounds and sizes, including Small to Medium Enterprises (SMEs) and also individuals

- Search online for ‘**MHRA Innovation Office**’ or email: [innovationoffice@mhra.gov.uk](mailto:innovationoffice@mhra.gov.uk)
MHRA CM Experience

• Inspected Drug Product CM sites for pre-approval and for routine re-inspections

• We have inspected a number of API CM Sites
  • both API and Non-Standard API

• The experience is with a core group of inspectors
  • number is increasing

• Increasing our knowledge and experience in a number of ways
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Issues Encountered on CM Inspections
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• We have observed a (limited) number of issues in:
  – Process stability (high reject volumes)
  – Calibration
  – Equipment malfunction
  – In-Process Testing results
  – Residence Time Distribution not known
  – Cleaning
  – Switch away from Real Time Release Testing (RTRT)

• Inspections currently infrequent enough that not yet able to define a set of ‘standard’ inspection issues for CM.
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Questions from (or for) you...
Grazzi