Cleaning / Cleaning Validation
Update on toxicological approach

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GMP Conference
12th November 2014
Content

• Section I - Introduction

• Section II – Toxicological Tool
  (refer to presentation by Sarah O’Meara)

• Section III – Implementation of New Guidance

• Section IV – Cleaning / Cleaning Validation
SECTION I

Introduction
Current GMP Guidance

Certain Antibiotics (Paragraph 3.6)

- Penicillin
- Cephalosporins
- Carbapenems
- Sulphonamides?
Current GMP Guidance

Certain Hormones (Paragraph 3.6)

• Estrogens
• Progestagens
• Testosterone

• Corticosteroids ?
• Levothyroxine ?
• Growth Hormone ?
Some Experiences

• Campaign manufacture of high potency products in a small scale facility.

• Re-designation of equipment / facilities from potent products to non potent products.

• Manufacture of penicillin products in a dedicated area but within the same building complex as non-penicillin products.

• Manufacture of cephalosporin and penicillin products in the same facility (non EU site for non EU market)
Guidance Revision Process

• Concept Paper published in February 2005

• Update on revision published by EMA December 2009
  - advised input of toxicologist for assessment of new products introduction.
  - advised consultation with Supervisory Authority

• Revised Chapters 3 & 5 published in August 2014

• Effective in March 2015
Guidance Revision Process

- consideration given to having a list of ‘certain’ products for which dedicated facilities would be mandatory.

- decision was to move away from use of product categories in the guidance.

- focus on methodology based on scientific principles
Guidance Revision Process

GMP inspectors to revise Chapters 3 & 5 with emphasis on:

- Use of QRM
- Refer to use of toxicological evaluation (but no details included)
- Guidance on technical & organisational measures to control cross contamination.

Leave the toxicological guidance (*toxicological tool*) to experts in this area.
Guidance Revision Process

Meeting with industry

• September 2013 at EMA

• Representatives from manufacturers of human and veterinary medicines

• Representatives from GMDPIWG and SWP

• Opportunity to discuss some concerns raised during the public consultation.

• Much of the discussion related to the toxicological tool.
Guidance Revision Process

Some concerns raised by industry

• Calculation of Permitted Daily Exposure for each product is time consuming and in many cases not value adding

• Traditional approaches for cleaning validation limits should still be acceptable (i.e. 1/1000th dose and 10ppm methods)

• Veterinary industry consider PDE not applicable
Guidance Revision Process

Some concerns raised by industry

• Alternative toxicological approaches to PDE e.g. Acceptable Daily Intake (ADI) should be acceptable.

• Long history of clinical experience with many products.

• IMPs – less data available, questioned relevance of PDE approach.

• APIs - intermediates
SECTION II

Toxicological Tool
Section III

Implementation of New Guidance
Active Substance Manufacturers

• Manufacturer may not know final usage of the API (i.e. dosage form, target patient group)
• Risk identification more problematic
• Part II – reference to dedication of facilities (4.4)
• Part II - reference to tox approach for cleaning limits (12.71)
• How to handle intermediate stages of synthesis - less knowledge

• Toxicological tool could be applied
Implementation of New Toxicological Approach

Revised Chapters 3 & 5 come into force 1st March 2015

Publication of “toxicological tool” anticipated shortly

Phased implementation

- new product introductions
- medicinal products for human use
- medicinal products for veterinary use
Implementation of New Toxicological Approach

Challenges for Manufacturers

- many manufacturers handle large numbers of products
- toxicological expertise may not be at the site
- cost
- rationale for prioritisation of work ….. worst case first.
Implementation of New Toxicological Approach

Challenges for Inspectors

• Oversight for correct application of the guidance lies with the inspectorates

• Toxicological guidance describes how a limit could be calculated but does not address how it is applied in the context of a manufacturing environment.

• Need for training in the application of the toxicological tool.

• Need to know when to seek specialist toxicological support within agencies.
Impact on Cleaning Validation

Cleaning Validation

• Some thoughts on application of the PDE approach and potential impact on existing cleaning validation:

A number of possible outcomes following PDE assessment to establish acceptable carryover limit.

1) PDE based limit $\geq$ Original limit:

Actions by Manufacturer: No further cleaning validation studies required but need to document rationale.
Impact on Cleaning Validation

2.1) PDE based limit < Original limit:

Scenario 1

- actual residue values obtained during the cleaning validation runs comply with the new limit.

- original cleaning validation data provide sufficient assurance

**Action by manufacturer**: no further cleaning validation needed but need to document rationale.
Impact on Cleaning Validation

2.2) PDE based limit < Original limit:

Scenario 2

Actual residue values obtained during the validation runs are too close to the limit to provide the necessary assurance

Possible actions by Manufacturer:

• Conduct additional cleaning validation studies
• Implement ongoing cleaning verification
• If unsuccessful refer to actions under scenario 3
Impact on Cleaning Validation

2.3) PDE based limit < Original limit:

Scenario 3
Actual residue values obtained during the validation runs are above PDE limit.

Possible actions by Manufacturer:
• Revise the cleaning method
• Revalidate to give necessary level of assurance.
• Notification of relevant competent authorities
Conclusion

New GMP guidance coming into force in March 2015

Consider strategy for implementation of the guidance at your manufacturing facility.
   i) New products
   ii) Legacy products

Consider impact on existing cleaning validation
Section IV

Cleaning / Cleaning Validation

Regulator’s Viewpoint
Content

- Important aspects of cleaning
- Points to consider for Cleaning Validation
- Campaign manufacture
Important aspects of Cleaning

• Identification of the residue in advance (what are you trying to remove)

• Knowledge of basic solubility is important

• Interaction of cleaning agent with the residue

• pH, temperature, peroxide, organic solvent.....they all can interact and need to be studied/assessed, if you are using them

• Calculations of residues – science based and understood
Important aspects of Cleaning

• What residues are you considering, at a minimum:
  – The residue of the active substance
  – The residues of excipients
  – The detergent residue
  – Microbiological residues

• If the cleaning agent interacts / degrades the active substance, you need to consider the degradation products
Points to consider for Cleaning Validation

- Risk assessment
- Equipment - Dedicated or multiproduct
- Product(s), worst case – solubility, toxicity
- Campaign size, proposed cleaning interval
- Product A - the formulation, the dosing, toxicity, route of administration.
- Product B - the product specifications, the formulation, the dosing, route of administration, batch size, shared equipment.
- Dosing should be comparable, daily/weekly
Points to consider for Cleaning Validation

- Target residue - API, excipient, cleaning agent, bioburden, endotoxin
- Degradation of the API during cleaning – Measure Degradant
- Order of manufacture - controls
- Potency, Toxicity (CVMP veterinary), Safety factor
- Method of cleaning: CIP/COP, Cleaning agent
- Rinse/Swab/Visual
Points to consider for Cleaning Validation

- Worst case locations clearly defined for sampling
- Surface Area (SA) calculation – entire/individual SA

- Analytical test method
- Recovery study
- Dirty/Clean hold time
- Periodic evaluation
- Introduction of new products – full cleaning assessment
Campaign Manufacture

• What is an acceptable limit for a campaign size?

• What is the defined frequency of cleaning between batches?

• An increase in campaign size may equate to a decrease in cleaning frequency which could be a potential increase in risk to product within the campaign.

• Requires a full risk evaluation
Conclusion

• Cleaning is **not that** easy

• Know your product and residue attributes – where they go and how they can be removed

• Production equipment is used to make products for people with varying degrees of illness.

• Your customer trusts you to ensure that the equipment you use to make product for them is clean.

• Consider the people you trust for keeping equipment clean.
Questions ??