GMP Regulatory Considerations

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REGULATORY CONSIDERATIONS
CONTAINMENT
PROTECTION METHODS
PROCESS CONSIDERATIONS
HVAC
REGULATORY CONSIDERATIONS

CONTAINMENT

PROTECTION METHODS

PROCESS CONSIDERATIONS

HVAC

BACKGROUND

Possible Health Hazards of Substances
- Pharmacological activity
- Acute toxicity
- Subchronic or chronic toxicity
- Mutagenicity
- Carcinogenicity
- Reproductive toxicity (aberration of fertility, embryo development)
- Sensitization / allergy
- Irritancy

Substances can enter the body in three ways
- Inhalation (OEL based on 10m$^3$/8h)
- Oral ingestion
- Skin absorption

OEL (Occupational Exposure Limit)
- Safe level of airborne exposure
- For a 8-hour workday, which does not impair health day after day at work (mg/m$^3$)
EXPOSURE TO STEROIDS

Occupational steroid exposure can occur when the active ingredients used in hormonal contraceptive manufacture are inhaled, ingested, or absorbed through exposed skin. Although exposure can occur at any point in the production process, the greatest potential for worker steroid exposure during hormonal contraceptive manufacture occurs during weighing, material transfers or loading of equipment, and milling of active ingredients. Because of the different manufacturing procedures used and the strict environmental control requirements necessary for the aseptic production of injectable contraceptives, risk of steroid exposure is greater during OC manufacture, especially during granulation, drying, tablet compression, and coating. Exposure also is possible:

- in the packaging area (particularly if uncoated bulk tablets are handled or if spills or leaks occur).
- during the sampling and quality control testing of raw materials, intermediate products, and finished products
- during maintenance and cleaning of the equipment and facilities, including ventilation systems and protective garments.

IMPACT OF STEROID EXPOSURE ON HEALTH

Both male and female employees can be adversely affected by exposure to exogenous estrogens and progestogens. Although most of the adverse health effects experienced by steroid workers result from estrogen exposure, exposure to progestogens also can be harmful. Reported effects of steroid exposure in men include gynecomastia (excessive development of the mammary glands), decreased libido, reduced testicular size, increased pigmentation of the nipple area, nipple sensitivity, dysspermia (the occurrence of pain during ejaculation), weight loss, and headaches. Reported effects in females include menstrual disorders (such as increased flow or intermenstrual spotting), nausea, headaches, breast pain, leukorrhea (vaginal discharge), and swollen ankles. In a few cases, steroid workers’ children also have been adversely affected after coming in contact with contaminated clothing. Although the symptoms of steroid exposure generally disappear following cessation of exposure, repeated exposure may have serious long-term effects on workers’ health. For example, there have been reports of death from breast cancer among male workers who were inadequately protected from steroids during OC production.
CROSS-CONTAMINATION

Cross contamination definition:
Contamination of a material or product with another material or product.
(ICH Q7A,GMP Guidance for APIs)
Any substance accidentally or unknowingly introduced into/onto a product. (E.Melendez FDA/ISPE Conf 9-23-2004)

Manufacturers have the responsibility to identify drugs with risks and set defined areas or controls necessary to eliminate risk of product cross contamination on a case-by-case basis.

DANGER TO OPERATOR

- SOLIDS
  - WEIGHING
  - GRANULATION
  - BLENDING
  - COMPRESSION
  - COATING
  - 1ARY PACKING
  - 2ARY PACKING

- INJECTABLES
  - WEIGHING
  - CHARGING / BLENDING
  - FILTRATION
  - FILLING
  - INSPECTION
  - 2ARY PACKING

+ INHALATION
+ CONTACT
+ CONTACT
PROCESS AND REGULATORY VIEWS

- Containment (weighing, production, sampling, washing)
- CIP and WIP to avoid product handling
- PAT to avoid product handling (no IPC sampling) (Process Analytical Technology)
- Necessity for complete integration of all process steps

TECHNOLOGY REDUCING SEGREGATION NEEDS

- Containment (weighing, production, sampling, washing)
- CIP and WIP to avoid product handling
- PAT to avoid product handling (no IPC sampling) (Process Analytical Technology)
  - coupled with PPE and Ventilation (Personnel Protective Equipment)
- Necessity for complete integration of all process steps
INTEGRATION NEED

Airlock  Weighing Isolator

How to remove weighed substances?
How to remove unweighed substances, going back to warehouse?
How to remove waste?

WHO GUIDANCE ON HORMONES (DRAFT)

GUIDELINE TO THE INSPECTION OF HORMONE PRODUCT MANUFACTURING FACILITIES

Please address comments on this proposal, by 13 May 2008, to Dr S. Koppa, Quality Assurance and Safety: Medicines, Medicines Policy and Standards, World Health Organization, 1211 Geneva 27, Switzerland, fax: (+41 22) 791 4720 or e-mail: koppa@who.int with a copy to tumey@who.int.
WHO GUIDANCE ON HORMONES (DRAFT)

3.4 Hormone facilities should be separate, dedicated facilities and should not form part of any other non-hormone facility. They may be in the same building as another facility but should be separated by a physical barrier and have separate entrances, staff facilities, air-handling systems, etc.

3.5 In general hormone facilities should be classified as containment facilities.

3.6 The effective operation of a hormone facility requires the combination of the following aspects:

3.6.1 Appropriate facility design and layout.

3.6.2 Manufacturing process controls including adherence to standard operating procedures (SOPs).

3.6.3 Environmental control systems (HVAC).

3.6.4 Extraction systems.

3.6.5 Personal protective equipment (PPE).

3.6.6 Industrial hygiene.

3.6.7 Medical surveillance (monitoring staff exposure levels).

3.6.8 Administrative controls.

4. RISK ASSESSMENT

4.1 Not all hormone products are equally potent and risk assessment should be carried out to determine the potential hazards to operators and to the environment.

The risk assessment should also determine which phases of the product production and control cycles, from API manufacture to finished product distribution, would fall under the requirements of this guideline.

Risk assessments applicable to the environment should include airborne contamination as well as liquid effluent contamination.

6. PERSONAL PROTECTION EQUIPMENT AND BREATHING AIR SYSTEMS

INDONESIAN OPERATIONAL MANUAL FOR IMPLEMENTATION OF GMP EDITION 2000

3.4.1. For the processing of products containing the highly toxic substances, cytotoxic agents and immunosuppressive compounds, facilities should be solely dedicated to the product. Outgoing air should be effectively filtered before discharging into the atmosphere using an air filter of minimum efficiency 98% or through other suitable system.

If production of those products is performed in the same building for non-penicillin products, the lay out should be arranged in such away that:

• the production area for those products is completely segregated from other area;
• entrance and exit of personnel and material are fully segregated from other building; and
• a separate air handling system is provided.
EU / EMEA POSITION

The current text of Chapter 3 section 6 of the GMP guide reads as follows:

“In order to minimise 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, such as highly sensitizing materials (e.g. penicillins) or biological preparations (e.g. from live micro-organisms).

The production of certain additional products, such as certain antibiotics, certain hormones, certain cytotoxics, certain highly active drugs and non-medicinal products should not be conducted in the same facilities.

For those products, in exceptional cases, the principle of campaign working in the same facilities can be accepted provided that…”
No guidance is given to clarify what is meant by “certain” and “exceptional cases” in this context.

EU / EMEA POSITION

At present the GMP/GDP Inspectors Working Group agrees that the Guide should indeed identify those products in which the use of dedicated facilities is mandatory.

It is acknowledged that the drafting group needs input from toxicological/pharmacological experts in order to develop this part of the guidance so that it is based on well grounded scientific principles and this expertise has now been made available.

EMEA’s Safety Working Party will be asked to endorse the outcome of this expert input before the new guidance is released for public consultation.

For other products, it is envisaged that those which combine relatively high-risk pharmacological/toxicological characteristics with high risk physico-chemical properties and process design, should not be manufactured using shared facilities unless justified after following a rigorous Quality Risk Management process and taking any appropriate risk mitigating measures for part or all of the process.

In this regard the drafting group is currently developing a table to identify those high risk physico-chemical and process characteristics and is working on definitions of some of the terms used in connection with this topic.
PRODUCTION HORMONES, CYTOTOXICS, ANTIBIOTICS, ETC.

- **DEDICATION** (Separate building, self-contained))
- **SEGREGATION** (Same building, but dedication)
- **CONTAINMENT** / Use of dedicated equipment
- **CAMPAIGN MANUFACTURING** / Use of dedicated equipment

- **WHICH HORMONES, WHICH ANTIBIOTICS ? FOR ALL FORMS ?**
  - Beta-lactames (PEN, Cepha but what about penems ?), others ?
  - Sexual hormones, corticosteroids ?

**Alpha-lactames**

![Prednisolone](image)

![Progesterone](image)

ALTERNATIVES

**DEDICATION**
- NO COMMON ACCESS
- SEPARATE HVAC
- SEPARATE UTILITIES
- WASTE TREATMENT

**SEGREGATION**
- COMMON ACCESS
- SEPARATE HVAC
- SEPARATE UTILITIES ?
- WASTE TREATMENT

**ISOLATION**
- DEDICATED EQUIPMENT
- SPECIAL TECHNOLOGY
- WASTE TREATMENT
ANY QUESTIONS ?