

Shared Facilities e Cross Contamination

il nuovo orientamento regolatorio

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Agenda

- * *Gli «impianti dedicati» nelle cGMP*
- * *Le proposte di modifica ai Capitoli 3 e 5 delle GMP-Part I*
- * *La nuova linea guida EMA sulle «shared facilities»*
- * *I commenti degli stakeholders e la posizione di EMA*

Impianti dedicati nelle cGMP

GMP-Part I – Chapter 3 - Premises and Equipment

Production Area (3.6)

- * “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, 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 specific precautions are taken and the necessary validations are made”

Impianti dedicati nelle cGMP

GMP-Part I – Chapter 5 - Production

Prevention of cross-contamination (5.18-5.20)

- * “Contamination of a starting material or of a product by another material or product must be avoided”
- * “Amongst the most hazardous contaminants are **highly sensitizing materials**, biological preparations containing living organisms, certain hormones, cytotoxics, and other highly active materials”
- * “**Cross-contamination should be avoided by appropriate technical or organizational measures**, for example:
 - * production in **segregated areas** (required for products such as penicillins, live vaccines, live bacterial preparations and some other biologicals), or by campaign (separation in time) followed by appropriate cleaning
 - * using “**closed systems**” of production
 - * using **cleaning** and **decontamination procedures** of known effectiveness

Impianti dedicati nelle cGMP

GMP-Part II – Chapter 4 – Building and Facilities

Containment (4.4)

- * “**Dedicated** production areas, which can include facilities, air handling equipment and/or process equipment , should be employed in the production of **highly sensitizing materials**, such as penicillins or cephalosporins.”
- * “**Dedicated** production areas should also be considered when material of an infectious nature or **high pharmacological activity or toxicity** is involved (e.g. certain steroids or cytotoxic anti-cancer agents) unless validated inactivation and/or cleaning procedures are established and maintained.”

Impianti dedicati nelle cGMP

GMP-Part II – Chapter 8 – Production and In-Process Controls

Contamination Control (8.5)

- * “**Residual materials** can be carried over into successive batches of the same intermediate or API if there is adequate control.... Such carryover should not result in the carryover of **degradants or microbial contamination** that may adversely alter the established API impurity profile”
- * “Production operations should be conducted in a manner that will prevent contamination of intermediates or APIs **by other material**”
- * “**Precautions to avoid contamination** should be taken when APIs are handled after purification”

Impianti dedicati nelle cGMP

Sviluppi normativi

2005

- * Pubblicazione **ICH Q9 (Step 4)**: Principi del Quality Risk Management (QRM)
- * **Concept Paper (GMP/GDP)**: proposta di applicazione del QRM ai criteri di scelta di un impianto dedicato

2008

- * Modifica **GMP Capitolo 1**: inserimento principi QRM
- * **ICH Q9** inclusa come *Annex 20* alle GMP Parte 1

2011

- * **ICH Q9** inclusa in GMP Parte III
- * **Concept Paper (SWP)**: annuncio elaborazione di una linea guida sui criteri tossicologici da applicare agli impianti dedicati
- * **ICH Q3C (R5)**: nuova linea guida sui solventi residui, che introduce criteri tossicologici di valutazione del cleaning

Impianti dedicati nelle cGMP

Sviluppi normativi

Dicembre 2012

* **EMA/CHMP/CVMP/169430/2012:**

Linea guida sui limiti di esposizione da usare per identificare rischio nella fabbricazione in impianti condivisi (*shared facilities*) - proposta in consultazione

Gennaio 2013

- * EC pubblica le proposte di modifica dei **Capitoli 3, 5, 6 e 8** delle **GMP Parte I**:
le modifiche proposte fanno riferimento alla nuova linea guida EMA

Giugno/Luglio 2013

- * Termine dei periodi di consultazione

Settembre 2013

* **EMA *Workshop on Shared Facilities*:**

Discussione con esponenti di associazioni imprenditoriali e professionali

Proposta di modifica

GMP Parte I - Chapter 3 – «Production Area»

- * “The measures to prevent cross-contamination should be **commensurate with the risks**”
- * “Risk assessment should include, among other parameters, a **toxicological evaluation** of the products being manufactured”
- * “**Dedicated facilities** are required for manufacturing **when** a medicinal product **presents a risk**:
 - * which **cannot be adequately controlled** by operational and/ or technical measures or
 - * **scientific data does not support threshold values** (e.g. allergenic potential from highly sensitising materials such as beta lactams) or
 - * **threshold values** derived from the toxicological evaluation **are below the levels of detection**

Proposta di modifica

GMP Part I - Chapter 5 – «Production»

- * “A **toxicological evaluation** should be the basis for the establishment of **threshold values** in relation to the products manufactured”
- * “The outcome of the **Quality Risk Management** process should be the basis for determining the necessity for and extent to which equipment and facilities should be **dedicated to a particular product or product family**”
- * “This may range from **dedicating specific product contact parts to dedication of the entire manufacturing facility**”
- * “It may be acceptable to confine manufacturing activities to a segregated, self contained production area within a multiproduct facility, where justified”
- * *Al punto **5.20** è inserita una lista (non esaustiva) di “**misure tecniche ed organizzative**” finalizzate alla riduzione del rischio di cross-contamination, tra le quali “**dedicated facilities**”*



EUROPEAN MEDICINES AGENCY
SCIENCE · MEDICINES · HEALTH

13 December 2012
EMA/CHMP/ CVMP/ SWP/169430/2012
Committee for medicinal products for human use (CHMP)
Committee for medicinal products for veterinary use (CVMP)

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

Draft

Draft Agreed by Safety Working Party	December 2012
Adoption by CVMP for release for consultation	November 2012
Adoption by CHMP for release for consultation	13 December 2012
Start of consultation	08 January 2013
End of consultation (deadline for comments)	30 June 2013

Comments should be provided using this [template](#). The completed comments form should be sent to SWP-H@ema.europa.eu

Keywords Shared facilities, risk identification, exposure limits

La nuova linea guida EMA

Obiettivi

- * Definire un approccio scientifico alla valutazione della *cross-contamination*
- * Sostituire i limiti attualmente in uso (1/1000 e 10ppm) che non tengono conto dei dati farmacologici e tossicologici
- * Introdurre una valutazione del rischio, basato su valori soglia
- * Definire le condizioni che richiedono l'uso di impianti dedicati

Campo di applicazione

- * Medicinali (umani e veterinari) - prodotti in fase clinica - API
- * Approccio omogeneo a tutti i processi di fabbricazione farmaceutica, con l'elaborazione di un «*Risk Assessment Report*»
- * Modifica i Capitoli 3 e 5 delle GMP

La nuova linea guida EMA

Calcolo limiti esposizione (cross-contamination)

- * Riferimento a Appendix 3 di **ICH Q3C (R5)** «*Impurities: Guideline for Residual Solvents*»
- * **PDE**: *Permitted Daily Exposure*

$$\text{PDE} = \frac{\text{NOEL} * \text{Weight Adjustment}}{\text{F1} * \text{F2} * \text{F3} * \text{F4} * \text{F5}}$$

Il valore di **PDE** è:

- * Specifico per ogni sostanza
- * Il livello di dose che non provoca effetti avversi
- * Riferito ad una esposizione per tutta la vita

La nuova linea guida EMA

PDE: criteri di valutazione

- * Necessità di disporre di **dati farmacodinamici e tossicologici** (clinici e non clinici)
- * Necessità di una **valutazione critica** dei dati, soprattutto se incompleti
- * Identificazione degli **effetti avversi** (clinici e non clinici)
- * Definizione di un **NOEL** oppure di un **LOEL** (basato sulla farmacodinamica)
- * Applicazione di «**fattori di aggiustamento**», analoghi a quelli riportati in ICH Q3C (R5), da giustificare
- * Valutazione e scelta del valore di PDE, **il più basso calcolato**

La nuova linea guida EMA

PDE: considerazioni specifiche

- * Valutazione dell'impatto della biodisponibilità in funzione della via di somministrazione (basato su dati nell'uomo)
- * Nel caso di **sostanze genotossiche**, dove non è determinabile un valore di soglia, è proposto il valore di **0.15 µg/day**, un approccio più conservativo rispetto a quello richiesto per le impurezze genotossiche (**TTC < 1.5 µg/day**)
- * Nel caso di **sostanze allergizzanti**:
 - * *se è stata definita una dose non allergizzante (es. via topica), si calcola il PDE*
 - * *se non è definita una dose non allergizzante (es. via orale), sono richiesti **impianti dedicati***
- * Nel caso di **macromolecole e peptidi** (non applicabile a ADC) si considera esclusivamente l'effetto farmacodinamico
- * In caso di **dati insufficienti** a definire un valore di PDE, sono richiesti **impianti dedicati**

La nuova linea guida EMA

Summary of Risk Assessment Report

Company Name

Company Address

Expert Name and Signature

Date

Assessment Review Date

Chemical Name/s

Hazards Identified

	YES	NO	UNKNOWN
Positive genotoxicant	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Reproductive developmental toxicant	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Potential carcinogen	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Sensitizing potential	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

Basis for the PDE

Critical effect observed
Dose upon which the PDE is based.

Reference/s

Publication/s used to identify the critical effect and dose

Derived PDE

Calculation

Summary of the Expert CV

EMA Workshop 2013



Parenteral Drug Association
Connecting People, Science and Regulation®



Making Medicines Affordable

APIC *Active Pharmaceutical
Ingredients Committee*



EMA Workshop 2013

Participants:

- * 3 EMA officers
- * 9 officers from 5 National Competent Authorities (UK, F, D, IRL, NL)
- * 30 representatives of 8 industry associations

Scope of the workshop

- * To allow both regulators and industry to clarify their respective positions and to discuss the main comments received during the public consultation

General considerations by industry:

- * Full agreement on the principles of avoiding cross contamination
- * General acceptance of the safety-based risk management
- * Need of a pragmatic approach for implementation and to consider a few critical issues

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Applicability

«Risk assessment for decision on the use of dedicated facilities should be carried out for **all products or only for products with elevated toxicity or highly sensitising?**»

Industry Associations (except ISPE)

- * In favour of applying risk assessment to categories of **products considered to be more at risk.**

ISPE

- * In favour of application **to all products.**

EMA and Regulators

- * **They recognize this is a very important point and a careful reflection is necessary before taking a decision.**

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Implementation period

Industry associations:

- * A careful consideration of the time given to industry to implement the new requirements to **existing products**, in particular if application of the risk assessment tool was required for all products
- * Need to clarify the meaning of «**new products**», which could be NCE or products that a given manufacturer has just started producing

EMA position:

- * *A different approach will be required for «legacy products», where old limit values could be accepted.*

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PDE methodology

Industry Associations:

- * Risk identification by PDE is **only part of a Risk Assessment** and Management
- * High Risk should be put in the context of **other aspects** such as: volume, engineering controls, etc.
- * Decisions on shared or dedicated facilities must be based on Risk Management approach as defined in **ICH Q9**

EMA position:

- * *The PDE methodology has been chosen as the preferred harmonized approach*
- * *Adjustment factors will be modified to increase flexibility*
- * *Health-based limits would replace toxicological limits*

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The Toxicological Tool

Industry Associations:

- * Some of the text in the guideline related to the decision making process for the use of dedicated facilities would be better placed **in the GMP guide**
- * A **more flexible approach** than the one in the current text fo setting the limits and for risk evaluation, as it is not possible to foresee all the possible cases that could present in practice

EMA position:

- * Agreement with the proposal to add a sentence e.g.:
«deviation from the main approach highlighted in the guideline can be accepted if adequately justified»

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Applicability to IMPs

Industry Associations:

- * The text relating to IMPs should be amended to reflect the fact that there may be little or **no toxicological knowledge** available
- * The **manufacturing scale** of IMPs evolves as the compound progresses
- * A flexibility in the methods of risk analysis: more emphasis on «**Read Across**» and default levels, in early phases

EMA position:

- * *Agreement with the amendment proposal of the text relating to IMPs, in particular for early phases IMPs*

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Applicability to APIs

Industry Associations:

- * The current text of the Guideline is **not suitable** to be applied to APIs
- * An Annex to EU GMP Part II could be created to give **specific guidance on API** operations, in relation with the toxicological approach in risk assessment on cross contamination

EMA position:

- * *The «toxicological tool» is not directly applicable to APIs*
- * *The QRM principles should be applied to APIs: the key issue stays in the intermediates*
- * *A specific guidance for APIs will be issued*

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Mutagenic Impurities

Industry Associations:

- * The genotoxic threshold limit (0.15 µg) would be inappropriate and would provide **no significant benefit**
- * The guideline should be aligned with **ICH M7** and EMA residual metals guidance
- * The 0.15 µg limit would drive toward the requirement of dedicated facilities not on the high risk basis but due to **analytical limitations**

EMA position:

- * *The threshold limit for genotoxic impurities was based on a conservative approach*
- * *Agreement on discussing further this issue and on the alignment with ICH M7*

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Sensitising Materials

Industry Associations:

- * For the greater majority of compounds, the frequency and severity of sensitisation is low with the exception, as noted in section 3.6 of the GMP Chapter (highly sensitising, e.g. **penicillins**)
- * A sensitising material as such does not indicate a requirement for a dedicated facility and this requirement **would be limited to highly sensitising materials**

EMA position:

- * *Agreement on replacing «sensitising» with «highly sensitising»*
- * *Definition of «highly sensitising material» will be included*
- * *A specific chapter about allergenes will be added*

Prospettive

- * **EMA** procederà ad una revisione dei documenti:
 - * *Revised Chapters 3 e 5 di EU GMP Part I*
 - * *Linea guida sulle “shared facilities”*
- * E' prevista una seconda consultazione pubblica.
- * E' prevista l'uscita di una revisione parziale dei Capitoli 3 e 5, limitata agli aspetti che non sono in relazione agli impianti dedicati.
- * **EMA** ha riconosciuto la necessità di un periodo di transizione abbastanza lungo (almeno 2 anni) per l'implementazione della nuova linea guida.

Grazie per l'attenzione