PHARMAprocess

Innovation Forum in Pharmaceutical Process

Annex 15 and new FDA/EMA validation guide

27-28/10/15

www.pharmaprocessforum.com

Fira Barcelona

Track 1: Novedades GMP.

EU-GMPs – Histórico de actualizaciones

2013

- Capítulo 1
- Sistemas de Calidad
- Capítulo 7
- Actividades Subcontratadas

2014

- Capítulo 2
- Personal
- Capítulo 6
- Control de Calidad
- Parte II-GMP
- Requisitos Sust. Activas

2015

- Capítulo 3
- Locales y equipos
- Capítulo 5
- Producción
- Capítulo 8
- Reclamaciones ,Defectos y Retiradas
- Anexo 15
- Cualificación y Validación
- Parte III-GMP
- Excipientes

Próximos

- Anexo 16
- Certificación por una persona cualificada y liberación
- Anexo 1
- Fabricación Medicamentos Estériles
- Anexo 21
- Importadores de Productos Medicinales

Continued/-ous Process Verification

(CPV)

Track 1: GMP (FDA, EU and others):

Building & Capturing Process Knowledge

Learning progression

New paradigm:

Good planning, expected path

Stage I	Stage II	Stage III
Comprehensive process design, scientific process understanding	Sound, thorough process qualification. Confirms design	Continued Verification, Process learning and improvement

Old paradigm:

Poor design, planning, process understanding

Poor, minimal design	PQ checklist exercise w/little understanding	Unexplained variation, Product and process problems. Process not in control. **Major learning!** Potentially substandard product on market

Track 1:
GMP (FDA, EU and others): New

U.S. Food and Drug Administration
Protecting and Promoting Public Health
www.fda.gov

Ref. Ares(2015)1380025 - 30/03/2015

EUROPEAN COMMISSION
DIRECTORATE-GENERAL FOR HEALTH AND FOOD SAFETY

Medicinal Products – Quality, Safety and Efficacy

Brussels, 30 March 2015

information and data to be provided in the regulatory submission only. However GMP requirements for process validation continue throughout the lifecycle of the process

Legal basis for publishing the detailed guidelines: Article 47 of Directive 2001/83/EC on the Community code relating to medicinal products for human use and Article 51 of Directive 2001/82/EC on the Community code relating to veterinary medicinal products. This document provides guidance for the interpretation of the principles and guidelines of good manufacturing practice (GMP) for medicinal products as laid down in Directive 2003/94/EC for medicinal products for human use and Directive 91/412/EEC for veterinary use.

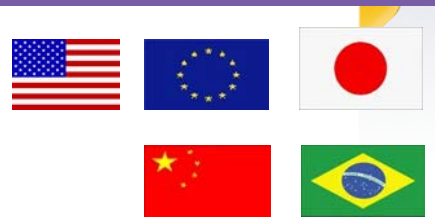
Status of the document: Revision

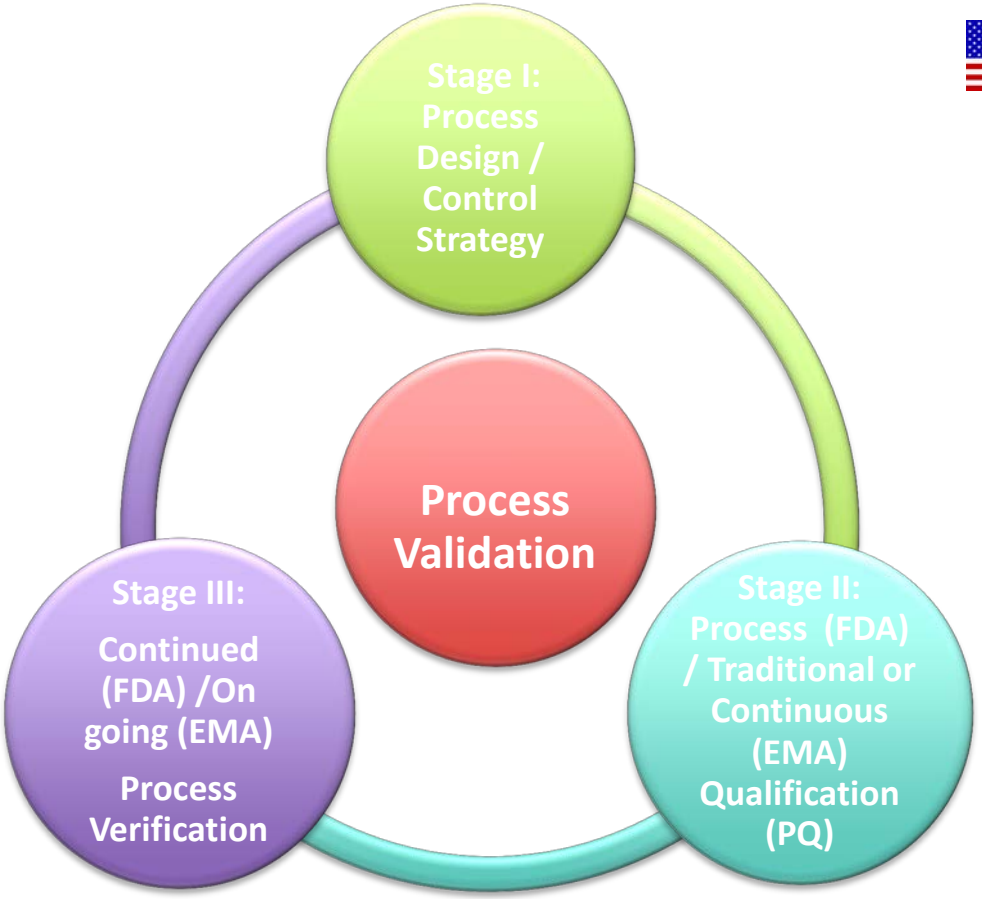
Reasons for changes: Since Annex 15 was published in 2001 the manufacturing and regulatory environment has changed significantly and an update is required to this Annex to reflect this changed environment. This revision to Annex 15 takes into account changes to other sections of the EudraLex, Volume 4, Part I, relationship to Part II, Annex 11, ICH Q8, Q9, Q10 and Q11, QWP guidance on process validation, and changes in manufacturing technology.

Deadline for coming into operation: 1 October 2015

Track 1: GMP (FDA, EU and others):

New concept: Lifecycle Model





Track 2: PROCESS VALIDATION: New

5.3. Manufacturing processes may be developed using a traditional approach or a continuous verification approach. However, irrespective of the approach used, processes must be shown to be robust and ensure consistent product quality before any product is released to the market. Manufacturing processes using the traditional approach should undergo a prospective validation programme, wherever possible, prior to certification of the product. Retrospective validation is no longer an acceptable approach.

Continuous process verification

5.23. For products developed by a quality by design approach, where it has been scientifically established during development that the established control strategy provides a high degree of assurance of product quality, then continuous process verification can be used as an alternative to traditional process validation.

5.24. The method by which the process will be verified should be defined. There should be a science based control strategy for the required attributes for incoming materials, critical quality attributes and critical process parameters to confirm product realisation. This should also include regular evaluation of the control strategy. Process Analytical Technology and multivariate statistical process control may be used as tools. Each manufacturer must determine and justify the number of batches necessary to demonstrate a high level of assurance that the

Track 2: PROCESS VALIDATION

Ongoing Process Verification during Lifecycle

5.28. Paragraphs 5.28-5.32 are applicable to all three approaches to process validation mentioned above, i.e. traditional, continuous and hybrid.

5.29. Manufacturers should monitor product quality to ensure that a state of control is maintained throughout the product lifecycle with the relevant process trends evaluated.

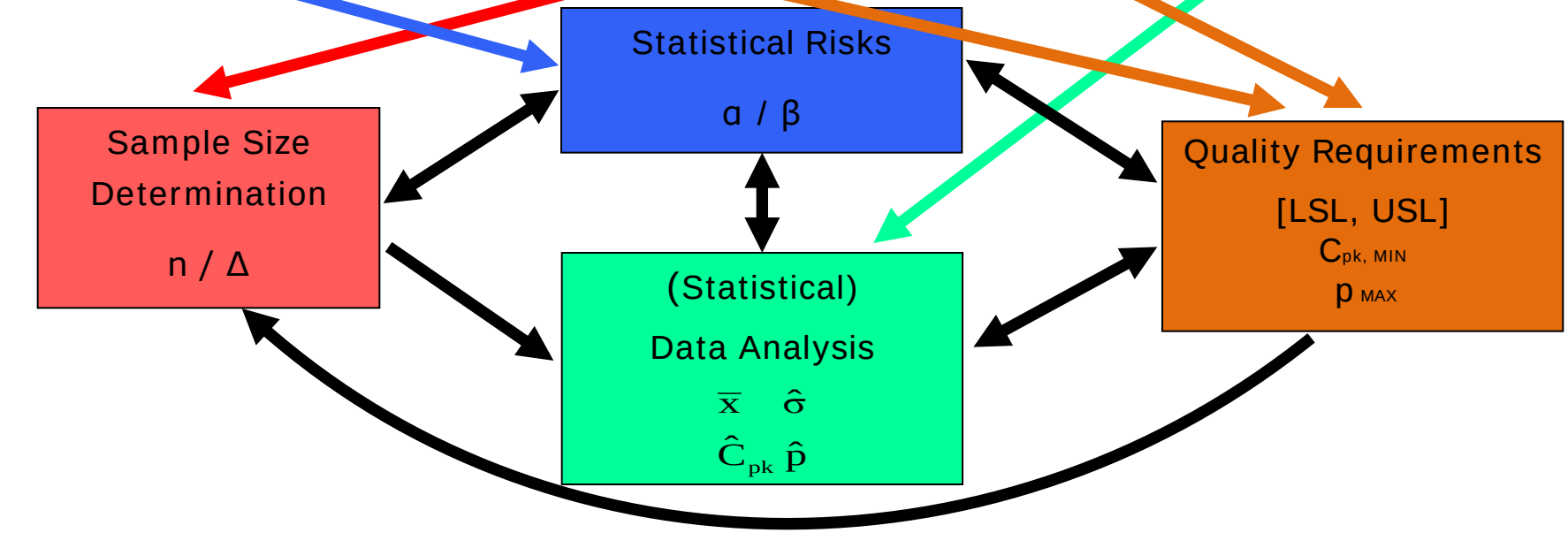
5.30. The extent and frequency of ongoing process verification should be reviewed periodically. At any point throughout the product lifecycle, it may be appropriate to modify the requirements taking into account the current level of process understanding and process performance.

5.31. Ongoing process verification should be conducted under an approved protocol or equivalent documents and a corresponding report should be prepared to document the results obtained. Statistical tools should be used, where appropriate, to support any conclusions with regard to the variability and capability of a given process and ensure a state of control.

5.32. Ongoing process verification should be used throughout the product lifecycle to support the validated status of the product as documented in the Product Quality Review. Incremental changes over time should also be considered and the need for any additional actions, e.g. enhanced sampling, should be assessed.

Track 3: DATA ANALYSIS
Translation into Statistics

For purposes of this guidance, *process validation* is defined as the collection and evaluation of data, from the process design stage through commercial production, which establishes scientific evidence that a process is capable of consistently delivering quality product. Process validation



The results derived from monitoring should be statistically trended and collaboratively reviewed by trained personnel from Operation and Quality Unit.

Track 4: Monitoring Plan: Control Strategy (Stage I & III)

Example 1

Menu

DP-CQA	(C)MAs / i(C)MAs / (C)PPs: process step	material / equipment	attribute/ parameter	criticality classification	risk level	justification / comment	Control Strategy (gives control measure for CQA related CMA/i-CMA/CPP(e.g. DS specification, excipients specifications, facility & equipment operating conditions, in-processcontrols, DP specifications)): type of control	range investigated	PAR	NOR	specification	method	frequency of testing	reference	monitoring
Drug content	---	---	---	---	---	---	Drug product Release Test	---	---	---	95.0 - 105.0% (for US: 90.0 - 110.0 %)	HPLC-UV	each batch	Release Testing Specifications TS-403 1.0	Yes
Drug content	Compression	Final blend	Water content	iCMA	high	Testing of LoD at final blend stage during process validation. Comparitive LoD-study with respect to different production steps (e.g. granules unsieved / final blend) will be carry out. **FMEA (1.2.1.a.6) RPZ = 120 --> Monitoring** Range investigated and PAR: Pharmaceutical development report U10-1536-02; NOR: Transfer report BIRI -ING 005-TFREP-	IPC: LoD at final blend level	2.0 - 4.8%	2.5 - 4.0 %	2.9 - 3.7% *: based on currently availalbe data	2.5 - 4.0 %	Microwave resonance moisture / Halogen Dryer	each batch	MBR /Monitoring Protocol	Yes
Drug content	Drying	wet granules	Water content	iCMA	high	Degradation products, water content, microbiological quality, Uniformity of drug content, mechanical strength, drug release, appearance: LoD results of all analyzed validation batches (granulate and final blend) are within specification. Comparitive LoD-study with respect to different production steps (e.g. granules unsieved / final blend) will carry out. **FMEA (1.1.1.e.3) RPZ = 120 --> Monitoring**	C: LoD at granules intermediate level	2.0 - 4.8%	2.5 - 4.0 %	2.9 - 3.7% *: based on currently availalbe data	2.5 - 4.0 %	Microwave resonance moisture / Halogen Dryer	each batch	MBR	Yes
Drug release	---	---	---	---	---	---	Drug product release test	---	---	---	Tightest Specification: % release of Linagliptin in 30min: Q=80%: Stage I (n=6):	HPLC-UV	each batch	Release Testing Specifications TS-403 1.0 in accordance with: Ph. Eur. 2.9.3 (S1, S2,	Yes
Drug release	Compression	Final blend	Water content	iCMA	high	Testing of LoD at final blend stage during process validation. Comparitive LoD-study with respect to different production steps (e.g. granules unsieved / final blend) will be carry out. **FMEA (1.2.1.a.6) RPZ = 120 --> Monitoring** Range investigated and PAR: Pharmaceutical development report U10-1536-02; NOR: Transfer report BIRI -ING 005-TFREP-	IPC: LoD at final blend level	2.0 - 4.8%	2.5 - 4.0 %	2.9 - 3.7% *: based on currently availalbe data	2.5 - 4.0 %	Microwave resonance moisture / Halogen Dryer	each batch	MBR /Monitoring Protocol	Yes
Drug release	Compression	Tabletting press	Main compression force	CPP	low	Automatic measurement of the main compression force. Monitoring of main compression force because of influence on the tablet hardness. **FMEA (1.2.2.a.14) RPZ = 40 --> Monitoring** Range investigated and PAR:Transfer report BC - BIRI APFE 2007/222; NOR: Transfer report BIRI -ING 005-TFREP-AA13305-01, Validation report ING 505-PVBE-AA15632-01 Evaluation report Doc.No. 505-EVBE-AA1828- 01	Equipment operation condition	6-20kN	8 -20 kN	9 -11 kN warning limit: < 14 kN*: based on currently available data	not defined	force measurement	each batch	Monitoring Protocol	Yes
Drug release	Drying	dried, unsieved granules	Inhomogeneous water distribution	iCMA	high	LoD results of all analyzed validation batches (granulate and final blend) are within specification. Comparitive LoD-study with respect to different production steps (e.g. granules unsieved / final blend) will carry out. **FMEA (1.1.1.e.3) RPZ = 120 --> Monitoring**	C: LoD at granules intermediate level	2.0 - 4.8%	2.5 - 4.0 %	2.9 - 3.7% *: based on currently availalbe data	2.5 - 4.0 %	Microwave resonance moisture / Halogen Dryer	each batch	MBR	Yes

DP-CQAs | **Related CMAs/iCMAs/CPPs** | **Established Control Measures**

Track 4: Monitoring Plan: Risk Assessment (Stage I & III)

Example 2

ANEXO 1: Análisis de Riesgos. Identificación de variables_Mucosolvan 2 ml ampollas

Definición Proceso					Sistemas de Control				Decisión	
Etapa	Equipo	Descripción etapa	Variable	Tipo	Rangos/Set-Point	Registros	Control	Seguimiento	Monit. (adicional)	Motivo
1. Preparación de la solución	Reactor de fabricación T-X2	Adición agua para inyectables y materias primas	Temperatura, Conductividad y TOC online Recuento microbiológico	MA	Cumple Ph Eur	SCADA Resultados monitorización	Setpoint PLC	On-line	No	SC/ PMT
							Plan monitorización WFI según NT-051-2CMMO-00091	Revisión resultados y tendencias semestral		
			Peso agua (kg)	CPP	Teor ± tolerancia (seg. tamaño lote)	GF SCADA	Setpoint PLC	Doble Chequeo Cada lote	No	SC
			Peso individual materias primas (kg)	CPP	Teor ± tolerancia (seg. tamaño lote)	GF Certificado Pesada	POMS	Doble Chequeo Cada lote	No	SC
			Temperatura (ºC)	CPP	37ºC (35-40)	GF SCADA	Setpoint PLC	Cada lote	No	SC
			Agitación (rpm)	PP	Teor ± tolerancia (según línea)	GF SCADA	Setpoint PLC	Cada lote	No	SC
			Tiempo (min)	PP	≥ Teórico (según validación)	GF	GF	Cada lote	Si	RGF
		Enfriamiento y Controles finales	Temperatura (ºC)	CPP	22ºC (20-25)	GF SCADA	Setpoint PLC	Cada lote	No	SC
			Agitación (rpm)	PP	Teor ± tolerancia (según línea)	GF SCADA	Setpoint PLC	Cada lote	No	SC
			pH	CQA	4,9-5,1	GF	GF-/-IPC	Cada lote PQR anual	Si	RGF
			Bioburden	CQA	≤100 UFC/100 ml	QDIS	Plan monitorización microbiológica según 051-2CMMT-00082	Cada lote Informe Anual	Si	PMT

Related CQAs/CMAs/iCMAs/CPPs

Established Control Measures

Cleaning Validation (ADE/PDE)

Track 1: GMP (FDA, EU and others):

U.S. Food and Drug Administration
Protecting and Promoting Public Health
www.fda.gov

Application of Risk and Science to Cleaning

Cleaning Risk Assessment

The subject of "risk" in pharmaceutical manufacturing has

Figure 1. Acceptable Daily Exposure (ADE).

21 CFR 211.67- EQUIPMENT CLEANING AND MAINTENANCE (2011)

Track 1:
Excerpt of EU GMP Annex 15 Qualification and Validation

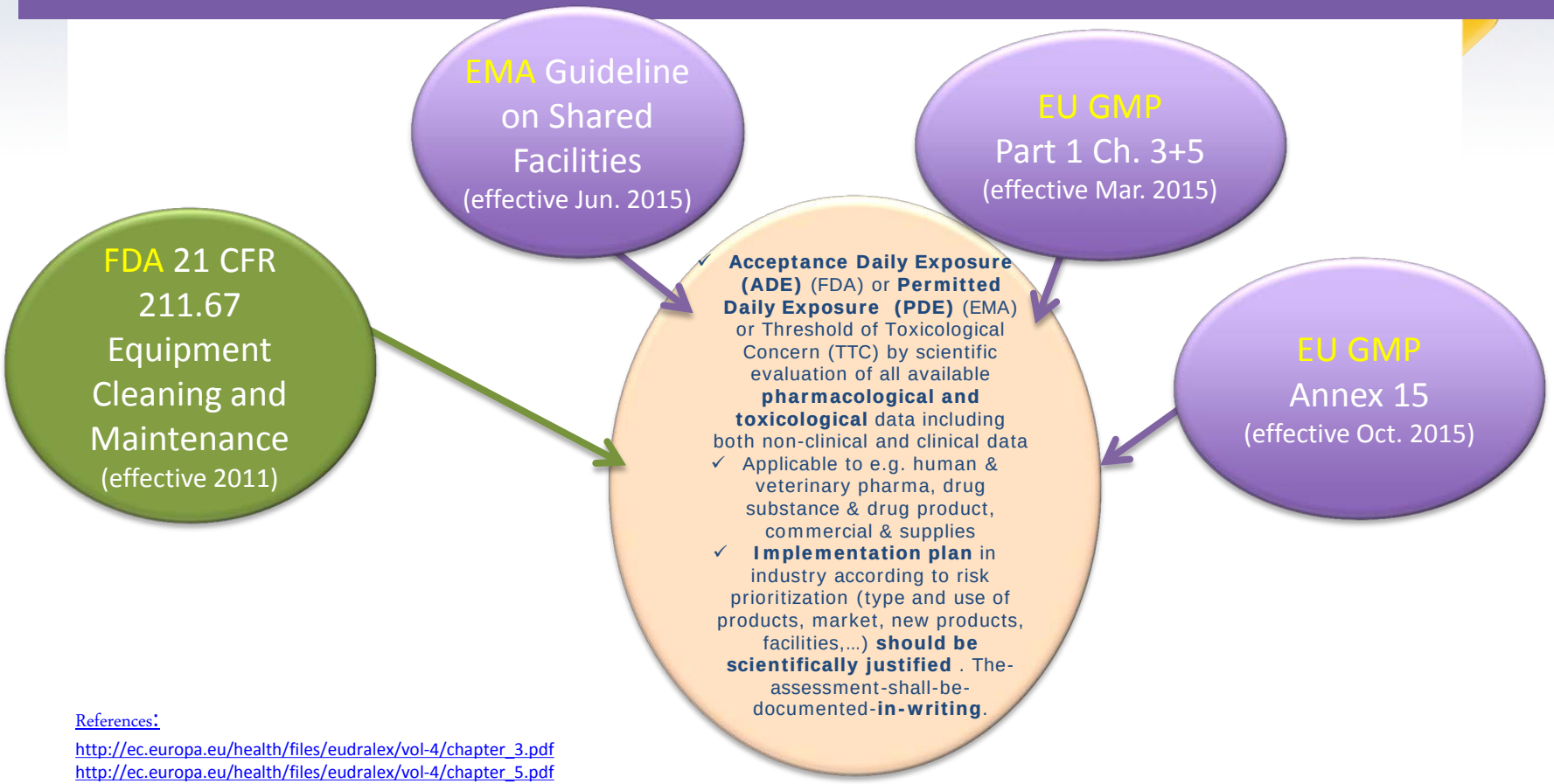
Previous version	Current version (effective October 1, 2015)
36. Cleaning validation should be performed in order to confirm the effectiveness of a cleaning procedure. The rationale for selecting limits of carry over of product residues, cleaning agents and microbial contamination should be logically based on the materials involved. The limits should be achievable and verifiable.	• 10.6. Limits for the carryover of product residues should be based on a toxicological evaluation (See EMA Guideline on setting health based exposure limits for use in risk identification in the manufacture of different medicinal products in shared facilities). The justification for the selected limits should be documented in a risk assessment which includes all the supporting references. Limits should be established for the removal of any cleaning agents used. Acceptance criteria should consider the potential cumulative effect of multiple items of equipment in the process equipment train.
40. Typically three consecutive applications of the cleaning procedure should be performed and shown to be successful in order to prove that the method is validated.	• 10.13. The cleaning procedure should be performed an appropriate number of times based on a risk assessment and meet the acceptance criteria in order to prove that • the cleaning method is validated. • http://ec.europa.eu/health/files/eudralex/vol-4/2015-10_annex15.pdf

Track 2: ADE (Acceptable Daily Exposure) or PDE (Permitted Daily Exposure) Definition

- The ADE (FDA) or PDE (EMA) is a **substance-specific dose** that is **unlikely to cause an adverse health event** or undesirable physiological effects, **if an individual is exposed to this dose** or to a lower dose every day for a lifetime.

- ADE (FDA) or PDE (EMA) are based on scientific evaluation of all available pharmacological and **toxicological data**, generally set **exposure-route specific**, in particular for the **parenteral**, the **oral** and the **inhalation route** [PDE (parenteral), PDE (oral) and PDE (inhalation)].

Track 2: Why are ADE/PDEs in Cleaning Process validation needed?



References:
http://ec.europa.eu/health/files/eudralex/vol-4/chapter_3.pdf
http://ec.europa.eu/health/files/eudralex/vol-4/chapter_5.pdf
http://ec.europa.eu/health/files/eudralex/vol-4/2015-10_annex15.pdf
http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2014/11/WC500177735.pdf
http://eur-lex.europa.eu/legal-content/EN/TXT/?uri=uriserv:OJ.L_.2014.337.01.0001.01.ENG

Track 3: ADE (FDA) / PDE (EMA) Calculation

How are ADE/PDEs calculated?

$$PDE = \frac{NO(A)EL \times Weight\ Adjustment}{F1 \times F2 \times F3 \times F4 \times F5}$$

NO(A)EL: NO(A)EL for critical effect

Weight Adjustment: 50 or 70 kg *(orientate)*

F1: Extrapolation between species

F2: Variability between individuals (10)

F3: Extrapolation to chronic exposure

F4: Severe toxicity (e.g. teratogenicity)

F5: LO(A)EL to NO(A)EL

If needed: Route-to-route extrapolation (→ $PDE_{parenteral}$, PDE_{oral} and $PDE_{inhalation}$)

Compounds with limited data, proposed default (categorized) PDE values: *(orientate)*

Compounds that are not likely to have a high pharmacological activity or toxicity: 100 µg/day
Compounds that may have a high pharmacological activity or toxicity: 10 µg/day
Compounds that may have a very high pharmacological activity or toxicity: 1 µg/day
Compounds known or expected to have an extremely high pharm. activity or toxicity: 0.1 µg/day

Reference: SOP (Scientific approach)

Track 4: Changes in Setting Acceptance Criterion

1/1000 of Dose Method; Changed to…

- **Acceptable Concentration in Next Product**

$$\text{Acceptable Residue } [\mu g/g] = \frac{MTD_p \cdot SF}{MDI_F}$$

- **Maximum Allowable Residue of previous product**

$$MAR_p \left[\frac{mg}{cm^2}\right] = \frac{MTD_p \cdot SF \cdot MBS_F}{W_F \cdot MDI_F \cdot A_{tot}}$$

- **Surface Criterion**

$$MAR_p \left[\frac{mg}{cm^2}\right] = \frac{MTD_p \cdot SF}{cm^2};$$

$$\text{Where } \frac{MBS_F}{W_F \cdot MDI_F \cdot A_{tot}} = 1.0$$

MTDp: Minimum Therapeutic Dose (mg/day)
SF: Safety factor (ex. 1/1000)
MDIF : Maximum Therapeutic Dose (following) (g/day)

Toxicology (PDE/ADE) Based

- **Acceptable Concentration in Next Product**

$$\text{Acceptable Residue } [\mu g/g] = \frac{PDE}{MDI_F}$$

- **Maximum Allowable Residue of previous product**

$$\text{MAR } [\mu g/cm^2] = PDE \cdot \frac{\text{MBS}_\text{F}}{\text{LDD}_\text{F} \cdot \text{SSA}}$$

- **Surface Area Generalization Factor**

$$\text{SAGF } \left[\frac{1}{cm^2}\right] = \frac{\text{MBS}_\text{F}}{\text{LDD}_\text{F} \cdot \text{SSA}};$$

$$MAR_p \left[\frac{mg}{cm^2}\right] = PDE \cdot \text{SAGF}$$

PDE: Permitted Daily Exposure (mg)
LDDF: Largest Daliy dose (following) (g/day)
MBSF: Minimum Batch Size (following) (g)
SSA: Total Shared Surface Area (cm2) or
V rinse: Total Volume rinse

Track 4: ADE / PDE Application in validated processes & equipment

- **PDEs mainly to be used in establishing thresholds for cleaning validation processes:**

☺ Established cleaning is acceptable, PDE (=risk) can be controlled

😐 Cleaning procedures / analytics to be confirmed/adapted

☹ **PDE cannot be kept: Consider organizational or technical remediation**

→ If no remediation possible, apply segregation or dedication

Track 5: References

THANK YOU !!!

- FDA: http://www.fda.gov/downloads/Drugs/.../Guidances/UCM070336.pdf
- EMA: http://ec.europa.eu/health/files/eudralex/vol-4/2015-10_annex15.pdf (NEW)
- AEMPS: http://www.aemps.gob.es/industria/inspeccionNCF/home.htm

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