Worst Case Residue Limits Calculations Matrix and Worst Production Selection

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Chapter 1

worst case residue limits calculation methodology

The Worst case residue limit calculations performed in this document are based on the principles outlined in the below reference documents:

- Fourman and Mullen, Determining Cleaning Validation Acceptance Limits for Pharmaceutical Manufacturing Operations
- PDA Technical Report No. 29, Revised 2012 Points to Consider for Cleaning Validation (TR29)

The acceptance level (i.e. concentration) of the target residue in the subsequently manufactured product may be called by different terms, but for this document that concentration will be called Maximum Allowed Carryover (abbreviated MAC).
This is an expression for the maximum concentration of residue allowed in that next product, as determined by medical, pharmacological, safety, stability and/or performance issues. For chemical residues (such as the drug active or cleaning agent), this concentration is typically given as g/g or g/mL (or an equivalent expression depending on the units selected).
MAC is generally expressed in various forms. The terminology used in this document is given below.
Surface Area Limit (SAL)
Surface Area Limit is the maximum allowed residue limit in the next product batch per shared surface area across the product equipment contact surface area. This is generally expressed in mg/square cm. For active pharmaceutical ingredients, Surface Area Limits is calculated using different criterias and are combined into one Worst Surface Area Limit (SAL) using the cleaning limit policy configured. For cleaning agent, only toxicity criteria is used to caculate the Surface Area Limit. The different criterias have been described below:

Name	Sampling Type	Product Type	Formula	Description
MAC based on dosage criteria	swab	solid	(1/SF) * (MDD_a) * (1/LDD_b) * (MBS_b) * (1/SSA_ab)	Based on minimum daily dose of the drug active in a maximum daily dose of the next drug product
MAC based on a general criteria	swab	solid	(1/100000) * (MBS_b) * (1/SSA_ab)	General 10ppm limit to be considered when it is lower than dosage/ toxicity based limits or when dosage/toxicity data is not available
MAC based on toxicity criteria	swab	solid	(PDE_a) * (1/LDD_b) * (MBS_b) * (1/SSA_ab)	Based on Risk-MaPP Acceptable Daily Exposure (ADE) approach

where,
SF: Safety factor for drug dosage and depends on the Product type.
MDD_a: Minimum daily dosage of the Active from previous Product (A)
LDD_b: Largest daily dosage of the next Product (B)
MBS_b: Minimum batch size of the next Product (B)
SSA_ab: Shared contact surface area between active (A) from previous product and next product (B)
PDE_a: Permitted daily exposure of the Active from previous Product or Cleaning Agent(A)
Worst Limit Swab
Worst Limit Swab = Worst Surface Area Limit * Swabbed Surface Area / Solvent Desorption Amount
Worst Limit Rinse
Worst Limit Rinse = Worst Surface Area Limit * Rinsed Surface Area / Rinse Volume
Actives Cleaning Limit Policy
The configured cleaning policy is used to combine different limits calcualted to give Worst Surface Area Limit Or Site Acceptance Limit. Based on the above methodology, «cleaningLimitPolicy».

Chapter 2

limits

2.1 Actives

cription
Product wise worst case residue limits are given below:

Production Id	Product	API	LOD	LOQ	Worst Limit Rinse	Worst Limit Swab	Next Production (Product)	Validation Group Id	SAL
Pr1	Febuxostat Tablets 40 mg 80 mg and 120 mg (P1)	Febuxostat	0.03	0.1	-	1813.458	Pr2 (Dabigatran Etexilate Capsules 75 mg 110 mg and 150 mg)	Production Group - ProductionGroup1 (PG1)	0.725
Pr2	Dabigatran Etexilate Capsules 75 mg 110 mg and 150 mg (P2)	Dabigatran Etexilate	0.03	0.1	-	5208.333	Pr1 (Febuxostat Tablets 40 mg 80 mg and 120 mg)	Production Group - ProductionGroup1 (PG1)	2.083
Pr3	Telmisartan Tablets 20 mg 40 mg and 80 mg (P3)	Telmisartan	0.03	0.1	11.412	114.124	Pr4 (Rosuvastatin Calcium Tablets 5 mg 10 mg 20 mg and 40 mg)	Production Group - ProductionGroup1 (PG1)	0.0456
Pr4	Rosuvastatin Calcium Tablets 5 mg 10 mg 20 mg and 40 mg (P4)	Rosuvastatin	-	-	13.695	-	Pr3 (Telmisartan Tablets 20 mg 40 mg and 80 mg)	Production Group - ProductionGroup1 (PG1)	0.0548
Pr5	Pregabalin Capsules 25 mg 50 mg 75 mg 100 mg 150 mg 200 mg 225 mg and 300 mg (P5)	Pregabalin	0.03	0.1	49.049	490.488	Pr4 (Rosuvastatin Calcium Tablets 5 mg 10 mg 20 mg and 40 mg)	Production - Pr5	0.196
Pr6	Test Product (P6)	Pregabalin	0.03	0.1	-	1813.458	Pr2 (Dabigatran	Production - Pr6	0.725

2.2 Cleaning Agent

cription

Equipment	Cleaning Agent	LOD	LOQ	Next Production (Product)	Worst Limit Rinse	Worst Limit Swab	Worst SAL
Scoop (DAPR009)	Methanol (Methanol)	0.03	0.1	Pr2 (Dabigatran Etexilate Capsules 75 mg 110 mg and 150 mg)	127576793.75	1275767937.5	510307.175
Scoop (DAWH001)	Methanol (Methanol)	0.03	0.1	Pr2 (Dabigatran Etexilate Capsules 75 mg 110 mg and 150 mg)	127576793.75	1275767937.5	510307.175
IdenticalGroup1 (EGI1)	Methanol (Methanol)	0.03	0.1	Pr5 (Pregabalin Capsules 25 mg 50 mg 75 mg 100 mg 150 mg 200 mg 225 mg and 300 mg)	-	-	57159.375

2.3 Microbial

cription

2.3.1 Bioburden

Room Grade	Contact Surface Type	Sampling Method	Limit	Residue Type
Unclassified	Direct	rinse	10	Bacterial
Unclassified	Direct	rinse	8	Fungal
Default (Grade A)	Direct	rinse	10	Bacterial
Default (Grade A)	Direct	rinse	8	Fungal
Default (Grade B)	Direct	rinse	10	Bacterial
Default (Grade B)	Direct	rinse	8	Fungal
Default (Grade C)	Direct	rinse	10	Bacterial
Default (Grade C)	Direct	rinse	8	Fungal
Default (Grade D)	Direct	rinse	10	Bacterial
Default (Grade D)	Direct	rinse	8	Fungal
Unclassified	Indirect	swab	10	BioBurden
Default (Grade A)	Indirect	swab	10	BioBurden
Default (Grade B)	Indirect	swab	10	BioBurden
Default (Grade C)	Indirect	swab	10	BioBurden
Default (Grade D)	Indirect	swab	10	BioBurden

2.3.2 Endotoxin

Room Grade	Contact Surface Type	Sampling Method	Limit
Unclassified	Indirect	rinse	10
Default (Grade A)	Indirect	rinse	10
Default (Grade B)	Indirect	rinse	10
Default (Grade C)	Indirect	rinse	10
Default (Grade D)	Indirect	rinse	10

Chapter 3

Worst Case Production Selection

C1.

- Production with API having the highest solubility rating will be selected as worst production.
- In case where solubility rating of two APIs are identical, Production with API having the highest Toxicity Risk category will be selected as worst production.
- In case where Toxicity Risk category of two APIs are identical, Production with API having the highest risk number as per RPN overall will be selected as worst production.

Validation Group	**Worst Case Production**	**Worst Case API**
product - Pr5	Pr5 (Pregabalin Capsules 25 mg 50 mg 75 mg 100 mg 150 mg 200 mg 225 mg and 300 mg)	Pregabalin
product - Pr6	Pr6 (Test Product)	Pregabalin
product group - ProductionGroup1 (PG1)	Pr1 (Febuxostat Tablets 40 mg 80 mg and 120 mg)	Febuxostat
product group - ProductionGroup1 (PG1)	Pr3 (Telmisartan Tablets 20 mg 40 mg and 80 mg)	Telmisartan

Chapter 4

Product attributes

The «prOrPrGroupString» attributes are given in the table below:

Production Group Id	**Production Group Name**	**Productions Mapped**
PG1	ProductionGroup1	Pr1,Pr2,Pr3,Pr4

Production	Product	API	Largest Daily Dosage	Minimum batch size	Strength	Type of Formulation
Pr1	Febuxostat Tablets 40 mg 80 mg and 120 mg (P1)	Febuxostat	40	125	120	Solution
Pr2	Dabigatran Etexilate Capsules 75 mg 110 mg and 150 mg (P2)	Dabigatran Etexilate	40	43.523	150	Suspension
Pr3	Telmisartan Tablets 20 mg 40 mg and 80 mg (P3)	Telmisartan	40	198	80	Solution
Pr4	Rosuvastatin Calcium Tablets 5 mg 10 mg 20 mg and 40 mg (P4)	Rosuvastatin	40	165	40	Oily Solution (Emulsion)
Pr5	Pregabalin Capsules 25 mg 50 mg 75 mg 100 mg 150 mg 200 mg 225 mg and 300 mg (P5)	Pregabalin	40	325	300	Solution
Pr6	Test Product (P6)	Pregabalin	40	325	200	Solution

API Name	Solubility in water	Min Therapeutic dose	Max Therapeutic dose	PDE	Is Genotoxic	OEB Rating
Febuxostat	7	40	240	0.12	-	1
Dabigatran Etexilate	6	150	300	20	true	2
Telmisartan	6	20	160	0.8	-	3
Rosuvastatin	4	5	80	0.15	true	4
Pregabalin	4	25	600	0.5	true	5

Chapter 5

equipment attributes

The «eqOrEqGroupString» attributes are given in the table below:

Equipment Group Id	Equipment Group Name	Equipments Mapped	Worst Equipments	Type
EGI1	IdenticalGroup1	EQG1,EQG2,EQG3	All equipments are identical.	Identical

Equipment Name	Equipment Id	Contact Surface area	Cleaning Procedure number
Scoop	DAPR009	300	CPN-Methanol
Scoop	DAWH001	300	CPN-Methanol
Compression Machine (39 stn)	DEPR022	18725	CPN-Water
Tablet deduster & metal detector	DEPR023	8410	CPN-GRAS
Tablet deduster & metal detector	DEPR024	8410	CPN-GRAS
Eq1	EQG1	10000	CPN-2
Eq2	EQG2	20000	CPN-2
Eq3	EQG3	40000	CPN-2

Chapter 6

product - equipment mapping

Product wise list of product-equipment mapping:

Product Name	**«eqOrEqGroupString» mapped (IDs)**	**Contact Surface Area**	**«eqOrEqGroupString» mapped count**	**Product ID**
Febuxostat Tablets 40 mg 80 mg and 120 mg	DAPR009,DAWH001	600	2	P1
Dabigatran Etexilate Capsules 75 mg 110 mg and 150 mg	DAPR009,DAWH001	600	2	P2
Telmisartan Tablets 20 mg 40 mg and 80 mg	DAPR009,DAWH001,DEPR023,DEPR024,DEPR025	36045	5	P3
Rosuvastatin Calcium Tablets 5 mg 10 mg 20 mg and 40 mg	DAPR009,DAWH001,DEPR023,DEPR024,DEPR025	36045	5	P4
Pregabalin Capsules 25 mg 50 mg 75 mg 100 mg 150 mg 200 mg 225 mg and 300 mg	DEPR024,EGI1	48410	2	P5
Test Product	DAPR009,DAWH001	600	2	P6

Chapter 7

limit calculation variables

The various variables used in the evaluation of the worst case limits and molecules are given in the table given below:

Name	**Short name**	**Unit**	**Value**	**Description**
Body weight (for LD50 dose)	bw	kg	50	body weight of patient taking next product
Indirect Surface Swab Chemical Limit L3	ind_swab_chemical_limit_l3	mg/sqcm	1	Default
Indirect Surface Swab Detergent Limit L3	ind_swab_detergent_limit_l3	mg/sqcm	1	Default
Modification factor	mf	no unit	1000	Cumulative modifying factor, selected by the toxicologist. generally no more than 1000
Safety Factor - Solids	sf_solid	no unit	1000	Safety Factor for Solids drug dosage
Verification Period	verifyPeriod	month	12	The frequency at which equipment needs to be verified.