CLEANING VALIDATION CONCEPT FOR INTRODUCTION OF PRODUCT WITH NEW ACTIVE PHARMACEUTICAL INGREDIENT IN PHARMACEUTICAL PRODUCTION

Elisaveta Adamova Abrasheva[1*]; Darko Atanasoski[1]; Natasha Kronevska[1]; Ana Ivcheska[1]; Elizabeta Karadzinska[1]; Olivera Paneva[1]

[1]ALKALOID AD Skopje, Pharmaceutical, Chemical and Cosmetics Company, Aleksandar Makedonski 12, 1000 Skopje, Republic of North Macedonia

INTRODUCTION

Equipment cleaning is a critical process in the manufacturing of different pharmaceutical products in shared facilities. The cleaning process must prevent cross contamination and reduce residues from previous product to levels that ensure patient safety and regulatory compliance.

Cleaning validation is documented evidence that an approved cleaning procedure will reproducibly remove the previous product and other residues from equipment surfaces below scientifically established acceptance criteria. Cleaning validation should be properly documented to demonstrate current Good Manufacturing Practice (cGMP) for finished medicinal products.

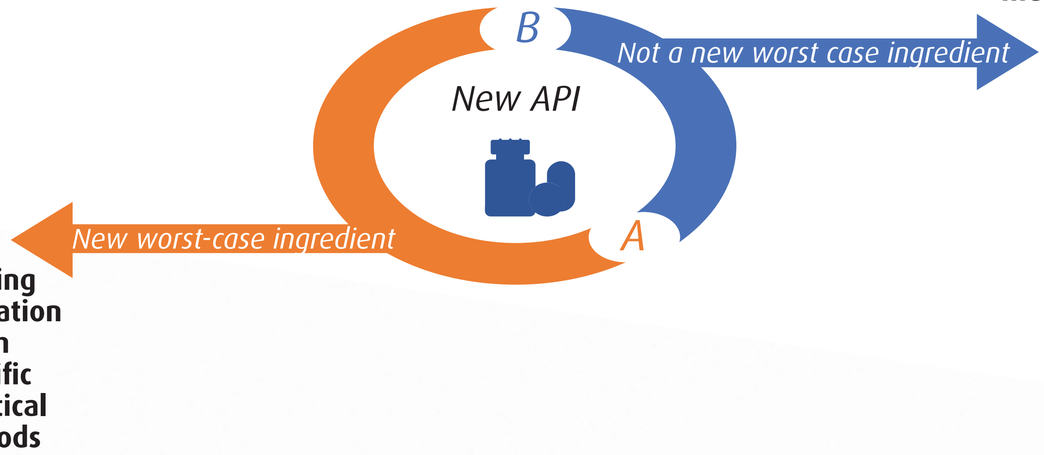
INTRODUCTION OF MEDICINAL PRODUCT WITH NEW ACTIVE PHARMACEUTICAL INGREDIENT

METHODOLOGY

Product name	PDE (µg/day)	P (PDE index 1-4)	S (Solubility index 1-4)	D (Difficulty of cleaning)	P*S*D = **RPN**
A	100,0	4,0	4,0	5,0	80,0
B	20,0	4,0	3,0	7,0	84,0
C	20,0	4,0	4,0	4,0	64,0

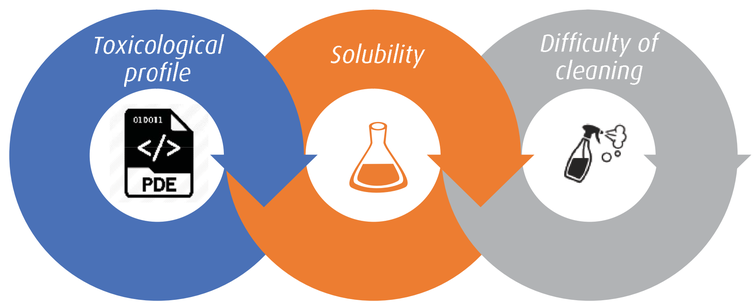
CLASSIFICATION CRITERIA		
PDE index (1-4)	**Solubility index of formulated product (1-4)**	**Difficulty (effort) of cleaning**
0-500 µg/day = 4,0	Insoluble = 4,0	Very difficult = 7,0
501-2000 µg/day = 3,0	Partly insoluble = 3,0	Difficult = 6,0
2001-5000 µg/day = 2,0	Soluble = 2,0	Medium difficult = 5,0
5001 – 10 000 µg/day = 1,0	Easily soluble = 1,0	Slightly difficult = 4,0
		Moderate to clean = 3,0
		Easy to clean = 1,0-2,0

Before introduction of a new active pharmaceutical ingredient in the production facility, a reevaluation of the risk assessment is performed, to characterize the degree of criticality and the specific requirements for active pharmaceutical ingredients with highly sensitizing or genotoxic potential.



ASSESSMENT APPROACH

New active pharmaceutical ingredient evaluation is based on a risk assessment matrix in which three main criteria of the active substance and the finished product are evaluated:



Worst case risk assesment for cleaning validation of solid dosage forms equipment					
Product name	**PDE (µg/day)**	**PDE index (1-4)**	**Solubilty index of formulated product (1-4)**	**Difficulty of cleaning index (1-7)**	**RPN**
DIAZEPAM 2 mg, 5 mg coated tbl.	**20,0**	**4,0**	**3,0**	**7,0**	**84,0**
SITAGLIPTIN 25 mg, 50 mg, 100 mg f.c.t.	1700,0	3,0	3,0	3,0	27,0

TOXICOLOGICAL PROFILE CRITERIA (PDE)

Sitagliptin

Occupational Exposure Limit (OEL)

330 µg/m³

Acceptable Daily Exposure (ADE)

1700 µg/day

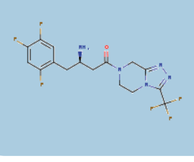
Classification

Category 1 - Low

Basis for Classification

- Long-elimination half-life
- Not carcinogenic
- Not genotoxic

Generic Name
Sitagliptin
Occupational Exposure Limit (OEL)
330 µg/m³
Acceptable Daily Exposure (ADE)
1700 µg/day
Classification
Category 1 – Low (5 band system)
C.A.S. #[1]
486460-32-6 (base)
486459-71-6 (hydrochloride)
654671-77-9 (phosphate monohydrate)
654671-78-0 (phosphate)
1169707-31-6 (sulphate)
Structure[1]



SOLUBILITY CRITERIA

Solubility evaluation is based on the rationale that any product less soluble in water, is more difficult to clean.

Solubility of the active substance and the finished product is tested in water, in alkaline and acidic pH environment, according to pH of the detergents in standard cleaning procedures.

	Descriptive term	Approximate volume of solvent in milliliters per gram of solute		
1	Very soluble	less than	1	
2	Freely soluble	from	1	to 10
3	Soluble	from	10	to 30
4	Sparingly soluble	from	30	to 100
5	Slightly soluble	from	100	to 1000
6	Very Slightly soluble	from	1000	to 10000
7	Practically insoluble	more than		10000

Active Pharmaceutical Ingredient	Solubility of API (according to European Pharmacopoeia)	Approximate volume of solvent in milliliters per gram of solute	Solubility index number for API (according to European Pharmacopoeia)
Diazepam	**Very Slightly Soluble**	**1000 ml – 10000 ml**	**6**
Sitagliptin	Soluble	10 ml – 30 ml	3

CLEANABILITY CRITERIA

Difficulty of cleaning matrix						
Products vs. Critical cleaning components	**Coloured API or pigments**	**Aroma (Flavour)**	**Extended/ prolonged release technology**	**Aqueous granulation technology**	**Excipients prone to microb. growth**	**Index number (1-7)**
DIAZEPAM 2 mg, 5 mg coated tbl.	1,0	/	/	1,0	5,0	7,0
SITAGLIPTIN 25 mg, 50 mg, 100 mg f.c.t.	2,0	/	/	1,0	/	3,0

CONCLUSION

In conclusion, when introducing a product with new active pharmaceutical ingredient in pharmaceutical production, for Cleaning validation a worst-case approach is used. Both active substance and the finished product are assessed. This is performed by risk assessment in which the relevant and scientifically justified criteria are evaluated.

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Health above all

REFERENCES

EMA's Guideline on setting health based exposure limits for use in risk identification in the manufacture of different medicinal products in shared facilities EMA/CHMP/CV MP/SWP/169430/2012;

ISPE® Guide: Cleaning validation lifecycle- Applications, Methods and Controls;

EudraLex - Volume 4 Good manufacturing practice (GMP) Guidelines. (Chapter 3 - "Premises and Equipment", Chapter 5- "Production", Annex 15- "Qualification and validation");