Implemetation of EMA's new toxicology-based regulation on setting cleaning limit – some practical aspects of cross-contamination

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It is obvious that cleaning limits is a critical question and establishing a safe carryover value is crucial part of pharmaceutical quality assurance (see e.g. [1]). On 20th November, 2014 the **European Medicines Agency (EMA)** accepted the **new guidline** [2] **on setting safe cleaning limits** in the pharmaceutical operational units. This guideline aims to regulate the quantity of residual active substances of human and/or veterinary medicinal products in order to ensure the safety of patients/treated animals. For this purpose an approach is recommended deriving a scientifically based threshold value for individual active substances to be applied for risk identification. In this context risk identification means a **complex approach** for analysing the different aspects and origins of possible cross-contamination in detail, including its toxicological concern as well, and then assessing the risk in the curse of continuous development of the pharmaceutical quality system.

From the point of view of risk evaluation, four groups of **failure modes** can be distinguished those result in cross-contamination, namely

1)mix-up,

2)retention,

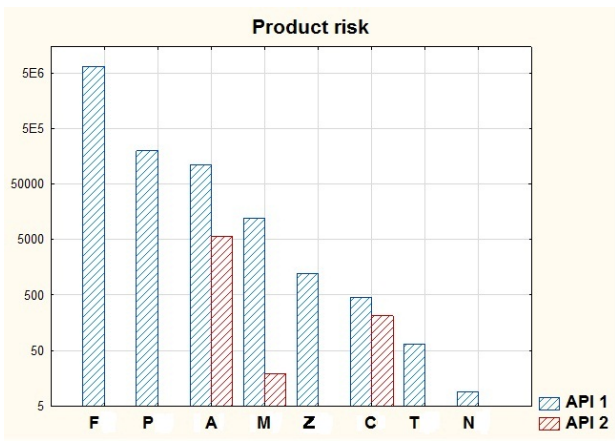
3)mechanical transfer and

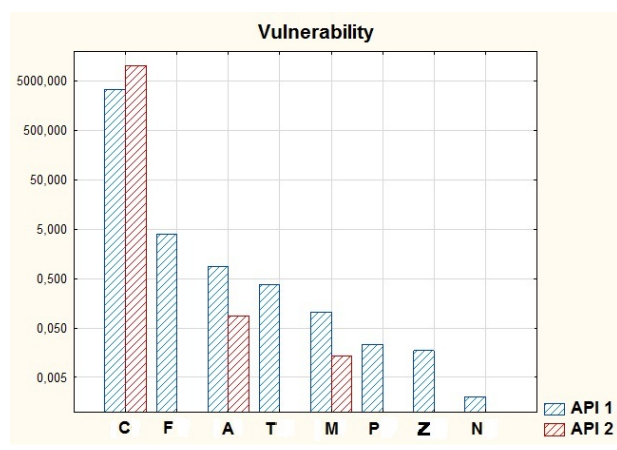
4)air transfer.

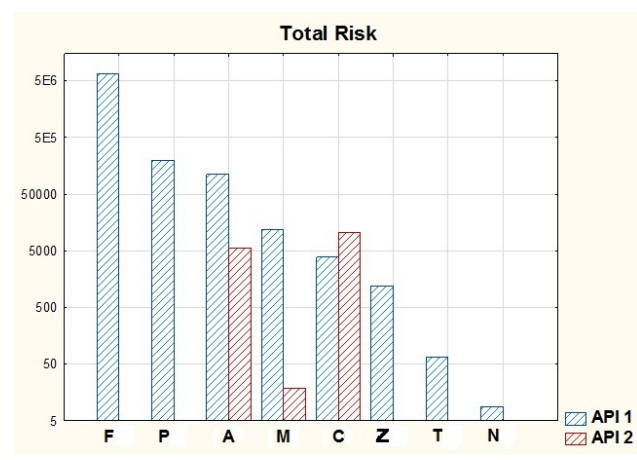
This classification is based on the recommendations of ISPE [3] which serves with a detailed practical guidence on how risk assessment of possible cross-contamination can be carried out.

Implementing the new EMA guide „**Guideline on setting health based exposure limits for use in risk identification in the manufacture of different medicinal products in shared facilities**" [2] is a real challenge in the contemporary pharma industry Europe-wide.

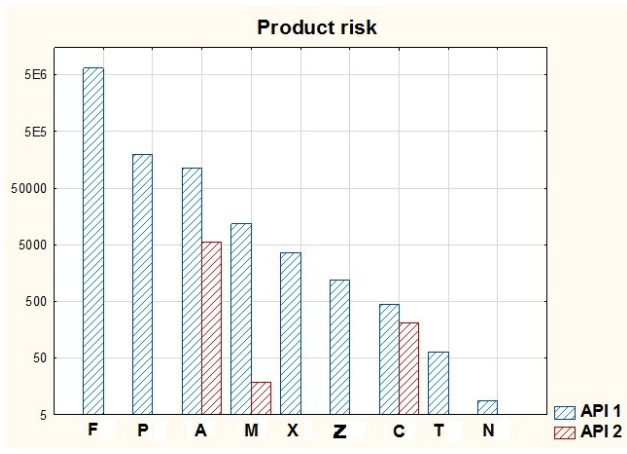
Case Study 1. Review of cleaning limits based on PDE values in a Plant and the analysis of risk of possible cross-contamination based on the knowledge of the production area

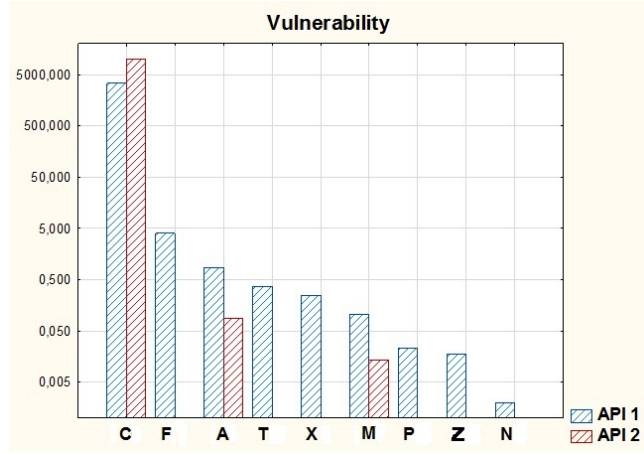


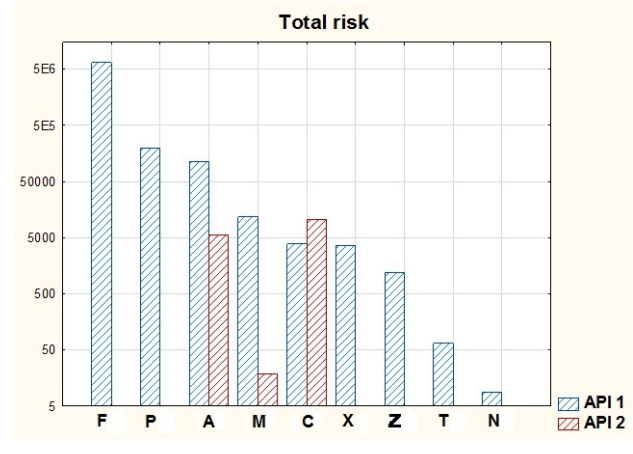




Case Study 2. Planning of a new product containing the active pharmaceutical ingredient „X" in the same Plant and the analysis of risk of possible cross-contamination based on the knowledge of the production area







Summary

Our risk evaluation on possible cross-contamination made clear some practical aspects due to the application of PDE-based calculations. 1) Very often „old" , well-known products may possess surprisingly toxic characteristics (or at least higher then expected). That extorts corrective actions in the cleaning process or in the controll of the cleaning process depending on the findings. 2) Not definetelly the hormonal active component is the most toxic. Traditionally, hormonal APIs are considered toxic while non-hormonal APIs not. The second part of the statement has to be revisied in the light of new rules (see ref [2]).

References

[1] I. Ziegler and B. Lugosi-Czangar: A practical approach to chemical cleaning validation planing of active pharmaceutical ingredients: establishing a safe maximum carryover value – present and future, Bilingual lecturebook on spectroscopy – On the 80th birthday of professor Dr. Ferenc Billes, private edition, Eds: I. Ziegler I. and I. Fejes, Esztergom, 2014, pp. 47-56., ISBN 978-963-08-9474-6

[2] EMA: Guideline on setting health based exposure limits for use in risk identification in the manufacture of different medicinal products in shared facilities, Brussels, 2014

[3] International Society for Pharmaceutical Engineering (ISPE): Risk-based manufacture of pharmaceutical products – A guide to managing risks associated to cross-contamination, Baseline Guide (Ser.) Vol. 7, 1st Ed., Sept. 2010.