Impact statement
Highly Potent Products – Dedicated Facilities

Background

EU GMP Ch 5 -Changes have been made to sections 17 to 21, including adding a new section, to improve the guidance on prevention of cross-contamination and to refer to toxicological assessment to determine safe threshold values of potential cross contaminants.

Deadline for coming into operation: 1 March 2015. However, the toxicological evaluation mentioned in section 20 has to be carried out:

- from 1 June 2015 for any medicinal product newly introduced into shared manufacturing facilities;
- before 1 December 2015 for medicinal products already produced in a shared manufacturing facility producing only medicinal products for human use or producing both medicinal products for human use and veterinary medicinal products on 31 May 2015;
- before 1 June 2016 for veterinary medicinal products already produced in a shared manufacturing facility producing only veterinary medicinal products on 31 May 2015.

PIC/S held closed sessions for regulators discussing the topic of dedicated facilities. PIC/S Inspectors agreed to establish an Expert Circle on Dedicated Facilities, which will draft an Aide Memoire on the inspection of dedicated facilities, as well as providing training to inspectors on this difficult issue. It was noted that 60% of all PIC/S inspectors have not yet received any training in this critical field. The Regulatory Authorities of Argentina, France, Ireland, Italy, Poland, South Africa, UK, and USA have committed to provide the necessary support to the PIC/S Expert Circle. Some Partner Organisations such as WHO will also be involved.

- ## What has changed

- The previous Chapter 5 gave a vague listing of certain types of product which might need to be manufactured in dedicated facilities. The new chapter 5 indicates that the need for dedicated facilities should be based on ICH Q9 (Quality Risk management) principles.
- Previously industry has made use of and regulators have in general accepted non scientific measures to define acceptable cross contamination / cleaning limits e.g. <1/1000of the low clinical dose,LD50 values and <10ppm of one product in another. This is no longer the case. Now a toxicological evaluation has to be carried out. Existing cleaning validation may no longer be valid
- Consolidation within the industry has led to increased transfers of product from one facility to another and often an increase in the type of products handled within any one facility. Some specialist dedicated facilities have been closed and production outsourced.
- New types of products are being introduced and this will in all probability proliferate in the future.
- Molecules are often more potent leading to lower dose products . Risk also exists from new and legacy high potency products in either low or high dose formats.

- New products often have a biological origin but are made / finished in non biological facilities
- New technologies including use of disposable or contained systems can significantly reduce cross contamination risks.
- Clean in place (CIP)/ wet or wash in place (WIP) systems are increasingly common and in turn lead to validateable plant cleaning.
- Regulators to be trained in the evaluation of the need for dedicated facilities and in the assessment of their effectiveness.

Impact

- Confirmation of, or increase in patient safety measures.**(Absolute requirement / peace of mind)**
- Present justifications for manufacture in common facilities, e.g cleaning validation based on non scientific values, may not hold up when subjected to toxicological evaluation. **(Risk of regulatory censure)**
- Regulators more aware of requirements and their effectiveness. **(Increased risk of regulatory censure unless industry keeps pace)**
- Current dedicated production / processes may be found to be no longer strictly required if subjected to toxicological evaluation and current containment /cleaning capability.**(un-necessary expense and restriction on versatility of production facilities**)
- Process improvement using new technologies and appropriate Quality Risk Management measures may remove the need for dedicated facilities. **(increased flexibility and production capacity through relatively low cost process refinement)**
- The incorporation of new technologies (single use, high containment / CIP,WIP etc.) may when scientifically evaluated Significantly reduce or eliminate cross contamination potential and subsequently the need for / frequency of monitoring. **(reduced long term costs)**

Dedicated facilities are in general a very expensive to build and operate. Only in exceptional circumstances would a company wish to build / operate them unless to do so was strictly necessary for patient safety reasons. The market is global so it is essential the regulators worldwide apply the same rationale to requiring such facilities.

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