



EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

<17 July 2013>

Submission of comments on

EU GMP Guide, Part 1, Draft revisions to Chapter 3: Premises and Equipment and Chapter 5: Production

Comments from:

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Please note that these comments and the identity of the sender will be published unless a specific justified objection is received.

When completed, this form should be sent to the European Medicines Agency electronically, in Word format (not PDF).



1. General comments

Stakeholder number	General comment (if any)	Outcome (if applicable)
<i>(To be completed by the Agency)</i>		<i>(To be completed by the Agency)</i>

Comment:

FDB supports the use of a risk-based approach for assessing and controlling cross contamination in shared equipment and facilities, based on a toxicological assessment of the product to be manufactured. This approach works well for products used in mid- to late-stage clinical trials, or marketed products.

FDB is however concerned that, as written, the revised chapters do not specifically address the challenges presented by the manufacture of Phase I investigational medicinal products in multi-product facilities and may result in a decrease in the flow of investigational medicinal products into clinical trials.

Chapter 3 section 6, and Chapter 5 section 19, require the calculation of a PDE based on the NOEL or LOEL, as set out in the Draft EMA Guidance: *Guideline on setting health based exposure limits for use in risk identification in the manufacture of different medicinal products in shared facilities* (EMA/CHMP/CVMP/SWP/169430/2012) This may be problematic for Manufacturing Organisations such as FDB, who make a range of biotechnology derived APIs, some of which are targeted for evaluation in early animal toxicology studies and Phase I clinical trials, where information is

very limited. Material used in toxicology studies is often also used for Phase I clinical trials, so at the time of the GMP manufacture, the information required to derive a PDE (as defined in the guidance) may not be available. In addition, at the time of equipment cleaning/changeover post manufacture, the identity of the next product to be manufactured in the same equipment, its batch size and dose, are also frequently not known, making an acceptable carryover limit difficult to determine. FDB routinely requests Material Safety Data Sheets (MSDSs) and Investigator Brochures from sponsor companies, who provide this information, in many cases. The concern is that this may not always be sufficient to meet the needs of the EMA guidance on PDE.

Recommendation:

FDB would like to propose that the approach required by the draft Chapters is applied where there is sufficient data to derive a PDE, but for early Toxicology/Phase I materials a Banding approach be considered, similar to that widely used in the Health and Safety environment, for deriving Occupational Exposure Bands (OEBs). The value of classifying chemicals into OEBs according to their hazards has been recognized for many years. Systems developed by a number of major pharmaceutical companies in the late 1980s classified compounds based on the severity of hazard, and the controls required to reduce exposures to acceptable levels, is described in an AIHAJ article (Naumann et al. 1996). About the same time "banding schemes" were being discussed in the US, the Association of the British Pharmaceutical Industry published a similar hazard categorization scheme (ABPI 1995). Meanwhile, the Health and Safety Executive (HSE) in the UK was developing a user-friendly banding scheme called COSHH Essentials (Brooke 1998; Gardener and Oldershaw 1991; HSE 1999; Maidment 1998). The International

Labor Organization is also supporting the use of control banding throughout the world, especially in less-developed countries. FDB is recommending the same concept be applied to the toxicology assessment for early phase APIs.

In the absence of the level of information cited in the EMA guideline, FDB would recommend a qualified/certified toxicologist be permitted to assign a 'Band', based on the available safety data for the product itself and/or information on products with a similar mode of action. The level of uncertainty in the assessment would be factored into the Band assignment, with those with the highest level of uncertainty defaulting to a higher risk Band.

A series of 4-5 Bands is recommended, each with an expected PDE range. The lower end of this PDE range for a given Band (i.e. worst case) could be used to calculate permitted carryover limits for equipment residues. The Band assigned would also define the scope of the risk mitigation required e.g. where equipment should be dedicated, single-use equipment should be substituted for reusable equipment, and/or where the entire processing scheme should be configured in an enclosed processing train etc. FDB is recommending each firm generate their own banding scheme and associated controls, based on their facility and risk assessments, similar to the approach taken in the Health and Safety models.

The risk associated with not being in a position to assign an acceptable carryover limit at the time of manufacture of a product, in the absence of information on the identity, batch size and/or dose of the next product into the equipment, could be mitigated by ensuring that a maximum allowable carryover calculation (MACO) is carried out as part of each new product introduction to confirm that the carryover limits determined are higher than the

verified residue levels post cleaning. In the event they were not, the equipment could not be shared with the follow on product. These considerations have been implemented in the manufacture of small-molecule pharmaceuticals that are designated as potent molecules (EU Directive 89/391 EEC).

References

ABPI. Association of the British Pharmaceutical Industry. Guidance on setting in-house occupational exposure limits for airborne therapeutic substances and their intermediates. London. England (1995).

Brooke, IM: A UK scheme to help small firms Control risks to health from exposure to chemicals: toxicological considerations. *Ann. Occup. Hyg.* 42:377-390 (1998).

Gardener RJ and PJ Oldershaw: Development of pragmatic exposure control concentrations based on packaging regulation risk phrases. *Ann. Occup. Hyg.* 35:51-59 (1991).

HSE. Health and Safety Executive: COSHH Essentials: Easy steps to control chemicals. London: UK Health and Safety Executive (1999). 200.

Maidment, SC: Occupational hygiene considerations in the development of a structured approach to select chemical control strategies. *Ann. Occup. Hyg.* 42:391-400 (1998).

Naumann, BD, EV Sargent, BS Starkman, WJ Fraser, GT Becker and DL Kirk: Performance-based exposure control limits for pharmaceutical active ingredients. *Am. Ind. Hyg. Assoc. J.* 57:33-42 (1996).

2. Specific comments on text

Line number(s) of the relevant text <i>(e.g. Lines 20-23)</i>	Stakeholder number <i>(To be completed by the Agency)</i>	Comment and rationale; proposed changes <i>(If changes to the wording are suggested, they should be highlighted using 'track changes')</i>	Outcome <i>(To be completed by the Agency)</i>
Chapter 3, section 3.6, paragraph 2		<p>Comment: The text requires that 'Dedicated facilities' are used when a medicinal product presents a risk as outlined in bullets a), b) and c). This could imply that rooms must always be dedicated, whereas adequate control may be achieved by e.g. the use of dedicated, or disposable equipment.</p> <p>Proposed change (if any): Dedicated facilities and/or equipment are required for manufacturing when a medicinal product present a risk:</p>	
Chapter 3, section 3.6, paragraph 3		<p>Comment: This paragraph references further guidance on some exemptions, including the EMA guidance on setting health based exposure limits for risk identification. FFDB would recommend an acknowledgement here that very early phase clinical trials could present a particular challenge that may be addressed by a Banding approach, applied by a certified toxicologist.</p> <p>Proposed change (if any): Further guidance including some exemptions could be found in Chapter 5 and in Annex 2,3,4,5 of the EU detailed guidelines on GMP and the guideline on setting health based exposure</p>	

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		<p>limits for use in risk identification in the manufacture of different medicinal products in shared facilities. The manufacture of toxicology materials and early Phase I materials, for which toxicology data may be very limited, presents a particular challenge. In these circumstances a toxicological assessment must still be undertaken based on available data and published information for products with a similar mode of action. A certified toxicologist should assign a risk category (or Band) to the product, which takes account of the level of uncertainty. Each risk category must have a PDE range assigned to it, the lower end of which can be applied for the determination of threshold levels.</p>	
		<p>Comment:</p> <p>Proposed change (if any):</p>	

Please add more rows if needed.