EMA works on Recalculation of Limits for Cleaning Validation

EMA 将重新计算清洁验证的限度标准

EMA's Inspector Working Group will get together at the end of February. According to the "Concept Paper on the development of toxicological guidance for use in risk identification in the manufacture of different medicinal products in shared facilities" published in October 2011, the question of "Dedicated Facilities" and the determination of limits for cleaning validation will be addressed.

EMA's 检查员工作团队将在 2 月底聚会，处理关于专用设施及确定清洁验证的限度标准，此次聚会是根据 2011 年 10 月出版的“发展毒理学指南用于风险识别在公用设施中生产不同产品”

Yet, a first internal draft for a guideline has been announced which is elaborated together with a specialists' team of EMA's Safety Working Party (SWP).

第一份内部的草案已经发布了，他是由专家团队和 SWP 共同完成的。

The key question which should be answered in this paper concerns the maximal acceptable carry over between products manufactured in the same facility or plant.

在这份文章中需要回答的主要问题就是公用工厂或车间的产品在生产过程中最大可以接受的转移量。

Limits which have been frequently used until now for cleaning validation (namely the 1/1000 dose and the 10ppm criterion) are being questioned by the inspectorate expert group as they do not take into account the available pharmacological/ toxicological data. For instance, the so-called *lead effect* of a substance is not taken into consideration. This is the first effect which occurs when increasing doses of a medicinal product.

现在被经常使用的清洁验证的标准是日常剂量的千分之一和 10ppm 的标准，这两种标准同样被专家检查员所质疑，因为他们没有考虑药理学及毒理学的数据。更进一步的说，这个所谓的能够引起作用或反应的成分没有考虑在内。这个效果最有可能发生，当你增加治疗的剂量的时候。

This may be the pharmacologically desired therapy effect (actually the basis for calculating) or undesired adverse effects like, for example, teratogenicity in case of a drug for cancer.

也许药物的治疗效果是我们最想得到的（实际上是我们计算的基础）而药物的不良反应是我们不想看到的，如癌症药物的致畸性有可能。

One of the possibilities to take into account these effects is to use the ADE (acceptable daily exposure) value. The calculation is based on the complete and actual toxicological and pharmacological properties of the substance.

一种可能就是在运用 ADE 时考虑这些可能的效果。这种计算是依据药物成分的完全及真实的药理学及毒理学数据来进行计算的。

Basically, these include information about the *lead effect* of the substance, the NOEL (No Observed Effect Level) for the lead effect concerned, indications regarding bioavaibility of the substance and appropriate safety factors.

一般的，这里应包括成分的起作用的部分，NOEL，生物利用度有关的参数，还有合适的安全系数都应该被考虑。

The maximal values calculated on the ADE basis generally exceed the previous limits which are based on the 10ppm criterion or 1/1000 daily dose. Substances with a lead effect - which is not the same as the pharmacological therapy effect - may lead to a stricter value for the cleaning limit.

这个基于 ADE 计算的最大值一般大于基于 10ppm 或 1/1000 日常剂量的计算值。但药物成分所引起的作用并不总是和药物的治疗效果一致，这有可能促使清洁验证制定更严格的限度标准。

Furthermore, the different dosage forms must be taken into account in the calculation. Indeed, when fixing the limit of a contaminating product A (for example to be taken orally), an important factor to consider is whether the subsequent product B is to be administered orally too or for parenteral use.

还有，在计算的时候同样要考虑药物的不同的剂型。当我们确定产品 A 的交叉污染的限度标准时（A 是口服制剂），一个重要的因素就是产品 B 是被口服还是做注射用。

It is still unclear if and to what extent the requirement for dedicated facilities for certain products (like antibiotics, hormones, cytostatics) will become more detailed, i.e. as a detailed products list.

如果还是不是很清楚和做到什么程度的要求对于专用设备的特定产品，根据详细的产品的列表将会很清晰。

Still, the manufacture of highly active substances in multipurpose facilities is permitted as long as the manufacturer has performed a scientific risk assessment which exempts him from the obligation of producing in a mono plant.

尽管如此，一种高活性的成分在公用设施中生产仍然是被允许的只要生产企业做了一个科学的风险认为他不必要为此设立一个单独的车间进行生产。

The new EMA Guideline should put an end to this grey area. It is expected that the guideline should contain certain cornerstones for the risk analyses concerned, i.e. indications for the calculation of acceptable residual contamination according to the respective ADEs. At the earliest, the draft should be published by June 2012. According to the current timetable, the guideline should become effective from March 2013 on with a 6-month implementation deadline.

这份新的 EMA 的指南就是弥补这个空白区域，希望指南包括一定的与风险分析有关的基础内容，例如，根据各自的 ADE 计算可接受残留的标志参数。

这份指南最早会在 2012 年 6 月出版，根据目前的时间计划，指南将会在 2013 年 3 月生效并将会有 6 个月的执行期限。

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翻译 kevin zhao 2012.03.11

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注：与药物的生物利用，毒性相关的因素数据将会被更多的考虑，在指南中将会提供一定的操作的具体的指导，而药物的非治疗作用也是制定更严格的清洁验证限度标准的一个主要原因，其实在 APIC 关于清洁验证的指南中已经有一小部分提到利用毒理学数据进行计算清洁验证标准的论述，希望能给你更多的思考。