Cleaning Memo for May 2015
EMA on Limits for Shared Facilities – Part 3

This is the third in a series of Cleaning Memos discussing the finalized version of EMA's "Guideline on setting health based exposure limits for use in risk identification in the manufacture of different medicinal products in shared facilities". It discusses still more additional specific issues in the November 2014 *finalized* version.

Data Gaps for Reproductive and Developmental Toxicity

The guideline refers to the possible lack of animal data on reproductive and developmental toxicity (which I will just refer to as "reproductive toxicity"), as well as "gaps in the scientific knowledge" for commercial products. One solution proposed is "the NOAEL of a sub-chronic/chronic study may be used in the calculation of a PDE with application of an additional adjustment factor (e.g. 10) if adequately justified." I am somewhat confused by this suggestion. If there is no animal reproductive toxicity, what is the NOAEL referring to? Is it a NOAEL on *another* critical effect, with the application of an additional safety factor? Or what?

A second option given is the "read-across" approach, where data from related compounds may be used. The "read-across" approach is utilized in the EU in its REACH initiative to control chemical entities in Europe. One way to think of the "read-across" approach is that it is a form of grouping, whereby data from one chemical compound is applied to other similar compounds. In the case in hand, data for reproductive toxicity for a given compound maybe used for another similar compound without formal studies to generate such data. The key, of course, is to decide what is *sufficiently similar* that such an approach is applicable. This does require the input of a toxicologist with experience in reproductive toxicology. (Note that one of the rationales for the read across approach is to reduce animal testing. Furthermore, while the EMA gives the application of the read-across approach in the context of reproductive toxicity, companies may want to consider that approach for other toxicity concerns.)

Investigational Medicinal Products (IMPs)

This section deals with Phase I/II products that may have limited data. EMA presents an "alternative" approach using default values tiered depending on *potency and toxicity*. It gives three references, but perhaps the most useful for pharmaceutical manufacturers would be the 2005 paper by Dolan et al, since it has a pharmaceutical focus. In that paper, three daily intake tiers are proposed for chemicals with *limited* toxicity data:

1 µg/day for compounds that *may be* carcinogenic
10 µg/day for compounds that *may be* potent or highly toxic
100 µg/day for compounds *not* likely to be potent, highly toxic, or carcinogenic

Although not mentioned by the EMA, it would seem that the "read-across" approach may also be applicable here.

Reporting of "PDE" Determination Strategy

In this section the EMA outlines documentation principles to be followed in determining a PDE. It includes a comprehensive literature search, the critical endpoints, the pivotal animal and human studies used for determination of the PDE, and a rationale for selection of adjustment factors. The EMA also provides a template for a cover page for clear communication to regulators of the results and strategy used. Note that while this section ostensibly applies only to the PDE value, it probably is meant also for any "safe threshold value" which may be determined by other means or approaches. [Note that this section was called "Risk Assessment Report" (a more general description) in the draft EMA document, but was changed to "Reporting of the PDE determination strategy" in the final version.]

Other Approaches

While the EMA gives several options for safe threshold values, such as the PDE approach and the TTC approach, and while it also gives cases where PDEs may not be applicable, it also states that other approaches may be accepted if "adequately justified". For example, in the executive summary, the EMA states:

> "Deviation from the main approach highlighted in this guideline to derive such safe threshold levels could be accepted if adequately justified."

Similar wording is repeated several times in the document in different contexts, such as at the end of Section 1 (Introduction) and in the middle of Section 4.1 (on calculation of PDE values).

Note: Both Risk-MaPP and the EMA refer to a "safe threshold value". However, that phrase is used differently in each document. For the EMA a safe threshold value is a generic or umbrella phrase that would include PDE and TTC values. In Risk-MaPP a safe threshold value is a value *derived from the ADE* which represents one of three limits: the total carryover to the next product, the amount per swab, or a concentration in a rinse solution (values that I commonly call L2, L4a, and L4c, respectively).

A More Scientific Approach

Those of you who have followed my critique of Risk-MaPP know that one of my objections to it involves various statements made by the Rick-MaPP authors that the traditional way of setting limits (such as 0.001 of a dose) is non-scientific and arbitrary. Fortunately, the EMA does *not* follow that approach, but rather calls its approach "more scientific". I don't object to that terminology (because at least concedes that there is some science before the traditional approach). However, I think a more helpful statement would be that the health-based limit is *more precise* than a 0.001 of a dose criterion. That is, the 0.001 dose criterion is a "one size fits all" approach for actives that are *not* highly hazardous. Using a "health-based" approach may allow manufacturers to set higher limits for certain actives that are not highly hazardous, as well as to manufacture highly hazardous drugs in shared facilities/equipment.

Definition of critical effect

While the EMA does list what is included in "critical effects", it does not really provide a clear definition. This probably is how it has to be; it is not unlike my definition for a "highly hazardous active", where I try to define it by giving examples. The EMA states that critical effects include "the most sensitive indicator of an adverse effect seen in non-clinical toxicity studies" and "any clinical therapeutic and adverse effect". This is good, because it clearly establishes that the *therapeutic effect* of an active *may be* the critical effect (which is probably the case for most drug actives that are not highly hazardous).

This is the last in this series. While these three Cleaning Memos may help you understand some of the issues, it is highly recommended that the EMA document be carefully reviewed in order to implement these approaches.