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Setting Limits for Cleaning Agents

In the last two months, I published Cleaning Memos critiquing the EMA approach to setting limits (November 2013) and then suggested a way forward for health-based limits (December 2013). I thought I was done with these issues for a few months; however, Andrew Walsh et al published an article in the November/December issue of Pharmaceutical Engineering critiquing the way limits are set for cleaning agents (based on a fraction of the LD50 value). The article is "Cleaning Validation for the 21st Century: Acceptance Limits for Cleaning Agents", Volume 33, no. 6, pp. 12-24. In addition to Andrew Walsh (who was prominent in ISPE's Risk-MaPP), the other authors are Edward Sargent (currently a consultant, but a toxicologist retired from Merck), Thomas Altmann (Application Specialist at Ecolab Pharmacos in Germany), and Mohammad Ovis (Pharmaceutical Scientist at Xepa-Soul Pattinson (M) Sdn. Bhd).

The basic argument made in this article is that limits for cleaning agents based on a fraction of the LD50 is overly conservative, and that limits for cleaning agents should be based on an ADE calculation (much like limits for actives in the Risk-MaPP document). I will focus on two issues. The first is setting limits for cleaning agents based on ADE values. The second is the authors' critique of the factors I have recommended for setting limits based on an LD50 value for cleaning agents. Obviously, some of the same criticisms I have made of Risk-MaPP also apply here, although I should give credit to the authors in that they have NOT stated that setting limits for cleaning agents based on LD50 values is "non-scientific" and "arbitrary".

So let's cover the main issue, that of setting limits for cleaning agents based on ADE values. Remember that an ADE value is an amount that can be taken daily for a lifetime and not be an unacceptable risk. The authors give examples of ADE values for some common generic cleaning agent chemicals (isopropyl alcohol, sodium lauryl sulfate, sodium dodecyl benzene sulfonate, and sodium hydroxide). I will just focus on one compound, sodium hydroxide, since it is widely used and the consequences are most extreme. The ADE value presented by the authors for NaOH is 20 mg/day. The details for the derivation of the value are not given, but it is stated that that the ADE was "calculated by a qualified toxicologist". The article then points out that this safe level of 20 mg/day is much higher than my suggested value of 0.0041 mg/day (based on applying a factor of 10-6 to the LD50). I should note that the ADE of 20 mg is also much higher than a factor of 0.041, which would be the result if a factor of 10-5 was applied to the LD50. (The conversion factors I recommend for LD50 values are 10-5 to 10-6.)

What is clear is that the Risk-MaPP ADE is considerably higher, by factors of about 500 to about 5000. There are two questions to ask about that ADE value. First, is that value a safe value to take on a daily basis for a lifetime, and secondly, is that value a safe level to be present in a pharmaceutical product that is taken for a lifetime? I have deliberately presented these as two questions. As to the first, I am not a toxicologist, so I would defer to qualified toxicologists (but I still would like to see the basis on which a value of 20 mg was selected for NaOH). The second is the more important question, and is the one the authors in this article (as well as the Risk-MaPP authors) fail to consider. Let's examine what it might mean for 20 mg of NaOH to be present in a daily dose of a pharmaceutical product.

Suppose we are dealing with tablets, and the gross tablet weight is 500 mg, and four tablets are taken every day. This means that I could have as much as 5 mg in each tablet, with a resulting concentration of NaOH in the drug product of 1% (or 10000 ppm). Leaving the toxicity concern behind, what effect would that concentration have on such issues as drug stability, drug bioavailability, tablet breaking strength, and

dissolution rate? I don't know, but I would never want to be in a position where I had to find out. It is just not CGMP to allow a concentration of 1% of NaOH to be present in a pharmaceutical tablet. Of course the acceptable concentration based on an ADE value would be much higher if I considered smaller tablets and tablets given less frequently than four a day.

Let's now consider an injectable product. Suppose I am dealing with a sterile injectable that is dosed twice a day at a dose of 10 mL (let's assume that is equivalent to 10 g). At 20 mg of NaOH per day, each dose could have as much as 10 mg of NaOH, or a concentration of 0.1% of NaOH (1000 ppm). Does anyone really think that would be acceptable in an injectable?

The authors point out other "facts" about NaOH. They point out that in one injectable drug product, the FDA allows as much as 19.27% NaOH. I think this argument is highly misleading; I am not sure what the product is, but I suspect that that the NaOH is added to an acidic material and the resulting product comes out fairly neutral. There is a significant difference between 19.27% NaOH being used to formulate a product, and 19.27% NaOH being present in a product. The authors also point out that NaOH is GRAS and is allowed by the FDA as a food additive. Again, this is misleading; GRAS status applies only to specified food products. "GRAS" does not mean it is a safe for any application. These "facts" are not very relevant to the argument as to whether 20 mg/day is a safe level for NaOH in drug products.

Essentially, my counterargument is that regardless of whether the 20 mg value is a responsibly calculated ADE value for NaOH, that value in no way should be allowed in most drug products. Now the authors might argue (but they didn't in this article) that while 20 mg/day is a safe value for sodium hydroxide, the intent for pharmaceutical manufacturers, as stated in Risk-MaPP, is that after cleaning residues "are as low as possible below the health-based criteria"; in other words, Walsh et al could counter that while the 20 mg value is a safe value, we really want residuals of sodium hydroxide to be as low as possible below that 20 mg value. I doubt if this argument would be used, because the emphasis of Risk-MaPP authors following publication of Risk-MaPP has been to ignore that statement in Risk-MaPP and emphasize higher limits to save money in cleaning processes. However, who knows how anyone will respond to my critique?

Before I go to my defense of how I recommend setting limits for cleaning agents, I would like to point out that my argument that it is not just toxicity that is of concern when setting limits is not a new argument. One of the publications referred to by Walsh et al is "Setting Health-Based Limits for Contamination in Pharmaceuticals and Medical Devices", by David L. Conine et al, published in Quality Assurance: Good Practice, Regulation, and the Law, Vol. 1, No. 3 June 1992, pp. 171-180. This article includes setting ADI values based on values such as subchronic and acute toxicity data. In a section on "Application to Pharmaceuticals", is the statement:

> "In practice, the actual allowable residue concentration in a pharmaceutical should be based upon both health and product quality concerns. Thus, the residue limit(s) derived from this procedure may not always be the binding constraint on an allowable residue concentration for a residue in a pharmaceutical. For example, if a residue limit were 1 mg per day and the maximum daily dose of the pharmaceutical were 10 mg per day, the residue could potentially make up a significant fraction of a daily dose without harming the patient. Obviously, a residue present at such concentrations would not be acceptable. In these cases, the allowable residue concentration should be controlled by product specifications, good manufacturing practices, or other quality-based requirements, and not by the health-based residue limit, so long as the health-based residual limit is always met."

Now it is most interesting that one of the authors of this 1992 article is Bruce Naumann, one of the lead

authors of Risk-MaPP (although the Conine et al article was written when Dr. Naumann was at Abbott; he is now at Merck). My question is "What has changed about setting limits from 1992 to the present?"

Now I'll get to the second issue, which is how I have recommended setting limits for cleaning agents. My general approach has been to apply a factor of 10-5 to 10-6 to an LD50, and then include the body weight adjustment. Walsh et al criticize me for not using the exact same values specifically from the three articles I usually cite (Conine et al, Kramer e al, and Layton et al). Let me first say that the reason I give a range is that each of the three articles gives a different value for an ADI value based on a short term (acute) toxicity study. For example, Layton et al suggest using factors of 5 X 10-6 to 1 X 10-5 to convert an LD50 to an ADI. This range of conversion factors is correctly cited by Walsh et al.

For the Conine et al paper, the values cited for "Lifetime Exposure Residue Limits" is given in Table 4 (in the Conine paper). The conversion factor for adjusting LD50 animal data is ≥ 1000. A general footnote applicable to "safety factor" is:

> "In each case, an additional modifying factor between 1 and 10 may be applied. In addition, since acute data represent the least acceptable data for calculation of acceptable daily intake values for lifetime exposure, the range of modifying factors based solely on such data may be expanded."

So, it is possible to use an additional factor of between 1 and 10, and the range can be further expanded. Now one reason I believe use of a factor greater than 1000 should be considered for lifetime exposure, is that the same value of ≥ 1000 is given by Conine et al for both lifetime exposure (Table 4) and prolonged use (Table 3). Simple logic suggests that if a value of 1000 were acceptable, for prolonged use, a more stringent value should be considered for lifetime use. Based on these considerations, it is not unreasonable to specify a factor of 10-5 to convert an LD50 to an ADI lifetime value.

Which brings us to the Kramer et al paper. The value cited specified by Kramer to convert an LD50 to an ADI is 1,700,000 (or written differently if you want to multiply the LD50 value by a number, a factor of about 5.8 X 10-7), a factor more stringent than what I usually recommend.

In other words, when correctly evaluating the data in these three publications, they are certainly in line with my values of a conversion factor of 10-5 to 10-6. It should not be surprising that the three authors come up with different conversion factors, since the databases evaluated were different, since the publication dates varied from 1987 to 1996, and since this approach is an attempt to arrive at a "one size fits all" (with the exception of carcinogens) conversion factor.

The other surprising thing about the Walsh et al criticism of the factors I advocate is that even if the conversion factors cited by Walsh et al were accurate, they still result in ADI values that are much more conservative than the proposed ADE values.

A final note related to why I selected the recommended limits I use for cleaning agents. If a safety factor of 1000 is appropriate for converting a pharmaceutical dose to a safe level, then a much more stringent factor should be considered to convert an LD50 to a safe level. Of course, that argument doesn't mean much to Risk-MaPP advocates, since they insist that application of the factor of 1000 to a pharmaceutical dose is "non-scientific" and "arbitrary".

I would hope there will be reasoned public discussion within the scientific community on appropriate ways to set limits for cleaning validation residues. So I ask, where is the FDA on this issue? Where is the PDA? I don't think I have to ask where the ISPE is.