Cleaning Memo for July 2015
Significance of GRAS

GRAS stands for "Generally Recognized As Safe". In a recent internet forum, there were questions and statements about applying the concept of GRAS to cleaning agent residues for cleaning validation. The general tenor of questions and comments were whether GRAS status of a cleaning agent or cleaning agent component affected how limits were set. There were also statements like "For GRAS materials there is no need to calculate anything. They are already at safe levels in everyday use." Before doing anything relating to GRAS, it helps to have an understanding of what GRAS means and how it is used.

The main use of GRAS is by the FDA for certain food ingredients. Other industries may also use the term GRAS, and may have certain definitions for use of that term. However, I believe the main use is related to food ingredient use. If you want to get reliable information on what GRAS means, the best source is the FDA website. There is a document (from December 2004) on the FDA website entitled "Guidance for Industry: Frequently Asked Questions About GRAS". It explains how the term is used by the FDA, and explains how GRAS status is established.

Below are key points from this FDA document.

1. GRAS status is established by public information widely accepted by qualified experts as to the safety in an intended application. The wording in the FDA FAQ is "For a GRAS substance, generally available data and information about the use of the substance are known and accepted widely by qualified experts, and there is a basis to conclude that there is consensus among qualified experts that those data and information establish that the substance is safe under the conditions of its intended use."
2. GRAS status is for a specific use, including type of food product and amount or concentration of the ingredient. The wording in the FDA FAQ is "A determination of the safety of the use of an ingredient includes information about the characteristics of the substance, the estimated dietary intake under the intended conditions of use, and the population that will consume the substance….. Dietary intake of a substance depends on the food categories in which it will be used and the level of use in each of those food categories."
3. Prior to1997 the FDA would "affirm" substances as GRAS, and would publish a GRAS lists (in 21CFR Parts 182, 184 and 186). Since then, the FDA operates by a voluntary notification procedure, where information is provided to the FDA notifying the FDA of the GRAS status for the intended application. The list of accepted voluntary notifications is on the FDA website under "GRAS Notification Inventory". However, the FDA repeats its criterion statement about what make a food ingredient GRAS, in that "The use of a substance is GRAS because of widespread knowledge among the community of qualified experts, not because of a listing or other administrative activity."

What does this mean for cleaning agent components? It probably means that GRAS status for foods is suggestive of a relative level of safety. However, that level of safety has certain significant constraints. For example, sodium hydroxide is on the GRAS list. Does that mean it is a safe as residue at all levels for all routes of administration? Clearly the answer is "No". I would be much more concerned about its use in the manufacture of parenterals and opthalmics than in oral dosages. Even for oral dosage forms, I have some concerns. Realize that the use of sodium hydroxide for certain food application may involve situations where there are already acids in the food, and I am using the sodium hydroxide for pH adjustment. Or perhaps the sodium hydroxide is used in combination with an acid and the resulting food product is near neutral pH. Some might object and state (correctly) that any sodium hydroxide in an oral product would be neutralized by stomach acids. While that is true, there may be concerns about the effect of sodium hydroxide in a tablet on other quality issues, such as stability or dissolution times.

This reflects a fundamental flaw in those who advocate only health-based limits for cleaning validation. While patient safety is a major concern, effects of residues on *other quality attributes* should also be evaluated in setting limits. For example, a paper published several years ago about ADE vs. LD_{50} values for cleaning agents gives an ADE value of 20 mg (that's milligrams, not micrograms) per day (Andrew Walsh et al, "Cleaning Validation for the 21st Century: Acceptance Limits for Cleaning Agents", *Pharmaceutical Engineering*, Vol. 33, no. 6, Nov/Dec 2013).

If an ADE as defined in Risk-MaPP is a "dose that is unlikely to cause an adverse effect if an individual is exposed, by any route, at or below this dose every day for a lifetime", I find it hard to believe that 20 mg of sodium hydroxide in *any* drug product would be a safe daily exposure amount. Just look at the math. Suppose I had an injectable product that was dosed at 5 mL (about 5 grams) per day. If that product contained 20 mg of sodium hydroxide, the concentration of one injection would be 0.4% sodium hydroxide. I am not a toxicologist, but it seems reasonable to believe that that would be unacceptable even for a single dose, much less for a lifetime.

You might object and state that while that might be true for an injectable, that we should really consider oral doses. Okay, let's take an example of a 0.5 gram tablet given once a day. At an ADE value of 20 mg, that would mean each tablet could have as much as 4% sodium hydroxide. In addition to detrimental effects on the patient, I would also have major concerns about effects on stability and dissolution.

I suspect that the reply to my concerns might be something like "Okay, 20 mg is an ADE for sodium hydroxide, but *all* drug manufacturers would certainly clean to a value *much below* that limit, so it is not really an issue." My reply would be something like this: "If 20 mg is the ADE value and my cleaning limit were set based on that ADE, then if a product contained an amount to give 20 mg daily, that product would be GMP material and could be released." However, it is clear that no company would release such products (at least those products I have illustrated above) with that level of sodium hydroxide.

I continue to be amazed as to why regulators, pharmaceutical scientific associations, and pharmaceutical manufacturers ignore these issues.

The two purposes of this Cleaning Memo are to present objective information about GRAS status and to again question the consistency of how ADE values are determined. For the later concern, it would be valuable for toxicologists in the industry to jointly publish ADE/PDE values for the most widely used generic APIs and cleaning agents, along with details of the supporting rationales.