Cleaning Memo for May 2019
Use of the Term "Product"

I have become more concerned in the last few years about the correct and consistent use of words, in particular in cleaning validation documents. The December 2018 Cleaning Memo dealt with "blanks/controls" and the October 2017 Cleaning Memo dealt with definitions of "dedicated". This month's Cleaning Memo will consider an additional example, that of the word "product". What does this refer to? Is this a "generic" use of the word "product", in that it could refer to almost anything? For example, I might refer to it meaning that the "product" could be the active, the "drug product" itself, a starting material, and excipient? If used in this generic sense, what constitutes a "product" may be left up to the interpretation of the reader/auditor. If what I really mean is the "drug product", then that term should be used. If I really mean product in a generic sense, then there may be other words to use so that I avoid any interpretation that I am referring to the "drug product". Examples of other words include "residue" and "materials".

An example of this confusing use of the word "product" is as old as limit setting in cleaning validation. In the classic "Fourmen and Mullen" 1993 paper on limits is a reference to a default limit as "No more than I0 ppm of any product will appear in another product." I have seen this interpreted as "10 ppm of one drug product in another drug product". Clearly this was not the intent of the authors. What was intended was ""No more than I0 ppm of any *active ingredient* will appear in another *drug product*"? At least the latter is how this has been historically applied.

One way to prevent confusion is to have glossary of typical terms that are used. For example, in a "drug product" manufacturing I might have both drug product and product defined. A definition of "drug product" might be the one typically used:

I. Drug Product: A finished dosage form that contains an active pharmaceutical ingredient, generally, but not necessarily, in association with inactive ingredients.

Then a definition of "product" might be something like:

II. Product: As referred to in this document, "product" is a generic term referring to any drug product, drug product intermediate or active ingredient.

On the other hand, in a "drug substance" (Active Pharmaceutical Ingredient or API) manufacturing facility, I might have definitions for "drug substance", but the following might be one definition for "Product":

III. Product: As referred to in this document, "product" is a generic term referring to any drug substance, crude drug substance, reactant, intermediate, or by-product.

Having such a definition in cleaning validation documents for drug substance manufacturing facility is important so that auditors don't assume that the cleaning validation approach for a drug product applies to the facility.

Realize that there may be situations where even the generic use of the term "product" might not be appropriate. For example, in determining whether a surface is visually clean, just saying the surface is free of "any product" might not be good enough, unless the concept of product were expanded to include cleaning agents. There are two possible approaches to address this. Here is one option for drug product manufacturing where the term "product" is not used at all:

IV. Visually clean: Free from visible residues including drug products, active ingredients, drug product intermediates, excipients, cleaning agents, foreign materials and by-products of the cleaning process under defined viewing conditions.

If I had my previous definition of "product" (II), then this could be shortened to:

V. Visually clean: Free from visible residues including products, excipients, cleaning agents, foreign materials and by-products of the cleaning process under defined viewing conditions.

[In IV and V, I do realize I used the term "by-product", which means I probably have to define it also.]

Here is an option for drug substance manufacture:

VI. Visually clean: Free from visible residues including drug substances, reactants, intermediates, by-products, cleaning agents, and foreign materials under defined viewing conditions.

Note that in this case, by-products could include by-products of a manufacturing step as well as by-products of a cleaning step.

As long as we are considering these definitions, it might also help to mention the difference between an "active ingredient" and an "active pharmaceutical ingredient" (or an "API"). As is typically used in the industry, an "active ingredient" is an API *in a drug product* (in the formulated drug product), while an "active pharmaceutical ingredient" is the drug *substance apart from (or before it is formulated into) a drug product*. To the lay person, this sounds like both terms are the same. Even to those in the drug industry, these terms may be used loosely as we talk to each other. However, as given in our formal cleaning validation documents (such as cleaning validation master plans, SOPs, protocols, and risk assessments) it is definitely better to use the terms correctly as defined in applicable glossaries.

Here is one more related clarification. Sometimes we use the word “drug” quite apart from specifying whether it is a “drug product” or a “drug substance”. Here is the FDA definition of “drug”:

VII. “The Federal Food Drug and Cosmetic Act (FD&C Act) and FDA regulations define the term drug, in part, by reference to its intended use, as “articles intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease” and “articles (other than food) intended to affect the structure or any function of the body of man or other animals.” Therefore, almost any ingested or topical or injectable product that, through its label or labeling (including internet websites, promotional pamphlets, and other marketing material), is claimed to be beneficial for such uses will be regulated by FDA as a drug. The definition also includes components of drugs, such as active pharmaceutical ingredients.”

After all this, here is a final concern on glossaries. Some companies like to have glossaries in each document, and some companies like to have one corporate glossary that all groups within the company refer to. The advantage of first option is that terms are readily accessible as the document is read. A possible downside is that the same term may be defined differently by different group within a company. The advantage of the latter approach is that consistency is assured across the firm. A possible downside is that a term one group might want to use might already be defined in an inconsistent manner in the corporate glossary.

After all this, I must confess that my writings have not always followed what I am saying here is good practice. So you are right to say, “Physician, heal thyself”.