CEFIC/APIC Position paper

CEFIC/APIC Position on statements requested by API customers, which are not required by regulatory guidelines or legislation.

The API Industry is experiencing a significant increase in requests for various statements relating to content, or absence of various substances in Active Pharmaceutical Ingredient's (API's) supplied for use in pharmaceutical dosage forms. APIC is concerned, because when answers to these questions are not actually required according to the pharmaceutical legislation or guidelines, there is a potential risk of API manufacturers wasting a lot of resources, time and money to accommodate all these requests, without any benefit to patient safety, and not adding anything to the quality or safety of the drug substances.

APIC would like the API industry to be conscious of why they issue these statements and if they are actually regulatory requirements or not. These types of requests typically arise from misinterpretation of the pharmaceutical legislation/guidelines, from confusion with the food or cosmetic legislation, or a desire to accommodate people who do not eat specific types of food or who suffer from allergies.

APIC suspect that many companies answer these requests to the best of their ability in order to provide "good customer service", but we see a risk in ending up with a self-imposed requirement of replying to "pseudo" regulatory requirements becoming an "industry standard".

Some examples collected from APIC members are listed below;

Frequently asked questions relate to use of GMO materials. These questions typically arise from an incorrect interpretation of NTA Part 1A item 2.6.4., which require the Applicant to state if the medicinal product contains or consists of a GMO. Contains or consists should not be interpreted to apply to raw materials used in the manufacture of the API and not present in the final medicinal product.

Statements are also requested on various components associated with allergy or toxicity e.g. lactose, gluten, latex, silicone, nuts, sesame seeds, fish, shellfish etc. These types of questions may originate from food or cosmetics regulations and/or directives or a general concern for patients with allergy problems. There are however, no requirements to limit these in pharmaceuticals. An exception is of course penicillin's as well as cephalosporins, which are known problem areas, which are normally controlled by GMP.

Content of dioxin is also a frequently asked question. Dioxin is a specific issue related to fat fish and mussel food products and specific contamination incidents. In the case of "risk raw materials", the question may be relevant, but generally not covered in the pharmaceutical legislation.

Other examples are pesticides, plant hormones or growth promoters, coal tar dye, benzoates, artificial sweeteners etc. the list of theoretical contaminants is endless, but again none of these are limited or considered specifically in the pharmaceutical legislation.

The regulatory requirements such as e.g. TSE/BSE information must of course be met and statements should be issued if information is not already covered in the DMF or other regulatory documents.

The non-regulatory requirements are left for the discretion of the company. APIC would like to encourage careful consideration before statements are issued, but if the API manufacturer decides to address the issues, new points to consider emerge;

How far back in the process is it necessary to go in order to provide an acceptable answer? Many raw materials are relatively complex, e.g. of vegetable origin, or from mines etc., with all the possible contamination issues involved. In order to provide a complete answer the API manufacturer should go back to the manufacturer of the raw materials,

which raises the issue of whether the raw material suppliers can be trusted - if they answer at all? Many of these suppliers sell only a fraction of their goods to the pharmaceutical industry and are typically not familiar with the requirements. When the raw material supplier is involved, a part of the responsibility regarding “how far to go further back” is also placed on the supplier. There may be several steps before the API raw material is created. They may not bother to answer and if they do, is the API manufacturer obliged to inspect/audit, check the information?

The critical issue here is that there is no general guidance (except for TSE/BSE) and the key problem is that before you know it the API manufacturer has spent resources completely out of proportion.

An obvious approach would be to limit the reply to the raw materials used for the API manufacturing process, but even if the material in question is not used directly as a raw material, is it reasonable to issue a statement of absence from the product without testing? Is it possible to test for e.g. plant hormones or egg derivatives? How often or how many batches should be tested? It quickly becomes very expensive, probably without adding anything to the quality of the product or safety of the patient.

APIC Recommendations

In general APIC will recommend the API supplier to ask the customer for the justification, explanation or indication of origin of inquiry. In most cases you will find that the inquiry originates from a misinterpretation of guidelines or is a “service” issue.

APIC do not think that the API industry should use resources to reply to non-regulatory requirements - it is not just up to the individual company, because this level of “service” may become an industry standard. To limit the workload, without jeopardising compliance, APIC proposes in general to only issue statements where this is really justified in applicable pharmaceutical guidelines/legislation.

We recognise the need for “customer service”, but we encourage API manufacturers to be conscious of the difference between regulatory and non-regulatory requirements. For other non-regulatory requirements, please consider carefully if statements are necessary. You may impose a lot of work and costs on other API manufacturers, without adding anything to patient safety or quality of the API.