Recent confusion and ongoing actions related to the FDA's Inactive Ingredient Database (IID) - What should be included in the ANDA?

David R. Schoneker *

Global Regulatory Affairs, Colorcon, Harleysville, PA

Received: August 31, 2015; *Accepted:* September 7, 2015

Opinion and Commentary Paper

KEY WORDS: FDA, IID, Inactive Ingredient Database, excipients, maximum daily intake, MDI, IPEC-Americas

For many years there has been confusion about what the levels in the Food and Drug Administration's (FDA) Inactive Ingredient Database (IID) actually mean. The excipient levels listed in this database under "Maximum Potency" are the levels that has been approved by the FDA in, at least one product, for a specific route of administration and dosage form. However, the levels listed in the IID are simply the maximum levels that was approved on a per dose basis! This establishes a precedence of use (per dose) for a particular route of administration that can be referenced when assessing excipient safety in drug applications. What matters for an excipient, when referencing a maximum potency in an Abbreviated New Drug Application (ANDA), is the highest level listed in the IID for a particular route of administration, not necessarily a particular dosage form. For example the highest level for any oral dosage form can be used to justify a level for any other oral dosage form. However, these levels are not necessarily the maximum daily intake levels that were approved which is an important distinction.

This causes confusion, particularly for generic companies because they must reference both the maximum potency in the IID and a maximum daily intake (MDI) level in their ANDAs to show that they do not exceed what has been used on a per day level of a specific excipient in a previously approved product. There is no database available at this time, accessible to either the public or the FDA, which includes information on the maximum daily intake level. All that is available is the IID, which only gives the approved, per dose levels, for different routes of administration. However, what it does not provide for a given excipient is, whether the approved drug which resulted in the maximum "per dose" level was dosed multiple times or only once per day. This causes the confusion prevalent today, especially in the generic industry.

* Corresponding author: David R. Schoneker, 275 Ruth Road Harleysville, Pennsylvania 19438, United States, Tel: 215- 661 2513, E-mail: dshoneker@colorcon.com

This situation creates a major data gap for the FDA as well. Currently there is no easy way to find out whether a maximum daily intake level is higher than what is listed in the IID for one dose. As a result many formulation scientists use the IID level as if it was the maximum daily intake level because they know that this is "safe" from a regulatory perspective. Unfortunately, in many cases, this approach can result in a poor formulation, that is only "good enough" to be approved but not necessarily be the best formulation that could be developed from a quality, performance and/or manufacturability perspective had greater levels of some excipients been used.

Instead of using QbD to develop drugs in these cases, consider this a Quality by IID Limitation (QbIL), which is counterproductive if the aim is to improve product quality, performance and consistency and move towards more advanced manufacturing methods and better products designed for specific target populations, such as, pediatrics. Unfortunately, this is what a number of generic companies actually do when they develop their formulations. They are reluctant to explore what they could possibly use in their formulations, without regulatory issues, because it takes significant time to assess and get the correct MDI information for a given excipient for a specific route of administration.

Currently, the only way a company can find out if an excipient level, higher than the IID level, would be acceptable when filing an ANDA, is for them to submit a controlled correspondence with the FDA with a request for the FDA to research the maximum daily intake levels for a particular, previously approved excipient, to find if the desired level they want to use is below an approved MDI level. It typically takes the FDA several months to respond since they can only determine the levels through manual research within their existing systems involving significant time and effort. In many cases, this type of delay can impact a generic company's filing and approval date which can have huge implications, especially in first to file situations.

The only other alternative for a generic company is to submit detailed toxicology data on the specific excipient to justify its level of use. However, this may also result in significant delays during the review process. It can also increase the risk of receiving a Refuse to Receive (RTR) notice at the time of filing should there be any disagreement on the type of data that should have been supplied.

IPEC-Americas has been working with the FDA since December 2011 to improve the IID and the policies that the FDA utilizes to determine IID Maximum Potency levels in ANDAs. The Generic Pharmaceutical Association (GPhA) is now also involved with this team. Currently, how the FDA handles the policies concerning the IID internally is, unclear at best, resulting in a number of RTR notifications that may be unnecessary. Progress has been made but it has been slow going so far due to the implementation of the Generic Drug User Fee Amendments of 2012 (GDUFA) and reorganization at the FDA Office of Pharmaceutical Quality over the last few years. That said, progress has been made behind the scenes and it is hoped that improvements will begin to show up in the near future.

The FDA is developing a new database for inactive ingredients which will include information on the MDI levels. The biggest part of this will be researching, currently done manually and, verifying the MDI levels for each route of administration. There has also been discussions about possible benefits of including, in the future, MDI levels for pediatric use. The FDA plans to use some of the resources they have acquired under GDUFA to carry out this research. IPEC-Americas will continue to actively work with the FDA on this project and is expected to present on this topic at a future joint AAPS and FDA webinar.

The following are some of the key issues identified by IPEC-Americas that still need to be addressed:

- The IID was not updated between September 2013 and May 2015. Many excipients and the levels used in drug products which were approved during this time were not entered into the IID. Additionally, there are a number of cases of inaccurate information and non-standardized names included in the current IID. Some levels are incorrect since they do not appear to be traceable to an actual approved drug which used the listed level. The FDA is committed to verifying all IID levels to establish accuracy and traceability.
- There are unclear requirements for how "families" of materials (e.g. Hypromelloses, Polyethylene Oxides, Silicones, Carbomers, etc.) should be handled and what data is needed to support safe use levels in ANDAs. Many discussions on this topic are ongoing since this issue has created many unjustified RTRs.
- The maximum potency levels that are listed in percentages cannot be converted to any type of weight per dose and are basically worthless for referencing in an ANDA. The FDA is aware of this and essentially cannot utilize this information when comparing any levels in other drugs. They intend to eliminate all these references in the future as they clean up the IID because these % levels have caused a lot of confusion and have resulted in a number of RTRs for ANDAs. In the future, the FDA hopes to convert some of the % information to milligrams if they can connect the IID listing to an actual application where they can find out the actual maximum per dose level in milligrams.
- It is still not possible to identify the maximum daily intake of ingredients required for ANDAs. This cannot be resolved until the FDA launches a new IID database.
- There is a lot of confusion regarding the Refuse to Receive (RTR) and Controlled Correspondence Guidances which actually conflict with what has already been agreed to between the FDA IID Expert Working Group (EWG) and the IPEC-Americas IID Team. These guidances need to be revised based on the ongoing discussions.

The IPEC-Americas IID Team (including a representative from GPhA) coordinated special meetings in December, 2014 and July, 2015 with personnel responsible for FDA policy and toxicology to try to accelerate progress on a number of these issues. IPEC-Americas presented strong scientific support for the family approach and requested that the FDA make a decision on this issue as soon as possible. Another meeting is planned with the FDA on September 18, 2015 where a number of topics, including the family approach, will be discussed.

Most recently, the FDA updated the Inactive Ingredient Database (IID) in May, 2015 and again on August 12, 2015. The August revision was the second update that FDA has done to try to "clean-up" the IID database and make sure that the information in the database can be traced to an actual approved drug application for a specific route of administration and dosage form.

Many changes have been made to the IID resulting in some of the names being changed to preferred nomenclature, as well as, changes to the maximum potency levels, increasing or decreasing from the previous listed levels based on the FDA's ongoing verification process. In some cases certain names or references have been removed completely from the IID or significantly renamed creating a number of questions throughout the industry.

The FDA is still working on this IID "clean-up" process and is expected to make additional changes to the IID in October, 2015. If you need to use the IID you should search the IID database, as soon as possible, to evaluate the listings for the materials that may have changed. The IPEC-Americas IID Team will be discussing the August 12th changes with FDA during a meeting scheduled for September 18, 2015. The minutes from this meeting, together with the minutes from all

previous meetings, will be posted on the FDA website (1).

IPEC-Americas will continue to work with the FDA to resolve this issue for the benefit of all stakeholders.

REFERENCES

(1) http://www.fda.gov/aboutfda/centersoffices/officeofmedicalproductsandtobacco/cder/ucm380688.htm