IPEC-Americas Publishes Position Paper on FDA Inactive Ingredient Database

IPEC-Americas Position Paper
United States Food and Drug Administration Inactive Ingredient Database

Current Issue / Event

Issues related to inaccurate and incomplete information on excipients referenced in the U.S. FDA Inactive Ingredient Database (IID) and FDA policies and guidance related to the review of inactive ingredients in ANDAs continue to create confusion for the pharmaceutical industry. As a result, pharmaceutical companies filing drug applications have encountered longer review cycles, unnecessary requests for additional safety studies/information and/or Refuse to Receive letters from the Agency.

Purpose of Position Paper

IPEC-Americas has developed this position paper to articulate its position regarding the current state of the Inactive Ingredients Database (IID) and specifically FDA's use of the data in the IID during the initial filing review to determine acceptance of ANDA applications.

Supporting background information

A sub-committee of IPEC-Americas members and GPhA[1] representatives, formed in 2011, has been working with FDA to communicate concerns related to the IID. The core mission of the sub-committee was/is to work towards improving and enhancing the information in the IID as well as reviewing how FDA assesses acceptance of a drug application during the filing review as it relates to inactive ingredient levels. Currently FDA reviewers rely on the data in the IID when reviewing acceptability of inactive ingredients in a proposed formulation in support of a drug application. Incomplete and inaccurate information as well as discrepancies in nomenclature related to inactive ingredients have impacted the ability of ANDA applicants to make timely and high quality submissions.

Although many applicants have turned to their inactive ingredient suppliers for assistance to

address issues identified in their deficiency letters from the FDA, the discrepancies in the IID and FDA policies documented in recent draft and final guidance documents limits the ability of inactive ingredient manufacturers to assist these customers. The types of deficiencies cited by reviewers include requests for complete pharmacology and toxicology data, Refusal to Receive if a different grade of an excipient is used as compared to those listed in the IID, justification for using ingredients that are GRAS, etc. Requirements cited by the Agency are placing inactive ingredient suppliers in a difficult position, since the data requested for these types of inactive ingredients do not exist. Further, the recent issuance of both the Refuse-To-Receive[2] (RTR) and Controlled Correspondence[3] guidances has created additional confusion in the industry. These two GDUFA guidances alone have had a negative impact on the timelines for ANDA submissions and approvals due to their restriction of access for excipient suppliers seeking clarity from the FDA. As a result, the generic pharmaceutical industry is not able to submit the "high quality applications" that FDA is seeking. It is apparent to industry that the FDA will not be able to reduce the number of review cycles, speaking directly to the quality of an application, without first addressing the fundamental issues and concerns with inactive ingredients and the IID.

Position on critical issues requiring immediate, short term actions

Industry needs a transparent process related to the IID to ensure that accurate and complete information is captured in the database for reference by both the FDA reviewers and industry. IPEC-Americas has identified the following critical issues that need to be immediately addressed:

- Quarterly updates to the IID listings (the last quarterly update to the IID was posted on October 2013, this update only captured data that was entered as of September 2013 therefore all data post September 2013 are omitted from the current IID posting);
- Timely communication to industry with regards to the FDA improvement strategies and status of the IID; and,
- Timeline and mechanism for updating inaccurate and incomplete data in the IID.

It is critical for both the industry and FDA to continue working together in order to provide clarification and revision to address the issues and concerns with the IID. It is further critical for both parties to work together to address the inconsistent and conflicting information found in FDA guidance's (RTR and Controlled Correspondence), which have created additional confusion throughout the industry as they relate to inactive ingredients. In addition, IPEC-Americas members have expressed concerns to FDA that these guidance's do not appear to take into account historically accepted scientific practices, for either the industry or FDA reviews, of inactive ingredient information. IPEC- Americas believes that these concerns are impacting the quality and timeliness of ANDA submissions and resulting in confusion pertaining to FDA's management and use of inactive ingredient data.

Recommendations / Suggested Next Steps

Institute policies based on sound science and risk for using IID excipient data in the evaluation of ANDA applications.

IPEC-Americas will continue its efforts to dialogue and collaborate with the FDA to ensure that historic dialogue and on-going inactive ingredients issues discussed with the FDA OGD IID EWG [4]

continues until a resolution is achieved. This will help the industry in making high quality submissions as well as help the FDA achieve its GDUFA goals and commitments.

- Based on the proposal made by IPEC-Americas in the IPEC-Americas – GPhA - OGD meeting minutes[5], IPEC-Americas has requested that FDA adopt and finalize the process for utilizing a family-based approach for assessing the safety of related grades of an excipient as is done by other global regulatory groups such as CFSAN[6], JECFA[7], EFSA [8] and REACH[9] initiatives. Establishing a maximum use level for a family of related grades is scientifically justified. The adoption of said practice will serve to minimize redundant FDA reviews of the same excipient toxicology data for every grade of an inactive ingredient. Further, this practice will improve the FDA's ability to more efficiently manage its workload to better maximize its resources to ensure goals, dates and commitments are achieved for both GDUFA and PDUFA user fee programs.
- As documented in FDA's own *Guidance for Industry - Nonclinical Studies for the Safety Evaluation of Pharmaceutical Excipients*, IPEC-Americas believes that the FDA should continue to allow for exceptions where prior human exposures under conditions and circumstances relevant to the proposed use would negate requirements for the full battery of toxicology studies. IPEC-Americas also believes that use of the following inactive ingredient categories should be considered as acceptable alternatives in most situations and not create a Refuse to Receive notification for an ANDA:
    - Inactive ingredients used in previously approved products
    - Those having GRAS status as a direct food additive when the ANDA is for an oral route of administration
    - Inactive ingredients with precedence of use in similar routes of administration (i.e.; oral and sublingual) where a bridging argument can easily be made
    - Similar level of exposure (potency), patient population, duration of exposure associated with prior use could qualify a new inactive ingredient

Conclusions

IPEC-Americas supports the FDA's GDUFA commitments as well as their efforts to help the industry submit high quality ANDA submissions. IPEC-Americas intends to continue to work collaboratively with the FDA and other stakeholders (such as GPhA) to address issues related to inactive ingredients, as highlighted above. IPEC-Americas believes that resolving IID related issues and conflicting information in guidances should facilitate high quality ANDA submissions while helping the FDA achieve its GDUFA goals and objectives and allow all stakeholders to focus on higher risk issues impacting patient safety. IPEC-Americas plans to continue to request a committed timeline from the FDA to address these issues.

IPEC-Americas understands the impact this issue is having on ANDA sponsors and believes that non- action by the FDA could lead to:

- Impeding GDUFA goal metrics for ANDA and Controlled Correspondence review
- Creating redundant, non-value added work for FDA and industry
- Impeding industry's ability to comply with new FDA quality standards
- Stifling innovation during the drug development phase
- Denying timely patient access to high quality affordable generic alternatives

[1] GPhA – Generic Pharmaceutical Association

[2] ANDA Submissions ? Final Guidance for Industry: Refuse-to-Receive Standards. U.S. Department of Health and Human Services, Food and Drug Administration Center for Drug Evaluation and Research (CDER). September 2014. Generic Drugs.

[3] Guidance for Industry: Controlled Correspondence Related to Generic Drug Development. Draft Guidance. U.S. Department of Health and Human Services, Food and Drug Administration Center for Drug Evaluation and Research (CDER). August 2014. Generics.

[4] Food and Drug Administration, Office of Generic Drugs, Inactive Ingredient Database, Expert Working Group

[5] http://www.fda.gov/aboutfda/centersoffices/officeofmedicalproductsandtobacco/cder/ucm380688.htm [1]

[6] CFSAN - Center for Food Safety and Applied Nutrition

[7] JECFA - Joint FAO/WHO Expert Committee on Food Additives

[8] EFSA - European Food Safety Authority

[9] REACh - Registration, Evaluation, Authorisation and Restriction of Chemicals

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Links
[1] http://www.fda.gov/aboutfda/centersoffices/officeofmedicalproductsandtobacco/cder/ucm380688.htm