Using the Inactive Ingredient Database

Guidance for Industry

DRAFT GUIDANCE

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U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)

July 2019
Pharmaceutical Quality/CMC

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Food and Drug Administration
Center for Drug Evaluation and Research (CDER)

July 2019
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Contains Nonbinding Recommendations

Draft — Not for Implementation

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Guidance for Industry[1]

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I. INTRODUCTION

This guidance describes the Food and Drug Administration's (FDA's) Inactive Ingredient Database (IID) and provides recommendations for how to use the IID in the development of drug products.[2] The guidance also describes how the IID can be used in evaluating excipient[3] safety, which can affect application filing and scientific review. In addition, this guidance discusses how the IID is structured; the data regarding excipients in the IID; and how nomenclature, maximum potency levels, and units of measure are presented in the IID. Lastly, the guidance is intended to give IID users a clearer understanding of the database's benefits and limitations.

In general, FDA's guidance documents do not establish legally enforceable responsibilities. Instead, guidances describe the Agency's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word *should* in Agency guidances means that something is suggested or recommended, but not required.

II. BACKGROUND

The IID provides information on excipients present in FDA-approved drug products.[4] Prior to the establishment of the IID, FDA made available information about excipients present in FDA-

[1] This guidance has been prepared by the Office of Pharmaceutical Quality in the Center for Drug Evaluation and Research at the Food and Drug Administration.

[2] The IID can be accessed at http://www.accessdata.fda.gov/scripts/cder/iig/index.cfm.

[3] In this draft guidance, we use the term "excipients" to mean any inactive ingredients that are added intentionally to therapeutic and diagnostic products, but that are not intended to exert therapeutic effects at the intended dosage, although they may act to improve product delivery (e.g., enhance absorption or control release of the drug substance). Historically, we used the term "inactive ingredient" in naming the database, however, we believe that the term "excipient" is more accurate because it recognizes that these ingredients may have some biological activity even though they are not intended to exert therapeutic effects. Therefore, the term "excipient" is used throughout this guidance in lieu of "inactive ingredient," although we are not changing the name of the database.

[4] The current IID includes excipients in drug products that are the subject of approved New Drug Applications (NDAs) and Abbreviated New Drug Applications (ANDAs). Excipients used in approved Biologics License Applications (BLAs) are not entered into the IID. If drug products are withdrawn from the market after approval or are reformulated for safety reasons, the excipients used in those products may be removed from the IID.

approved drug products by making available an inactive ingredient guide. The inactive ingredient guide was first made available in 1987 in a hardcopy paper format. FDA began making the information available in an online database in 2003. This information about excipients has been used by all segments of industry as an aid in developing new drug products. If an excipient is used in approved drug products for a particular route of administration, the excipient generally is not considered new and may warrant less extensive review the next time it is included in a new drug product. For example, if the IID includes a particular excipient at a specified potency for a certain route of administration, a sponsor could generally consider the excipient at that potency safe for use in a similar manner for a similar type of product.[5]

The Agency may consult the IID when performing regulatory filing reviews of applications and during the technical review of applications as part of an evaluation of whether the levels of excipients in drug product formulations are acceptable or require additional documentation to support the proposed level. The IID, however, does not currently provide information regarding the different exposure models (e.g., maximum daily intake based on the dosing recommendations indicated in the labeling, safety in pediatric populations, acute versus chronic use) that may be needed during such a technical review, nor does inclusion of an excipient at a level described in the IID necessarily satisfy the requirements in FDA regulations with respect to maximum allowable limits for specific categories of products.[6] However, the IID is one of the tools the Agency uses to confirm prior use of particular excipients.

The Agency has solicited stakeholder engagement and feedback to improve the IID. For example, FDA's Inactive Ingredients Database Working Group (IID Working Group), created in September 2011, has worked with industry stakeholders to identify the IID's limitations and improve the IID. FDA also published a *Federal Register* notice in 2015 to obtain input from stakeholders and invited questions and corrections directly from a wide range of individual IID users through an electronic mailbox (see section VI).[7] Upon consideration of that input, this guidance provides recommendations for how applicants can optimize use of the IID.

The Agency notes that changes will be made to the IID in the future in accordance with the GDUFA II commitments letter.[8] "By October 1, 2020, FDA will complete enhancements to the

[5] In this guidance, the term "sponsor" is used to denote the submitter of an Investigational New Drug Application (IND), NDA, or ANDA.

[6] For example, during technical review, the Maximum Daily Intake (MDI) of elemental iron and any color additive must be verified to not exceed the maximum amount specified in 21 CFR 73.1200(c) (i.e., 5 mg/day) for iron and in 21 CFR Parts 73 (subpart B), 74 (subpart B), or 82 (subparts B and C) for color additives. As prescribed by law, a color additive must be shown to be safe and be listed in the CFR before it may be used to color foods, drugs, cosmetics, or certain medical devices. Refer to the guidance for industry *Color Additive Petitions - FDA Recommendations for Submission of Chemical and Technological Data on Color Additives for Food, Drugs, Cosmetics, or Medical Devices* (July 2009) for additional recommendations. Applicants should reference relevant CFR sections in their submissions. We update guidances periodically. To make sure you have the most recent version of a guidance, check the FDA Drugs guidance web page at http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm.

[7] See *Federal Register* Volume 80, Number 161 [FR Doc No: 2015-20556] August 20, 2015, Technical Document for Using the Inactive Ingredient Database, Establishment of a Public Docket, Government Publishing Office.

[8] GDUFA Reauthorization Performance Goals and Program Enhancements Fiscal Years 2018-2022 (GDUFA II Commitment Letter) at 17.

Inactive Ingredient Database so users can perform electronic queries to obtain accurate Maximum Daily Intake and Maximum Daily Exposure[9] information for each route of administration for which data is available. FDA will update the Inactive Ingredient Database on an ongoing basis, and post quarterly notice of updates made. Such notices will include each change made and, for each change, the information replaced."

III. DEFINITION OF IID

A. IID Contents

The IID is a listing of excipients used in approved New Drug Application (NDA) and Abbreviated New Drug Application (ANDA) products, regardless of whether the products remain on the market, if no safety concerns have been identified. It includes the following specific information about each excipient:

1. Ingredient Name

The ingredient name is the preferred term for the excipient as it appears in the Global Substance Registration System (GSRS).[10]

2. Route of Administration

The route of administration refers to the route of administration of the approved drugs in which the excipient was or is currently used that are the basis for the listing.

3. Dosage Form

The dosage form of the excipient is the dosage form of the approved drugs in which the excipient was or is currently used that are the basis for the listing.

4. Chemical Abstracts Service (CAS) Registry Number[11]

The CAS Registry Number associated with the excipient is a recognized chemical identifier linked to chemical structure and other information associated with the excipient.

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[9] Maximum Daily Exposure (MDE) is the total amount of the excipient that would be taken or used in a day based on the maximum daily dose (MDD) of the drug product in which it is used. MDE is calculated as the dosage unit level of the excipient multiplied by the maximum number of dosage units recommended per day (excipient (mg) x number units). MDE may also be referred to as maximum daily intake (MDI) for oral drug products. Where an MDD is not provided in the product labeling, FDA will consider the applicant's rationale for an MDD when calculating excipient MDE.

[10] See https://fdasis.nlm.nih.gov/srs. The GSRS (also known as SRS) is used to generate permanent, unique, unambiguous identifiers for substances in regulated products, such as ingredients in drug products.

[11] See http://www.cas.org/content/chemical-substances/faqs.

5. Unique Ingredient Identifier (UNII)[12]

Assigned by GSRS, a UNII is a unique alphanumeric code that identifies a substance based on molecular structure and/or descriptive information. A UNII is displayed with excipients to facilitate Structured Product Labeling (SPL), which requires that a UNII be used for all ingredients, including excipients used in FDA-approved drugs.[13]

6. Maximum Potency

Maximum potency is the highest level of the excipient used in approved products. The IID lists the highest level per dosage unit of the excipient in each dosage form in which it is used. For topical products and other products where excipients are expressed as a percentage of the product formula, maximum potency is the highest formula percentage for products included in the IID.

B. IID System

1. IID Excipient Data

All product formulas are entered into the Agency's internal master database as part of the application record. The IID is a public database that is a subset of information derived from FDA's internal master database. When an excipient is included in the IID, the IID will list the largest value for each route of administration and dosage form available for listing from FDA's master database, but does not reveal the formulation of any particular product. The retrieved largest value appears as the maximum potency listed for the excipient for that route of administration and dosage form in the published IID on the FDA website.

2. IID Dynamics

With each subsequent IID update, the IID grows longer as new excipients, routes of administration, and dosage forms are added. This reflects the growing number of approved drug products. However, FDA may also remove entries from the IID if the Agency has reason to question the safety of excipients, including when drug products are reformulated or withdrawn from sale for safety reasons that implicate the excipients. Further, FDA updates the IID with corrected information if FDA identifies a discrepancy. If an applicant wishes to search previously published versions of the IID for an ingredient, archival files, organized by fiscal quarter from 2009 to present, can be downloaded through the IID web page.[14]

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[12] See https://www.fda.gov/ForIndustry/DataStandards/SubstanceRegistrationSystem-UniqueIngredientIdentifierUNII/ucm127839.htm.

[13] See http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm.

[14] Applicants generally should not reference archival records to justify a proposed level of excipient. An applicant should rely on current IID information as the most up-to-date information to support a proposed route of administration and level of use of an excipient, or should provide other adequate justification for Agency review and consideration.

IV. SPECIFIC TOPICS

A. Nomenclature and Identity

1. Excipient Preferred Terms

The identities of most excipients in the IID are drawn from GSRS. Although applicants may provide a trade name or common name of an excipient in the original application, the IID displays the preferred term for the excipient as it appears in GSRS to promote consistency in nomenclature in the IID. GSRS preferred terms generally identify single ingredient substances. When the United States Pharmacopeia/National Formulary (USP/NF) identifies an excipient as a single ingredient substance, the GSRS preferred term is the same as the USP/NF monograph title for that excipient. However, in cases where the USP/NF monograph title covers multiple substances, the GSRS preferred terms for each of those ingredient substances might differ from the monograph. In such cases, the preferred term in the IID and the USP/NF monograph title may differ.

Co-processed excipients and excipient mixtures that have USP/NF monographs generally retain their monograph names in GSRS and the IID and are updated in GSRS and the IID to be consistent with the USP/NF monograph if the monograph title is revised. One example is emulsifying wax, which is an excipient mixture with a USP/NF monograph. This excipient appears in the IID under the USP/NF name. If a co-processed excipient or excipient mixture does not have a USP/NF monograph or GSRS preferred term, it will generally be listed in the IID by the name provided in the source applications or some other unique identifier provided by applicants. One example is the excipient mixture glyceryl oleate/propylene glycol, which appears in the IID under the name the applicants provided.

2. Unique Ingredient Identifier (UNII)

Most entries in the IID now have a UNII, a unique alphanumeric code that identifies the substance. The UNII, which is generated by GSRS, has been designed to support health information technology initiatives by providing unique identifiers for substances in drugs, biologics, foods, and devices based on molecular structure and/or descriptive information. In the IID, the UNII is displayed with excipients to facilitate Structured Product Labeling (SPL), which includes UNIIs for all ingredients, including excipients.

Not all excipients have been assigned UNIIs. Certain ingredients and mixtures are considered formulations and are not currently assigned UNIIs.[15] When an excipient does not have a UNII, the IID UNII field displays NA (not applicable). For excipients that should be assigned but have not yet been assigned a UNII, a request for UNII assignment by industry may be made directly to GSRS.

[15] The IID, however, does not disclose the specific formulation (i.e., each ingredient and the quantity of each ingredient) for these excipients.

B. Excipient Level Listing (Maximum Potency)

When an excipient is included in the IID, the maximum potency shown is generally described as the maximum level of the excipient per dosage unit for each route of administration and dosage form in which the excipient has been used. Maximum potency does not represent the maximum daily exposure (MDE) of an excipient unless the MDE of products that were the basis for the listing is only a single unit. Maximum potency does not represent a maximum permissible daily intake or acceptable daily intake of the excipient; rather, maximum potency reflects the level per unit of the excipient that has been used previously in approved drug products.

1. Difference Between Maximum Potency and Maximum Daily Exposure (MDE)

Because there has been confusion over the years about the difference between maximum potency and MDE, an example is provided here to illustrate the difference. In a hypothetical case, where the maximum potency of an excipient is listed as 500 mg in the IID for the oral route of administration in oral capsules, if the maximum daily dose (MDD), the highest level of active ingredient dosed in a day (generally determined by following the instructions on the product labeling) is provided by two capsules per day, then the MDE would be 1,000 mg of the excipient. The MDE would not be reflected in the IID because the IID currently only shows the maximum potency (the maximum amount per dosage unit), which is 500 mg. Although the IID currently provides only the maximum potency per unit dose, it is important for applicants to consider the total daily exposure of excipients when developing new drug products.

2. Listing of Maximum Potency for Various Dosage Forms

The units of measure differ for different dosage forms. For example, the IID provides the maximum potency for solid oral dosage forms in weight, typically in milligrams (mg).

Excipients in liquid oral dosage forms are also provided as weight per dosage unit; however, the dosage unit of a liquid oral dosage form is a volume, typically in milliliters (mL). Therefore, excipients in this dosage form are listed as weight per volume (X mg/X mL), where the weight is the level of the excipient (X mg), and the volume (X mL) is the liquid volume of one dose. Until 2015, liquid oral dosage forms were listed in the IID as a percentage of total formula weight. The conversion to weight per dosage unit was done to standardize the units and facilitate better use of the IID.

Topical products are listed in percentage weight/weight (%w/w), weight/volume (%w/v), or volume/volume (%v/v). Since topical dosage forms often do not have an exact dosage unit, FDA has determined that percentage is the best representation of the maximum potency. The maximum potency of excipients in parenteral dosage forms is also shown as a percentage of the total formula weight, in which percentage is the percent weight per volume (%w/v). Excipient potencies of parenteral products that are marketed as powders or lyophilized powders for reconstitution are generally shown as the percentage of the excipient in the product after reconstitution. The IID Working Group is working to standardize potency units in the IID to provide consistent representation of maximum potency for excipients listed in the IID. IID users

are encouraged to contact the IID Update mailbox if the units for an entry differ from the descriptions provided above.

3. Omissions

A small number of entries in the IID lack a maximum potency value. In some cases, this is intentional; some values are difficult to verify because they are associated with very old products. In other cases, the use of the term "NA" in place of a maximum potency may be used when the quantity of the excipient is variable (e.g., pH adjusters that are indicated in the formula as "quantity sufficient"). There are also IID entries for excipients where the potency of the excipient is not relevant. For example, the excipients in certain drug-device combination products are included in the IID, but no potency is specified for device components. This is because the device components are not evaluated in the same manner as excipients in drugs. Since a 'potency' level generally is not appropriate for components of devices, the IID contains qualitative information for such components (e.g., components of membranes and films of transdermal systems and insoluble polymers in vaginal drug-delivery systems).[16] The Agency periodically reviews the IID and makes corrections if the omission of maximum potency was not intentional, but rather found to be an error.

V. INVESTIGATIONAL NEW DRUG APPLICATIONS (INDs), NDAs, AND ANDAs

The IID is often used by applicants to help justify the levels of excipients in Investigational New Drug Applications (INDs), NDAs, and ANDAs. An applicant may wish to use an excipient that is found in the IID, but at a higher level or in a different route of administration than listed in the IID. In such cases, the IID alone does not provide sufficient information to determine the safety of the proposed level of the excipient, and the applicant should provide evidence of safety for the excipient at the proposed level or for the proposed route of administration taking into consideration the context of use (e.g., patient population, dosage, and duration of exposure). For additional information on the type of data recommended for review, applicants should refer to the guidance for industry on *Nonclinical Studies for the Safety Evaluation of Pharmaceutical Excipients.*

In an application, when referencing the IID to justify the use of an excipient, additional information may be warranted. For example, when referencing the IID for an excipient with multiple grades, it is best to specify the proposed grade and reference the IID listing for that grade, or if that is not possible, explain the link between the grade in the referenced IID listing and the excipient grade being proposed. When referencing the IID for complex mixtures, including color additives, flavorings, and combinations of pre-existing excipients, a quantitative breakdown of the mixture is recommended so that individual excipients in the mixture may be easily referenced to IID listings.[17]

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[16] The safety of these components will be the subject of interdisciplinary review for INDs, NDAs, and ANDAs, and additional studies and safety justification may be requested.

[17] If Generally Recognized as Safe (GRAS) status or FDA food regulations are referenced in the application, supporting information should be provided that is relevant to the context of use of the drug product when the IID alone does not support the excipient and its level. When the submission is for an NDA, contact the specific drug

A. INVESTIGATIONAL NEW DRUGS (INDs)

During the IND stage, excipients are reviewed for safety as appropriate for the phase of study. The IID may be consulted for evidence of previous use. In addition, any nonclinical or clinical studies conducted with the excipients or proposed clinical formulations submitted in the IND application are evaluated. An overall assessment of the appropriateness of excipients in the formulation is conducted by the review team and can be based on several factors, including, for example, total daily exposure, dosage form, route of administration, and patient population.

FDA encourages innovations in drug development during the IND stage, including use of novel excipients to address drug development problems and produce new drug products. The Agency recommends that sponsors have early discussions regarding formulations proposed for use in clinical trials.[18]

B. NEW DRUG APPLICATIONS (NDAs)

As noted above, the IID is often used by applicants to help justify the levels of excipients in NDAs. An applicant may wish to use an excipient that is found in the IID, but at a higher level or in a different route of administration than listed in the IID. In such cases, the IID alone does not provide sufficient information to determine the safety of the proposed level of the excipient for the proposed route of administration, and the applicant should provide evidence of safety for the excipient in its NDA.[19]

C. ABBREVIATED NEW DRUG APPLICATIONS (ANDAs)

The Agency evaluates each submitted ANDA individually to determine whether the ANDA can be received. The receipt of an ANDA means that the Agency made a threshold determination that the ANDA is substantially complete; that is, that the ANDA on its face is sufficiently complete to permit a substantive review.[20] The excipients proposed in the ANDA are initially assessed during this filing review. For ANDA receipt, applicants can justify excipient levels by

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product's review division with questions. When the submission is for an ANDA, submit a controlled correspondence via email to GenericDrugs@fda.hhs.gov. For the definition of a controlled correspondence as well as the process to submit a controlled correspondence, see the draft guidance for industry *Controlled Correspondence Related to Generic Drug Development*. When final, this guidance will represent the FDA's current thinking on this topic.

[18] Sponsors are encouraged to follow FDA's guidance to industry *Nonclinical Studies for the Safety Evaluation of Pharmaceutical Excipients* (May 2005) in developing their safety rationale to support the use of novel excipients. To avoid subsequent delays in development programs, the use of any novel excipients should be noted in original INDs and subsequent amendments.

[19] Novel excipients should be addressed during the IND stage (see V.A Investigational New Drugs (INDs)). If the first appearance of a novel excipient is in an NDA, this is a cause for concern as it suggests that information has not been communicated to the Agency during clinical development and that subjects in a clinical trial may have been exposed to an unknown risk. As noted in section V.A. of this draft guidance (Investigational New Drugs (INDs)), early discussions during clinical development before use in clinical trials will facilitate a full safety evaluation of excipients before submission of an NDA.

[20] See 21 CFR 314.101(b)(1).

referencing the applicable current IID listing or submit a justification supporting the safety of the excipient at the proposed level.[21]

The multidisciplinary technical review of an ANDA includes evaluation of the acceptability of each excipient in the generic drug formulation. Although the IID currently provides only the maximum potency per dosage unit, during the technical assessment of an ANDA the MDE of excipients is considered for the proposed context of use. If evidence of safety for the appropriate route of administration cannot be determined by reference to the IID and any additional information submitted by the applicant, the Agency may request supporting safety information.[22]

VI. QUESTIONS AND COMMUNICATIONS WITH FDA

The Agency welcomes input from IID users. Different FDA mailboxes are available depending on the subject of the communication. The IID Update mailbox was established to allow users to inform FDA of errors in the IID and to ask questions about IID listings. Questions about the preferred terms in the IID should be addressed to the GSRS mailbox. Questions related to the use of excipients in generic products under development should be addressed to OGD as Controlled Correspondence. A brief description of each of these mailboxes follows.

A. IID Update Mailbox

The IID update mailbox can be contacted via email to IIDUpdate@FDA.HHS.GOV. This mailbox is used to receive questions about changes in the IID listings, reports of errors, requests for clarification of units or names, and other questions that are not application-specific. The inquiries are assigned to IID working group staff in the Office of Policy for Pharmaceutical Quality in the Office of Pharmaceutical Quality.

B. GSRS Mailbox

The GSRS mailbox can be contacted via email to FDA-GSRS@FDA.HHS.GOV. This mailbox is used primarily for UNII requests, but also to communicate questions about specific UNIIs and other general GSRS questions such as the preferred term for an excipient listed in the IID. These inquiries are assigned to GSRS staff in the Office of Health Informatics.

C. Controlled Correspondence

Controlled Correspondence should be submitted to OGD via email to GenericDrugs@FDA.HHS.GOV. Applicants preparing ANDAs may submit application-specific questions relating to drug development, including questions about the acceptability of excipient

[21] When referencing an IID listing that differs from the proposed excipient in nomenclature, molecular weight, viscosity, or grade, applicants should provide justification for citing the IID listing as the basis for the excipient and its proposed level of use.

[22] A proposed drug product that contains an excipient that would require clinical investigations to establish safety of the excipient for use in a particular drug product would not be permitted in an ANDA, but may be submitted in a 505(b)(2) application. See guidance for industry *Determining Whether to Submit an ANDA or a 505(b)(2) Application.*

levels, to the Agency as a Controlled Correspondence as recommended in the guidance for industry on *Controlled Correspondence Related to Generic Drug Development*. The Controlled Correspondence will be processed in accordance with current GDUFA timelines. If the response to a Controlled Correspondence is relevant to an original ANDA, applicants should include a copy of the response within the ANDA submission.