Guidance for Industry

Incorporation of Physical-Chemical Identifiers into Solid Oral Dosage Form Drug Products for Anticounterfeiting

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

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Contains Nonbinding Recommendations

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This guidance represents the Food and Drug Administration's (FDA's) current thinking on this topic. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. You can use an alternative approach if the approach satisfies the requirements of the applicable statutes and regulations. If you want to discuss an alternative approach, contact the FDA staff responsible for implementing this guidance. If you cannot identify the appropriate FDA staff, call the appropriate number listed on the title page of this guidance.

I. INTRODUCTION

This document is intended to provide guidance to pharmaceutical manufacturers who want to use physical-chemical identifiers (PCIDs) in solid oral dosage forms (SODFs). A PCID is a substance or combination of substances possessing a unique physical or chemical property that unequivocally identifies and authenticates a drug product or dosage form.

This guidance provides recommendations to pharmaceutical manufacturers on (1) design considerations for incorporating PCIDS into SODFs, (2) supporting documentation to be submitted in new drug applications (NDAs) and abbreviated new drug applications (ANDAs) to address the proposed incorporation of PCIDs in SODFs, (3) supporting documentation to be submitted in postapproval submissions to report or request approval to incorporate PCIDs into SODFs, and (4) procedures for reporting or requesting approval to incorporate PCIDs into SODFs as a postapproval change.

The incorporation of components or features used in radiofrequency identification for drug products is outside the scope of this guidance. In addition, this guidance does not apply to manufacturing or formulation changes, made in conjunction with the addition of a PCID, that go beyond simply inserting the PCID into a blending or mixing operation (e.g., adding a PCID to a non-functional tablet film coating is covered by this guidance, but adding a non-functional film coating that contains a PCID to a previously uncoated tablet involves manufacturing changes that are not covered by this guidance). The incorporation of a PCID into the packaging or labeling is not covered in this guidance.

Other guidance documents, which may be applicable to proposed changes outside the scope of this guidance, are located on FDA's guidance Web site[2] and should be consulted to help to

[1] This guidance has been prepared by the Office of New Drug Quality Assessment, Office of Pharmaceutical Science in the Center for Drug Evaluation and Research (CDER) at the Food and Drug Administration.

[2] CDER guidance documents can be found on the Internet at http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm. We update guidances periodically. To make sure you have the most recent version of a guidance, check the CDER guidance Web site.

determine whether additional reporting or approval procedures may apply to proposed changes outside the scope of this guidance.

FDA's guidance documents, including this guidance, do not establish legally enforceable responsibilities. Instead, guidance documents 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 an Agency guidance document means that something is suggested or recommended, but not required.

II. BACKGROUND

Pharmaceutical manufacturers aiming to thwart drug product counterfeiting have been investigating readily available technologies that may make drug products more difficult to duplicate. One approach that pharmaceutical manufacturers appear to be considering involves adding a trace amount of an inactive ingredient(s) to an existing *section*[3] of the dosage form. A unique physical-chemical characteristic of that ingredient makes it possible to detect and authenticate legitimate dosage forms, and to identify counterfeits.

Examples of substances that may be incorporated into SODFs as PCIDs include inks, pigments, flavors, and molecular taggants. Such PCIDs may allow product authentication by their presence alone or may be used to code the product identity into or onto the SODF.

There are various available means for presentation and detection of PCIDs (e.g., photolithography, holography, optical microscopy, laser scanning devices, excitation/fluorescence detection). Some identifying characteristics, such as pigments or flavors, could be easily observed by patients, healthcare practitioners, and pharmacies. Others could require the use of a detection instrument (e.g., a scanner, photometric detector, mass spectrometry).

FDA anticipates that many of the ingredients that will ultimately be employed as PCIDs are already used as food additives, colorants, or excipients with established safety profiles.

III. DESIGN CONSIDERATIONS FOR INCORPORATION OF PCIDs IN SOLID ORAL DOSAGE FORMS

A. Pharmacological and Toxicological Considerations

If an applicant incorporates a PCID into a solid oral dosage form, we recommend that the ingredients comprising the PCID be pharmacologically inactive so the ingredients can be treated as excipients.

To minimize toxicological risk, FDA recommends using permissible direct food additives,[4] food substances that are generally recognized as safe (GRAS) (including direct food substances

[3] *Section* is the term used for a discrete, contained solid or a layer in a solid oral dosage form. Any section can be described by its composition, the functional characteristics that distinguish it from other sections in that dosage form, and its position relative to other sections that may be present (e.g., coatings, capsule shells, encapsulated particles, a layer in a bi-layer tablet, and compressed powders).

[4] See 21 CFR parts 172.

affirmed as GRAS),[5] or those ingredients listed in the FDA Inactive Ingredient Guide (IIG) that have been used in SODFs.[6]

Certain substances could present a toxicological risk when used as a PCID in a SODF if the substance is:

- Used at a level in excess of the limitations provided in the relevant IIG listing or Code of Federal Regulations (CFR) chapter for direct food additives
- An ingredient that has never been used in an SODF or as a direct food additive
- An ingredient that poses risk of adverse reaction (e.g., allergic reaction or irritation), including an ingredient derived from a major food allergen (i.e., milk, eggs, fish, Crustacean shellfish, tree nuts, peanuts, wheat and soybeans)[7]

We recommend that applicants contact the appropriate clinical review division for more information on how to assess the safety of such proposed PCIDs.

B. Other Design Considerations

A substance employed as a PCID should not adversely affect the identity, strength, quality, purity, potency, or bioavailability of the SODF. To minimize the risk of adverse effects on these characteristics, FDA recommends that applicants add a PCID to an SODF at the lowest level that ensures identification of the dosage unit. Applicants also can minimize the potential for adverse interactions by using a PCID that is relatively inert (i.e., unreactive). Applicants also should consider the potential effect of a PCID on the quality, performance, and stability of the SODF both during the selection of a PCID and during the design of an SODF that will include a PCID.

Another factor that applicants should consider is the location of the PCID within the drug product. When considering where to place a PCID, the applicant may find it helpful to conceptually subdivide an SODF into sections that differ in composition that may or may not contain active drug substance. For example, a core section in an SODF is likely to contain one or more drug substances,[8] while the external sections of the SODF may not. If an applicant places a PCID inside a core section of the SODF, that placement may increase the chances of interactions with the drug substance that could result in degradation. If the applicant is concerned the PCID will interact with core components, incorporating the PCID into an external section of the SODF (e.g., in a coating or an ink-imprinted logo) may reduce the possibility of such interaction.

The applicant should also consider whether the presence of the PCID might interfere with control of the release rate of modified-release SODFs (SODF-MRs), including extended-release and delayed-release dosage forms. Thus, FDA recommends that the applicant consider incorporating the PCID into a section of the SODF-MR that does not contain any *release-controlling excipient*.[9] Since the mechanisms that impart modified-release characteristics are varied, the

[5] See 21 CFR parts 182 and 184.
[6] See http://www.accessdata.fda.gov/scripts/cder/iig/index.cfm.
[7] See section 201(qq) of the Federal Food, Drug, and Cosmetic Act.
[8] The term *drug substance* is defined in FDA's regulations at 21 CFR 314.3.
[9] A *release-controlling excipient* is any ingredient in the SODF that controls the rate at which a drug substance is made available for absorption in the gastrointestinal tract after it is administered.

potential impact on drug product release rate and stability should be evaluated by the applicant prior to incorporating a PCID into an SODF-MR, regardless of the location of the PCID relative to the drug substance and release-controlling excipients.

IV. SUPPORTING DOCUMENTATION TO ADDRESS THE PROPOSED INCORPORATION OF PCIDs IN SOLID ORAL DOSAGE FORMS

Section A below describes FDA's recommendations for documentation to be submitted both by applicants proposing to incorporate PCIDs into new SODFs in an NDA or ANDA for initial approval of a drug product and by applicants proposing to incorporate PCIDs into SODFs as a postapproval change. In addition, as described in section B below, FDA recommends that applicants proposing to incorporate PCIDs into SODFs as a postapproval change submit certain additional documentation.

A. Documentation Regarding Incorporation of PCIDs into Solid Oral Dosage Forms to be Included in any Premarketing or Postapproval Regulatory Submission

FDA recommends that applicants include the following information in appropriate sections of any premarketing or postapproval regulatory submission proposing the incorporation of a PCID in a SODF:

1. Chemical composition (names and relative amounts of each component) of the PCID.
2. Rationale for selection and incorporation of the PCID and description of how the PCID is integrated into the design of the SODF.
3. An illustration showing the location of the PCID in the SODF, unless the location can be easily explained without the use of an illustration.
4. Relevant physical-chemical attributes of the PCID (e.g., those relating to identity, strength, quality and purity) including those attributes that make the material useful as a PCID.
5. Specification[10] for the PCID.
6. Information on the impurities that may be present in the PCID.
7. Justification for safety of the PCID including any toxicological assessment.
8. Information on product development pertaining to incorporation of the PCID. (This information should include any study conducted during development to assess compatibility of a PCID with other formulation components.)
9. Description of manufacturing steps and controls associated with the incorporation of the PCID in the drug product.
10. Assurance and verification of quality, performance, and stability of the drug product containing the PCID.[11]
11. A summary of a product quality and performance risk assessment associated with the incorporation of the PCID.

The amount of information provided for a PCID will depend on its pharmacological and toxicological characteristics as well as the design of the SODF. For example, less

[10] The term *specification* is defined in FDA's regulations at 21 CFR 314.3.
[11] See also section IV.B. regarding postapproval regulatory submissions.

information would be expected for a PCID, which is a permissible direct food additive, a food substance that is GRAS, or listed in the IIG, than for a novel PCID.

B. Documentation Regarding Incorporation of PCIDs into Solid Oral Dosage Forms to be Included in any Postapproval Regulatory Submission

When an applicant proposes to incorporate a PCID into an SODF that has already been approved and marketed without the PCID, we expect that the applicant will be able to conduct certain assessments comparing the product without the PCID and with the PCID. Assessments of impurity profile, stability, and dissolution data as described below may be sufficient to address item 10 in the list in section IV, A above. We recommend that such applicants provide documentation regarding the assessments described below in the appropriate section of any postapproval regulatory submission proposing the incorporation of a PCID in a SODF:

- The applicant should perform analyses to determine whether the impurity profile of the drug product has been altered by the addition of the PCID, either through the presence of new impurities or increased levels of previously detected impurities. To prepare your submission in accordance with 21 CFR 314.70, FDA suggests that applicants follow the recommendations in the International Conference on Harmonisation guidance entitled "Q3B(R2) Impurities in New Drug Products"[12] regarding the reporting, identification, and qualification thresholds, even if the PCID is a permissible direct food additive, a food substance that is GRAS, or listed in the IIG.

- If the addition of the PCID to the SODF has the potential to significantly affect drug release rates, FDA recommends that applicants conduct evaluations of dissolution profiles. The applicant should perform dissolution testing using methods and apparatus specified in the approved application. Where applicable, the submission should include a statistical comparative assessment of multipoint dissolution profiles for the prechange and postchange batches obtained in one or more dissolution media simulating physiologically-relevant conditions.

- The applicant should use long-term and accelerated stability studies to evaluate impurity formation and the effect of the PCID on the dissolution profile. One should conduct such stability studies through the drug product expiration date, although the studies need not be completed prior to submission of the change. The initial report of the change, whether in an annual report or supplemental application, should include the most current stability data, and the applicant should continue to provide updated data in subsequent annual reports.

The applicant should also ascertain whether any analytical procedures should be revalidated as a consequence of adding the PCID.

V. DETERMINING REPORTING CATEGORY FOR POSTAPPROVAL CHANGES TO INCORPORATE PCIDs INTO SOLID ORAL DOSAGE FORMS

Applicants that propose to incorporate a PCID into a SODF as a postapproval change should report the change in a prior approval supplement, a changes being effected (CBE-30)

[12] This guidance is available on FDA's website. See footnote 2.

supplement, or an annual report according to the recommendations described in section A below.[13] Section B below describes our recommendations regarding revising the labeling of the SODF to indicate that a PCID has been incorporated.

A. Reporting Categories

The applicant should perform a risk assessment to determine the appropriate reporting category and type of drug product testing needed to evaluate the proposed change on a case-by-case basis, regardless of previous use of the same PCID in other SODF drug products.

1. Prior Approval Supplement

If the incorporation of a PCID in a SODF would have a substantial potential to have an adverse effect on the identity, strength, quality, purity, or potency of a drug product, the applicant may not market the drug product with the PCID unless a prior approval supplement is submitted and approved.[14] Examples of situations in which an applicant should submit a prior approval supplement include, but are not limited to, when a substance in a proposed PCID is not a permissible food additive, a food substance that is GRAS, or an inactive ingredient used in a CDER-approved SODF (as indicated by IIG), or if it poses the risk of an adverse reaction in patients. In such circumstances, FDA encourages the applicant to contact the appropriate clinical review division for guidance on how to provide a toxicological assessment to the Agency.

2. Changes Being Effected Supplement

If the incorporation of a PCID in a SODF would have a moderate potential to have an adverse effect on the identity, strength, quality, purity, or potency of a drug product, the applicant should submit a CBE-30 supplement at least 30 days before distribution of the drug product made using the change.[15] Examples of situations in which an applicant should submit a CBE-30 include, but are not limited to, a situation in which the applicant proposes to add a PCID (which is not a PCID for which a prior approval supplement should be submitted) to a core section of the SODF or to a section of an SODF-MR that contains a release-controlling excipient.

3. Annual Report

If the incorporation of a PCID in a SODF would have a minimal potential to have an adverse effect on the identity, strength, quality, purity, or potency of a drug product, the applicant should describe the addition of a PCID to the drug product in its next annual report.[16]

B. Labeling

Applicants should review the statute and all regulations to determine how the incorporation of a PCID may impact the labeling of their drug. FDA does not intend to object if ingredients used as PCIDs are not included in the list of ingredients in a drug's labeling. If the incorporation of a PCID changes the identifying characteristics (e.g., color) of the SODF, then the labeling must be

[13] See 21 CFR 314.70.
[14] See 21 CFR 314.70(b)(1)
[15] See 21 CFR 314.70(c)(1) and 314.70(c)(4).
[16] See 21 CFR 314.70(d)(1)

revised in accordance with 21 CFR 201.57(c)(4). All labeling changes are subject to the submission and approval requirements under 21 CFR 314.70.