Guidance for Industry

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

DRAFT GUIDANCE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 2009
CMC

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This draft guidance, when finalized, will represent the Food and Drug Administration's (FDA's) current thinking on this topic.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This draft guidance provides recommendations to pharmaceutical manufacturers on (1) design considerations for incorporating PCIDS into SODFs, (2) supporting documentation to be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. This guidance also provides our recommendations regarding (1) evaluation of toxicological and other concerns for PCIDs that are incorporated into packaging and labeling and (2) procedures for reporting or requesting approval to add PCIDs to packaging and containers 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).

Other applicable guidance documents are located on FDA's guidance Web site[2] and should be consulted to determine whether additional reporting or approval procedures may apply to other proposed changes.

[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.

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 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, laser scanning devices, and excitation/fluorescence detection). Many identifying characteristics, such as pigments or flavors, could be easily observed by patients, healthcare practitioners, and pharmacies. Some could require the use of instrumental detection (e.g., a scanner or photometric detector).

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.

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

[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 and functional characteristics that distinguish it from other sections in that dosage form and by 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).

To minimize toxicological risk, FDA recommends using permissible direct food additives,[4] including those affirmed as generally recognized as safe (GRAS),[5] or those ingredients listed in the FDA Inactive Ingredient Guide (IIG).[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 a direct food additive; or
- An ingredient that poses risk of adverse reaction (e.g., allergic reaction or irritation).

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, 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. 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 active drug substances, 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 a modified-release SODF (SODF-MR), which includes 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*.[7] Since the mechanisms that impart modified-release characteristics are varied, the potential impact on drug product release rate and stability should be evaluated by the

[4] 21 CFR parts 172, 182, and 184
[5] 21 CFR part 184
[6] http://www.fda.gov/search/databases.html
[7] 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.

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.
4. Relevant physical-chemical attributes of the PCID (e.g., those relating to identity, strength, quality, purity, and potency) including those attributes that make the material useful as a PCID.
5. Information on the impurities that may be present in the PCID.
6. Justification for safety of the PCID including any toxicological assessment.
7. 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.)
8. Description of manufacturing steps and controls associated with the incorporation of the PCID in the drug product.
9. Assurance and verification of quality, performance, and stability of the drug product containing the PCID.[8]
10. A summary of a product quality and performance risk assessment associated with the incorporation of the 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

[8] See also section IV.B regarding postapproval regulatory submissions.

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 9 in the list in section IV, A above. We recommend that such applicants provide documentation regarding the assessments described below in any appropriate section of any postapproval regulatory submission proposing the incorporation of a PCID in a SODF:

- The applicant should perform evaluations of the drug product containing the PCID to ascertain that there is no significant increase in previously detected impurities. The evaluations should be able to detect the presence of significant new impurities at levels that may have toxicological consequence. Toxicological assessment, which is usually not required for PCIDs that are GRAS, may be warranted if the impurity profile of the drug product is altered significantly by the addition of a PCID.

- 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.

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 an annual report or submit a changes being effected (CBE-30) or prior approval supplement according to the recommendations described below.[9] We also describe below our recommendations regarding revising the labeling of the SODF to indicate the incorporation of a PCID.

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. It is our hope that the majority of these changes will be designed to present minimal potential to have an adverse effect on the identity, strength, quality, purity, or potency of the drug product and therefore can be

[9] See 21 CFR 314.70.

reported in an annual report. We therefore have described the reporting categories below in order of least to most risk presented by the proposed change.

1. Annual Report

In situations where PCID toxicological considerations and SODF design factors reduce the risk such that the change would have a minimal potential to have an adverse effect on the identity, strength, quality, purity, or potency of a drug product and the applicant's evaluation of the drug product containing the PCID finds no adverse effect, the applicant may report the addition of the PCID to the SODF in its next annual report.[10]

2. Changes Being Effected Supplement

Certain SODF design factors elevate the risk of the change. Examples of such design factors are adding a PCID to a core section of the SODF or adding a PCID to a section of an SODF-MR that contains a release-controlling excipient. In such cases, the applicant should report the addition of a PCID to the drug product by submitting a CBE-30 supplement.[11]

3. 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.[12] For example, if a substance in a proposed PCID neither appears on the GRAS list nor is an inactive ingredient used in a CDER-approved SODF (as indicated by IIG), the applicant should submit a prior approval supplement. In this case, FDA encourages the applicant to contact the appropriate clinical review division for guidance on how to provide a toxicological assessment to the Agency.

B. Labeling

At their discretion, applicants may decide whether or not to revise the labeling of the SODF to indicate the incorporation of a PCID. For example, applicants may wish to revise the labeling to alert healthcare practitioners and patients that the SODF has a PCID with unique visual features so that the practitioners and patients can verify that the drug product they receive contains the PCID. If an applicant decides to revise the labeling, any labeling changes are subject to the reporting and approval requirements under 21 CFR 314.70.

VI. POTENTIAL MIGRATION OF PCIDs ADDED TO PACKAGING OR CONTAINER LABELING

Some pharmaceutical manufacturers may consider adding PCIDs into the packaging and labeling of SODFs. We describe below our recommendations regarding (1) evaluation of toxicological and other concerns for PCIDs that are incorporated into packaging and labeling and (2)

[10] 21 CFR 314.70(d)(1)
[11] 21 CFR 314.70(c)(1)
[12] 21 CFR 314.70(b)(1)

procedures for reporting and requesting approval to add PCIDs to packaging and containers as a postapproval change.

A. Information Regarding Toxicological and Other Concerns

If an applicant proposes to affix or incorporate a PCID into a primary packaging component for a SODF, the applicant should assess PCID toxicology and the potential for an adverse effect on SODF quality, performance, and stability.

FDA's toxicological concerns are mitigated if the added substance(s) is a permitted direct or indirect food additive[13] or listed in FDA IIG. Applicants proposing to use any additive as a PCID in primary packaging where toxicology has not been established should provide assurance that there is no migration of the PCID into the SODF.

We recommend that applicants identifying toxicological concerns with a proposed PCID in primary packaging contact the appropriate clinical review division and/or the appropriate chemistry, manufacturing, and controls review division before proceeding to discuss possible adverse interactions of a proposed PCID added to packaging with the SODF.

Applicants proposing to use a PCID in primary packaging for a SODF in an initial NDA or ANDA should include supporting information in their application addressing toxicological concerns.

B. Reporting Categories for Adding PCIDs to Packaging or Container Labeling Postapproval

An applicant proposing to add a PCID to primary packaging for a SODF as a postapproval change should report the change in an annual report or submit a CBE-30 or prior approval supplement according to the recommendations described below.[14]

1. Annual Report

If the substance(s) in the PCID is a permitted direct or indirect food additive[15] or listed in FDA IIG, or if the added substance(s) has been previously approved for use in the primary packaging of another CDER approved SODF, an applicant may report the addition of a PCID to primary packaging for a SODF in its next annual report.

2. Changes Being Effected Supplement

If the toxicology of the added substance has not previously been established (as provided for in the above paragraph), applicants proposing to use the substance as a PCID in primary or secondary packaging may submit the change in a CBE-30 supplement if the supplement includes data providing assurance that there will be no migration of the PCID into the SODF. The supplement should also include information addressing toxicological concerns.

[13] 21 CFR parts 172, 174-178, 182, 184, and 186
[14] 21 CFR 314.70.
[15] 21 CFR parts 172, 174-178, 182, 184, and 186

3. Prior Approval Supplement

If the safe use of a PCID cannot be ensured (i.e., if the toxicology has not previously been established and migration potential exists), the applicant may not market the drug product using the PCID in primary or secondary packaging unless a prior approval supplement is submitted and approved.