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

[*1]Dr. Sushil Kumar Sharma [2]Dr. Ajay Mishra; [3]Dr. Ekta Sharma; & [4]Yatendra Sharma

[*1]*Freelance Consultant, ISO 9001, 14001 & GMP. LIG 56, Pkt-1, Sector-A9, Narela, Delhi (India)*
[2]*MD (Neuropsychiatry), Consultant, MLN Hospital, Allahabad, U.P (E) (India)*
[3]*Assist Prof & In charge, Dept. of Textiles and Apparel Designing, Ethelind College of Home Science, SHUATS, Allahabad (India)*
[4]*Young Professional, Ministry of Youth Affairs and Sports (India)*

1. 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 design considerations for incorporating PCIDS into SODFs, 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, supporting documentation to be submitted in post-approval submissions to report or request approval to incorporate PCIDs into SODFs, and procedures for reporting or requesting approval to incorporate PCIDs into SODFs as a post-approval 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 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.

2. 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.

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).

3. 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, food substances that are generally recognized as safe (GRAS) (including direct food substances affirmed as GRAS), or those ingredients listed in the FDA Inactive Ingredient Guide (IIG) that have been used in SODFs. 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

*Corresponding Author: *drsharmasushil[at]gmail.com*

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, 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.

4. 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 post-approval change. In addition, as described in section B below, FDA recommends that applicants proposing to incorporate PCIDs into SODFs as a post-approval change submit certain additional documentation.

a) Documentation Regarding Incorporation of PCIDs into Solid Oral Dosage Forms to be Included in any Premarketing or Post-approval Regulatory Submission

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

- Chemical composition (names and relative amounts of each component) of the PCID.
- Rationale for selection and incorporation of the PCID and description of how the PCID is integrated into the design of the SODF.
- An illustration showing the location of the PCID in the SODF, unless the location can be easily explained without the use of an illustration.
- 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.
- Specification for the PCID.
- Information on the impurities that may be present in the PCID.
- 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.
- Assurance and verification of quality, performance, and stability of the drug product containing the PCID.

b) Documentation Regarding Incorporation of PCIDs into Solid Oral Dosage Forms to be Included in any Post-approval 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 post-approval 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 Harmonization 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 pre-change and post-change 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.

5. Determining reporting category for postapproval changes to incorporate PCIDs into solid oral dosage forms

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
2. Changes Being Effected Supplement
3. Annual Report

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 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.

The specific approach to assuring the protection from counterfeit drugs includes the following critical elements:

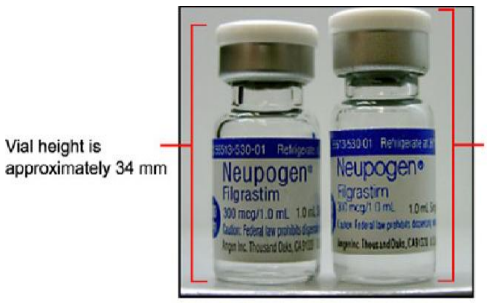
1. *Implementation of new technologies*
    a. *Common use of reliable track and trace technology*
    b. *Authentication technologies*
2. *Adoption of electronic track and trace technology*
3. *Adoption and enforcement of strong, proven anti-counterfeiting laws and regulations*
4. *Increased criminal penalties*
5. *Adoption of secure business practices*
6. *Development of a system that helps ensure effective reporting*
7. *Education of consumers and health professionals*
8. *Collaboration with foreign stakeholders to develop strategies to deter and detect counterfeit drugs globally*

6. Technologies to secure the drug supply

A. **Authentication Technology:** There is a considerable debate where FDA has initiated Proposals to the industry to secure our medicinal drug products from counterfeit

Practices in the drug supply chain. These proposals are listed below:

a) Whether to incorporate at least two types of anti-counterfeiting technologies into the packaging and labeling of all drugs, at the point of manufacture, with at least one of those technologies being covert *(i.e., not made public, and requiring special equipment or knowledge for detection)* starting with those products at high risk of being counterfeited and where the introduction of counterfeit product poses a serious health risk;

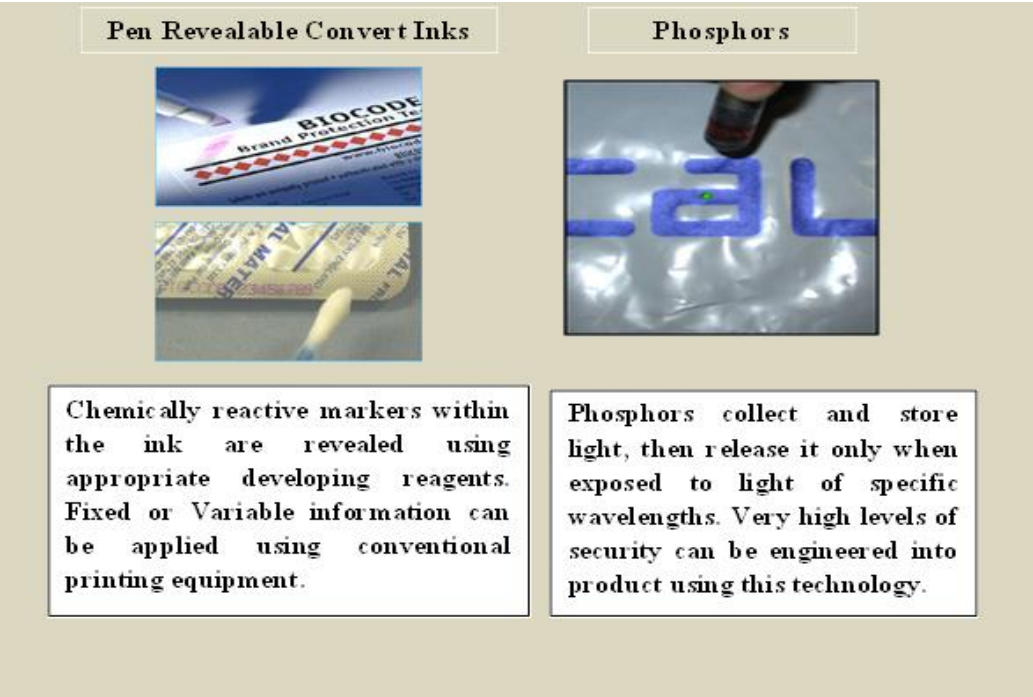


Counterfeit Neupogen - No active ingredient

b) Whether to incorporate a taggant chemical marker, or other unique characteristics into manufacturing process of all drugs that is only identifiable with the use of sophisticated analytic techniques starting with those products at high risk of being counterfeited and where the introduction of counterfeit product poses a serious health risk;

c) Whether to issue FDA guidance concerning the appropriate use of anti-counterfeiting technologies And the application and review process for labeling and packaging changes or

product changes such as incorporation of taggants, chemical markers, or other unique characteristic(s) into the product for the purpose of product authentication.



B. Identification of Products likely to be counterfeited

All Products are at high risk for being counterfeited. Most of the comments FDA received supported the idea of developing criteria by which stakeholders could determine which products are likely to be counterfeited and/or developing a national list of products likely to be counterfeited based on these criteria. There was general agreement that the existence of state specific lists, each with its own regulatory requirements, could inhibit commerce and adversely affect the availability of drugs.

C. Radio-frequency Identification (RFID) Technology

RFID was cited as being the technology with strongest potential for securing the supply chain but that it was not ready for widespread commercial use with pharmaceutical products. Many costs potential benefits, and unresolved issues related to RFID were cited. The potential benefits included the ability to control inventory and conduct rapid, efficient recall, while costs that could hinder the adoption of RFID included purchase of tags and other hardware, integration into existing information systems and compliance with regulatory requirements (e.g, labeling, electronic records). Important unsolved issues included the need to develop standards and business rules for RFID, the need to address database management issues, and the need to determine the effect of RFID on product quality.

References

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2. http://whqlibdoc.who.int/trs/who_trs_902.pdf, accessed 24 Sept. 2016.
3. FDA 21 CFR 314.70, 70 (b), (c) and (d)
4. http://www.gmp-compliance.org/guidemgr/files/UCM171575

