



# Combating Counterfeit Drug Products

*New guidance explores PCIDs*

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THE PUBLIC FRUSTRATION OVER THE LACK of available H1N1 flu virus vaccine has been widely publicized. Due to slow growth in the eggs used to produce the vaccine, by the end of October the Centers for Disease Control and Prevention (CDC) had a relatively low supply of doses available: just 26.6 million, or more than one-third less than projected earlier in the year. With consumer concern bordering on public panic as 48 states reported widespread influenza activity, would-be vaccine recipients have naturally been seeking out additional methods to protect themselves and their loved ones. This includes using one or more of the plethora of swine flu prevention or treatment options available online, including miraculous offers for the vaccine itself or for Tamiflu or Relenza, two drug products for which the FDA has issued emergency use authorizations allowing the use of these products beyond their approved indications. Many, if not all, of these products are likely counterfeit.

Consistent with this wave of consumer activity, FDA has heightened enforcement activity against these products. In fact, in the five-month period spanning May to November, FDA issued warnings to more than 75 websites illegally marketing more than 135 different unapproved, uncleared, or unauthorized products. In addition, FDA has been encouraging consumer vigilance regarding promotions and Internet sites offering products for sale claiming to diagnose, prevent, mitigate, treat or cure H1N1 flu, has increased efforts to publicize warnings regarding potentially deceptive H1N1 products, and has joined with the Federal Trade Commission to issue a warning letter to a website marketing fraudulent supplements claiming to prevent H1N1.

These actions focused on H1N1 are just the latest in ongoing efforts by the FDA to deal with the consumer risks raised by unapproved, uncleared, unauthorized or counterfeit products. The agency has begun developing and implementing new tools to address the issue. One of the areas it has focused on is the issue of counterfeit products. The Federal Food, Drug, and Cosmetics Act defines a counterfeit drug product as "a drug which, or the container or labeling of which, without authorization, bears the trademark, trade name, or other identifying mark, imprint, or device, or any likeness thereof, of a drug manufacturer, processor, packer, or distributor other than the person or persons who in fact manufactured, processed, packed, or distributed such drug and which thereby falsely purports or is represented to be the product of, or to have been packed or distributed by, such other drug manufacturer, processor, packer, or distributor." Generally, a counterfeit drug

is one sold under a product name, without proper authorization, and is represented, labeled, or packaged in a manner that suggests it is an authentic approved product. These products may be contaminated, provide an incorrect dosage, or include incorrect ingredients.

While FDA believes the quality of approved products is high and the public can have confidence that products sold in the U.S. market are authentic, it considers allegations or information regarding the counterfeiting of products grievous and recognizes that, as the manufacturing and distribution system has become more global in nature, protecting against counterfeit products has become more challenging. One action taken by the agency places additional power in the hands of industry via a draft guidance document published in July 2009 regarding the use of certain anti-counterfeiting methods by manufacturers. Specifically, the document is intended to provide guidance to pharmaceutical manufacturers who want to use physical-chemical identifiers (PCIDs) — a substance or combination of substances possessing a unique physical or chemical property that unequivocally identifies and authenticates a drug product or dosage form — in solid oral dosage forms.

While drug manufacturers have been investigating a number of available technologies to make replication of their drug products more difficult, one approach being considered involves the addition of trace amounts of an inactive ingredient or ingredients to an existing section (a discrete contained solid or a layer in a solid oral dosage form) of the dosage form. A unique physical-chemical characteristic of that added ingredient makes it possible to detect and authenticate legitimate dosage forms and identify counterfeits. Examples given in the draft guidance document as substances that may be incorporated into solid drugs as PCIDs include inks, pigments, flavors, and molecular taggants that may allow product authentication by their presence alone or code the product identity into or onto the product.

The draft guidance document provides

- recommendations to pharmaceutical manufacturers on design considerations for incorporating PCIDs into solid drugs,
- supporting documentation to be submitted in new drug applications and abbreviated new drug applications to

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address the proposed incorporation of PCIDs in solid drugs,

- supporting documentation to be submitted in post-approval submissions to report or request approval to incorporate PCIDs into solid drugs; procedures for reporting or requesting approval to incorporate PCIDs into solid drugs as a post-approval change
- recommendations regarding the evaluation of toxicological and other concerns for PCIDs incorporated into packaging and labeling, and
- recommendations regarding procedures for reporting or requesting approval to add PCIDs to packaging and containers as a post-approval change.

With respect to design considerations for incorporating PCIDs into solid oral dosage forms, FDA recommends that the ingredients constituting the PCID be pharmacologically inactive, allowing them to be treated as excipients. FDA anticipates that

substance employed as a PCID should not adversely affect the identity, strength, quality, purity, potency, or bioavailability of the product, and that applicants should add a PCID at the lowest level required to ensure identification, in order to minimize the risk of adverse events. To minimize potential safety issues, FDA also recommends that applicants use a PCID that is relatively inert, with appropriate consideration for the potential effect of a PCID on the quality, performance, and stability of the solid drug both during the selection of a PCID and during the design of the drug that will include a PCID.

The draft guidance document also indicates that sponsors should consider the location of the PCID within the drug product, or the section into which the PCID is built. FDA suggests that manufacturers may find it helpful to “conceptually subdivide” the solid oral dosage formulation into sections differing in composition that may or may not contain active drug substances. For example, placing a PCID inside a core section of the drug where one or more active drug ingredients are located may increase the chance of interactions with or degradation

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many of the ingredients that will ultimately be used as PCIDs are already used as food additives, colorants, or excipients with established safety profiles. To that end, to reduce or minimize toxicological risks, FDA suggests considering approved or authorized direct food additives, including those considered generally recognized as safe (GRAS) or listed in the FDA Inactive Ingredient Guide. FDA does note in its draft guidance document, however, that certain substances could present a toxicological risk if used as a PCID. This could occur if a PCID ingredient is used at a level in excess of the limitations provided in the relevant listing for inactive ingredients or direct food additives, or for ingredients that have never been used in solid oral dosage form or as a direct food additive. There is also the possibility an ingredient could pose risks of adverse experiences such as allergic reactions or irritation. In light of this, FDA recommends that manufacturers contact the relevant review division for more specific information on how to assess proposed PCIDs.

Additionally, the draft guidance document specifies that a

of the drug substance. Engineering a PCID into an external or non-core section of the drug product may reduce the possibility of such interaction or degradation. In a similar fashion, the sponsor should consider whether the addition or inclusion of the PCID may affect the release of modified-release formulations. Due to the potential effect on the product, FDA recommends in the draft guidance document that the manufacturer incorporate the PCID into a section that does not contain any ingredient that controls the rate at which a drug substance is made available for absorption in the gastrointestinal tract after it is administered, and evaluate the potential impact of the PCID on drug product release rate and stability before incorporating the PCID into a modified release product, regardless of section.

While this column contemplates only the design elements, manufacturers should familiarize themselves with the draft guidance document. It represents one potential way for manufacturers to address potential counterfeiting threats. ■

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