

The final rule does not require these tests to be submitted to FDA at the time of patent submission, nor does it require the NDA applicant or holder to conduct the tests itself. The testing requirements, however, will ensure that only relevant polymorphs are submitted for listing.

Whether two different polymorphs are the "same" active ingredient for purposes of drug approval is a scientific determination based upon the specific characteristics of the forms of the drug substance involved. Only with testing can the scientific determination be made that the drug product containing the polymorph will perform the same as the drug product described in the NDA. The test data that the NDA applicant or holder or patent owner must certify exist at the time of patent submission are similar to the type of information required under §§ 314.50 and 314.94. The following explains more fully the required tests or data that would support the statement in the declaration forms:

- A full description of the polymorphic form of the drug substance, including its physical and chemical characteristics and stability; the method of synthesis (or isolation) and purification of the drug substance; the process controls used during manufacture and packaging; and such specifications and analytical methods as are necessary to assure the identity, strength, quality, and purity of the polymorphic form of the drug substance;

- The executed batch record for a drug product containing the polymorphic form of the drug substance and documentation that the batch was manufactured under current good manufacturing practice requirements;

- Demonstration of bioequivalence between the executed batch of the drug product that contains the polymorphic form of the drug substance and the drug product as described in the NDA;

- A list of all components used in the manufacture of the drug product containing the polymorphic form and a statement of the composition of the drug product; a statement of the specifications and analytical methods for each component; a description of the manufacturing and packaging procedures and in-process controls for the drug product; such specifications and analytical methods as are necessary to assure the identity, strength, quality, purity, and bioavailability of the drug product, including release and stability data complying with the approved product specifications to demonstrate pharmaceutical equivalence and comparable product stability; and

- Comparative in vitro dissolution testing on 12 dosage units each of the executed test batch and the NDA product.

This test data requirement corresponds to the test data required of ANDA applicants to demonstrate the drug product containing the polymorph described in the ANDA will perform the same as the drug product described in the NDA. In addition to the data requirements described in our regulations cited above (§§ 314.50 and 314.94), we have published guidance documents describing the test data ANDA applicants may use to demonstrate that the drug product will perform the same as the drug product described in the NDA. (See "Guidance for Industry: Changes to an Approved NDA or ANDA" (November 1999) and "Guidance for Industry: Immediate Release Solid Oral Dosage Forms CMS 5" (November 1995); these guidances are available at www.fda.gov/opacom/morechoices/industry/guidedc.htm.)

The stringency of these requirements regarding "sameness" also should address the concerns that the submission of polymorph patents might lead to submission of other patents claiming components which are not, but might be, included in a drug described in an NDA. Given the narrow legal and scientific basis for submission of polymorph patents, the final rule does not open the door to submission of any patents claiming formulations or inactive ingredients not contained in the drug product described in the NDA.

We believe that these changes will help deter submission of inappropriate polymorph patents. The assumption that a product containing a polymorph will perform the same as the product containing a different polymorph and described in the NDA will have to be substantiated.

b. Product-by-Process Patents—Should These Patents Be Listed? Proposed § 314.53(b) would allow an NDA applicant or holder or patent owner to submit information on product-by-process patents. The act requires that NDA holders submit patents that claim the drug product. However, NDA applicants or holders must not submit patents that claim a process for making that product.

We explained that a product-by-process patent claims a product by describing or listing process steps to wholly or partially define the claimed product. In a product-by-process patent, the patented, novel invention is the product and not the process that is used to make the product. We recognized that the distinction between a product-by-process patent and a process patent

might not be readily apparent to persons who are unfamiliar with patent law. We sought comment on ways to ensure that only appropriate product-by-process patents are listed in the Orange Book.

(Comment 2) Several comments argued that product-by-process patents must not be listed. Some comments stated that product-by-process patents "closely resemble" process patents and that the act does not allow listing of process patents. One comment asserted that listing product-by-process patents would have a "profound negative effect" on generic drug approvals because NDA applicants and holders or patent owners would attempt to list any product-by-process patent, whether or not the process defined in the patent was actually used to manufacture the drug product approved in the NDA.

Similarly, other comments sought to limit the type of product-by-process patents that could be listed. Several comments would revise the rule to require the product-by-process patent to claim a "novel" product, so that if the drug product described by the product-by-process patent was a "known" drug product or the product already had been listed in the Orange Book, we would not list the product-by-process patent. In other words, the comments sought to ensure that the product-by-process patent covered a product that was "new and patentably distinct" from previously-approved drug products. One comment suggested adding a new paragraph to the patent declaration to read as follows:

F. For each drug substance or drug product claim that was (1) identified as listable in subparts B and C and (2) is drafted in product-by-process format, please provide the following information:

1. Is the product of the recited process novel? [If the answer to question F.1 is "no," stop. The patent cannot be listed. If yes, please identify the claim(s) by number.]

Another comment thought that few drugs would be the subject of a product-by-process patent. The comment recommended that we investigate any product-by-process patents that were listed in the Orange Book to see if these related to the NDA drug product. Yet another comment would amend the patent declaration to identify the product-by-process claims in the patent, the effective filing date of the patent application, whether the product has been previously sold, and, if the product had been previously sold, whether such sales occurred more than 1 year before the effective filing date of the patent application. The comment explained that if the drug's active ingredient has been previously sold for more than 1 year before the effective filing date of the product-by-process patent