

rule would clarify that we would list only patents that claim:

- The drug substance (ingredient);
- The drug product (formulation and composition); and
- Method of use.

Proposed § 314.53(b) would not allow listing of process patents and patents claiming packaging, metabolites, or intermediates.

a. *Patents Claiming a Drug Substance—Must Patents that Claim the “Same” Active Ingredient Be Submitted and Listed?* For patents that claim a drug substance, the proposal stated that an applicant “shall submit information only on those patents that claim the form of the drug substance that is the subject of the pending or approved application or that claim a drug substance that is the same as the active ingredient that is the subject of the approved or pending application.” We explained that an NDA applicant or holder would determine whether the drug substance was the “same” as the active ingredient in the NDA by considering “whether the drug substances can be expected to perform the same with respect to such characteristics as dissolution, solubility, and bioavailability” (see 67 FR 65448 at 65452).

Drug substances that are the same active ingredient, but that are in different physical forms, are often called “polymorphs.” For example, the different crystalline forms of a drug substance are sometimes known collectively as polymorphs, and drug substances with different waters of hydration are sometimes referred to as “polymorphs” as well. (For purposes of this final rule, polymorphs include chemicals with different crystalline structures, different waters of hydration, solvates, and amorphous forms.) Under the proposed rule, an NDA applicant or holder would be required to submit a patent claiming a different polymorph from that of the drug substance described in the NDA if a drug product containing the polymorph will perform the same as the drug product described in the NDA with respect to dissolution, solubility, and bioavailability.

The proposed rule would make the patent listing standards generally consistent with the ANDA approval standards. For ANDA approval purposes, the active ingredient in a generic drug product can be the “same” as that in the reference listed drug notwithstanding differences in the physical forms of their active ingredient if the drug product performs the same. Thus, we stated that it would be consistent to interpret “drug substance” for patent submission and listing

purposes as including certain drug substances having different physical forms if they would be considered the same active ingredient for ANDA approval purposes (*id.*).

We invited comment on whether we should revise the codified language to require an NDA holder to submit additional information regarding the basis for its assertion that the drug substances are the “same” active ingredient. We also invited comment on the potential impact of the change (allowing the submission of patents claiming different polymorphs) on the submission of ANDA and 505(b)(2) applications.

(Comment 1) Several comments disagreed with our proposal to allow listing of patents claiming different polymorphs of the active ingredient in the listed drug. Some comments stated that section 505(b)(1) of the act requires the patent to claim the drug substance that is the subject of the NDA. Several comments asserted that a patent claiming a polymorph that was not the subject of an NDA did not satisfy section 505(b)(1) of the act. Other comments argued that “sameness” for ANDA approval purposes differed from “sameness” in patent law, so we did not have to develop an identical interpretation of the two concepts. Several comments maintained that no such patents could exist if the active ingredients were truly the “same” because a subsequent patent for the “same” active ingredient should not have been issued. Some comments agreed that patents claiming different polymorphs of the same active ingredient should be listed, but only with submission of additional information such as clinical trial data required for FDA approval or proof that “sameness” is beneficial. A few comments maintained that the proposal did not change our pre-existing position because we have permitted NDA holders and applicants to submit patents claiming different polymorphs of the active ingredient. In response to our request for comment on the impact on ANDA and 505(b)(2) applications, one comment expressed the belief that listing patents claiming different polymorphs of the active ingredient would reduce the ability of generic manufacturers to “design around” the existing patents, an option which was contemplated by the Hatch-Waxman Amendments.

(Response) We decline to modify our position taken in the proposed rule which would require patents to be submitted for listing that claim different polymorphs of the active ingredient described in the NDA. If the NDA

applicant or holder is able to establish that a polymorph claimed in a patent is the “same” active ingredient (i.e., that a drug product containing the polymorph will perform the same as the drug product described in the NDA with respect to such characteristics as dissolution, solubility, and bioavailability), the NDA applicant or holder must submit the patent to us for listing. We acknowledge that there may be some legitimate confusion regarding our prior position concerning submission of such patents for listing, which resulted in the listing of some polymorph patents in the Orange Book. The uncertainty over our policy resulted from certain court decisions, our response to those court decisions, and other public statements. The FTC Citizen Petition highlighted the need for clarification and is one reason we decided to implement this final rule and clarify our position. For the reasons explained in the preamble to the proposed rule (see 67 FR 65448 at 65452 to 65453), it is appropriate to have a consistent interpretation of the “sameness” principle in the patent listing and ANDA approval contexts. Accordingly, we will not treat polymorphs differently for patent submission and listings and ANDA approval. The argument that certain polymorph patents should never have been issued is not a matter for us to address. The Patent and Trademark Office (PTO) is responsible for reviewing and issuing patents. We will not question whether the PTO should have issued a particular patent, nor will we conduct a “patent law” or other analysis to determine “sameness.”

We agree with the comments that suggested we needed to take additional steps to help ensure that the submitted patents claim the “same” active ingredient as that described in the NDA. A polymorph patent must claim the drug substance (active ingredient) to meet the statutory requirements for submission. We have modified the declaration requirement and created forms to help ensure that the NDA applicant or holder or patent owner confirms that the patent does claim the “same” active ingredient. The final rule and the declaration forms require that the NDA applicant or holder or patent owner certify that test data exist demonstrating that a drug product containing the polymorph will perform the same as the drug product described in the NDA. If a patent claims more than one polymorph, each polymorph for which the required test data are available must be identified by claim or description in the declaration forms.