

17 January, 2023

Joint USPTO-FDA Collaboration Initiatives; Notice of Public Listening Session

FDA Guidance on Polymorphs and Patenting Practices

This comment relates to FDA guidance for companies in relation to monitoring, controlling and the timing of providing information to the FDA on polymorphic forms during the development of new drug substances/products that are based on small molecules and the patenting practices of these forms.

Background:

On 29 December 2000 the FDA published a guidance entitled 'Q6A Specifications: Test Procedures and Acceptance Criteria for New Drug Substances and New Drug Products: Chemical Substances.' The guidance document can be found here:

<https://www.federalregister.gov/documents/2000/12/29/00-33369/international-conference-on-harmonisation-guidance-on-q6a-specifications-test-procedures-and>

In this guidance, the FDA sets out how polymorphic forms should be monitored and controlled by companies for new drug substances and products. As the guideline states, some new drug substances exist in different crystalline forms that differ in their physical properties. In cases where differences exist that have been shown to affect drug product performance, bioavailability, or stability, then the appropriate solid state should be specified. The guidance provides how physicochemical measurements and techniques are commonly used to determine whether multiple forms exist, including hot-stage microscopy, solid state IP, X-ray powder diffraction, thermal analysis procedures such as differential scanning calorimetry (DSC), Raman spectroscopy and solid state nuclear magnetic resonance spectroscopy. Furthermore, additional guidance is provided, by way of decision trees (see attached Decision Tree #4), on when and how polymorphic forms should be monitored and controlled.

In addition to the above guidance, the FDA's page on Investigational New Drug (IND) Application states:

"Current Federal law requires that a drug be the subject of an approved marketing application before it is transported or distributed across state lines. Because a sponsor will probably want

to ship the investigational drug to clinical investigators in many states, it must seek an exemption from that legal requirement. The IND is the means through which the sponsor technically obtains this exemption from the FDA.

“The IND application must contain information in three broad areas [including] manufacturing information pertaining to the composition, manufacturer, stability, and controls used for manufacturing the drug substance and the drug product. This information is assessed to ensure the company can adequately produce and supply consistent batches of the drug.”

<https://www.fda.gov/drugs/types-applications/investigational-new-drug-ind-application>

Accordingly, the FDA requires polymorphic screening data to be submitted by a company seeking to bring a new product to market in its original IND application before Phase 1 clinical trials. Therefore, polymorphic data on a new drug can be available to the FDA anywhere between 3-6 years before the drug is finally approved.

Polymorph Patenting in Practice

Despite the FDA guidance for routine testing for polymorphs (see Decision Tree #4) and that such information is provided to the FDA as early as the IND application stage of a new drug's development, our review of patent filings for polymorphic forms for a number of drugs shows that they are being filed by companies considerably later.

While it is recognised that information on polymorphs provided through an IND to the FDA is treated as confidential information, it appears companies are using this confidentiality to delay the filing of the patents on these polymorphs in order to stretch out their patent protection for as long as they possibly can. In essence, companies are being allowed to protect the polymorphic data they provide to the FDA as a trade secret until they decide to file the relevant polymorph patent(s) for the purpose of meeting the listing requirements on the U.S FDA Orange Book as required under Hatch Waxman or simply for defensive litigation purposes to block competitors finding alternative polymorphs that would enable them to work around the patented form.

Example - Revlimid

The main compound patent for the drug lenalidomide (Revlimid) as developed by Celgene, U.S 5635517, was filed on 7/24/1996 and expired 10/4/2019. According to a source at the Mayo Clinic who worked on the preclinical trials for lenalidomide, it is understood that the drug was under clinical investigation in 1999/2000, which would have required an IND and the submission of relevant polymorph data to the FDA as described above.

However, Celgene did not submit its patent application for a polymorphic form of lenalidomide until 9/3/2004 (U.S 7465800), which expires on 4/27/2027 – some 4-5 years after clinical

investigation commenced and adding another 8 years of patent protection beyond the main compound patent. Between 2008-2020, Celgene then applied for several other patents covering polymorphic forms of lenalidomide, many as divisionals of US7465800, but also a completely new patent application for a different polymorph e.g. U.S 9808450 filed on 3/25/2014, expiring 3/25/2034. (Patent data is available at <https://drugpatentbook.i-mak.org/>).

Revlimid was approved by the FDA for treating multiple myeloma on 12/27/2005.

Celgene has entered into settlements with a handful of companies, but which only allows for a very limited generic volume launch until 2026. Only after 2026 will the U.S market see unfettered competition. A key to extending the limited volume launch of generic versions until 2026 was Celgene's polymorph patents, in particular U.S 7465800, which expires 4/27/2027. As a result of the delay to unlimited competition for the drug Revlimid, Americans will be paying several billion dollars more than they would otherwise. Meanwhile, in Europe, companies have been able to manufacture unlimited volumes of generic versions of Revlimid since 2022 and patients have seen the benefit of lower prices.

Given FDA guidelines on polymorph screening being a routine and required part of drug development for small molecule drugs, and what appears to be a deliberate delay by companies filing for patents on them, we believe the FDA and USPTO need to work more closely to remedy these abusive patenting practices that are blocking earlier generic competition and lower drug prices.

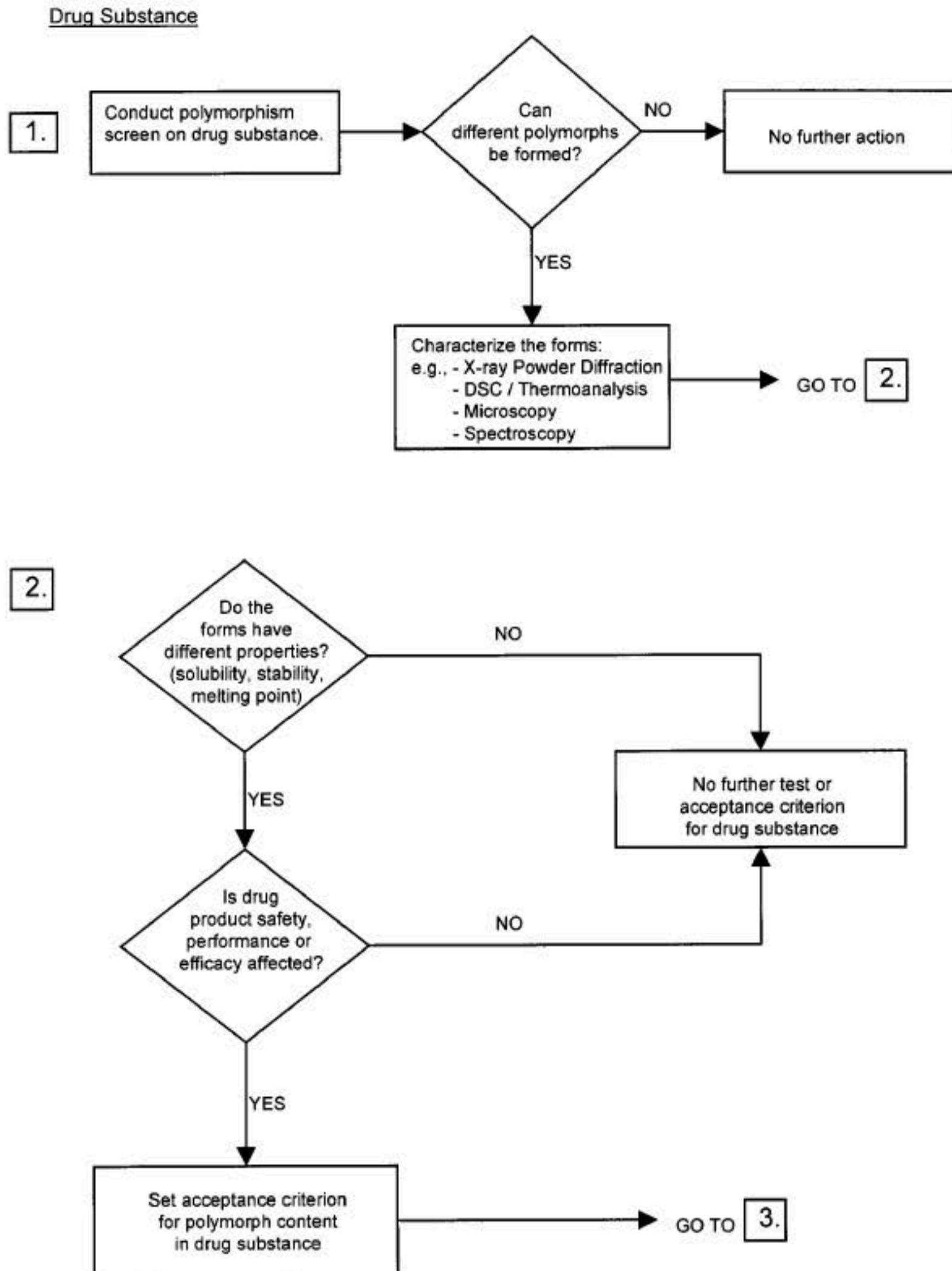
Recommendations

The following are some recommendations that the FDA and USPTO should consider in relation to the current practice around the patenting of polymorphs:

1. Currently the courts and USPTO view polymorphs are "unpredictable" and, therefore, patentable. However, given polymorphs are inherent in the original compound and the FDA requires companies to find them as a matter of routine testing/experimentation for the purpose of marketing approval, the USPTO should revise its examination practice such that polymorphs are *prima facie* obvious.
2. Where companies are filing patents for other polymorphic versions much later than the first polymorph patent (even if as a continuation or divisional application that does not extend the expiry of the patent) and claiming surprising or unexpected advantages such as stability, flow or bulk density, these patents should be refused if the FDA had knowledge of these other forms at the time of the IND or during the approval process.
3. Alternatively, and without prejudice to the above, once a company has submitted polymorph screening data to the FDA as part of its IND, it has 30 days within which to

file patent applications for all polymorphs identified with the USPTO. Failure to meet this requirement means the USPTO should refuse to accept the application. This would require the FDA to share the IND materials with the USPTO.

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DECISION TREE #4: INVESTIGATING THE NEED TO SET
ACCEPTANCE CRITERIA FOR POLYMORPHISM
IN DRUG SUBSTANCES AND DRUG PRODUCTS

DECISION TREE #4: INVESTIGATING THE NEED TO SET ACCEPTANCE CRITERIA FOR POLYMORPHISM IN DRUG SUBSTANCES AND DRUG PRODUCTS

Drug Product - Solid Dosage Form or Liquid Containing Undissolved Drug Substance

N.B.: Undertake the following processes only if technically possible to measure polymorph content in the drug product.

3.

