



Marketed Unapproved Drugs: FDA to Take Immediate Enforcement Action at Any Time, Without Prior Notice

FDANEWS

Kurt R. Karst
Hyman, Phelps & McNamara, P.C.
700 Thirteenth Street, N.W., Suite 1200
Washington, D.C. 20005, U.S.A.
202-737-5600 • www.hpm.com
kkarst@hpm.com
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Today's Agenda

- **Essential Concepts – What is a “Drug;” What is a “New Drug”?**
- **Historical Development of the Federal Food, Drug, and Cosmetic Act (“FDC Act”) and the Different “Categories” of Drugs.**
- **FDA’s Compliance Policy Guide (“CPG”) – What are FDA’s Enforcement Policies and Priorities?**
- **September 19, 2011 – The Line in the Sand**
- **Challenging FDA**

Essential Concepts – What is a “Drug;” What is a “New Drug”?

Essential Concepts – What is a “Drug;” What is a “New Drug”?

- FDC Act § 201(g)(1) defines the term “drug” as:
 - (A) articles recognized in the official United State Pharmacopeia, official Homeopathic Pharmacopeia of the United States, or official National Formulary, or any supplement to any of them; and
 - (B) articles intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease in man or other animals; and
 - (C) articles (other than food) intended to affect the structure or any function of the body of man or other animals; and
 - (D) articles intended for use as a component of any articles specified in clause (A), (B), or (C)....
- Thus, whether a product is a “drug” generally depends on its “intended use.” See generally 21 C.F.R. § 201.128.

Background – What is a “Drug;” What is a “New Drug”?

- FDC Act § 201(p) defines the term “new drug” so that a drug is not a “new drug” if:
 - (1) it is Generally Recognized As Safe and Effective (“GRASE”) under the conditions of use for which it is labeled; and
 - (2) it has been used “to a material extent or for a material time under those conditions.”
- A product that is a “new drug” may not be introduced into interstate commerce unless there is an approved marketing application (e.g., an NDA), or unless an exemption has been granted permitting the introduction of the drug into interstate commerce (e.g., an effective IND).

Historical Development of the FDC Act and the Different “Categories” of Drugs

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- **The 1906 Federal Food and Drugs Act**
 - First brought drug regulation under federal law by prohibiting the sale of adulterated or misbranded drugs.
 - The statute did not require that drugs be approved by FDA in order to be marketed.

Historical Development of the FDC Act and the Different “Categories” of Drugs

- **The 1938 FDC Act**
 - Enacted on June 25, 1938.
 - Added the requirement that “new drugs,” that is, drugs not Generally Recognized As Safe (“GRAS”), be approved for safety in an NDA.
 - Drugs on the market prior to that date are exempt from “new drug” status under a “grandfather clause.”
 - “Pre-1938 grandfathered drugs” are exempt from the requirement of submitting an NDA, provided the drug contains the same chemical composition, indications, and other conditions for use as the original “grandfathered drug.”
 - The active ingredients in many currently marketed drugs were first introduced, at least in some form, before June 25, 1938.

Historical Development of the FDC Act and the Different “Categories” of Drugs

- If FDA approved a drug between 1938 and 1962, FDA generally permitted Identical, Related, or Similar (“IRS”) drugs to the approved drug to be marketed without independent approval.
- Many manufacturers also introduced drugs onto the market between 1938 and 1962 based on:
 - Their own conclusion that the products were GRAS (i.e., not a “new drug”); or
 - A formal opinion from FDA that the products were not “new drugs.”

Historical Development of the FDC Act and the Different “Categories” of Drugs

- **The 1962 Drug Amendments and the Drug Efficacy Study Implementation (“DESI”) Program**
 - In 1962, Congress amended the FDC Act to require that a “new drug” be demonstrated to be effective, as well as safe, in order to obtain FDA approval.

Historical Development of the FDC Act and the Different “Categories” of Drugs

- Under a “grandfather clause” included in the 1962 Drug Amendments, a drug is exempt from the effectiveness requirement if:
 - (1) Its composition and labeling has not changed since October 10, 1962 (the date on which the 1962 Drug Amendments were enacted); and
 - (2) If, on the day before the 1962 Drug Amendments became effective, the drug was:
 - Used or sold commercially in the United States;
 - Not a “new drug” as defined by the FDC Act at that time; and
 - Not covered by an effective application.

Historical Development of the FDC Act and the Different “Categories” of Drugs

- The 1962 Drug Amendments required FDA to conduct a retrospective evaluation of the effectiveness of the drug products approved as safe between 1938 and 1962 (to which FDA added IRS drugs).
- FDA's administrative implementation of the effort was called the DESI program.

Historical Development of the FDC Act and the Different “Categories” of Drugs

- Some currently marketed products are subject to completed DESI proceedings, but nevertheless lack approved marketing applications.
 - FDA considers all of these products to be unapproved and marketed illegally, but uses its enforcement discretion.
- Some products currently on the market are unapproved but are still undergoing DESI reviews in which a final determination regarding efficacy has not yet been made.
 - Products subject to an ongoing DESI proceeding may remain on the market during the pendency of the proceeding.

Historical Development of the FDC Act and the Different “Categories” of Drugs

- “Products first marketed after a hearing notice is issued ***with a different formulation than those covered by the notice are not considered subject to the DESI proceeding. Rather, they need approval prior to marketing.*** Under longstanding Agency policies, a firm holding an NDA on a product for which a DESI hearing is pending must submit a supplement prior to reformulating that product. The changed formulation may not be marketed as a related product under the pending DESI proceeding; it is a new drug, and it must be approved for safety and efficacy before it can be legally marketed. . . . Similarly, firms without NDAs cannot market new formulations of a drug without first getting approval of an NDA.”

Historical Development of the FDC Act and the Different “Categories” of Drugs

- **The Prescription Drug Wrap-Up**
 - Drugs that did not have pre-1962 approvals or were not IRS to drugs with pre-1962 approvals were not subject to DESI.
 - For a period of time, FDA allowed these drugs to remain on the market and allowed new unapproved drugs that were IRS to these pre-1962 drugs to enter the market without approval.

Historical Development of the FDC Act and the Different “Categories” of Drugs

- In 1984, FDA assessed pre-1962 non-DESI marketed drug products. The program for addressing these products became known as the “Prescription Drug Wrap-Up.”
- FDA believes that drugs that were subject to the Prescription Drug Wrap-Up are all marketed illegally, unless a manufacturer of such a drug can establish that the drug is “grandfathered” or otherwise not a “new drug.”

Historical Development of the FDC Act and the Different “Categories” of Drugs

■ New Unapproved Drugs

- Some unapproved drugs were first marketed, or were changed, after the 1962 Drug Amendments were enacted (i.e., drugs that were not covered in the Prescription Drug Wrap-Up).
- Still other drugs are the subject of a formal “new drug” finding (e.g., timed-release drugs, and parenteral drugs in plastic containers).
- FDA has taken the position that drugs in this category are all marketed illegally and are subject to enforcement action, unless covered by an approved marketing application.

Historical Development of the FDC Act and the Different “Categories” of Drugs

- **Scope of the “Grandfather Clauses” and the GRASE Exemption**
 - The 1938 and 1962 “grandfather clauses” have been construed very narrowly by FDA and the courts.
 - FDA believes that there are few, if any, marketed drugs that are actually entitled to “grandfather” status.
 - If a company claims that its product is “grandfathered,” FDA considers it the firm’s burden to prove that assertion.

Historical Development of the FDC Act and the Different “Categories” of Drugs

■ Over-the-Counter (“OTC”) Drugs

- FDA has taken the position that OTC drugs covered by ongoing OTC monograph proceedings may remain on the market, subject to current enforcement policies.
- FDA has extended these policies to products sold as prescription drugs with ingredients under the OTC Drug Review, deferring action until the monograph is final.
- OTC drugs that require approval because their ingredients or claims are not within the scope of the OTC Drug Review, or are not allowed under a final monograph or another final rule, are illegally marketed unless they are the subject of an approved marketing application.

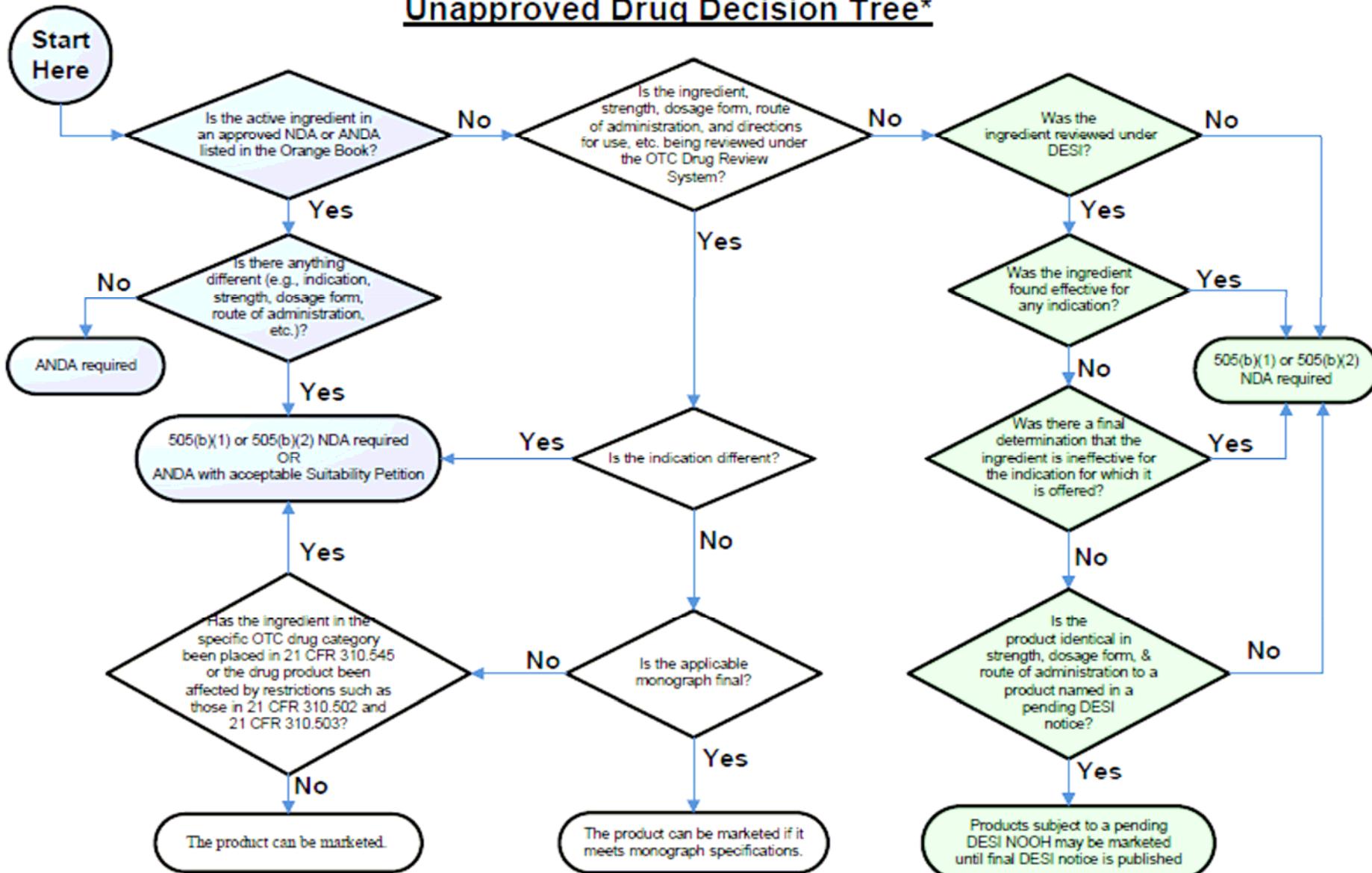
Historical Development of the FDC Act and the Different “Categories” of Drugs

- **Legally marketed drugs are those drugs:**
 - Marketed in accordance with an approved NDA (and generic copies of such drugs marketed under an approved ANDA); and
 - Drugs that are exempt from the NDA requirement, which includes:
 - Pre-1938 and pre-1962 “grandfathered” drugs;
 - Drugs subject to an ongoing DESI proceeding;
 - GRASE drugs; and
 - Drugs marketed in accordance with a final or tentative OTC drug monograph.

Historical Development of the FDC Act and the Different “Categories” of Drugs

- **Illegally marketed drugs subject to FDA enforcement action include, according to FDA:**
 - Drugs marketed outside of an OTC drug final or tentative final monograph;
 - Drugs found to be effective under DESI but for which an NDA or ANDA has not been submitted;
 - Drugs subject to a completed DESI proceeding that found them to be not effective;
 - Drugs subject to the Prescription Drug Wrap-Up;
 - New unapproved drugs; and
 - Drugs that do not meet the GRASE requirements or that differ in some respect from pre-1938 or pre-1962 “grandfathered” drugs.

Unapproved Drug Decision Tree*



FDA's CPG – What are FDA's Enforcement Policies and Priorities?

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- Draft CPG issued in October 2003.
- Final CPG issued in June 2006; Revised on September 19, 2011.
 - Supersedes CPG Manual, Sec. 450.100 –Marketed New Drugs Without Approved NDAs or ANDAs (CPG 7132c.02), as established in 1976, and subsequently amended in the 1980s and 1990s.
 - FDA revised the draft October 2003 CPG to, among other things, clarify when and how the Agency intends to exercise its enforcement discretion.
- FDA's CPG discusses the Agency's risk-based enforcement approach with regard to marketed unapproved drug products.

FDA's CPG – What are FDA's Enforcement Policies and Priorities?

- FDA gives higher priority to enforcement action against unapproved drugs in the following categories:
 - (1) Drugs with potential safety risks;
 - (2) Drugs that lack evidence of effectiveness;
 - (3) Drugs that present a “health fraud;”
 - FDA defines health fraud to mean “[t]he deceptive promotion, advertisement, distribution or sale of articles . . . that are represented as being effective to diagnose, prevent, cure, treat, or mitigate disease (or other conditions), or provide a beneficial effect on health, but which have not been scientifically proven safe and effective for such purposes. Such practices may be deliberate, or done without adequate knowledge or understanding of the article.”

FDA's CPG – What are FDA's Enforcement Policies and Priorities?

- (4) Drugs that present direct challenges to the “new drug” approval and OTC drug monograph systems;
- (5) Unapproved “new drugs” that are also violative of the FDC Act in other ways;
 - E.g., Current Good Manufacturing Practice (“CGMP”) regulation violations, misbranding, and failure to register and list; and
- (6) Drugs that are reformulated to evade an FDA enforcement action
 - E.g., when a firm, in anticipation of FDA enforcement action, changes its unapproved drug product by, for example, adding an active ingredient, in an attempt to evade such enforcement action.

FDA's CPG – What are FDA's Enforcement Policies and Priorities?

- FDA evaluates whether to initiate enforcement action on a case-by-case basis, consistent with the Agency's risk-based enforcement approach.
- FDA generally does not intend to give special or advance notice that an unapproved drug may be subject to enforcement action, but may allow a grace period using the following factors:
 - (1) the effects on the public health of proceeding immediately to remove the illegal products from the market (e.g., medically necessary drugs);
 - (2) the difficulty associated with conducting any required studies, preparing and submitting applications, and obtaining approval of an application;
 - (3) the burden on affected parties of immediately removing the products from the market;
 - (4) the Agency's available enforcement resources; and
 - (5) special circumstances relevant to the particular case under consideration (e.g., a newly approved drug).

FDA's CPG – What are FDA's Enforcement Policies and Priorities?

- Newly Approved Drugs
 - Because FDA wants to encourage the submission of marketing applications, and because the approval of a drug that is also marketed without FDA approval is a direct challenge to the integrity of the drug approval system, "FDA is more likely to take enforcement action against remaining unapproved drugs in this kind of situation."
 - In addition to the factors listed on the previous slide concerning when FDA might take enforcement action against companies marketing unapproved drugs, and how much of a grace period (if any) should generally be anticipated, FDA will also consider in the case of a newly approved drug whether the effort to obtain FDA approval was publicly disclosed.
 - FDA normally intends to allow a 1-year grace period from the date of approval before initiating enforcement action.

FDA's CPG – What are FDA's Enforcement Policies and Priorities?

- Once a risk-based assessment has been made, FDA can take any number of enforcement actions, including , for example:
 - Requesting voluntary compliance
 - Providing notice of action in a Federal Register notice
 - Issuing an Untitled Letter
 - Issuing a Warning Letter, or
 - initiating a seizure, injunction, or other proceeding.
- FDA Marketed Unapproved Drugs Website -
<http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/EnforcementActivitiesbyFDA/SelectedEnforcementActionsonUnapprovedDrugs/default.htm>.

FDA's CPG – What are FDA's Enforcement Policies and Priorities?

- Exceptions to FDA's Enforcement Policy
 - FDA has taken the position that OTC drugs covered by ongoing OTC monograph proceedings may remain on the market, subject to current enforcement policies. FDA has extended these policies to products sold as prescription drugs with ingredients under the OTC Drug Review, deferring action until the monograph is final.
 - Products subject to an ongoing DESI proceeding may remain on the market during the pendency of the proceeding.

FDA's CPG – What are FDA's Enforcement Policies and Priorities?

- Required Reporting of Adverse Events
 - FDA expects that manufacturers of unapproved prescription products will report unexpected, serious adverse events to the Agency per 21 C.F.R. § 310.305.
 - Adverse events should be reported to FDA on Form FDA 3500A, which is for use by user facilities, distributors, importers, applicants, and manufacturers for mandatory reporting of adverse events and product problems.

September 19, 2011 – The Line in the Sand

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- FDA, Notice of Compliance Policy Guide, Revised Guidance on Marketed Unapproved Drugs; Compliance Policy Guide Sec. 440.100; Marketed New Drugs Without Approved NDAs or ANDAs, 76 Fed. Reg. 58,398 (Sept. 21, 2011).
 - “Despite both the long-standing statutory requirement that new drugs must obtain approval prior to marketing (21 U.S.C. 355) and FDA's outreach efforts under the Marketed Unapproved Drugs Initiative, FDA is aware that unapproved new drugs have continued to come onto the market after the issuance of the 2006 CPG.”

September 19, 2011 – The Line in the Sand

- “In some cases, these unapproved new drugs come onto the market to compete with other unapproved new drugs that are already on the market. In other cases, unapproved new drugs are introduced to the market when a manufacturer perceives that there may be an ‘opportunity’ to gain a share of the market after actions taken by FDA, including enforcement actions that remove similar unapproved new drugs from the market.”
- “In either case, FDA must expend additional scarce resources to address unapproved products in situations where manufacturers and distributors have had ample notice that the products they are introducing onto the market cannot be legally marketed without approval.”

September 19, 2011 – The Line in the Sand

- Revised CPG:
 - For unapproved drugs commercially used or sold as of September 19, 2011, FDA's enforcement priorities described in the CPG are in effect, but

September 19, 2011 – The Line in the Sand

- “The enforcement priorities and potential exercise of enforcement discretion discussed in [the CPG] ***apply only to unapproved drug products that are being commercially used or sold as of September 19, 2011. All unapproved drugs introduced onto the market after that date are subject to immediate enforcement action at any time, without prior notice and without regard to the enforcement priorities set forth [in the CPG].*** In light of the notice provided by this guidance, we believe it is inappropriate to exercise enforcement discretion with respect to unapproved drugs that a company (including a manufacturer or distributor) begins marketing after September 19, 2011.” (Emphasis added.)

September 19, 2011 – The Line in the Sand

- FDA will likely rely on marketing information submitted to the Agency and reflected in the National Drug Code Directory to determine whether a drug product is introduced onto the market after September 19, 2011.
 - NDC Directory recently revamped to include a “Start Marketing Date” category.
- FDA Warning Letters to Glenmark Generics and Konec Inc. for marketed unapproved nitroglycerin sublingual tablets.
 - Cite to drug listing submissions as the basis for the information contained in Warning Letters.

V Challenging FDA

Challenging FDA

- Cody/Lannett v. FDA
 - Case stems from FDA's March 2009 Warning Letters to Cody/Lannett (among other companies) to stop manufacturing certain unapproved narcotic drugs, including morphine sulfate oral solutions.
 - At that time, FDA concluded that marketed unapproved morphine sulfate products are "new drugs [under the FDCA] and not grandfathered and that manufacturing and marketing of these products without an approved application constituted a violation of the Act."

Challenging FDA

- In subsequent communications with Cody/Lannett, FDA stated that the Agency would exercise enforcement discretion with regard to the shipment and distribution of Cody's/Lannett's unapproved Morphine Sulfate Solution Immediate-Release 20mg/mL drug products until July 24, 2010, which is 180 days after FDA approved Roxane's NDA for the drug product.
- Meanwhile, Lannett submitted its own NDA to FDA for Morphine Sulfate Solution Immediate-Release 20mg/mL in late February 2010.

Challenging FDA

- Cody/Lannett raised three issues in the litigation:
 - (1) FDA's alleged determination that Cody/Lannett's product is a "new drug;"
 - (2) FDA's alleged failure to develop an administrative record for its determination that Cody/Lannett's Morphine Sulfate Oral Solution 20mg/mL product is a "new drug;" and
 - (3) FDA's alleged disparate treatment of Cody/Lannett's standard review NDA compared to a competitor, which obtained priority NDA review status and NDA approval in January 2010.

Challenging FDA

- On November 16, 2010, the U.S. District Court for the District of Wyoming granted FDA's Motion to Dismiss the case.
- Judge Johnson ruled that the court "does not have jurisdiction over any of the agency actions [Cody/Lannett] ask this Court to review, as the FDA has yet to complete a final agency action," and that "[a]ny attempt to review such actions would be premature and contrary to law."

Challenging FDA

- Cody/Lannett appealed the decision to the U.S. Court of Appeals for the Tenth Circuit.
- On June 23, 2011, FDA approved Lannett Holdings, Inc.'s NDA No. 201517 for Morphine Sulfate Oral Solution, 100 mg per 5 mL (20 mg per mL).
- FDA's Motion to Dismiss the case on mootness grounds (in light of the NDA approval) has been met with opposition from Cody/Lannett.

Challenging FDA

- According to Cody/Lannett, FDA's NDA approval did not moot the case:
 - "If this appeal were to be dismissed at this point in the litigation, Cody/Lannett would be forced to endure forever the additional financial and administrative burdens of manufacturing and selling the Product under a NDA rather than as a grandfathered product. Furthermore, Cody/Lannett would never have an opportunity to obtain judicial review of their disparate treatment claim, though Cody/Lannett would suffer ongoing harm as a result of such disparate treatment. They would likely face similar disparate treatment by the FDA in the future."

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