



U.S. Food and Drug Administration

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# The Unapproved Universe

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Deborah M. Autor, Esq.

Director,

CDER Office of Compliance

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# Overview of Presentation

- Why FDA is concerned about unapproved drugs
- Legal description of the “unapproved universe”
- The unapproved drugs initiative: the 2006 CPG (“Marketed Unapproved Drugs - Compliance Policy Guide”) and the multi-pronged approach
- Workshop overview

# Why Is FDA Concerned About Unapproved Drugs?

- Physicians and consumers cannot assume that marketed drugs have been found by FDA to be safe and effective
  - even if those drugs are listed in the Physician's Desk Reference (PDR)
- Potential for drug labeling deficiencies
- Potential for drug quality deficiencies

# Why Is FDA Concerned About Unapproved Drugs?

- Limited post-market surveillance and no periodic reporting
- In some cases, there may not be a documented safety risk
  - But, the absence of proof of a problem is not proof of the absence of a problem
- Challenge the integrity of the drug approval system
  - Reduce incentives for research to prove safety/effectiveness
  - Inequitable: unapproved drugs compete unfairly with approved ones

# **“Unapproved Universe” Legal Description: Introduction**

- FDA estimates that there are several thousand illegal marketed unapproved drugs
- Three main categories of marketed unapproved drugs
  - DESI Drugs
  - Prescription “Wrap-Up”
  - Post '62 Drugs

# “Unapproved Universe” Legal Description: Details

- DESI Drugs
  - DESI means Drug Efficacy Study Implementation
  - Refers to drugs that were the subject of 1938-1962 NDAs (safety only) and drugs that are identical, related, and similar to such drugs
  - DESI drugs are *not* “grandfathered” or generally recognized as safe and effective (GRAS/E)
- Prescription “Wrap-Up”
  - Refers to drugs that are on the market based on a claim of being a pre-’38 or pre-’62 product or identical, related, or similar to such a product
- Post ’62 Drugs
  - Drugs initially marketed after 1962

# **“Unapproved Universe” Legal Description: Bottom Line**

- All drugs must have FDA approval or comply with an Over the Counter monograph, unless:
  - DESI pending or OTC monograph pending
    - Less than 20 DESI proceedings pending (out of almost 600)
    - Many OTC monographs have been finalized
  - Generally recognized as safe and effective (GRAS/E)
    - The agency believes it is not likely that any currently marketed prescription drug is GRAS/E
    - For example, a GRAS/E finding requires a consensus among experts that the product is safe and effective based on published scientific literature regarding the finished drug product of the same quality and quantity needed to approve a drug

# **“Unapproved Universe” Legal Description: Bottom Line**

- All drugs must have FDA approval or comply with an Over the Counter monograph, unless:
  - Grandfathered
    - The agency believes it is not likely that any currently marketed prescription drug is grandfathered
    - For example, for grandfather status, a firm must document that its product is identical in formulation, strength, dosage form, route of administration, indications, intended patient population, and other conditions of use to a drug marketed on the relevant date for the 1938 or 1962 grandfather clause
    - For the 1962 grandfather clause, the firm must also document that the drug was GRAS in 1962 based on published scientific literature

# The Unapproved Drugs Initiative: Goals of the 2006 CPG

- Improve the safety of the drug supply by enforcement and by bolstering incentives to submit applications for marketed unapproved drugs
- Encourage companies to comply with the drug approval process, while minimizing disruption to the marketplace
- Provide notice that any product that is being marketed illegally is subject to FDA enforcement action at any time (CPG, page 4)

# The Unapproved Drugs Initiative: Enforcement Priorities in the CPG

- For all unapproved drugs (DESI, Wrap-Up, Post-62):
  - Drugs with potential safety risks
  - Drugs that lack evidence of effectiveness
  - Fraudulent drugs
  - Unapproved drugs that directly compete with an approved drug
  - Drugs from manufacturers that are otherwise violating the Act
    - Examples: GMP violations, ADE reporting violations
  - Drugs with formulation changes made as a pretext to avoid enforcement

# The Unapproved Drugs Initiative: Multi-Pronged Approach

- FDA is committed to tackling the unapproved drugs problem
- The agency's multi-pronged approach includes
  - Enforcement
  - Education
  - Incentives
  - Other Measures

# Workshop Overview: Why

- Product of the CDER/ORA unapproved drugs working group that meets weekly to further this initiative
- Modeled on questions frequently asked by industry
- Intent is to educate, especially small businesses
- We hope that, with education and incentives, companies will take the initiative to get approval, and enforcement will be necessary in fewer cases

# Workshop Overview: What

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- We will talk in generalities today
- Specific scientific questions will need to be addressed to the relevant Division of the Office of New Drugs
- Legal questions can be addressed to the Office of Compliance

# Workshop Overview: Agenda

- Regulatory Pathways for Legal Marketing
  - OTC Monograph
  - ANDA
  - NDA (505(b)(1) and 505(b)(2))
- Other Important Issues for Applicants
  - Chemistry, Manufacturing, and Controls
  - Pediatric Considerations
  - Exclusivities
  - User Fees and Waivers
  - Role of the Unapproved Drugs Coordinator

# Workshop Overview: Spectrum of Uncertainty

From

- Active ingredients that are unknown (from FDA's regulatory standpoint), such as
  - New molecule never previously approved

To

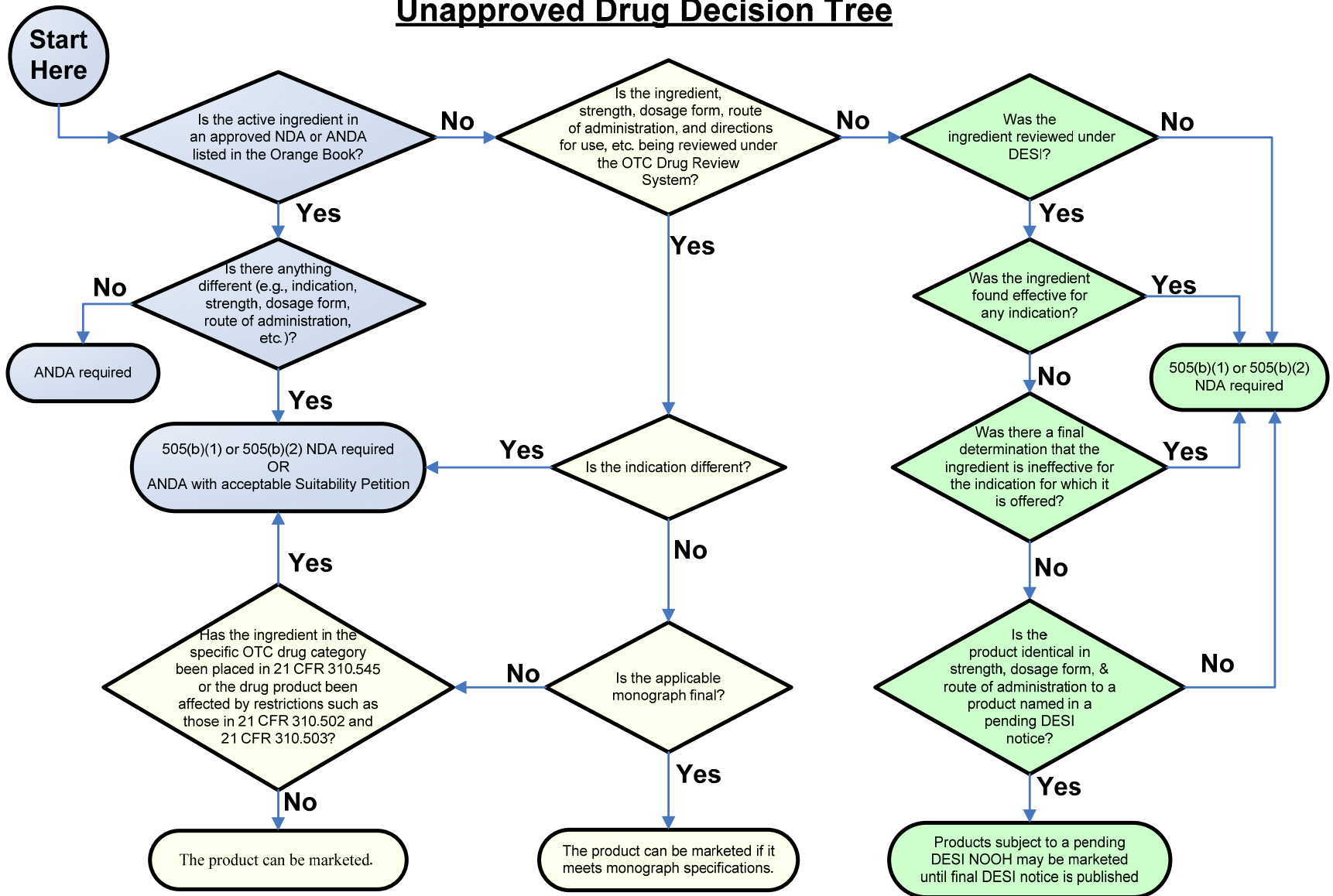
- Active ingredients that are well known, such as
  - Already approved for another firm
  - DESI final effective (or those identical, related, or similar to it)

# Workshop Overview: Use of the Decision Tree

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- Simply a guide
- Will become more clear during the course of the day

## Unapproved Drug Decision Tree



# Workshop Overview: Conclusion

- We can only brush the surface today, but we hope this workshop will help manufacturers of unapproved drugs to understand how to comply with the law
- Slides and links to relevant guidances will be posted on the unapproved drugs web page: [www.fda.gov/cder/drug/unapproved\\_drugs](http://www.fda.gov/cder/drug/unapproved_drugs)