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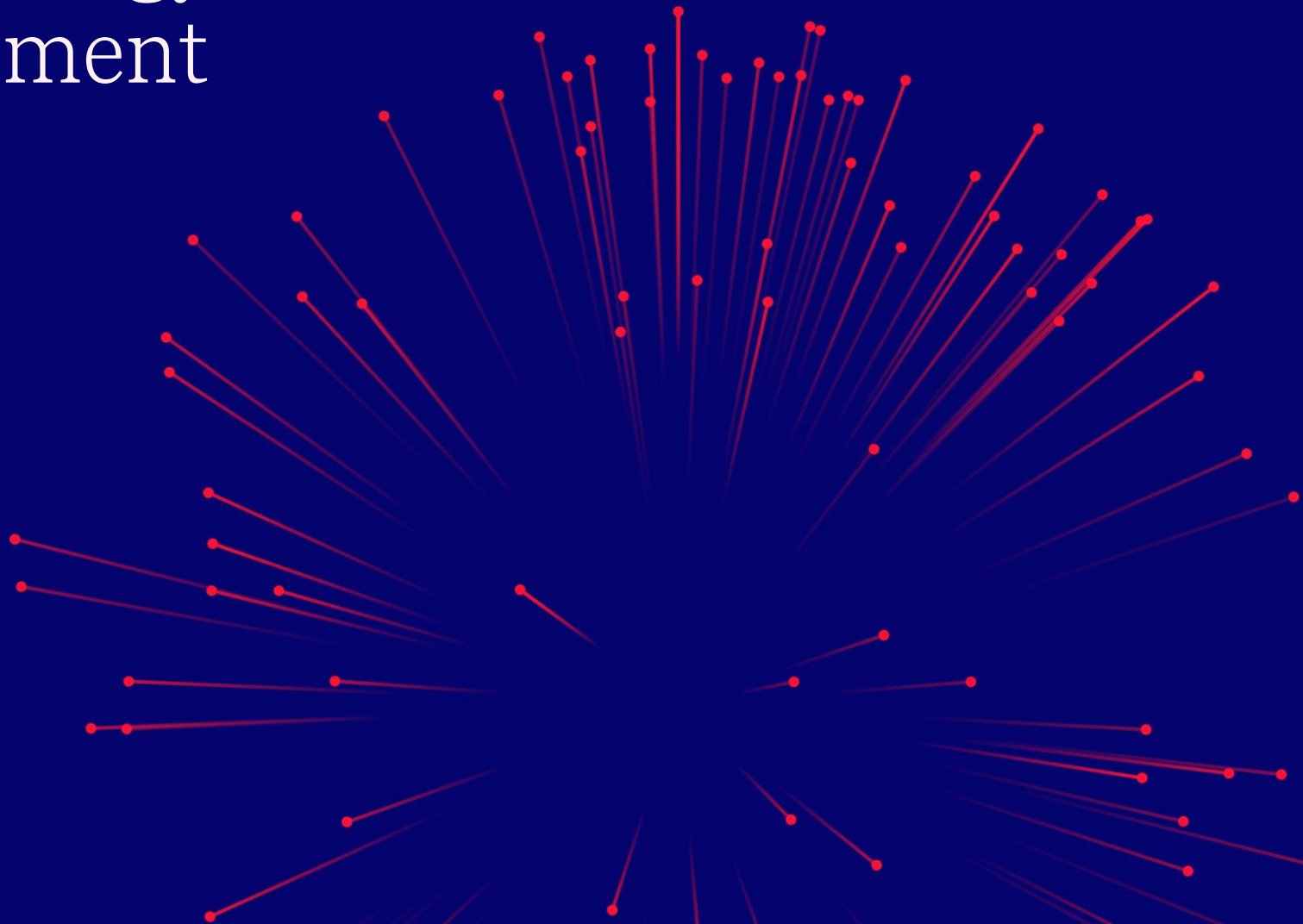
# The Interplay Between Regulatory and IP Strategy During Drug Development and Beyond

**2025 – 2026 Legal Insights: A CLE Webinar Series**



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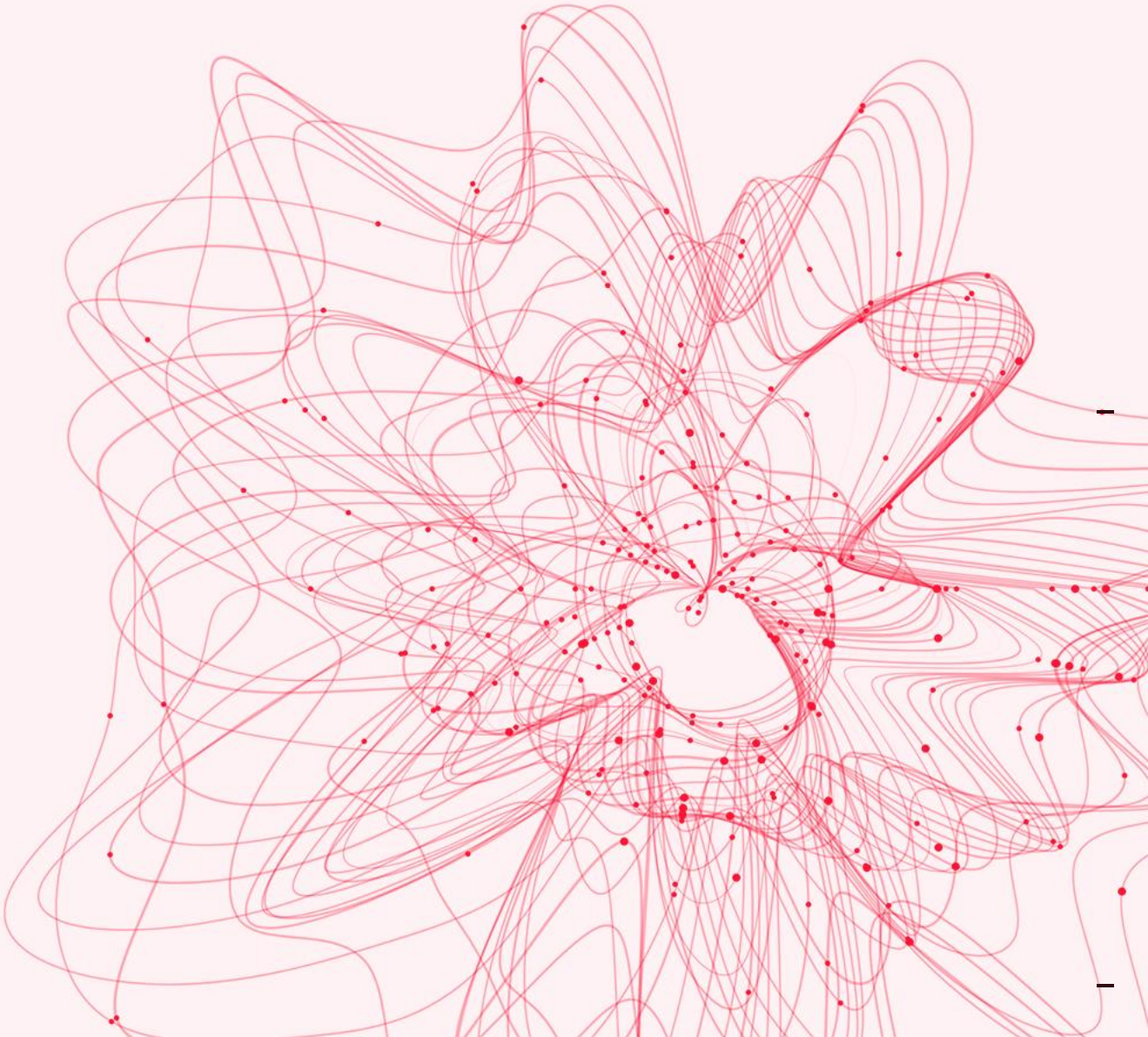
# Background



# Hatch Waxman Act: A Policy Compromise

"The Hatch-Waxman Act strikes a balance between two potentially competing policy interests—inducing pioneering development of pharmaceutical formulations and methods and facilitating efficient transition to a market with low cost, generic copies of those pioneering inventions at the close of a patent term."

*Novo Nordisk A/S, et al. v. Caraco Pharmaceutical Laboratories, Ltd.*, 601 F.3d 1359, 1360 (Fed. Cir. 2010).

# What Each Side Got

**New Chemical Entity Exclusivity (NCE):**

- 5 years of exclusivity for a drug product that contains a new chemical entity
- **Precludes submission** of a 505(b)(2) or ANDA application for a drug product with the same active moiety
- An ANDA or 505(b)(2) application can be submitted in year 4 with a Paragraph 4 certification if the NDA has patentslisted in the Orange Book

**New Clinical Investigation Exclusivity (NCI):**

- 3 years of exclusivity to NDAs and supplemental NDAs that contain new clinical investigations (other than bioavailabilitystudies) essential to approval of the application.
- FDA may accept and review ANDA or 505(b)(2) applications but **cannot grant full approval** until the exclusivity ends.

**180-Day Exclusivity for Generic Drugs:**

- 180-day exclusivity for the first applicant to file an ANDA that contains a Paragraph IV certification.
- **Precludes approval** of subsequent ANDAs during this 180-day period
- **Biological Product Exclusivity: Blocks submission** of biosimilar application **for 4 years and approval** of a biosimilar application **for12 years** from date of first licensure

# Other Regulatory Exclusivities

**Pediatric Exclusivity:**

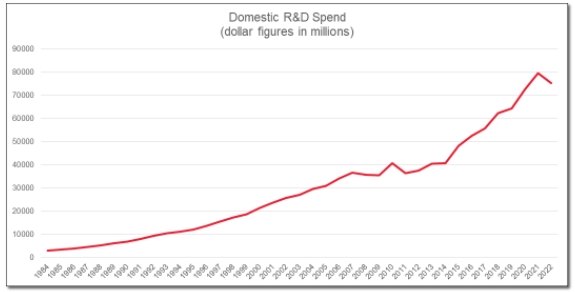
- Adds 6 months of exclusivity to the end of listed patents or other regulatory exclusivities for sponsors that conduct a pediatric study at FDA's written request
- Does not extend the patent term but **precludes FDA from approving** a 505(b)(2), ANDA, or Section 351(k) biosimilar application during the 6-month period

**Orphan Drug Exclusivity (ODE)**:

- 7 years of exclusivity for use in the rare disease or condition for which it was designated.
- A rare disease or condition affects less than 200,000 people in the United States; orphan subsets may also be eligible
- During the exclusivity period, FDA **will not approve** another application for “same drug” for the “same disease or condition” unless clinically superior

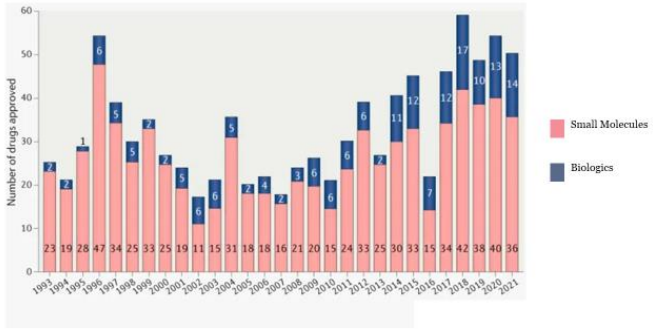
# Hatch Waxman Act has been Wildly Successful

## Branded Research and Development




2023 PhRMA Annual Membership Survey 20

## New Drugs Approved

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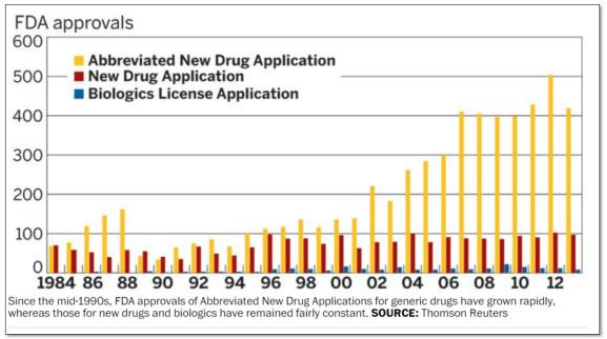
## Approved Generic Products




Since the mid-1990s, FDA approvals of Abbreviated New Drug Applications for generic drugs have grown rapidly, whereas those for new drugs and biologics have remained fairly constant. **SOURCE:** Thomson Reuters

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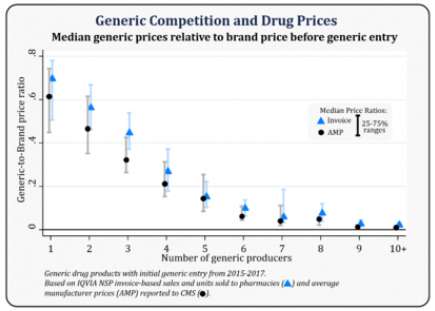
## Effect of Generic Entry on Brand Prices




https://www.fda.gov/about-fda/center-drug-evaluation-and-research-cder/generic-competition-and-drug-prices 23

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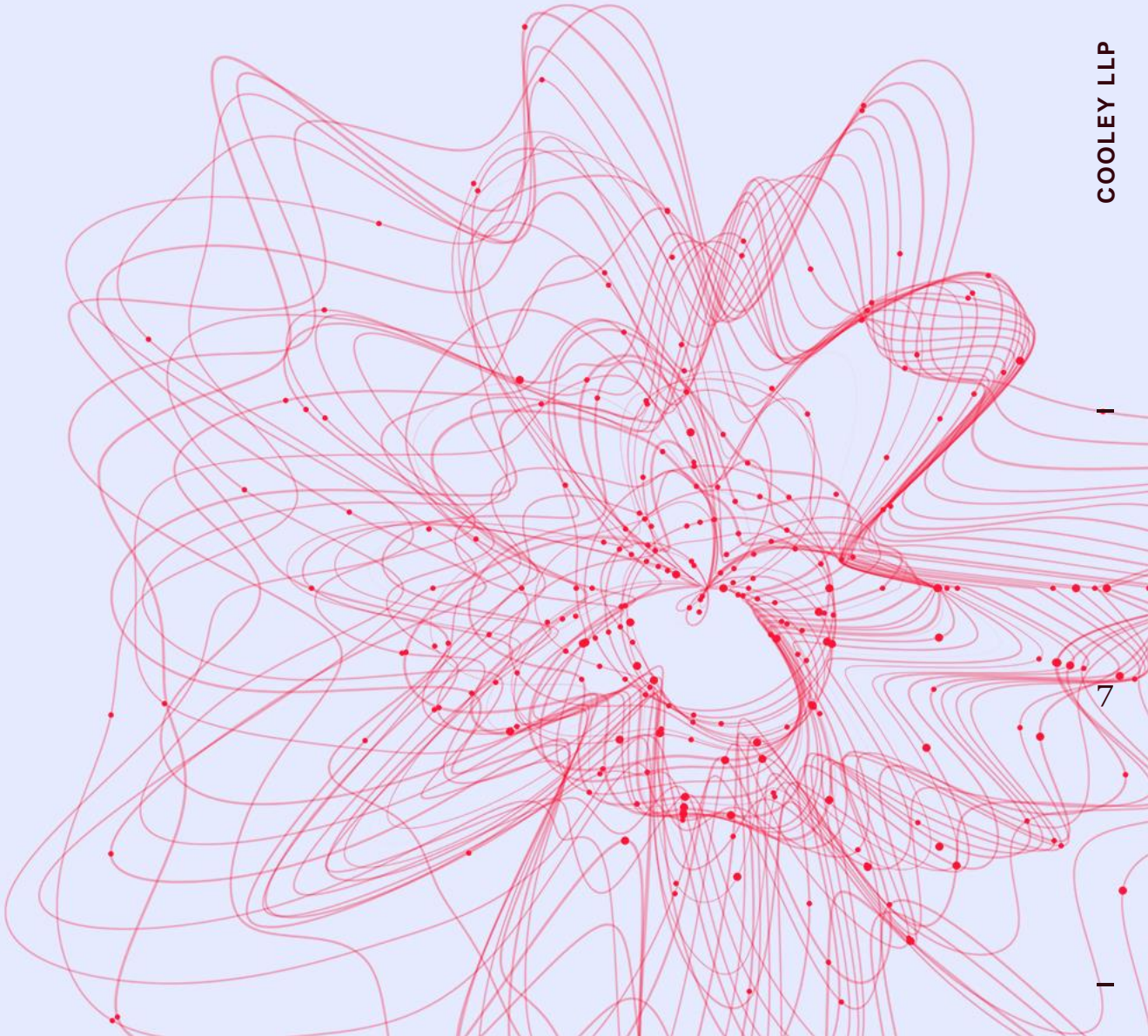
# Drug Development



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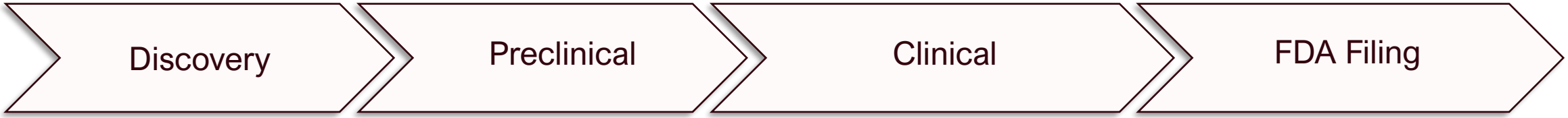
# Modern Day Drug Development



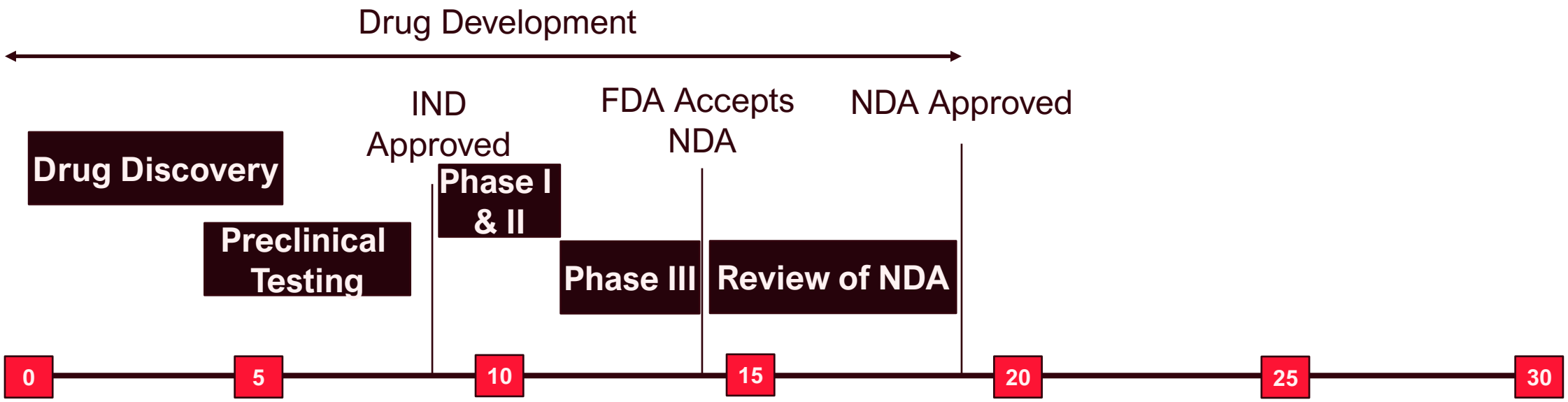

- Target Selection
- Lead Compound
- SAR optimization
- Pharmacological assessment

- Toxicology
- Formulation
- Pharmacokinetics
- Large scale synthesis

- Phase I
  - Safety in volunteers, PK studies
- Phase II
  - Smaller scale trials in patients to assess efficacy
  - Longer term tox studies
- Phase III
  - Large scale clinical trials assessing efficacy and safety

- Comprehensive data analyzed and submitted to FDA

# A Drug's Life


Drug Development
IND Approved
FDA Accepts NDA
NDA Approved
Drug Discovery
Preclinical Testing
Phase I & II
Phase III
Review of NDA
0
5
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25
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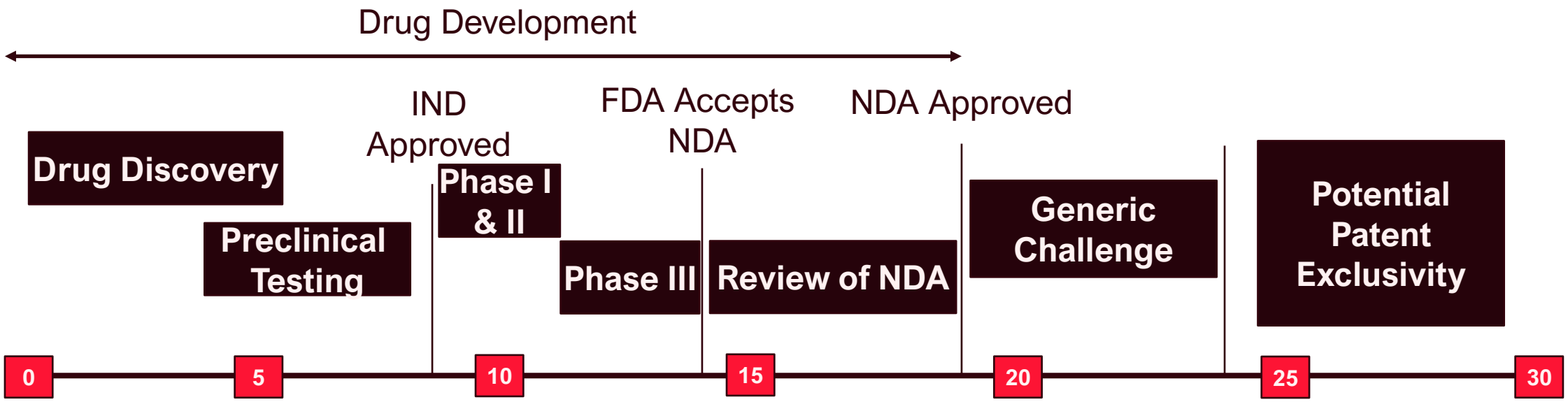
# Typical Types of Patents

- Orange Book-Listed Patents
  - Compound
  - Formulation
  - Methods of Treatment
  - Crystalline Form/Polymorph
- Devices (sometimes listable)
- Process Patents
- Metabolite Patents

# A Drug's Life


Drug Development
IND Approved
FDA Accepts NDA
NDA Approved
Drug Discovery
Preclinical Testing
Phase I & II
Phase III
Review of NDA
Generic Challenge
Potential Patent Exclusivity
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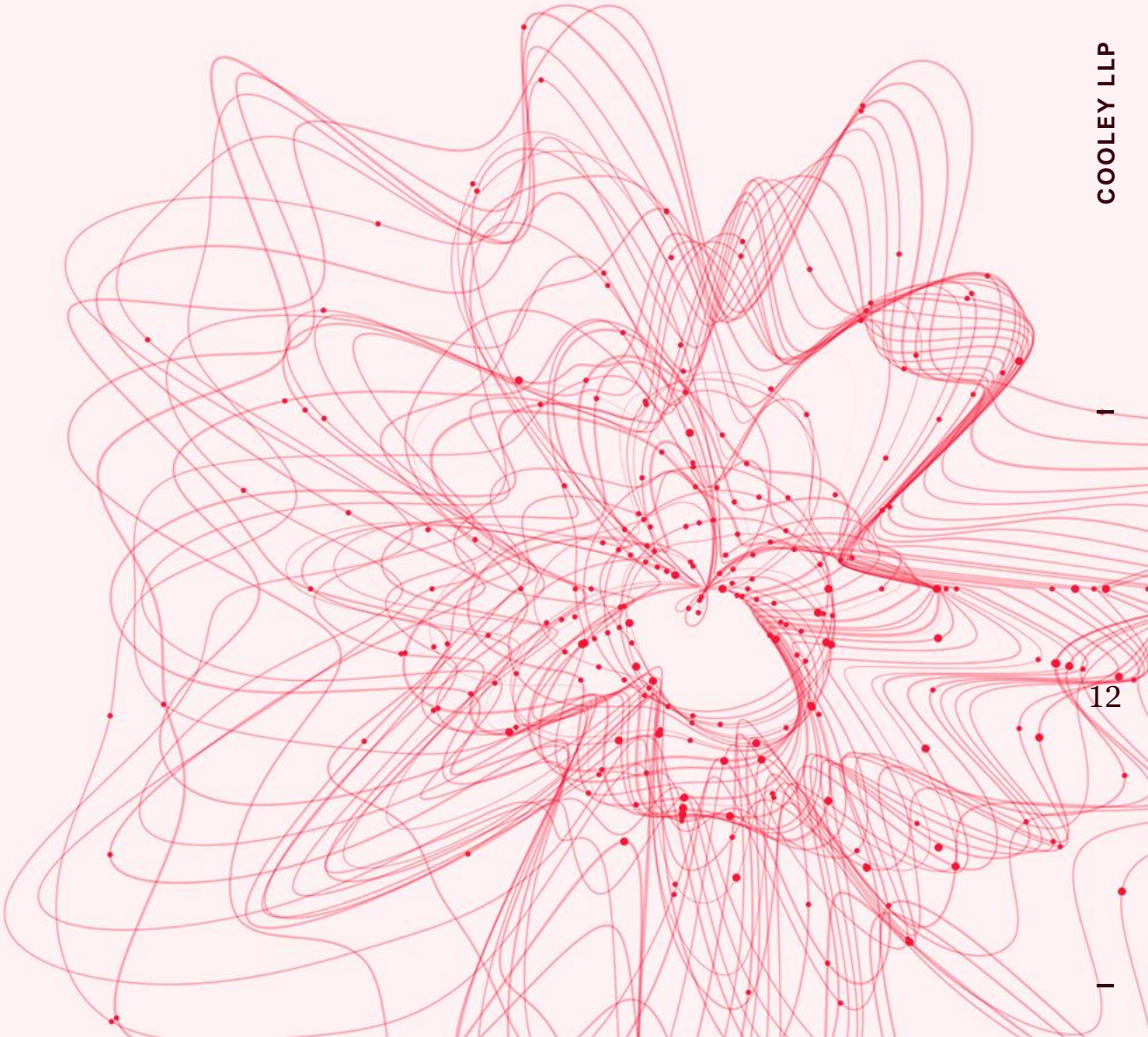
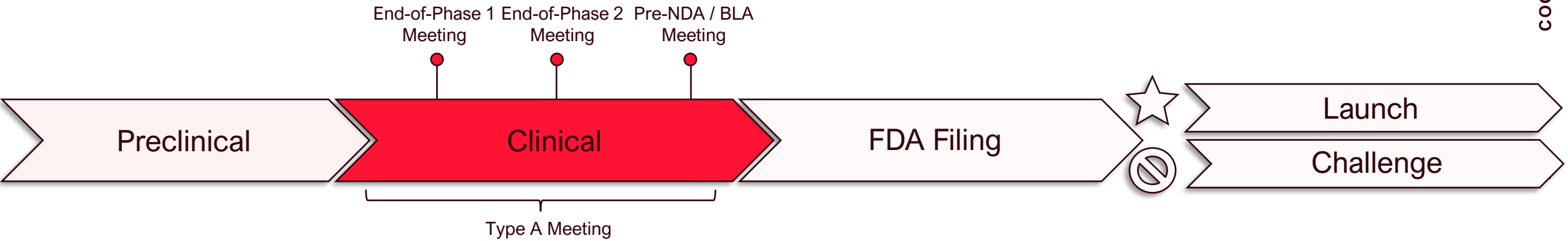
# FDA



# Lifecycle of an FDA-Regulated Product

## Clinical Phase




- **End-of-Phase 1 Meeting:** For biologics that treat life-threatening and debilitating illnesses or drugs under accelerated approval for serious/life-threatening illnesses, discuss proposed phase 2 protocol, identify population for phase 3 trials
- **End-of-Phase 2 Meeting:** Discuss trial designs, modeling strategies, and clinical trial simulation
- **Pre NDA/BLA Meeting:** "Preview" of general information to be provided in application, discuss appropriate methods for statistical analysis approach to presentation and formatting of the data
- **Type A Meeting:** To discuss otherwise stalled product development or address an important safety issue

# FDA Formal Meeting Types

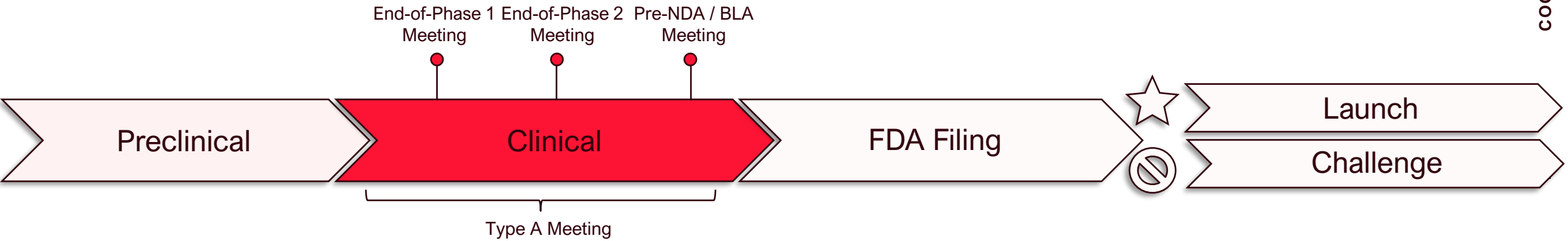
Each of the four meeting types has different aims and procedures.

| | Type A | Type B | Type C | Type D |
|---|---|---|---|---|
| **Purpose / Aims**  | • Scheduled to help an otherwise stalled product development program including dispute resolution. | • Pre-investigational new drug application (Pre-IND) meetings<br>• Pre-new drug application/biologics license (Pre-NDA/BLA) application meetings<br>• Certain end-of-phase 1 meetings<br>• End-of-phase 2 and Pre-phase 3 meetings<br>• Development for breakthrough designation products | • Any meeting other than a Type A or Type B regarding the development and review of a product. | • Focused on a narrow set of issues (Ideally no more than 2 focused topics) and should not require input from more than 3 disciplines or Divisions. |
| **Timing**  | • Typically scheduled to occur within **30 days** of FDA receipt of a meeting request.<br>• FDA will grant or deny the request within 14 days of receipt | • Typically scheduled to occur within **60 days** of FDA receipt of the meeting request.<br>• FDA will grant or deny the request within 21 days of receipt | • Typically scheduled to occur within **75 days** of FDA receipt of the meeting request.<br>• FDA will grant or deny the request within 21 days of receipt | • Typically scheduled to occur within 50 days of receipt of the meeting request<br>• FDA will respond within 14 days of receipt. |

*See*, U.S. Food and Drug Admin., *Guidance for Industry Formal Meetings Between the FDA and Sponsors or Applicants (2017), https://www.fda.gov/media/109951/download; SOPP 8101.1: Regulatory Meetings with Sponsors and Applicants for Drugs and Biological Products (Mar, 2023), https://www.fda.gov/media/84040/download#:~:text=Type%20D%20Meeting%20-%20A%20meeting,than%203%20disciplines%20or%20Divisions.*

# Lifecycle of an FDA-Regulated Product

## Clinical Phase




**Patent Opportunities:**

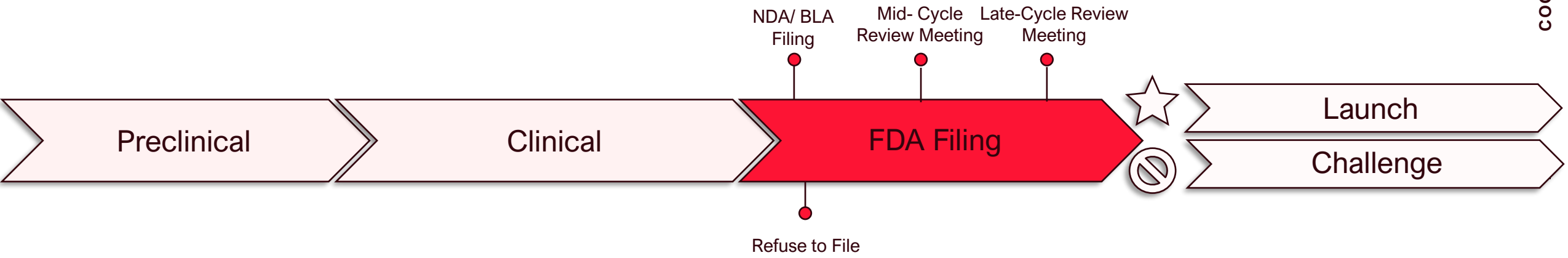
- Formulation
- Pharmacokinetics/Pharmacodynamics
- Dosing Regimen
- Method of treatment
- Large Scale production
- Crystalline form/polymorphs

**Coordination Opportunities:**

- Label (Product Insert)
  - Indication and usage
  - Clinical trials
  - Patient counseling
- Investigator's Brochure
- Formulation
- Manufacturing concerns
- Stability

# Lifecycle of an FDA-Regulated Product

## Submission and FDA Review

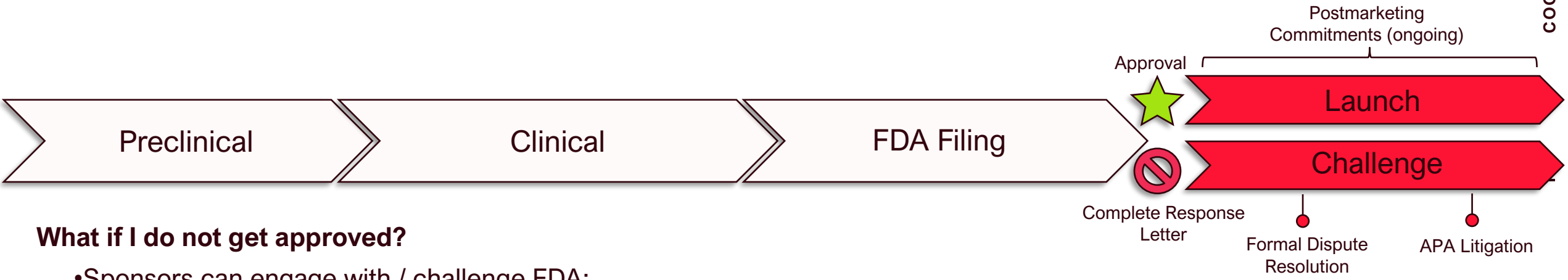



**What are the steps once I submit?**

- **Refuse to File:** FDA may refuse to file if application is incomplete or not submitted in the proper form/format
- **Mid-Cycle Review Meeting:** Discuss review status, flag issues, update timelines, determination on need for post-marketing commitments including REMS.
- **Late Cycle Review Meeting:** Topics can include major deficiencies identified, potential issues to be discussed by an Advisory Committee, status update of FDA review activities
- **Label Negotiations:** Negotiation of the drug's final package label with FDA.

# Lifecycle of an FDA-Regulated Product

## Post-FDA Decision




**What if I do not get approved?**

- Sponsors can engage with / challenge FDA:
  - **Formal Dispute Resolution:** Sponsor / Applicant can obtain formal review to resolve scientific or medical disputes by the supervisor of the employee who made the decision
  - **Administrative Procedures Act (APA) Litigation:** Challenge FDA in court for arbitrary or capricious actions or ctions that exceed the agency's statutory authority. Post *Loper-Bright* such challenges may be more likely but also require sponsors to more seriously consider intervening

**What if I get approved with the label I want?**

- Sue competitors for infringement

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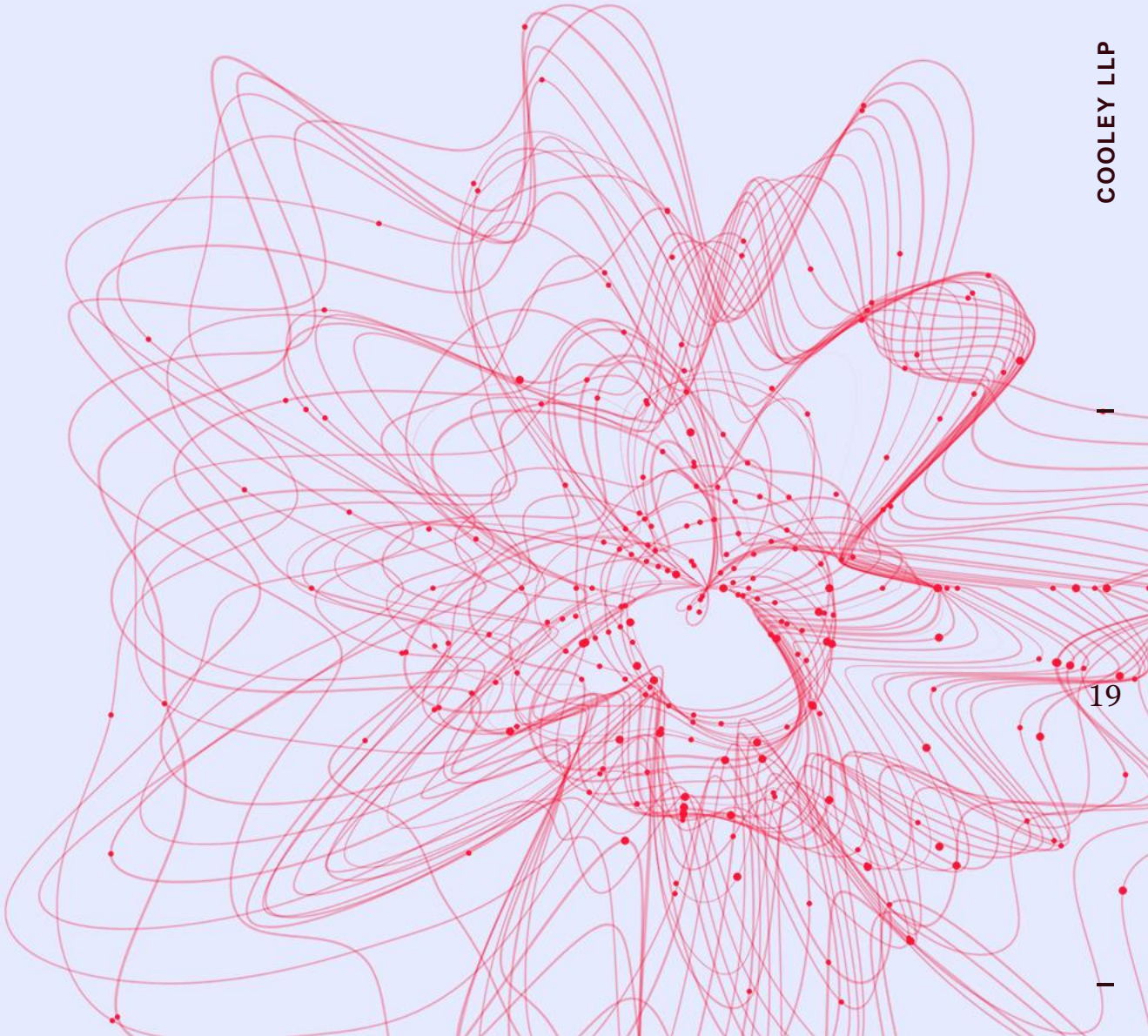
# The Importance of the Label

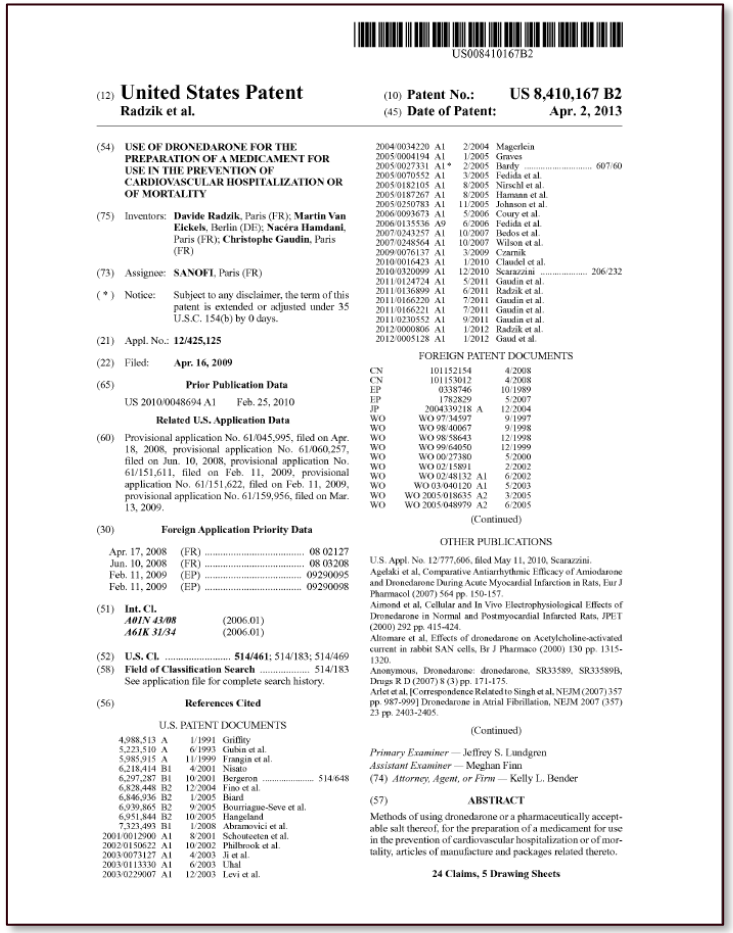


# Induced Infringement

"[F]or a court to find induced infringement, it must be established that the defendant possessed specific intent to encourage another's infringement . . . When proof of intent to encourage depends on the label accompanying the marketing of a drug, the label must encourage, recommend, or promote infringement."

*Sanofi v. Watson Lab'ys Inc.*, 875 F.3d 636, 644 (Fed. Cir. 2017) (internal quotations and citations omitted).

# Induced Infringement



US008410167B2

(12) **United States Patent**
**Radzik et al.**

(10) **Patent No.: US 8,410,167 B2**
(45) **Date of Patent: Apr. 2, 2013**

(54) **USE OF DRONEDARONE FOR THE PREPARATION OF A MEDICAMENT FOR USE IN THE PREVENTION OF CARDIOVASCULAR HOSPITALIZATION OR OF MORTALITY**

(75) Inventors: **Davide Radzik**, Paris (FR); **Martin Van Eickels**, Berlin (DE); **Nacéra Hamdani**, Paris (FR); **Christophe Gaudin**, Paris (FR)

(73) Assignee: **SANOFI**, Paris (FR)

( * ) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 0 days.

(21) Appl. No.: **12/425,125**

(22) Filed: **Apr. 16, 2009**

(65) **Prior Publication Data**

US 2010/0048694 A1 Feb. 25, 2010

**Related U.S. Application Data**

(60) Provisional application No. 61/045,995, filed on Apr. 18, 2008, provisional application No. 61/060,257, filed on Jun. 10, 2008, provisional application No. 61/151,611, filed on Feb. 11, 2009, provisional application No. 61/151,622, filed on Feb. 11, 2009, provisional application No. 61/159,956, filed on Mar. 13, 2009.

(30) **Foreign Application Priority Data**

Apr. 17, 2008 (FR) ..... 08 02127
Jun. 10, 2008 (FR) ..... 08 03208
Feb. 11, 2009 (EP) ..... 09290095
Feb. 11, 2009 (EP) ..... 09290098

(51) **Int. Cl.**
***A01N 43/08*** (2006.01)
***A61K 31/34*** (2006.01)

(52) **U.S. Cl.** ..... **514/461**; 514/183; 514/469
(58) **Field of Classification Search** ..... 514/183
See application file for complete search history.

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(Continued)

*Primary Examiner* — Jeffrey S. Lundgren
*Assistant Examiner* — Meghan Finn
(74) *Attorney, Agent, or Firm* — Kelly L. Bender

(57) **ABSTRACT**

Methods of using dronedarone or a pharmaceutically acceptable salt thereof, for the preparation of a medicament for use in the prevention of cardiovascular hospitalization or of mortality, articles of manufacture and packages related thereto.

**24 Claims, 5 Drawing Sheets**

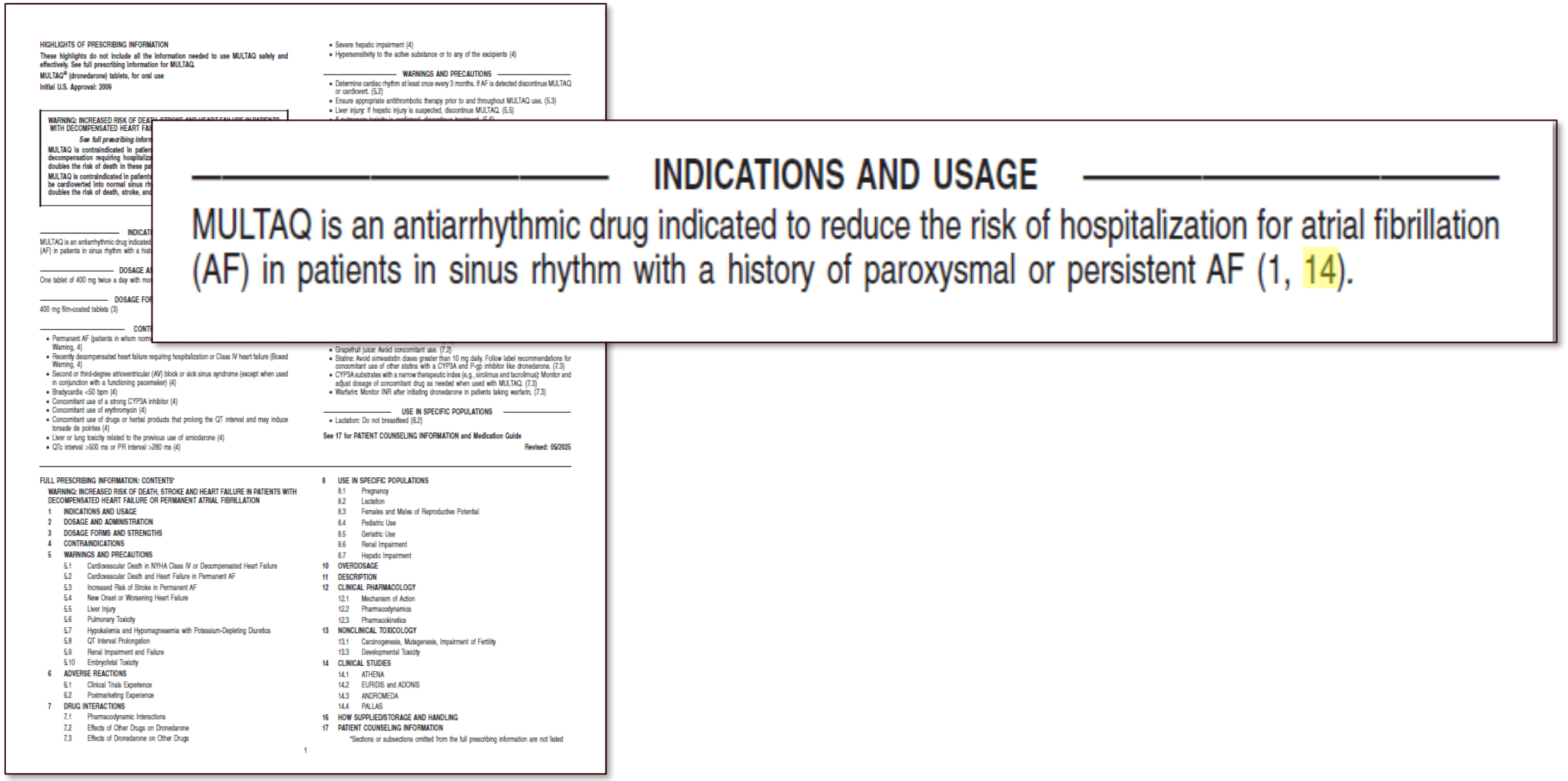
What is claimed is:

**1**. A method of decreasing a risk of cardiovascular hospitalization in a patient, said method comprising administering to said patient an effective amount of dronedarone or a pharmaceutically acceptable salt thereof, twice a day with a morning and an evening meal, wherein said patient does not have severe heart failure, (i) wherein severe heart failure is indicated by: a) NYHA Class IV heart failure or b) hospitalization for heart failure within the last month; and (ii) wherein said patient has a history of, or current, paroxysmal or persistent non-permanent atrial fibrillation or flutter; and (iii) wherein the patient has at least one cardiovascular risk factor selected from the group consisting of:

i. an age greater than or equal to 75;
ii. hypertension;
iii. diabetes;
iv. a history of cerebral stroke or of systemic embolism;
v. a left atrial diameter greater than or equal to 50 mm; and
vi. a left ventricular ejection fraction less than 40%.

**2**. The method according to claim **1**, wherein said cardiovascular hospitalization is hospitalization for atrial fibrillation.

# Induced Infringement



HIGHLIGHTS OF PRESCRIBING INFORMATION

**These highlights do not include all the information needed to use MULTAQ safely and effectively. See full prescribing information for MULTAQ.**

**MULTAQ® (dronedarone) tablets, for oral use**

**Initial U.S. Approval: 2009**

WARNING: INCREASED RISK OF DEATH, STROKE AND HEART FAILURE IN PATIENTS WITH DECOMPENSATED HEART FAILURE OR PERMANENT ATRIAL FIBRILLATION

*See full prescribing information for complete boxed warning.*

MULTAQ is contraindicated in patients with NYHA Class IV heart failure or decompensated heart failure requiring hospitalization because it doubles the risk of death in these patients. (4)

MULTAQ is contraindicated in patients in atrial fibrillation who will be cardioverted into normal sinus rhythm because it doubles the risk of death, stroke, and heart failure. (4)

## INDICATIONS AND USAGE

MULTAQ is an antiarrhythmic drug indicated to reduce the risk of hospitalization for atrial fibrillation (AF) in patients in sinus rhythm with a history of paroxysmal or persistent AF (1, 14).

## DOSAGE AND ADMINISTRATION

One tablet of 400 mg twice a day with meals (2.1)

## DOSAGE FORMS AND STRENGTHS

400 mg film-coated tablets (3)

## CONTRAINDICATIONS

- Permanent AF (patients in whom normal sinus rhythm cannot be maintained) (4, Boxed Warning, 4)
- Recently decompensated heart failure requiring hospitalization or Class IV heart failure (Boxed Warning, 4)
- Second or third-degree atrioventricular (AV) block or sick sinus syndrome (except when used in conjunction with a functioning pacemaker) (4)
- Bradycardia <50 bpm (4)
- Concomitant use of a strong CYP3A inhibitor (4)
- Concomitant use of erythromycin (4)
- Concomitant use of drugs or herbal products that prolong the QT interval and may induce torsade de pointes (4)
- Liver or lung toxicity related to the previous use of amiodarone (4)
- QTc interval >500 ms or PR interval >280 ms (4)
- Severe hepatic impairment (4)
- Hypersensitivity to the active substance or to any of the excipients (4)

## WARNINGS AND PRECAUTIONS

- Determine cardiac rhythm at least once every 3 months. If AF is detected discontinue MULTAQ or cardiovert. (5.2)
- Ensure appropriate antithrombotic therapy prior to and throughout MULTAQ use. (5.3)
- Liver injury: If hepatic injury is suspected, discontinue MULTAQ. (5.5)
- [illegible] confirmed, discontinue treatment. (5.6)
- Grapefruit juice: Avoid concomitant use. (7.2)
- Statins: Avoid simvastatin doses greater than 10 mg daily. Follow label recommendations for concomitant use of other statins with a CYP3A and P-gp inhibitor like dronedarone. (7.3)
- CYP3A substrates with a narrow therapeutic index (e.g., sirolimus and tacrolimus): Monitor and adjust dosage of concomitant drug as needed when used with MULTAQ. (7.3)
- Warfarin: Monitor INR after initiating dronedarone in patients taking warfarin. (7.3)

## USE IN SPECIFIC POPULATIONS

- Lactation: Do not breastfeed (8.2)

**See 17 for PATIENT COUNSELING INFORMATION and Medication Guide**

**Revised: 05/2025**

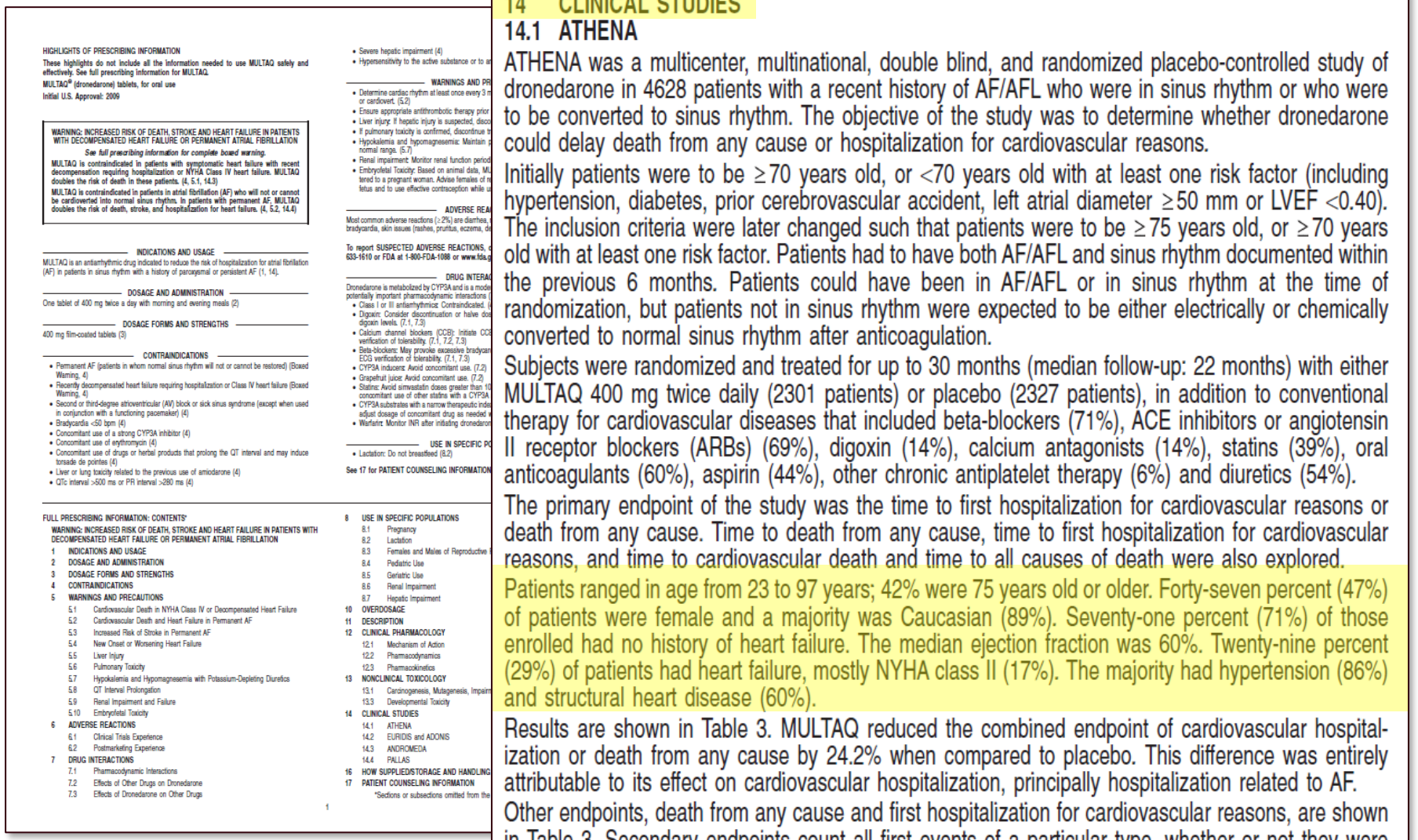
FULL PRESCRIBING INFORMATION: CONTENTS*



*Sections or subsections omitted from the full prescribing information are not listed

1

# Induced Infringement



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MULTAQ® (dronedarone) tablets, for oral use

Initial U.S. Approval: 2009

WARNING: INCREASED RISK OF DEATH, STROKE AND HEART FAILURE IN PATIENTS WITH DECOMPENSATED HEART FAILURE OR PERMANENT ATRIAL FIBRILLATION

*See full prescribing information for complete boxed warning.*

MULTAQ is contraindicated in patients with symptomatic heart failure with recent decompensation requiring hospitalization or NYHA Class IV heart failure. MULTAQ doubles the risk of death in these patients. (4, 5.1, 14.3)

MULTAQ is contraindicated in patients in atrial fibrillation (AF) who will not or cannot be cardioverted into normal sinus rhythm. In patients with permanent AF, MULTAQ doubles the risk of death, stroke, and hospitalization for heart failure. (4, 5.2, 14.4)

INDICATIONS AND USAGE

MULTAQ is an antiarrhythmic drug indicated to reduce the risk of hospitalization for atrial fibrillation (AF) in patients in sinus rhythm with a history of paroxysmal or persistent AF (1, 14).

DOSAGE AND ADMINISTRATION

One tablet of 400 mg twice a day with morning and evening meals (2)

DOSAGE FORMS AND STRENGTHS

400 mg film-coated tablets (3)

CONTRAINDICATIONS

- Permanent AF (patients in whom normal sinus rhythm will not or cannot be restored) (Boxed Warning, 4)
- Recently decompensated heart failure requiring hospitalization or Class IV heart failure (Boxed Warning, 4)
- Second or third-degree atrioventricular (AV) block or sick sinus syndrome (except when used in conjunction with a functioning pacemaker) (4)
- Bradycardia <50 bpm (4)
- Concomitant use of a strong CYP3A inhibitor (4)
- Concomitant use of erythromycin (4)
- Concomitant use of drugs or herbal products that prolong the QT interval and may induce torsade de pointes (4)
- Liver or lung toxicity related to the previous use of amiodarone (4)
- QTc interval >500 ms or PR interval >280 ms (4)

FULL PRESCRIBING INFORMATION: CONTENTS*



*Sections or subsections omitted from the

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- Severe hepatic impairment (4)
- Hypersensitivity to the active substance or to a

WARNINGS AND PR

- Determine cardiac rhythm at least once every 3 m or cardiovert. (5.2)
- Ensure appropriate antithrombotic therapy prior
- Liver injury: If hepatic injury is suspected, disco
- If pulmonary toxicity is confirmed, discontinue tr
- Hypokalemia and hypomagnesemia: Maintain normal range. (5.7)
- Renal impairment: Monitor renal function period
- Embryofetal Toxicity: Based on animal data, MU tered to a pregnant woman. Advise females of re fetus and to use effective contraception while u

ADVERSE REA

Most common adverse reactions (≥2%) are diarrhea, bradycardia, skin issues (rashes, pruritus, eczema, de

To report SUSPECTED ADVERSE REACTIONS, c 633-1610 or FDA at 1-800-FDA-1088 or www.fda.g

DRUG INTERA

Dronedarone is metabolized by CYP3A and is a mode potentially important pharmacodynamic interactions (

- Class I or III antiarrhythmics: Contraindicated. (
- Digoxin: Consider discontinuation or halve dos digoxin levels. (7.1, 7.3)
- Calcium channel blockers (CCB): Initiate CC verification of tolerability. (7.1, 7.2, 7.3)
- Beta-blockers: May provoke excessive bradycar ECG verification of tolerability. (7.1, 7.3)
- CYP3A inducers: Avoid concomitant use. (7.2)
- Grapefruit juice: Avoid concomitant use. (7.2)
- Statins: Avoid simvastatin doses greater than 10 concomitant use of other statins with a CYP3A
- CYP3A substrates with a narrow therapeutic inde adjust dosage of concomitant drug as needed
- Warfarin: Monitor INR after initiating dronedaron

USE IN SPECIFIC PO

- Lactation: Do not breastfeed (8.2)

See 17 for PATIENT COUNSELING INFORMATION

## 14 CLINICAL STUDIES

### 14.1 ATHENA

ATHENA was a multicenter, multinational, double blind, and randomized placebo-controlled study of dronedarone in 4628 patients with a recent history of AF/AFL who were in sinus rhythm or who were to be converted to sinus rhythm. The objective of the study was to determine whether dronedarone could delay death from any cause or hospitalization for cardiovascular reasons.

Initially patients were to be ≥70 years old, or <70 years old with at least one risk factor (including hypertension, diabetes, prior cerebrovascular accident, left atrial diameter ≥50 mm or LVEF <0.40). The inclusion criteria were later changed such that patients were to be ≥75 years old, or ≥70 years old with at least one risk factor. Patients had to have both AF/AFL and sinus rhythm documented within the previous 6 months. Patients could have been in AF/AFL or in sinus rhythm at the time of randomization, but patients not in sinus rhythm were expected to be either electrically or chemically converted to normal sinus rhythm after anticoagulation.

Subjects were randomized and treated for up to 30 months (median follow-up: 22 months) with either MULTAQ 400 mg twice daily (2301 patients) or placebo (2327 patients), in addition to conventional therapy for cardiovascular diseases that included beta-blockers (71%), ACE inhibitors or angiotensin II receptor blockers (ARBs) (69%), digoxin (14%), calcium antagonists (14%), statins (39%), oral anticoagulants (60%), aspirin (44%), other chronic antiplatelet therapy (6%) and diuretics (54%).

The primary endpoint of the study was the time to first hospitalization for cardiovascular reasons or death from any cause. Time to death from any cause, time to first hospitalization for cardiovascular reasons, and time to cardiovascular death and time to all causes of death were also explored.

Patients ranged in age from 23 to 97 years; 42% were 75 years old or older. Forty-seven percent (47%) of patients were female and a majority was Caucasian (89%). Seventy-one percent (71%) of those enrolled had no history of heart failure. The median ejection fraction was 60%. Twenty-nine percent (29%) of patients had heart failure, mostly NYHA class II (17%). The majority had hypertension (86%) and structural heart disease (60%).

Results are shown in Table 3. MULTAQ reduced the combined endpoint of cardiovascular hospitalization or death from any cause by 24.2% when compared to placebo. This difference was entirely attributable to its effect on cardiovascular hospitalization, principally hospitalization related to AF.

Other endpoints, death from any cause and first hospitalization for cardiovascular reasons, are shown in Table 3. Secondary endpoints count all first events of a particular type, whether or not they were preceded by a different type of event.

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# Thank you.