# Exclusivity–Which one is for me?

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# Disclaimer

- This presentation is intended to provide general descriptions of exclusivities under the Food Drug and Cosmetic Act.
- Refer to the relevant statute and regulations regarding exclusivity in order to make regulatory related decisions.

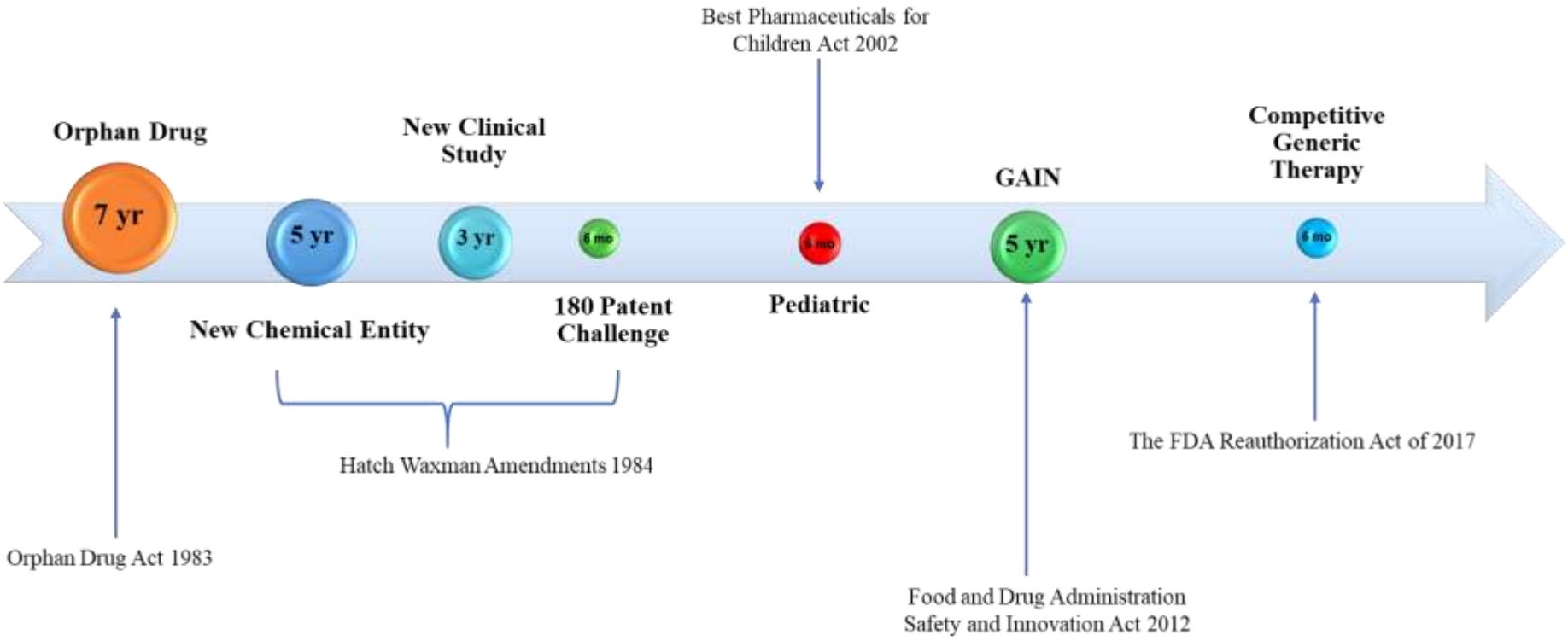
# Overview

- Considerations CDER uses to make exclusivity determinations
- Case Study - Crestor (rosuvastatin calcium tablets)
- Broad overview of FDA exclusivities and how they work
- Strategies to maximize the benefits of exclusivity in the current landscape
- Resources and References

# Drug Price Competition and Patent Term Restoration Act of 1984 – Grand Bargain

- Brand Industry Gains:
  - 5-year New Chemical Entity Exclusivity
  - 3-year New Clinical Investigation Exclusivity
  - Patent Term Extension to account for time patented product is under review by FDA
- Generic Industry Gains:
  - Abbreviated New Drug Application (ANDA) pathway
  - 180-day Generic Drug Exclusivity
    - Artificial act of infringement
      - Challenge brand patents in court prior to marketing
- Exclusivity: is granted for a drug product by the FDA upon approval that affects the timing of submission and/or approval of certain other applications and may run concurrently with a patent but does not need to do so.

# Exclusivity through the years



# CDER Exclusivity Board

- Majority of exclusivity determinations are made by Orange Book staff
- CDER established the Board to provide oversight and recommendations regarding exclusivity determinations made by the Center, with a primary focus on clarity and consistency of decisions
- Board relies on various FDA offices to handle challenges:
  - **Office of Generic Drugs**
  - Office of Regulatory Policy
  - Office of Chief Counsel
  - Office of New Drugs
  - Office of Pharmaceutical Quality
- Meets on a monthly basis to discuss whether and what type of exclusivity should be granted and the appropriate scope of exclusivity grants

# CDER Exclusivity Board

## The Board will focus on:

- New chemical entity exclusivity (NCE)
- New clinical investigation exclusivity (H-W)
- Exclusivity for biological products

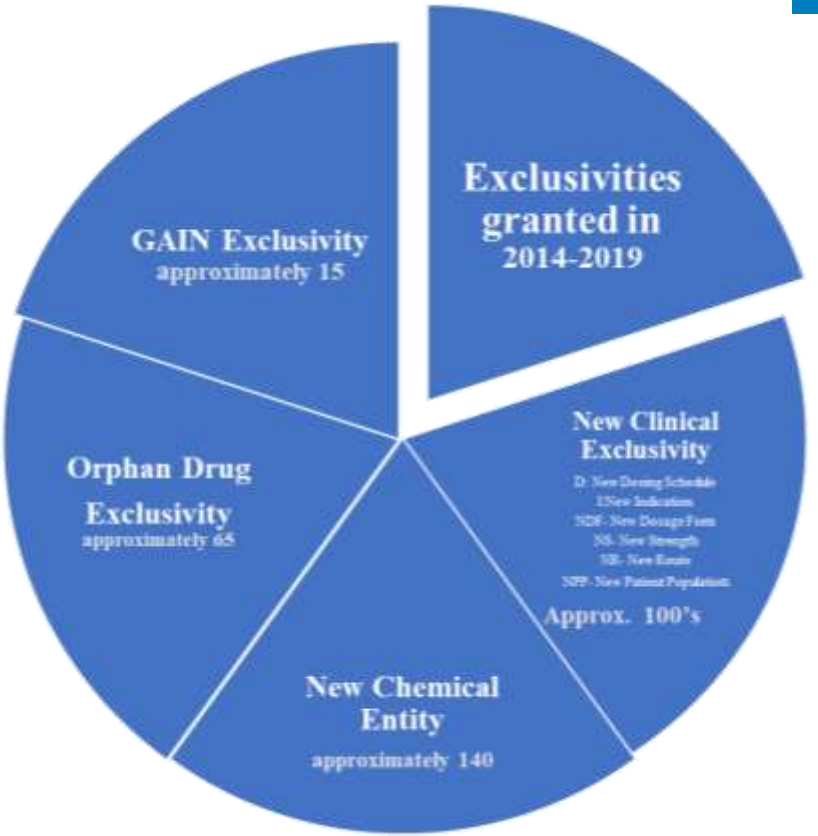
## The Board generally does NOT review:

- Orphan drug exclusivity (ODE)
- Pediatric exclusivity (PED)
- Generating Antibiotic Incentives Now (GAIN)
- 180-day patent challenge exclusivity (PC)
- Competitive Generic Therapy exclusivity (CGT)

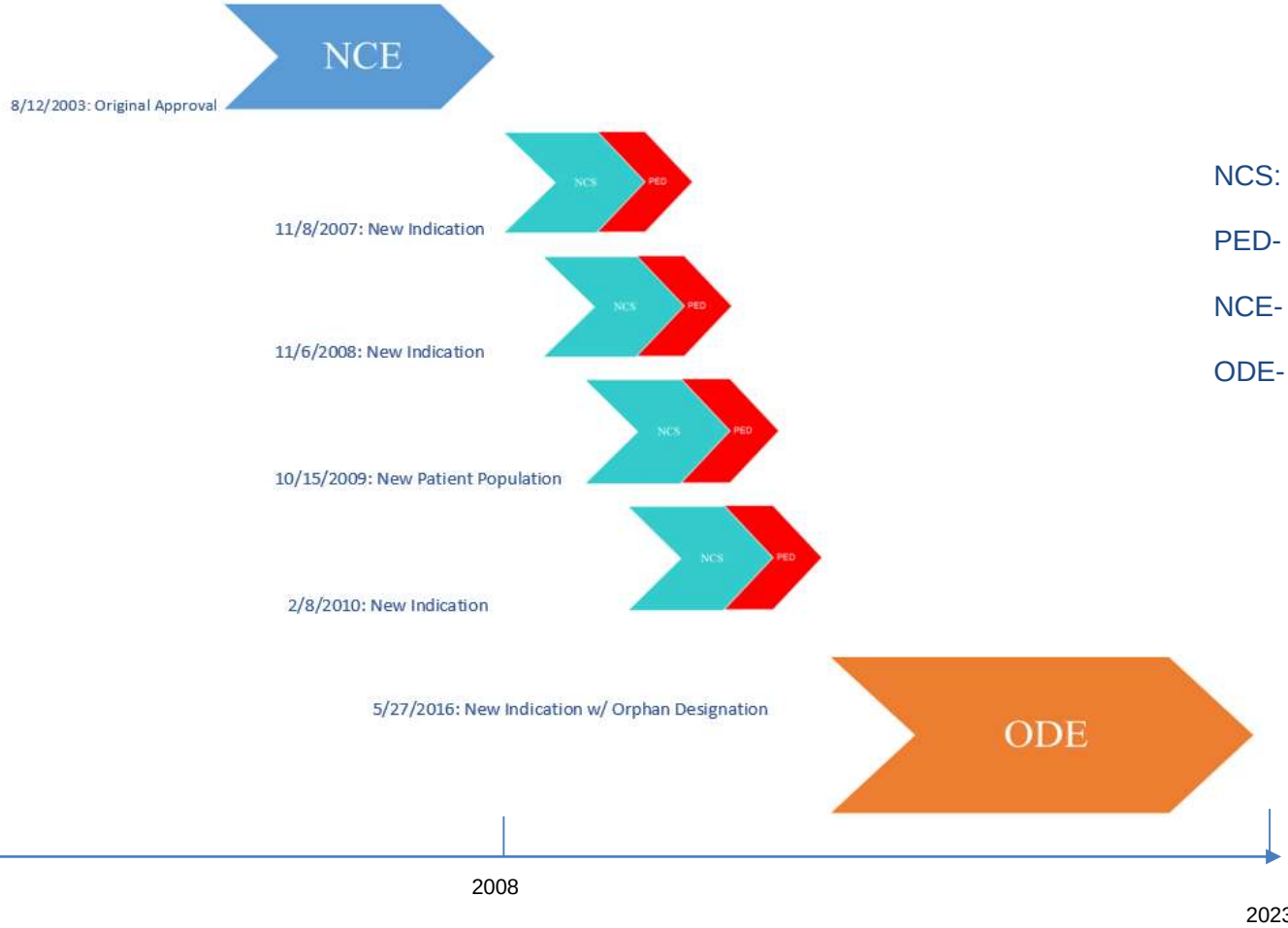
# Orange Book

**MONITOR**
**MONITOR**
**MONITOR**

Publishes
all exclusivities
in the Orange Book



# Crestor™ (rosuvastatin) Tablets Case Study




NCS: New Clinical Study

PED- Pediatric Exclusivity

NCE- New Chemical Exclusivity

ODE- Orphan Drug Exclusivity

# New Chemical Entity Exclusivity

- NCE is granted to "a drug that contains no active moiety that has been approved by FDA in any other application submitted under section 505(b) of the Act"
- Generally, a salt of an approved drug is not considered a new active moiety and so is not eligible for NCE exclusivity.
- FDA will grant NCE exclusivity to:
  - Active moiety not previously approved in a single-ingredient drug product

    i.e., Farxiga NDA 202293 Dapagliflozin Tablets [Approved on 1/8/2014, NCE expired on 1/8/2019]
  - A fixed-combination in which at least one active moiety is new even if the drug product also contains an active moiety previously approved

    i.e., Xigduo XR NDA 205649 Dapagliflozin and Metformin Extended Release Tablets [Approved on 5/28/2017, NCE expired on 1/8/2019]
  - A fixed-combination where both active moieties have not previously been approved

    i.e., Mavyret NDA 209394 Glecaprevir and Pibrentasvir Tablets [Approved on 8/3/2017, NCE expires on 8/3/2022]

NCE

# NCE Exclusivity Pearls

- Implementing regulation is found at 21 CFR 314.108
- CDER reviews all relevant applications, with or without a request from the applicant, for an exclusivity determination
- There is no requirement to apply
- Runs concurrently with the term of any patent claiming the drug
- 5-year NCE exclusivity does not block the submission, review, or approval of a 505(b)(1) NDA
- During this 5-year period no applicant can submit an ANDA or 505(b)(2) to FDA seeking regulatory approval of a drug product containing the same active moiety- exception to this on the next slide
- NCE applies to all dosage forms containing the active moiety regardless of who owns the application

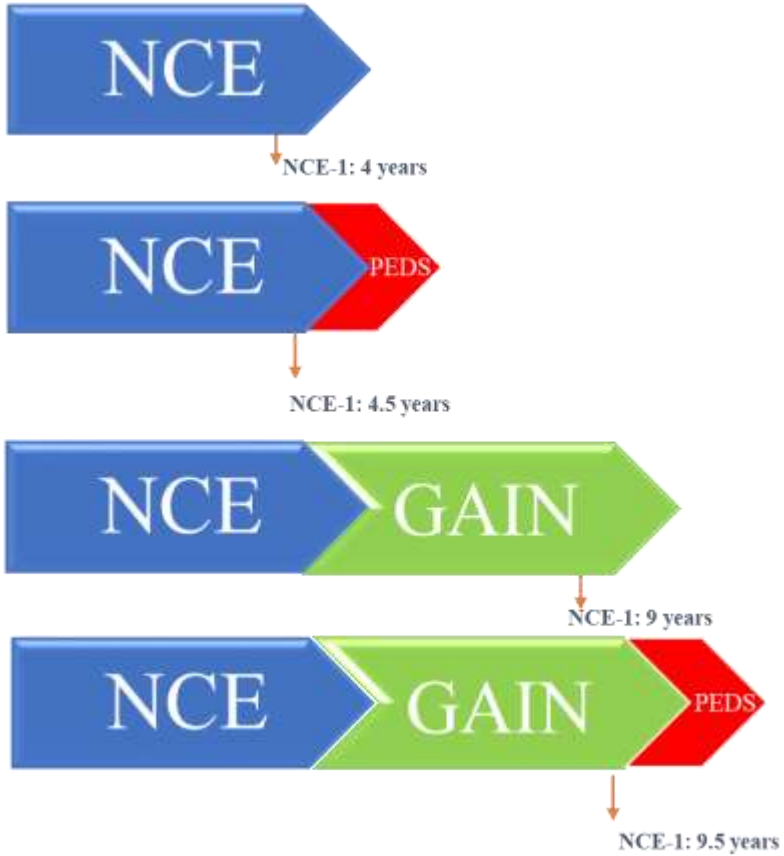
NCE

# NCE Exclusivity Pearls

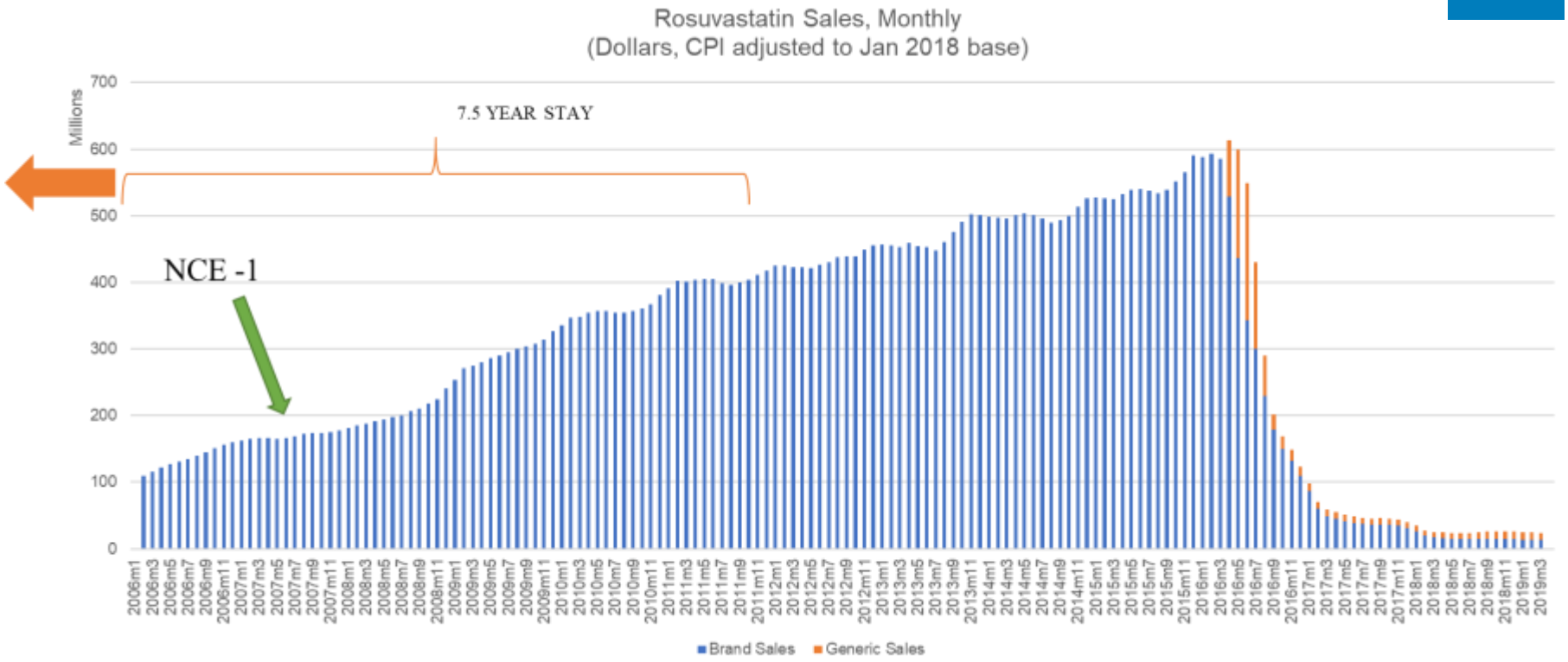
FDA

- If there are patents listed in Orange Book under the NDA, an ANDA or 505(b)(2) can be submitted with a Paragraph IV certification at “NCE -1” date (Year 4)
- If suit filed within the 1-year period beginning 4 years after NDA approval, the 30-month stay is extended by amount of time such that 7.5 years will elapse from the date of NDA approval

# New Chemical Entity Exclusivity- Generic Entry



# Crestor™ (rosuvastatin) Tablets: NCE -1




Data obtained from IQIVIA on 5/31/2019

New Clinical Investigation Exclusivity

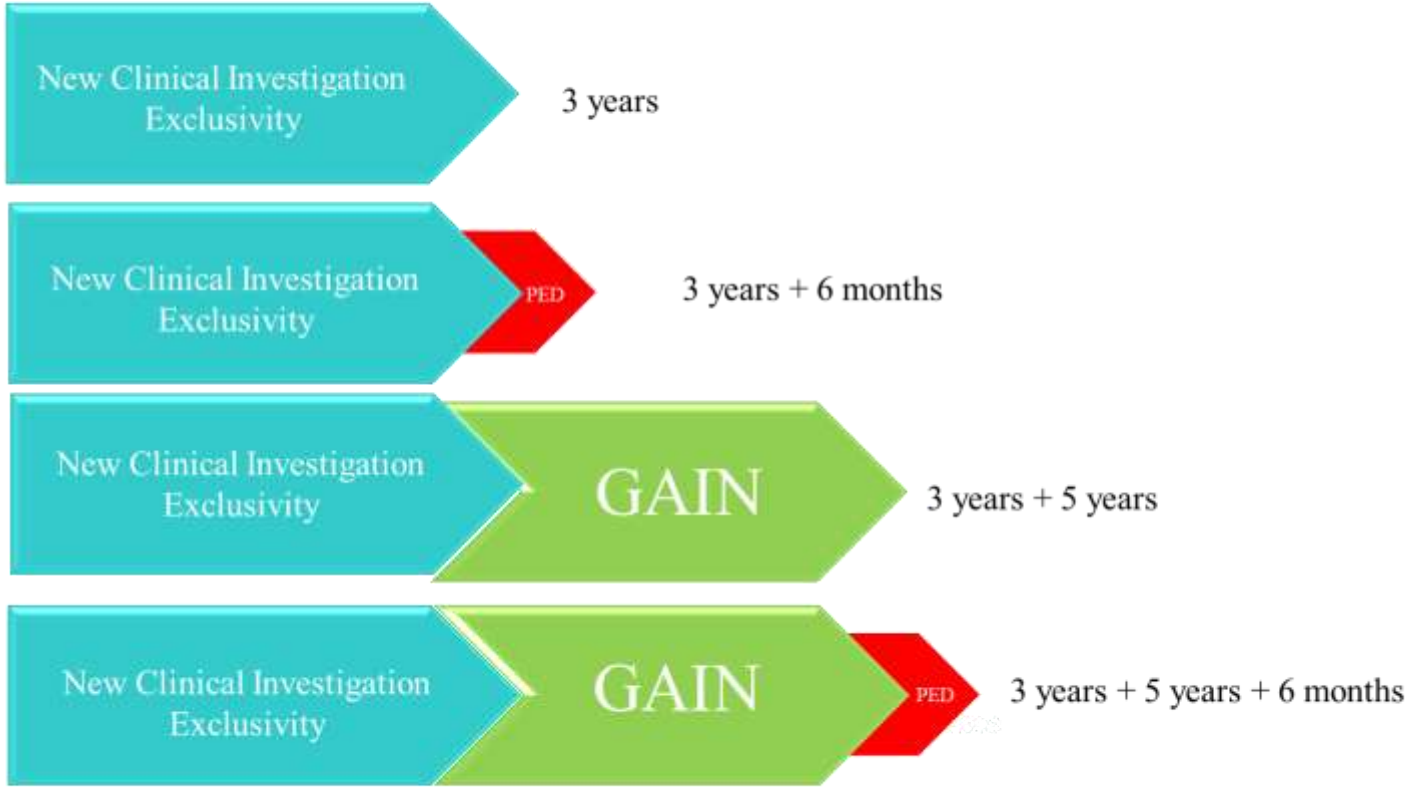
# New Clinical Investigation Exclusivity

- Available to original NDAs and for efficacy supplements
- 3-year period of exclusivity granted for a drug product that contains an active moiety that has been previously approved when the application contains “new” clinical investigations (other than bioavailability studies) conducted or sponsored by the sponsor that were “essential "to the approval
- Examples include: new indications, dosing regimens, patient population; Rx to OTC switches

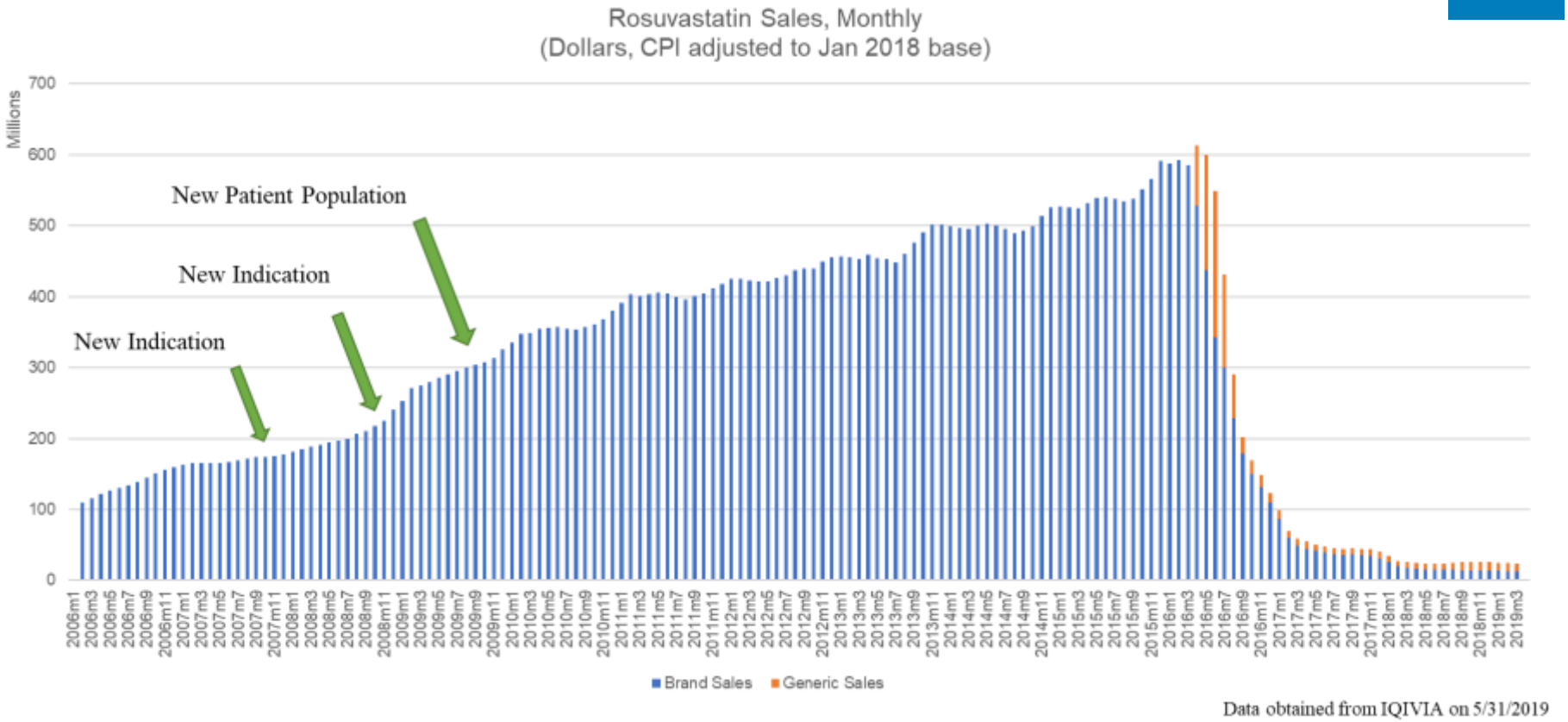
# New Clinical Investigation Exclusivity Pearls

- 3-year exclusivity period runs irrespective of, but concurrent with, any applicable patent term
- ANDAs may be received and assessed but will not be approved until exclusivity expires
  - Exception is if the exclusivity protected information can be “carved out” of the labeling
- Generally, exclusivities that are not carved out are:
  - Rx to OTC switches
  - New dosage form

# New Clinical Investigation Exclusivity



# Crestor™ (rosuvastatin) Tablets: New Clinical Investigation Exclusivity




Data obtained from IQIVIA on 5/31/2019

# Pediatric Exclusivity

- Since pediatric information was often missing from drug labeling, Congress passed the two major pediatric drug laws:
  - Best Pharmaceuticals for Children Act (BPCA) in 2002: provides a financial incentive (pediatric exclusivity) to pharmaceutical companies that conduct pediatric studies
  - Pediatric Research Equity Act (PREA) in 2003: requires pharmaceutical companies to access safety and effectiveness of new drug products in pediatric patients
- Granted when the sponsor has conducted and submitted pediatric studies on the **active moiety** in response to a Written Request from FDA
  - Will always result in pediatric exclusivity when sponsor 'fairly responds' to the written request regardless of changes to labeling

# Pediatric Exclusivity Pearls

- Additional 6 months of exclusivity added to the end of listed patents and/or exclusivity
  - Unique as the only exclusivity that also attaches to listed patents
  - Applies to all existing patents and exclusivities on ALL drug products held by the sponsor of the active moiety at time of grant
- 6-month pediatric exclusivity period can NOT be “carved out” of labeling
- 6-month pediatric exclusivity is NOT an extension of the patent
- ANDA not eligible for full approval during pediatric exclusivity “window” unless:
  - Applicant has secured a waiver of pediatric exclusivity from the NDA holder
  - Applicant has obtained a ruling from a Court finding the patent to subject to pediatric exclusivity invalid, not-infringed or unenforceable
  - Dismissal of civil action: Must secure a waiver
  - Not sued within 45 days: Must secure a waiver

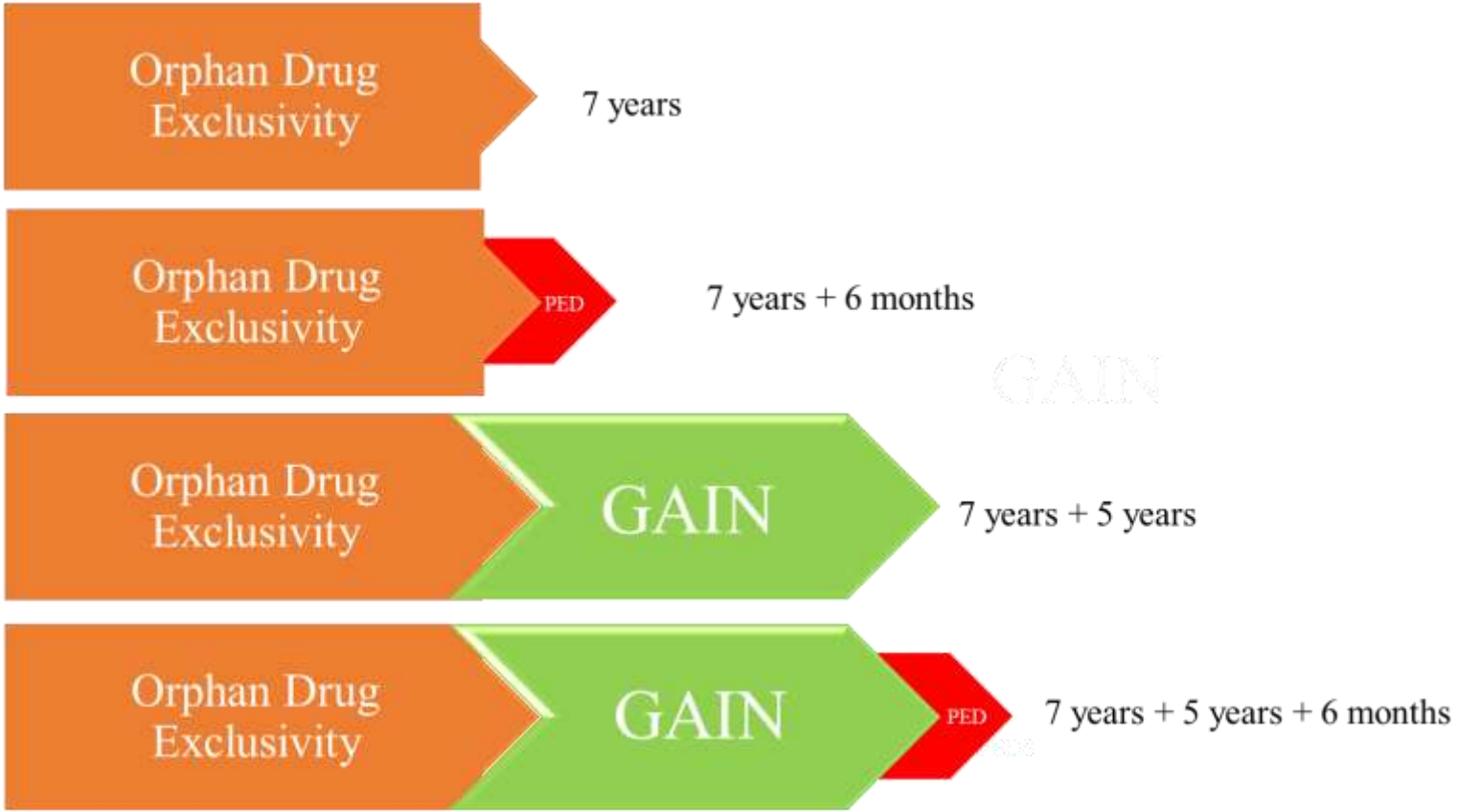
# The Power of Pediatric Exclusivity

| Appl No | Prod No | Patent No | Patent Expiration | Drug Substance Claim | Drug Product Claim | Patent Use Code | Delist Requested |
|---|---|---|---|---|---|---|---|
| N021153 | 001 | 5690960 | Nov 25, 2014 | | Y | U - 373 | |
| N021153 | 001 | 5690960 | Nov 25, 2014 | | Y | U - 729 | |
| N021153 | 001 | 5690960 | Nov 25, 2014 | | Y | U - 770 | |
| N021153 | 001 | 5690960*PED | May 25, 2015 | | | | |
| N021153 | 001 | 5714504 | Feb 3, 2015 | | Y | U - 373 | |
| N021153 | 001 | 5714504 | Feb 3, 2015 | | Y | U - 729 | |
| N021153 | 001 | 5714504 | Feb 3, 2015 | | Y | U - 770 | |
| N021153 | 001 | 5714504*PED | Aug 3, 2015 | | | | |
| N021153 | 001 | 5877192*PED | Nov 27, 2014 | | | | |
| N021153 | 001 | 5900424 | May 4, 2016 | Y | | U - 373 | |
| N021153 | 001 | 5900424 | May 4, 2016 | Y | | U - 729 | |
| N021153 | 001 | 5900424 | May 4, 2016 | Y | | U - 770 | |
| N021153 | 001 | 5900424*PED | Nov 4, 2016 | | | | |

NDA: Nexium Delayed Release Capsules

- Ped window for '192 extended from 5/27/2014 until 11/27/2014.
- Ped window for '960 currently extended from 11/25/2014 until 5/25/2015
- Ped window for '504 currently extended from 2/3/2015 until 8/3/2015.

# Orphan Drug Exclusivity

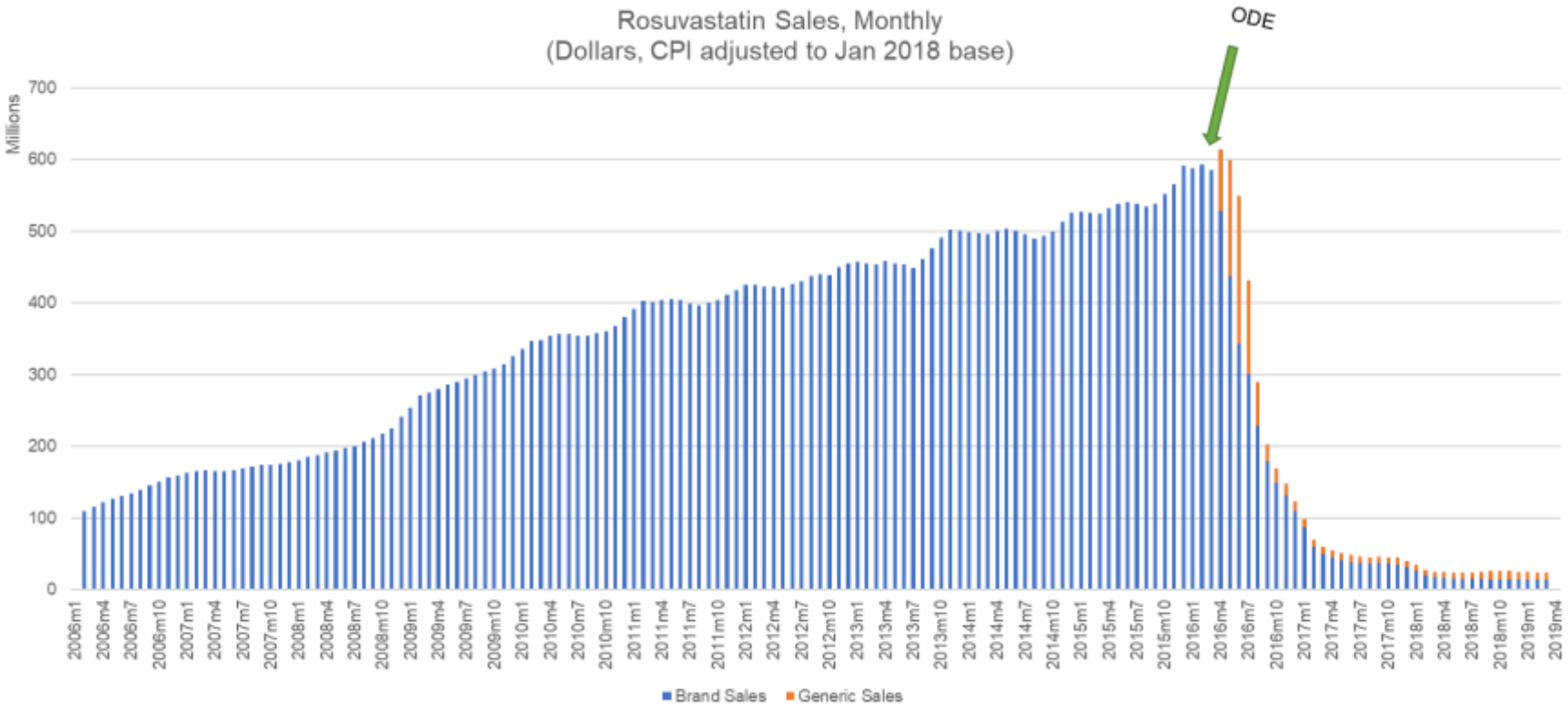


Orphan Drug Exclusivity

# Orphan Drug Exclusivity

- Will be discussed by Roberta Szydlo
  - Orphan Drug designation and grants are handled by Office of Orphan Products Development
- Once granted, Orphan Drug Exclusivities are listed in Orange Book

# Crestor™ (rosuvastatin) Tablets: Orphan Drug Exclusivity (ODE)




Data obtained from IQIVIA on 5/31/2019

# Generating Antibiotic Incentives Now (GAIN)

- Offers incentives for the development of antibacterial and antifungal drugs for human use to treat serious or life-threatening infections.
  - FDA will consider a drug to be “intended to treat a serious or life-threatening infection” if it is intended to “diagnose, prevent, or treat such an infection.”
- The primary incentive is a 5-year exclusivity extension for drug products that have been designated as qualified infectious disease product (QIDP)
  - Exclusivity is added to NCE, H-W and ODE for which the application qualifies for upon approval
- Once granted QIDP designation:
  - FDA will give priority review for the first application or efficacy supplement for a specific drug product and indication for which QIDP designation was granted
  - Upon the request from the applicant, eligible for fast track designation

GAIN

# GAIN/QIDP Pearls

FDA

- Sponsors can request a QIDP designation any time prior to the submission of the NDA either to an IND or as pre-IND correspondence
- QIDP designation applies to a specific drug product from a specific sponsor for a specified use for which the drug is being studied
  - Designation does not apply to a drug substance in general or beyond the specified indications
- GAIN exclusivity does not apply to:
  - Approved drug products
  - Supplements to NDAs that have been granted GAIN exclusivity

# List of Qualifying Pathogens: 21 CFR 317.2

| |
|---|
| Acinetobacter species |
| Aspergillus species |
| Burkholderia cepacia complex |
| Campylobacter species |
| Candida species |
| Clostridium difficile |
| Coccidioides species |
| Cryptococcus species |
| Enterobacteriaceae (e.g., Klebsiella pneumoniae) |
| Enterococcus species |
| Helicobacter pylori |
| Mycobacterium tuberculosis complex |
| Neisseria gonorrhoeae |
| N. meningitidis |
| Non-tuberculous mycobacteria species |
| Pseudomonas species |
| Staphylococcus aureus |
| Streptococcus agalactiae |
| S. pneumoniae |
| S. pyogenes |
| Vibrio cholerae |

# 180-Day Exclusivity

- Incentive for ANDA applicants to challenge patent(s) listed in the Orange Book
- Reward for being First Applicant to submit substantially complete ANDA containing Paragraph IV challenge (PIV)
  - PIV challenge: assertion by ANDA applicant that a patent is invalid, unenforceable, or will not be infringed
- 180-day Exclusivity will block approval of all non-First Applicants both prior to approval and after approval of the First Applicant(s) until exclusivity has run or has been forfeited
- Substantial incentive as ANDA(s) may face limited competition in market with NDA prior to entry by multiple ANDAs.

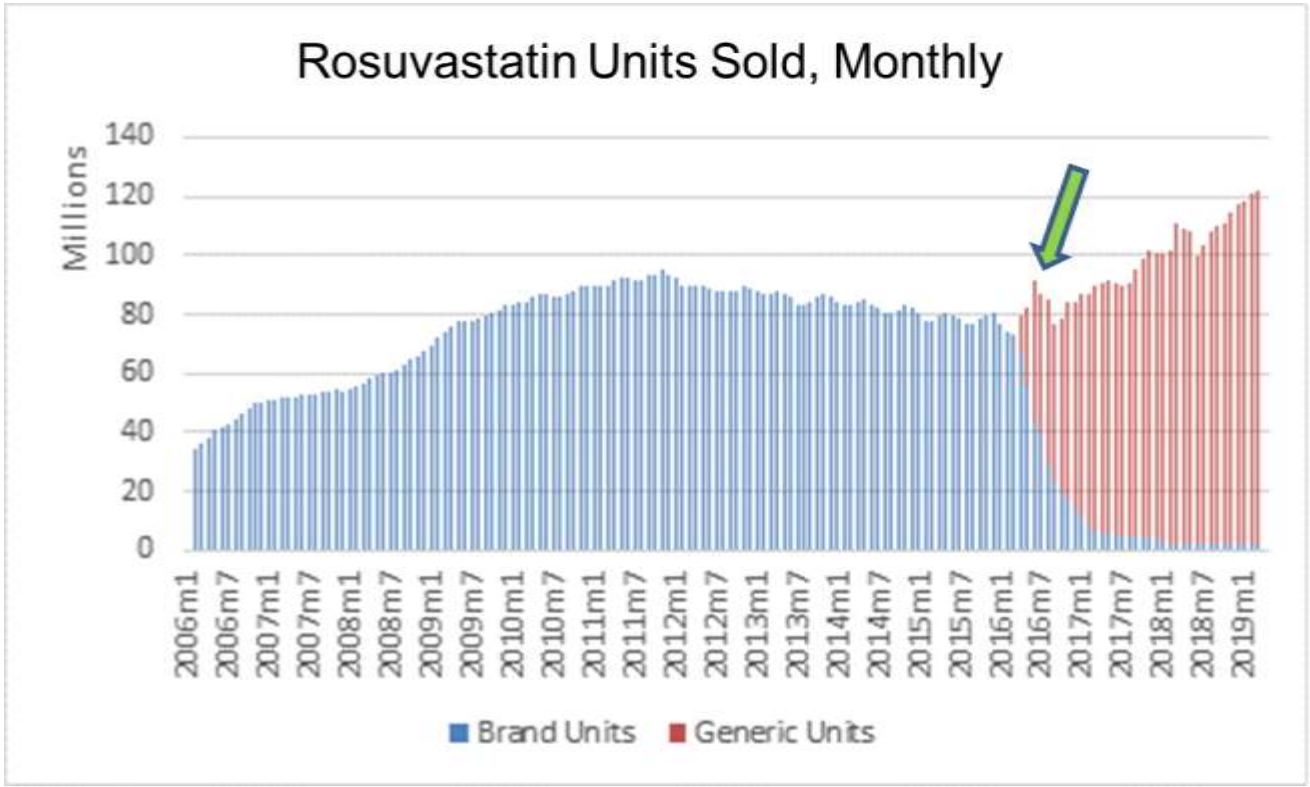
# 180-Day Exclusivity Pearls

- Plan ahead! Take time to submit a substantially complete application and check the PIV website
  - Paragraph IV Certifications List: To assist generic drug applicants in preparing their applications, FDA regularly publishes a list of drug products for which an ANDA has been received by the Office of Generic Drugs (OGD) containing a Paragraph IV patent certification.
- Approval letter denotes whether the applicant may be **eligible** for or forfeited 180-day exclusivity
- 180-day is triggered by first commercial marketing by any First Applicant
  - 314.107(c) requirement: Applicant must submit notification of commercial marketing
  - Once triggered, the 180-day period runs without interruption


# 180-Day Exclusivity Pearls

- 180 day trigger is designated in the Orange Book by the code Patent Challenge (PC)
- Never extends beyond those patents which qualified the First Applicant(s) for exclusivity
- 180-day exclusivity blocks only the approval of subsequent ANDAs that also contain a paragraph IV certification
- Does not affect the approval of marketing under NDAs, including marketing of authorized generics
- Applicants who provide a section viii statement to the same patent are never blocked
- Can be forfeited under certain conditions

# Crestor™ (rosuvastatin) Tablets: 180 day Exclusivity




## Rosuvastatin Exclusivity

- Cohort of First Filers submitted on NCE-1 date.
- No First filer secured Tentative Approval within 30 months of submission
- Exclusivity was shared and potentially subject to mass forfeiture by all First Filers
- Forfeiture analysis competed showing that there was a change in or review of the requirements for approval of at least one First Filer
- Non-forfeiture by one First Filer in the cohort preserves exclusivity per the Agency's Nateglinide precedent
- First application approved on April 29, 2016 due to pediatric waiver during pediatric window for the RE37314 patent
- First approved application launched on May 4, 2016

Data obtained from IQIVIA on 5/31/2019

# Competitive Generic Therapy

- CGT may be available to a drug product for which there is inadequate generic competition:
  - Request submitted by an ANDA applicant, designation is application specific
  - Must be made concurrent with or at any time prior to the submission of an original ANDA
  - Must be for a drug product for which there is inadequate generic competition
    - Inadequate Generic Competition: when "there is not more than one approved drugs on the list of drugs described in section 505(j)(7)(A) (not including drugs on the discontinued section of such list) that is
      - The reference listed drug
      - A generic with the same reference listed drug as the drug for which designation as a competitive generic therapy is sought
  - FDA will determine whether the request satisfies designation criteria within 60 days of request
  - Letter issued to applicant either granting or denying designation

# Competitive Generic Therapy

- The first approved applicant of a product designated as CGT is eligible for 180 day exclusivity
- "First approved applicant" for CGT exclusivity does not necessarily mean the first applicant to have their ANDA approved for the drug product.
  - In some cases, there may be an already approved ANDA that references the same RLD, but that did not receive a CGT designation.
- However, the applicant must obtain approval of its ANDA for a CGT on the first day that the FDA approves an ANDA for that particular CGT.
  - There may be multiple ANDA applicants approved on the same day for the same CGT, which means that there may be multiple "first approved applicants."

# CGT Exclusivity Pearls

- ANDA must have been granted CGT designation
- ANDA must meet statutory definition of First Approved Applicant
- Drug product was not eligible for 180-day exclusivity that's been triggered or forfeited
  - Monitor the Paragraph IV List

If all of these criteria are met, then an ANDA will be granted CGT 180-day exclusivity in the approval letter.

Exclusivity granted in final approval letter with explicit instructions for applicant to follow with respect to notification of commercial marketing

# CGT Exclusivity Pearls

- CGT exclusivity only blocks other approvals after the first approved applicant(s) begin marketing
  - "the application shall be made effective on the date that is 180 days after the date of the first commercial marketing of the competitive generic therapy (including the commercial marketing of the listed drug) by any first approved applicant"
- Applicants must inform the Office of Generic Drugs (OGD) once marketing has commenced in order for subsequent approvals to be halted by this exclusivity.
- OGD will continue to approve other ANDAs for the CGT drug until we receive notice of marketing.

# Resources and References

- Draft guidance for industry *Competitive Generic Therapies*
- Guidance for industry *New Chemical Entity Exclusivity Determinations for Certain Fixed-Combination Drug Products*
- Draft guidance for industry *180-Day Exclusivity: Questions and Answers*
- Draft guidance for industry *Qualified Infectious Disease Product Designation Questions and Answers*
- Guidance for Industry *Guidance for Industry, Qualifying for Pediatric Exclusivity Under Section 505A of the Federal Food, Drug, and Cosmetic Act*
- "*Approved Drug Products with Therapeutic Equivalence Evaluations* (the Orange Book)

# Resources and References

| Exclusivity | Legislation | Statue and Regulations |
|---|---|---|
| New Chemical Entity Exclusivity | Drug Price Competition and Patent Term Restoration Act, 1984 & Food and Drug Administration Amendments Act, 2007 | Statutes: 21 USC 355(c)(3)(E)(ii) –505(b)(2)<br>21 USC 355(j)(5)(F)(ii) – ANDA<br>Regs: 21 CFR 314.108(b)(2) |
| New Clinical Study Exclusivity | Drug Price Competition and Patent Term Restoration Act, 1984 | Statutes: 21 USC 355(c)(3)(E)(iii, iv) –505(b)(2)<br>21 USC 355(j)(5)(F)(iii, iv) – ANDA<br>Regs: 21 CFR 314.108(b)(4) and (5) |
| Generating Antibiotic Incentives Now Exclusivity | Food and Drug Administration Safety and Innovation Act, 2012 | Statute: 21 USC 355(f)(a), 21 USC 360n-1, 21 USC 356(b)(1)<br>Regulation: 21 CFR 317.2 |
| Orphan Drug Exclusivity | Orphan Drug Act, 1983 | Statute: 21 USC 360aa-dd<br>Regs: 21 CFR 316 |
| Pediatric Exclusivity | Best Pharmaceuticals for Children Act, 2002 | Statute: 21 USC 355A |
| 180 Patent Challenge Exclusivity | Drug Price Competition and Patent Term Restoration Act, 1984 | Statute: 21 USC 355(j)(5)(B)(iv) |
| Competitive Generic Therapy Exclusivity | Food and Drug Administration Reauthorization Act of 2017 | Statute: 21 U.S.C. 356h(b)(3),(e)(2), (j)(5)(B)(iv) |

# Challenge Question 1

Which of the following exclusivities attaches to patents and other exclusivities?

A. Pediatric Exclusivity

B. Competitive Generic Exclusivity

C. New Chemical Entity Exclusivity

D. Orphan Drug Exclusivity

# Challenge Question 2

Which of the following exclusivities was passed under Food and Drug Administration Reauthorization Act of 2017?

A. Competitive Generic Therapy

B. New Clinical Study Exclusivity

C. Pediatric Exclusivity

D. Generating Antibiotic Incentives Now Exclusivity

**Center for Drug Evaluation and Research**

**Office of Generic Drugs**

**Division of Regulatory Support**

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