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Pediatric Studies and Pediatric Exclusivity

Developing Drugs and biologics for children

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George works with life sciences companies of all sizes to assist them in developing and marketing innovative products that are regulated by the US Food and Drug Administration, including drugs and biologics, medical devices, drug-device combination products, CBD and botanical products, medical foods and dietary supplements.

George has deep experience providing regulatory advice to pharmaceutical and biotech companies on lifecycle management issues, including regulatory exclusivities and FDA-facing patent issues. He is a leading expert on orphan drug matters, including orphan designation and exclusivity, and has successfully advocated on behalf of clients to FDA on matters related to prevalence, orphan subsets, and clinical superiority. George also regularly advises pharmaceutical and biotechnology companies on pediatric study and pediatric exclusivity issues arising under the Best Pharmaceuticals for Children Act and the Pediatric Research Equity Act.

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Introduction

- Welcome to Mayer Brown's FDA Lifecycle Management webinar series
  - Monthly installments addressing issues affecting lifecycle of pharma and biotech products

- Four installments covering four key types of regulatory exclusivity
  - New Chemical Entity and Reference Product Exclusivity (February 23, 2023)
  - Orphan Drug Exclusivity (March 16, 2023)
  - **Pediatric Studies and Exclusivity**
  - 3-Year "New Clinical Investigation" Exclusivity (May 11, 2023)

Today's Agenda: FDA's Pediatric Programs

- Pediatric Research Equity Act (PREA)
- Best Pharmaceuticals for Children Act (BPCA)
  - Qualifying for Pediatric Exclusivity
  - Effects of Pediatric Exclusivity
- Rare Pediatric Disease Priority Review Voucher Program

Incentivizing Pediatric Product Development

- FDA has long-term experience with off-label use of "adult" medications in pediatric patients
  - However, pediatric patients may respond differently than adults, particularly in the youngest age groups
  - Pharmacokinetics (PK) and pharmacodynamics (PD) likely vary
  - Safety and dosing concerns
- Beginning in the 1990s, several approaches were taken, effectively arriving at the two-pronged approach we have today with the BPCA and PREA
  - Orphan drug designation for pediatric populations – FDA has moved away from this policy
  - Rare Pediatric Disease Priority Review Voucher program – sunsetting in 2024
- FDA posts vast amounts of information, data and reports on pediatric studies on the agency website

PREA and BPCA: A Complementary Approach to Drug Development

- **Pediatric Research Equity Act (PREA)**
  - Authorizes FDA to **require** pediatric research for indications approved or pending approval in adults, including development of age-appropriate formulations
  - The "stick"
- **Best Pharmaceuticals for Children Act (BPCA)**
  - Provides a financial incentive (6 months of additional exclusivity) to encourage companies to **voluntarily** conduct pediatric studies in both approved and unapproved uses
  - The "carrot"
- Together, PREA and BPCA are designed to support development of ***meaningful pediatric labeling*** for approved drug and biologic products

PREA vs. BPCA: What's the Difference?

PREA	BPCA
Drugs and biologics	Drugs and biologics
Studies are **mandatory**	Studies are **voluntary**
Requires studies **only on approved or pending indications ("on-label")**	Studies can include **approved and/or unapproved uses ("off-label")**
Orphan indications **exempt** from studies	FDA can request studies be conducted for orphan indications
Pediatric studies must be labeled	Pediatric studies must be labeled
No exclusivity	Provides financial incentive (exclusivity) to submit studies to meet Written Requests

THE PEDIATRIC RESEARCH EQUITY ACT

Pediatric Research Equity Act (PREA)

- PREA **mandates** that applicants conduct a **pediatric assessment** for a given drug or biologic
  - Pediatric studies using appropriate formulations for each age group
    - **Assess safety and effectiveness** of a drug/biologic for the claimed indications in all relevant pediatric subpopulations
    - **Support dosing and administration** for each pediatric subpopulation for which the drug/biologic is **safe and effective**
- Requirement applies upon submission of an NDA/BLA (or supplement) for a:
  - New indication
  - New dosage form, dosing regimen, route of administration
  - New active ingredient/biological substance (which includes new salts and new fixed combinations)
  - "Certain molecularly targeted cancer indications"

Pediatric Research Equity Act (PREA)

- **Key aspects of PREA**
  - Limited to approved indication(s); not "off-label" uses
  - Full or partial waiver of requirements is available for one or more pediatric subpopulations
  - Deferral of studies until after approval of relevant adult application is also available
- Orphan-designated drugs are generally exempt from PREA requirements
- Potential enforcement for non-compliance

How to Satisfy the Requirements of PREA

- Sponsor must submit a **Pediatric Study Plan (PSP)** during clinical development phase
  - Outline of the pediatric studies the sponsor plans to conduct
  - Including study objectives and design, age groups, relevant endpoints, and statistical approach)
  - Intention to request a deferral, partial waiver, or full waiver
- Sponsor must **complete required studies** and **submit labeling supplement** to add relevant pediatric information
- Develop age-appropriate formulation, as needed

Pediatric Study Plans: Contents and Procedure

- **Timing of Submission:**
  - If End-of-Phase 2 (EOP2) meeting, "initial PSP" (iPSP) must be submitted within 60 days after
  - If no EOP2 meeting, PSP should be submitted "as early as practicable" and at a time agreed upon by FDA and sponsor.
    - FDA strongly encourages submission before initiation of Phase 3 studies
    - At least 210 days prior to submission of NDA/BLA
  - FDA response within 90 days: Division will consult with Pediatric Review Committee (PERC)
  - Sponsor has 90 days to continue negotiations and/or submit "agreed iPSP"
  - FDA has 30 days to confirm agreed iPSP
- Non-agreed iPSP: can meet or further negotiate; no timelines
- Amendments permitted, follow similar process

Contents of an iPSP

- *See Guidance for Industry, Pediatric Study Plans: Content of and Process for Submitting Initial Pediatric Study Plans and Amended Initial Pediatric Study Plans* (July 2020), which includes a template iPSP:
  - Overview of the Disease/Condition in the Pediatric Population
  - Overview of the Drug or Biological Product
  - Overview of Planned Extrapolation to Specific Pediatric Populations
  - Planned Request for Drug-Specific Waiver(s)
  - Planned Request for Deferral(s) of Pediatric Studies
  - Tabular Summary of Planned Nonclinical and Clinical Development
  - Age-Appropriate Formulation Development
  - Nonclinical Studies
  - Planned Pediatric Clinical Studies (PK, PK/PD, Clinical safety and efficacy)
  - Timelines

Certain Molecularly Targeted Cancer Indications

- Added to PREA in 2017 (FDARA), this provision applies to sponsors of original NDAs and BLAs for "new active ingredients" that are:
  - Intended to treat adult cancer **and** are directed at a molecular target that is "substantially relevant to the growth or progression of a pediatric cancer"
- If meet these criteria, sponsor must conduct and submit reports of pediatric investigations, submit an iPSP, etc.
- Applies even where:
  - Adult cancer indication does not occur in pediatric patients, or
  - Adult indication is otherwise exempt as orphan-designated
- "Substantially relevant"
  - FDA maintains list of "relevant" and "non-relevant molecular targets," the latter of which can support a waiver request; not all inclusive
  - Review literature, consult pediatric oncology experts

Deferral and Waiver of Studies under PREA

- **Deferral**
  - Submission of some or all pediatric assessments may be deferred until after approval of drug/biologic for adults
- **Waiver**
  - Under certain circumstances, requirement for pediatric assessments may be waived
    - Full waiver (all pediatric patients)
    - Partial waiver (subset of pediatric populations)
- Decided by FDA ***at time of application approval***

Deferral Criteria

- **Pediatric studies may be postponed until after approval of the drug in adults if:**
  - The drug/biologic is ready for approval for use in adults before pediatric studies are complete,
  - Pediatric studies should be delayed until additional safety or effectiveness data have been collected, OR
  - Another appropriate reason for deferral (catch-all)
    - *E.g.*, Scientific issues concerning study design or endpoints
    - *E.g.*, Development of a pediatric formulation is not complete
- Deferred pediatric studies will need to be conducted and submitted to FDA according to timelines agreed upon with agency as part of PSP

Deferral Statistics

- ***Very common*** to have studies deferred until post-approval
  - Must nevertheless include iPSP in marketing application when submitting a deferral request
- FDA reports indicate that vast majority of deferrals are because drug/biologic is "Ready for approval for use in adults and the pediatric study has not been completed"
  - Less commonly, "Pediatric studies should be delayed until additional safety or effectiveness data have been collected"

Deferral Extensions

- Sponsor can request deferral extension no later than 90 days prior to deferred study deadline
  - FDA will respond within 45 days
  - Commonly granted if just extending timelines and information provided to FDA to support delay, *e.g.*, enrollment difficulties, COVID
- Can also be requested in response to a PREA Non-Compliance Letter (more on this below)
- FDA reports indicate that most common reason for deferral extension are delays:
  - Due to issues with the study drug and/or comparator drug
  - Involving study participants, sites, and/or management
  - Due to continuing interaction between the applicant and the FDA

Waiver Criteria

- **Required pediatric assessments may be waived if:**
  - Necessary studies are impossible or highly impracticable,
    - FDA maintains a non-exhaustive list of conditions "automatically" eligible for waiver
  - Evidence strongly suggests the drug/biologic would be ineffective or unsafe in children,
  - Drug/biologic (1) does not represent a meaningful therapeutic benefit over existing therapies in pediatric patients AND (2) is unlikely to be used by a substantial number of pediatric patients
    - *Meaningful therapeutic benefit*: if approved, the drug would provide an improvement in the treatment, diagnosis, or prevention of a disease, or there is a need for additional options for that indication or class of products
    - *Substantial number*: 50,000 patients
  - Reasonable attempts to produce a pediatric formulation necessary for that age group have failed (partial waiver only) (will also be published on FDA website)

Waiver Statistics

- CDER's most recent report states that ***1660 waivers have been granted*** based on ***1944 waiver requests***:

Reason for Waiver	Number of waivers granted
Necessary Studies Impossible or Highly Impracticable	1337
Evidence Strongly Suggests Product Would be Ineffective/Unsafe/Both	10/117/39
Product Does Not Represent a Meaningful Therapeutic Benefit	168
Reasonable Attempts to Produce a Pediatric Formulation Necessary for that Age Group Have Failed	6

Deferrals and Waivers: *Practical Considerations*

- PSP must include plans to request deferrals or waivers, including supporting data and reasons
- Know the precedent!
  - FDA maintains huge amounts of pediatric data and reports on its website
- Show your work
  - The agency will not take a sponsor's word, particularly in support of deferral extension and/or formulation problems
- It is possible to be "released" from a deferred study, based on waiver criteria
  - Commercial reasons not sufficient

PREA Non-Compliance

- If a sponsor fails to comply with PREA (*e.g.*, by not completing deferred studies within timelines), FDA will send a PREA Non-Compliance Letter
  - Sponsor must respond in writing within 45 days; can include a deferral extension request
  - Both letters are posted publicly on FDA website
- Failure to comply with PREA also results in product being considered misbranded and potentially subject to additional enforcement:
  - NOT: criminal penalties or civil monetary penalties under FDCA 303
  - NOT: withdrawal of marketing application
  - Seizure, injunction, etc.

BEST PHARMACEUTICALS FOR CHILDREN ACT

QUALIFYING FOR PEDIATRIC EXCLUSIVITY

Background on Pediatric Exclusivity

- **Best Pharmaceuticals for Children Act (BPCA):**
  - A **voluntary** incentive for sponsors to study their drugs in pediatric populations. 21 USC 355a.
  - Provides a 6-month extension of patents and other regulatory exclusivities listed in the Orange Book/Purple Book
    - With some important limitations
  - Designed to incentivize the development of meaningful pediatric labeling where use of approved drug or biologic is anticipated or foreseeable

Pediatric Exclusivity

- Overview of pediatric exclusivity
  - How does a sponsor obtain pediatric exclusivity?
  - What are the benefits of pediatric exclusivity?
- What are the relevant timing considerations?
  - Pre-approval vs. post-approval
  - Statutory limitations and submission timelines
- How does pediatric exclusivity interact with other regulatory exclusivities?
- How is pediatric exclusivity applied to patents listed the Orange Book?

How to Qualify for Pediatric Exclusivity

- Pediatric exclusivity will be awarded to a sponsor that conducts pediatric studies in accordance with a "Written Request" issued by FDA
  - FDA can issue the Written Request on its own
  - More commonly, a sponsor asks FDA to issue a Written Request by submitting a Proposed Pediatric Study Request (PPSR) to the agency
- A sponsor must submit reports of the pediatric studies as part of a marketing application to add labeling regarding the pediatric use
  - The ***studies are not required to show safety or efficacy in the pediatric population(s)***
    - Do not have to support a new pediatric indication in the drug product's labeling
  - Study results may demonstrate that the drug is not safe or effective for pediatric population(s), or even be inconclusive

Contents of a Written Request

- FDA has broad discretion in deciding what studies to include
  - Generally will include **all** relevant pediatric subpopulations, from neonates to adolescents
  - May include studies in the proposed adult indication and/or known "off-label" uses
- A single Written Request can include multiple studies
  - Pharmacokinetic and/or non-clinical
  - Safety and efficacy
  - FDA may require staggered sequence, *e.g.*, begin study in children aged 6-11 only after completion of study in adolescents aged 12-17
- The Written Request will describe the study or studies in detail
  - Objective(s) of study or studies
  - Study design: Patient population, age groups, study size, endpoints, statistical considerations
  - Deadlines for submission to FDA

Qualifying for Pediatric Exclusivity: Interaction with PREA

- Studies required under PREA can be used to qualify for pediatric exclusivity
  - Must be included in a Written Request
  - Remember that FDA can also include additional studies in Written Request
- iPSP should describe intent to submit a PPSR and seek pediatric exclusivity, if any
  - Ordinarily, PPSR submitted after iPSP; however, can be submitted concurrently (as separate documents)

FDA's Pediatric Exclusivity Determination

- Following submission of reports of the studies, FDA has 180 days to make a pediatric exclusivity determination (in parallel, sNDA subject to 6-month Priority Review)
- FDA will award pediatric exclusivity if:
  - The studies "fairly respond" to the Written Request
    - Meet each and every term of the Written Request **OR** otherwise lead to "clinically meaningful labeling across all age groups and uses" cited in the Written Request
    - REMINDER: Study results may be inconclusive and still qualify for exclusivity
  - The studies were submitted as part of a labeling supplement, AND
  - The studies were conducted in accordance with commonly accepted scientific principles
- A sponsor must also develop and seek approval of any new formulation necessary for the pediatric studies

Practical Timing Considerations

- Pediatric exclusivity can be awarded for pediatric studies conducted after a drug is approved for use in adults or for pediatric studies conducted prior to the initial approval in adults
  - It is uncommon for a sponsor to conduct pediatric studies in advance of approval in order to earn pediatric exclusivity at the time of initial approval
  - Most sponsors elect to obtain approval of adult indication first
- Practically speaking, it may be difficult to accomplish prior to approval
  - Need to sequence studies, for example
- FDA has 120 days to respond to PPSR
  - That response will not always be a finalized Written Request
  - The agency can request additional information, propose alternative studies or study designs, or suggest a meeting with a sponsor

BEST PHARMACEUTICALS FOR CHILDREN ACT

EFFECTS OF PEDIATRIC EXCLUSIVITY

The Effect of Pediatric Exclusivity: *Basic Operation*

- Pediatric exclusivity ***extends*** listed patents and other regulatory exclusivity periods by ***6 months***:
  - Exclusivities and patents listed in the Orange Book or Purple Book ***at the time of the pediatric exclusivity award*** (or at the time of initial approval for a new drug or biologic), or that will be listed with pending application(s) (*e.g.* the pediatric application responding to the WR)
  - For all of the sponsor's products containing the same drug (active moiety) or biologic
    - *E.g.*, multiple NDAs/BLAs for different dosage forms
  - In certain cases, 6-month extension will also be applied to:
    - Later-submitted applications and/or
    - Later-listed patents

Limitations on Pediatric Exclusivity: *Statutory Limitations and Submission Timelines*

- ***Statutory limitation***: Pediatric exclusivity will not be applied to any patent or exclusivity period that expires within 9 months of the award of pediatric exclusivity
- In addition, FDA has 180 days to review the study reports to determine whether they "fairly respond" to the Written Request
  - We advise sponsors to submit their final study reports ***at least 15 months*** (approximately 9 months + 180 days) before the expiration of the relevant patent(s) or exclusivity period(s)
- A sponsor must also allow time for submission of the PPSR, issuance of the Written Request, and the conduct of the pediatric clinical trial(s)
- Generally, a second period of pediatric exclusivity is rare and requires second Written Request
  - Will only extend the 3-year exclusivity awarded for the pediatric studies
  - In other words, no way to get 12-month pediatric extension

The Effect of Pediatric Exclusivity: *Effect on Other Regulatory Exclusivities*

- Pediatric exclusivity is awarded ***only as an add-on to other*** regulatory exclusivities; it is not an independent exclusivity period
  - Drugs approved under NDAs:
    - 5-year "NCE" exclusivity extended to 5.5 years
      - See additional details on next two slides
    - 3-year "new use" exclusivity extended to 3.5 years
  - Biologics approved under BLAs:
    - 12-year reference product exclusivity extended to 12.5 years
      - 4-year bar on submission of biosimilar extended to 4.5 years
  - Both drugs and biologics:
    - 7-year orphan exclusivity extended to 7.5 years

New Chemical Entity (NCE) Exclusivity and Pediatric Exclusivity
Basic Operation of NCE Exclusivity

- Generally, 5-year New Chemical Entity (NCE) exclusivity is awarded upon approval of a drug product that contains a "drug" (an active moiety) that has not previously been approved
  - ***5-Year NCE Exclusivity Period:*** a competitor cannot submit an ANDA or 505(b)(2) NDA with the same active moiety for 5 years
  - ***4-Year "NCE minus 1" (NCE-1) Date:*** the 5-year period is reduced to 4 years, if competitor 505(b)(2) NDA or ANDA challenges listed patent(s) by submitting a paragraph IV certification
  - ***7.5-Year Regulatory Stay:*** If a competitor submits an application with a paragraph IV certification between the NCE-1 date and the end of the 5-year exclusivity period, and the innovator sponsor files infringement litigation, a regulatory stay will arise
    - FDA cannot approve the competitor ANDA or 505(b)(2) NDA until 7.5 years from the date of the innovator's approval, ***unless patent litigation resolved or patent expires before then***
    - Similar to the "30-month stay" (7.5 years = 5 years + 30 months)

New Chemical Entity (NCE) Exclusivity and Pediatric Exclusivity
Application of Pediatric Exclusivity

- Pediatric exclusivity will extend by six months ***each*** of the periods described in the NCE exclusivity provision
  - 5-Year NCE Exclusivity Period becomes 5.5 years
  - 4-Year NCE-1 Date becomes 4.5 years
  - 7.5-Year Regulatory Stay becomes 8 years
- Remember the 9-month statutory limitation and the 180-day FDA review = submission 15 months in advance
  - For NCE exclusivity, the key is the 5-year NCE period, which means submission of pediatric study reports no later than 3 years 9 months post approval = 15 months before end of 5-year period
  - Difficult to extend NCE period unless Written Request obtained prior to original NDA approval

The Effect of Pediatric Exclusivity: *Listed Patents*

- Pediatric exclusivity is not a true extension of the ***term of the patent*** (unlike PTA and PTE)
  - Instead, pediatric exclusivity extends by 6 months any limits the patent imposes on FDA's authority to grant final approval to a competitor product
    - FDA will issue a tentative approval if a competitor product is blocked by the patent – including pediatric exclusivity extension – but is otherwise eligible for final approval
  - There can be no infringement or damages during the 6-month pediatric extension because the underlying patent has expired
- ***Applies only to drug products*** – not biologics
  - Under the BPCIA, patents do not limit FDA's authority to approve biosimilars, unlike patent linkage system under Hatch-Waxman

The Effect of Pediatric Exclusivity: *Listed Patents*

- The effect of pediatric exclusivity will depend on the patent certification filed by the competitor ANDA or 505(b)(2) NDA applicant
  - Pediatric exclusivity will apply **automatically** if:
    - The competitor submits a **Paragraph II certification** (meaning that the patent has expired)
    - The competitor submits a **Paragraph III certification** (meaning that competitor does not seek approval until expiration of the patent)
  - If the competitor submits a **Paragraph IV certification** (claiming that the patent is invalid or will not be infringed by competitor's product), **pediatric exclusivity will not apply unless innovator wins in patent litigation** (*i.e.,* the court finds that the patent is valid and infringed)
- If patent expires during litigation, PIV is deemed to be converted to PII, and the pediatric exclusivity automatically attaches
- Pediatric exclusivity will often impact settlement negotiations

Orange Book Example

- Symbicort was awarded pediatric exclusivity on **January 25, 2017**

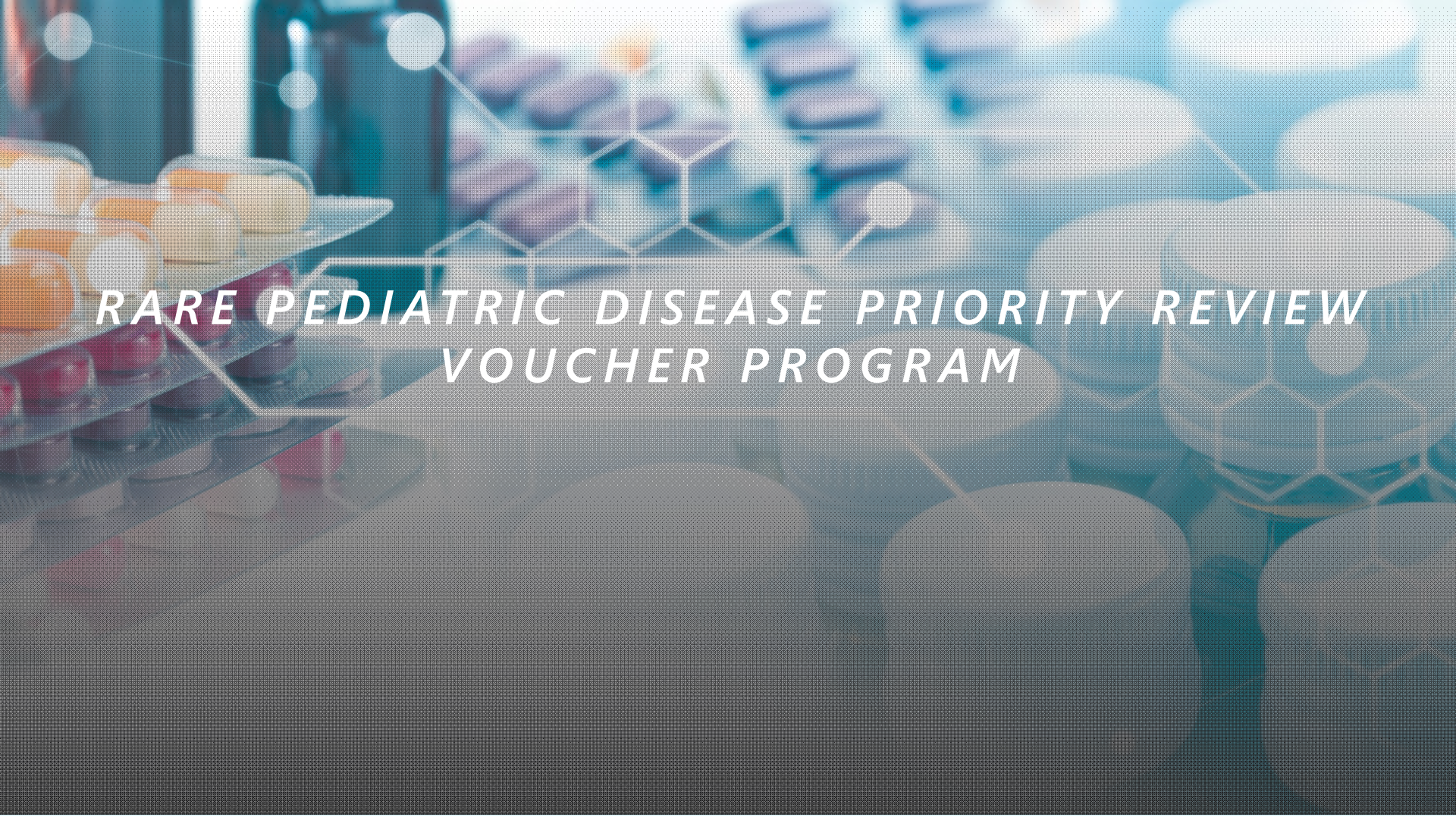
APPL/PROD NO	PATENT NO	PATENT EXPIRATION DATE	PATENT CODES	PATENT DELIST REQUESTED	EXCLUSIVITY CODE(S)	EXCLUSIVITY EXPIRATION DATE
BUDESONIDE; FORMOTEROL FUMARATE DIHYDRATE - SYMBICORT						
N 021929 001	6123924	Sep 26, 2017	DP		M-210	Sep 11, 2020
	7367333	Nov 11, 2018	DP		M-214	Dec 20, 2020
	7367333*PED	May 11, 2019			NPP	Jan 27, 2020
	7587988	Apr 10, 2026	DP		PED	Jul 27, 2020
	7587988*PED	Oct 10, 2026				

These exclusivities **not extended** because they were awarded after January 25, 2017.

Basic operation: These two listed patents **extended** by pediatric exclusivity.

Patent **not extended** because expired within 9 months of January 25, 2017.

These exclusivities **extended** because application pending on January 25, 2017.



RARE PEDIATRIC DISEASE PRIORITY REVIEW VOUCHER PROGRAM

Other Pediatric Programs:
Rare Pediatric Disease Priority Review Voucher Program

- Awards a voucher for a shorter review period on a subsequent application, if sponsor obtains approval of an application for a "rare pediatric disease product application" (21 USC 360ff)
  - Pediatric: a "serious or life-threatening disease in which the serious or life-threatening manifestations primarily affect individuals aged from birth to 18 years"
  - Rare: affects fewer than 200,000 persons in the United States
- Operates independently from pediatric exclusivity
- Rare pediatric disease product application
  - NDA or full BLA
  - Application eligible for Priority Review
  - New active moiety/biological substance
  - Does not seek approval for additional adult indication

Other Pediatric Programs:
Rare Pediatric Disease Priority Review Voucher Program

- 2-step process: RPD designation prior to submission of marketing application
  - At same time as orphan drug or Fast Track designation request(s)
- Sunset provision in the statute:
  - After September 30, 2024, FDA may only award a voucher for an approved rare pediatric disease product application if the sponsor has rare pediatric disease designation for the drug, and that designation was granted by September 30, 2024.
  - After September 30, 2026, FDA may not award any rare pediatric disease priority review vouchers.

Key Resources

- **PREA**
  - Draft Guidance, How to Comply with the Pediatric Research Equity Act (September 2005)
  - Guidance for Industry, Pediatric Study Plans: Content of and Process for Submitting Initial Pediatric Study Plans and Amended Initial Pediatric Study Plans (July 2020)
  - Draft Guidance, Pediatric Study Plans for Oncology Drugs: Transitional Information Until Full Implementation of FDARA Section 504 Questions and Answers (January 2020)
  - Guidance for Industry, FDARA Implementation Guidance for Pediatric Studies of Molecularly Targeted Oncology Drugs: Amendments to Sec. 505B of the FD&C Act (May 2021)
- **BPCA**
  - Draft Guidance, Qualifying for Pediatric Exclusivity Under Section 505A of the Federal Food, Drug, and Cosmetic Act (Sept. 1999) (withdrawn)
- **RPDPRV**
  - Draft Guidance, Rare Pediatric Disease Priority Review Vouchers (July 2019)

BACKUP SLIDES

PREA: Biologics and Biosimilars

- PREA states that non-interchangeable biosimilars are considered to have a "new active ingredient," and therefore may be subject to PREA requirements
  - Submission of iPSP
- But FDA's biosimilars guidance effectively exempts most biosimilars from PREA:
  - If reference product BLA has adequate pediatric labeling, biosimilar can use that (assuming extrapolation shown)
  - If reference product BLA doesn't have adequate pediatric labeling because of a deferral, biosimilar applicant should request a deferral, too, then add labeling once reference product BLA adds it
  - FDA takes the position that interaction of BPCIA and PREA cannot result in (1) a condition of use that has not been previously approved for the reference product, or (2) a dosage form, strength, or route of administration that differs from that of the reference product

The Effect of Pediatric Exclusivity: *Later-Listed Patents*

- **Later-listed patent**: a patent that issues and is listed in the Orange Book after the award of pediatric exclusivity
  - Will be extended by pediatric exclusivity only if it claims the product as it was approved at the time the pediatric exclusivity was awarded
- **Example**: Formulation patent issues 1 year after pediatric exclusivity award, but covers the product formulation that was approved at the time of pediatric exclusivity award
  - When listed in the Orange Book, that patent will be extended by pediatric exclusivity
- **Counter-example**: Supplement for new indication is approved 1 year after pediatric exclusivity award, and method patent covering new indication is listed in Orange Book
  - That patent will not be extended by pediatric exclusivity because it covers a product change that occurred after the award of pediatric exclusivity

The Effect of Pediatric Exclusivity: *Later-Submitted applications*

- **Later-Submitted Applications**: products approved after award of pediatric exclusivity
  - Remember, pending applications get benefit of pediatric exclusivity
  - Patents and regulatory exclusivities that are extended by pediatric exclusivity will also be extended if they are subsequently listed with a later-submitted application
  - However, patents and exclusivities listed for the first time with the new approval will not be extended
- **Example**: NDA for oral tablets approved for orphan indication; Orange Book listing includes orphan exclusivity and a patent covering active ingredient (drug substance)
  - Pediatric exclusivity is awarded and extends the orphan exclusivity and the patent
  - Assume a new NDA is approved for an injectable solution product for the same orphan indication; Orange Book listing includes same orphan exclusivity and same patent covering active ingredient, as well as a second patent covering injectable formulation
  - Pediatric exclusivity will extend the orphan exclusivity and active ingredient patent, but not the newly-listed injectable formulation patent

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