15 February 2024

Dockets Management
Division of Dockets Management
Department of Health and Human Services
Food and Drug Administration
5630 Fishers Lane,
Room 1061, HFA-305
Rockville, MD 20852

AMENDMENT TO DOCKET ID FDA-2024-P-0427

Dear Sir/Madam:

This is in reference to suitability petition FDA-2024-P-0427, the undersigned, hereby submits the complete response to the information request as an amendment to the petition for submission of an ANDA for a Progesterone-based pessary formulation.

Comment 1
You have failed to identify a reference listed drug for which you are proposing a change. Pursuant to 21 CFR 314.93(d), identify the reference listed drug that is the subject of your petition. Additionally, ensure that a copy of the approved labeling for the listed drug has been provided.

Response: The details of the reference listed drug in accordance with 21 CFR 314.93(d) is provided below:

- Active Ingredient: Progesterone
- Proprietary Name: CRINONE
- Strength: 8%
- Dosage Form: Gel
- Route of Administration: Vaginal
- Application Number: N020701
- Approval Date: Jul 31, 1997
- Applicant Holder: Allergan Sales LLC
- Marketing Status: Prescription

The approved prescribing information for Crinone is provided as ***Attachment-I***.

DDReg Pharma INC. 1201 North Market Street Suite 111, Wilmington, DE 19801
Ph: +1 (302) 391-6010 | FAX: +1 (302) 391-6009 | Email: info@ddregpharma.com |
Website: www.ddregpharma.com

Comment 2

Your petition proposes a change in strength from a listed drug. In accordance with 21 CFR 314.93(b), provide the strength(s) of your proposed drug product.

Response: The strength of the reference listed drug is 8% containing 90mg of Progesterone, being released sustainably in the gel form and the proposed formulation strength shall be 400mg.

Comment 3

Your petition proposes a change in dosage form from a listed drug. In accordance with 21 CFR 314.93(b), specify the dosage form of your proposed drug product.

Response: The dosage form of the reference listed drug is Gel which is administered via vaginal route and the proposed formulation form shall be a pessary which is also administered via vaginal route.

Comment 4

Pursuant to 21 CFR 314.93(d), provide the proposed drug product labeling.

Response: The proposed prescribing information of the Progesterone pessary 400mg is provided as ***Attachment-II***. The proposed prescribing information has been provided in the non-PLR format in accordance with the available information of the reference listed drug in the same format.

Comment 5

You are requesting that FDA permit the filing of an Abbreviated New Drug Application (ANDA) under an approved suitability petition under section 505(j)(2)(C) of Federal Food, Drug, and Cosmetic Act ("the Act") for a change in dosage form. This type of change is subject to the pediatric assessment requirements imposed by the Pediatric Research Equity Act (PREA) as amended in 505B(a)(5) and 505B(e)(2)(B)(ii) of the Act. To request a waiver of the requirement to submit pediatric assessments, please include in your waiver the statutory reason(s) for requesting a waiver, including reference to the applicable statutory authority. The request should also include evidence that the request meets the statutory reason(s) for waiver. For additional information, please refer to the draft guidance for industry on *Pediatric Drug Development: Regulatory Considerations – Complying With the Pediatric Research Equity Act and Qualifying for Pediatric Exclusivity Under the Best Pharmaceuticals for Children Act* (May 2023) which replaces the draft guidance for industry *How to Comply With the Pediatric Research Equity Act*.

Response: The pediatric requirements in accordance with PREA is not applicable to the proposed progesterone pessary formulation because Progesterone formulations are generally indicated for supplementation or replacement as part of an Assisted Reproductive Technology ("ART") treatment for infertile women with progesterone deficiency. The justification report for waiver to these assessments is provided as ***Attachment-III***.

Sincerely,

Andrej Gasperlin

DDReg Pharma INC. 1201 North Market Street Suite 111, Wilmington, DE 19801
Ph: +1 (302) 391-6010 | FAX: +1 (302) 391-6009 | Email: info@ddregpharma.com |
Website: www.ddregpharma.com

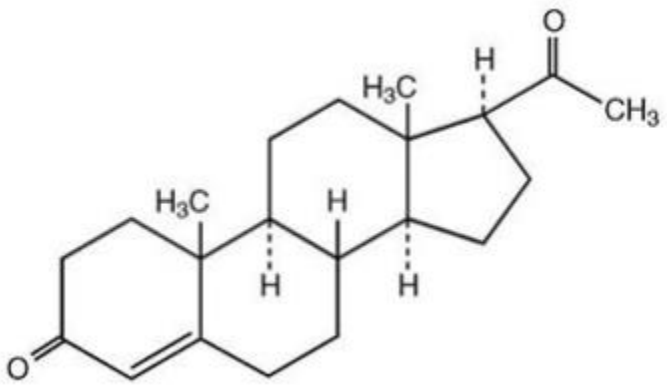
Crinone® 4% and Crinone® 8%
(progesterone gel)
PHYSICIAN INFORMATION
For Vaginal Use Only
Rx only

DESCRIPTION

Crinone® (progesterone gel) is a bioadhesive vaginal gel containing micronized progesterone in an emulsion system, which is contained in single use, polypropylene vaginal applicators. The carrier vehicle is an oil in water emulsion containing the water swellable, but insoluble polymer, polycarbophil. The progesterone is partially soluble in both the oil and water phase of the vehicle, with the majority of the progesterone existing as a suspension. Physically, Crinone has the appearance of a soft, white to off-white gel.

The active ingredient, progesterone, is present in either a 4% or an 8% concentration (w/w). The chemical name for progesterone is pregn-4-ene-3,20-dione. It has an empirical formula of $C_{21}H_{30}O_2$ and a molecular weight of 314.5.

The structural formula is:



Progesterone exists in two polymorphic forms. Form 1, which is the form used in Crinone, exists as white orthorhombic prisms with a melting point of 127-131°C.

Each applicator delivers 1.125 grams of Crinone gel containing either 45 mg (4% gel) or 90 mg (8% gel) of progesterone in a base containing glycerin, light mineral oil, polycarbophil, carbomer homopolymer Type B, hydrogenated palm oil glyceride, sorbic acid, purified water and may contain sodium hydroxide.

CLINICAL PHARMACOLOGY

Progesterone is a naturally occurring steroid that is secreted by the ovary, placenta, and adrenal gland. In the presence of adequate estrogen, progesterone transforms a proliferative endometrium into a secretory endometrium. Progesterone is essential for the development of decidual tissue, and the effect of progesterone on the differentiation of glandular epithelia and stroma has been extensively studied. Progesterone is necessary to increase endometrial receptivity for implantation of an embryo. Once an embryo is implanted, progesterone acts to maintain the pregnancy. Normal or near-normal endometrial responses to oral estradiol and intramuscular progesterone have been noted in functionally agonadal women through the sixth decade of life. Progesterone administration decreases the circulatory levels of gonadotropins.

Pharmacokinetics

Absorption

Due to the sustained release properties of Crinone, progesterone absorption is prolonged with an absorption half-life of approximately 25 to 50 hours, and an elimination half-life of 5 to 20 minutes. Therefore, the pharmacokinetics of Crinone are rate-limited by absorption rather than by elimination.

The bioavailability of progesterone in Crinone was determined relative to progesterone administered intramuscularly. In a single dose crossover study, 20 healthy, estrogenized postmenopausal women received 45 mg or 90 mg progesterone vaginally in Crinone 4% or Crinone 8%, or 45 mg or 90 mg progesterone intramuscularly. The pharmacokinetic parameters (mean ± standard deviation) are shown in Table 1.

TABLE 1 Single Dose Relative Bioavailability

	Crinone 4%	**45 mg Intramuscular Progesterone**	**Crinone 8%**	**90 mg Intramuscular Progesterone**
C_{max} (ng/mL)	13.15 ± 6.49	39.06 ± 13.68	14.87 ± 6.32	53.76 ± 14.9
$C_{avg\ 0\text{-}24}$ (ng/mL)	6.94 ± 4.24	22.41 ± 4.92	6.98 ± 3.21	28.98 ± 8.75
$AUC_{0\text{-}96}$ (ng·hr/mL)	288.63 ± 273.72	806.26 ± 102.75	296.78 ± 129.90	1378.91 ± 176.39
T_{max} (hr)	5.6 ± 1.84	8.2 ± 6.43	6.8 ± 3.3	9.2 ± 2.7
$t_{1/2}$ (hr)	55.13 ± 28.04	28.05 ± 16.87	34.8 ± 11.3	19.6 ± 6.0
F (%)	27.6		19.8	

C_{max} - maximum progesterone serum concentration
$C_{avg\ 0\text{-}24}$ - average progesterone serum concentration over 24 hours
$AUC_{0\text{-}96}$ - area under the drug concentration versus time curve from 0-96 hours post dose
T_{max} - time to maximum progesterone concentration
$t_{1/2}$ - elimination half-life
F - relative bioavailability

The multiple dose pharmacokinetics of Crinone 4% and Crinone 8% administered every other day and Crinone 8% administered daily or twice daily for 12 days were studied in 10 healthy, estrogenized postmenopausal women in two separate studies. Steady state was achieved within the first 24 hours after initiation of treatment. The pharmacokinetic parameters (mean ± standard deviation) after the last administration of Crinone 4% or 8% derived from these studies are shown in Table 2.

TABLE 2 Multiple Dose Pharmacokinetics

	Assisted Reproductive Technology		**Secondary Amenorrhea**	
	Daily Dosing 8%	**Twice Daily Dosing 8%**	**Every Other Day Dosing 4%**	**Every Other Day Dosing 8%**
C_{max} (ng/mL)	15.97± 5.05	14.57 ± 4.49	13.21± 9.46	13.67 ± 3.58
C_{avg} (ng/mL)	8.99 ± 3.53	11.6 ± 3.47	4.05 ± 2.85	6.75 ± 2.83
T_{max} (hr)	5.40 ± 0.97	3.55 ± 2.48	6.67 ± 3.16	7.00 ± 2.88
$AUC_{0\text{-}t}$ (ng·hr/mL)	391.98 ±153.28	138.72 ± 41.58	242.15 ± 167.88	438.36 ± 223.36
$t_{1/2}$ (hr)	45.00 ± 34.70	25.91 ± 6.15	49.87 ± 31.20	39.08 ± 12.88

C_{max} -maximum progesterone serum concentration
C_{avg} -average progesterone serum concentration
T_{max} -time to maximum progesterone concentration
AUC_{0-t} -area under the drug concentration versus time curve
$t_{1/2}$ -elimination half-life

Distribution

Progesterone is extensively bound to serum proteins (~ 96-99%), primarily to serum albumin and corticosteroid binding globulin.

Metabolism

The major urinary metabolite of oral progesterone is 5β-pregnan-3α, 20α-diol glucuronide which is present in plasma in the conjugated form only. Plasma metabolites also include 5β-pregnan-3α-ol-20-one (5β-pregnanolone) and 5α-pregnan-3α-ol-20-one (5α-pregnanolone).

Excretion

Progesterone undergoes both biliary and renal elimination. Following an injection of labeled progesterone, 50-60% of the excretion of progesterone metabolites occurs via the kidney; approximately 10% occurs via the bile and feces, the second major excretory pathway. Overall recovery of labeled material accounts for 70% of an administered dose, with the remainder of the dose not characterized with respect to elimination. Only a small portion of unchanged progesterone is excreted in the bile.

CLINICAL STUDIES

Assisted Reproductive Technology

In a single-center, open-label study (COL1620-007US), 99 women (aged 28-47 years) with either partial (n = 84) or premature ovarian failure (n = 15) who were candidates to receive a donor oocyte transfer as an Assisted Reproductive Technology ("ART") procedure were randomized to receive either Crinone 8% twice daily (n = 68) or intramuscular progesterone 100 mg daily (n = 31). The study was divided into three phases (Pilot, Donor Egg and Treatment). The first phase of the study consisted of a test Pilot Cycle to ensure that the administration of transdermal estradiol and progesterone would adequately prime the endometrium to receive the donor egg. The second phase was the Donor Egg Cycle during which a fertilized oocyte was implanted. Crinone 8% was administered beginning the evening of Day 14 of the Pilot and Donor Egg cycles. Subjects with partial ovarian function also underwent a Pre-Pilot Cycle and a Pre-Donor Egg Cycle during which time they were administered only leuprolide acetate to suppress remaining ovarian function. The Pre-Pilot Cycle, Pilot Cycle, Pre-Donor Egg Cycle, and Donor Egg Cycle each lasted approximately 34 days. The third phase of the study consisted of a 10-week treatment period to maintain a pregnancy until placental autonomy was achieved.

Sixty-one women received Crinone 8% as part of the Pilot Cycle to determine their endometrial response. Of the 55 evaluable endometrial biopsies in the Crinone 8% group performed on Day 25 to 27, all were histologically "in-phase", consistent with luteal phase biopsy specimens of menstruating women at comparable time intervals. Fifty-four women who received Crinone 8% and had a histologically "in-phase" biopsy received a donor oocyte transfer. Among these 54 Crinone-treated women, clinical pregnancies (assessed about week 10 after transfer by clinical examination, ultrasound and/or ß-hCG levels) occurred in 26 women (48%). Seventeen women (31%) delivered a total of 25 newborns, seven women (13%) had spontaneous abortions and two women (4%) had elective abortions.

In a second study (COL1620-F01), Crinone 8% was used in luteal phase support of women with tubal or idiopathic infertility due to endometriosis and normal ovulatory cycles, undergoing *in vitro* fertilization ("IVF") procedures. All women received a GnRH analog to suppress endogenous progesterone, human menopausal gonadotropins, and human chorionic gonadotropin. In this multi-center, open-label study, 139 women (aged 22-38 years) received Crinone 8% once daily beginning within 24 hours of embryo transfer and continuing through Day 30 post-transfer. Clinical pregnancies assessed at Day 90 post-transfer were seen in 36 (26%) of women.

Thirty-two women (23%) delivered newborns and four women (3%) had spontaneous abortions. *(See PRECAUTIONS, Pregnancy)*

Secondary Amenorrhea

In three parallel, open-label studies (COL1620-004US, COL1620-005US, COL1620-009US), 127 women (aged 18-44) with hypothalamic amenorrhea or premature ovarian failure were randomized to receive either Crinone 4% (n = 62) or Crinone 8% (n = 65). All women were treated with either conjugated estrogens 0.625 mg daily (n = 100) or transdermal estradiol (delivering 50 mcg/day) twice weekly (n = 27).

Estrogen therapy was continuous for the entire three 28-day cycle studies. At Day 15 of the second cycle (six weeks after initiating estrogen replacement), women who demonstrated adequate response to estrogen therapy (by ultrasound) and who continued to be amenorrheic received Crinone every other day for six doses (Day 15 through Day 25 of the cycle).

In cycle 2, Crinone 4% induced bleeding in 79% of women and Crinone 8% induced bleeding in 77% of women. In the third cycle, estrogen was continued and Crinone was administered every other day beginning on Day 15 for six doses. On Day 24 an endometrial biopsy was performed. In 53 women who received Crinone 4%, biopsy results were as follows: 7% proliferative, 40% late secretory, 19% mid secretory, 13% early secretory, 7% atrophic, 6% menstrual endometrium, 6% inactive endometrium and 2% negative endometrium. In 54 women who received Crinone 8%, biopsy results were as follows: 44% late secretory, 19% mid secretory, 11% early secretory, 19% atrophic, 5% menstrual endometrium and 2% "oral contraceptive like" endometrium.

INDICATIONS AND USAGE

Assisted Reproductive Technology

Crinone 8% is indicated for progesterone supplementation or replacement as part of an Assisted Reproductive Technology ("ART") treatment for infertile women with progesterone deficiency.

Secondary Amenorrhea

Crinone 4% is indicated for the treatment of secondary amenorrhea. Crinone 8% is indicated for use in women who have failed to respond to treatment with Crinone 4%.

CONTRAINDICATIONS

Crinone should not be used in individuals with any of the following conditions:

1. Known sensitivity to Crinone (progesterone or any of the other ingredients)
2. Undiagnosed vaginal bleeding
3. Liver dysfunction or disease
4. Known or suspected malignancy of the breast or genital organs
5. Missed abortion
6. Active thrombophlebitis or thromboembolic disorders, or a history of hormone-associated thrombophlebitis or thromboembolic disorders

WARNINGS

The physician should be alert to the earliest manifestations of thrombotic disorders (thrombophlebitis, cerebrovascular disorders, pulmonary embolism, and retinal thrombosis). Should any of these occur or be suspected, the drug should be discontinued immediately.

Progesterone and progestins have been used to prevent miscarriage in women with a history of recurrent spontaneous pregnancy losses. No adequate evidence is available to show that they are effective for this purpose.

PRECAUTIONS

General

1. The pretreatment physical examination should include special reference to breast and pelvic organs, as well as Papanicolaou smear.
2. In cases of breakthrough bleeding, as in all cases of irregular vaginal bleeding, nonfunctional causes should be considered. In cases of undiagnosed vaginal bleeding, adequate diagnostic measures should be undertaken.
3. Because progestogens may cause some degree of fluid retention, conditions which might be influenced by this factor (e.g., epilepsy, migraine, asthma, cardiac or renal dysfunction) require careful observation.
4. The pathologist should be advised of progesterone therapy when relevant specimens are submitted.
5. Patients who have a history of psychic depression should be carefully observed and the drug discontinued if the depression recurs to a serious degree.
6. A decrease in glucose tolerance has been observed in a small percentage of patients on estrogen-progestin combination drugs. The mechanism of this decrease is not known. For this reason, diabetic patients should be carefully observed while receiving progestin therapy.

Information for Patients

The product should not be used concurrently with other local intravaginal therapy. If other local intravaginal therapy is to be used concurrently, there should be at least a 6-hour period before or after Crinone administration. Small, white globules may appear as a vaginal discharge possibly due to gel accumulation, even several days after usage.

Drug Interactions

No drug interactions have been assessed with Crinone.

Carcinogenesis, Mutagenesis, Impairment of Fertility

Nonclinical toxicity studies to determine the potential of Crinone to cause carcinogenicity or mutagenicity have not been performed. The effect of Crinone on fertility has not been evaluated in animals.

Pregnancy

[See CLINICAL STUDIES, Assisted Reproductive Technology]

Crinone 8% has been used to support embryo implantation and maintain pregnancies through its use as part of ART treatment regimens in two clinical studies (studies COL1620-007US and COL1620-F01). In the first study (COL1620-007US), 54 Crinone-treated women had donor oocyte transfer procedures, and clinical pregnancies occurred in 26 women (48%). The outcomes of these 26 pregnancies were as follows: one woman had an elective termination of pregnancy at 19 weeks due to congenital malformations (omphalocele) associated with a chromosomal abnormality; one woman pregnant with triplets had an elective termination of her pregnancy; seven women had spontaneous abortions; and 17 women delivered 25 apparently normal newborns.

In the second study (COL1620-F01), Crinone 8% was used in the luteal phase support of women undergoing *in vitro* fertilization ("IVF") procedures. In this multi-center, open-label study, 139 women received Crinone 8% once daily beginning within 24 hours of embryo transfer and continuing through Day 30 post-transfer.

Clinical pregnancies assessed at Day 90 post-transfer were seen in 36 (26%) of women. Thirty-two women (23%) delivered newborns and four women (3%) had spontaneous abortions. Of the 47 newborns delivered, one had a teratoma associated with a cleft palate; one had respiratory distress syndrome; 44 were apparently normal and one was lost to follow-up.

Geriatric Use

The safety and effectiveness in geriatric patients (over age 65) have not been established.

Pediatric Use

Safety and effectiveness in pediatric patients have not been established.

Nursing Mothers

Detectable amounts of progestins have been identified in the milk of mothers receiving them. The effect of this on the nursing infant has not been determined.

ADVERSE REACTIONS

Assisted Reproductive Technology

In a study of 61 women with ovarian failure undergoing a donor oocyte transfer procedure receiving Crinone 8% twice daily, treatment-emergent adverse events occurring in 5% or more of the women are shown in Table 3.

TABLE 3 Treatment-Emergent Adverse Events in ≥ 5% of Women Receiving Crinone 8% Twice Daily Study COL1620-007US (n = 61)

Body as a Whole	
Bloating	7%
Cramps NOS	15%
Pain	8%
Central and Peripheral Nervous System	
Dizziness	5%
Headache	13%
Gastro-Intestinal System	
Nausea	7%
Reproductive, Female	
Breast Pain	13%
Moniliasis Genital	5%
Vaginal Discharge	7%
Skin and Appendages	
Pruritus Genital	5%

In a second clinical study of 139 women using Crinone 8% once daily for luteal phase support while undergoing an *in vitro* fertilization procedure, treatment-emergent adverse events reported in ≥ 5% of the women are shown in Table 4.

TABLE 4 Treatment-Emergent Adverse Events in ≥ 5% of Women Receiving Crinone 8% Once Daily Study COL1620-F01 (n = 139)

Body as a Whole	
Abdominal Pain	12%
Perineal Pain Female	17%
Central and Peripheral Nervous System	
Headache	17%
Gastro-Intestinal System	

Constipation	27%
Diarrhea	8%
Nausea	22%
Vomiting	5%
Musculo-Skeletal System	
Arthralgia	8%
Psychiatric	
Depression	11%
Libido Decreased	10%
Nervousness	16%
Somnolence	27%
Reproductive, Female	
Breast Enlargement	40%
Dyspareunia	6%
Urinary System	
Nocturia	13%

Secondary Amenorrhea

In three studies, 127 women with secondary amenorrhea received estrogen replacement therapy and Crinone 4% or 8% every other day for six doses. Treatment-emergent adverse events during estrogen and Crinone treatment that occurred in 5% or more of women are shown in Table 5.

TABLE 5 Treatment-Emergent Adverse Events in ≥ 5% of Women Receiving Estrogen Treatment and Crinone Every Other Day Studies COL1620-004US, COL1620-005US, COL1620-009US

	Estrogen + Crinone 4% n = 62	**Estrogen + Crinone 8% n = 65**
Body as a Whole		
Abdominal Pain	3 (5%)	6 (9%)
Appetite Increased	3 (5%)	5 (8%)
Bloating	8 (13%)	8 (12%)
Cramps NOS	12 (19%)	17 (26%)
Fatigue	13 (21%)	14 (22%)
Central and Peripheral Nervous System		
Headache	12 (19%)	10 (15%)
Gastro-Intestinal System		
Nausea	5 (8%)	4 (6%)
Musculo-Skeletal System		
Back Pain	5 (8%)	2 (3%)
Myalgia	5 (8%)	0 (0%)
Psychiatric		
Depression	12 (19%)	10 (15%)
Emotional Lability	14 (23%)	14 (22%)
Sleep Disorder	11 (18%)	12 (18%)
Reproductive, Female		

Vaginal Discharge	7 (11%)	2 (3%)
Resistance Mechanism		
Upper Respiratory Tract Infection	3 (5%)	5 (8%)
Skin and Appendages		
Pruritus Genital	1 (2%)	4 (6%)

OVERDOSAGE

There have been no reports of overdosage with Crinone. In the case of overdosage, however, discontinue Crinone, treat the patient symptomatically, and institute supportive measures.

As with all prescription drugs, this medicine should be kept out of the reach of children.

DOSAGE AND ADMINISTRATION

Assisted Reproductive Technology

Crinone 8% is administered vaginally at a dose of 90 mg once daily in women who require progesterone supplementation. Crinone 8% is administered vaginally at a dose of 90 mg twice daily in women with partial or complete ovarian failure who require progesterone replacement. If pregnancy occurs, treatment may be continued until placental autonomy is achieved, up to 10 to 12 weeks.

Secondary Amenorrhea

Crinone 4% is administered vaginally every other day up to a total of six doses. For women who fail to respond, a trial of Crinone 8% every other day up to a total of six doses may be instituted.

It is important to note that a dosage increase from the 4% gel can only be accomplished by using the 8% gel. Increasing the volume of gel administered does not increase the amount of progesterone absorbed.

HOW SUPPLIED

Crinone is available in the following strengths:

4% gel (45 mg) in a single use, disposable, white polypropylene vaginal applicator with a teal twist-off cap. Each applicator contains 1.3 g of gel and delivers 1.125 g of gel.

NDC 0023-6150-04: 6 Single-use prefilled applicators.

8% gel (90 mg) in a single use, disposable, white polypropylene vaginal applicator with a teal twist-off cap. Each applicator contains 1.3 g of gel and delivers 1.125 g of gel.

NDC 0023-6151-08: 15 Single-use prefilled applicators.

Each applicator is wrapped and sealed in a foil overwrap.

Store at 20-25ºC (68-77ºF). [See USP controlled room temperature.]

Keep out of reach of children.

Rx only

For all medical inquiries contact:

Allergan USA, Inc.
Irvine, CA 92612

1-800-678-1605

Distributed by: Allergan USA, Inc.
Irvine, CA 92612

Content Updated: June 2017

Product of the Netherlands.

PATIENT INFORMATION

Crinone® 4% and **Crinone® 8%**
(progesterone gel)
For Vaginal Use Only

Please read this information carefully before you start to use Crinone and each time your prescription is renewed, in case anything has changed. This leaflet does not take the place of discussions with your doctor. If you still have any questions, ask your doctor or healthcare provider.

What is Crinone?

Crinone is medicine that contains the female hormone called progesterone.

What is Crinone used for?

- Crinone 4% and Crinone 8% are used to treat the absence of a menstrual period in a woman who has previously had a menstrual period. Progesterone is one of the hormones that allows women to have regular menstrual periods. When you do not produce enough progesterone, menstrual irregularities can occur. Crinone may be prescribed to increase your progesterone.
- Crinone 8% is also used as part of a program for women who are undergoing fertility treatments to get pregnant. Progesterone is one of the hormones that helps to prepare the lining of your uterus so that it is ready to receive and nourish a fertilized egg and to continue a pregnancy. If you are undergoing ART treatment and your doctor has determined your body does not produce enough progesterone on its own, Crinone may be prescribed to increase your progesterone.
- If pregnancy occurs, Crinone may be supplemented for 10 to 12 weeks until production of progesterone by the placenta is adequate.

Who should not use Crinone?

Do not start using Crinone if you:

- Are allergic to progesterone, progesterone-like drugs, or any of the inactive ingredients in the gel (ask a pharmacist if you are not sure about the inactive ingredients in Crinone).
- Have unusual vaginal bleeding which has not been evaluated by a doctor.
- Have or have had a liver disease.
- Have or have had cancer of the breast or genital organs.
- Have had a miscarriage and your physician suspects some tissue is still in the uterus.
- Have or have had blood clots in the legs, lungs, eyes, or elsewhere.

What are the possible side effects of Crinone?

Serious side effects include:

- Blood clots. Progestational drug products may increase your chance of having blood clots in your blood vessels. Blood clots can cause:
  - blood vessel problems (thrombophlebitis)
  - stroke

    - loss of your arm or leg
    - blood clot in your lungs (pulmonary embolus)
    - heart attack
    - death

- Birth defects. Abdominal wall defect and cleft palate have been reported with Crinone use in early pregnancy. It is not known if these defects were caused by Crinone.

Call your healthcare provider right away if you get any of the following warning signs or any other unusual symptoms that concern you:

- Pains in the calves or chest, a sudden shortness of breath or coughing blood indicating possible clots in the legs, heart, or lungs.
- Severe headache or vomiting, dizziness, faintness, or changes in vision or speech, weakness or numbness of an arm or leg indicating possible clots in the brain or eye.

Common side effects include:

- abdominal pain
- perineal pain (the perineum is the area between the vagina and the rectum)
- cramps
- bloating
- headache
- fatigue
- increased appetite
- constipation
- diarrhea
- nausea
- joint pain
- depression
- mood swings
- sleep disorder
- nervousness
- decreased libido
- breast enlargement
- excessive urination at night
- vaginal discharge
- upper respiratory tract infection

These are not all the possible side effects of Crinone. For more information, ask your healthcare provider or pharmacist for advice about side effects. **To report SUSPECTED ADVERSE REACTIONS, contact Allergan at 1-800-678-1605 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.**

How should I use Crinone?

Use as directed by your healthcare provider.

Read the Instructions for Use included in this leaflet for information on the right way to use Crinone.

Additional information about Crinone

- You may see a small amount of white discharge that may look like a vaginal discharge. This discharge may be caused by gel that can remain in your vagina, even several days after use. Gel discharge from your vagina is normal, but if you are concerned, talk to your healthcare provider.
- If you miss a dose of Crinone, use it as soon as you remember.

- **Do not** use more Crinone than the dose prescribed by your doctor.
- Talk to your healthcare provider about whether to use other vaginal medicines when you are using Crinone.

General information about the safe and effective use of Crinone

Medicines are sometimes prescribed for purposes other than those listed in a Patient Information Leaflet. Do not use Crinone for another condition. Your doctor has prescribed this drug for you and you alone. Do not give this drug to anyone else, even if they have the same condition.

Keep Crinone out of the reach of children

This leaflet provides the most important information about Crinone. If you would like more information, talk with your healthcare provider or pharmacist. You can ask for information about Crinone that is written for health professionals.

You can get more information by calling the toll free number 1-888-776-4358 or visit www.crinoneusa.com.

What are the ingredients in Crinone?

Crinone contains either 45 mg (4% gel) or 90 mg (8% gel) of progesterone in a base containing glycerin, light mineral oil, polycarbophil, carbomer homopolymer Type B, hydrogenated palm oil glyceride, sorbic acid, purified water and may contain sodium hydroxide.

How should I store Crinone?

Store Crinone at room temperature between 68°F to 77°F (20°C to 25°C).
Do not use Crinone after the expiration date printed on the box.

INSTRUCTIONS FOR USE

Crinone® 4% and Crinone® 8% ("KRI-noan")
(progesterone gel)

For Vaginal Use Only

You will need the following supplies: See Figure A.

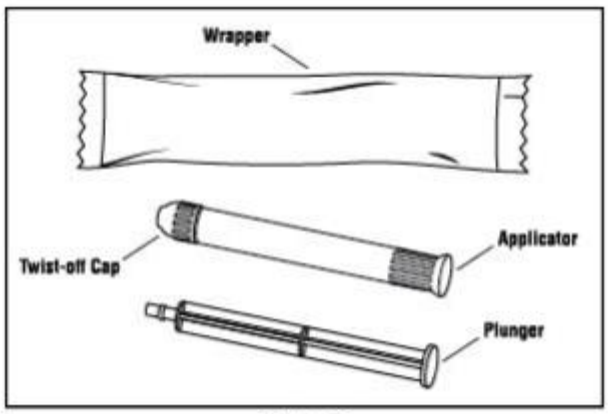


Figure A

Step 1. Remove the applicator from the sealed wrapper.

- Open the sealed wrapper and remove the applicator. Do not remove the twist-off cap at this time. **See Figure B.**

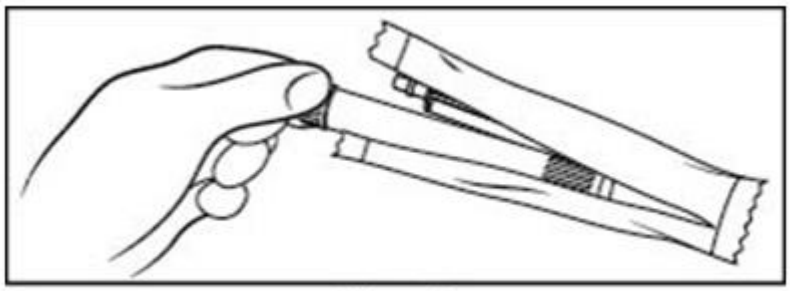


Figure B

Step 2. Insert the plunger into the open end of the applicator. See Figure C.

- Hold the applicator on each side and push the plunger into the applicator until the plunger snaps into place.
- You will see about 1 inch of the plunger outside of the applicator.

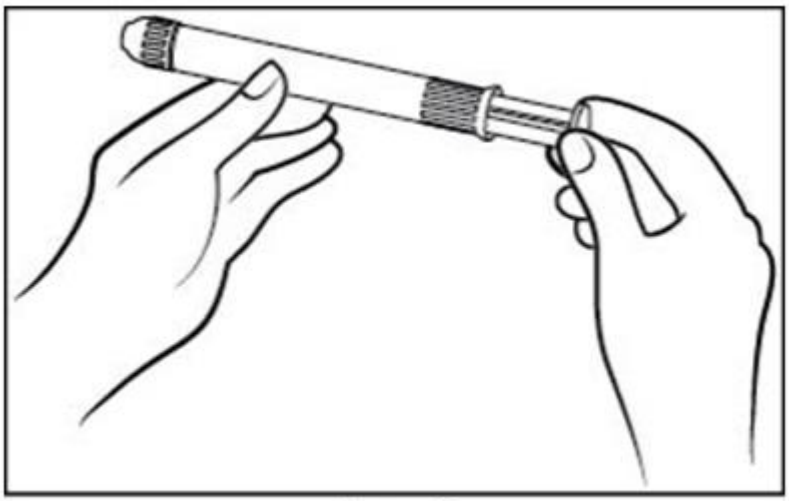


Figure C

Step 3. Remove the cap. See Figures D and E.

- Remove the cap from the tip of the applicator by twisting it counterclockwise.
- Do not push the plunger while you are removing the cap. This could cause some gel to come out.

Figure D

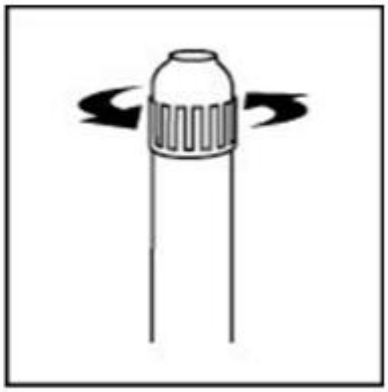


Figure E

Step 4. Prepare to insert the applicator. See Figure F.

Choose the position that is most comfortable for you. For example, lying down on your back with your knees bent.

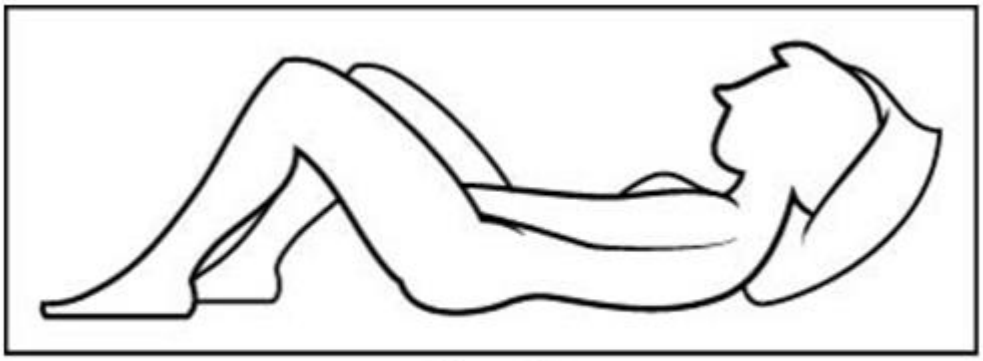


Figure F

Step 5. Insert the applicator. See Figure G.

- After you are in a comfortable position, gently insert the rounded tip of the applicator into your vagina.

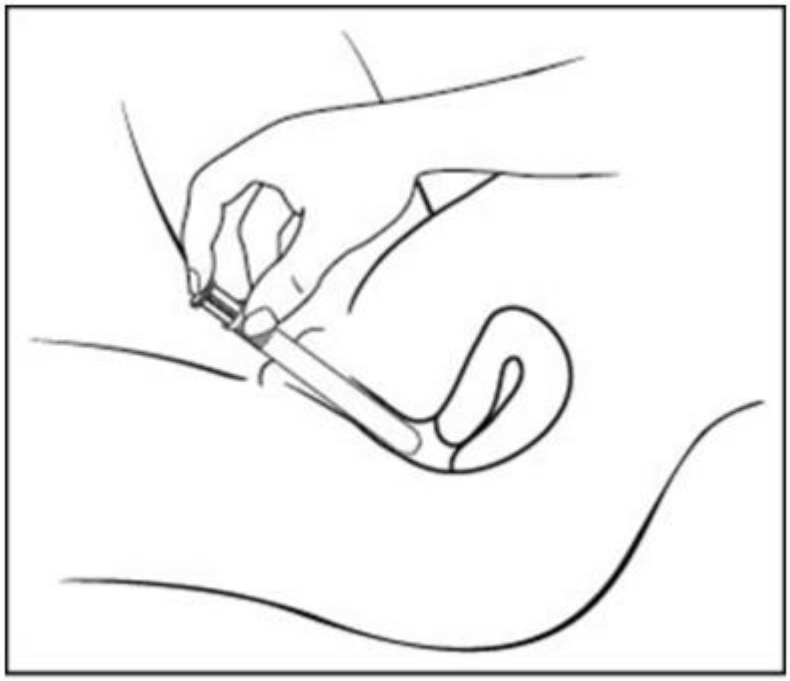


Figure G

Step 6. Push the plunger. See Figure H.

- While the applicator is inserted in your vagina, push the plunger to release the gel into your vagina.

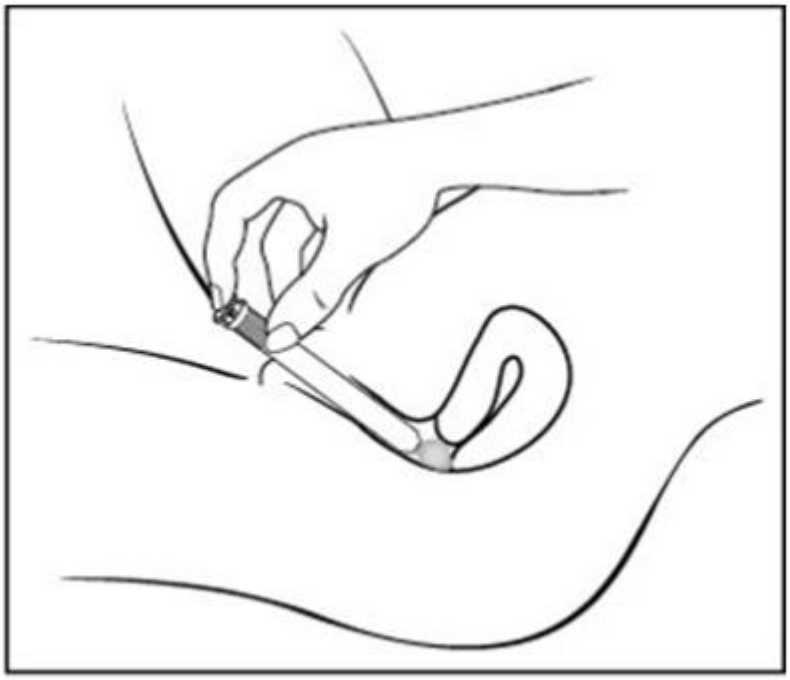


Figure H

Step 7. Remove the applicator from your vagina and throw it away in your household trash.

- It is normal for a small amount of gel to be left in the applicator. You will still get the right dose of medicine.

This Instructions for Use has been approved by the U.S. Food and Drug Administration.

Rx only

For all medical inquiries contact:
Allergan USA, Inc.

Irvine, CA 92612
1-800-678-1605

Distributed by:
Allergan USA, Inc.

Irvine, CA 92612

Content Updated: June 2017

Product of the Netherlands.

73343US10

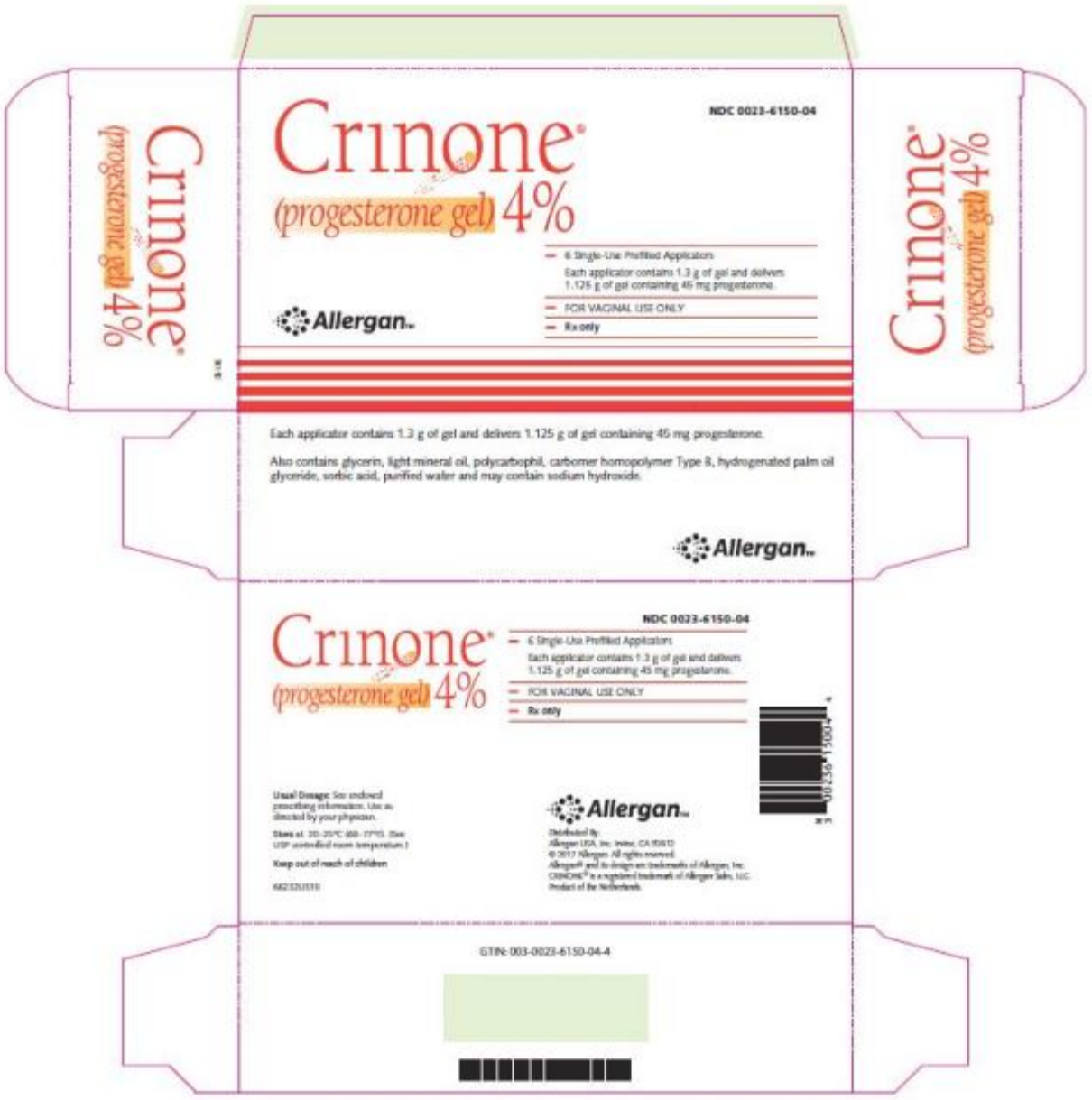
PRINCIPAL DISPLAY PANEL

NDC 0023-6150-04

Crinone®
(progesterone gel) 4%
6 Single-Use Prefilled Applicators
Each applicator contains 1.3 g of gel and delivers
1.125 g of gel containing 45 mg progesterone.

FOR VAGINAL USE ONLY

Rx only



PRINCIPAL DISPLAY PANEL

NDC 0023-6151-08

Crinone®
(progesterone gel) 8%
15 Single-Use Prefilled Applicators
Each applicator contains 1.3 g of gel and delivers
1.125 g of gel containing 90 mg progesterone.

FOR VAGINAL USE ONLY

Rx only

CRINONE

progesterone gel

Product Information

Product Type	HUMAN PRESCRIPTION DRUG	**Item Code (Source)**	NDC:0023-6150
Route of Administration	VAGINAL		

Active Ingredient/Active Moiety

Ingredient Name	Basis of Strength	Strength
PROGESTERONE (UNII: 4G7DS2Q64Y) (PROGESTERONE - UNII:4G7DS2Q64Y)	PROGESTERONE	45 mg in 1.125 g

Inactive Ingredients

Ingredient Name	Strength
GLYCERIN (UNII: PDC6A3C0OX)	
MINERAL OIL (UNII: T5L8T28FGP)	
POLYCARBOPHIL (UNII: W25LM17A4W)	
HYDROGENATED PALM OIL (UNII: 257THB963H)	
SORBIC ACID (UNII: X045WJ989B)	
WATER (UNII: 059QF0KO0R)	
SODIUM HYDROXIDE (UNII: 55X04QC32I)	
CARBOMER HOMOPOLYMER TYPE B (ALLYL SUCROSE CROSSLINKED) (UNII: Z135WT9208)	

Packaging

#	Item Code	Package Description	Marketing Start Date	Marketing End Date

1	NDC:0023-6150-04	6 in 1 CARTON	05/13/1997	
1		1.125 g in 1 APPLICATOR; Type 2: Prefilled Drug Delivery Device/System (syringe, patch, etc.)		

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
NDA	NDA020701	05/13/1997	

CRINONE

progesterone gel

Product Information

Product Type	HUMAN PRESCRIPTION DRUG	**Item Code (Source)**	NDC:0023-6151
Route of Administration	VAGINAL		

Active Ingredient/Active Moiety

Ingredient Name	Basis of Strength	Strength
PROGESTERONE (UNII: 4G7DS2Q64Y) (PROGESTERONE - UNII:4G7DS2Q64Y)	PROGESTERONE	90 mg in 1.125 g

Inactive Ingredients

Ingredient Name	Strength
GLYCERIN (UNII: PDC6A3C0OX)	
MINERAL OIL (UNII: T5L8T28FGP)	
POLYCARBOPHIL (UNII: W25LM17A4W)	
CARBOMER HOMOPOLYMER TYPE B (ALLYL SUCROSE CROSSLINKED) (UNII: Z135WT9208)	
HYDROGENATED PALM OIL (UNII: 257THB963H)	
SORBIC ACID (UNII: X045WJ989B)	
WATER (UNII: 059QF0KO0R)	
SODIUM HYDROXIDE (UNII: 55X04QC32I)	

Packaging

#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:0023-6151-08	15 in 1 CARTON	05/13/1997	
1		1.125 g in 1 APPLICATOR; Type 2: Prefilled Drug Delivery Device/System (syringe, patch, etc.)		

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
NDA	NDA020701	05/13/1997	

Labeler - Allergan, Inc. (144796497)

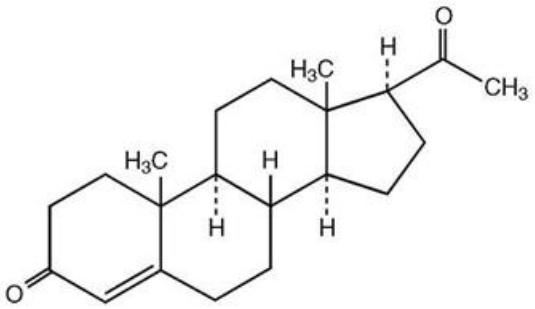
Revised: 1/2019 Allergan, Inc.

Progesterone pessary 400 mg
(micronized progesterone pessary)
PHYSICIAN INFORMATION
For Vaginal Use Only
Rx only
Revised: February 2024

DESCRIPTION

Progesterone pessary 400 mg contains micronized progesterone. They are off-white, torpedo-shaped pessaries. The chemical name for progesterone is pregn-4-ene-3,20-dione. It has an empirical formula of $C_{21}H_{30}O_2$ and a molecular weight of 314.5.

The structural formula is:



Progesterone is a white or almost white crystalline powder or colourless crystals. Progesterone is practically insoluble in water, freely soluble in dehydrated alcohol and sparingly soluble in acetone and fatty oils.

Progesterone is synthesized from a starting material from a plant source and is chemically identical to progesterone of human ovarian origin. Each pessary contains 400 mg micronized progesterone for vaginal administration. The inactive ingredient is hard fat.

CLINICAL PHARMACOLOGY

Progesterone is a naturally occurring steroid that is secreted by the ovary, placenta, and adrenal gland. In the presence of adequate estrogen, progesterone transforms a proliferative endometrium into a secretory endometrium. Progesterone is necessary to increase endometrial receptivity for implantation of an embryo. Once an embryo is implanted, progesterone acts to maintain the pregnancy.

Pharmacokinetics

Absorption

Vaginal administration of Progesterone pessary 400 mg every 12 h in healthy women has been shown effective in rapidly achieving and maintaining serum progesterone concentrations at physiological levels appropriate to the midluteal phase of the ovarian cycle and early pregnancy.

The mean C_{max} after 10 days of multiple dosing was 18.4 [ng/mL] and C_{trough} was 10.5 [ng/mL].

Distribution

Progesterone is approximately 96 % to 99 % bound to serum proteins, primarily to serum albumin and corticosteroid binding globulin.

Metabolism

Progesterone is metabolized primarily by the liver largely to pregnanediols and pregnanolones. Pregnanediols and pregnanolones are conjugated in the liver to glucuronide and sulfate metabolites. Progesterone metabolites that are excreted in the bile may be deconjugated and may be further metabolized in the gut via reduction, dehydroxylation, and epimerization.

Excretion

Progesterone undergoes renal and biliary elimination.

Special Populations

Hepatic Insufficiency:

No formal studies have evaluated the effect of hepatic disease on the disposition of progesterone. However, since progesterone is metabolized by the liver, use in patients with severe liver dysfunction or disease is contraindicated (See **CONTRAINDICATIONS**). If treatment with progesterone is indicated in patients with mild to moderate hepatic dysfunction, these patients should be monitored carefully. (See **PRECAUTIONS**)

Renal Insufficiency:

No formal studies have evaluated the effect of renal disease on the disposition of progesterone. Since progesterone metabolites are eliminated mainly by the kidneys, Progesterone pessary should be used with caution and only with careful monitoring in patients with renal dysfunction. (See **PRECAUTIONS**)

CLINICAL STUDIES

Clinical efficacy and safety

In a Phase III clinical trial, pre-menopausal women subjected to ART and IVF were randomized to receive either Progesterone pessary 400 mg twice daily (n = 385) or progesterone 8% gel once daily (n = 383) via vaginal route. The pregnancy rates after vaginally applied Progesterone pessary (400 mg twice daily) was found to be 38.3% (FAS) and 38.1% (PP) after 38 days of luteal phase support. The clinical pregnancy rate was 34.5% after 70 days of luteal phase support. Comparable results were obtained for the clinical implantation rates after 70 days (22.5% vs 24.5%, respectively), biochemical pregnancy rate after 18 and 38 days, and the implantation rate after 38 days (24.6% and 26.5%, respectively). No differences between Progesterone pessary 400 mg and progesterone 8% gel were recognized with regard to effects of age, number of embryos, and occurrence of blood loss based on diary information. Treatments were both safe and well tolerated by the patients.

INDICATIONS AND USAGE

Progesterone pessary is indicated for the luteal phase support as part of an Assisted Reproductive Technology (ART) treatment for women.

CONTRAINDICATIONS

- Hypersensitivity to the active substance or to any of the excipients.
- Undiagnosed vaginal bleeding
- Severe liver dysfunction or disease
- Known or suspected progesterone sensitive malignant tumors.
- Porphyria
- Known missed abortion or ectopic pregnancy.
- Active arterial or venous thromboembolism or severe thrombophlebitis, or a history of these events

WARNINGS

Progesterone pessary is not indicated in threatened miscarriage. Treatment should be discontinued in the event of a missed miscarriage.

Progesterone pessary should be discontinued if any of the following conditions are suspected: myocardial infarction, cerebrovascular disorders, arterial or venous thromboembolism (venous thromboembolism or pulmonary embolism), thrombophlebitis or retinal thrombosis.

Although risk of thromboembolism has been associated with estrogens, a link with progestins remains questionable. Therefore, in women with generally recognized risk factors for thromboembolic events, such as personal or family history, treatment with Progesterone pessary may further increase the risk. In these women, the benefits of Progesterone pessary administration need to be weighed against the risks. It should be noted however, that pregnancy itself carries an increased risk of thrombo-embolic events.

PRECAUTIONS

Patients with a history of depression need to be closely observed. Consider discontinuation if symptoms worsen.

Because progesterone may cause some degree of fluid retention, conditions that might be influenced by this factor (e.g. epilepsy, migraine, asthma, cardiac or renal dysfunction) require careful observation.

A decrease in glucose tolerance has been observed in a small number of patients on estrogen-progestin combination drugs. The mechanism of this decrease is not known. For this reason, diabetic patients should be carefully observed while receiving progestin therapy.

Progesterone is metabolized in the liver and should be used with caution in patients with hepatic dysfunction.

Progesterone pessary contains the hormone progesterone which is present in significant concentrations in women during the second half of the menstrual cycle and during pregnancy. This should be borne in mind when treating patients with conditions that may be hormone-sensitive.

Abrupt discontinuation of progesterone dosing may cause increased anxiety, moodiness, and increased sensibility to seizures.

Drug Interactions

Drugs known to induce the hepatic cytochrome-P450-3A4 system (e.g. rifampicin, carbamazepine or phenytoin) may increase the elimination rate and thereby decrease the bioavailability of progesterone.

The effect of concomitant vaginal products on the exposure of progesterone from Progesterone pessary has not been assessed and is therefore not recommended.

Carcinogenesis, Mutagenesis, Impairment of Fertility

Nonclinical toxicity studies to determine the potential of Progesterone pessary to cause carcinogenicity or mutagenicity have not been performed. The effect of progesterone on fertility has not been evaluated in animals.

Pregnancy

Progesterone pessary should not be used during pregnancy except as indicated during the first trimester of pregnancy for use as part of an assisted reproduction (ART) treatment (see **INDICATIONS AND USAGE** for full details). There is limited and inconclusive data on the risk of congenital anomalies, including genital abnormalities in male or female infants, following intrauterine exposure during pregnancy. The rates of congenital anomalies, spontaneous abortion and ectopic pregnancies observed during the clinical trial were comparable with the event rate described in the general population although the total exposure is too low to allow conclusions to be drawn.

Nursing Mothers

Progesterone is excreted in human milk and Progesterone pessary should not be used during breast-feeding.

Pediatric Use

There is no relevant use of Progesterone pessary in the pediatric population.

Geriatric Use

No clinical data have been collected in patients over age 65.

Hepatic Insufficiency

There is no experience with use of Progesterone pessary in patients with impaired liver function.

ADVERSE REACTIONS

Very common (≥ 1/10), Common (≥ 1/100 to < 1/10), Uncommon (≥ 1/1,000 to < 1/100), Rare (≥ 1/10,000 to < 1/1,000), Very rare (< 1/10,000), Not known (cannot be estimated from the available data).

SYSTEM ORGAN CLASS	Common	Uncommon	Not known
Nervous system disorder	Somnolence		
Gastrointestinal disorders	Abdominal pain, Abdominal discomfort		Diarrhea and flatulence may occur with rectal administration.
Skin and subcutaneous tissue disorders		Hypersensitivity reactions (e.g. rash, pruritus)	
Reproductive system and breast disorders	Breast pain		Menstruation may occur earlier than expected, or, more rarely, menstruation may be delayed.
General disorders and administration site conditions			Soreness, some leakage of the pessary base

Adverse reactions in patients undergoing luteal support as a part of ART treatment is presented in the table below:

SYSTEM ORGAN CLASS	Common	Uncommon
Psychiatric disorders		Mood altered
Nervous system disorder	Somnolence	Headache, dizziness, dysgeusia
Vascular disorders	Hot flush	Hemorrhage
Gastrointestinal disorders	Abdominal distension, abdominal pain, constipation	Diarrhea, vomiting, flatulence, gastric dilatation
Skin and subcutaneous tissue disorders		Rash, pruritus, night sweats
Musculoskeletal and connective tissue disorders		Arthralgia
Renal and urinary disorders		Pollakiuria, incontinence
Reproductive system and	Breast pain	Vaginal hemorrhage, pelvic pain,

SYSTEM ORGAN CLASS	Common	Uncommon
breast disorders		metrorrhagia, ovarian enlargement, vulvovaginal pruritus
General disorders and administration site conditions	Fatigue	Feeling cold, feeling of body temperature change, application site pruritus, discomfort
Investigations		Weight increased

To report SUSPECTED ADVERSE REACTIONS, contact FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

OVERDOSAGE

There is a wide margin of safety with Progesterone pessary, but overdosage may produce euphoria or dysmenorrhea.

DOSAGE AND ADMINISTRATION

400 mg administered vaginally twice a day starting at oocyte retrieval. The administration of Progesterone pessary should be continued for 38 days, if pregnancy has been confirmed.

HOW SUPPLIED

Progesterone pessary are off-white, torpedo-shaped pessaries. The product may be supplied in strip packs contained in cartons:
Carton: *White backed folding box board printed on white.*
Strip pack: *Aluminum foil lacquer-laminated to 20µm polypropylene foil and coated on the reverse with polythene (20mg/m²). The alternative is thermoplastic film and laminated PVC to 95µm and polyethylene to 27-33µm.*

Strip of 15 pessaries NDC XXXXX-**XXX**-XX[1]

Store at 20-25ºC (68-77ºF). [See USP controlled room temperature.]

Keep out of reach of children.

Rx only

Distributed by:
XXXX

XX

Revised: 02/2024

[1] NDC numbers pending for all three counts. It will be available prior to marketing/distribution.

Justification for waiver to pediatric study

The Best Pharmaceuticals for Children Act (BPCA) defines pediatric studies to mean at least one clinical investigation in "pediatric age groups (including neonates in appropriate cases) in which a drug is anticipated to be used, and, at the discretion of the Secretary, may include preclinical studies." For purposes of satisfying the requirements of Pediatric Research Equity Act (PREA), assessments of safety and effectiveness must be performed in all relevant pediatric age groups, unless the assessments are waived or deferred.

The BPCA and PREA are designed to work together to encourage the development of data to inform the safe and effective use of drugs in pediatric populations. Under PREA, pediatric assessments are required for drug products with a new active ingredient, new indication, new dosage form, new dosing regimen, or new route of administration unless the drug is for an indication for which orphan designation has been granted.

As per the draft guidance for industry on ***Pediatric Drug Development: Regulatory Considerations – Complying With the Pediatric Research Equity Act and Qualifying for Pediatric Exclusivity Under the Best Pharmaceuticals for Children Act*** (May 2023), FDA will, as appropriate, grant a full waiver of the requirement to submit pediatric assessments or reports on the molecularly targeted pediatric cancer investigation if the applicant certifies and FDA finds one or more of the following criteria:

- Necessary studies are impossible or highly impracticable (because, for example, the number of patients is so small, or the patients are geographically dispersed).
- There is evidence strongly suggesting that the drug would be ineffective or unsafe in all pediatric age groups.
- The drug (1) does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients; and (2) is not likely to be used in a substantial number of pediatric patients.

Petitioner asserts that PREA is not applicable to the proposed progesterone pessary formulation because the progesterone formulations are indicated for luteal phase support as part of an Assisted Reproductive Technology (ART) treatment for women. The condition "infertility & reproductive technology (including /Assisted Reproductive Technology (ART))" is also in the *Adult-Related Conditions that qualify for a waiver because they rarely or never occur in pediatrics* list published on the FDA's website and thus the requirement of conducting pediatric studies should be waived.

As this fulfils the first criteria accordingly, PREA should not serve as an impediment to the agency granting this petition.

References:

1. Pediatric Drug Development: Regulatory Considerations — Complying With the Pediatric Research Equity Act and Qualifying for Pediatric Exclusivity Under the Best Pharmaceuticals for Children Act (fda.gov)
2. Adult-Related Conditions that qualify for a waiver because they rarely or never occur in pediatrics* (fda.gov)

Pediatric Drug Development: Regulatory Considerations — Complying With the Pediatric Research Equity Act and Qualifying for Pediatric Exclusivity Under the Best Pharmaceuticals for Children Act

Guidance for Industry

DRAFT GUIDANCE

This guidance document is being distributed for comment purposes only.

Comments and suggestions regarding this draft document should be submitted within 60 days of publication in the *Federal Register* of the notice announcing the availability of the draft guidance. Submit electronic comments to https://www.regulations.gov. Submit written comments to the Dockets Management Staff (HFA-305), Food and Drug Administration, 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852. All comments should be identified with the docket number listed in the notice of availability that publishes in the *Federal Register*.

For questions regarding this draft document, contact (CDER) Rosemary Addy at 301-796-1640 or (CBER) the Office of Communication, Outreach, and Development at 800-835-4709 or 240-402-8010.

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)

May 2023
Administrative/Procedural

Revision 1

Pediatric Drug Development: Regulatory Considerations — Complying With the Pediatric Research Equity Act and Qualifying for Pediatric Exclusivity Under the Best Pharmaceuticals for Children Act

Guidance for Industry

Additional copies are available from:

Office of Communications, Division of Drug Information
Center for Drug Evaluation and Research
Food and Drug Administration
10001 New Hampshire Ave., Hillandale Bldg., 4th Floor
Silver Spring, MD 20993-0002
Phone: 855-543-3784 or 301-796-3400; Fax: 301-431-6353; Email: druginfo@fda.hhs.gov
https://www.fda.gov/drugs/guidance-compliance-regulatory-information/guidances-drugs

and/or

Office of Communication, Outreach, and Development
Center for Biologics Evaluation and Research
Food and Drug Administration
10903 New Hampshire Ave., Bldg. 71, Room 3128
Silver Spring, MD 20993-0002
Phone: 800-835-4709 or 240-402-8010; Email: ocod@fda.hhs.gov
https://www.fda.gov/vaccines-blood-biologics/guidance-compliance-regulatory-information-biologics/biologics-guidances

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)

May 2023
Administrative/Procedural

Revision 1

TABLE OF CONTENTS

Pediatric Drug Development: Regulatory Considerations — Complying With the Pediatric Research Equity Act and Qualifying for Pediatric Exclusivity Under the Best Pharmaceuticals for Children Act Guidance for Industry[1]

This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA or Agency) on this topic. It does not establish any rights for any person and is not binding on FDA or the public. You can use an alternative approach if it satisfies the requirements of the applicable statutes and regulations. To discuss an alternative approach, contact the FDA staff responsible for this guidance as listed on the title page.

I. INTRODUCTION

This guidance is intended to assist industry developing drug products[2] to comply with the pediatric study requirements under the Pediatric Research Equity Act (PREA),[3] and to describe the process for qualifying for pediatric exclusivity and the protections that pediatric exclusivity offers under the Best Pharmaceuticals for Children Act (BPCA).[4] In 2010, the Biologics Price Competition and Innovation Act of 2009 extended provisions of the BPCA to biological products.[5]

[1] This guidance has been prepared by the Division of Pediatrics and Maternal Health in the Center for Drug Evaluation and Research in cooperation with the Center for Biologics Evaluation and Research at the Food and Drug Administration.

[2] For the purposes of this guidance, unless otherwise specified, references to *drugs* or *drug products* include drugs approved under section 505 of the Federal Food, Drug, and Cosmetic Act (FD&C Act) (21 U.S.C. 355) and biological products licensed under section 351 of the Public Health Service (PHS) Act (42 U.S.C. 262) that are regulated as drugs.

[3] Public Law 108-155 (2003), codified at section 505B of the FD&C Act (21 U.S.C. 355c). Although section 505B has been amended since the passage of PREA, by convention, that section of the FD&C Act is often referred to by the acronym for the Act that created it, PREA. We adopt that convention in this guidance.

[4] Public Law 107-109 (2002), codified at section 505A of the FD&C Act (21 U.S.C. 355a). Although section 505A has been amended since the passage of the BPCA, by convention, that section of the FD&C Act is often referred to by the acronym for the Act that created it, the BPCA. We adopt that convention in this guidance.

[5] See section 351(m) of the PHS Act (42 U.S.C. 262(m)).

Note that section 505B(b) of the Federal Food, Drug, and Cosmetic (FD&C) Act on already-marketed drugs and section 409I of the Public Health Service (PHS) Act are only briefly addressed in this guidance. Future guidance may address these issues in greater detail. Furthermore, this guidance only briefly addresses the Food and Drug Administration Reauthorization Act of 2017's (FDARA's) amendments to section 505B of the FD&C Act relating to requirements that sponsors of certain adult oncology drugs with molecular targets that are determined to be substantially relevant to the growth or progression of a pediatric cancer submit reports on ***molecularly targeted pediatric cancer investigations***.[6,7]

The scientific aspects of a pediatric program (e.g., considerations regarding data in pediatric subjects, timing of pediatric studies) are addressed in the draft guidance for industry *Pediatric Drug Development Under the Pediatric Research Equity Act and the Best Pharmaceuticals for Children Act: Scientific Considerations* (May 2023).[8]

This guidance, along with the draft guidance for industry *Pediatric Drug Development Under the Pediatric Research Equity Act and the Best Pharmaceuticals for Children Act: Scientific Considerations*,[9] revises and replaces the draft guidance for industry *How to Comply With the Pediatric Research Equity Act*.[10] In addition to addressing the PREA topics covered in the earlier draft guidance (i.e., the pediatric ***assessment***, pediatric plan, ***waivers*** and ***deferrals***, compliance issues, and pediatric exclusivity provisions), this guidance addresses statutory changes relating to adverse event reporting, ***pediatric study plans (PSPs)***, deferral extensions, and noncompliance.

In general, FDA's guidance documents do not establish legally enforceable responsibilities. Instead, guidances describe the Agency's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word *should* in Agency guidances means that something is suggested or recommended, but not required.

---

[6] Certain terms used in this guidance, which appear in bold italics at first mention, are defined for purposes of this guidance in the Glossary.

[7] For additional information on FDA's implementation of these amendments to section 505B of the FD&C Act, see the 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). We update guidances periodically. To make sure you have the most recent version of a guidance, check the FDA guidance web page at https://www.fda.gov/regulatory-information/search-fda-guidance-documents.

[8] When final, this guidance will represent the FDA's current thinking on this topic. For the most recent version of a guidance, check the FDA guidance web page at https://www.fda.gov/regulatory-information/search-fda-guidance-documents.

[9] When final, this guidance will represent the FDA's current thinking on this topic.

[10] This guidance also addresses certain topics previously addressed in the guidance for industry *Qualifying for Pediatric Exclusivity Under Section 505A of the Federal Food, Drug, and Cosmetic Act*. That guidance was withdrawn August 7, 2013 (78 FR 48175).

II. OVERVIEW OF REGULATORY STRATEGY FOR PEDIATRIC DRUG DEVELOPMENT

A. General Approach

For purposes of pediatric drug development, FDA generally considers the pediatric population to include those patients from birth to younger than 17 years (i.e., birth through 16 years of age), and to include the subpopulation age groups of neonates, infants, children, and adolescents.[11] Consistent with International Council for Harmonisation (ICH) guidelines,[12] FDA considers these subpopulation age groups to be divided as follows:

- Neonates: birth through 27 days (corrected gestational age)
- Infants: 28 days to 23 months
- Children: 2 years to 11 years
- Adolescents: 12 years to younger than 17 years

The BPCA defines *pediatric studies* to mean at least one clinical investigation in "pediatric age groups (including neonates in appropriate cases) in which a drug is anticipated to be used, and, at the discretion of the Secretary, may include preclinical studies."[13] For purposes of satisfying the requirements of PREA, assessments of safety and effectiveness must be performed in all relevant pediatric age groups, unless the assessments are waived or deferred.[14]

The BPCA and PREA are designed to work together to encourage the development of data to inform the safe and effective use of drugs in pediatric populations. Under PREA, pediatric assessments are *required* for drug products with a new active ingredient, new indication, new dosage form, new dosing regimen, or new route of administration unless the drug is for an indication for which orphan designation has been granted.[15] Also under PREA, molecularly targeted pediatric cancer investigations are *required* for original new drug applications (NDAs) or biologics license applications (BLAs) submitted on or after August 18, 2020, for a new active ingredient, if the drug that is the subject of the application is intended for the treatment of an

[11] See 21 CFR 201.57(c)(9)(iv)(A) ("the terms *pediatric population(s)* and *pediatric patient(s)* are defined as the pediatric age group, from birth to 16 years, including age groups often called neonates, infants, children, and adolescents"). FDA interprets "birth to 16 years" in 21 CFR 201.57(c)(9)(iv)(A) to mean from birth to younger than 17 years old. See, for example, the guidance for industry *Pediatric Information Incorporated Into Human Prescription Drug and Biological Product Labeling* (March 2019).

[12] For additional information, see the ICH guidances for industry *E11 Clinical Investigation of Medicinal Products in the Pediatric Population* (December 2000) and *E11(R1) Addendum: Clinical Investigation of Medicinal Products in the Pediatric Population* (April 2018).

[13] See section 505A(a) of the FD&C Act (21 U.S.C. 355a(a)).

[14] See sections 505B(a)(2)(A), 505B(a)(4), and 505B(a)(5) of the FD&C Act (21 U.S.C. 355c(a)(2)(A), 21 U.S.C. 355c(a)(4), and 21 U.S.C. 355c(a)(5)).

[15] See sections 505B(a)(1)(A) and 505B(k)(1) of the FD&C Act (21 U.S.C. 355c(a)(1)(A) and 21 U.S.C. 355c(k)(1)).

adult cancer, and directed at a molecular target that FDA determines to be substantially relevant to the growth or progression of a pediatric cancer.[16] Studies conducted under the BPCA, on the other hand, are *optional* because sponsors have the option of declining to undertake them in response to a ***written request*** (WR). Nevertheless, it is critical that sponsors consider both laws when planning their pediatric clinical development programs.

PREA requires that any application falling within the requirements of section 505B(a)(1) of the FD&C Act for a new active ingredient, new indication, new dosage form, new dosing regimen, or new route of administration must either include pediatric assessments or reports on the molecularly targeted pediatric cancer investigation (as appropriate);[17] or a request for waiver and/or deferral of the pediatric assessments or reports on the molecularly targeted pediatric cancer investigation.[18] There are certain exceptions; for example, PREA requirements generally do not apply to a drug for an indication for which orphan designation has been granted (see section II.B.4., Orphan Products).[19]

The FD&C Act requires sponsors to submit an initial pediatric study plan (iPSP) during the investigational phase of development, which helps to ensure that sponsors thoroughly consider a pediatric clinical development program earlier in their overall clinical development program.[20] See sections III., Pediatric Research Equity Act, and V., Elements Common to PREA and the BPCA, for additional information about PREA.

While addressing PREA, sponsors should also consider whether to seek a WR under the BPCA. It is important to note that sponsors may qualify for pediatric exclusivity under the BPCA for completed PREA studies when those studies are described in a WR,[21] and the WR is issued by FDA before the sponsor submits any reports about the studies described in the WR.[22] If FDA determines that "information relating to the use of a new drug in the pediatric population may produce health benefits in that population" and issues a WR, a sponsor may qualify for 6 months of exclusivity under the BPCA for conducting studies that are required under PREA.[23] However, as discussed in Section IV. A. 2., Written Request Studies, FDA does not expect to issue WRs solely for studies or planned studies that are required under PREA.

---

[16] Section 505B(a)(1)(B) of the FD&C Act (21 U.S.C. 355c(a)(1)(B)).

[17] For additional information, see the guidance for industry *FDARA Implementation Guidance for Pediatric Studies of Molecularly Targeted Oncology Drugs: Amendments to Sec. 505B of the FD&C Act*.

[18] See sections 505B(a)(1), 505B(a)(4), and 505B(a)(5) of the FD&C Act (21 U.S.C. 355c(a)(1), 21 U.S.C. 355c(a)(4), and 21 U.S.C. 355c(a)(5)).

[19] See section 505B(k)(1) of the FD&C Act (21 U.S.C. 355c(k)(1)). Under section 505B(k)(2) of the FD&C Act, this orphan exemption does not apply to products that trigger PREA under section 505B(a)(1)(B) of the FD&C Act.

[20] See section 505B(e) of the FD&C Act (21 U.S.C. 355c(e)).

[21] See section 505A(h) of the FD&C Act (21 U.S.C. 355a(h)).

[22] See section 505A(b)(1) of the FD&C Act (21 U.S.C. 355a(b)(1)).

[23] See section 505A(b)(1) of the FD&C Act (21 U.S.C. 355a(b)(1)).

In addition, sponsors should consider other indications for development in the pediatric population based on the current understanding of the effect of the drug (e.g., mechanism of action), and include them as appropriate when seeking a WR. FDA reviews adult safety and effectiveness data and, in some instances, information from postmarketing safety reports, information regarding unapproved uses, and the scientific literature to identify a potential health benefit in pediatric populations when contemplating a WR. This knowledge not only informs FDA's decision to issue a WR for a given indication, but also whether to include a request to study additional indications in children beyond those already approved in adults. See sections IV., Best Pharmaceuticals for Children Act, and V., Elements Common to PREA and the BPCA, for more information about the BPCA.

B. Developing Drugs for Pediatric Use

During clinical development programs, a sponsor should consider whether the eventual marketing application will trigger the requirements of PREA. FDA encourages sponsors to interact with FDA early, including, when applicable, to discuss studies to meet PREA and other requirements. See section III., Pediatric Research Equity Act, for information about the requirements of PREA.

FDA has identified a number of scenarios and considerations that may affect a sponsor's approach to developing a drug product for use in pediatric patients. Some common ones are described below.

1. Drugs for Life-Threatening or Severely Debilitating Conditions and Unmet Medical Needs

Early consultation and discussions are particularly important for drugs intended for life-threatening or severely debilitating conditions.[24] For these drugs, FDA encourages sponsors to discuss the pediatric plan at pre-investigational new drug application (pre-IND) and end-of-phase 1 meetings.[25] In some cases, pediatric studies of drugs for life-threatening or severely debilitating conditions that lack adequate therapies might begin earlier than usual in the drug development process. The need for new therapies might justify early trials despite the relative lack of safety and effectiveness information in humans. Pediatric studies might be considered appropriate when prospects of direct benefit to the enrolled children are sufficient to justify the risks.[26]

[24] See the guidance for industry *Expedited Programs for Serious Conditions — Drugs and Biologics* (May 2014) for more information.

[25] See section 505B(e)(2)(C)(i)(I) of the FD&C Act (21 U.S.C. 355c(e)(2)(C)(i)(I)).

[26] See 21 CFR 50.52.

2. Drugs for Diseases or Conditions That Occur Primarily in Pediatric Populations

Sponsors developing drug products for diseases or conditions that primarily or substantially occur in the pediatric population should discuss their plans with FDA as early as possible (e.g., pre-IND meeting). They should consider submitting an iPSP earlier than is required under PREA because the initial clinical studies will likely include pediatric subjects (see section III.B.1., Pediatric Study Plans).

3. Neonates

The complex medical state of neonates makes it critical to evaluate drugs specifically for their use. However, FDA is aware that studies in neonates present special challenges, including the short time period to conduct studies during the neonatal period (e.g., birth through 27 days corrected gestational age), the differences in neonatal physiology that may affect dose and endpoint selection, as well as ethical issues that may be age-specific. Under PREA, studies in neonates may be required. However, it is possible that partial waivers for this and other specific age groups might be appropriate under certain circumstances.[27]

FDA encourages specific activities regarding neonates. Under PREA, if a sponsor does not plan to study an investigational drug in neonates, the rationale and supporting data explaining why the drug is not appropriate for use in this population should be included in the iPSP.[28] Under the BPCA, similar rationale and supporting data explaining why the investigational drug is not appropriate for use in this population should be included in the ***proposed pediatric study request (PPSR)*** if a sponsor does not plan to study the drug in neonates. When FDA issues a WR that does not include studies in neonates, the WR must state the rationale for not including neonates.[29] See sections IV.A.1., Description of the Written Request, and IV.B., How to Obtain a Written Request, as well as the draft guidance for industry *Pediatric Drug Development Under the Pediatric Research Equity Act and the Best Pharmaceuticals for Children Act: Scientific Considerations*[30] for more information regarding clinical studies in neonates.

4. Orphan Products

PREA requirements generally do not apply "to any drug or biological product for an indication for which orphan designation has been granted;" however, this *orphan exemption* does not apply to drugs that trigger the PREA requirement for submission of reports on the molecularly targeted

[27] See section 505B(a)(5)(B) of the FD&C Act (21 U.S.C. 355c(a)(5)(B)).

[28] See section 505B(e)(2)(B) of the FD&C Act (21 U.S.C. 355c(e)(2)(B)) and the guidance for industry *Pediatric Study Plans: Content of and Process for Submitting Initial Pediatric Study Plans and Amended Initial Pediatric Study Plans* (July 2020).

[29] See section 505A(d)(1)(A) of the FD&C Act (21 U.S.C. 355a(d)(1)(A)).

[30] When final, this guidance will represent FDA's current thinking on this topic.

pediatric cancer investigation.[31] Thus, PREA does not require submission of pediatric assessments for an application (or supplemental application) to market a drug for an indication for which orphan designation has been granted.[32] As FDA has interpreted PREA, if orphan designation is granted after approval of a drug, and postmarketing studies were required under PREA at the time of the drug's approval, the granting of orphan designation does not alter the already existing requirement for such studies.[33] The PREA orphan exemption is not revisited to retroactively abrogate a PREA requirement that was properly imposed before orphan designation was granted. Additionally, if marketing approval is sought for multiple indications for a drug product, some of which have not been granted orphan designation, the sponsor must submit pediatric assessments for all indications that do not have an orphan designation, unless the assessments are waived or deferred.[34] If the orphan-designated indication(s) involve the pediatric population, we encourage sponsors to conduct studies in the relevant age group(s) whenever appropriate.

Despite this orphan exemption under PREA, a sponsor that submits an application to market a drug for an indication for which orphan designation has been granted may be eligible to qualify for pediatric exclusivity if FDA issues a WR to the sponsor in connection with the application and the sponsor accepts. Sponsors should contact FDA about the feasibility and timing of a WR and about submitting a PPSR, if appropriate. For more information, see sections III.C.2., Submission of Pediatric Assessments or Reports on the Molecularly Targeted Pediatric Cancer Investigation, IV.F.2., Biological Products, and V.B.1., Pediatric Exclusivity Determinations, as well as FDA's Office of Orphan Products Development web page on developing drug products for rare diseases and conditions,[35] and the guidance for industry *Clarification of Orphan Designation of Drugs and Biologics for Pediatric Subpopulations of Common Diseases* (July 2018).

[31] See sections 505B(a)(1)(B), 505B(a)(3), and 505B(k) of the FD&C Act (21 U.S.C. 355c(a)(1)(B), 21 U.S.C. 355c(a)(3), and 21 U.S.C. 355c(k)). Note that, although section 505B(k) authorizes FDA to issue regulations that would alter the orphan exemption, as of the date of publication of this guidance, FDA has not issued any such regulations.

[32] See section 505B(k)(1) of the FD&C Act (21 U.S.C. 355c(k)(1)). For products meeting the criteria in section 505B(a)(1)(B) of the FD&C Act, the requirement to submit reports on the investigation described in section 505B(a)(3) of the FD&C Act applies even if the drug is for an adult indication for which orphan designation has been granted. See section 505B(k)(2) of the FD&C Act (21 U.S.C. 355c(k)(2)). See also the guidance for industry *FDARA Implementation Guidance for Pediatric Studies of Molecularly Targeted Oncology Drugs: Amendments to Sec. 505B of the FD&C Act.*

[33] Because the orphan exemption in section 505B(k)(1) of the FD&C Act can affect whether PREA applies to a particular application or supplement submitted to the Agency for review, FDA evaluates whether the orphan exemption is applicable at the time it evaluates whether PREA would otherwise be triggered for any application or supplement under section 505B(a)(1)(A).

[34] See sections 505B(a)(1)(A), 505B(a)(4), 505B(a)(5), and 505B(k)(1) of the FD&C Act (21 U.S.C. 355c(a)(1)(A), 21 U.S.C. 355c(a)(4), 21 U.S.C. 355c(a)(5), and 21 U.S.C. 355c(k)(1)).

[35] See the Medical Products for Rare Diseases and Conditions web page at https://www.fda.gov/ForIndustry/DevelopingProductsforRareDiseasesConditions/default.htm.

5. Drug Development in Foreign Countries

Many sponsors conduct their entire clinical programs in other countries and occasionally submit a marketing application with little, if any, prior interaction with FDA. All sponsors who seek to market their drugs in the United States are strongly encouraged to contact FDA as early as possible to avoid any delay in providing any required pediatric information in their applications. Sponsors should include an agreed iPSP in any NDA, BLA, or supplement that is required by PREA to include pediatric assessments or reports on the molecularly targeted pediatric cancer investigation. PREA requirements are described in more detail in section III., Pediatric Research Equity Act.

6. Drugs for Diseases or Conditions That Only Occur in Adults

Sponsors focusing on clinical development programs for drugs for diseases and conditions that only occur in adults must submit an iPSP, assuming the application triggers PREA.[36] A list of diseases and conditions that rarely or never occur in pediatrics can be found on FDA's website.[37] Generally, applications for drugs for such diseases or conditions that rarely or never occur in pediatrics will qualify for a waiver because the necessary studies would be impossible or highly impracticable.[38] However, sponsors should consider all potential pediatric indications for their drugs. FDA may consider issuance of a WR for other indications that may have health benefits in the pediatric population.

III. PEDIATRIC RESEARCH EQUITY ACT

A. Overview — Requirements of PREA

1. PREA Applicability

With limited exception (for example, the orphan exemption described in section II.B.4., Orphan Products), PREA applies to the following:

- Applications (or supplements to an application) submitted under section 505 of the FD&C Act or section 351 of the PHS Act for a new active ingredient, new indication, new dosage form, new dosing regimen, or new route of administration, and

[36] See section 505B(e)(1) of the FD&C Act (21 U.S.C. 355c(e)(1)); see also section 505B(a)(1) of the FD&C Act (21 U.S.C. 355c(a)(1)).

[37] See Adult-Related Conditions That Qualify for a Waiver Because They Rarely or Never Occur in Pediatrics, available at https://www.fda.gov/media/101440/download.

[38] See section 505B(a)(5) of the FD&C Act (21 U.S.C. 355c(a)(5)). FDA anticipates that there will be additional considerations for applications described in section 505B(a)(1)(B) of the FD&C Act that require submission of reports on the molecularly targeted pediatric cancer investigation described in section 505B(a)(3) of the FD&C Act. For additional information, see the guidance for industry *FDARA Implementation Guidance for Pediatric Studies of Molecularly Targeted Oncology Drugs: Amendments to Sec. 505B of the FD&C Act*.

- Original applications for a new active ingredient submitted under section 505 of the FD&C Act or section 351 of the PHS Act on or after August 18, 2020, if the drug that is the subject of the application is intended for the treatment of an adult cancer and is directed at a molecular target that FDA determines to be substantially relevant to the growth or progression of a pediatric cancer.[39]

PREA also authorizes FDA to require holders of already approved applications to conduct pediatric assessments under certain circumstances.[40]

2. Scope of Requirements — Generic drugs

Abbreviated new drug applications (ANDAs) submitted under section 505(j) of the FD&C Act most often are applications for drugs containing the *same* active ingredient(s), strength(s), indication(s), dosage form(s), dosing regimen(s), and route(s) of administration as the listed drugs they reference and are not subject to PREA. ANDA applicants may petition the Agency to request a change from a listed drug per section 505(j)(2)(C) of the FD&C Act and 21 CFR 314.93, a process referred to as a suitability petition. The regulation at 314.93 limits the types of changes that may be permitted to changes in strength, dosage form, route of administration, or of a single active ingredient in a combination drug subject to the restrictions identified in 314.93(d)(1) through (3). ANDAs submitted pursuant to an approved suitability petition for changes in dosage form, route of administration, or for a change in active ingredient in a combination drug do trigger PREA, but they are only eligible for submission as ANDAs if the pediatric assessment or molecularly targeted pediatric cancer investigation requirements are waived.[41] If a change proposed in a suitability petition triggers PREA and FDA does not waive the requirement to submit pediatric assessments or reports on the molecularly targeted pediatric cancer investigation, the suitability petition will be denied, and the proposed drug product will not be eligible for submission as an ANDA.[42]

B. Development of Drugs for Pediatric Use

1. Pediatric Study Plans

A sponsor planning to submit a marketing application or supplement that is subject to PREA is required to submit an iPSP before submission of pediatric assessments or reports on the molecularly targeted pediatric cancer investigation.[43] A sponsor should submit an iPSP to its investigational new drug application (IND) for review by the appropriate review division as early

[39] See section 505B(a)(1) of the FD&C Act (21 U.S.C. 355c(a)(1)).

[40] See section 505B(b) of the FD&C Act (21 U.S.C. 355c(b)).

[41] See section 505(j)(2)(C) of the FD&C Act (21 U.S.C. 355(j)(2)(C)) and section 505B(a)(1) of the FD&C Act (21 U.S.C. 355c(a)(1)).

[42] See, for example, 21 CFR 314.93.

[43] See section 505B(e)(1) of the FD&C Act (21 U.S.C. 355c(e)(1)).

as practicable and must submit it no later than 60 calendar days after the date of the end-of-phase 2 meeting or such other time as agreed upon between FDA and the applicant.[44] More information on the timing and contents of iPSPs, the process for reaching agreement with FDA on iPSPs, and the process for amending an agreed iPSP can be found in the guidance for industry *Pediatric Study Plans: Content of and Process for Submitting Initial Pediatric Study Plans and Amended Initial Pediatric Study Plans* (July 2020). Sponsors are also encouraged to consider the possibility of submitting a PPSR to obtain a WR during the PSP process. An iPSP and a PPSR are different documents and have different considerations for submission; the former is a requirement for compliance with PREA and the latter may be submitted at a sponsor's discretion to seek a WR under the BPCA. See sections IV.A., Written Requests, and IV.B., How to Obtain a Written Request, for further discussion about PPSRs and WRs.

2. Developing a Pediatric Formulation

Under PREA, sponsors are required to conduct pediatric studies "using appropriate formulations for each age group" for which the assessment or investigation is required.[45] However, FDA may grant a partial waiver if a sponsor is unable to develop an age-appropriate formulation after reasonable attempts to do so.[46] (See discussion of waivers in section III.D., Waivers and Deferrals Under PREA.) Under PREA, sponsors must submit "a request for approval of a pediatric formulation" used in their pediatric studies, and if a sponsor fails to submit such a request, the drug may be considered misbranded.[47] Accordingly, sponsors should submit an application or supplemental application for any formulation(s) not previously approved that were used during pediatric studies and for which the sponsor has data to assess the safety and effectiveness and to support dosing and administration. To avoid delays in initiation of pediatric clinical studies, sponsors should begin the development of an age-appropriate formulation as early as possible.

C. Pediatric Assessments and Molecularly Targeted Pediatric Cancer Investigations Under PREA

1. Definitions

Pediatric assessments must contain data, gathered using appropriate formulations for each age group for which the assessment is required and that are adequate to:

- Assess the safety and effectiveness of the drug for the claimed indications in all relevant pediatric subpopulations; and

[44] See section 505B(e)(2)(A)(ii) of the FD&C Act (21 U.S.C. 355c(e)(2)(A)(ii)).

[45] See section 505B(a)(2)(A) and 505B(a)(3)(A) of the FD&C Act (21 U.S.C. 355c(a)(2)(A) and 355c(a)(3)(A)).

[46] See section 505B(a)(5)(B)(iv) of the FD&C Act (21 U.S.C. 355c(a)(5)(B)(iv)).

[47] See section 505B(d) of the FD&C Act (21 U.S.C. 355c(d)).

- Support dosing and administration for each pediatric subpopulation for which the drug is safe and effective.[48]

A molecularly targeted pediatric cancer investigation "shall be designed to yield clinically meaningful pediatric study data, gathered using appropriate formulations for each age group for which the study is required, regarding dosing, safety, and preliminary efficacy to inform potential pediatric labeling."[49]

2. Submission of Pediatric Assessments or Reports on the Molecularly Targeted Pediatric Cancer Investigation

Sponsors must submit pediatric assessments or reports on the molecularly targeted pediatric cancer investigation with any application for which such assessments or reports are required by PREA, unless FDA defers and/or waives the requirement.[50] (For pediatric assessments, if the drug is for an indication for which orphan designation has been granted, the requirements of PREA do not apply.)[51] See section III.D., Waivers and Deferrals Under PREA, for discussion of waivers and deferrals. In general, sponsors should include pediatric studies at the time of submission of an application when there is sufficient knowledge to proceed and it is feasible to complete studies in children in parallel with adult studies.

Information about the results of pediatric assessments under PREA must be included in product labeling whether findings are positive, negative, or inconclusive.[52] Labeling changes for approved products must be submitted in accordance with applicable requirements in 21 CFR 601.12 and 21 CFR 314.70. For more information about labeling, see section V.D., Considerations for Labeling of Drug Products, and the guidance for industry *Pediatric Information Incorporated Into Human Prescription Drug and Biological Product Labeling* (March 2019).

For information about the specific types of data that may be needed to complete a pediatric assessment, refer to the draft guidance for industry *Pediatric Drug Development Under the Pediatric Research Equity Act and the Best Pharmaceuticals for Children Act: Scientific Considerations*.[53]

[48] See section 505B(a)(2)(A) of the FD&C Act (21 U.S.C. 355c(a)(2)(A)).

[49] Section 505B(a)(3)(A) of the FD&C Act (21 U.S.C. 355c(a)(3)(A)).

[50] See sections 505B(a)(1), 505B(a)(4), and 505B(a)(5) of the FD&C Act (21 U.S.C. 355c(a)(1), 21 U.S.C. 355c(a)(4), and 21 U.S.C. 355c(a)(5)).

[51] See section 505B(k)(1) of the FD&C Act (21 U.S.C. 355c(k)(1)).

[52] See section 505B(g)(2) of the FD&C Act (21 U.S.C. 355c(g)(2)).

[53] When final, this guidance will represent FDA's current thinking on this topic.

D. Waivers and Deferrals Under PREA

1. Waivers

PREA authorizes FDA to waive the requirement to submit pediatric assessments or reports on the molecularly targeted pediatric cancer investigation, based on established criteria, for some or all pediatric age groups.[54] FDA can grant a full or partial waiver of the requirements on its own initiative or at the request of an applicant.[55] Any applicant requesting a waiver should provide written justification for the waiver and evidence to support the request.

a. Criteria for full waiver

FDA will, as appropriate, grant a full waiver of the requirement to submit pediatric assessments or reports on the molecularly targeted pediatric cancer investigation if the applicant ***certifies*** and FDA finds one or more of the following criteria:

- Necessary studies are impossible or highly impracticable (because, for example, the number of patients is so small or the patients are geographically dispersed).[56] For further information, see Section II.B.6., Drugs for Diseases or Conditions That Only Occur in Adults.

- There is evidence strongly suggesting that the drug would be ineffective or unsafe in all pediatric age groups.[57]

- The drug (1) does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients; and (2) is not likely to be used in a substantial number of pediatric patients.[58]

  — Importantly, we note that *both* criteria must be met for this waiver justification to apply. A drug is considered to represent a meaningful therapeutic benefit over existing therapies if FDA determines that (1) "if approved, the drug or biological product could represent an improvement in the treatment, diagnosis, or prevention of a disease, compared with marketed products adequately labeled for that use in the relevant pediatric population;" or (2) "the drug or biological product is in a class of products or for an indication for which there is a need for additional options."[59] FDA anticipates that improvement over marketed drugs might be demonstrated by

[54] See section 505B(a)(5) of the FD&C Act (21 U.S.C. 355c(a)(5)).

[55] See section 505B(a)(5) of the FD&C Act (21 U.S.C. 355c(a)(5)).

[56] See section 505B(a)(5)(A)(i) of the FD&C Act (21 U.S.C. 355c(a)(5)(A)(i)).

[57] See section 505B(a)(5)(A)(ii) of the FD&C Act (21 U.S.C. 355c(a)(5)(A)(ii)).

[58] See section 505B(a)(5)(A)(iii) of the FD&C Act (21 U.S.C. 355c(a)(5)(A)(iii)).

[59] See section 505B(c) of the FD&C Act (21 U.S.C. 355c(c)).

showing, for example (1) evidence of increased effectiveness in treatment, prevention, or diagnosis of disease; (2) an improved safety profile; (3) enhancement of compliance (e.g., by virtue of less frequent dosing or mode of delivery); or (4) safety and effectiveness in a new subpopulation for which marketed drugs are not currently labeled.

b. Criteria for partial waiver

FDA will, as appropriate, grant a partial waiver of the requirement to submit pediatric assessments or reports on the molecularly targeted pediatric cancer investigation with respect to a specific pediatric age group, if the applicant certifies and FDA finds one or more of the following criteria:

- Necessary studies are impossible or highly impracticable (because, for example, the number of patients in that age group is so small or patients in that age group are geographically dispersed);[60]

- There is evidence strongly suggesting that the drug would be ineffective or unsafe in that age group;[61]

- The drug (1) does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients in that age group; and (2) is not likely to be used in a substantial number of pediatric patients in that age group;[62]

- The applicant can demonstrate that reasonable attempts to produce a pediatric formulation necessary for that age group have failed.[63]

We note that if a partial waiver is granted on the basis that it is not possible to develop a pediatric formulation, the waiver will cover only the pediatric age groups requiring that formulation.[64]

FDA believes that a partial waiver granted based on the inability to develop a pediatric formulation generally should apply to situations in which the applicant can demonstrate that unusually difficult technological problems prevented it from developing a pediatric formulation. In certain cases, FDA may seek appropriate external expert opinion (e.g., from an advisory committee) to help assess whether to grant such a waiver.

[60] See section 505B(a)(5)(B)(i) of the FD&C Act (21 U.S.C. 355c(a)(5)(B)(i)).

[61] See section 505B(a)(5)(B)(ii) of the FD&C Act (21 U.S.C. 355c(a)(5)(B)(ii)).

[62] See section 505B(a)(5)(B)(iii) of the FD&C Act (21 U.S.C. 355c(a)(5)(B)(iii)).

[63] See section 505B(a)(5)(B)(iv) of the FD&C Act (21 U.S.C. 355c(a)(5)(B)(iv)).

[64] See section 505B(a)(5)(C) of the FD&C Act (21 U.S.C. 355c(a)(5)(C)).

If the sponsor seeks a partial waiver on the grounds that it is not possible to develop a pediatric formulation, the sponsor must submit documentation detailing why a pediatric formulation cannot be developed.[65] This should include a detailed description of the sponsor's efforts to develop a pediatric formulation.[66] If FDA grants such a waiver, the sponsor's submission will be made publicly available.[67]

c. Information for requesting a waiver

To request a waiver, sponsors should provide the following:

- The drug name, applicant name, and indication.
- The age group(s) included in the waiver request.
- The statutory reason(s) for requesting a waiver, including reference to the applicable statutory authority.[68]
- Evidence that the request meets the statutory reason(s) for waiver.[69] All relevant scientific/clinical justifications for the waiver request should be included.

d. Waiver decision

FDA grants a waiver at the time of approval of an application that triggers PREA if it determines that the application satisfies the statutory requirements for a waiver. FDA generally includes a preliminary evaluation of the sponsor's plan to request a waiver in FDA's comments on the iPSP (see section III.B.1., Pediatric Study Plans). This evaluation reflects FDA's best judgment at that time.

2. Deferrals

PREA authorizes FDA to defer the requirement to submit pediatric assessments or reports on the molecularly targeted pediatric cancer investigation, based on established criteria.[70] A deferral acknowledges that pediatric assessments or reports on the molecularly targeted pediatric cancer investigation are required, but permits the applicant to submit the assessments or reports after the

[65] See section 505B(a)(5)(C) of the FD&C Act (21 U.S.C. 355c(a)(5)(C)).

[66] A partial waiver on this basis hinges on whether "the applicant can demonstrate" the failure of reasonable attempts to produce a pediatric formulation (section 505B(a)(5)(B)(iv) (21 U.S.C. 355c(a)(5)(B)(iv)).

[67] See section 505B(a)(5)(C) of the FD&C Act (21 U.S.C. 355c(a)(5)(C)).

[68] See sections 505B(a)(5) and 505B(e)(2)(B)(ii) of the FD&C Act (21 U.S.C. 355c(a)(5) and 21 U.S.C. 355c(e)(2)(B)(ii)).

[69] See, for example, section 505B(e)(2)(B)(ii) of the FD&C Act (21 U.S.C. 355c(e)(2)(B)(ii)).

[70] See section 505B(a)(4) of the FD&C Act (21 U.S.C. 355c(a)(4)).

approval of an NDA, BLA, or supplement. FDA may, on its own initiative or at the request of an applicant, defer the submission of some or all of the pediatric assessments or reports on the molecularly targeted pediatric cancer investigation until a specified date after approval of the drug.[71]

a. Timeline

Sponsors can discuss a plan for a deferral and the status of a deferred study with FDA as follows:

- Premarketing — It is important to include in the iPSP any plans for a deferral request. In certain cases it may be appropriate to initiate early discussion of a plan for deferral, for example, as part of a pre-IND meeting or during phase 1 of clinical development.

- Application review — FDA grants the deferral, as appropriate, upon approval of the application or supplement.

- Postmarketing — The applicant must submit an annual review of the status of a deferred pediatric study (PREA postmarketing requirement) to FDA until it has submitted the final study report.[72] The final due date of a deferred pediatric study may be extended under certain circumstances (see section III.D.2.e., Deferral extensions).

b. Criteria for deferral

FDA may defer the timing of submission of some or all required assessments or reports on the molecularly targeted pediatric cancer investigation if the applicant submits certain required information to FDA, as discussed below, and FDA finds one or more of the following:[73]

- The drug 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

- There is another appropriate reason for deferral

An "appropriate reason" for deferral may include, for example, that development of a pediatric formulation is not complete.

[71] See section 505B(a)(4) of the FD&C Act (21 U.S.C. 355c(a)(3)).

[72] See section 505B(a)(4)(C) of the FD&C Act (21 U.S.C. 355c(a)(4)(C)).

[73] See section 505B(a)(4)(A)(i) of the FD&C Act (21 U.S.C. 355c(a)(4)(A)(i)).

c. Information for requesting a deferral

To request a deferral, an applicant must provide the following:[74]

- A certification of the grounds for deferral;
- A pediatric study plan as described in section 505B(e) of the FD&C Act (see section III.B.1., Pediatric Study Plans);
- Evidence that the studies are being conducted or will be conducted with due diligence and at the earliest possible time; and
- A timeline for completion of such studies.

d. Deferral review and decision

The decision to defer and the deferral date are determined on a case-by-case basis. FDA may, as appropriate, consider the following in determining whether and how long to defer submission of a pediatric assessment:

- The need for the drug in pediatric patients;
- Availability of sufficient safety data to initiate pediatric clinical studies;
- The nature and extent of pediatric data needed to support pediatric labeling;
- The existence of clearly documented difficulties in enrolling subjects; and/or
- Evidence of technical problems in developing pediatric formulations.

For additional information on the circumstances in which a deferral may be appropriate for a molecularly targeted pediatric cancer investigation, see the guidance for industry *FDARA Implementation Guidance for Pediatric Studies of Molecularly Targeted Oncology Drugs: Amendments to Sec. 505B of the FD&C Act*.

The iPSP, agreed iPSP, and any subsequent amendments should include the key elements of any planned deferred studies. FDA does not intend to make recommendations on planned deferral requests that are submitted in the absence of an iPSP, except under rare circumstances (e.g., urgent public health need).

FDA grants a deferral, as appropriate, in the approval letter for an NDA, BLA, or supplement.

e. Deferral extensions

The FD&C Act provides a mechanism for FDA to grant an extension of the timeline for a deferral granted by FDA.[75] Examples of reasons assessments or investigations may be delayed

[74] See section 505B(a)(4)(A)(ii) of the FD&C Act (21 U.S.C. 355c(a)(4)(A)(ii)).

[75] See section 505B(a)(4)(B) of the FD&C Act (21 U.S.C. 355c(a)(4)(B)).

include, but are not limited to, unexpected difficulties with enrollment, unexpected delays in reaching agreement with FDA on protocols for the pediatric clinical studies, or an unanticipated need for additional safety or effectiveness data before proceeding with studies in children. During consideration of the deferral extension request, in general, FDA considers whether the applicant could have prevented or foreseen the delay. FDA also generally considers the likelihood that studies can be completed given the circumstances.

To request a deferral extension, an applicant must submit a new timeline for the completion of pediatric studies along with any significant updates to the following information from the original deferral request:[76]

- A certification of the grounds for deferral;
- PSP; and
- Evidence that the studies are being conducted or will be conducted with due diligence and at the earliest possible time.

Applicants should submit information to support the need for an extension of the timeline for deferred studies. For example, if an applicant needs additional time to complete the deferred pediatric studies because of difficulty recruiting subjects, the applicant should provide information outlining the reasons for the difficulties, evidence supporting the reasons outlined (including information on the incidence of the condition and global geographic distribution, if applicable), and information outlining its efforts to increase enrollment such as the number of clinical sites contacted and the number of subjects screened and enrolled.

An applicant must submit a request for deferral extension, along with the required information, at least 90 days before the date that the studies are due.[77] FDA will respond to such request within 45 days of receipt of the request.[78] If FDA grants the deferral extension, the specified date will be the new due date for submission of the deferred assessments or deferred reports on the molecularly targeted pediatric cancer investigation.[79]

3. Annual Review

Pediatric assessments deferred under PREA are required postmarketing studies subject to annual status reporting requirements under PREA and FDA regulations.[80]

[76] See section 505B(a)(4)(B)(i)(II) of the FD&C Act (21 U.S.C. 355c(a)(4)(B)(i)(II)).

[77] See section 505B(a)(4)(B)(ii) of the FD&C Act (21 U.S.C. 355c(a)(4)(B)(ii)).

[78] See section 505B(a)(4)(B)(ii) of the FD&C Act (21 U.S.C. 355c(a)(4)(B)(ii)).

[79] See section 505B(a)(4)(B)(ii) of the FD&C Act (21 U.S.C. 355c(a)(4)(B)(ii)).

[80] See section 505B(a)(4)(C) of the FD&C Act (21 U.S.C. 355c(a)(4)(C)); 21 CFR 314.81(b)(2)(vii), and 21 CFR 601.70.

An applicant's annual status report under PREA must contain the following:[81]

- Information detailing the progress made in conducting pediatric studies
- If no progress has been made in conducting such studies, evidence and documentation that such studies will be conducted with due diligence and at the earliest possible time
- The projected completion date for pediatric studies
- The reason(s) that a deferral or deferral extension continues to be necessary

E. Compliance With PREA

If an applicant submits an application or supplement subject to PREA and fails to comply with applicable PREA requirements, FDA may, as appropriate, refuse to file the application or issue a complete response letter after reviewing the application.[82] If an applicant fails to fulfill required deferred pediatric studies under PREA that were established in the approval letter, FDA will issue to the applicant a noncompliance letter that informs it of such failure.[83] The applicant must respond to this letter in writing within 45 days and may request a deferral extension as part of that response.[84]

FDA will post the noncompliance letter and the applicant's response on the FDA public website after redacting any information protected by applicable law.[85] If FDA grants a deferral extension before the initial study due date, FDA does not intend to issue a noncompliance letter unless and until the newly established due date has passed.

After FDA issues a noncompliance letter, it may take additional steps to ensure compliance if needed. The drug may be considered misbranded solely because of the applicant's failure to comply with PREA and subject to relevant enforcement action.[86] For an approved drug, the failure to submit pediatric assessments or reports on the molecularly targeted pediatric cancer investigation, or a request for waiver or deferral of those studies, will not be the basis for

[81] See section 505B(a)(4)(C)(i) of the FD&C Act (21 U.S.C. 355c(a)(4)(C)(i)).

[82] See 21 CFR 314.101(d), 21 CFR 314.110, and 21 CFR 601.3.

[83] See section 505B(d)(1) of the FD&C Act (21 U.S.C. 355c(d)(1)).

[84] See section 505B(d)(1) of the FD&C Act (21 U.S.C. 355c(d)(1)).

[85] See 505B(d)(1) of the FD&C Act (21 U.S.C. 355c(d)(1)). See also the Noncompliance Letters Under 505B(d)(1) of the FD&C Act web page at https://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/ucm343203.htm.

[86] See section 505B(d)(2) of the FD&C Act (21 U.S.C. 355c(d)(2)).

612 withdrawing approval of a drug or revoking a license for a biological product.[87] However, if
613 FDA finds a drug to be misbranded, the drug could be subject to an injunction or seizure
614 proceedings.[88]
615
616
617 **IV. BEST PHARMACEUTICALS FOR CHILDREN ACT**
618
619 **A. Written Requests**
620
621 *1. Description of the Written Request*
622
623 A WR is a document issued by FDA requesting submission of a study or studies intended to
624 provide meaningful health benefits in the pediatric population. The WR specifies the elements
625 of the study or studies that the sponsor or application holder must complete to qualify for
626 pediatric exclusivity.[89] FDA can issue a WR at the request of an interested party or on its own
627 initiative. Completion of studies described in a WR is voluntary.[90] FDA does not limit issuance
628 of a WR to a specific drug product, and the WR can result in only one 6-month period of
629 pediatric exclusivity for that sponsor, as described in section IV.F., Attaching the Period of
630 Pediatric Exclusivity After a Determination That a Drug Qualifies for Pediatric Exclusivity.
631 FDA's authority to issue a WR extends to use of an active moiety for indications that may
632 produce health benefits in the pediatric population, regardless of whether the indications have
633 been previously approved in adults.[91]
634
635 Generally, a WR seeks all applicable information necessary to establish safety and effectiveness
636 of a drug for use in all relevant pediatric populations, including study information (e.g., type,
637 timing, endpoints), drug-specific safety concerns to be monitored, statistical analysis plan, and
638 timeline for completing the studies.
639
640 FDA can use a PPSR to develop a WR or use alternative information (see section IV.B., How to
641 Obtain a Written Request). As a greater understanding of the indication or of the mechanism of
642 action of a particular drug or drug class develops, WRs, including elements within a study or
643 studies necessary to qualify for pediatric exclusivity, may evolve.
644

[87] See section 505B(d)(2) of the FD&C Act (21 U.S.C. 355c(d)(2)).

[88] See sections 302 and 304 of the FD&C Act (21 U.S.C. 332 and 21 U.S.C. 334).

[89] See sections 505A(b)(1) and 505A(c)(1) of the FD&C Act (21 U.S.C. 355a(b)(1) and 21 U.S.C. 355a(c)(1)).

[90] Section 505A of the FD&C Act does not require the sponsor or application holder to conduct pediatric studies; instead, it creates an exclusivity incentive to encourage such studies. However, the sponsor or application holder may be required to conduct pediatric studies of certain new and marketed drugs under section 505B of the FD&C Act.

[91] See sections 505A(a), 505A(b)(1), 505A(c)(1), and 505A(d)(1)(B) of the FD&C Act (21 U.S.C. 355a(a), 21 U.S.C. 355a(b)(1), 21 U.S.C. 355a(c)(1), and 21 U.S.C. 355a(d)(1)(B)).

In addition, the BPCA requires that, in issuing a WR, FDA take into account adequate representation of children of ethnic and racial minorities.[92] If a WR does not request studies in neonates, the request will include a statement describing the rationale for not requesting such studies.[93]

A sponsor will not be eligible for pediatric exclusivity based on requirements or requests to conduct postmarketing studies (e.g., studies required under PREA) or other communications about pediatric studies unless it is in receipt of a WR.[94]

2. Written Request Studies

In general, FDA decides what studies to include in a WR by determining what information is needed to use the drug appropriately in the pediatric population. When making this determination, in general, FDA obtains the following from the sponsor:

- Information on any other indications for this product that may have health benefits in children. For example, the sponsor should provide information on any indications for which there are ongoing clinical studies in adults and/or children or for which the sponsor has opened an IND.

- Information that exists in the literature on the drug or on pharmacologically related drugs.

In some instances, FDA may ask a sponsor to submit information to an IND before issuing a WR. Similarly, in some cases, a sponsor may wish to submit pediatric study data to its IND in support of an amendment to its WR. Pediatric studies previously submitted to an IND can be used as the basis of a PPSR or can be submitted to an NDA or BLA to qualify for pediatric exclusivity in response to a WR; however, FDA does not consider pediatric studies a sponsor submits to an NDA or BLA (either in an original application, amendment, or supplement) before FDA issues a WR as being responsive to that WR.

In certain situations, FDA may determine that a WR for additional pediatric studies will **not** be issued. Such situations may include the following:

- Sufficient pediatric information has already been submitted to the NDA or BLA, even if the pediatric information is not yet included in the labeling;

- Study of the drug for the specified indication(s) in the pediatric population would not offer a health benefit in that population;

[92] See section 505A(d)(1)(A) of the FD&C Act (21 U.S.C. 355a(d)(1)(A)).

[93] See section 505A(d)(1)(A) of the FD&C Act (21 U.S.C. 355a(d)(1)(A)).

[94] See sections 505A(b)(1) and 505A(c)(1) of the FD&C Act (21 U.S.C. 355a(b)(1) and 21 U.S.C. 355a(c)(1)).

- It is not possible to conduct a study or studies of the drug for the specified indications in the pediatric population in a manner that would provide useful information (e.g., the study population is too small to yield interpretable results); and/or

- Outstanding safety concerns from studies or significant theoretical concerns need to be clarified with additional studies to support conducting studies in the pediatric population.

Historically, FDA has at times issued WRs solely for studies required under PREA, even if there were no other indications that may produce health benefits in the pediatric population. However, over time, data on pediatric labeling changes pursuant to BPCA and/or PREA have been collected. Between 2002 and 2019, there were 768 products with pediatric labeling changes under BPCA and/or PREA. Sixty-three percent of these labeling changes were based on studies conducted under PREA/Pediatric Rule alone; 21 percent were based on studies conducted under BPCA alone; 16 percent were based on studies conducted under both the BPCA and PREA. These data suggest that studies required under PREA are successfully completed, and that PREA requirements have resulted in an increase in pediatric labeling, even without the added incentive of the BPCA.

The BPCA provides FDA with discretion to determine whether to issue, and the appropriate scope of, WRs based on the information that "may produce health benefits" in the pediatric population.[95] In light of the data on pediatric labeling changes pursuant to the BPCA and/or PREA, FDA believes WRs should be reserved for those sponsors who conduct additional pediatric studies — beyond what is required under PREA — that may produce health benefits in children. Thus, upon finalization of this guidance, FDA does not expect to issue WRs solely for studies or planned studies that are required under PREA. In general, FDA expects that a WR that includes studies or planned studies required under PREA will also include additional indications or populations. If there are no additional studies for indications or populations that may produce health benefits in the pediatric population beyond the studies or planned studies required under PREA, then FDA does not expect to issue a WR for that drug. For example, if a sponsor has an iPSP that includes a plan for deferred studies of a drug for pediatric juvenile idiopathic arthritis (pJIA), FDA does not expect to issue a WR solely for studies of pJIA in the same pediatric population. However, if FDA determines that this drug may produce health benefits in pediatric systemic juvenile idiopathic arthritis (sJIA), and there are no studies or planned studies required under PREA for this indication, then it may be appropriate for FDA to issue a WR for pediatric studies for *both* pJIA and sJIA.

In general, when considering issuance of a WR, FDA evaluates the need for studies for all pediatric subpopulations and for all indications for which the drug is being used or could be used in the pediatric population. In general, FDA considers the indications already approved for adults, indications pending for adults, and unapproved uses including uses that might be specific to the pediatric population. A single WR may address multiple indications and uses that are both approved and unapproved.[96]

[95] See sections 505A(b)(1) and 505A(c)(1) of the FD&C Act (21 U.S.C. 355a(b)(1) and 21 U.S.C. 355a(c)(1)).

[96] See section 505A(d)(1)(B) of the FD&C Act (21 U.S.C. 355a(d)(1)(B)).

FDA can issue a WR that includes nonclinical studies.[97] Section 505A(a) of the FD&C Act defines the term *pediatric studies* to mean "at least one clinical investigation (that, at the Secretary's discretion, may include pharmacokinetic studies) in pediatric age groups (including neonates in appropriate cases) in which a drug is anticipated to be used, and, at the discretion of the Secretary, may include preclinical studies." FDA may need certain toxicology studies in immature animals to evaluate the safety of drugs for use in pediatric populations.[98] Accordingly, FDA may request that a sponsor or holder of an approved application conduct nonclinical studies before completing pediatric studies in humans. FDA may need to review such studies before it can determine whether information relating to use of the drug could produce health benefits in the pediatric population; thus, FDA may need these studies to determine if it will issue a WR.

In response to a WR, sponsors may, as appropriate, submit studies conducted by a third party. However, the sponsor should submit reports of studies that it has not conducted only if (1) the data from the studies appear to provide useful pediatric information that *fairly responds* to the WR issued by FDA; **and** (2) the sponsor obtains a right of reference to submit the reports of studies along with the underlying data.

A sponsor can use data it collects before or after FDA issues a WR to respond to the WR. Although FDA can request literature reviews as part of a larger WR, reviews of published literature alone are not pediatric studies that will qualify a drug for pediatric exclusivity.[99]

Although a sponsor may, as appropriate, use studies it conducts to meet PREA requirements to qualify also for pediatric exclusivity,[100] as mentioned, FDA does not consider pediatric studies a sponsor submits to an NDA or BLA (either in an original application, amendment, or supplement) before FDA issues a WR as being responsive to that WR. To qualify for pediatric exclusivity, sponsors and holders of an approved application should obtain a WR or an amendment to an existing WR before submitting the pediatric studies to an application.

3. Amended Written Requests

Each WR states that the WR may be amended. A sponsor may request an amendment to the WR, or FDA may issue an amendment on its own initiative. However, FDA does not anticipate amending WRs in the absence of scientific, medical, or regulatory justification.

---

[97] See section 505A(a) of the FD&C Act (21 U.S.C. 355a(a)).

[98] We support the principles of the 3Rs (reduce/refine/replace) for animal use in testing when feasible. The FDA encourages sponsors to consult with review divisions when considering a nonanimal testing method believed to be suitable, adequate, validated, and feasible. The FDA will consider if the alternative method could be assessed for equivalency to an animal test method.

[99] See sections 505A(a), 505A(b), and 505A(c) of the FD&C Act (21 U.S.C. 355a(a), 21 U.S.C. 355a(b), and 21 U.S.C 355a(c)).

[100] As noted earlier in this section, going forward, FDA does not expect to issue WRs solely for studies or planned studies that are required under PREA.

Sponsors can request a change in the studies' due date in the WR by submitting a proposed amendment to the WR. If a sponsor believes it will be unable to meet the time frames in a WR, it should contact FDA to request such a change as soon as possible. If FDA agrees to the change, it intends to notify the sponsor in writing regarding the extension time. Any request for an extension of time should take into consideration that completed reports of all studies should be submitted for filing at least 15 months before the expiration of the patent or exclusivity to which the pediatric exclusivity would attach. Sponsors should be aware that if they choose to submit within less than 15 months, FDA may not be able to complete the review and make a determination in time to meet the 9-month deadline.[101]

FDA intends to issue all amendments to a WR in writing. Sponsors should also request any amendments to a WR in writing. Discussion of a proposed amendment at a meeting with FDA does not constitute a request to amend a WR nor does it constitute FDA's amendment of the WR. In addition, if a sponsor has submitted a protocol that is inconsistent with the WR, and FDA has not commented on the protocol, the sponsor should not assume FDA agrees that the protocol is consistent with the WR. Even a minor change to a study, such as a change in the number of subjects, the age groups enrolled, or the elimination of certain testing requirements, may warrant a change in the protocol and a revision of the WR if it relates to a specified term of the WR.

Sponsors can submit preliminary data to an IND in support of a request for amendment. Sponsors that believe that their studies may not fairly respond to the WR as issued but nonetheless provide valuable pediatric information should (1) seek to obtain an amended WR *before* submitting any pediatric study reports to their NDAs or BLAs; and (2) submit proposed amendments to their WRs early enough to ensure enough time for FDA to issue an amended WR and to ensure the sponsor has enough time to submit its studies at least 15 months before the expiration of any patent or exclusivity to which pediatric exclusivity would attach.

Sponsors should not submit the requested study reports to their NDAs or BLAs until *after* they have received FDA's response to requested amendments in writing. Reports of studies that do not fairly respond to the existing WR will *not* qualify for pediatric exclusivity (see sections IV.C., How to Submit Study Reports in Response to a Written Request, IV.D., Qualifying for Pediatric Exclusivity, and IV.E., Determining Eligibility For Pediatric Exclusivity).[102]

B. How to Obtain a Written Request

Historically, WRs have generally been issued after a drug is approved for use in adults. However, there may be situations in which it is appropriate to issue a WR before such an action. See sections II., Overview of Regulatory Strategy for Pediatric Drug Development, and III.B.1., Pediatric Study Plans, and previous subsections of this section for additional considerations relating to timing of a WR. Additionally, the appropriate timing of the submission of a specific

[101] See sections 505A(b)(2), 505A(c)(2), and 505A(d)(4) of the FD&C Act (21 U.S.C. 355a(b)(2), 21 U.S.C. 355a(c)(2), and 21 U.S.C. 355a(d)(4)).

[102] See sections 505A(b)(1), 505A(c)(1), 505A(d)(4), and 505A(h) of the FD&C Act (21 U.S.C. 355a(b)(1), 21 U.S.C. 355a(c)(1), 21 U.S.C. 355a(d)(4), and 21 U.S.C. 355a(h)).

PPSR can be discussed with the relevant review division(s). FDA may issue a WR either in response to a PPSR **or** on its own initiative (see sections IV.A., Written Requests).

1. Submitting a PPSR

If a sponsor has exclusivity or patent protection for a drug or exclusivity for a biological product, or anticipates that it will have such exclusivity or patent protection, the sponsor can submit a PPSR to the appropriate review division (such a proposal can help to expedite FDA's issuance of a WR). Sponsors should mark PPSRs with the header PROPOSED PEDIATRIC STUDY REQUEST and submit it to the appropriate IND. Sponsors that seek to qualify for pediatric exclusivity to attach to existing patents and/or exclusivities should plan to submit their PPSRs with sufficient time to:

- Permit FDA to review the PPSR, confer with the party submitting the PPSR as necessary, and issue the WR (including review by the FDA's internal pediatric review committee (the PeRC) as required before issuance[103]);

- Allow time for the sponsor, after the WR is issued, to initiate the studies, complete the studies, and submit the reports for filing; **and**

- Provide FDA 180 days to review the studies and make an exclusivity determination, with a remaining, nonoverlapping 9 months before expiration of the patent or exclusivity period.[104]

The PPSR should describe the studies the sponsor or application holder proposes to conduct to qualify for pediatric exclusivity. The PPSR should include (1) a background section, (2) nonclinical studies, (3) drug information, (4) clinical studies, (5) known drug safety concerns and monitoring, (6) statistical information, including power of studies and statistical assessments, and (7) time frame for submitting reports of the study or studies.

It is important to note that a PPSR is not a substitute for an iPSP (section III.B.1., Pediatric Study Plans). Although these submissions may have some similarities, each one is submitted under a different statutory scheme and serves a distinct purpose. See sections II., Overview of Regulatory Strategy for Pediatric Drug Development, III., Pediatric Research Equity Act, and V.C., PREA and Pediatric Exclusivity, for additional information.

FDA intends to consider PPSRs that include requests to study multiple pediatric age groups in the same study, as appropriate. FDA recognizes that studies defined by age may be inappropriate when it is reasonable to define subgroups using methods other than age, such as development stage. If the sponsor submits data as part of a PPSR to indicate that a drug should

[103] See section 505A(f) of the FD&C Act (21 U.S.C. 355a(f)).

[104] See sections 505A(b)(2), 505A(c)(2), and 505A(d)(4) of the FD&C Act (21 U.S.C. 355a(b)(2), 21 U.S.C. 355a(c)(2), and 21 U.S.C. 355a(d)(4)).

be studied in pediatric groups identified by characteristics other than age, in general, FDA intends to consider that data when developing the WR.

FDA has 120 days after a sponsor submits a PPSR to review and act on the submission.[105] Our response to the PPSR is either a WR or a PPSR inadequate letter, in which we inform the sponsor of the reasons we will not issue a WR at this time. In general, FDA also makes suggestions as to what the sponsor should include in a resubmitted PPSR that might support our issuance of a WR.

2. Issuance and Acceptance of a WR

The sponsor or application holder must respond to FDA within 180 days after receiving the WR indicating whether it will conduct the studies and, if so, indicate when it will initiate the studies.[106]

The procedure for qualifying for exclusivity and the protections that exclusivity will confer are described in more detail in sections IV.E., Determining Eligibility For Pediatric Exclusivity, and IV.F., Attaching the Period of Pediatric Exclusivity After a Determination That a Drug Qualifies for Pediatric Exclusivity.

If a sponsor declines a WR that is issued by FDA, the sponsor must provide the reasons it declined the request.[107] If the sponsor declines the WR because it is not possible to develop an appropriate pediatric formulation, the sponsor must submit to FDA the reasons such pediatric formulation cannot be developed.[108] If a sponsor declines a WR, the sponsor is not eligible to qualify for pediatric exclusivity for the studies under that WR.

C. How to Submit Study Reports in Response to a Written Request

To qualify for pediatric exclusivity, sponsors or application holders must submit study reports in accordance with FDA requirements for filing.[109] Studies submitted in an application or supplement that does not meet requirements for filing of an NDA, BLA, or supplement (i.e., FDA refuses to file the application or supplement) are not considered submitted to FDA.

In general, sponsors should also submit study reports in accordance with the guidance for industry *Guideline for the Format and Content of the Clinical and Statistical Sections of an Application* (July 1988) and the ICH guidance for industry *E3 Structure and Content of Clinical Study Reports* (July 1996).

---

[105] See section 505A(d)(3) of the FD&C Act (21 U.S.C. 355a(d)(3)).

[106] See section 505A(d)(2)(A)(i) of the FD&C Act (21 U.S.C. 355a(d)(2)(A)(i)).

[107] See section 505A(d)(2)(A)(i) of the FD&C Act (21 U.S.C. 355a(d)(2)(A)(i)).

[108] See section 505A(d)(2)(A)(ii) of the FD&C Act (21 U.S.C. 355a(d)(2)(A)(ii)).

[109] See section 505A(d)(4) of the FD&C Act (21 U.S.C. 355a(d)(4)). For additional information on filing requirements and refusal to file, see, for example, 21 CFR 314.50, 21 CFR 314.101, and 21 CFR 601.2.

To help ensure that pediatric study reports are evaluated for eligibility for pediatric exclusivity in a timely manner, sponsors should include the following with the application or supplement:

- A header that states SUBMISSION OF PEDIATRIC STUDY REPORTS — PEDIATRIC EXCLUSIVITY DETERMINATION REQUESTED;
- A copy of the WR and any amendments;
- A summary of the pediatric studies conducted in response to the WR;
- An annotated WR indicating how and where in the submitted study reports each term of the WR has been addressed; and
- Proposed labeling that includes information regarding the results of the study or studies.

If there is information that is adequate to support the evaluation of dosing, safety, and efficacy in a subpopulation of the population included in the WR, FDA encourages the sponsor to submit an NDA, BLA, or supplement to incorporate that information into labeling for the drug before the determination of exclusivity. If making multiple submissions in response to a single WR, the sponsor should, in the final submission, reference prior submissions (including relevant submission dates) and mark only the last submission as described above.

D. Qualifying for Pediatric Exclusivity

We note at the outset that a commitment to complete a study at some future date is not sufficient to qualify a drug for pediatric exclusivity.[110] Rather, to qualify for an initial period of pediatric exclusivity, a sponsor must submit study reports that fairly respond to an issued WR, were conducted in accordance with commonly accepted scientific principles and protocols, and have been reported in accordance with filing requirements.[111] It is not necessary for the uses studied under the WR to be approved.[112]

1. For a Drug Product That Is the Subject of a New Drug Application or Biologics License Application

A drug product qualifies for pediatric exclusivity when all of the following have occurred:[113]

[110] See sections 505A(b) and 505A(c) of the FD&C Act (21 U.S.C. 355a(b) and 21 U.S.C. 355A(c)).

[111] See sections 505A(b), 505A(c), and 505A(d)(4) of the FD&C Act (21 U.S.C. 355a(b), 21 U.S.C. 355a(c), and 21 U.S.C. 355a(d)(4)).

[112] Approval is required for a sponsor to qualify for a second 6-month period of pediatric exclusivity under section 505A(g) of the FD&C Act (21 U.S.C. 355a(g)). See section IV.F.1.b., A second 6-month period of pediatric exclusivity, for further discussion of that process.

[113] See sections 505A(b), 505A(c), and 505A(d)(4) of the FD&C Act (21 U.S.C. 355a(b), 21 U.S.C. 355a(c), and 21 U.S.C. 355a(d)(4)).

- FDA issued a WR for pediatric studies, and the sponsor or holder of an approved application agreed to the request.

- The sponsor or the holder of an approved application has submitted reports of the requested studies. Such reports should be submitted to the NDA or BLA **after** FDA issues the WR.

- The studies were completed using appropriate formulations for each age group and within the requested time frame.

- FDA has determined the studies fairly respond to the WR, have been conducted in accordance with commonly accepted scientific principles and protocols, and have been reported in accordance with filing requirements.

- FDA makes an exclusivity determination at least 9 months before the expiration date of the patent and/or exclusivity protection to which the pediatric exclusivity will attach.[114]

2. Nonprescription Drugs

Nonprescription drugs marketed under an approved application may be eligible for pediatric exclusivity, and the recommendations in this guidance apply to those nonprescription drugs.

Nonprescription drugs that are marketed pursuant to a monograph developed under the over-the-counter drug review are not eligible for exclusivity under section 505A of the FD&C Act.

E. Determining Eligibility For Pediatric Exclusivity

For a drug to be considered eligible for pediatric exclusivity, FDA recommends that the sponsor submit a complete report of all studies to FDA at least 15 months before the expiration of any existing patent or exclusivity it wishes to protect (i.e., the 9-month time period[115] plus the 180-day exclusivity determination review period[116]). If sponsors choose to submit within less than 15 months, FDA may not be able to complete its review of such studies and make a determination about the drug's eligibility for pediatric exclusivity in time to meet the 9-month deadline.

In making an eligibility determination, FDA will evaluate whether the studies fairly respond to the WR, were conducted in accordance with commonly accepted scientific principles and

[114] See section 505A(b)(2) and 505A(c)(2) of the FD&C Act (21 U.S.C. 355a(b)(2) and 21 U.S.C. 355a(c)(2)) and section 351(m)(4) of the PHS Act (42 U.S.C. 262(m)(4)).

[115] See section 505A(b)(2) and 505A(c)(2) of the FD&C Act; 21 U.S.C. 355a(b)(2) and 21 U.S.C. 355a(c)(2).

[116] See section 505A(d)(4) of the FD&C Act (21 U.S.C. 355a(d)(4)).

protocols, and have been reported in accordance with filing requirements.[117] FDA's pediatric exclusivity boards (Boards), which are comprised of representatives from the Center for Drug Evaluation and Research or the Center for Biologics Evaluation and Research, including representatives with pediatric expertise, make this determination. In general, the Boards consider the following when assessing, as required by statute, whether the studies *fairly respond* to a WR:

- The purpose of the pediatric exclusivity provision as described in the statute, with reference to the legislative history. The statute makes clear that its purpose is to generate meaningful clinical information on the use of drug products in children that will result in a health benefit to pediatric populations.[118]

- Whether the sponsor met the terms of a WR.

- The information sought in the WR and the objectives stated in the WR.

In general, the Boards ask whether the studies were designed and carried out by the sponsor in a way likely to meet those objectives specified in the WR and underlying the exclusivity provision as a whole. When a sponsor meets the terms of a WR, the resulting studies fairly respond to that WR because studies that are carried out in accordance with the trial's plans and objectives, as expressed in the WR, generally satisfy the statutory goal of obtaining meaningful pediatric use information. Sometimes, a sponsor fails to produce meaningful pediatric information despite conducting the studies in the manner requested. Under such circumstances, FDA nevertheless considers the sponsor to have fairly responded to the WR. FDA understands that the failure to generate meaningful information in such cases is at least partially attributable to study design, and FDA and the sponsor generally design studies described in a WR jointly.

Where the sponsor has not met the terms of the WR, FDA evaluates whether the information generated by the studies is nevertheless sufficient to meet the objectives of the WR in light of the information sought in the WR. If FDA determines that the objectives of the WR were met, then FDA concludes that the sponsor has fairly responded, even if it did not meet the terms of the WR. FDA considers studies that do not meet the terms of the written request to have fairly responded if, considering the data provided by the sponsor as a whole (i.e., by considering all relevant data, and not just data generated by those studies), the sponsor meets the objectives of the WR by generating clinically meaningful information of the general type (quality and quantity) the WR contemplates.

[117] See section 505A(d)(4) of the FD&C Act (21 U.S.C. 355a(d)(4)).

[118] See, for example, section 505A(b)(1) and 505A(c)(1) of the FD&C Act (21 U.S.C. 355a(b)(1) and 21 U.S.C. 355a(c)(1)) requiring FDA to determine "that information relating to the use of a new drug in the pediatric population may produce health benefits," section 505A(f)(2) of the FD&C Act (21 U.S.C. 355a(f)(2)) requiring review by the PeRC before FDA issues a WR, section 505A(f)(3) of the FD&C Act, providing that the same committee may review the reports of studies conducted in response to a WR before FDA makes a determination regarding pediatric exclusivity, section 505A(f)(6)(E) of the FD&C Act (21 U.S.C. 355a(f)(6)(E)) requiring FDA to publicly report, among other things, labeling changes made as a result of studies conducted in response to a WR, and section 505A(k)(2) of the FD&C Act (21 U.S.C. 355a(k)(2)) requiring sponsors to distribute the same to physicians and other health care providers.

For example, if a specific number of subjects is requested or a specific study duration or endpoint is specified to ensure that the study will generate adequate data to provide a health benefit, failure to comply with these elements of the WR may result in a denial of exclusivity. Denial is likely if, in the absence of compliance with the terms of the WR, the studies are not expected to be interpretable or will not provide information that otherwise yields a health benefit to the pediatric populations addressed in the WR.

Where a WR is capable of more than one interpretation, the Boards generally consider a fair response to be one that interprets the WR in a manner likely to generate information that will provide a health benefit (including meaningful pediatric labeling) in the relevant populations that the WR asked the sponsor to study. If the studies submitted fairly respond to the WR, the Boards will recommend that the drug is eligible for pediatric exclusivity (assuming the other statutory requirements for pediatric exclusivity are met).[119] If, on the other hand, the sponsor responds to the WR in such a way that the possibility of a health benefit (including meaningful pediatric labeling in relevant age groups) from the studies conducted is not likely, the Boards are likely to conclude that the submission does not fairly respond to the WR.

Generally, FDA expects to notify sponsors or holders of an approved application within the 180-day period after the study reports are submitted whether the study reports fairly responded to the WR and the drug qualifies for pediatric exclusivity.[120]

F. Attaching the Period of Pediatric Exclusivity After a Determination That a Drug Qualifies for Pediatric Exclusivity

1. Drug Products[121]

a. An initial 6-month period of pediatric exclusivity

Pediatric exclusivity will attach to all unexpired exclusivities and patents[122] listed in the *Approved Drug Products With Therapeutic Equivalence Evaluations* publication (the Orange

[119] See sections 505A(b)(1), 505A(c)(1), and 505A(d)(4) of the FD&C Act (21 U.S.C. 355a(b)(1), 21 U.S.C. 355a(c)(1), and 21 U.S.C. 355a(d)(4)).

[120] See section 505A(d)(4) of the FD&C Act (21 U.S.C. 355a(d)(4)).

[121] For the purposes of this section IV.F.1., references to *drugs* or *drug products* do not include biological products licensed under section 351 of the PHS Act (42 U.S.C. 262). Although the considerations in this section are generally relevant to such biological products, pediatric exclusivity for biological products differs in certain ways from pediatric exclusivity for other drug products. For more information see section IV.F.2., Biological Products, below.

[122] Pediatric exclusivity that has attached to the end of the patent term will block for an additional 6 months after the patent expires approval of an ANDA or 505(b)(2) application if (1) the ANDA or 505(b)(2) sponsor did not seek approval until the end of the patent term; or (2) the ANDA or 505(b)(2) sponsor's patent challenge has been unsuccessful. See, for example, sections 505A(b)(1) and 505A(c)(1) of the FD&C Act (21 U.S.C. 355a(b)(1) and 21 U.S.C. 355a(c)(1)). In addition, if an ANDA or 505(b)(2) sponsor files a paragraph IV certification challenging a listed patent, and the patent litigation is ongoing when the patent expires, the pediatric exclusivity will attach at the

Book)[123] for any drug product containing the drug the sponsor studies and for which it holds the approved NDA.[124] For studies a sponsor conducts on a previously unapproved drug, pediatric exclusivity will attach to any exclusivities or patents that will be listed in the Orange Book upon approval of that drug and to certain later listed patents or exclusivities.[125] For studies a sponsor conducts on a previously approved drug, pediatric exclusivity will attach to protections listed for the previously approved drug *at the time the drug qualifies for pediatric exclusivity* and to certain later listed patents and exclusivities,[126] as described further in section IV.F.1.c., Later-filed applications containing the same drug. Pediatric exclusivity for combination drugs may raise additional considerations that are not addressed in this guidance.

b. A second 6-month period of pediatric exclusivity

Each WR may result in only one 6-month period of pediatric exclusivity.[127] However, after a drug has qualified for an initial period of pediatric exclusivity, a sponsor submitting a supplement to an application can submit additional pediatric studies meeting the relevant statutory requirements in response to a second WR.[128] The second 6-month period of pediatric exclusivity will attach only to any new 3-year exclusivity period for which the supplemental application qualifies.[129] In addition, several other considerations regarding a second period of pediatric exclusivity are presented as follows:[130]

- A second WR can result in a 6-month period of exclusivity only if the response to the WR results in an approved *supplemental application* for a new use.

- A new use is a use not included in the approved labeling of an approved drug.[131] For example, expansion of the labeling to include a new pediatric population constitutes a new use.

---

end of the patent term to block approval of that ANDA or 505(b)(2) application for an additional 6 months after the patent expires (*Ranbaxy Labs.* v. *FDA*).

[123] The Orange Book is available at https://www.accessdata.fda.gov/scripts/cder/ob/index.cfm.

[124] See section 505A(c) of the FD&C Act (21 U.S.C. 355a(c)).

[125] See section 505A(b) of the FD&C Act (21 U.S.C. 355a(b)).

[126] See section 505A(c) of the FD&C Act (21 U.S.C. 355a(c)).

[127] See sections 505A(b)(1) and 505A(c)(1) of the FD&C Act (21 U.S.C. 355a(b)(1) and 21 U.S.C. 355a(c)(1)).

[128] See section 505A(g) of the FD&C Act (21 U.S.C. 355a(g)).

[129] See section 505A(g) of the FD&C Act (21 U.S.C. 355a(g)).

[130] See section 505A(g) of the FD&C Act (21 U.S.C. 355a(g)).

[131] See 21 CFR 99.3(g).

- The supplement for a new use submitted in response to the second WR must qualify for 3-year exclusivity[132] or no 6-month period of pediatric exclusivity will attach.

- The second 6-month period of pediatric exclusivity attaches *only* to the 3-year exclusivity applied to the supplement for a new use containing the studies submitted in response to the second WR and not to any other exclusivity or patent protections applicable to the drug.

- No more than two 6-month periods of exclusivity under the BPCA are possible for any specific drug product.

c. Later-filed applications containing the same drug

In situations where a sponsor submits an application or supplement containing an active moiety for which the sponsor previously qualified for pediatric exclusivity, pediatric exclusivity does not attach to new (not previously listed) patents or exclusivity covering the later filed applications or supplements unless the subsequent drug product could not be labeled without the data that qualified the previously approved drug product for the prior pediatric exclusivity.[133]

FDA notes that if pediatric exclusivity for which a drug product previously qualified has attached to a listed patent or exclusivity protecting the previously approved application that also protects the new application or new supplement held by the same sponsor, the pediatric exclusivity also attaches to that patent in conjunction with the new application or supplement.[134] For example, if a sponsor qualifies for a 6-month pediatric exclusivity that attaches to a 5-year exclusivity, that exclusivity attaches to each of the sponsor's NDAs protected by that 5-year exclusivity, regardless of when the new application or supplement is filed or what it contains. The following examples are provided:

- **Example 1** — Drug 1 (D1) qualifies for pediatric exclusivity. The sponsor or holder of an approved application for D1 later files a different application for a drug product containing D1 or a supplement to an existing application for a drug product containing D1. FDA does not need any of the data the sponsor or holder of an approved application submitted for pediatric exclusivity to approve the new application or new supplement. The pediatric exclusivity does not attach to any exclusivities or patents that apply solely to the new application or the new supplement.

- **Example 2** — D1 qualifies for pediatric exclusivity. The sponsor or holder of the approved application for D1 later files a different application for a drug product containing D1 or a supplement to an existing application for a drug product containing D1. The drug product could not be labeled with the data submitted in the later-filed applications or supplements without the data the sponsor or holder of an approved

[132] See sections 505(c)(3)(E)(iv) and 505(j)(5)(F)(iv) of the FD&C Act (21 U.S.C. 355(c)(3)(E)(iv) and 21 U.S.C. (j)(5)(F)(iv)).

[133] See sections 505A(b)(1) and 505A(c)(1) of the FD&C Act (21 U.S.C. 355a(b)(1) and 21 U.S.C. 355a(c)(1)).

[134] See sections 505A(b)(1) and 505A(c)(1) of the FD&C Act (21 U.S.C. 355a(b)(1) and 21 U.S.C. 355a(c)(1)).

application previously submitted for pediatric exclusivity. The pediatric exclusivity attaches to any exclusivities or patents that apply to the new application or the new supplement. In addition, if the pediatric exclusivity attaches to a patent or exclusivity that also protects the new application or new supplement, the pediatric exclusivity applies to the new application or supplement to the same extent it applies to the previously approved application.

2. Biological Products

Pediatric exclusivity for biological products differs in some ways from provisions applicable to other drug products. First, as described below, pediatric exclusivity only attaches to reference product and orphan drug exclusivity periods. Second, unlike other drug products, pediatric exclusivity does not attach to patents for biological products.[135]

Under section 351(k)(7)(A) of the PHS Act, approval of an application for a biosimilar or interchangeable biological product submitted under section 351(k) of the PHS Act may not be made effective until 12 years after the date on which the reference product was first licensed under section 351(a) of the PHS Act. Moreover, under section 351(k)(7)(B) of the PHS Act, an application for a biosimilar or interchangeable biological product submitted under section 351(k) of the PHS Act may not be submitted for review until 4 years after the date on which the reference product was first licensed under section 351(a) of the PHS Act. An additional 6-month period of pediatric exclusivity will attach to the 12- and 4-year periods if the sponsor meets the requirements for pediatric exclusivity pursuant to section 505A of the FD&C Act.[136] Furthermore, an additional 6-month period of pediatric exclusivity will also attach to the 7 years of orphan drug exclusivity for a biological product designated under section 526 of the FD&C Act for a rare disease or condition.[137]

V. ELEMENTS COMMON TO PREA AND THE BPCA

A. The Pediatric Review Committee

Section 505C of the FD&C Act directed FDA to establish the PeRC that must review all WRs and all requests for deferrals, deferral extensions, and waivers.[138] The PeRC also provides consultation on pediatric assessments and on iPSPs, agreed iPSPs, and any significant amendments to such plans.[139]

[135] See section 351(m) of the PHS Act (42 U.S.C. 262(m)).

[136] See section 351(m) of the PHS Act (42 U.S.C. 262(m)).

[137] See section 527(a) of the FD&C Act and section 351(m) of the PHS Act (21 U.S.C. 360cc(a); 42 U.S.C. 262(m)).

[138] See sections 505C, 505A(f), and 505B(f) of the FD&C Act (21 U.S.C. 355d, 21 U.S.C. 355a(f), and 21 U.S.C. 355c(f)).

[139] See section 505B(f) of the FD&C Act (21 U.S.C. 355c(f)).

As a general matter, the PeRC also reviews significant amendments to WRs and PPSR inadequate letters to ensure consistency.

Members of the PeRC include FDA employees with expertise in pediatrics (including representation from the Office of Pediatric Therapeutics (OPT)), neonatology, biopharmacology (i.e., pharmacology/toxicology), statistics, chemistry, legal issues, pediatric ethics, the appropriate expertise pertaining to the pediatric drug under review, and other individuals as needed.[140] In addition to the responsibilities above, the PeRC also provides consultation on tracking information regarding pediatric assessments and labeling changes.[141] As a general matter, members of the relevant drug review division provide background information to the PeRC and are present during the discussion of an application.

B. Publishing Information About Pediatric Studies

1. Pediatric Exclusivity Determinations

FDA posts on its website a list of exclusivity determinations on approved drugs that have qualified for pediatric exclusivity.[142] FDA also publishes pediatric exclusivity information for drugs in the Patent and Exclusivity Information section of the Orange Book and its supplements in the same manner as FDA publishes information regarding 5-year exclusivity, 3-year exclusivity, patent listings, and orphan drug exclusivity.[143]

2. Medical, Statistical, and Clinical Pharmacology Reviews

Sections 505A(k) and 505B(h) of the FD&C Act require that FDA publish the medical, statistical, and clinical pharmacology reviews of pediatric studies conducted under the BPCA and of pediatric assessments under PREA. For studies submitted in response to a WR, FDA must do so within 210 days after the submission.[144] For most pediatric assessments submitted under PREA, FDA must do so within 330 days after the submission.[145] FDA makes such

[140] See section 505C of the FD&C Act (21 U.S.C. 355d).

[141] See sections 505A(f)(6) and 505B(f)(6) of the FD&C Act (21 U.S.C. 355a(f)(6) and 21 U.S.C. 355c(f)(6)).

[142] See the FDA's Pediatric Exclusivity Granted web page at https://www.fda.gov/drugs/development-resources/pediatric-exclusivity-granted.

[143] See the Orange Book available at https://www.accessdata.fda.gov/scripts/cder/ob/default.cfm.

[144] See section 505A(k)(1) of the FD&C Act (21 U.S.C. 355a(k)(1)). For drug products for which exclusivity determinations were made before September 27, 2007, we have posted summaries of medical and clinical pharmacology reviews of studies conducted under section 505A of the FD&C Act, consistent with applicable BPCA requirements at that time.

[145] See section 505B(h)(1) of the FD&C Act (21 U.S.C. 355c(h)(1)). This provision of the law first went into effect on September 27, 2007.

information publicly available consistent with section 301(j) of the FD&C Act, the Freedom of Information Act, and the Trade Secrets Act.[146]

Before disclosure, the medical, statistical, and clinical pharmacology reviews are redacted, as appropriate, for trade secret information and for confidential commercial information.[147]

As FDA interprets section 505A(k) of the FD&C Act, the 210-day BPCA disclosure requirement is triggered when a sponsor or holder of an approved application submits an application or a supplement in response to a WR that FDA determines meets filing requirements (see section IV.C., How to Submit Study Reports in Response to a Written Request). FDA interprets the disclosure requirement to apply to such applications and supplements submitted in response to a WR under the BPCA, regardless of whether (1) the application process is completed or it is later withdrawn; (2) the drug qualifies for pediatric exclusivity; or (3) the application or supplement is approved or the sponsor receives a complete response letter. In addition, FDA interprets the disclosure requirement to apply to partial responses to a WR under the BPCA that meet the filing requirements. (See section IV.C., How to Submit Study Reports in Response to a Written Request, for a discussion of partial responses.)

3. Other Pediatric Information

FDA maintains a web page[148] containing extensive information about pediatric studies conducted under sections 505A and 505B of the FD&C Act. The web page includes, among other things, statistics and other information regarding the relevant studies, drugs, labeling changes, and reports. Statistics we post include the number of waivers, deferrals, and deferral extensions granted; the number of pediatric formulations developed; and the number of formulations not developed (including the reason they were not developed).[149] The web page also identifies drugs approved for use in a pediatric population for which a pediatric formulation

---

[146] See 5 U.S.C. 552 and 18 U.S.C. 1905.

[147] 21 CFR 314.430 is FDA's regulation regarding the public disclosure of information in a drug application or abbreviated application. 21 CFR 601.51 is FDA's regulation regarding the public disclosure of information in a biological product file. Under 21 CFR 314.430(b), we will not publicly disclose the existence of an application or abbreviated application before an approval or tentative approval letter is sent, unless the existence of the application or abbreviated application has been previously publicly disclosed or acknowledged. Under 21 CFR 601.51(b), we will not disclose the existence of a biological product file before the application has been approved if the existence of the file has not been previously publicly disclosed or acknowledged. Under 21 CFR 314.430(d)(1) and 601.51(d)(1), if the existence of the application or biological product file has been publicly disclosed or acknowledged, as a general matter, no data or information contained in the application, abbreviated application, or biological product file is available for public disclosure before we send an approval letter or before a license is issued. We note that 21 CFR 314.430 and 601.51 were promulgated before the passage of PREA and the BPCA and do not specifically discuss the disclosure of medical, statistical, and clinical pharmacology reviews of pediatric studies conducted under the BPCA and of pediatric assessments under PREA. As a general matter, FDA discloses such reviews only to the extent the drug product studied has already been approved. Additionally, the protected status of particular information in the reviews is determined on a case-by-case basis.

[148] See the Pediatric Reports, Statistics, Reviews, and Databases web page at https://www.fda.gov/science-research/pediatrics/reports-statistics-reviews-and-databases.

[149] See section 505B(f)(6) of the FD&C Act (21 U.S.C. 355c(f)(6)).

was developed and that qualified for pediatric exclusivity, but the formulation was not marketed within 1 year of the exclusivity determination.[150] FDA also maintains a web page containing information about section 409I of the PHS Act.[151]

A list of approved drugs for which WRs have been issued is published on the FDA website.[152] In addition, WRs, including any amendment(s) if not otherwise incorporated into one document, are posted on the FDA website within 30 days of the determination that the requirements for exclusivity have been met.[153]

Information from a required annual review following the granting of a deferral will be posted publicly within 90 days of submission.[154] The posting will include the information submitted through the annual review, the name of the applicant, the date on which the drug was approved, and the date of each deferral or deferral extension.[155]

Finally, FDA posts guidances, relevant regulations, relevant presentations from conferences, press releases, and reports, among other information. Transcripts from Pediatric Advisory Committee meetings, beginning September 2004, are posted as well, as are transcripts from past meetings of the Pediatric Advisory Subcommittee of the Anti-Infective Drugs Advisory Committee, held between April 1999 and June 2004.[156] FDA intends to update these sites regularly.

C. PREA and Pediatric Exclusivity

To qualify for pediatric exclusivity, the pediatric studies conducted to satisfy the requirements of PREA must be the subject of a WR and satisfy all other requirements for pediatric exclusivity

[150] See section 505A(e)(2) of the FD&C Act (21 U.S.C. 355a(e)(2)).

[151] See the Off-Patent Studies Under BPCA web page at https://www.fda.gov/drugs/development-resources/patent-studies-under-bpca.

[152] See the Written Requests Issued web page at https://www.fda.gov/drugs/development-resources/written-requests-issued. On occasion, information obtained by FDA subsequent to issuance of a WR causes FDA to rescind the WR. This list is not updated to indicate when a WR has been rescinded.

[153] See section 505A(e)(1) of the FD&C Act (21 U.S.C. 355a(e)(1)). See also the FDA's Pediatric Exclusivity Granted web page at https://www.fda.gov/drugs/development-resources/pediatric-exclusivity-granted.

[154] See section 505B(a)(4)(C)(ii) of the FD&C Act (21 U.S.C. 355c(a)(4)(C)(ii)). See also FDA's Postmarket Requirements and Commitments web page at https://www.accessdata.fda.gov/scripts/cder/pmc/index.cfm.

[155] See section 505B(a)(4)(C)(ii) of the FD&C Act (21 U.S.C. 355c(a)(4)(C)(ii)).

[156] See https://www.fda.gov/advisory-committees/pediatric-advisory-committee/past-meeting-materials-pediatric-advisory-committee.

under the BPCA.[157] As discussed in section IV.A.2., Written Request Studies, FDA does not expect to issue WRs solely for studies or planned studies that are required under PREA.

For already marketed drugs, FDA may require pediatric assessments under PREA if it finds, for example, that the drug is used for a substantial number of pediatric patients for the labeled indications and adequate pediatric labeling could confer a benefit on pediatric patients.[158] In some cases, FDA may first issue a WR under section 505A of the FD&C Act before requiring studies under section 505B(b). In those cases, if the sponsor declines the WR for the labeled indication(s), FDA may still require those studies under PREA.[159]

It is important to note the distinction between the scope of the studies FDA requests under the BPCA and those required under PREA. The scope of studies described in a WR may be broader than those required under PREA. FDA's authority to issue a WR extends to the use of an active moiety for indications that may produce health benefits in the pediatric population, regardless of whether it has previously approved the indications in adults.[160] Under PREA, pediatric assessments are required only for those indications the sponsor has included in the pending application.[161] To learn more about eligibility for pediatric exclusivity, see section IV., Best Pharmaceuticals for Children Act, or contact the relevant review division.

D. Considerations for Labeling of Drug Products

1. Labeling Study Results

Study results submitted in response to PREA or a WR must be described in labeling regardless of whether these findings support safety and/or effectiveness, do not support safety and/or

[157] See sections 505A(b)(1), 505A(c)(1), 505A(d) and 505A(h) of the FD&C Act (21 U.S.C. 355a(b)(1), 21 U.S.C. 355a(c)(1), 21 U.S.C. 355a(d), and 21 U.S.C. 355a(h)).

[158] See section 505B(b)(1) of the FD&C Act (21 U.S.C. 355c(b)(1)).

[159] See section 505B(b) of the FD&C Act (21 U.S.C. 355c(b)). This section states that the Secretary may require a sponsor or holder of an approved application to submit pediatric assessments as described under section 505B(a)(2) of the FD&C Act if the Secretary finds that "(A) (i) the drug or biological product is used for a substantial number of pediatric patients for the labeled indications; and (ii) adequate pediatric labeling could confer a benefit on pediatric patients; (B) there is reason to believe that the drug or biological product would represent a meaningful therapeutic benefit over existing therapies for pediatric patients for 1 or more of the claimed indications; or (C) the absence of adequate pediatric labeling could pose a risk to pediatric patients."

[160] See sections 505A(a), 505A(b)(1), 505A(c)(1), and 505A(d)(1)(B) of the FD&C Act (21 U.S.C. 355a(a); 21 U.S.C. 355a(a), 21 U.S.C. 355a(b)(1), 21 U.S.C. 355a(c)(1), and 21 U.S.C. 355a(d)(1)(B)).

[161] See sections 505B(a)(1)(A) and 505B(a)(2) of the FD&C Act (21 U.S.C. 355c(a)(1)(A) and 21 U.S.C. 355c(a)(2)). Note, however, that molecularly targeted pediatric cancer investigations are based on molecular mechanism of action rather than clinical indication. See sections 505B(a)(1)(B) and 505B(a)(3) of the FD&C Act (21 U.S.C. 355c(a)(1)(B) and 21 U.S.C. 355c(a)(3)). For additional information, see the guidance for industry *FDARA Implementation Guidance for Pediatric Studies of Molecularly Targeted Oncology Drugs: Amendments to Sec. 505B of the FD&C Act*.

effectiveness, or are inconclusive.[162] If a full or partial waiver is granted because there is evidence that a drug would be unsafe or ineffective in pediatric populations, applicants must include this information in labeling.[163]

Applicants must distribute information to health care providers describing any labeling changes that are approved as a result of these studies as required by FDA.[164]

2. Dispute Resolution

The BPCA and PREA provide for a dispute resolution process when FDA and the applicant fail to agree on appropriate labeling changes.[165] If the applicant does not agree within the specified time period after FDA's request to make labeling changes, FDA must refer the matter to the Pediatric Advisory Committee (PAC).[166] The PAC then has 90 days after receiving the referral to review the pediatric study reports and make a recommendation to FDA.[167] FDA will consider the recommendation, and, if appropriate, within 30 days after receiving the recommendation, make a request to the applicant to make the labeling changes FDA determines to be appropriate.[168] If the applicant fails to agree to make the labeling changes within 30 days after receiving such a request, the drug may be deemed misbranded.[169]

3. Priority Review of Applications and Labeling Supplements

Any application or supplement to an application that proposes a labeling change as a result of pediatric studies a sponsor conducts under section 505A of the FD&C Act will be considered a priority application or supplement.[170] This priority status applies even if the studies submitted

---

[162] See sections 505A(j) and 505B(g)(2) of the FD&C Act (21 U.S.C. 355a(j) and 21 U.S.C. 355c(g)(2)). See also the guidance for industry *Pediatric Information Incorporated Into Human Prescription Drug and Biological Product Labeling*.

[163] See section 505B(a)(5)(D) of the FD&C Act (21 U.S.C. 355c(a)(5)(D)).

[164] See sections 505A(k)(2) and 505B(h)(2) of the FD&C Act (21 U.S.C. 355a(k)(2) and 355c(h)(2)).

[165] See sections 505A(i)(2) and 505B(g)(1) of the FD&C Act (21 U.S.C. 355a(i)(2) and 355c(g)(1)).

[166] See sections 505A(i)(2)(A) and 505B(g)(1)(A) of the FD&C Act (21 U.S.C. 355a(i)(2)(A) and 355c(g)(1)(A)).

[167] See sections 505A(i)(2)(B) and 505B(g)(1)(B) of the FD&C Act (21 U.S.C. 355a(i)(2)(B) and 355c(g)(1)(B)).

[168] See sections 505A(i)(2)(C) and 505B(g)(1)(C) of the FD&C Act (21 U.S.C. 355a(i)(2)(C) and 355c(g)(1)(C)).

[169] See sections 505A(i)(2)(D) and 505B(g)(1)(D) of the FD&C Act (21 U.S.C. 355a(i)(2)(D) and 355c(g)(1)(D)).

[170] See section 505A(i)(1) of the FD&C Act (21 U.S.C. 355a(i)(1)). This priority review provision applies only to applications and supplements containing studies conducted under section 505A of the FD&C Act; it does not apply to an application or supplement solely because it contains pediatric information. Note that NDAs and BLAs may be otherwise eligible for priority review. For information on Prescription Drug User Fee Act VI performance goals and procedures, see https://www.fda.gov/industry/fda-user-fee-programs/prescription-drug-user-fee-amendments.

did not respond completely to the WR or did not otherwise qualify for pediatric exclusivity.[171] Applications that include a pediatric assessment submitted with the sole intention of responding to PREA requirements do not necessarily receive priority review.

For more information about priority review, see FDA's Prescription Drug User Fee Act reauthorization performance goals and procedures document.[172]

E. Adverse Event Reporting for Drug Products Subject to the BPCA and PREA

At the same time that a sponsor submits reports of studies responding to a WR, the sponsor must also provide FDA with all available postmarketing adverse event reports regarding the studied drug.[173] The format of the postmarketing adverse event report should follow the model for a periodic safety update report described in the ICH guidance for industry *E2C(R2) Periodic Benefit-Risk Evaluation Report (PBRER)* (July 2016). In addition, the sponsor may contact the review division for further information.

Eighteen months after the date of a labeling change made to reflect studies conducted under PREA or the BPCA, the applicable center refers to OPT a report of all adverse events received by FDA for the drug product.[174] As a general matter, OPT presents a report and analysis to the PAC, and the PAC reviews this analysis and recommends whether additional monitoring (other than the usual surveillance) is necessary. When the PAC considers additional monitoring necessary after the 18-month period, the center generally continues to refer adverse event reports to OPT.

VI. ADDITIONAL INFORMATION

The Division of Pediatrics and Maternal Health can provide general information about complying with PREA and the BPCA. Additional pediatric information and contact information is available on the Pediatric Product Development web page.[175]

[171] See section 505A(i)(1) of the FD&C Act (21 U.S.C. 355a(i)(1)).

[172] See PDUFA Reauthorization Performance Goals and Procedures Fiscal Years 2013 Through 2017 at https://www.fda.gov/media/81306/download.

[173] See section 505A(d)(2)(B) of the FD&C Act (21 U.S.C. 355a(d)(2)(B)).

[174] See sections 505A(l) and 505B(i) of the FD&C Act (21 U.S.C. 355a(l) and 355c(i)).

[175] Available at https://www.fda.gov/drugs/development-resources/pediatric-and-maternal-health-product-development.

GLOSSARY

Assessment — Contains data, gathered using appropriate formulations for each age group for which the assessment is required, that are adequate to assess the safety and effectiveness as well as support the dosing and administration of a drug product for each relevant pediatric age group (see section 505B(a)(2) of the FD&C Act (21 U.S.C. 355c(a)(2))).

Certify/Certification — In general, a certification is a statement from the applicant that the data provided to support a deferral[1] and/or waiver[2] request are accurate and complete.

Deferral — Defers submission of some or all of the required assessments or reports on the molecularly targeted pediatric cancer investigation until a specified date (see section 505B(a)(4) of the FD&C Act (21 U.S.C. 355c(a)(4))).

Pediatric Study Plan (PSP) — An outline of planned pediatric studies, along with any deferral and/or waiver requests, that is submitted by a sponsor for an application subject to PREA before the submission of assessments or reports on the molecularly targeted pediatric cancer investigation (see section 505B(e) of FD&C Act (21 U.S.C. 355c(e))). For more information, see the guidance for industry *Pediatric Study Plans: Content of and Process for Submitting Initial Pediatric Study Plans and Amended Initial Pediatric Study Plans* (July 2020).[3]

Proposed Pediatric Study Request (PPSR) — In general, a PPSR is a submission describing what pediatric studies a sponsor or application holder believes will yield information about the use of a drug that may produce health benefits in the pediatric population.

Molecularly Targeted Pediatric Cancer Investigation — An investigation of a drug described in section 505B(a)(1)(B) of the FD&C Act that must be designed to yield clinically meaningful pediatric study data, gathered using appropriate formulations for each age group for which the study is required, regarding dosing, safety, and preliminary efficacy to inform potential pediatric labeling (see section 505B(a)(3) of the FD&C Act (21 U.S.C. 355c(a)(3))).

Waiver — Waives the requirement to submit assessments or reports on the molecularly targeted pediatric cancer investigation for the entire pediatric population or specific age group(s) (see section 505B(a)(5) of the FD&C Act (21 U.S.C. 355c(a)(5))).

Written Request (WR) — In general, a WR is a document from FDA, signed by the applicable office director(s), requesting submission of a certain study or studies to determine whether the use of a drug could provide a meaningful health benefit in the pediatric population that is issued under section 505A of the FD&C Act (21 U.S.C. 355a) or section 351(m) of the PHS Act (42 U.S.C. 262(m)).

---

[1] See section 505B(a)(4)(A)(ii)(I) of the FD&C Act (21 U.S.C. 355c(a)(4)(A)(ii)(I)).

[2] See section 505B(a)(5) of the FD&C Act (21 U.S.C. 355c(a)(5)).

[3] We update guidances periodically. To make sure you have the most recent version of a guidance, check the FDA guidance web page at https://www.fda.gov/regulatory-information/search-fda-guidance-documents.

Adult-Related Conditions that qualify for a waiver because they rarely or never occur in pediatrics*

These conditions qualify for waiver because studies would be impossible or highly impractical.

actinic keratosis
acute bacterial exacerbations of chronic bronchitis (a complication of chronic obstructive pulmonary disease)
adjunctive treatment of major depressive disorder (MDD)
age-related macular degeneration (AMD)
Alzheimer's disease amyloidosis
amyotrophic lateral sclerosis
androgenic alopecia
atherosclerotic cardiovascular disease (excluding genetic causes and including acute myocardial infarction due to ASCD)
benign monoclonal gammopathy
benign prostatic hyperplasia
bullous pemphigoid
Cancer:
- basal cell and squamous cell skin cancer;
- bladder;
- breast;
- cervical;
- colorectal;
- cholangiocarcinoma;
- chronic lymphocytic leukemia (CLL);
- endometrial;
- esophageal;
- fallopian tube;
- follicular lymphoma;
- gastric;
- hairy cell leukemia;
- hepatocellular;
- indolent non-Hodgkin lymphoma;
- liposarcoma; lung (small & non-small cell);
- multiple myeloma;
- oropharynx (squamous cell);
- ovarian (non-germ cell);
- pancreatic;
- peritoneal;
- prostate;
- renal cell;
- uterine;

chronic obstructive pulmonary disease (COPD)
cryoglobulinemia
degenerative intervertebral disc disease
diabetic foot infections
diabetic gastroparesis
diabetic peripheral neuropathy/macular edema
diabetic retinopathy (DR)
digestive disorders (gallstones)
dry eye syndrome (keratoconjunctivitis sicca)
Dupuytren's disease and manifestations
erectile dysfunction
essential thrombocytosis
Fuchs endothelial corneal dystrophy
giant cell arteritis
gout
heavy menstrual bleeding associated with uterine fibroids
Huntington's chorea
idiopathic pulmonary fibrosis
infertility & reproductive technology (including Assisted Reproductive Technology (ART))
memory loss
menopause and perimenopausal disorders mesothelioma
microscopic polyangiitis
myelodysplasia
myelofibrosis & myeloproliferative disorders
Myopic Choroidal Neovascularization (mCNV)
opioid induced constipation in chronic, non-cancer pain
osteoarthritis
overactive bladder
Parkinson's disease
paroxysmal nocturnal hemoglobinuria
pemphigus vulgaris
Peripheral arterial disease (PAD) due to T2 diabetes mellitus
peripheral vascular disease
plasma cells and antibody production disorders
polycythemia vera
polymyalgia rheumatica (PMR)
postmenopausal osteoporosis
presbyopia
prevention of stroke and systemic embolic events in atrial fibrillation
reduction of thrombotic cardiovascular events in patients with coronary artery disease
retinal vein occlusions (RVO)
rosacea
Sjogren's Syndrome
stress urinary incontinence
temporary improvement in the appearance of glabellar, canthal, and/or forehead lines
thyroid eye disease
treatment of incompetent great saphenous veins and varicosities
treatment of Hypoactive Sexual Desire Disorder (HSDD) in postmenopausal women
type 2 diabetic mellitus with cardiovascular disease
type 2 diabetic nephropathy
vascular dementia/vascular cognitive disorder/ impairment