U.S. FOOD & DRUG ADMINISTRATION

Drug Safety and Risk Management Advisory Committee and the
Dermatologic and Ophthalmologic Drugs Advisory Committee Meeting
March 28-29, 2023

Isotretinoin Background and Regulatory History

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Objectives

- Isotretinoin background
- Overview of isotretinoin risk management programs
- Regulatory history of modifications to the risk management programs

Isotretinoin

- Chemical name: 13-cis retinoic acid
- Class: Retinoid
- First-generation
- Related to vitamin A

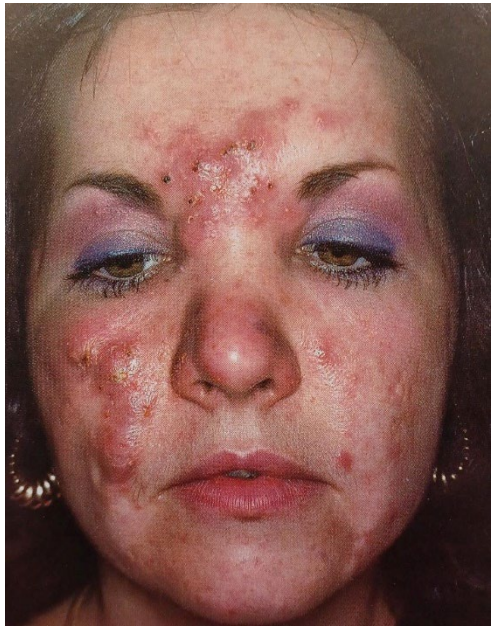
Isotretinoin

- Accutane® (isotretinoin) capsules approved in May 1982
  - Indication: Severe recalcitrant nodular acne, 12 years and older
  - Treatment: dosed by patient weight; duration for 16 to 20 weeks

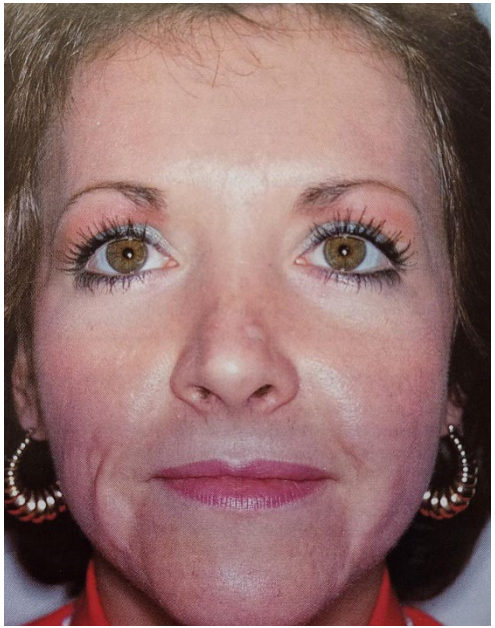
Nodular Acne Treated with Isotretinoin

From: Fitzpatrick, 1993

Before



After



Isotretinoin Drug Products

Accutane brand removed from market in 2009

Currently Marketed Drugs (Approval month/year)

- NDAs
  - Absorica® – 5/2012
  - Absorica LD™ – 11/2019
- ANDAs
  - Isotretinoin (5 manufacturers) - since 2002
  - Amnesteem – 11/2002
  - Claravis – 4/2003
  - Myorisan – 1/2012
  - Zenatane – 3/2013

Isotretinoin

- Remains the only FDA-approved drug product for the nodular acne indication
- Highly efficacious
- Many patients require one course of therapy only

Isotretinoin – Teratogen

- 1982 – Pregnancy Category X
  - Studies in pregnant women demonstrated a risk to the fetus, and/or
  - Human or animal studies have shown fetal abnormalities
  - No benefit of use in pregnancy
- 1983 – First report of exposed infant, malformation

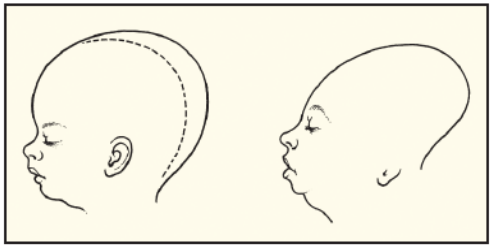
Isotretinoin - Embryofetal Toxicity Malformations

External Abnormalities

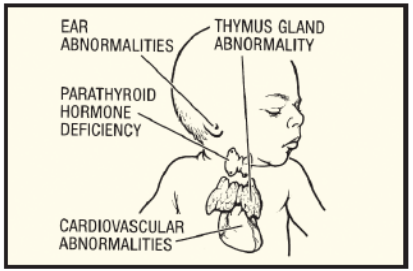
Skull abnormality; ear abnormalities (including anotia, micropinna, small or absent external auditory canals); eye abnormalities (including microphthalmia); facial dysmorphia; cleft palate.

Internal Abnormalities

CNS abnormalities including cerebral abnormalities, cerebellar malformation, hydrocephalus, microcephaly, cranial nerve deficit, cardiovascular abnormalities, thymus gland abnormalities, parathyroid hormone deficiencies. In some cases, death has occurred with certain of the abnormalities noted.



Line drawing represents the possible abnormalities of the low-set, deformed, or absent ears; wide-set eyes; depressed bridge of the nose; enlarged head; and small chin.



Line drawing represents the possible abnormalities of the brain, heart, and thymus gland that may occur.

Accutane® Labeling Modifications

- 1984 – Boxed Warning
- Added information to labeling:
  - Use of contraception for 1 month prior to treatment
  - Pregnancy testing
  - Patients must discontinue treatment immediately if they become pregnant

Reports of Isotretinoin Embryo-Fetal Toxicity and Pregnancy Loss

- **April 1984 –** Centers for Disease Control and Prevention (CDC) published their first report which identified isotretinoin (Accutane®) as cause of:
  - Specific pattern of birth defects of the brain, head and face, and heart
  - Miscarriage (spontaneous abortion)

- **May 1984** – results of American Academy of Dermatology (AAD) requesting members report outcome of pregnancies exposed to isotretinoin (Accutane®) to its Adverse Drug Reaction Reporting System (ADRRS), and FDA
  - 35 reported to ADRRS and FDA: 29 (83%) spontaneous abortion or "birth anomalies"

CDC – Morbidity and Mortality Weekly Report – Epidemiologic Notes and Reports Isotretinoin -- A Newly Recognized Human Teratogen. https://www.cdc.gov/mmwr/preview/mmwrhtml/00000310.htm. April 6, 1984.

Stern RS, Rosa F, Baum C. Isotretinoin and pregnancy. *J Am Acad Dermatol*. 1984;10(5 Pt 1):851-854.

Retinoic Acid Embryopathy
Exposed Pregnancies

1985 – Evaluated 154 isotretinoin-exposed pregnancies voluntarily reported to Hoffmann-LaRoche, FDA, CDC between September 1982 and July 5, 1984. Exposure: 7 to 124 days

Outcomes:

- 62% elective first-trimester abortions
- 17% infants without major malformations
- 13% malformed infants
- 8% spontaneous abortions

For subset of 36 of the 154 pregnancies observed prospectively.

Outcomes:

- 64% without major malformations
- 22% spontaneous abortions (first trimester)
- 14% malformed infants (one was stillborn)

Lammer EJ, Chen DT, Hoar RM, et al. Retinoic acid embryopathy. *N Engl J Med*. 1985;313(14):837-841.

Retinoic Acid Embryopathy
Malformation Pattern and Relative Risk

- Malformations formed recognizable pattern = embryopathy: cranium and face; heart; brain; thymus
- High relative risk for group of selected major malformations (relative risk = 25.6; 95% confidence interval, 11.4 to 57.5)

Lammer EJ, Chen DT, Hoar RM, et al. Retinoic acid embryopathy. *N Engl J Med*. 1985;313(14):837-841.

Isotretinoin - Embryopathy Summary

- Severe, life-threatening birth defects
- Severe birth defects may occur if pregnancy is exposed
  - Any amount of isotretinoin
  - Even for short periods of time
- In 1985, there was no accurate means to determine prenatally whether or not an exposed fetus has been affected

Advisory Committee and Stakeholder Input

- Eleven Advisory Committee meetings have been held regarding isotretinoin
- Included expert committee member discussion, open public comment and recommendations
- Pertinent advisory committee meetings and modifications are highlighted

Accutane Pregnancy Prevention Program (APPP) 1988 Advisory Committee

- New education-based program and reminder tools
- Negative Pregnancy test before initiating treatment
- Monthly pregnancy testing
- Limited to 30-day supply
- Stakeholders were not required to comply

Dermatology and Ophthalmology Advisory Committee (DODAC) September 2000

Recommendations:

- Augmentation of patient education
- Link prescription dispensing to negative pregnancy test
- Mandatory registration of patients and prescribers
- Implement pregnancy registry (voluntary)

System to Manage Accutane Related Teratogenicity (S.M.A.R.T.) October 2001

- Sticker-based program for prescription
- Sticker intended to verify:
  - Two negative pregnancy tests
  - Two forms of contraception
  - Signed patient information/consent form
- Medication Guide
- Prescription compliance survey

Risk Management Plans

- Additional isotretinoin safety programs developed 2002-2003
- Manufacturers operated programs individually
- Not centralized

Drug Safety and Risk Management (DSaRM) Advisory Committee and DODAC February 2004

Recommendations:

- Registration of all patients, prescribers, pharmacies
- Tighter linkage of pregnancy testing to prescription dispensing
- Implement pregnancy registry including analysis of the pregnancy occurrence
- Participation of all manufacturers in a single risk minimization action plan

iPLEDGE Program - 2005

- Single, consolidated risk minimization action plan for isotretinoin (innovator and generic versions)
- **Risk Evaluation and Mitigation Strategy (REMS) Goals**:
  - To prevent fetal exposure to isotretinoin
  - To inform prescribers, pharmacists, and patients about isotretinoin's serious risks and safe-use conditions
- First access system for isotretinoin
  - Only registered and qualified patients receive isotretinoin

iPLEDGE REMS Program
Elements To Assure Safe Use (ETASU)

- Prescriber certification
- Pharmacy certification
- Patient qualification and documentation:
  - Monthly counseling (all patients)
  - Monthly pregnancy testing, all females of childbearing potential (FCBP)
  - FCBPs demonstrate comprehension by monthly questions
  - Prescriber and patient identify chosen contraceptive methods
- Pregnancy registry for data, analysis

Qualification for Male and Female of Nonchildbearing Potential (FNCBP)

- Prescriber registered patient with iPLEDGE
- Counseling patient reg. teratogenic risk, safety, confirmed in iPLEDGE system
- Patient filled prescription in registered pharmacy
  - Pick up Rx within 7 days
  - If not picked up, 23-day lockout period

iPledge program, 2006

iPLEDGE
Milestones and Implementation

- Approved August 2005
- Transition completed March 2006
- Slow registration/activation of stakeholders
- Call center overload
- 7-day window/23-day lockout →many Rx denied, delay treatment

iPLEDGE Program Modifications 2006

- Removal of 23-day lockout for Males and FNCBP
  - Did not require labeling change
  - More flexibility for this subset of patients
  - Reduced treatment interruptions
  - Reduced burden for stakeholders

DSaRM and DODAC
Advisory Committee Meeting 2007

- Updated risk management since iPLEDGE implementation
- Enrollment
- Pregnancy data

iPLEDGE Program Modifications after 2007 AC Meeting

- Terminology – 3 categories
  - Females of Childbearing Potential → Females of Reproductive Potential
  - Females of Nonchildbearing Potential → Females Not of Reproductive Potential
  - Males – no change
- For Females of Reproductive Potential (FRP):
  - 23-day lockout removed for isotretinoin refills
  - Interval to repeat the pregnancy test should be ≥ 19 days, if initial 7-day window is missed
  - Link 7-day prescription window to date of pregnancy test collection, rather than office visit
- For Females Not of Reproductive Potential (FNRP) and Males
  - Extended prescription window from 7 days to 30 days

iPLEDGE Program Modifications 2008

- Sponsors developed a non-compliance action policy for manufacturers, distributors, pharmacies, prescribers
- Examples: Not registered; Patient/counseling not confirmed; report different pregnancy test result; misidentify patient pregnancy risk category (i.e., FRP, FNRP, Males) in the iPLEDGE program

iPLEDGE Program Modifications 2009

- Further definition of childbearing potential
- Urine pregnancy test, hCG with sensitivity of at least 25 mIU/mL
- Accept qualitative and quantitative pregnancy tests
- Confirmatory pregnancy test in CLIA-certified lab
- Confirmatory pregnancy test obtained at menses onset
- Clarification of abstinence in program
- System prompts and changes allowed without call center

DSaRM and DODAC
Joint Advisory Committee Meeting 2011

Purpose of Meeting Discussion:

- Does iPLEDGE program assure the safe use of isotretinoin?
- Is iPLEDGE excessively burdensome on patients who require access to isotretinoin therapy?
- To the extent possible, are there ways to minimize inconvenience of iPLEDGE on healthcare delivery?

DSaRM and DODAC
Joint Advisory Committee Meeting 2012

- The FDA's framework for selecting strategies to manage the teratogenic risk of drug products:
  - The "at-risk" populations for teratogenicity
  - The benefits and drawbacks of targeting a REMS to only the "at-risk" populations
  - The risk management approach for a teratogenic drug when it is used to treat different medical conditions
- Committee's views on the risk management tools for contraception use and pregnancy testing that should be considered when dealing with teratogenic drug products
- Discussion did not include in-depth discussion of any drug-specific information

Ongoing Evaluation and Modification

Multidisciplinary Team:

- Regularly assesses REMS, pregnancy data
- Reviews safety, adverse event reports- reference, generic drugs
- Reviews iPLEDGE educational materials– video, print, digital
- Receives stakeholder input

Pregnancy and Lactation Labeling Rule (PLLR) 2014

- FDA: *Content and Format of Labeling for Human Prescription Drug and Biological Products; Requirements for Pregnancy and Lactation Labeling*
- Removed Pregnancy Categories A, B, C, D, X
- Replaced categories with narrative summaries of risk

Source: 21 CFR Part 201

Absorica® and Absorica LD™ Labeling Boxed Warning – 2019

WARNING: EMBRYO-FETAL TOXICITY – CONTRAINDICATED IN PREGNANCY

ABSORICA/ABSORICA LD can cause severe life-threatening birth defects and is contraindicated in pregnancy. There is an extremely high risk that severe birth defects will result if pregnancy occurs while taking any amount of ABSORICA/ABSORICA LD even for short periods of time. Potentially any fetus exposed during pregnancy can be affected. There are no accurate means of determining prenatally whether an exposed fetus has been affected. If pregnancy occurs, discontinue ABSORICA/ABSORICA LD immediately and refer the patient to an Obstetrician-Gynecologist experienced in reproductive toxicity for further evaluation and counseling *[see Contraindications (4), Warnings and Precautions (5.1), and Use in Specific Populations (8.1)]*.

Because of the risk of embryo-fetal toxicity, ABSORICA and ABSORICA LD are available only through a restricted program under a Risk Evaluation and Mitigation Strategy (REMS) called the iPLEDGE REMS *[see Warnings and Precautions (5.2)]*.

iPLEDGE Program Modification
Pregnancy Risk Categories

- In 2016, Katz a Viewpoint: “Transgender Patients, Isotretinoin, and US Food and Drug Administration-Mandated Risk Evaluation and Mitigation Strategies: A Prescription for Inclusion”.
- Safety and compliance issue: misidentify pregnancy risk by gender rather than if they can become pregnant
- Initiated review, stakeholder input, and Center Director Workshop with LGBTQ+ representatives

- Katz KA. Transgender Patients, Isotretinoin, and US Food and Drug Administration-Mandated Risk Evaluation and Mitigation Strategies: A Prescription for Inclusion. JAMA Dermatol. 2016 May 1;152(5):513-4. doi: 10.1001/jamadermatol.2015.5547. PMID: 26762226.

iPLEDGE Program Modification
October 2021

- Change in patient pregnancy risk categories from three to two
- Females of Reproductive Potential → **Patients who <u>can</u> get pregnant**
- Females Not of Reproductive Potential and Males → **Patients who <u>cannot</u> get pregnant**

iPLEDGE System Transition in December 2021

- No changes to the iPLEDGE Program safety requirements.
- iPLEDGE Program changes implemented upon transition to a new system:
  - **RMAs must be obtained via the iPLEDGE Program website or interactive voice response system (IVRS)**
  - Three patient categories will be consolidated into **two gender neutral categories (patients who can get pregnant and patients who cannot get pregnant)**

iPLEDGE Modification
December 2021 Transition

- The transition was difficult logistically
  - Difficult platform access for stakeholders
  - Delays in patient access after launch
  - Multiple meetings with stakeholders
- Platform operations improved
- Agency reevaluation continues

iPLEDGE Summary

- iPLEDGE program, in place for 18 years, is complex, with interdependent features and requirements.
- iPLEDGE modifications have been ongoing and multidisciplinary, and systematic.

Conclusion

- There is benefit of isotretinoin for patients.
- The risks are serious, so that some inconvenience is expected to ensure safety and to prevent harm.

References

- 21 CFR Part 201 [Docket No. FDA-2006-N-0515 (formerly Docket No. 2006N-0467)] RIN 0910-AF11 Content and Format of Labeling for Human Prescription Drug and Biological Products; Requirements for Pregnancy and Lactation Labeling

- Epidemiologic Notes and Reports Isotretinoin -- A Newly Recognized Human Teratogen. **MMWR** Weekly Rep [Internet]. 1984 Apr 6 [cited (2023 Mar 20)];33(13):171-3. Available from: https://www.cdc.gov/mmwr/preview/mmwrhtml/00000310.htm

- Fitzpatrick TB, Eisen AZ, Wolff K, Freedberg IM, Austen KF, ed: Dermatology in General Medicine, Fourth Edition. McGraw-Hill, Inc., 1993.

- Katz KA. Transgender Patients, Isotretinoin, and US Food and Drug Administration-Mandated Risk Evaluation and Mitigation Strategies: A Prescription for Inclusion. JAMA Dermatol. 2016 May 1;152(5):513-4. doi: 10.1001/jamadermatol.2015.5547. PMID: 26762226.

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- Stern RS, Rosa F, Baum C. Isotretinoin and pregnancy. *J Am Acad Dermatol*. 1984;10(5 Pt 1):851-854. doi:10.1016/s0190-9622(84)80142-5


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ADMINISTRATION

Contraception and Pregnancy Testing Requirements to Prevent Exposure in Pregnancy

iPLEDGE Advisory Meeting

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Division of Pediatrics and Maternal Health
Office of Rare Diseases, Pediatrics, Urologic and Reproductive Medicine
Office of New Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
March 28, 2023

Outline

- Contraception requirements
- Pregnancy testing requirements
- Rationale for 19-day lockout when the initial 7 day-prescription window is missed

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Factors that Affect Contraception Recommendations

- Medical conditions and/or co-morbidities*
  - smoking
  - chronic/acute medical conditions
  - age
- Adverse reactions
- Drug-drug (contraceptive) interactions
  - resulting in possible decrease in contraceptive efficacy
- Ability to correctly and consistently use a contraception method
- Patient's preference

*Update to U.S. Medical Eligibility Criteria for Contraceptive Use. CDC MMWR 2020;69(14): 405-410

Factors Affecting Contraception Effectiveness Rate

- Intrinsic efficacy under clinical trial conditions
- Typical use effectiveness rate
  - lower than failure rate observed during clinical trials
  - reflects failure rates during everyday life, including inconsistent or incorrect use

Trussell J. Understanding contraceptive failure. Best Pract Res Clin Obstet Gynaecol. 2009 Apr;23(2):199-209.

Contraceptive Typical Use Failure Rates**

Contraceptives	Failure Rate during First Year (Typical Use)
Sterilization surgery for female and male	0.15-0.5%
IUDs (progestin, copper)	0.1-0.8%
Implantable rod	0.1%
Injection	4%
Patch, vaginal contraceptive ring, combined birth control pills	7%
Male condom	13%
Diaphragm (with spermicide), sponge	9-20%

**Hatcher R, et al. 2018, Contraceptive Technology, 21st edition, New York, NY: Ayer Company Publishers, Inc.

iPLEDGE Acceptable Contraception Methods*

Patient must choose 2 forms of contraception unless the patient commits to continuous abstinence from having any sexual contact (penis-vaginal) with a partner that could result in pregnancy

Primary

- Hormonal Implant
- IUD (hormonal and non-hormonal)
- Tubal Sterilization
- Male Vasectomy
- Hormonal Shot
- Vaginal Ring
- Hormonal Patch
- Birth Control Pill (Combination Type)

Secondary

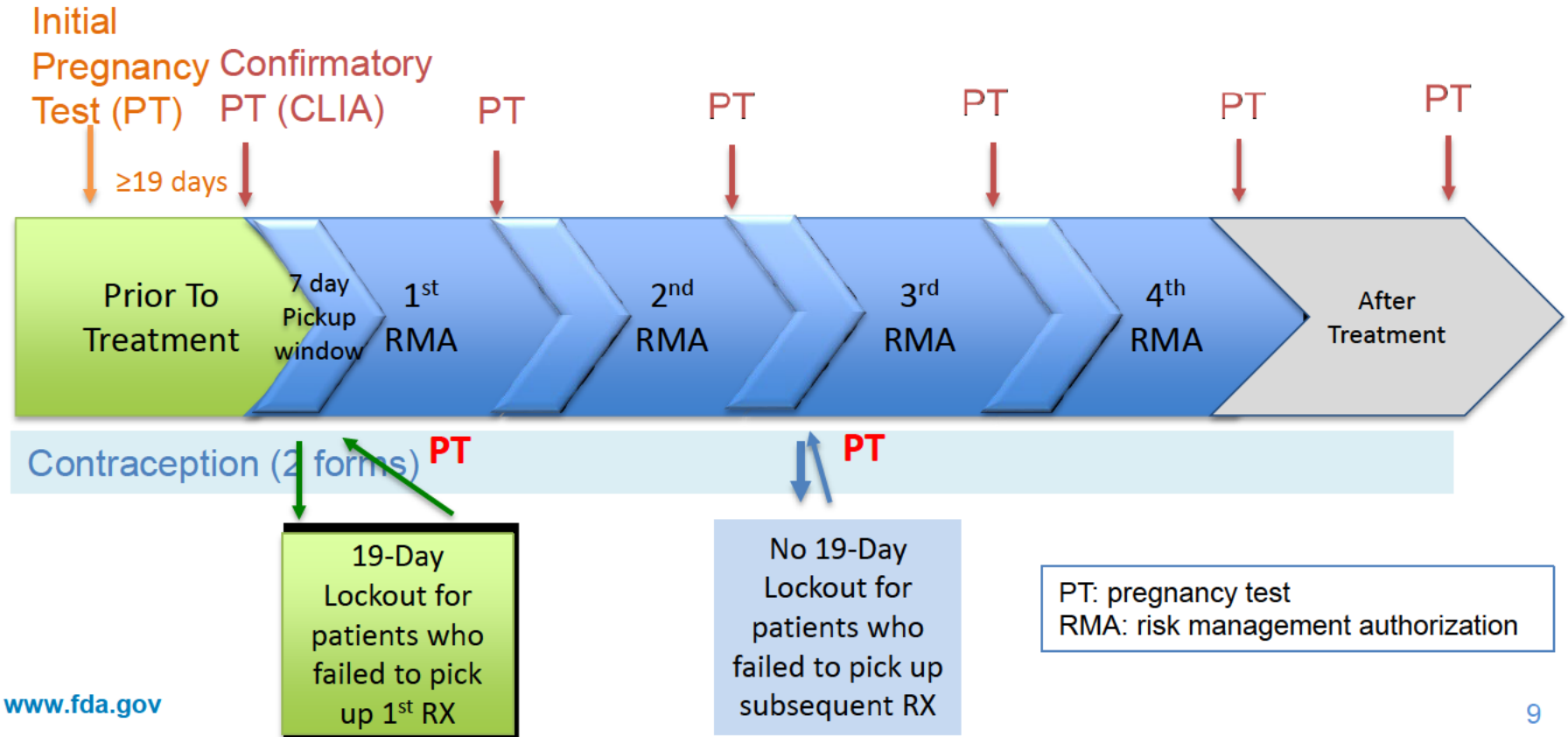
- Male Latex Condoms (with or without spermicide)
- Cervical cap or diaphragm with spermicide; vaginal sponge

*iPLEDGE Prescriber Guide

Outline

- Contraception requirements
- Pregnancy testing requirements
- Rationale for 19-day lockout when the initial 7 day-prescription window is missed

Pregnancy Testing Requirements for Patients Who Can Become Pregnant



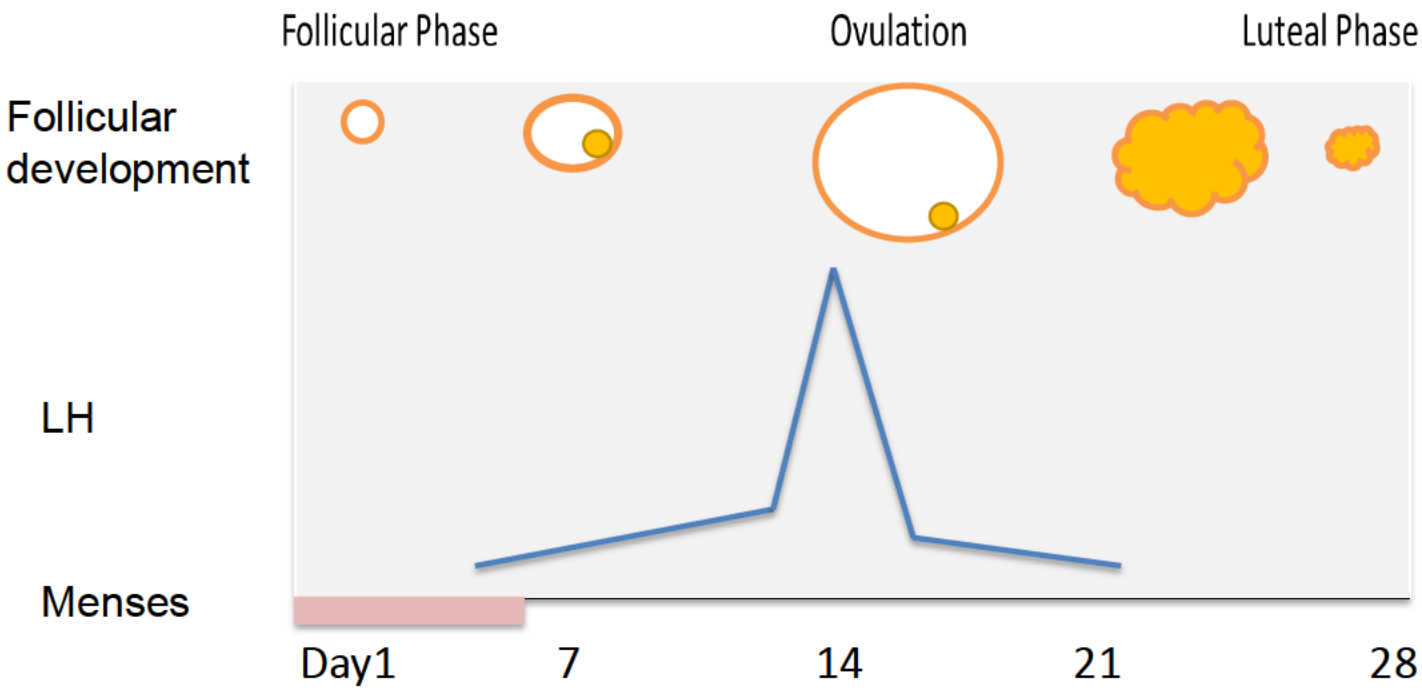
Outline

- Contraception requirements
- Pregnancy testing requirements
- Rationale for 19-day lockout when the initial 7 day-prescription window is missed

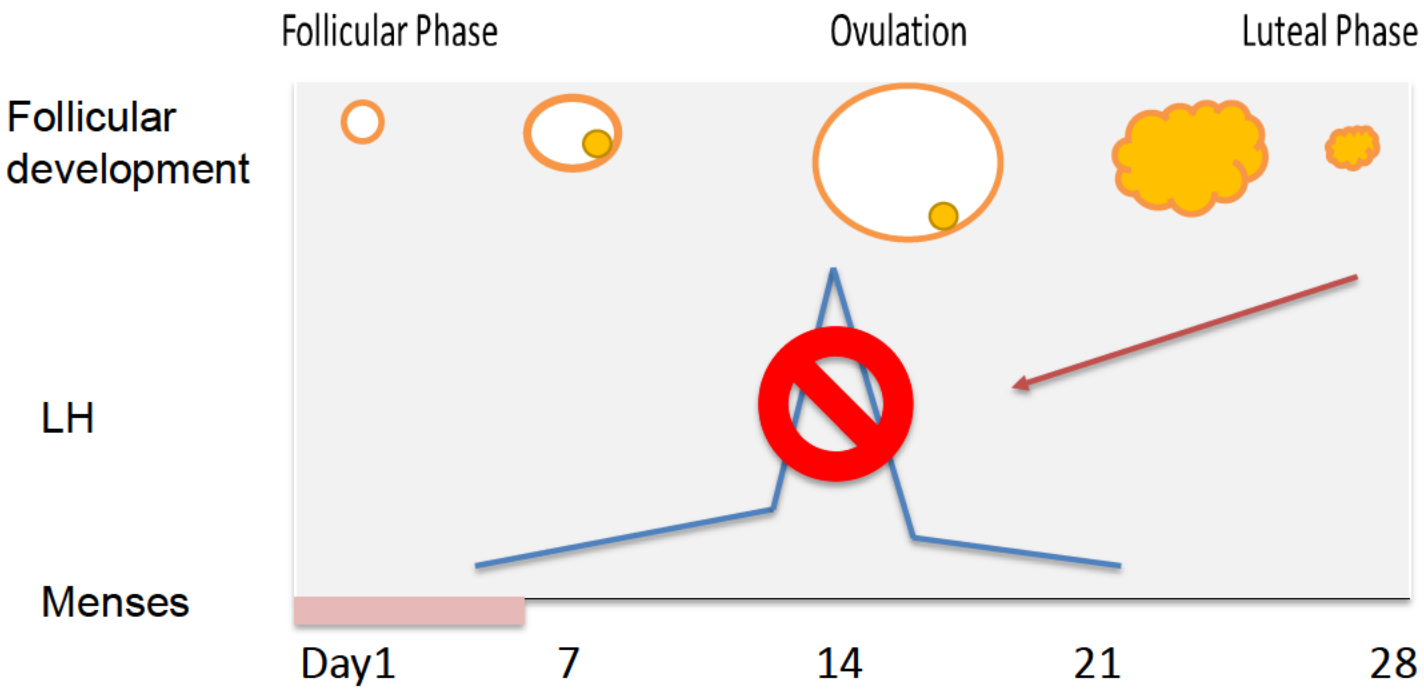
The Rationale of 19-Day Lockout

- **First Prescription:**
  - Patient has not started isotretinoin treatment
  - The 19-day lockout applies only to the first prescription where the goal is to prevent exposure to isotretinoin.
- **Subsequent Prescriptions:**
  - Patient has already started isotretinoin treatment
  - Therefore, exposure cannot prevented
  - No 19-day lockout
  - The 19-day lockout does not apply to subsequent prescriptions where the goal is to minimize exposure to isotretinoin.

The Menstrual Cycle



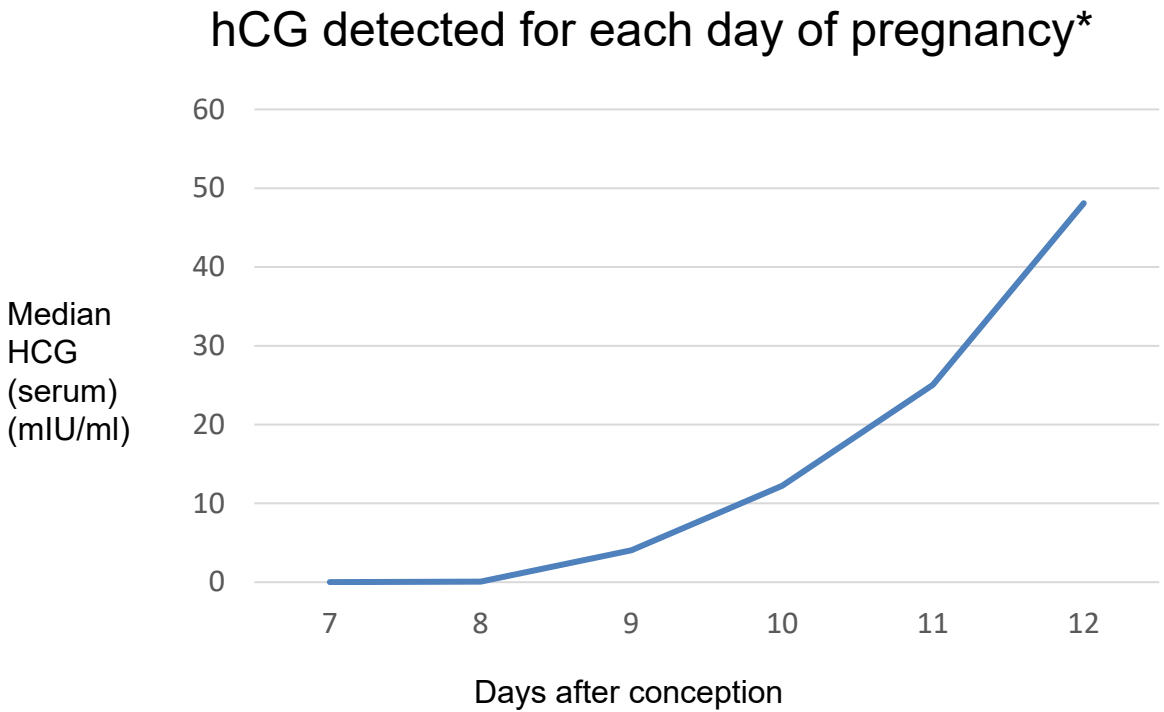
The Menstrual Cycle



Hormonal Contraceptives:

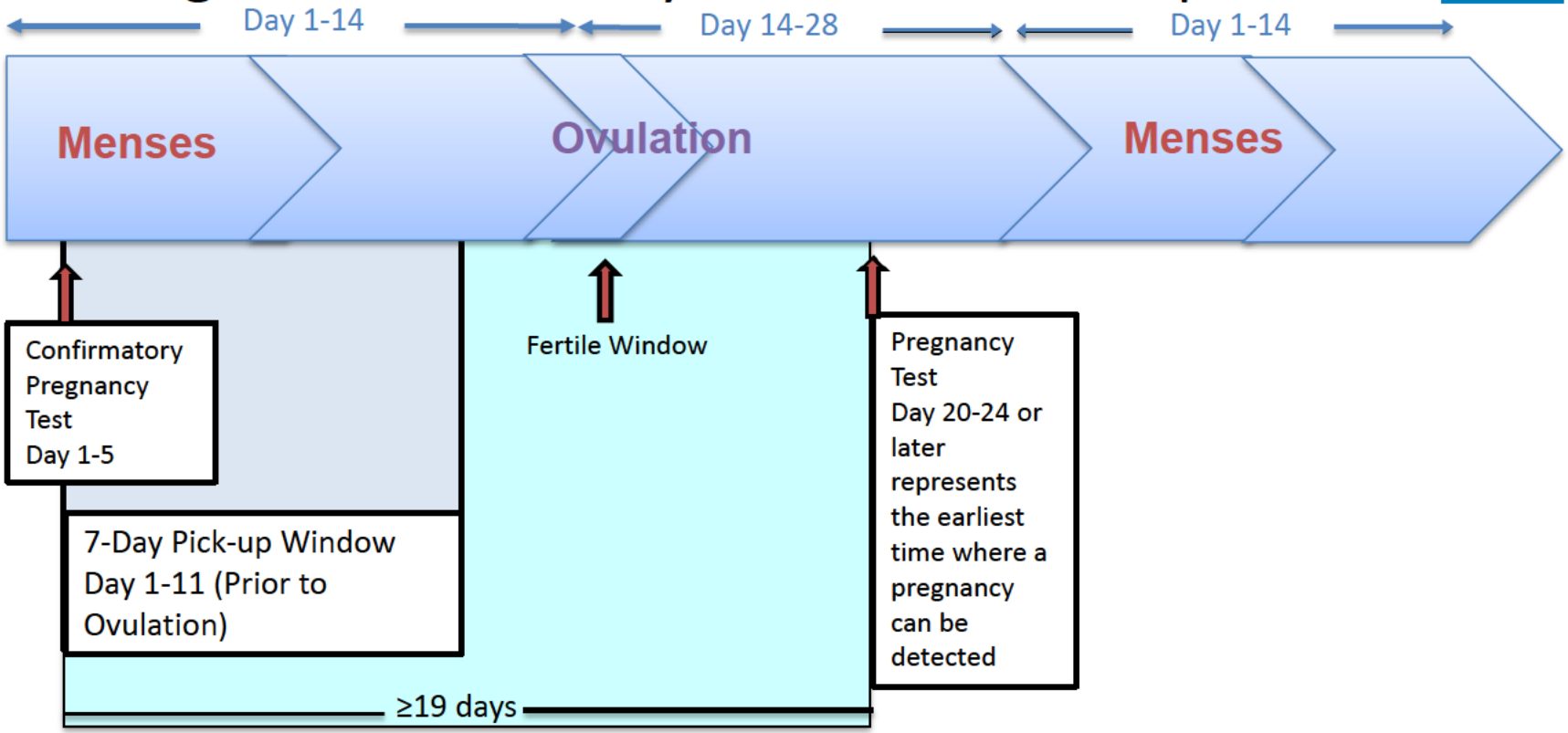
- Suppress FSH release
- Block LH surge

Early Pregnancy



Gnoth C, et al. Strips of Hope: Accuracy of Home Pregnancy Tests and New Developments. Geburtshilfe Frauenheilkd. 2014

19-Day Lockout in Patients with Regular Menstrual Cycle for First Prescription Fill



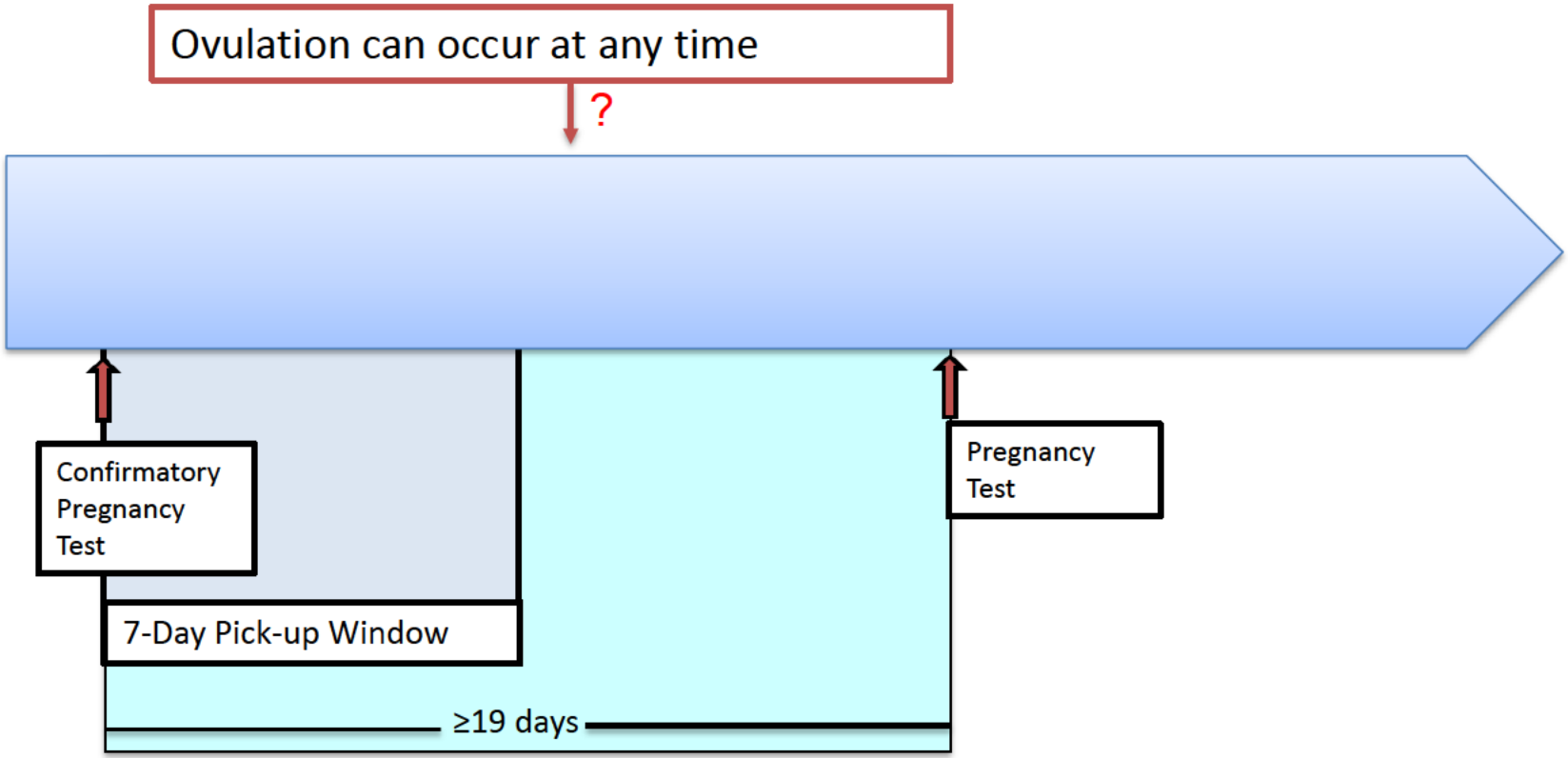
Pregnancy Testing

A prospective cohort study of 221 healthy females (1982-1986) with a mean age of 30 years who were planning to get pregnant were tested daily using a urine pregnancy test with an immunoradiometric assay with a detection limit of 0.01 ng/mL. This study found the following:

- At ~7 to 10 days after conception, or day 21-24 of the cycle, 40-66% of pregnancies were detected.
- At day 14 after conception (on the day of the expected menstrual period), 90% of pregnancies were detected
- At 19 days after conception, 97% of pregnancies were detected

Wilcox AJ, Time of implantation of the conceptus and loss of pregnancy. N Engl J Med. 1999

19-Day Lockout in Patients Who have Unpredictable Ovulation for First Prescription Fill



In Summary: Purpose of 19-Day Lockout

- **Summary:**
  - The 19-day lockout only applies to the first isotretinoin prescription and starts from date when the confirmatory pregnancy test was performed
  - It represents the earliest time when a pregnancy can be detected
- **First Prescription:**
  - Patient has not started isotretinoin treatment
  - The 19-day lockout applies only to the first prescription where the goal is to prevent exposure to isotretinoin.
- **Subsequent Prescriptions:**
  - Patient has already started isotretinoin treatment
  - Therefore, exposure cannot prevented
  - No 19-day lockout
  - The 19-day lockout does not apply to subsequent prescriptions where the goal is to minimize exposure to isotretinoin.

Thank You

- Thank you for your attention
- Special thanks to the FDA teams:
  - Office of Surveillance and Epidemiology
    - Office of Medication Error Prevention and Risk Management
      - Division of Risk Management
      - Division of Mitigation Assessment and Medication Error Surveillance
    - Office of Pharmacovigilance and Epidemiology
      - Division of Pharmacovigilance
      - Division of Epidemiology
  - Office of Immunology and Inflammation
    - Division of Dermatology and Dentistry

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Potential Modifications to the iPLEDGE REMS

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Division of Risk Management
Office of Medication Error Prevention and Risk Management
Office of Surveillance and Epidemiology
Center for Drug Evaluation and Research

Presentation Overview

- Approach for the FDA review team's evaluation of the iPLEDGE REMS
- FDA review team recommendations on REMS requirements and potential REMS modifications to reduce burden
- Summary of issues for Committee discussion

Risk Evaluation and Mitigation Strategies

- May be required for certain medications with serious safety concerns to help ensure the benefits of the medication outweigh its risks

- Use risk minimization tools and interventions to reinforce necessary medication use behaviors and actions that support the safe use of a medication

- The required interventions inherently impose burden on the healthcare system and may create unintended barriers to patient access

Burden Associated with REMS

- In the context of REMS, **burden** is the additional effort that healthcare professionals and other stakeholders expend in complying with the REMS requirements*

- Potential negative impacts
  - Prescribing preference for other therapies without REMS
  - Interruption of typical prescriber or pharmacy workflow due to performing or documenting REMS requirements
  - Need for additional administrative time and resources for healthcare provider or pharmacy staff to complete REMS requirements
  - Barriers to patient access resulting in treatment delays or interruption

*Source: *FDA Background Document: Impact of REMS on the Healthcare Delivery System and Patient Access. Public Meeting, October 5-6, 2015.*

Evaluation of iPLEDGE REMS

Systematic evaluation of all iPLEDGE REMS elements to assure safe use and requirements

Purpose was to identify any opportunities to minimize burden without compromising patient safety

Focused on requirements that may contribute to stakeholder burden, impact patient access, or cause delays in treatment

Approved iPLEDGE REMS Goals

The goals of the isotretinoin risk evaluation and mitigation strategy are:

- To prevent fetal exposure to isotretinoin
- To inform prescribers, pharmacists, and patients about isotretinoin's serious risks and safe-use conditions

Approved REMS Patient Risk Categories

Patients who <u>can</u> become pregnant	Patients who <u>cannot</u> become pregnant
• **Cisgender females:** born female with a uterus and at least one ovary • **Transgender males:** born female with a uterus and at least one ovary, transitioned to a male	• **Cisgender male:** born a male • **Cisgender females and transgender males**: - undergone a **hysterectomy** - undergone a **bilateral oophorectomy** - who are **post-menopausal** according to the iPLEDGE REMS definition • **Transgender female:** born male and transitioned to female
Previously referred to as females of reproductive potential or females of childbearing potential	*Previously referred to as male or females of non-reproductive potential or females not of childbearing potential*

Source: Adapted from *iPLEDGE REMS Prescriber Guide*

REMS Program Overview

Prescribers

Certification

Pharmacy

Certification

Obtain authorization for every dispense from iPLEDGE REMS

Only dispense within prescription window

iPLEDGE REMS

iPLEDGE Website and Call Center

	Patients who <u>can</u> get pregnant	Patients who <u>cannot</u> get pregnant
Before Treatment	• Counseling • Required pregnancy tests • Enrollment and informed consent • Prescriber confirms counseling, enters contraception methods, and enters negative pregnancy test result in iPLEDGE system • 30-day supply prescription • Patient completes comprehension questions	• Counseling • Enrollment and informed consent • Prescriber confirms counseling in iPLEDGE system • 30-day supply prescription
During Treatment	• Monthly counseling • Required pregnancy tests • Prescriber confirms counseling, enters contraception methods, and enters pregnancy test results in iPLEDGE system • Patient completes comprehension questions • Must pick up prescription from pharmacy within 7-day window	• Monthly counseling • Prescriber confirms counseling in iPLEDGE system • Must pick up prescription from pharmacy within 30-day window
After Treatment	• Counseling • Required pregnancy tests • Prescriber enters pregnancy test results in iPLEDGE	• Counseling

Prescription Authorization Process

Risk Management Authorization (RMA)

- Unique number generated by the REMS during the prescription authorization process verifying that all safe-use requirements have been met

RMA Denial

- Occurs if any of the safe-use requirements have not been completed or documented by the prescriber or patient
- Denials may result in potential delays in therapy
- The prescription may ultimately be authorized and dispensed when evidence of the missing requirements is obtained and an RMA is generated

Review Team Analysis of REMS Requirements

- Patient Enrollment Requirements
- Limitation on Prescription Days' Supply
- Patient Counseling Requirements
- Contraception Requirements
- Pregnancy Testing Requirements
- iPLEDGE Pregnancy Registry

Patient Enrollment Requirements

REMS Requirement

- All patients are required to be enrolled in the REMS, regardless of patient risk category

FDA Review Team Recommendation

- Continue to require enrollment of all patients

Supporting Rationale

- Ensures prescribers thoroughly assess and document a patient's risk category prior to initiation of therapy and throughout therapy
- Pharmacists cannot determine patient risk categories based on patient's name or perceived sex

Limitation on Prescription Days' Supply

REMS Requirement

- A maximum 30-days' supply with no refills may be prescribed and dispensed

FDA Review Team Recommendation

- Maintain 30-days' supply limit

Supporting Rationale

- Ensures verification of safe-use requirements monthly prior to each dispense of isotretinoin
- Limits patients from using extra or leftover medication or sharing among friends and family
- A range of 1 to 8 pregnancies were reported per year where patients took leftover medication*

*Source: *iPLEDGE Assessment Reports Years 12–16.*

Patient Counseling Requirements

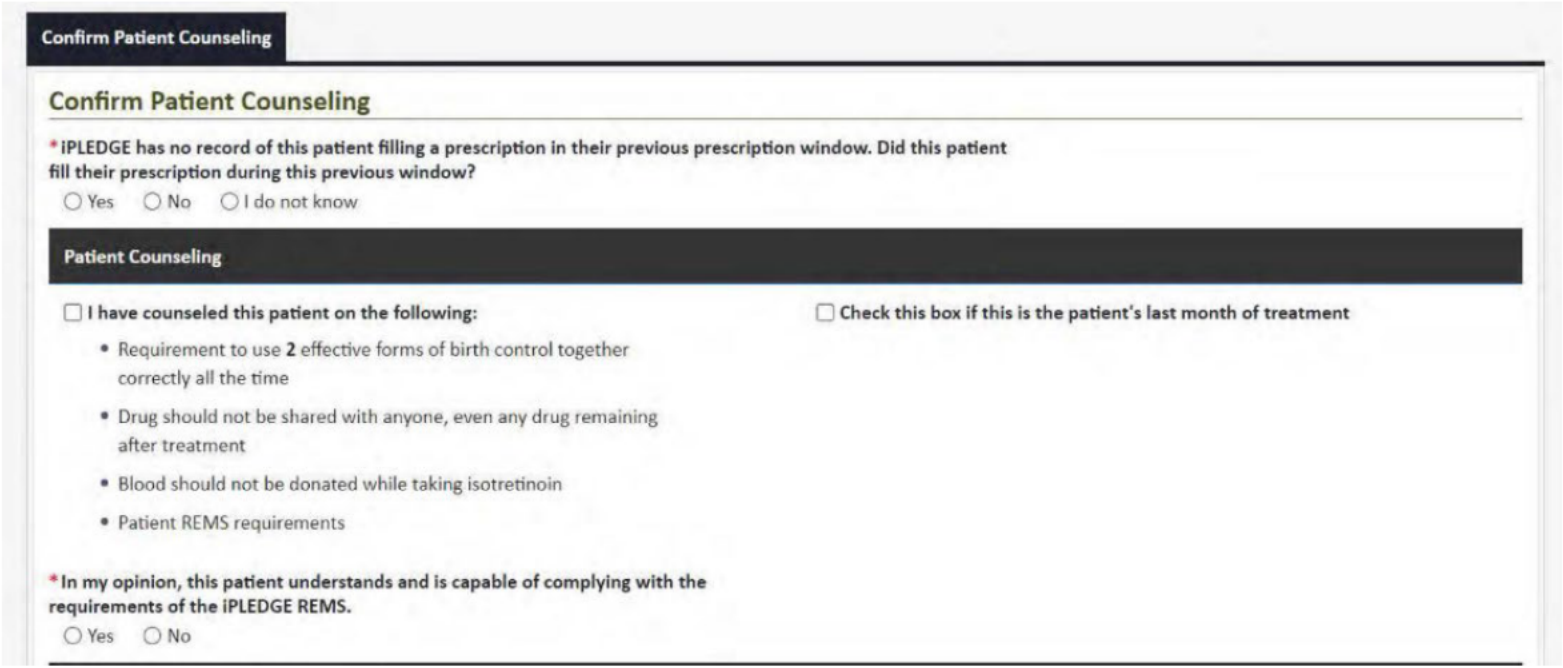
Patients who can become pregnant

REMS Requirement

- Prescribers must document (i.e., confirm) that monthly counseling was completed at treatment initiation and prior to each monthly prescription
- Counseling is only one aspect of the required monthly prescriber documentation for this patient risk category

Prescriber Confirmation of Counseling

Patients who can become pregnant



Confirm Patient Counseling

Confirm Patient Counseling

*iPLEDGE has no record of this patient filling a prescription in their previous prescription window. Did this patient fill their prescription during this previous window?

○ Yes ○ No ○ I do not know

Patient Counseling

☐ I have counseled this patient on the following:

- Requirement to use **2** effective forms of birth control together correctly all the time
- Drug should not be shared with anyone, even any drug remaining after treatment
- Blood should not be donated while taking isotretinoin
- Patient REMS requirements

☐ Check this box if this is the patient's last month of treatment

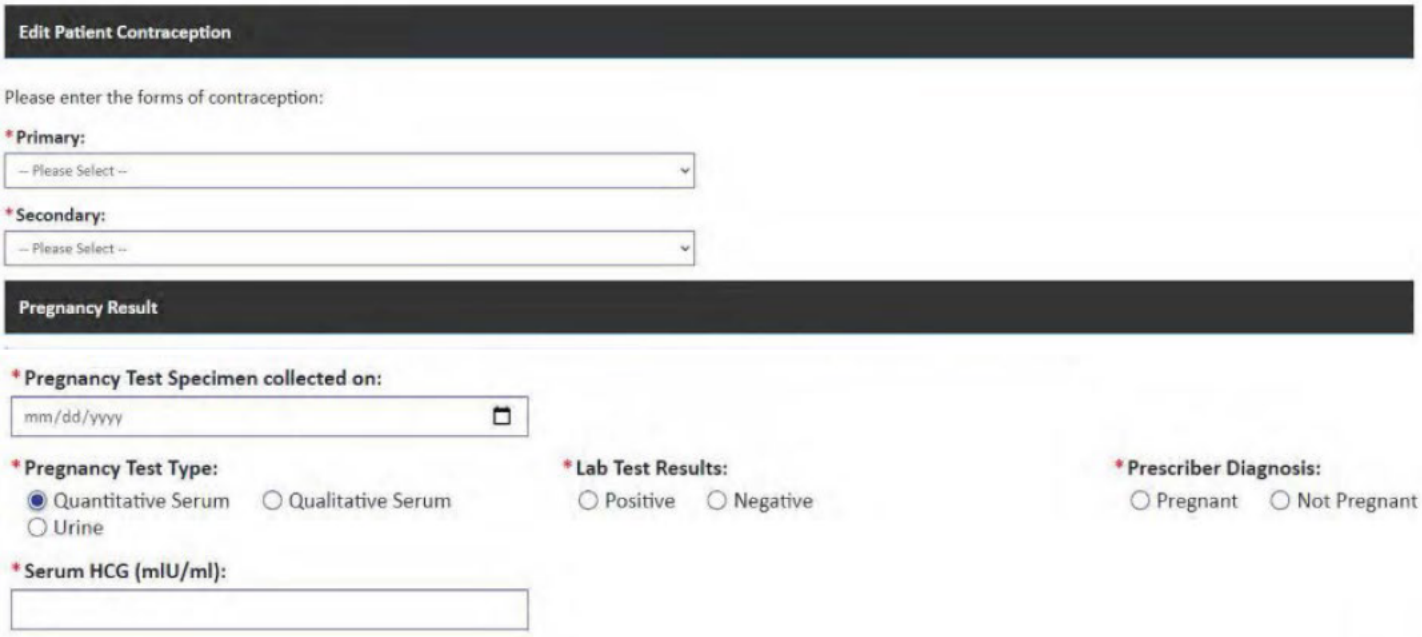
*In my opinion, this patient understands and is capable of complying with the requirements of the iPLEDGE REMS.

○ Yes ○ No

Source: *iPLEDGE REMS Website Screenshots*

Prescriber Confirmation of Contraception Forms and Pregnancy Test Result

Patients who can become pregnant



Source: *iPLEDGE REMS Website Screenshots*

Patient Counseling Requirements

Patients who can become pregnant

REMS Requirement

- Prescribers must **document (i.e., confirm) that monthly counseling** was completed at treatment initiation and prior to each monthly prescription

FDA Review Team Recommendation

- Maintain monthly documentation of counseling

Supporting Rationale

- Given the safe-use requirements for patients who can become pregnant and need for prescribers to interact with iPLEDGE REMS monthly, documentation of counseling is not an extra administrative step
- Failure to complete documentation of counseling accounts for approximately 11–14% of denials for this patient risk category*

*Source: *Supplemental data from IPMG metric reports submitted February 2022 through February 2023.*

Patient Counseling Requirements

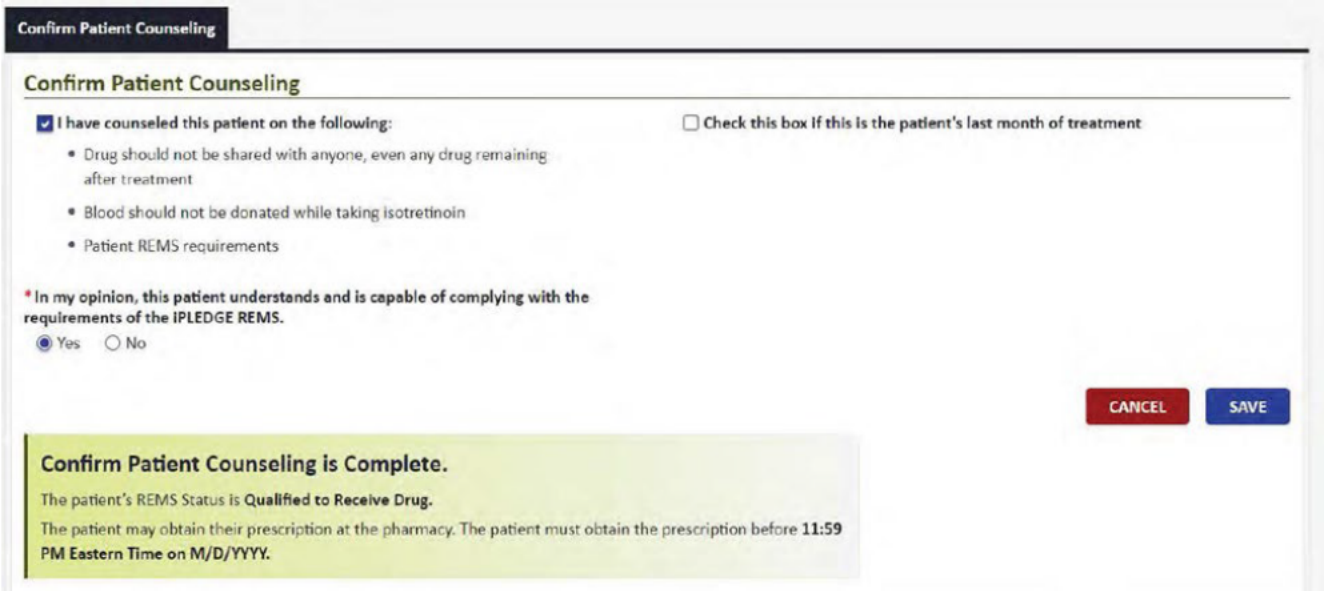
Patients who cannot become pregnant

REMS Requirement

- Prescribers must document (i.e., confirm) counseling was completed within iPLEDGE REMS at treatment initiation and prior to each monthly prescription
- Counseling focuses on not sharing isotretinoin and not donating blood

Prescriber Confirmation of Patient Counseling

Patients who cannot become pregnant



Patients who cannot become pregnant do not need to interact with the iPLEDGE system monthly

Source: *iPLEDGE REMS Website Screenshots*

Patient Counseling Requirements

Patients who cannot become pregnant

REMS Requirement

- Prescribers must **document (i.e., confirm) counseling** was completed within iPLEDGE REMS at treatment initiation and prior to each monthly prescription

FDA Review Team Seeks Advice

- Reduce the frequency for documenting counseling to every 120 days or remove monthly documentation

Supporting Rationale

- Prescribers would not need to access the iPLEDGE REMS system each month for a patient who cannot become pregnant resulting in reduced administrative burden
- Removal should eliminate 72–78% of RMA denials for this patient risk category*

*Source: *Supplemental data from IPMG metric reports submitted February 2022 through February 2023.*

Contraception Requirements

Patients who can become pregnant

REMS Requirement

- Use 2 forms of approved contraception for at least 30 days prior to treatment initiation, throughout treatment, and for 30 days after treatment
  - *Alternatively, iPLEDGE allows patients to commit to continuous abstinence as a lifestyle choice*

iPLEDGE Approved Forms of Contraception

Patient must choose 2 forms of contraception unless the patient commits to continuous abstinence from having any sexual contact (penis-vaginal) with a partner that could result in pregnancy

Primary

- Hormonal implant
- IUD (hormonal and non-hormonal)
- Tubal sterilization
- Male vasectomy
- Hormonal shot
- Vaginal ring
- Hormonal patch
- Birth control pill

Secondary

- Condom
- Cervical cap or diaphragm with spermicide; vaginal sponge

Contraception Requirements

Patients who can become pregnant

REMS Requirement

- Use **2 forms of approved contraception** for at least 30 days prior to treatment initiation, throughout treatment, and for 30 days after treatment
  - *Alternatively, iPLEDGE allows patients to commit to continuous abstinence as a lifestyle choice*

FDA Review Team Recommendation

- Maintain the contraception requirements at this time

Supporting Rationale*

- Abstinence is typically one of the top two choices by patients during isotretinoin therapy
- Most common contraception choices are birth control pills and male condoms
- Most common reasons cited by prescribers for unintended pregnancy are not using two forms of contraception, contraceptive failure, and unsuccessful abstinence

*Source: *iPLEDGE Assessment Report Year 12–16*

Contraception Requirements

Patients who can become pregnant

REMS Requirement

- Prescribers and patients must enter the patient's contraception methods (or designate their commitment to abstinence) within the iPLEDGE REMS monthly
- The primary contraception method entered monthly by the prescriber and patient must match

FDA Review Team Recommendation

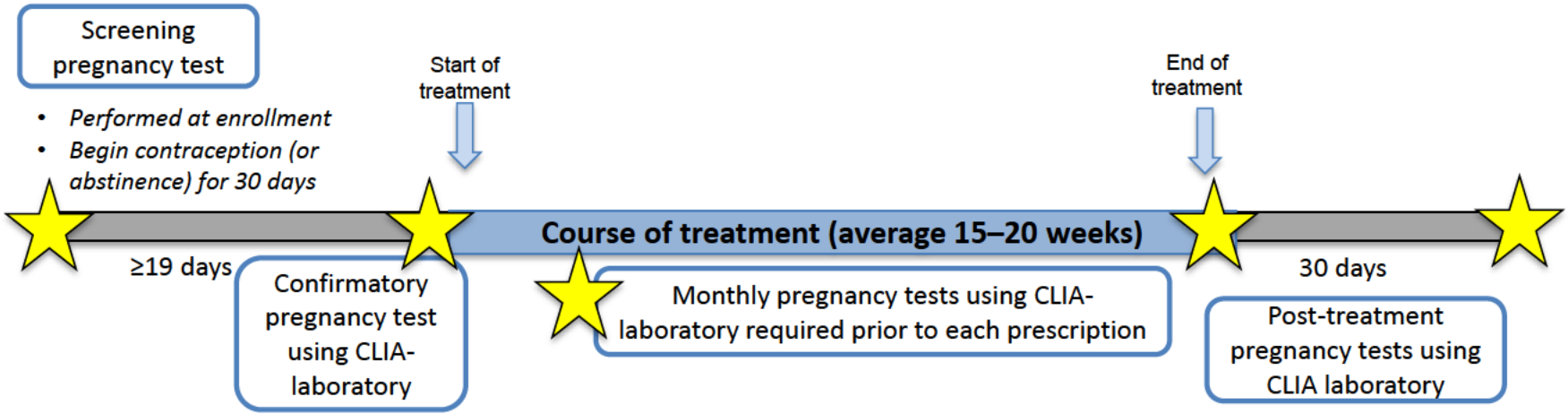
- Maintain the need for monthly contraception documentation and alignment

Supporting Rationale

- Although requiring entering and alignment for contraception methods may be considered an administrative burden, it allows for continual communication and re-evaluation of contraception choices between prescriber and patient
  - Facilitates discussions related to contraception method switches throughout therapy
  - Important as a way to reassess patient's commitment to abstinence as a lifestyle choice

Pregnancy Testing Requirements

Patients who can become pregnant



*Sensitivity of pregnancy tests must be at least 25 mIU/mL

^Figure is not to scale for timepoints

Source: Adapted from *Isotretinoin Prescribing Information* & *iPLEDGE REMS Materials*

Clinical Laboratory Improvement Amendments (CLIA)

- CLIA established quality standards for laboratory testing to ensure accuracy, reliability and timeliness of test results, regardless of where test was performed

- CLIA regulations and certifications are based on complexity of test method – more stringent requirements for more complex tests

- CLIA-waived tests are “simple laboratory examinations and procedures that have an insignificant risk of an erroneous result”
  - Most urine pregnancy tests are intended for over-the-counter use and are CLIA waived by regulation

Sources: *FDA. Clinical Laboratory Improvement Amendments (CLIA), CMS. Clinical Laboratory Improvement Amendments (CLIA),* and *CDC. CLIA Law & Regulations*

Pregnancy Testing Requirements

Patients who can become pregnant

FDA review team will provide our analysis on the following:

- Use of a CLIA-certified laboratory
- At-home pregnancy testing
- 7-day prescription window
- 19-day lockout period
- Post-treatment pregnancy testing

Pregnancy Testing Requirements

Patients who can become pregnant

REMS Requirement

- Use a CLIA-certified laboratory for the confirmatory pregnancy test and all subsequent tests

FDA Review Team Recommendation

- Remove the requirement to only use a CLIA-certified laboratory
- Allow for FDA-cleared pregnancy tests to be performed in a providers' office as an alternative provided they meet a sensitivity of at least 25 mIU/mL

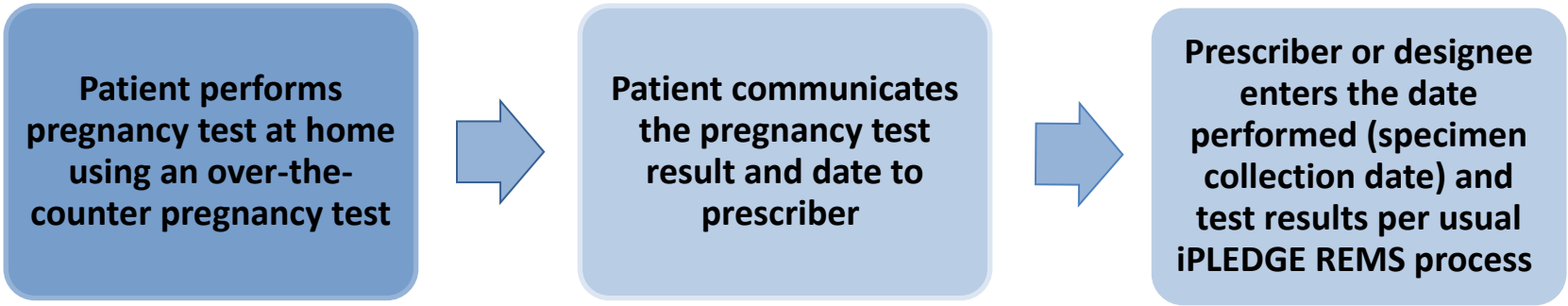
Supporting Rationale

- Most urine pregnancy tests are CLIA-waived by regulation and meet specific performance criteria
- Allowing in-office FDA cleared tests may reduce the need for separate office and laboratory visits and improve the patient experience

COVID-19 Public Health Emergency

At-Home Pregnancy Testing

Allowance of home pregnancy testing, using over-the-counter tests to minimize potential patient access issues when patients self-isolate or are subject to quarantine



Sources: *FDA Policy for Certain REMS Requirements During the COVID-19 Public Health Emergency. Guidance 2020* and *iPLEDGE Assessment Report Year 16*

Pregnancy Testing Requirements

Patients who can become pregnant

REMS Requirement

- Allowed **at-home testing** during the Public Health Emergency (PHE)

FDA Review Team Recommendation

- Do not recommend the continued use of home pregnancy testing outside of the PHE

Supporting Rationale and Considerations for Discussion

- Insufficient data to understand the impact of home testing
  - iPLEDGE REMS system does not have a mechanism for capturing the setting of pregnancy test for all patients
  - Reported pregnancies exposed to isotretinoin are comparable to previous years (outside of the PHE)[1]
- Published literature on home pregnancy testing during PHE identify cases of intentional falsifications
  - Falsification of home pregnancy test results reported in 15.7% of patients taking isotretinoin (N=89)[2]
  - Falsification examples included use of stock images, repeated use of same test result & editing previous test images[2]

Sources: *1. IPMG Year 16 Assessment Report* 2. Smith GP. *J Am Acad Dermatol.* 2022;87(5):1129-1130.

Pregnancy Testing Requirements

Patients who can become pregnant

REMS Requirement

- Complete all safe-use requirements and obtain the prescription within the **7-day prescription window**

FDA Review Team Recommendation

- Maintain the 7-day prescription window

Supporting Rationale*

- Median time to pick up first prescription is 2 days and mean time is 2.31–2.44 days
- About 80–85% of patients who can become pregnant pick up the first prescription within the 7-day window

*Source: *IPMG Information Request Response December 22, 2022.*

Pregnancy Testing Requirements

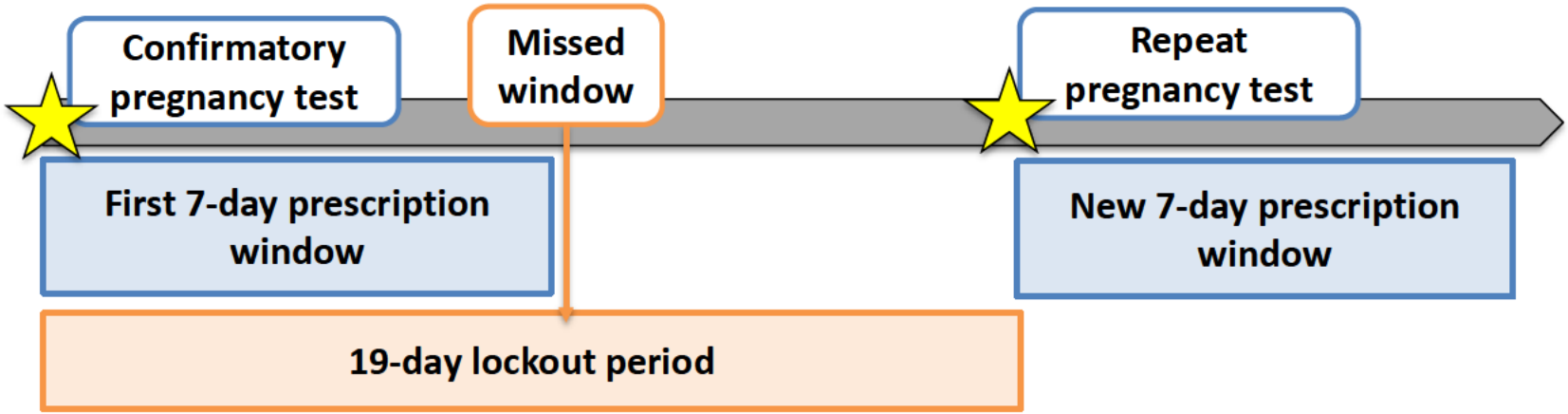
Patients who can become pregnant

REMS Requirement

- Enter a 19-day lockout if the first prescription is not obtained within the 7-day prescription window

19-day Lockout for Missing First Prescription Window

Patients who can become pregnant who miss the 7-day prescription window for obtaining the **first** isotretinoin prescription must **wait at least 19 days from their confirmatory pregnancy test** before getting a new pregnancy test



Source: *iPLEDGE REMS Prescriber Guide*

Pregnancy Testing Requirements

Patients who can become pregnant

REMS Requirement

- Enter a **19-day lockout** if the first prescription is not obtained within the 7-day window

FDA Review Team Seeks Advice

- Retain or change the 19-day lockout

Considerations for Discussion

- *Considerations for retaining a lockout*
  - Last opportunity to detect pregnancy and prevent exposure
  - At least 12 pregnancies have been reported to iPLEDGE during the 19-day lockout from March 2017 through September 2022[1]
- *Considerations for changes*
  - About 15–20% of patients who can become pregnant miss the first window and enter the 19-day lockout leading to delays in treatment initiation and increased costs for patients due to additional follow up and testing[2]
    - 173,311 patients entered the 19-day lockout from March 2017 through September 2022. This represents 15.6% of the total patients who can become pregnant who received at least one RMA[1]
  - There will always be a gap in pregnancy detection

Sources: *1. IPMG Information Request Response February 9, 2023; 2. IPMG Information Request Response. December 22, 2022*

Pregnancy Testing Requirements

Patients who can become pregnant

REMS Requirement

- A **pregnancy test** is required at the **end of the treatment course** and repeated **30 days after treatment discontinuation**

FDA Review Team Recommendation

- Maintain post-treatment pregnancy test requirements

Supporting Rationale*

- 83.4% of patients correctly answered comprehension question regarding need for these pregnancy tests
- Approximately 14% of patients completed either the **first or second** post-treatment pregnancy test. Only 5.36% completed **both** post-treatment pregnancy tests.
- From March 2021 to December 2021, 16 of the total reported pregnancies (N=184) occurred within 30 days of stopping isotretinoin

Source: *iPLEDGE Assessment Report Year 16*

iPLEDGE Pregnancy Registry

REMS Requirement

- Maintain a centralized pregnancy registry for all patients who become pregnant

iPLEDGE Pregnancy Registry Objectives

1. Determine isotretinoin exposure status for each reported pregnancy
2. Document the outcome of each isotretinoin exposed pregnancy
3. Determine, document, and analyze causes contributing to fetal exposure [root cause analysis (RCA)]

Source: *IPMG. iPLEDGE Pregnancy Registry Protocol. September 2021*

iPLEDGE Pregnancy Registry

REMS Requirement

- Maintain a centralized pregnancy registry for all patients who become pregnant

FDA Review Team Seeks Advice

- Ways to streamline the pregnancy registry to encourage more participation to yield high quality data
- Whether pregnancy and fetal outcome data collection continues to be necessary

Considerations for Discussion

- Pregnancy exposure data is valuable in evaluating the REMS success over time
- RCA identifies contributing factors to pregnancy exposure and possible opportunities to improve the program
- Pregnancy outcome and fetal outcome data are incomplete and at least a third of pregnancies are lost to follow up
  - Extensive knowledge on teratogenicity of isotretinoin available
  - Patient privacy concerns may impact participation

Source: *iPLEDGE Assessment Report Year 12–16*

Summary

FDA Review Team's recommendations

- ***For all patients***
  - Continue to require enrollment
  - Maintain a 30 days' supply limit for all prescriptions
- ***For patients who can become pregnant***
  - Maintain monthly documentation of counseling
  - Maintain the contraception requirements and the need for monthly contraception documentation and alignment
  - Maintain the 7-day prescription window
  - Maintain post-treatment pregnancy test requirements
  - Remove the requirement to only use a CLIA-certified laboratory and allow pregnancy tests to be performed in a providers' office

Summary

Seeking Committee advice on the following four topic areas related to potential modifications to the iPLEDGE REMS to reduce burden without impacting safe use of isotretinoin:

Documentation of monthly counseling for *patients who cannot become pregnant*

At-home pregnancy testing

19-day lockout when the initial prescription window is missed by a *patient who can become pregnant*

Pregnancy registry

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