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Committed to Pregnancy Prevention

Overview of the iPLEDGE REMS

James Shamp

VP of Data Intelligence and Program Analytics

UBC

Topics for Discussion

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iPLEDGE REMS:

- Minimize risk of isotretinoin's teratogenicity
- Minimize fetal exposure
- Required by FDA to help to ensure the benefits of isotretinoin outweigh its risks

What you will hear today:

- Evolution of iPLEDGE REMS
- Evidence iPLEDGE REMS is meeting its goals
- Proposed modifications to minimize stakeholder burden while maintaining safe use

FDA = United States Food and Drug Administration; REMS = Risk Evaluation and Mitigation Strategy.

iPLEDGE Representatives

Presenters	Role in iPLEDGE	Presentation
James Shamp UBC	REMS Administrator	Overview of iPLEDGE REMS
Sara Ephross, PhD Syneos Health	Pregnancy Registry	Overview of Pregnancy Registry
Gregory P. Wedin, PharmD Upsher-Smith Laboratories, LLC	iPLEDGE Sponsor	Modifications to iPLEDGE REMS

Additional Team Members	Role in iPLEDGE
Maryann Major, Independent REMS/Regulatory Consultant	Regulatory Consultant
Christine Manley, UBC	REMS Administrator
Sheline Way, MBA, Teva Pharmaceuticals USA, Inc.	iPLEDGE Sponsor
Herman Weiss, MD, MBA, FACOG, ProVation Life, LLC	OB/GYN Consultant

Isotretinoin Manufacturers

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- Akorn Inc.
- Amneal Pharmaceuticals LLC
- Dr. Reddy's Laboratories Ltd.
- Mylan Pharmaceuticals Inc.
- Sun Pharmaceutical Industries, Inc.
- Teva Pharmaceuticals USA, Inc.
- Upsher-Smith Laboratories, LLC

Severe Recalcitrant Nodular Acne

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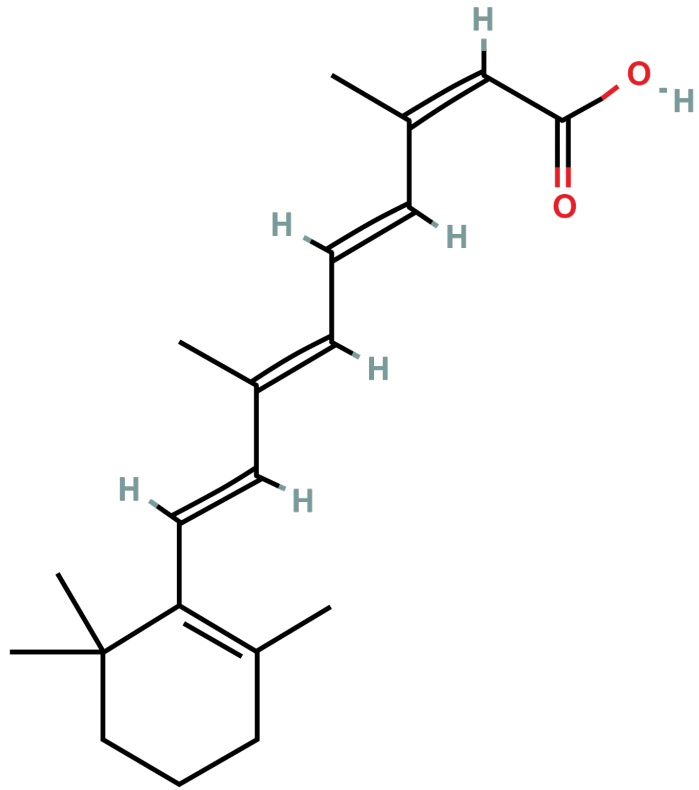
- Acne is the most common skin condition in the US, affecting about 50 million people, **with ~20% being a severe type**[1,2,3]
- Nodular acne is a severe, extremely painful, inflammatory acne[2,3]
  - Bacteria trapped under skin causes hard lumps to form[2,3]
  - Requires treatment by a dermatologist[2]
- Nodules that form lead to
  - Pain and sensitivity[2,3]
  - Lifelong scarring when untreated or improperly treated[2,3]
  - Decreased quality of life[2]
    - Including increased emotional distress and depression and decreased self-esteem[2,3]

1. American Academy of Dermatology. Skin Conditions by the Numbers. https://www.aad.org/media/stats-numbers.
2. Cleveland Clinic. Nodular Acne: What It Looks Like, Causes & Treatment. https://my.clevelandclinic.org/health/diseases/22888-nodular-acne.
3. Institute for Quality and Efficiency in Health Care. Acne: Overview. https://www.informedhealth.org/acne.html.

Efficacy of Isotretinoin

- Oral retinoid treatment for severe, recalcitrant, nodular acne
  - Patients unresponsive to conventional therapy
- Effective and prolonged disease remission
  - 70% of patients achieved 90% reduction in total nodular lesion count from baseline to week 20[1]



1. Isotretinoin label.
Image reprinted from National Center for Biotechnology Information. PubChem Compound Summary for CID 5282379, Isotretinoin. https://pubchem.ncbi.nlm.nih.gov/compound/Isotretinoin. Accessed January 18, 2023.

Isotretinoin Associated With High Risk of Severe Birth Defects

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- Teratogenic: Must not be used by patients who are or may become pregnant[1]
- Extremely high risk of life-threatening birth defects if pregnancy occurs while taking isotretinoin
  - In any amount, for any period of time[1,2]
- Patients advised not to become pregnant during treatment
  - Or for 1 month after discontinuing treatment[1,3]
- Must be discontinued immediately if pregnant
  - Refer patient to obstetrician/gynecologist (OB/GYN) experienced in reproductive toxicity[1]

1. The iPLEDGE REMS Prescriber Guide. October 2021 Modification.
2. Sladden MJ, et al. *Arch Dermatol*. 2007;143(9):1187-1188.
3. Dai WS, Hsu M-A, Itri LM. *Arch Dermatol*. 1989;125(3):362-365.

Birth Defects Associated With Fetal Isotretinoin Exposure

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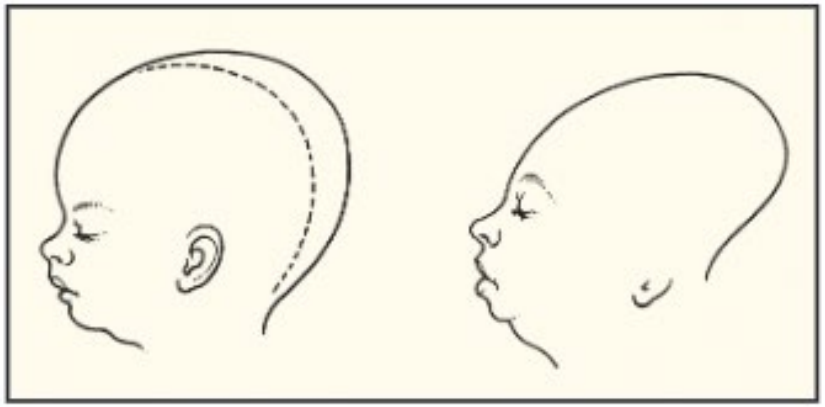
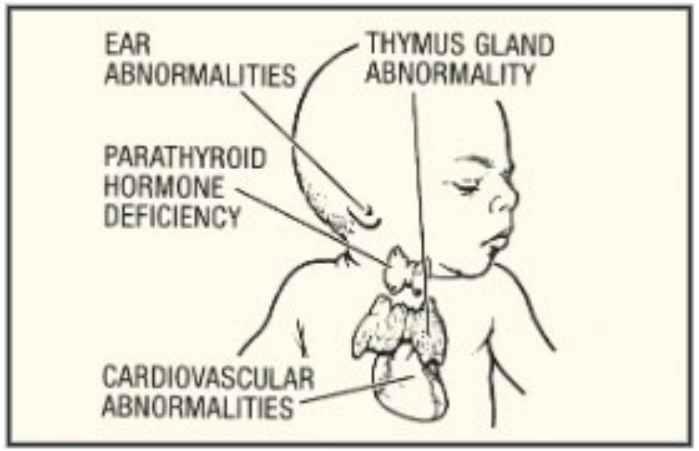
External Abnormalities



- Malformation of the skull, ears, eyes
- Facial dysmorphia
- Cleft palate

Internal Abnormalities



- Central nervous system
- Cardiovascular system
- Thymus gland and parathyroid hormone deficiencies

In some cases, death has occurred

Historical Evolution of Isotretinoin Risk Management Programs and Labeling

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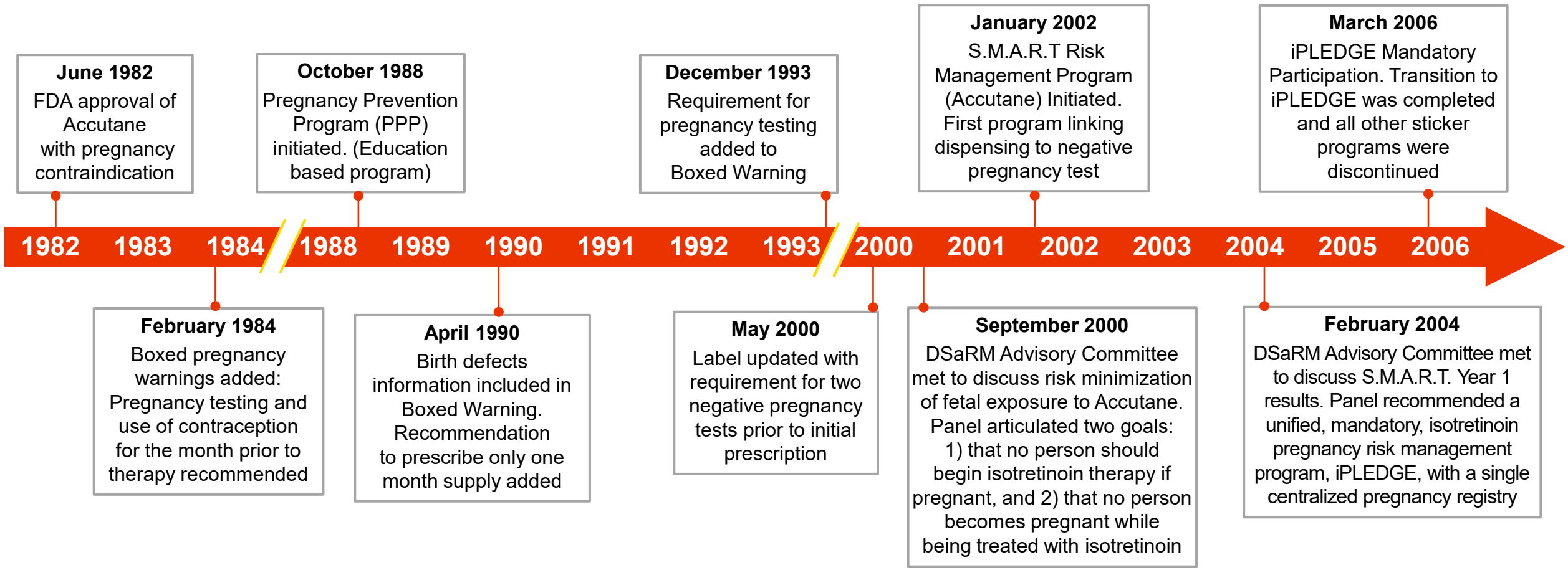
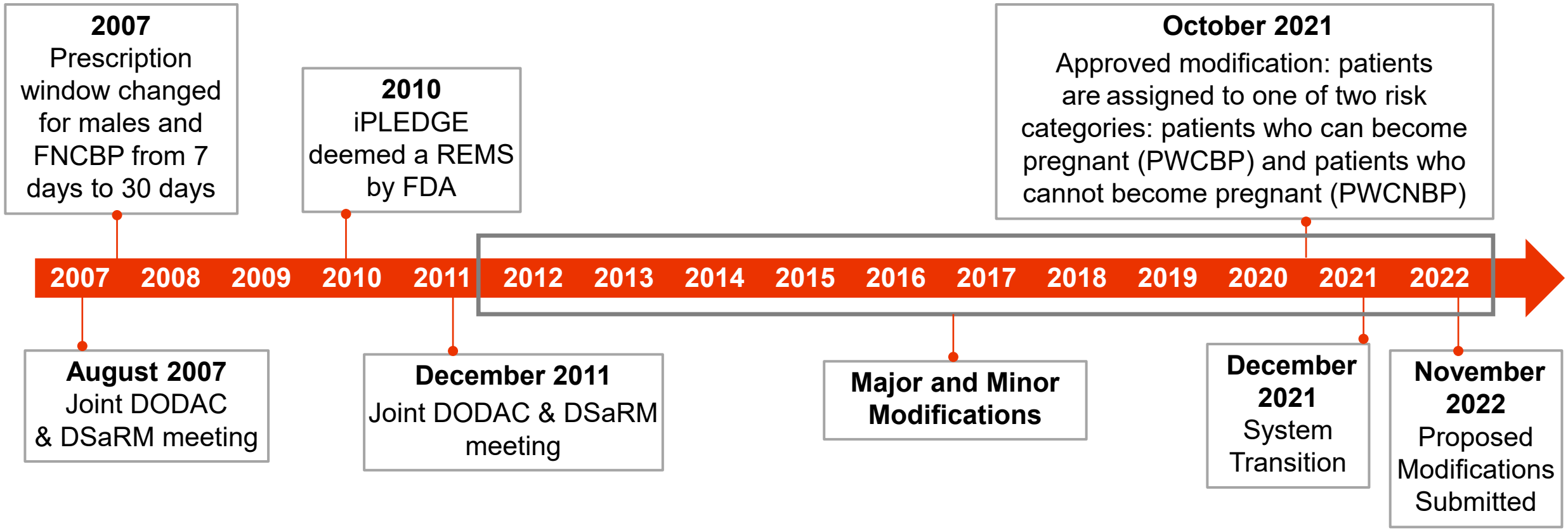


DSaRM = Drug Safety and Risk Management.

Evolution of the iPLEDGE REMS



DODAC = Dermatologic and Ophthalmic Drugs Advisory Committee; DSaRM = Drug Safety Risk Management; FNCBP = females not capable of becoming pregnant; PWCBP = patients who can become pregnant; PWCNBP = patients who cannot become pregnant.

iPLEDGE REMS—Key Modifications

Date Approved or Implemented	Description of Modification
Major Modification; April 12, 2012	• Editorial changes to the REMS documents to remove Roche and Accutane from the materials • Relocated documents from REMS document into the REMS Supporting Document (NCAP, webpages, What's New)
Major Modification; September 15, 2015	• Modifications to the Serious Medical Reason Exemption (SMRE) form to add Tanner Staging, clarify the request for FRPs is for first month only, added attestation relating to pregnancy tests
Minor Modification; February 4, 2016	• Added a Notice to Deter Patient Misclassification of female patients of reproductive potential on prescriber and designee screens
Major Modification; June 17, 2017	• Added the pharmacy network connectivity as an additional new method for obtaining an RMA to dispense isotretinoin • Added iPLEDGE REMS Program Birth control information sheet/iPLEDGE Program checklist
Major Modification; October 8, 2021	• Alignment of REMS document and materials with labeling changes related to gender-neutral patient risk categories • Addition of the requirement for pharmacies and wholesalers to comply with audits • Changes to pharmacy operations to verify safe-use conditions for the REMS RMA • Remove the Medication Guide as an element of the REMS • Add an optional quick reference (QR) code for use by patients enrolled in the REMS
Minor Modification; October 6, 2022	• Make changes to the REMS document including the Non-Compliance Action Policy regarding the requirement for pharmacies and wholesalers to comply with audits

FRP = females of reproductive potential; NCAP = Non-Compliance Action Policy; RMA = Risk Management Authorization.

Risk Categorization Update

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Classifications Prior to October 2021

Females of Reproductive Potential (FRP)	Females of Non-Reproductive Potential (FNRP) or Males

Current Classifications

Patients Who Can Become Pregnant (PWCBP)

- Cisgender females (born a female with a uterus and at least one ovary, aka cis-female)
- Transgender males (born female with a uterus and at least one ovary, transitioned to a male, aka trans-male)

Patients Who Can NOT Become Pregnant (PWCNBP)

- Cisgender male (born a male, aka cis-male)
- Cisgender females and transgender males who have undergone a hysterectomy (surgical removal of the uterus)
- Cisgender females and transgender males who have undergone a bi-lateral oophorectomy (surgical removal of both ovaries)
- Cisgender females and transgender males who are post-menopausal according to the iPLEDGE REMS definition
- Transgender female (born male and transitioned to female)

iPLEDGE REMS Goals

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1

To prevent
fetal exposure
to isotretinoin

2

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

Elements to Assure Safe Use (ETASUs)

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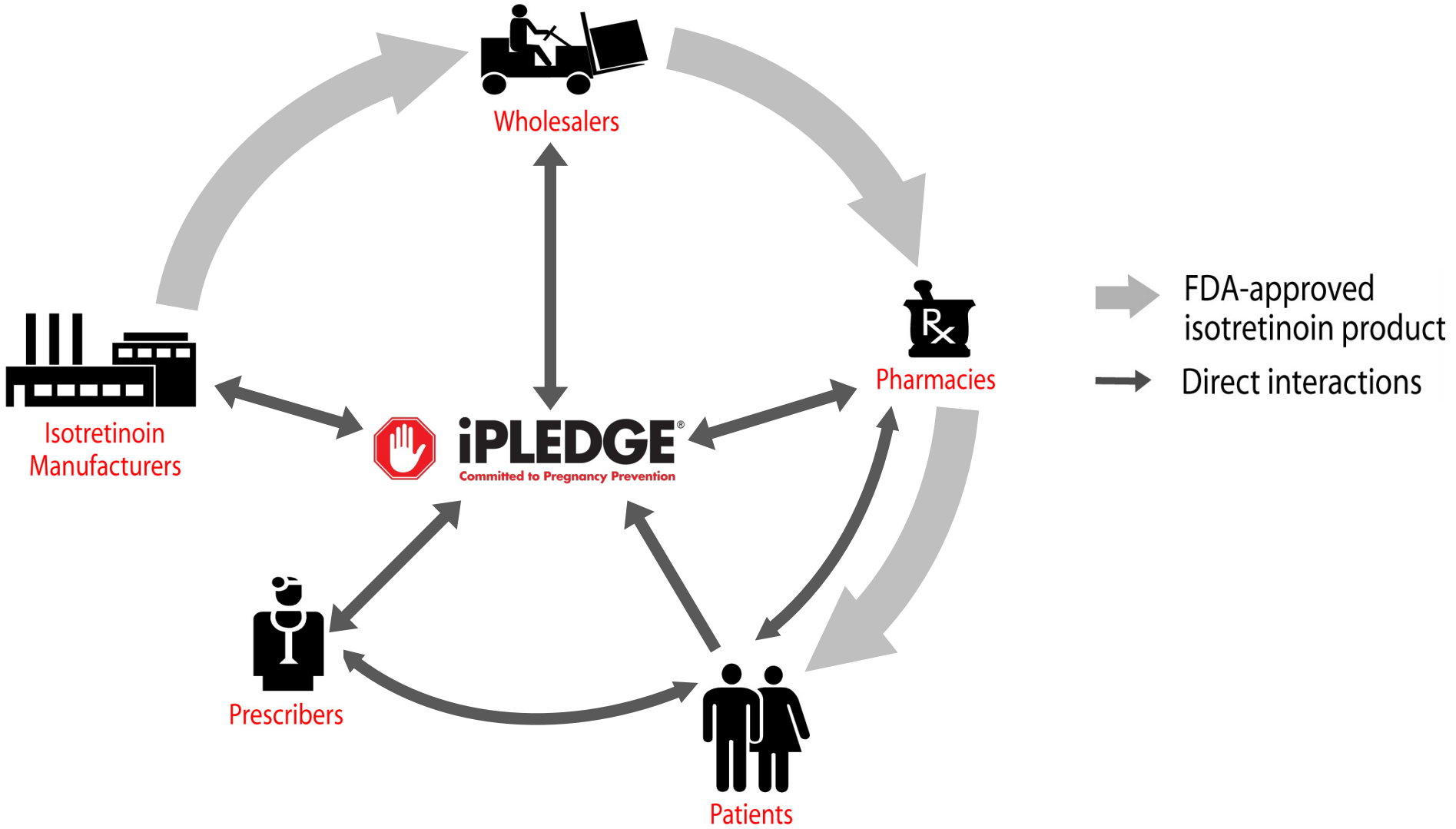
- Isotretinoin will only be
  - Prescribed by healthcare providers specially certified in the iPLEDGE REMS
  - Dispensed by pharmacies specially certified in the iPLEDGE REMS
  - Dispensed to patients enrolled in the iPLEDGE REMS with evidence or other documentation of safe-use conditions
- Centralized pregnancy registry
  - For enrolled patients who become pregnant
  - And for pregnancies reported from other sources, i.e., published literature, non-enrolled PWCBP

What Is iPLEDGE?



iPLEDGE REMS Reporting Years

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iPLEDGE Year	Reporting Period March 1 to February 28/29
1	2006 - 2007
2	2007 - 2008
3	2008 - 2009
4	2009 - 2010
5	2010 - 2011
6	2011 - 2012
7	2012 - 2013
8	2013 - 2014
9	2014 - 2015
10	2015 - 2016
11	2016 - 2017
12	2017 - 2018
13	2018 - 2019
14	2019 - 2020
15	2020 - 2021
16	March 1, 2021 to December 10, 2021

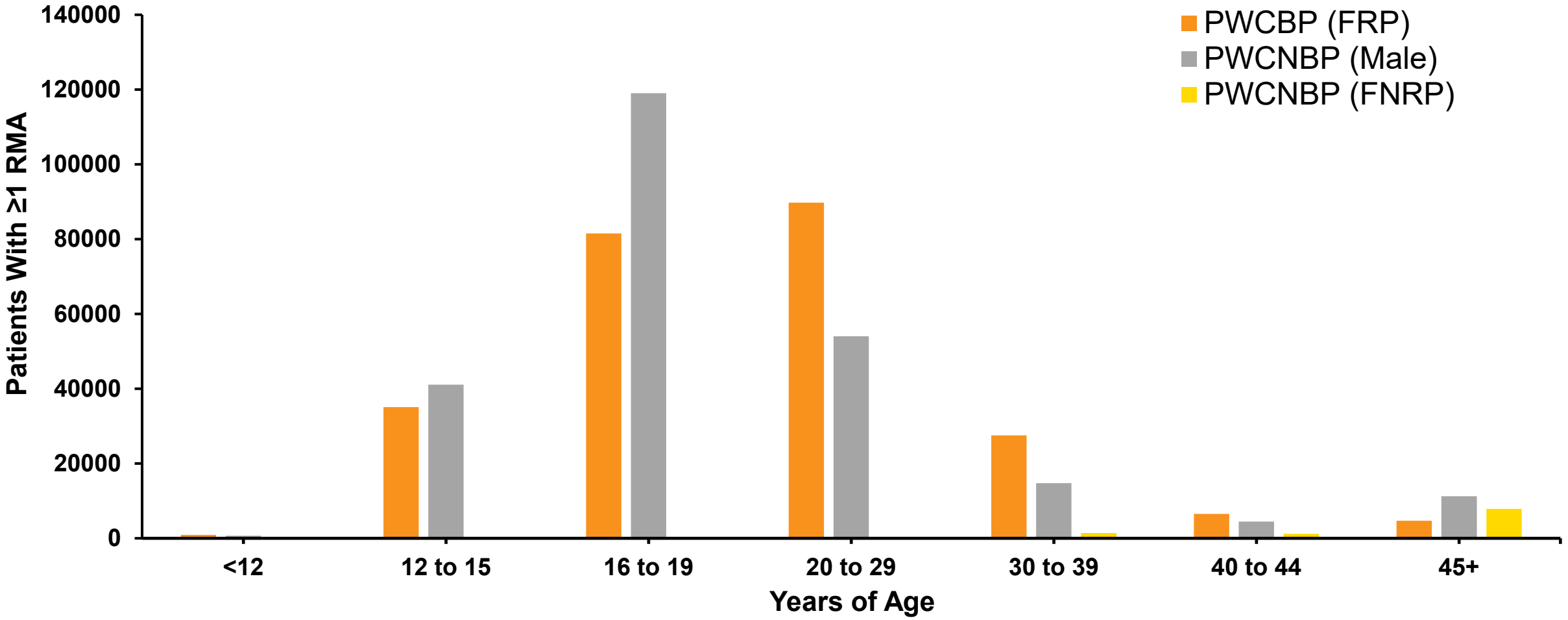
Patients Enrolled in iPLEDGE and RMAs by Risk Category

Risk Category		Year 16: Newly Enrolled in iPLEDGE, N (%)	Year 16: Number of Risk Management Authorizations (RMAs)	Years 1-16: Cumulative Enrollment in iPLEDGE, N (%)	Years 1-16: Cumulative Number of Risk Management Authorizations (RMAs)
PWCBP	(FRP)	151,735 (51.0)	927,284	2,020,745 (48.2)	9,707,159
PWCNBP	(FNRP)	5872 (2.0)	34,655	113,821 (2.7)	517,965
	(Male)	140,138 (47.1)	871,769	2,061,877 (49.1)	10,765,500
Total		**297,745 (100)**	**1,833,708**	**4,196,443 (100)**	**20,990,624**

Note: Prior to October 8, 2021, Patients Who Cannot Become Pregnant were categorized as either Females of Non-Reproductive Potential or Males.
FNRP = Females of Non-Reproductive Potential; PWCBP = Patients Who Can Become Pregnant; PWCNBP = Patients Who Cannot Become Pregnant; RMA = Risk Management Authorization.

Patients With ≥1 RMA by Risk Category and Age

Year 16



Note: Prior to October 8, 2021, Patients Who Cannot Become Pregnant were categorized as either Females of Non-Reproductive Potential or Males.
FNRP = Females of Non-Reproductive Potential; PWCBP = Patients Who Can Become Pregnant; PWCNBP = Patients Who Cannot Become Pregnant; RMA = Risk Management Authorization.

iPLEDGE REMS Journey for Patients Who Can Become Pregnant

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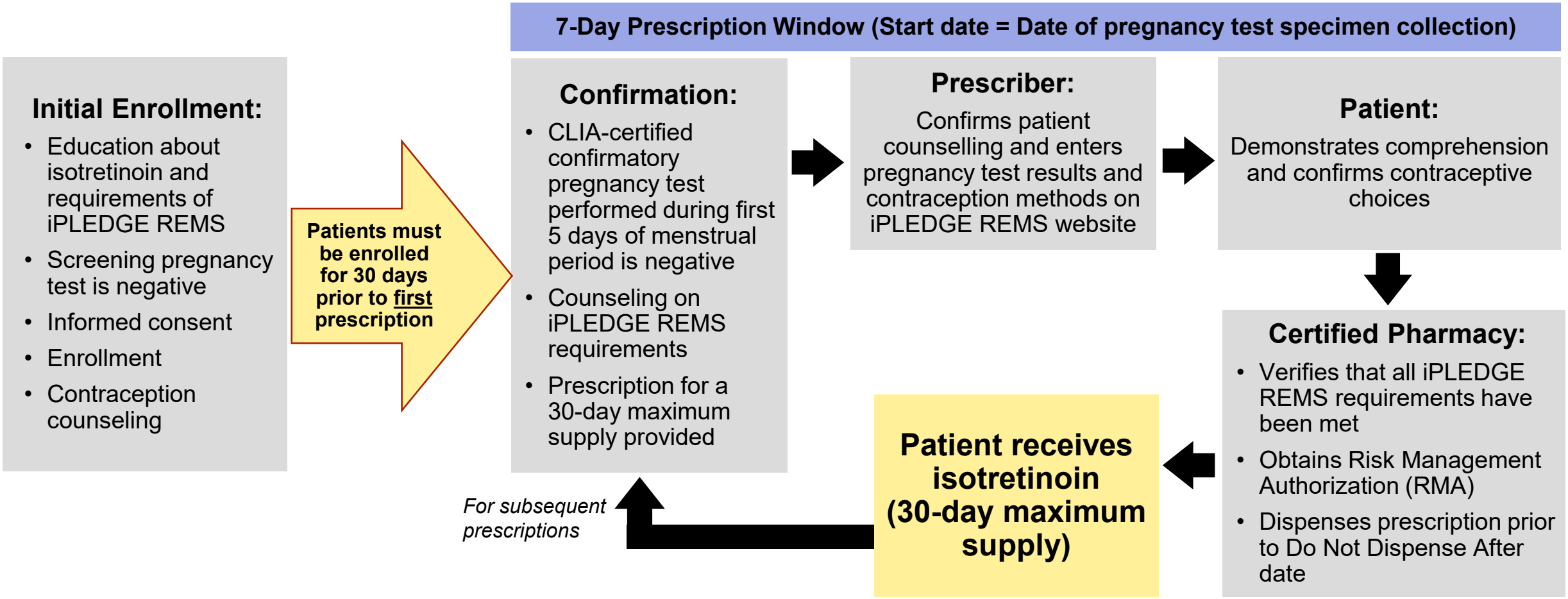

CLIA = Clinical Laboratory Improvement Amendment.

iPLEDGE REMS Journey for Patients Who Cannot Become Pregnant

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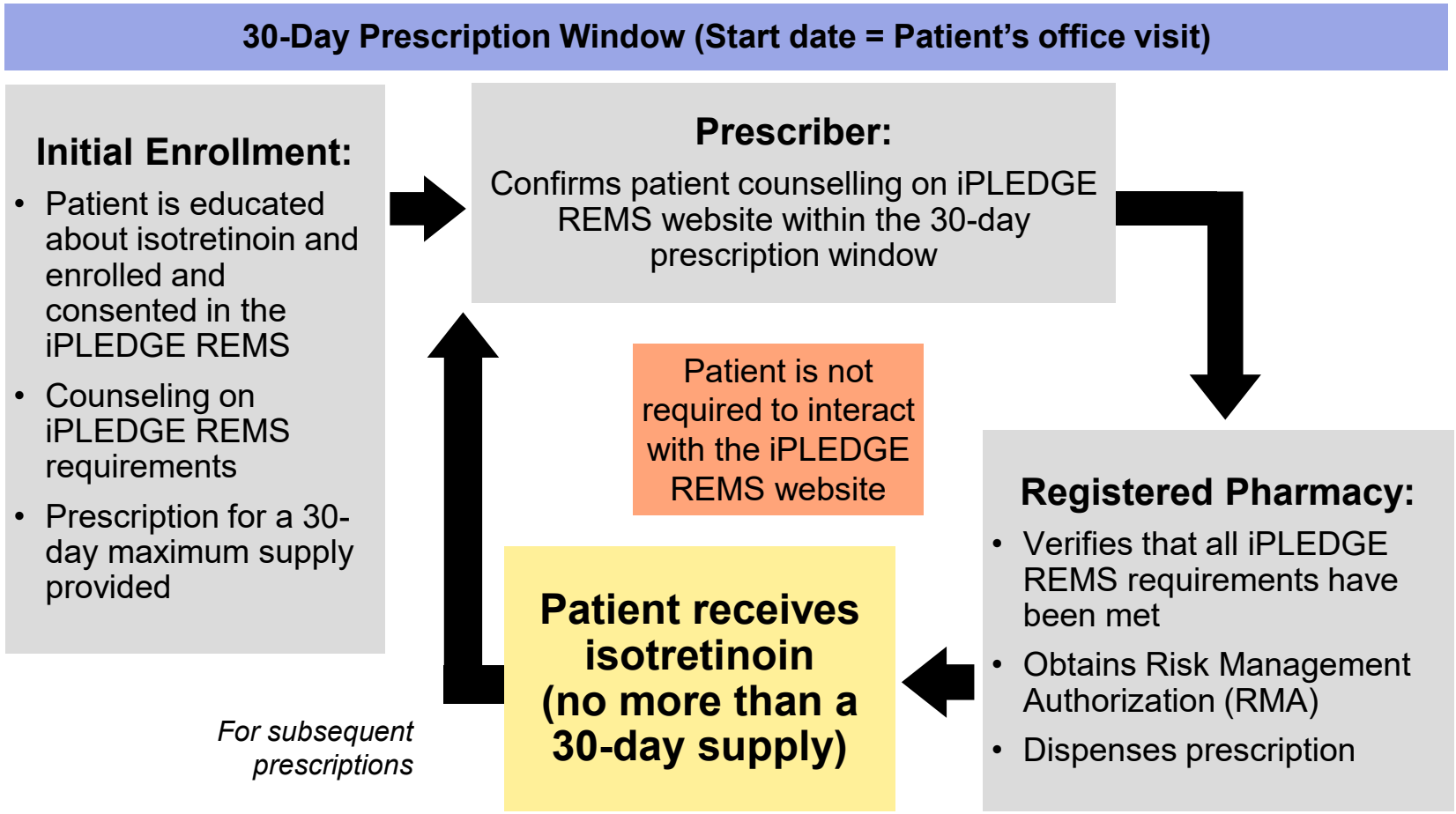

The iPLEDGE REMS Goals

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1

To prevent
fetal exposure
to isotretinoin

2

To inform
prescribers,
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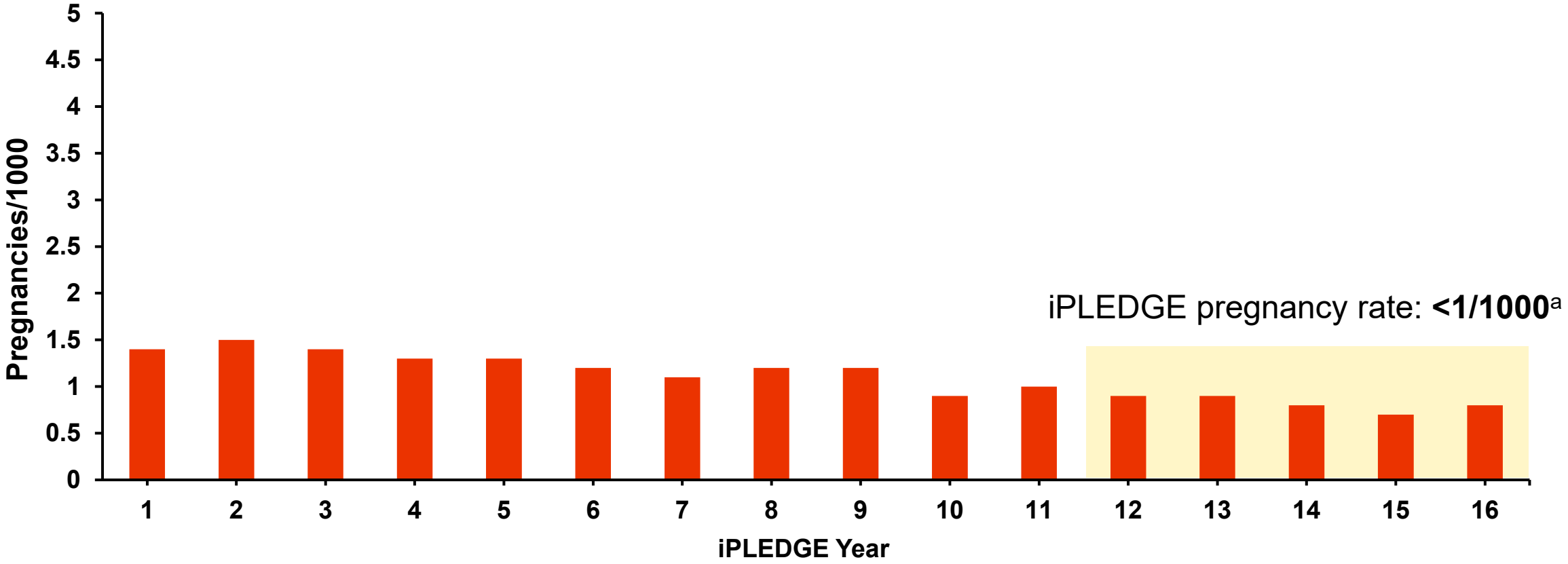
conditions

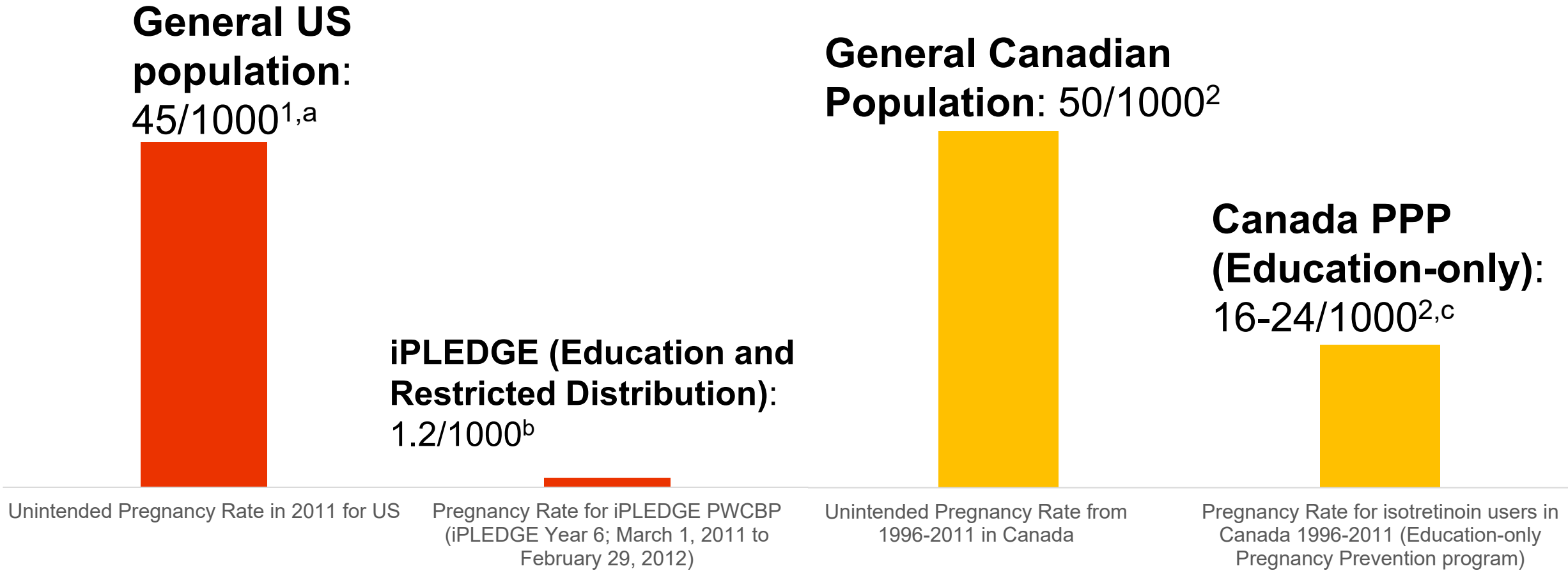
iPLEDGE Pregnancy Rate Has Been Consistently Low

Years 1-16



[a] PWCBP enrolled in iPLEDGE with at least one RMA.

iPLEDGE Pregnancy Rate Comparisons



[a] Rate for women and girls 15-44 years of age; [b] PWCBP enrolled in iPLEDGE with at least one RMA; [c] Female isotretinoin users in 4 Canadian provinces from 1996-2011.

1. Finer MB and Zolna MR. *N Engl J Med*. 2016;374(9):843-852; 2. Henry D, et al. *CMAJ*. 2016;188(10):723-730.

Pregnancies Detected by iPLEDGE Before Initiation of Isotretinoin Treatment

Years 1-16

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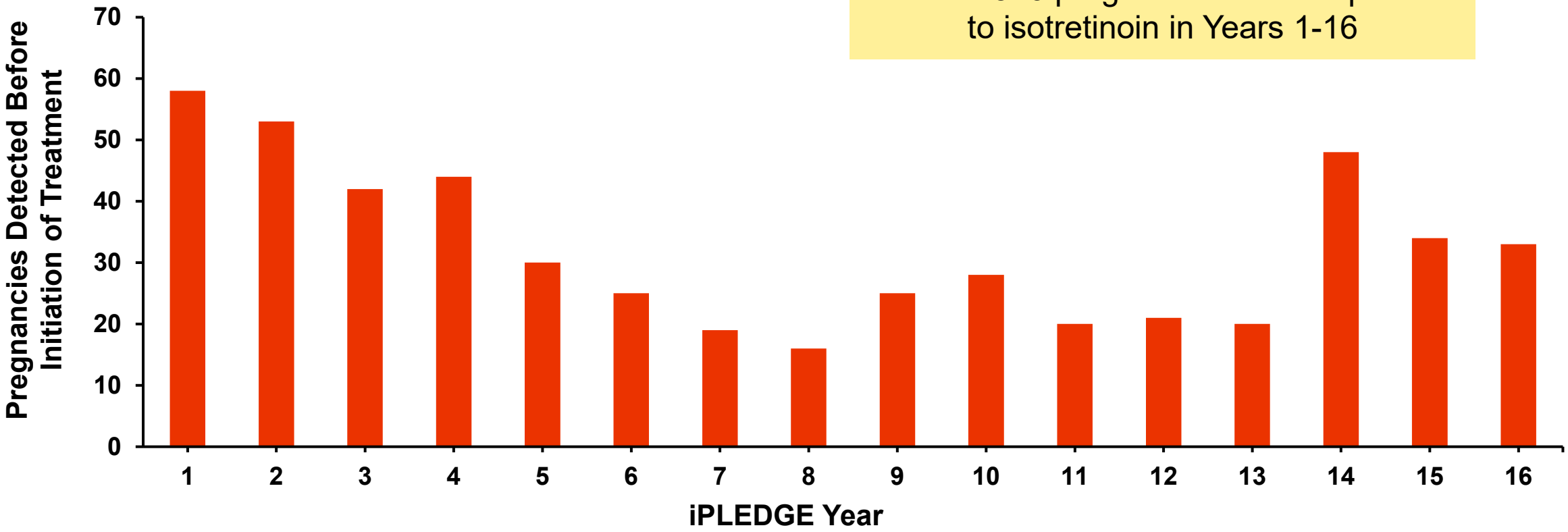
iPLEDGE detected and prevented at least **516** pregnancies from exposure to isotretinoin in Years 1-16



The iPLEDGE REMS Goals

iPLEDGE
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1

To prevent fetal exposure to isotretinoin

2

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

Patient Recall of Educational Components Before Starting Treatment

Years 14-16

	Patients Responding Affirmatively,[a,b] n (%)					
	Year 14[a]		Year 15[a]		Year 16[a]	
	Non-Pregnant N=293,055	Pregnant N=171	Non-Pregnant N=324,526	Pregnant N=165	Non-Pregnant N=307,032	Pregnant N=182
Told to avoid pregnancy	292,217 (99.7)	171 (100)	323,586 (99.7)	165 (100)	306,148 (99.7)	180 (98.9)
Read guide to isotretinoin for PWCBP	275,211 (93.9)	161 (94.2)	304,642 (93.9)	146 (88.5)	287,908 (93.8)	165 (90.7)
Read Birth Control Workbook	271,143 (92.5)	160 (93.6)	300,842 (92.7)	143 (86.7)	284,706 (92.7)	164 (90.1)

[a] Patients may have had multiple courses of therapies represented in the data.
[b] Not all pregnant and non-pregnant patients answer the required first month questions.

Monthly Patient Comprehension of Contraception Use and Risk of Birth Defects

Years 12-16

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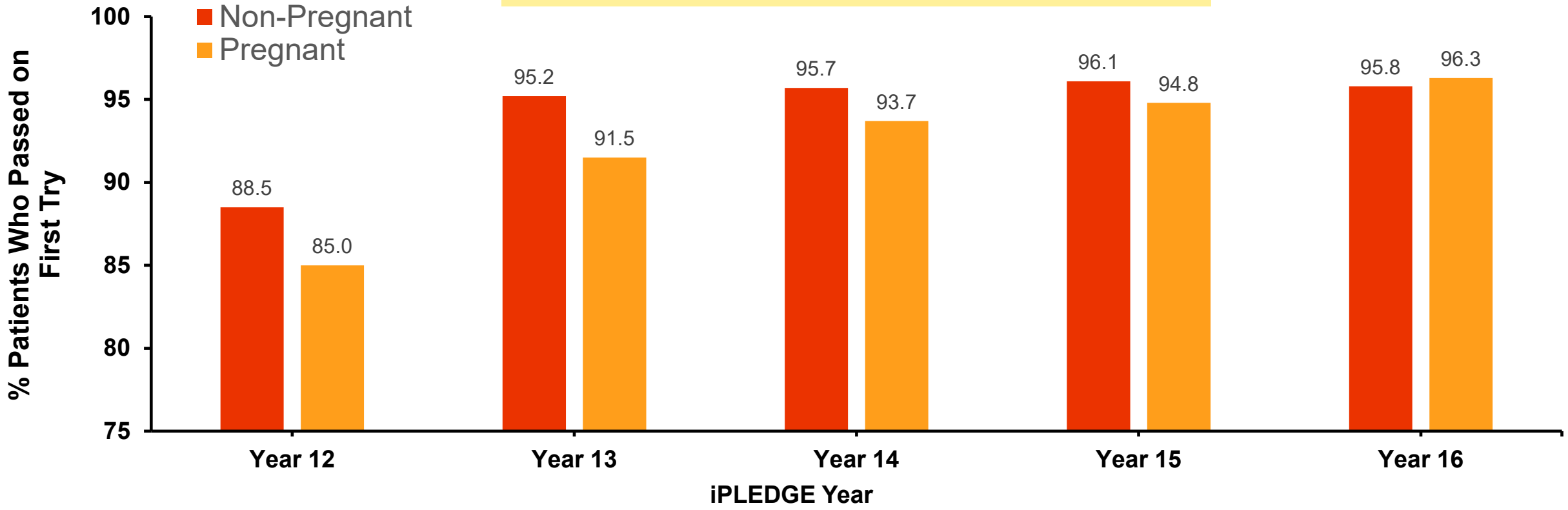
>95% of PWCBP passed monthly comprehension tests on first try in Year 16



	Year 12	Year 13	Year 14	Year 15	Year 16
Non-Pregnant N=	250,535	161,085	176,012	195,544	163,369
Pregnant N=	173	106	111	115	108

Quantitative Testing of Prescriber's Understanding of iPLEDGE

Year 16

Key Risk Message	Unadjusted Demonstrated Understanding Rate[a] N=224[b] n (% [95% CI])[c]
1) The Prescriber must know the risk and severity of fetal injury/birth defects from isotretinoin	222 (99.1 [96.8, 99.9])
2) Prescribers should understand the iPLEDGE REMS requirements regarding pregnancies	194 (86.6 [81.4, 90.8])
3) Prescribers should understand the effective measures for avoidance of unplanned pregnancy	200 (89.3 [84.5, 93.0])
4) Prescribers must comply with the iPLEDGE Program requirements described in the booklets entitled *The Guide To Best Practices for the iPLEDGE Program* and *The iPLEDGE Program Prescriber Contraception Counseling Guide*	188 (83.9 [78.5, 88.5])

- Met goal of >80% comprehension rates for each of the 4 key risk messages
- 66% of Prescribers demonstrated understanding of all 4 key risk messages

[a] Unadjusted rates have not been adjusted for medical specialty and geographic region.
[b] Number of eligible prescribers completing the survey.
[c] Exact binomial two-sided 95% confidence intervals (CI) are calculated using the Clopper-Pearson method.

Quantitative Testing of Pharmacist's Understanding of iPLEDGE

Year 16

Key Risk Message	Unadjusted Demonstrated Understanding Rate[a] N=292[b] n (% [95% CI])[c]
1) The Pharmacist must know the risk and severity of fetal injury/birth defects from isotretinoin	283 (96.9 [94.2, 98.6])
2) Responsible Site Pharmacists (RSPs) are responsible for training all pharmacists who participate in the filling and dispensing of isotretinoin prescriptions at their location on the iPLEDGE program requirements	269 (92.1 [88.4, 94.9])
3) RSPs must comply and seek to ensure all pharmacists who participate in the filling and dispensing of isotretinoin prescriptions comply with the iPLEDGE program requirements	267 (91.4 [87.6, 94.4])
4) Isotretinoin product should be obtained from only iPLEDGE-registered wholesalers, and pharmacies must not sell, buy, borrow, loan, or otherwise transfer isotretinoin in any manner to or from another pharmacy	204 (69.9 [64.2, 75.1])

[a] Unadjusted rates have not been adjusted for pharmacy type and number of Risk Management Authorizations by pharmacy in the last 120 days.
[b] Number of eligible pharmacists completing the survey.
[c] Exact binomial two-sided 95% confidence intervals (CI) are calculated using the Clopper-Pearson method.

iPLEDGE REMS Helps Ensure Benefits of Isotretinoin Outweigh Risks

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1 To prevent fetal exposure to isotretinoin

2 To inform prescribers, pharmacists, and patients about isotretinoin's serious risks and safe-use conditions

- Evidenced by
  - Consistently low pregnancy rates
  - Prevention of patients who become pregnant prior to starting therapy from receiving drug
  - High comprehension and understanding scores
- Any proposed modification to reduce stakeholder burden must be carefully weighed against the increased risk of fetal exposure to isotretinoin

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Overview of Pregnancy Registry

Sara Ephross, PhD

Syneos Health

Overview of Presentation

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- Summary of the Pregnancy Registry including role in the REMS
- Scope of, and process for, data collection in the Registry, including
  - Pregnancy and fetal outcomes
  - Root cause analysis of pregnancy
- Opportunities to streamline data collection

iPLEDGE Pregnancy Registry

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- Patients who become pregnant while on isotretinoin are eligible for inclusion in the Registry
- Objectives
  - Determine the isotretinoin exposure status for each reported pregnancy
  - Document the outcome for each pregnancy
  - Obtain additional information for each pregnancy to allow for evaluation of the underlying root cause(s)

How Pregnancies Are Reported

Entry of either a positive pregnancy test and/or a diagnosis of pregnant in the iPLEDGE REMS database

Via phone call, either directly to the Registry or triaged through the call center

Discontinuation of a patient in the iPLEDGE REMS due to a reason of pregnancy

All other pregnancy reports from various sources are evaluated for eligibility for inclusion in the iPLEDGE Pregnancy Registry

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Current Pregnancy Registry Data Collection Flow

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Initial Pregnancy Report

Exposure
- Exposed
- Indeterminate

- Non-exposed[a]

Data Collection

Initial Data Collection
- Extracted from iPLEDGE REMS
- Requested from reporter

30 Days & Interim (1st, 2nd, 3rd Trimester)

Pregnancy Outcome

Live Births Outcomes (Post 30 Days, 6 Months, 12 Months)

Birth defect may be noted at any data collection point

[a] Non-exposed cases are not reported to the agency or included in statistical analyses.

Communications When a Pregnancy Is Reported

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Pregnancy Data
from Prescriber or OB/GYN[a]

1st, 2nd, 3rd trimester[b]

Infant Data
from Prescriber or pediatrician[a]

Birth, 1 month, 6 months, 1 year

Case Classification

- Reason and outcome provided: Case closed
- Reason and/or outcome not provided: Lost to follow-up

[a] If patient consent is obtained.
[b] Registry makes a minimum of 3 attempts at each specified timeframe.

Key Data Collected for Reported Pregnancies

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Data Extracted From iPLEDGE REMS

- Patient demographics
- hCG — Pregnancy test type & results
- Course of Treatment (dose, RMA)

Data Requested From Reporter

- First day of last menstrual period and approximate date of conception
- Exposure status (non-exposed, indeterminately exposed, or exposed)
- Treatment start & stop dates
- Root cause (contributing reason)
- Outcome: defined as live birth, still birth, spontaneous abortion, elective termination, or ectopic pregnancy

Pregnancy Outcome Status Has Been Stable Over 16 Years

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Status	Year 14 N=186 n (%)	Year 15 N=189 n (%)	Year 16 N=184 n (%)	Cumulative Years 1-16 N=2720 n (%)
Outcome known	116 (62.4%)	112 (59.3%)	83 (45.1%)	**1707 (62.8%)**
Outcome unknown	7 (3.8%)	4 (2.1%)	5 (2.7%)	**44 (1.6%)**
Lost to follow-up	64 (34.4%)	72 (38.1%)	43 (23.4%)	**919 (33.8%)**
Still continuing	—	—	53 (28.8%)	**54 (2.0%)**

Pregnancy Outcomes

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Pregnancy Outcome	Year 14 N=186	Year 15 N=189	Year 16 N=184	Cumulative Since iPLEDGE REMS Inception N=2720
Number of Outcomes[a]	**187**	**189**	**184**	**2724[a]**
Outcome				
Elective termination	88	74	62	1263
Spontaneous abortion	18	22	15	262
Missed abortion	2	1	1	17
Ectopic pregnancy	2	5	5	39
Still birth	0	0	0	2
Live birth	6	10	0	124
Still continuing	0	0	53	54
Unknown	7	4	5	44
Lost to follow-up[b]	64	72	43	919

[a] The number of outcomes includes multiple birth outcomes.
[b] Lost to follow-up includes cases where outcome is unknown and cases where outcome is known to have occurred but specifics surrounding outcome of pregnancy are unknown.

Root Causes of Pregnancy Have Remained Stable

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Prescriber-Reported Reason for Pregnancy[a]	Year 14 N=186 n (%)	Year 15 N=189 n (%)	Year 16 N=184 n (%)
Unsuccessful at abstinence	49 (26.3)	43 (22.8)	41 (22.3)
Did not use 2 forms of birth control	48 (25.8)	43 (22.8)	41 (22.3)
Unknown (no additional information provided)	49 (26.3)	44 (23.3)	43 (23.4)
Contraceptive failure	26 (14.0)	38 (20.1)	30 (16.3)
Failure to use contraceptive on date of conception	7 (3.8)	8 (4.2)	3 (1.6)
Used ineffective contraception	0	4 (2.1)	3 (1.6)
Other	6 (3.2)	5 (2.6)	9 (4.9)
Missing	9 (4.8)	15 (7.9)	15 (8.2)

Patient-Reported Reason for Pregnancy[a]	Year 14 (n=186)	Year 15 (n=189)	Year 16 (n=184)
Not reported	150 (80.6%)	152 (80.4%)	159 (86.4%)

[a] Categories are not mutually exclusive. Patients may appear in multiple categories.

iPLEDGE Sponsors' Recommendations for Data Collection

- Continue collecting fetal exposure information and root cause analysis for pregnancies
  - Can inform whether REMS is meeting goals and if changes in the program are needed to prevent further pregnancies
  - Consider streamlined processes and more succinct data collection forms

- Reevaluate the Pregnancy Registry collecting pregnancy outcomes and fetal outcomes given the extensive knowledge of teratogenic effects of isotretinoin

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Modifications to iPLEDGE REMS Program

Gregory P. Wedin, PharmD

Pharmacovigilance and Risk Management Director

Upsher-Smith Laboratories, LLC

Technology Platform Transition Challenges

December 2021

- Legacy system was discontinued
  - Passwords were encrypted and could not be migrated
- Stakeholders needed to use a secondary identifier, which most did not remember
  - Date of Personal Significance (DOPS)
- As a result, stakeholders could not login to the iPLEDGE Web site
  - Influx of calls to the newly established Contact Center

Restoring Functionality While Preserving Safe Use

- Goals:
  - Restoring stakeholder access to the iPLEDGE website
  - Returning call volume to the Contact Center to pre-transition levels
  - Returning daily prescription volume to pre-transition levels
- Acting to restore full functionality of iPLEDGE while preserving the elements to assure safe use (ETASUs)

Technology Platform Transition Resolutions

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- Actions taken to facilitate access:

Communications to medical and pharmacy organizations, Call Center, and public website

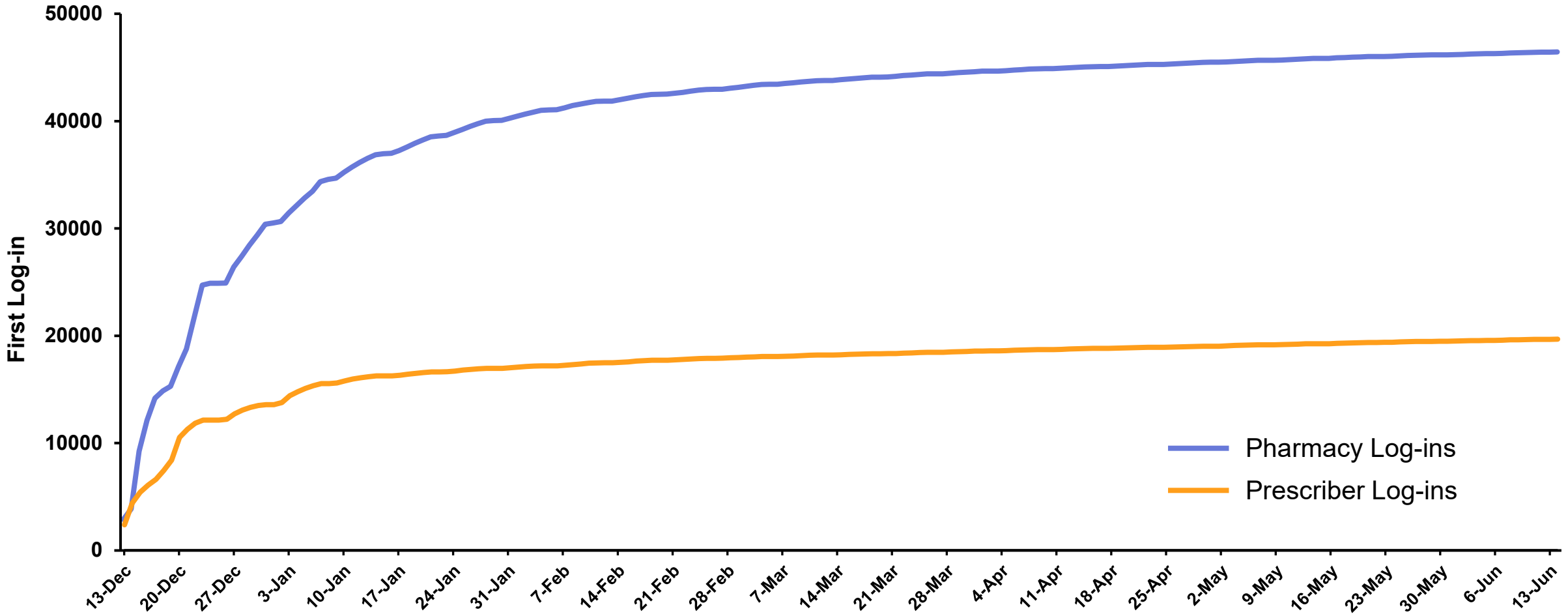
Troubleshooting Tips posted on the public home page

Additional options added to Forgot Username/Forgot DOPS for users to update accounts

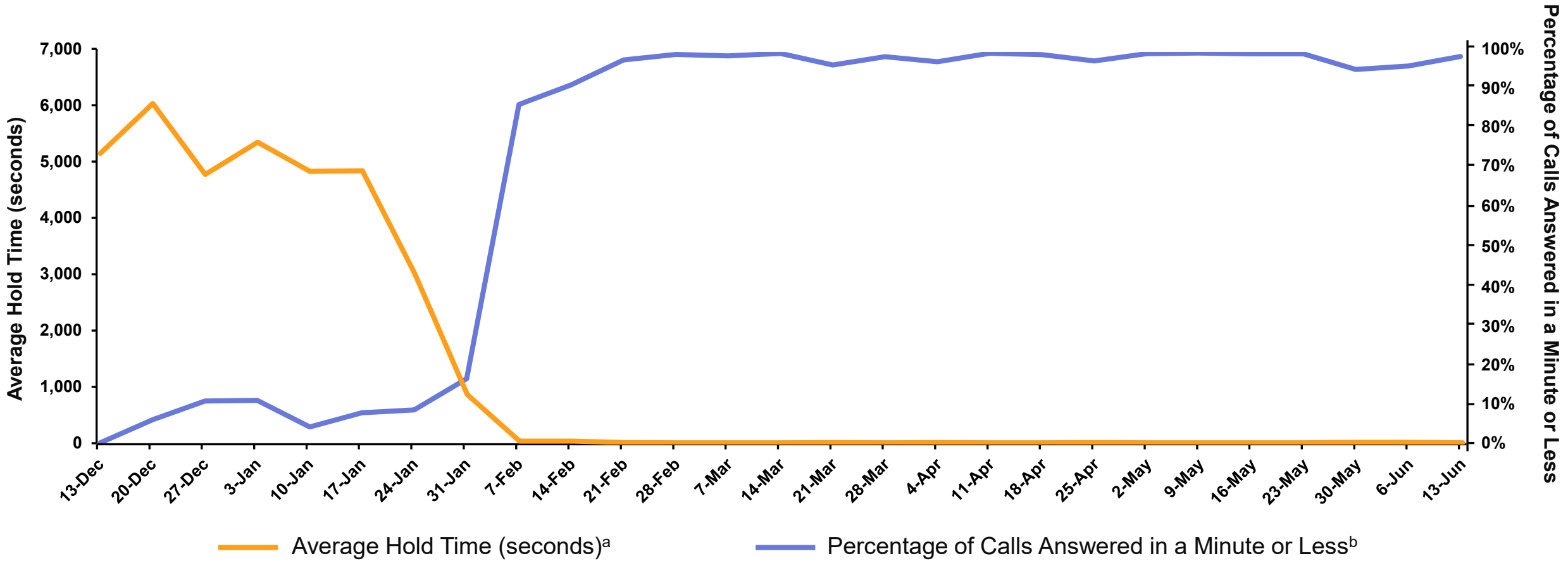
Emails with quick log-in links sent to prescribers to forward to patients and staff

- Operations at pre-transition levels for more than a year

Login Trends

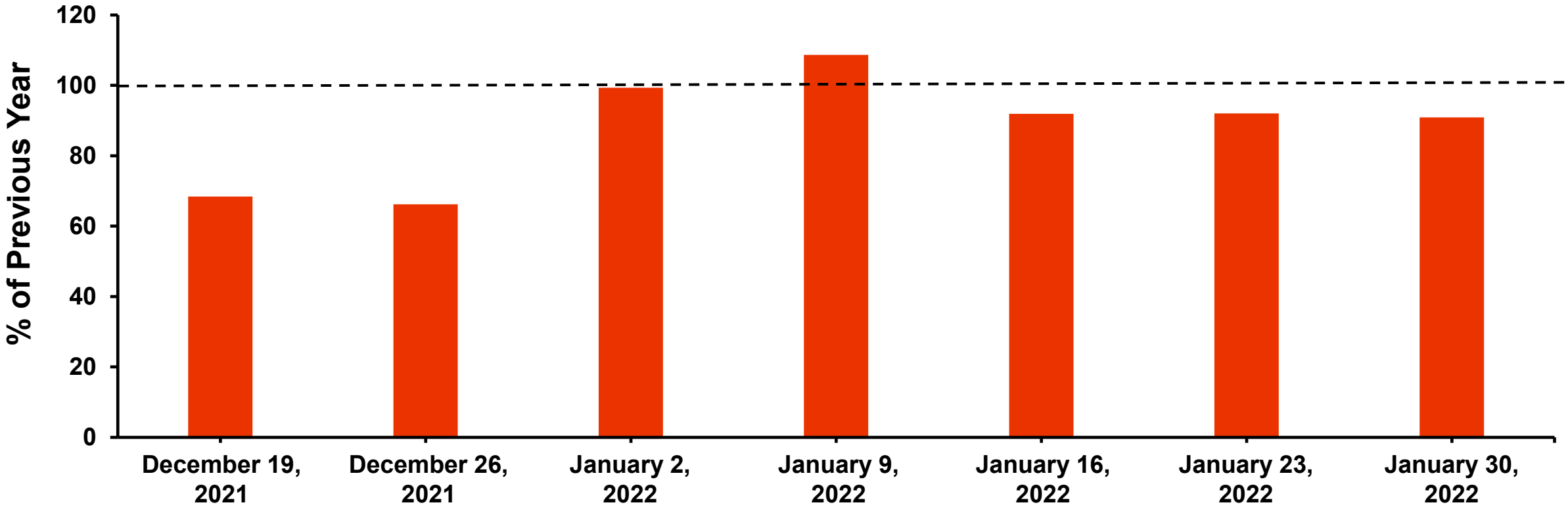


Average Hold Time and Calls Answered in Less Than One Minute



[a] Average queue wait time for all answered calls and queue callbacks requested. Does not include callers who abandon the call while in the Interactive Voice Response System (IVRS) queue.
[b] Percentage of calls answered by agents (including automatic queue callbacks when active). Includes Compliance and Spanish.

Total RMAs Approved Post-Transition



100% is defined as the average weekly volume of RMAs approved in the same time period in the previous year.

Prescriber Interviews
(9/13/2022 – 10/17/2022)

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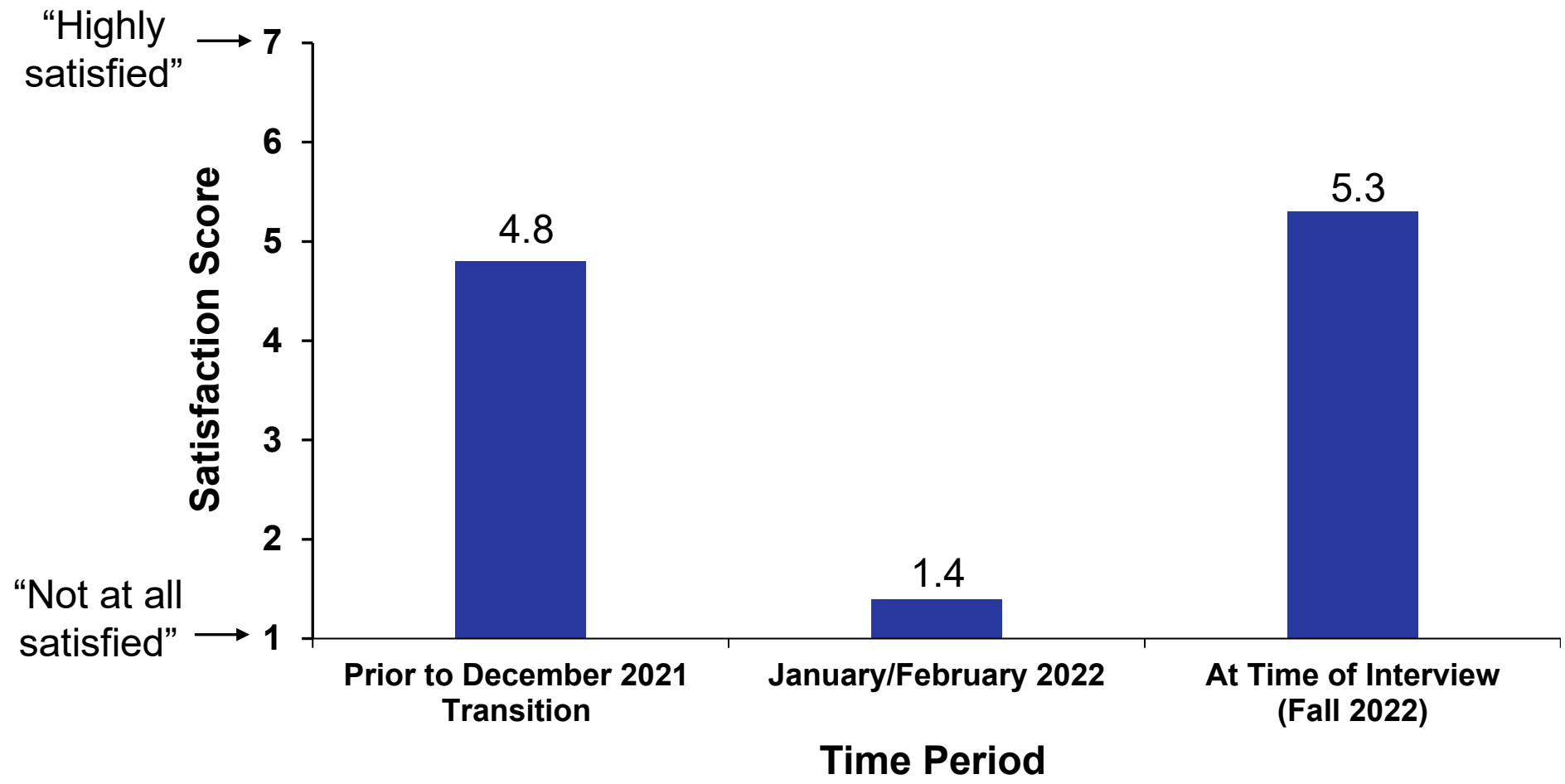
39 phone interviews (45 minutes each) with practicing community-based dermatologists

Average 106 acne patients per month

Most have 11-50 patients currently on isotretinoin

Queried perceptions about iPLEDGE and the modifications being considered for proposal to FDA

Prescriber Satisfaction: 2021 Modification



Criteria for Modifications to iPLEDGE REMS

- Much was learned during this recovery, including that there were opportunities for improvement of iPLEDGE and burdens that needed to be addressed
- The iPLEDGE Sponsors submitted a Major REMS Modification in November 2022 that included proposed changes based on stakeholder feedback
- iPLEDGE REMS modifications to reduce stakeholder burden must be carefully weighed against the potential impact on the safe use of isotretinoin

Overview of Proposed Modifications

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1. Change in Confirmation Interval for PWCNBP

- The iPLEDGE Sponsors propose to extend the confirmation interval for Patients Who Cannot Become Pregnant (PWCNBP) to every 120 days, rather than the current 30 days

2. Enhanced Enrollment Process

- A Designee will be able to enter all enrollment information (including pregnancy test results and patient categorization); this information can be saved at any time in the process
- To complete the process, the Prescriber will need to attest that the information is correct, complete the informed consent(s) with the patient, and provide an electronic signature

3. Calendar Feature

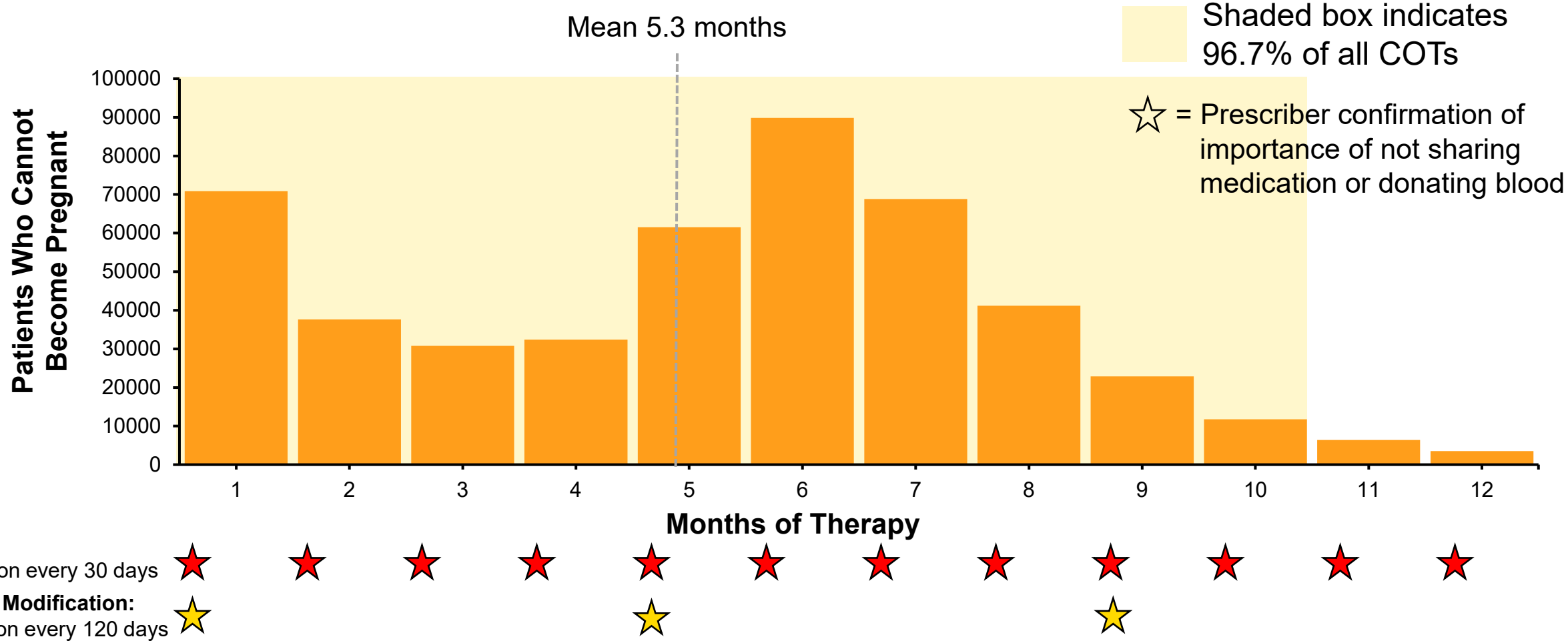
- The iPLEDGE Sponsors plan to reinstate the calendar functionality to better communicate the patient's course of therapy

4. Website Updates for Prescribers and Designees

- Website revisions will be made to reduce data-entry errors
- This will reduce delays in patients receiving drug

Rationale for Proposed 120-Day Confirmation Interval for Patients Who Cannot Become Pregnant

Year 16



COT = course of treatment.

A Confirmation Interval of 120 Days Reduces Stakeholder Burden

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- Extending the confirmation interval to every 120 days for Patients Who Cannot Become Pregnant reduces stakeholder burden
  - These patients are under the care of a certified Prescriber
  - Monthly prescriptions and counseling are required
- A confirmation coinciding with the mean duration of therapy provides documentation that counseling took place, that important safety reminders are being reinforced, and that the Prescriber has deemed that additional therapy is necessary
- Extending the confirmation interval beyond the typical course of therapy could interfere with the restricted distribution of the drug and increase the risk for misuse

Benefit/Risk of Proposed 120-Day Confirmation Interval for Patients Who Cannot Become Pregnant

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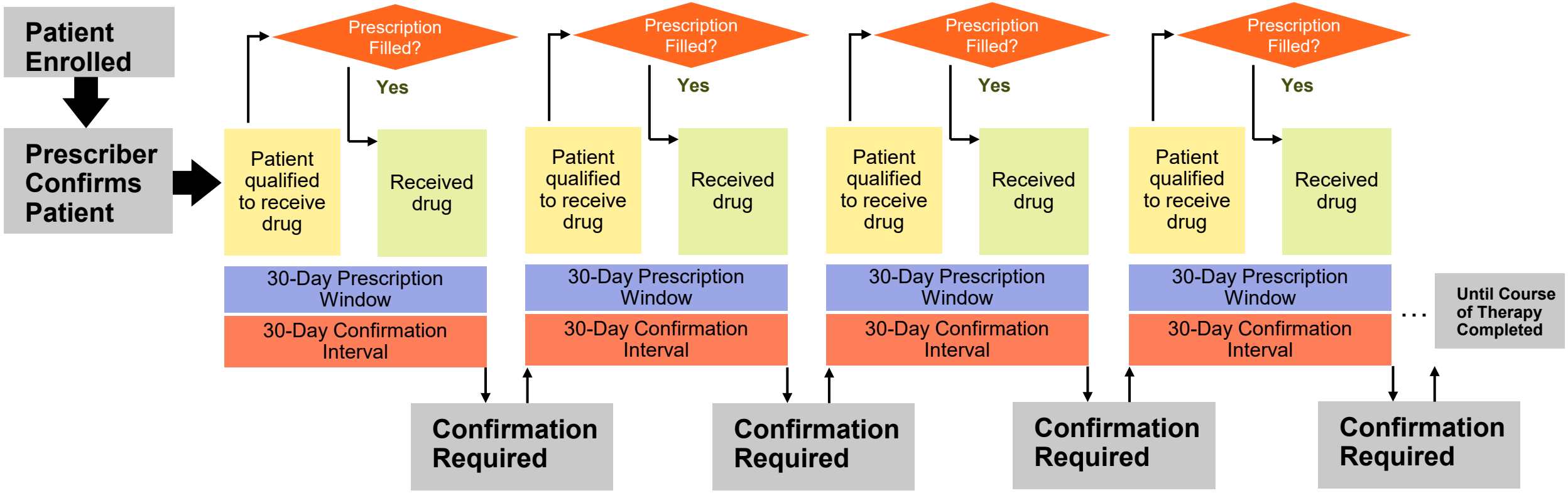

Benefit/Risk of Proposed 120-Day Confirmation Interval for Patients Who Cannot Become Pregnant (cont)

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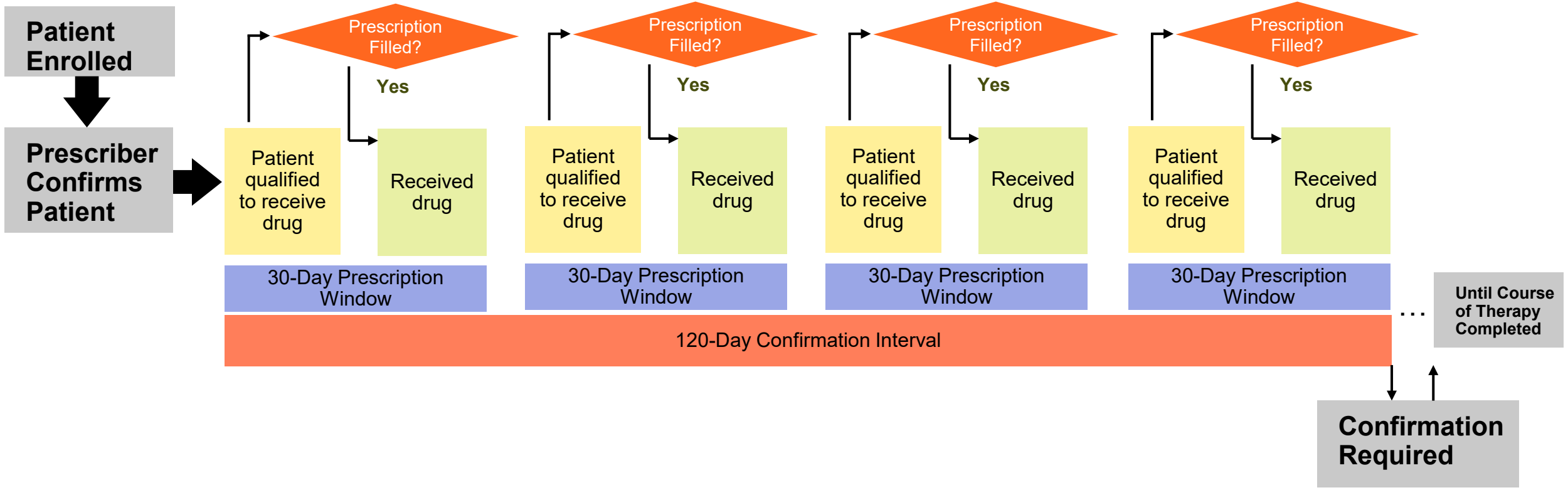
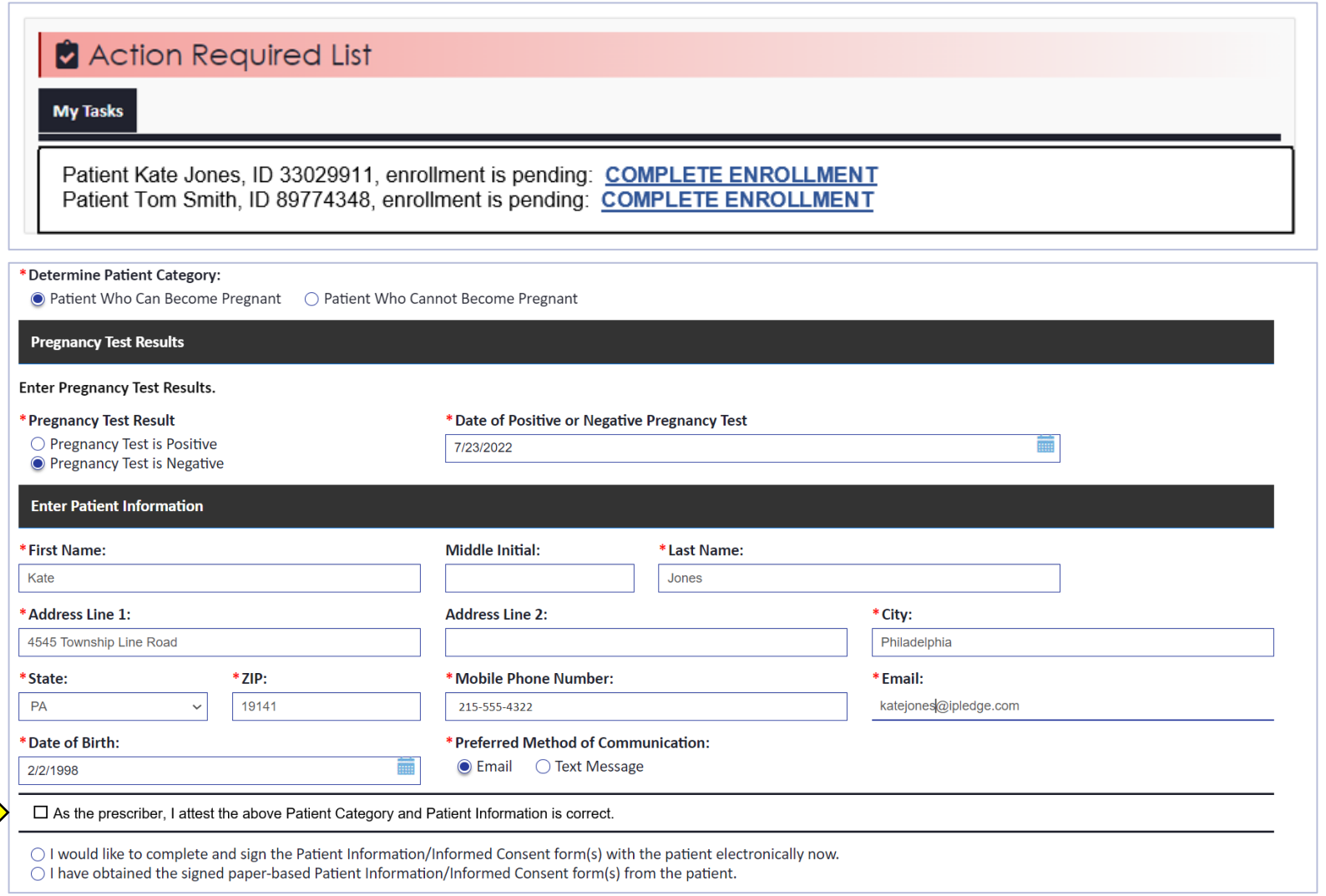


The Proposed Enhanced Enrollment Process Reduces Prescriber Burden

- Designees will enter enrollment information
- Includes “Save and Complete” functionality
- Once complete, the Prescriber will attest that the information is correct, complete the informed consents(s) with the patient, and provide an electronic signature



Reinstating the Calendar Functionality Is Proposed to Improve the iPLEDGE User Interface

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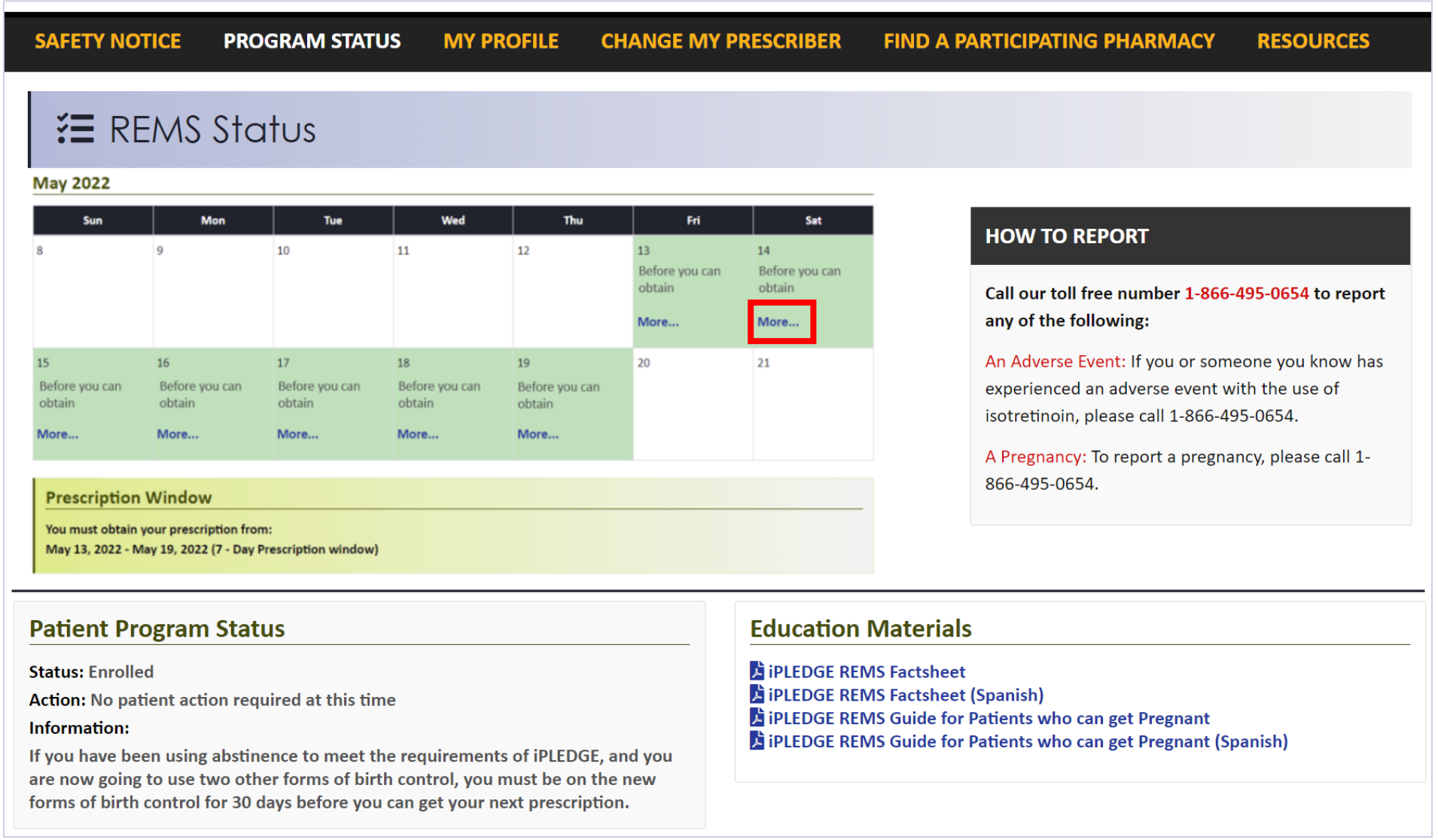

- The Calendar provides prescribers, designees, and patients a graphical view of the course of treatment and program requirements

Elements of the iPLEDGE REMS That Should Be Preserved

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1. 30-Day and 19-Day Waiting Periods
2. Abstinence Switch Wait
3. Laboratory-Confirmed Pregnancy Testing

30-Day Wait: Minimizes Risk of Fetal Exposure to Isotretinoin

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- Provide a negative pregnancy test
- Allow 30 days to select and begin contraception
  - Enable contraception to reach full effect
- Provide second negative pregnancy test
  - Must occur within the first 5 days of the menstrual cycle
- Complete comprehension questions

Rationale for 19-Day Wait

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Pregnancy Test

Menstrual Period

7-day Prescription Window

Fertile Window

28-Day Menstrual Cycle

★ 1	2	3	4	5	6	7
8	9	10	11	12	13	14
15	16	17	18	19	★ 20	21
22	23	24	25	26	27	28
1	2	3	4	5	6	7

19-Day Wait: Minimizes Risk of Fetal Exposure to Isotretinoin

Years 12-17

iPLEDGE® Committed to Pregnancy Prevention

	Years 12-17
PWCBP who obtained an RMA during their first treatment window	990,118
PWCBP who entered a 19-day wait	173,311
PWCBP who entered a 19-day wait and had an iPLEDGE-detected pregnancy prior to isotretinoin exposure	**12**

12 pregnancies have been detected during the 19-day wait in iPLEDGE Years 12-17

Elements of the iPLEDGE REMS That Should Be Preserved

iPLEDGE®
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1. 30-Day and 19-Day Waiting Periods

2. Abstinence Switch Wait

3. Laboratory-Confirmed Pregnancy Testing

Abstinence Switch Wait: Minimizes Risk of Fetal Exposure to Isotretinoin

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- **Abstinence Switch Wait:**
  A patient transitioning from abstinence to birth control is essentially the same as a PWCBP who is initiating therapy for the first time and is required to wait 30 days while on two forms of contraception

Eliminating these waiting periods increases the risk of fetal exposure to isotretinoin

Elements of the iPLEDGE REMS That Should Be Preserved

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1. 30-Day and 19-Day Waiting Periods

2. Abstinence Switch Wait

3. Laboratory-Confirmed Pregnancy Testing

Limitations of "At-Home" Pregnancy Testing

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- A rate of 15.7% of deliberate noncompliance with at-home pregnancy tests[1]
  - Similar methods of falsification were identified in a subsequent publication[2]
- In-office pregnancy testing with a sensitivity detection limit of at least 25 mIU/mL administered in a providers' office is an acceptable alternative to using a CLIA-certified laboratory

Long term use of "At-home" pregnancy tests has the potential for an increased risk of fetal exposure to isotretinoin

1. Smith GP and Machavariani L. *J Am Acad Dermatol*. 2022;87(5):1129-1130; 2. Johnson H, et al. *JAAD Case Report*. 2022;28:49-53.

Conclusions

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Carefully considered Stakeholder suggestions

Proposed modifications to reduce burden without increasing risk

Maintained elements that preserve effectiveness and safe use

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Supportive Slides

Pregnancies Detected in Patients Who Were Put Into 19-day Wait

Year 12-17

- 12 Pregnancies were detected in patients who were placed in the 19-day wait
  - 3 pregnancies were detected within the 19-day wait period
  - 7 pregnancies were detected after the 19-day wait period
  - 1 pregnancy was found to have occurred prior to the 19-day wait period
  - 1 pregnancy was unknown due to no pregnancy test reported; pregnancy ended in spontaneous abortion

Most Common Contraception Methods and Pregnancy Rates by Contraception Method

Years 14-16

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	Year 14 N (%)			Year 15 N (%)			Year 16 N (%)		
Primary / Secondary Contraception Methods	**Patients[b]**	**Pregnant Patients[c]**	**Rate of Pregnancy[d]**	**Patients[b]**	**Pregnant Patients[c]**	**Rate of Pregnancy[d]**	**Patients[b]**	**Pregnant Patients[c]**	**Rate of Pregnancy[d]**
Abstinence / n/a	101691 (44.0)	48 (26.1)	0.5	115852 (45.2)	45 (23.8)	0.4	115028 (47.0)	47 (25.5)	0.4
Birth control Pill (combination type) / Male Latex condoms	79472 (34.4)	106 (57.6)	1.3	85001 (33.1)	100 (52.9)	1.2	76335 (31.2)	107 (58.2)	1.4
Hormonal IUD / Male Latex condoms	18064 (7.8)	5 (2.7)	0.3	21187 (8.3)	5 (2.6)	0.2	21020 (8.6)	7 (3.8)	0.3
Hormonal Implants Under-the-skin / Male Latex condoms	6851 (3.0)	2 (1.1)	0.3	7872 (3.1)	0 (0)	0	7203 (2.9)	3 (1.6)	0.4
Non-Hormonal IUD / Male Latex condoms	6525 (2.8)	3 (1.6)	0.5	7219 (2.8)	6 (3.2)	0.8	6888 (2.8)	4 (2.2)	0.6
Other[a]	18559 (8.0)	22 (12.0)	1.2	19344 (7.5)	33 (17.5)	1.7	18327 (7.5)	16 (8.7)	0.9
Total Individuals[b]	**231162 (100)**	**186 (100)**	**-**	**256475 (100)**	**189 (100)**	**-**	**244801 (100)**	**184 (100)**	**-**

[a] Other includes primary contraceptive methods of tubal sterilization, male vasectomy, birth control patch, vaginal ring, or hormonal shot; [b] Patients who switched contraception methods during their treatment may be counted in more than one category; [c] Patients who became pregnant during the treatment window where they attested to using the indicated contraception method; [d] Number of patients who became pregnant out of 1000 patients who attested to using the indicated contraception method at some point during their treatment.

PWCBP Who Were Exposed to Isotretinoin and Lost to Follow-up

	Total No. by Year		
	Year 14 N (%)	**Year 15 N (%)**	**Year 16 N (%)**
Count of patients who registered and went to Inactive, LTFU or PLTFU without any activity during the assessment period i.e., had no approved RMAs and no confirmations within the COT	34,681 (16.6)	33,801 (15.8)	29,726 (14.5)
Pregnancy test results were not entered into iPLEDGE within 44 days after the date of the last isotretinoin dose[a]	174,068 (83.4)	180,470 (84.2)	175,547 (85.5)
Total	**208,749**	**214,271**	**205,273**

[a]Represents all patients that were expected to have completed both post-therapy pregnancy tests in Year Sixteen but did not complete both.
The average number of RMAs

Top 10 Most Common Contraception Methods Based on Monthly Interactions

Year 16

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Primary / Secondary Contraception Methods	N	%
Abstinence / n/a	702,822	46.2
Birth Control Pill / Male Latex Condom	479,766	31.6
Male Latex Condom / Hormonal IUD	120,894	8.0
Hormonal Implant / Male Latex Condom	43,031	2.8
Male Latex Condom / Non-Hormonal IUD	42,418	2.8
Male Vasectomy / Male Latex Condom	23,701	1.6
Tubal Sterilization / Male Latex Condom	23,219	1.5
Hormone Shot / Male Latex Condom	18,992	1.3
Vaginal Ring / Male Latex Condom	13,736	0.9
Birth Control Pills / Male Vasectomy	6,692	0.4

Table displays the number of monthly interactions where the contraception methods were selected.

Protocol: Appendix A

Information Requested		Contact w/Patient or Treating Dermatologist, Maternal Obstetric HCP, Primary Care Physician			For Live Birth Outcomes of Exposed or Indeterminate Cases Contact w/Patient or Infant HCP		
	iPLEDGE PROGRAM	Regis-tra-tion	Interim Follow-Up (each trime-ster)	Follow-Up at Out-come	Follow-Up (30 day)	Follow-Up (6 mon.)	Follow-Up (12 mon.)
Reporter Information and Permissions							
FRP consent to report pregnancy to the iPLEDGE Pregnancy Registry	X						
Maternal consent to participate in the iPLEDGE Pregnancy Registry Refer to section 12.2 for consent details		X					
Maternal Information							
Maternal characteristics (age, ethnicity,)	X	X					
Family history (maternal)		X	X				
Maternal prenatal test results & timing		X	X	X			
Isotretinoin therapy (dosage, start/stop date of administration)	X	X					
Maternal medications/products (Rx, OTC, dietary supplements, herbals) during pregnancy (dosage, routes, start/stop date of administration)		X	X	X			
Maternal concurrent medical conditions			X	X			
Patient and secondary contact information		X	X	X	X	X	X
Health Care Provider contact information	X	X	X	X	X	X	X

Information Requested		Contact w/Patient or Treating Dermatologist, Maternal Obstetric HCP, Primary Care Physician			For Live Birth Outcomes of Exposed or Indeterminate Cases Contact w/Patient or Infant HCP		
	iPLEDGE PROGRAM	Regis-tra-tion	Interim Follow-Up (each trime-ster)	Follow-Up at Out-come	Follow-Up (30 day)	Follow-Up (6 mon.)	Follow-Up (12 mon.)
Outcome of Pregnancy Information							
Pregnancy status		X	X	X			
Outcome information (fetal loss or live birth, gestation age, weight, length, head circumference)				X			
Birth defect/developmental milestones noted, description		X	X	X	X	X	X
Other factors that may have contributed to outcome (etiology)			X	X	X	X	
Infant Information							
Infant testing and results				X	X	X	X
Isotretinoin exposure assessment		X					
Infant characteristics (age, weight, length, head circumference, disease status)				X	X	X	X
Infant medications (dosage, routes, start/stop date of administration)				X	X	X	X
Authorization for Release of Medical Information has been incorporated into iPLEDGE Pregnancy Registry Patient Consent Form							
Maternal provider will be asked to obtain signed authorization for release of medical information for self and infant		X	X	X	X		