

Oncology Center of Excellence Project Renewal

Weighing evidence to update oncology drug labels

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- ✓ **FDA Product Labeling Rule and Project Renewal**
- ✓ Updating Product Labels with Current Scientific Evidence
- ✓ Expanding Indications – Substantial Evidence of Efficacy

History of Project Renewal

2006 Physician Labeling Rule (PLR)

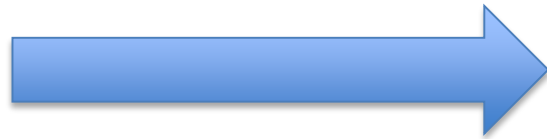
- “PLR Format”
- Drugs approved before 6/30/2001 are not required to be in PLR format

Long-standing off-patent FDA labels can become outdated

- Dose, administration schedules
- New Pharmacologic Data
- Data in special populations
- Old indications that may no longer be supported
- Standard of Care off-label Indications



History of Project Renewal

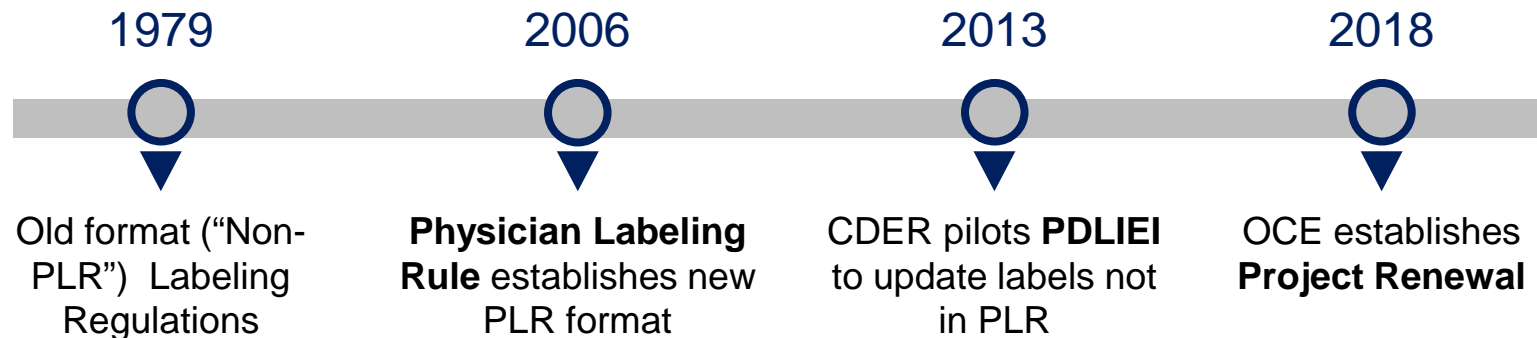


2013 PDLIEI Pilot

FDA piloted the **Prescription Drug Labeling Improvement and Enhancement Initiative (PDLIEI)** in February 2013 to update labels not in PLR format

PDLIEI encountered **several challenges**:

- User Fees for Efficacy Supplements
- Limited subject matter expertise with Contractor
- **Substantial divisional resources** needed to “fix” the labels



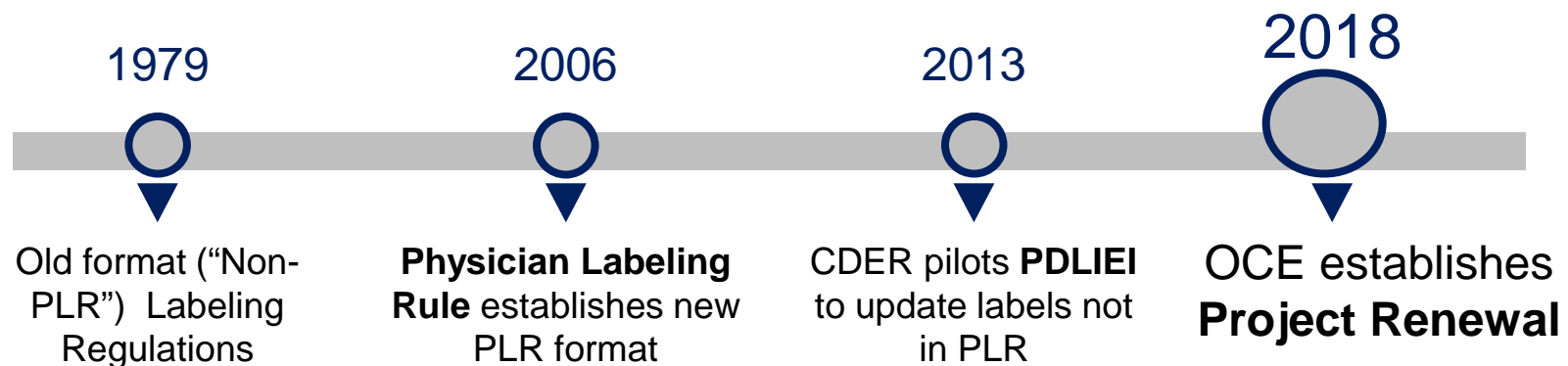
History of Project Renewal



Overcoming challenges:

- ~~User Fees for Efficacy Supplements~~

- Reach out to Oncology Community
- Clinical and regulatory expertise
- ***Reduce need for lengthy divisional review***



Project Renewal



Aligned with the U.S. Food and Drug Administration (FDA)'s mission to promote and **protect public health**, the **Project Renewal** initiative will provide healthcare providers - with the most accurate labeling information to inform prescribing decisions.




-
- Establish repeatable, objective and scientific processes for efficient label updates
 - Engage the Oncology Community
 - Create an educational opportunity and foster transparency

Label updates- potential indication expansion






Project Renewal is a **public health initiative** that aims to update the safety and efficacy information for oncology product labeling by establishing a set of repeatable processes to evaluate scientific evidence from available published literature.

Project Renewal **IS**:

-  An FDA pilot to update longstanding labels for off-patent products
-  Initially only reviewing a subset of high priority indications
-  An opportunity to collaborate on a transparent review of evidence

Project Renewal **IS NOT**:

-  A way to expand indications for drugs on patent or with exclusivity
-  A review of all possible indications that may be in use
-  Related to cost, payment, or coverage decisions

- ✓ FDA Product Labeling Rule and Project Renewal
- ✓ **Updating Product Labels with Current Scientific Evidence**
- ✓ Expanding Indications – Substantial Evidence of Efficacy

Updated product labels – more than just indications

FULL PRESCRIBING INFORMATION: CONTENTS*

WARNING: [SUBJECT OF WARNING]

1 INDICATIONS AND USAGE

1.1 [text]

1.2 [text]

2 DOSAGE AND ADMINISTRATION

2.1 [text]

2.2 [text]

3 DOSAGE FORMS AND STRENGTHS

4 CONTRAINDICATIONS

5 WARNINGS AND PRECAUTIONS

5.1 [text]

5.2 [text]

6 ADVERSE REACTIONS

6.1 [text]

6.2 [text]

7 DRUG INTERACTIONS

7.1 [text]

7.2 [text]

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

8.2 Labor and Delivery

8.3 Nursing Mothers

8.4 Pediatric Use

8.5 Geriatric Use

9 DRUG ABUSE AND DEPENDENCE

9.1 Controlled Substance

9.2 Abuse

9.3 Dependence

10 OVERDOSAGE

11 DESCRIPTION

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

12.2 Pharmacodynamics

12.3 Pharmacokinetics

12.4 Microbiology

12.5 Pharmacogenomics

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

13.2 Animal Toxicology and/or Pharmacology

14 CLINICAL STUDIES

14.1 [text]

14.2 [text]

15 REFERENCES

16 HOW SUPPLIED/STORAGE AND HANDLING

17 PATIENT COUNSELING INFORMATION

PLR Labeling Guidance for Industry <https://www.fda.gov/downloads/drugs/guidances/ucm075082.pdf>

Example: Fluorouracil (5-FU)



- **Label was updated to adhere to PLR format in 2016**
 - Dose and administration:
 - Indications were reorganized, clarified, and dose and administration for each indication were updated
 - Safety:
 - Contraindications were revised
 - New warnings for cardiotoxicity, neurologic toxicity, hyperammonemic encephalopathy and increased INR with concomitant warfarin use
 - Clinical Pharmacology:
 - Warning added regarding increased risk in those with low or absent Dipyrimidine Dehydrogenase (DPD) Activity

5-FU: We may also **remove** out of date information



- 5-FU labeling revision removed an outdated boxed warning

WARNING

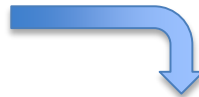
It is recommended that fluorouracil be given only by or under the supervision of a qualified physician who is experienced in cancer chemotherapy and who is well versed in the use of potent antimetabolites. Because of the possibility of severe toxic reactions, it is recommended that patients be hospitalized at least during the initial course of therapy.

Moving Cisplatin Contraindications to Warnings

- **CONTRAINDICATIONS**

PLATINOL is contraindicated in patients with **preexisting renal impairment**. PLATINOL **should not be employed in myelosuppressed patients, or in patients with hearing impairment**. PLATINOL is contraindicated in patients with a history of allergic reactions to PLATINOL or other platinum-containing compounds.

- **The Cisplatin product label was revised to:**



- **CONTRAINDICATIONS**

Cisplatin for injection is contraindicated in patients with severe hypersensitivity to cisplatin.

- Additional information added in warnings to allow safe use in those with renal, bone marrow and hearing impairment...

INDICATIONS AND USAGE

Fluorouracil is a nucleoside metabolic inhibitor indicated for the treatment of patients with

- Adenocarcinoma of the Colon and Rectum (1.1)
- Adenocarcinoma of the Breast (1.2)
- Gastric Adenocarcinoma (1.3)
- Pancreatic Adenocarcinoma (1.4)

More detail provided in dose and administration section:

2.2 Recommended Dosage for Adenocarcinoma of the Colon and Rectum

- The recommended dose of fluorouracil, administered in an infusional regimen in combination with leucovorin alone, or in combination with leucovorin and oxaliplatin or irinotecan, is 400 mg/m² by intravenous bolus on Day 1, followed by 2400 mg/m² to 3000 mg/m² intravenously as a continuous infusion over 46 hours every two weeks.
- The recommended dose of fluorouracil, if administered in a bolus dosing regimen in combination with leucovorin, is 500 mg/m² by intravenous bolus on Days 1, 8, 15, 22, 29, and 36 in 8-week cycles.

Project Renewal will generate a product report that characterizes the evidence to support a subset of commonly used off-label indications

- ✓ FDA Product Labeling Rule and Project Renewal
- ✓ Updating Product Labels with Current Scientific Evidence
- ✓ **Expanding Indications – Substantial Evidence of Efficacy**

- **Quantity of Evidence**
 - # of trials and supportive evidence
- **Quality of Evidence**
 - Adequate and well-controlled trials
- **Magnitude and Statistical Persuasiveness of Result**
 - E.g., large median OS improvement $p < 0.001$
- **Source of Evidence**
 - Controlled Clinical Trial, Real World Evidence, Published Literature
- **Context**
 - Rarity of disease, unmet need, additional safety and efficacy data across diseases

*“Reports of **adequate and well-controlled investigations** provide the primary basis for determining whether there is ‘substantial evidence’ to support the claims of effectiveness for new drugs.”*

1. Clear statement of objectives – prespecified analyses
2. Trial design – valid comparison to a control
3. Subjects are selected with disease being studied
4. Treatment assignment minimizes bias
5. Minimize bias for subjects, observers and data analysts
6. Well-defined and reliable assessments

- Well defined natural history of disease
- External control well matched to treatment group
- Outcome is compelling evidence of change in disease progression

e.g., Regression of metastases

In oncology, we have most commonly used external controls for single arm trials with response rate as the endpoint

Published Literature

Registry / Real-World Data

Patient Level Commercial Trial Data Sets



Limitation of published literature: Lacks patient level data and source validation FDA normally reviews for commercial trials

- Who conducted the study?
- How detailed is the published report?
- How many sites?
- How objective are the outcomes?
- Was the analysis prespecified?
- Clinically meaningful and statistically persuasive result?
- Additional internal consistency within trial secondary outcomes?
- Are there multiple studies? (external validation?)

Does the published report provide enough detail to be considered substantial evidence from an adequate and well-controlled trial?



DISEASE CONTEXT

- Severe, life-threatening or debilitating diseases
- Rarity of the condition



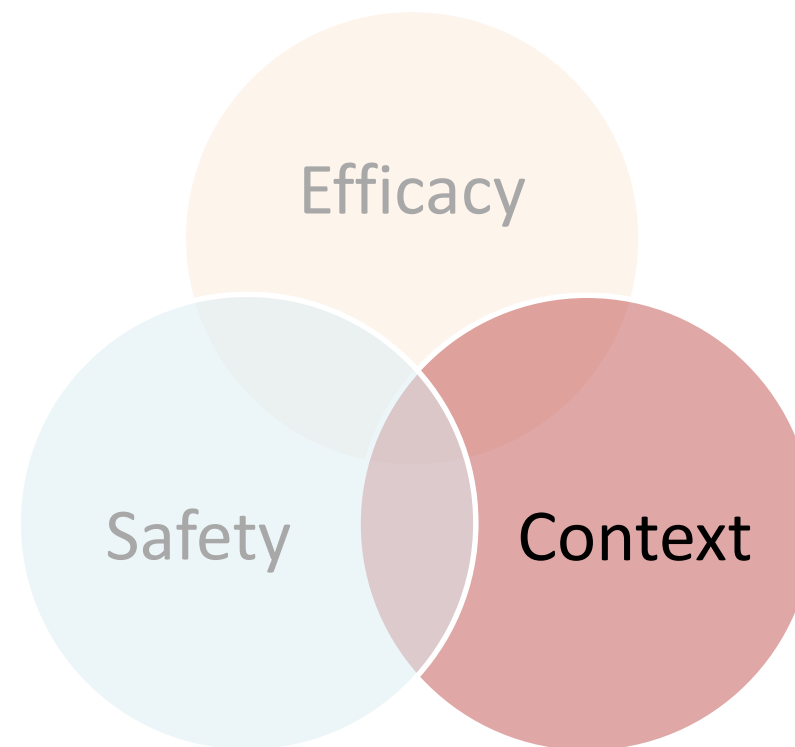
THERAPEUTIC CONTEXT

- Available therapies
- Unmet medical need



TEMPORAL CONTEXT

- Significant cumulative experience for older drugs
- OLD published studies in from different scientific era



- Project Renewal is a **public health initiative** to update longstanding outdated cancer product labeling

- Labeling information that may need to be updated spans dosage, administration, safety, special populations, and may include expanding the label to include new indications **based on substantial evidence of effectiveness**

- “**Substantial Evidence**” takes into account the quantity, quality, magnitude, source, and context of clinical trial and other data

- This NAS workshop is an opportunity for FDA to have an **open dialogue** with scientific leaders to understand their perspective on evidence to consider when updating cancer drug labeling

- How do you evaluate published literature when making your treatment or policy decisions?
- What components of the FDA label for longstanding drugs would you prioritize as critical to update with contemporary information?
- Are there considerations other than those discussed in this presentation that should be taken into account when deciding whether to expand the indication section for commonly used standard regimens?