FDALabel: A Tool to Manage Drug-Labeling Documents with Flexible Search Capabilities Used in Drug Reviews at FDA

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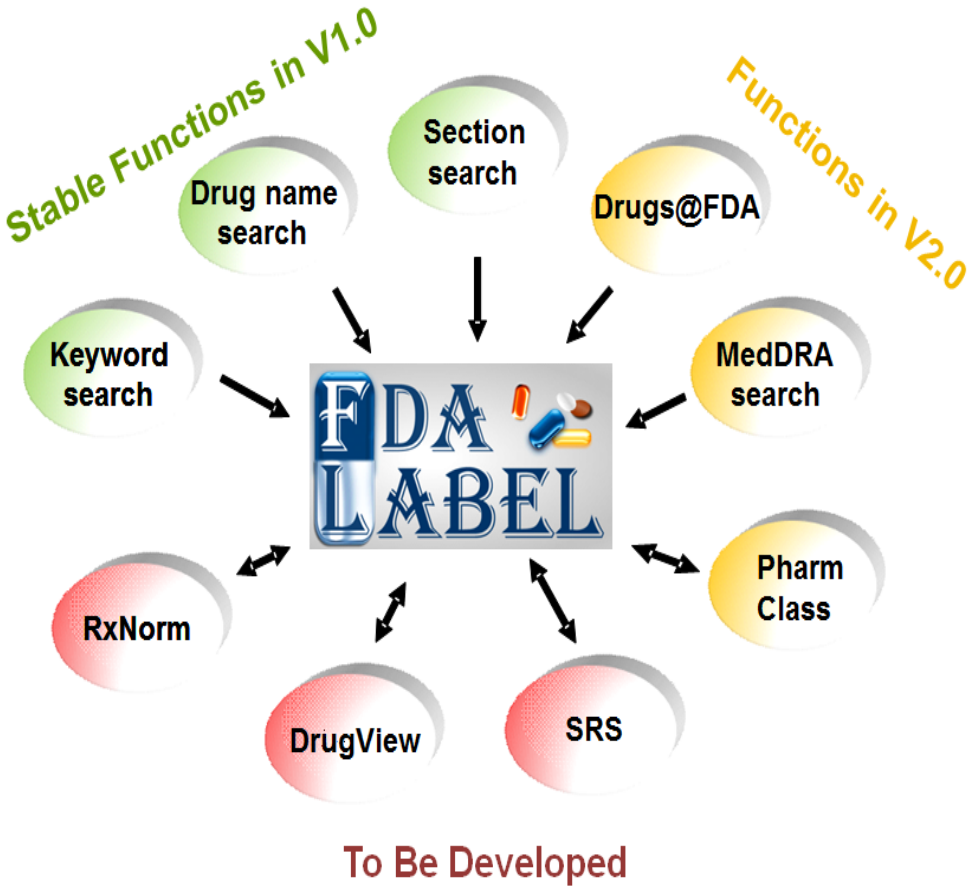
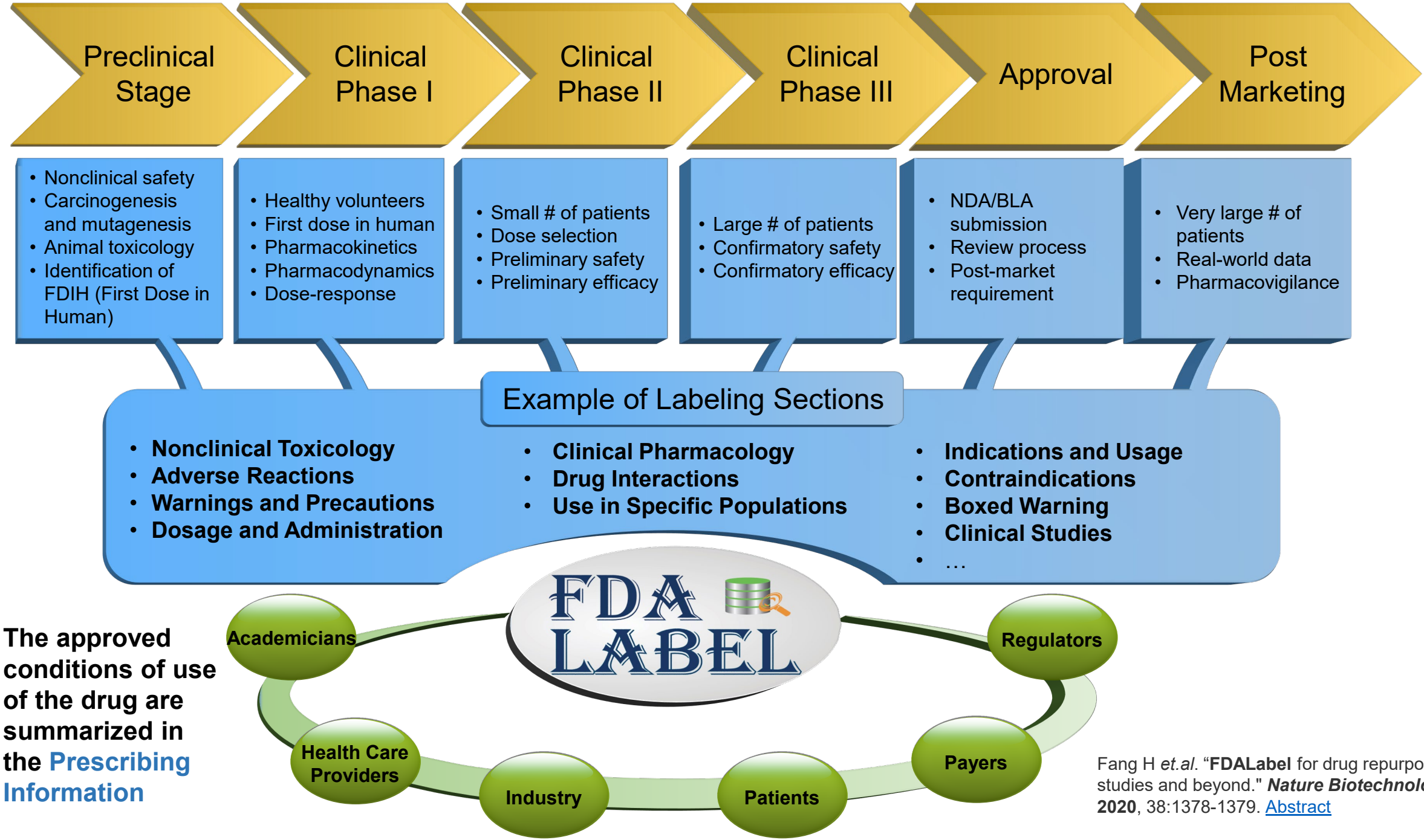
Disclaimer

This presentation reflects the views of the author and does not necessarily reflect those of the US Food and Drug Administration. Any mention of commercial products is for clarification and is not intended as an endorsement.

FDALabel Overview

- Web-based database for managing, querying and organizing drug labeling and other product labeling
  - Data source: FDA's SPL (Structured Product Labeling): for human and animal prescription and nonprescription drugs and biological products downloaded from DailyMed
  - Currently with >140,000 labeling, updated regularly
  - User-friendly interface that searches against the entire text of drug labeling
  - Publicly available at AWS
- Advanced future query features for **Translational and Regulatory Science**
  - Integrate with Drugs@FDA and Orange Book
  - Integrate with MedDRA
  - Integrate with Pharmacologic Class
  - Integrate with GSRS (Global Substance Registration System)





The approved conditions of use of the drug are summarized in the Prescribing Information

Fang H *et.al*. "**FDALabel** for drug repurposing studies and beyond." ***Nature Biotechnology***. **2020**, 38:1378-1379. Abstract

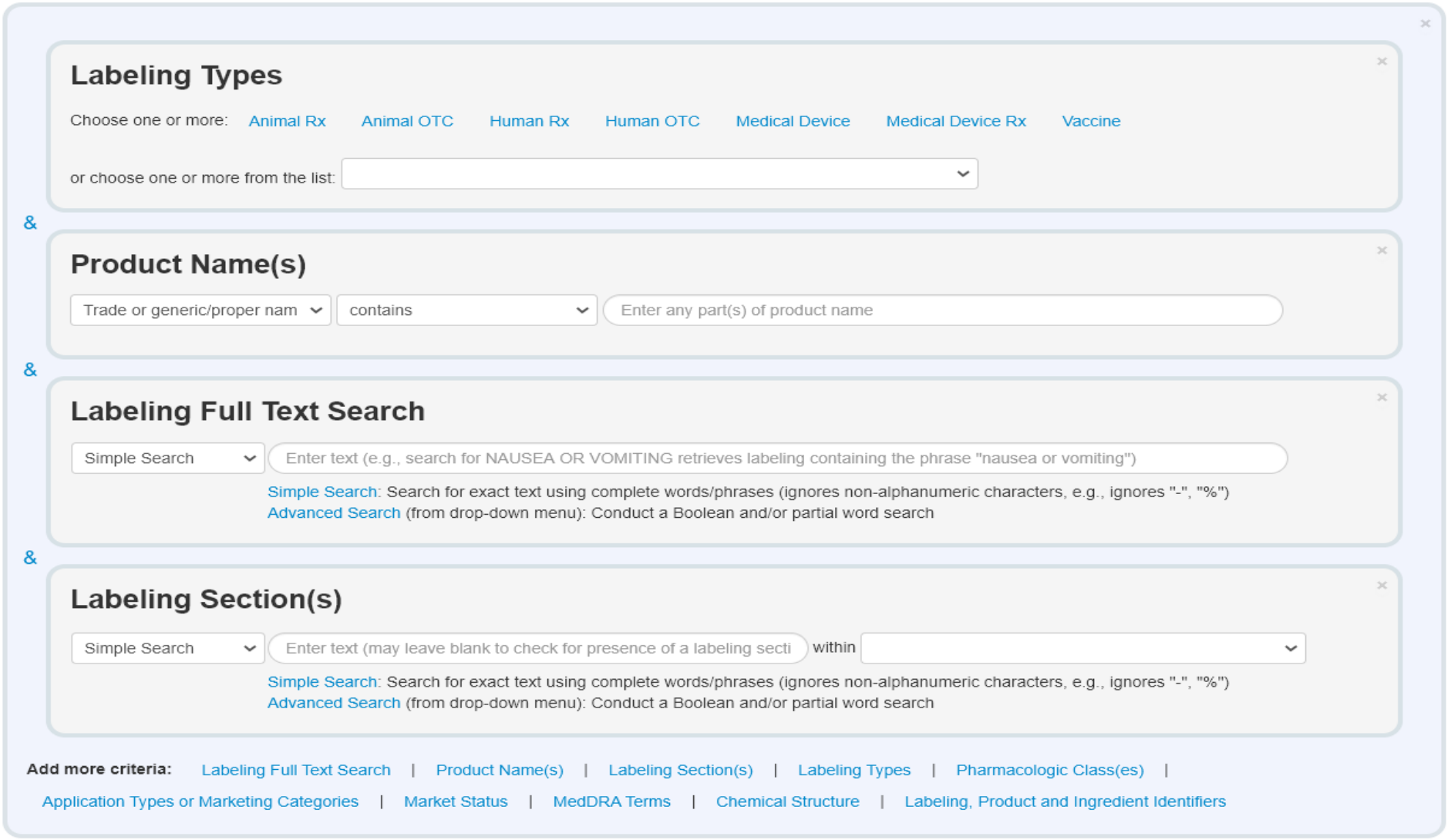
FDA-Approved Prescription Drug Labeling

- **Prepared by manufacturers and approved by FDA**
  - Data is from preclinical and clinical trials and updated with post-market case reports (e.g., FAERS).
  - Wording in approved prescription drug labeling is ordinarily based on an agreement between the FDA and the drug company.
- **Format and Content of Prescribing Information specified by Code of Federal Regulations, Title 21 (21 C.F.R. § 201.56, 201.57 and 201.80)**
  - In 1979, FDA established a Final Rule "Old" labeling format (non-PLR) (currently 21 C.F.R. §201.80)
  - In 2006, the Physician Labeling Rule (PLR) (see 21 C.F.R. §201.56) amended regulations regarding format and content of the Prescribing Information.
  - All drugs approved (under NDAs/BLAs) since June 2001 and certain drugs approved (under NDAs/BLAs) before June 2001 (e.g., those approved for new uses after June 2001), must have Prescribing Information in PLR format.
    - The amount of information captured in drug labeling has grown rapidly; labeling is updated (e.g., with new essential scientific information for the safe and effective use of the drug, to meet statutory/regulatory requirements).
    - Additional prescription drug labeling resources including specific recommendations for sections of labeling are available.

FDALabel Tool Features for Searching Drug Labeling Documents

- **Complex structure of drug labeling requires a flexible, powerful, and fast search engine to search against the entire text**
  - Query text within any specific or combination of product names (e.g., generic or trade), labeling types (e.g., Rx and OTC), sections/subsections (e.g., Indications and Usage, Dosage and Administration, Warnings and Precautions), Pharmacologic Class information, etc.
  - Export labeling results to a spreadsheet to open in Excel
  - Direct links to the SPL document, DailyMed, Drugs@FDA, and Orange Book for the product
- **Repeat and reproduce the same complex queries**
  - Customized queries and results can be created, saved, and shared with other users for later viewing and updating

FDALabel User Interface (Version 2.5)



FDALabel **on Amazon Cloud:**
https://www.fda.gov/fdalabeltool

Fang H *et.al*. "**FDALabel** for drug repurposing studies and beyond." ***Nature Biotechnology***. **2020**, 38:1378-1379. Abstract

Example of Highlights in Drug Labeling
Remdesivir (VEKLURY®, approved by FDA in 2020)

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use VEKLURY safely and effectively. See full prescribing information for VEKLURY.

VEKLURY® (remdesivir) for injection, for intravenous use
VEKLURY® (remdesivir) injection, for intravenous use
Initial U.S. Approval: 2020

---------- **INDICATIONS AND USAGE** ----------
VEKLURY is a SARS-CoV-2 nucleotide analog RNA polymerase inhibitor indicated for adults and pediatric patients (12 years of age and older and weighing at least 40 kg) for the treatment of coronavirus disease 2019 (COVID-19) requiring hospitalization. VEKLURY should only be administered in a hospital or in a healthcare setting capable of providing acute care comparable to inpatient hospital care. (1)

---------- **DOSAGE AND ADMINISTRATION** ----------
- Testing: In all patients, before initiating VEKLURY and during treatment as clinically appropriate, perform renal and hepatic laboratory testing and assess prothrombin time. (2.1)
- Recommended dosage in adults and pediatric patients 12 years of age and older and weighing at least 40 kg: a single loading dose of VEKLURY 200 mg on Day 1 followed by once-daily maintenance doses of VEKLURY 100 mg from Day 2 infused over 30 to 120 minutes. (2.2)
- For patients not requiring invasive mechanical ventilation and/or ECMO, the recommended total treatment duration is 5 days. If a patient does not demonstrate clinical improvement, treatment may be extended for up to 5 additional days for a total treatment duration of up to 10 days. (2.2)
- For patients requiring invasive mechanical ventilation and/or ECMO, the recommended total treatment duration is 10 days. (2.2)
- Administer VEKLURY via intravenous (IV) infusion over 30 to 120 minutes. (2.2, 2.4)
- Renal impairment: VEKLURY is not recommended in patients with eGFR less than 30 mL/min. (2.3)
- Dose preparation and administration: Refer to the full prescribing information for further details for both formulations. (2.4)
- Storage of prepared dosages: VEKLURY contains no preservative. (2.5)

---------- **DOSAGE FORMS AND STRENGTHS** ----------
- For injection: 100 mg of remdesivir as a lyophilized powder, in a single-dose vial. (3)
- Injection: 100 mg/20 mL (5 mg/mL) remdesivir, in a single-dose vial. (3)

---------- **CONTRAINDICATIONS** ----------
VEKLURY is contraindicated in patients with a history of clinically significant hypersensitivity reactions to VEKLURY or any components of the product. (4)

---------- **WARNINGS AND PRECAUTIONS** ----------
- Hypersensitivity including infusion-related and anaphylactic reactions: Hypersensitivity reactions have been observed during and following administration of VEKLURY. Slower infusion rates, with a maximum infusion time of up to 120 minutes, can be considered to potentially prevent signs and symptoms of hypersensitivity. If signs and symptoms of a clinically significant hypersensitivity reaction occur, immediately discontinue administration of VEKLURY and initiate appropriate treatment. (5.1)
- Increased risk of transaminase elevations: Transaminase elevations have been observed in healthy volunteers and have also been reported in patients with COVID-19 who received VEKLURY.
  Perform hepatic laboratory testing in all patients before starting VEKLURY and while receiving VEKLURY as clinically appropriate. Consider discontinuing VEKLURY if ALT levels increase to greater than 10 times the upper limit of normal. Discontinue VEKLURY if ALT elevation is accompanied by signs or symptoms of liver inflammation. (5.2)
- Risk of reduced antiviral activity when coadministered with chloroquine phosphate or hydroxychloroquine sulfate: Coadministration of VEKLURY and chloroquine phosphate or hydroxychloroquine sulfate is not recommended based on data from cell culture experiments demonstrating a potential antagonistic effect of chloroquine on the intracellular metabolic activation and antiviral activity of VEKLURY. (5.3)

---------- **ADVERSE REACTIONS** ----------
The most common adverse reactions (incidence greater than or equal to 5%, all grades) observed with treatment with VEKLURY are nausea, ALT increased, and AST increased. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Gilead Sciences, Inc. at 1-800-GILEAD-5 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.
See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.

Revised: 02/2021

FULL PRESCRIBING INFORMATION: CONTENTS*

Remdesivir (VEKLURY®)

*The letter of authorization that FDA issues to the sponsor (upon authorization) includes authorization of the content of the fact sheets and specifies the authorized Fact Sheets must be distributed with the product. Fact Sheets will always be available when a product is authorized for emergency use.

Indications and Usage (approved):

- VEKLURY is a SARS-CoV-2 nucleotide analog RNA polymerase inhibitor indicated for ***adults and pediatric patients (12 years of age and older and weighing at least 40 kg)*** for the treatment of coronavirus disease 2019 (***COVID-19***) requiring hospitalization.
- VEKLURY should only be administered in a hospital or in a healthcare setting capable of providing acute care comparable to inpatient hospital care.

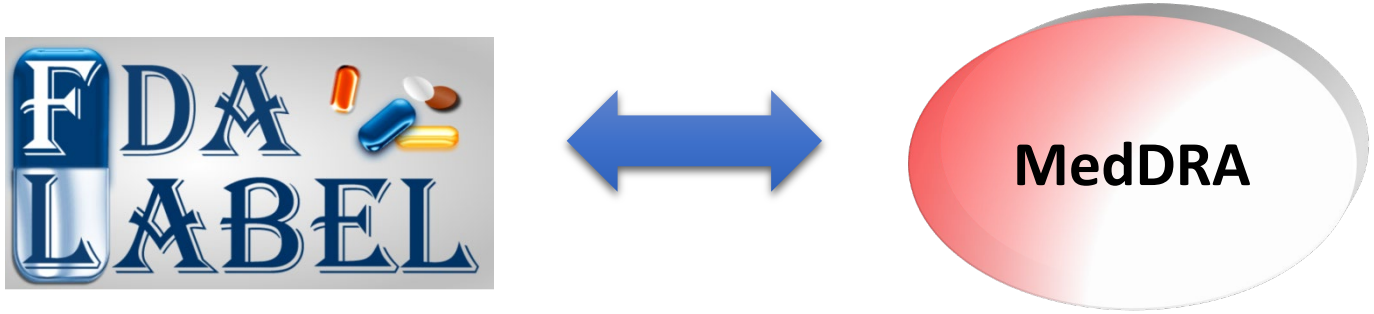
Emergency Use Authorization (EUA)*

- Updated EUA for hospitalized ***pediatric patients weighing 3.5 kg to less than 40 kg or hospitalized pediatric patients less than 12 years of age weighing at least 3.5 kg*** with suspected or laboratory-confirmed **COVID-19 (**up-to-date info see **EUA official webpage)**.

Applications of FDALabel in the Study of ADRs and Precision Medicine

FDALabel Integrated with MedDRA

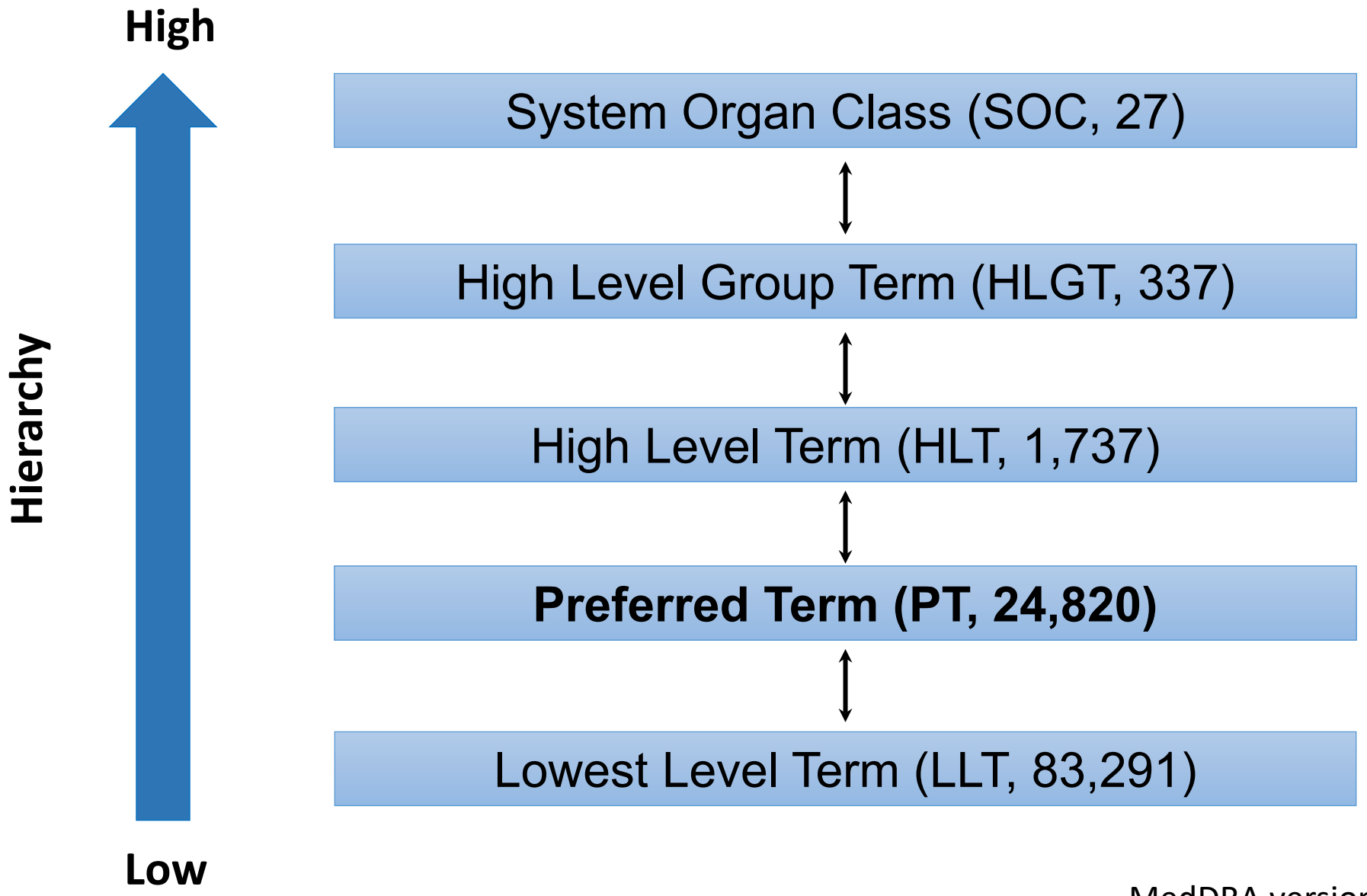
(Medical Dictionary and Standard Terminology)



Medical Dictionary for Regulatory Activities (MedDRA):
The terminology is used through the entire regulatory process, from pre-marketing to post-marketing, and for data entry, retrieval, evaluation, and presentation.

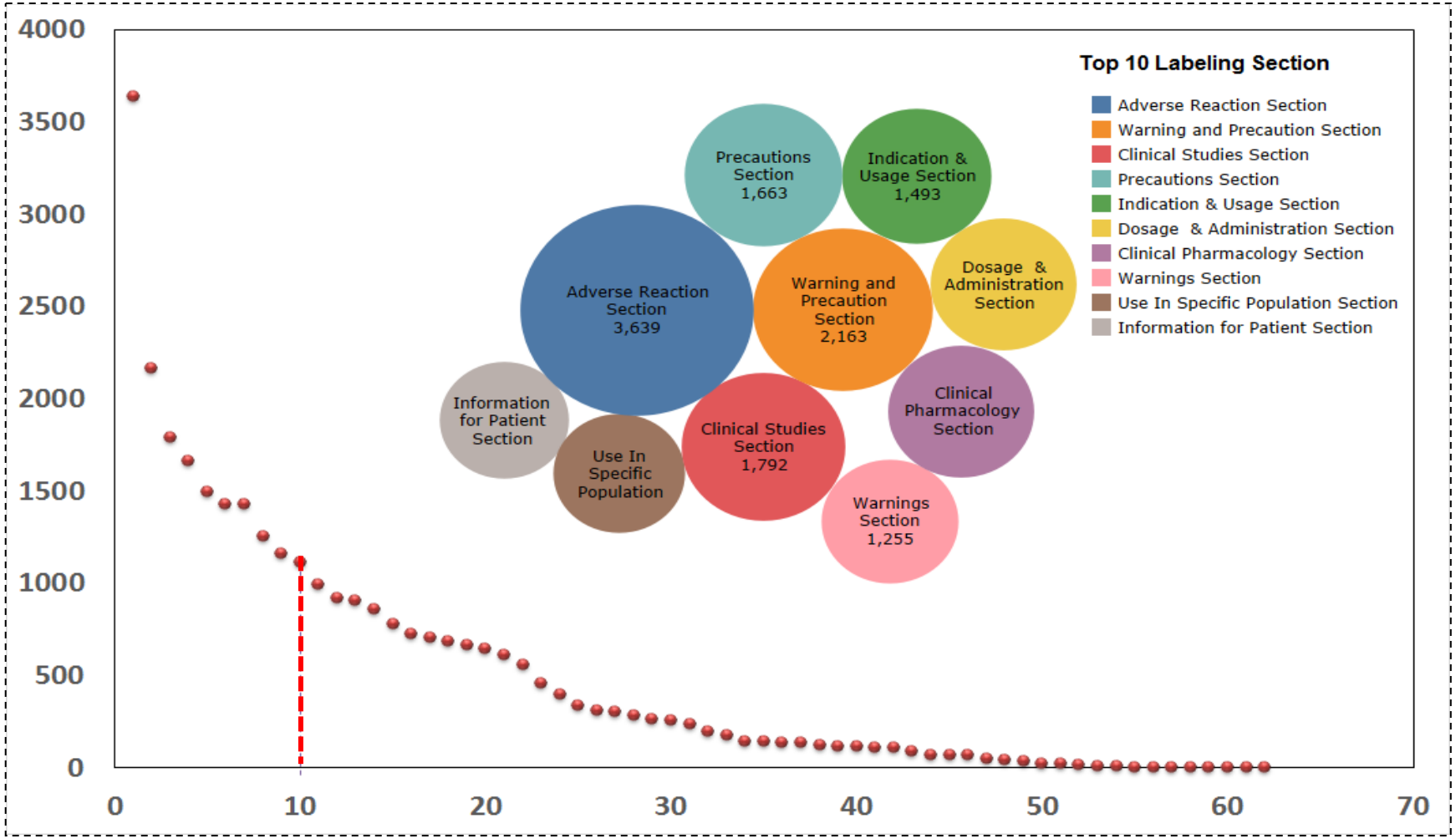
- FAERS codes adverse event using MedDRA
- MedDRA is widely used internationally, including in the United States, European Union and Japan.
- Originally available in English and Japanese, MedDRA is now also translated into Chinese, Czech, Dutch, French, German, Hungarian, Italian, Portuguese and Spanish.
- Its use is currently mandated in Europe and Japan for safety reporting.
- Eventually, standardized MedDRA Queries (SMQs) allow the computer automation.

MedDRA Hierarchy



MedDRA version 24.0

Distribution of MedDRA (PTs) in All Drug Labeling Sections

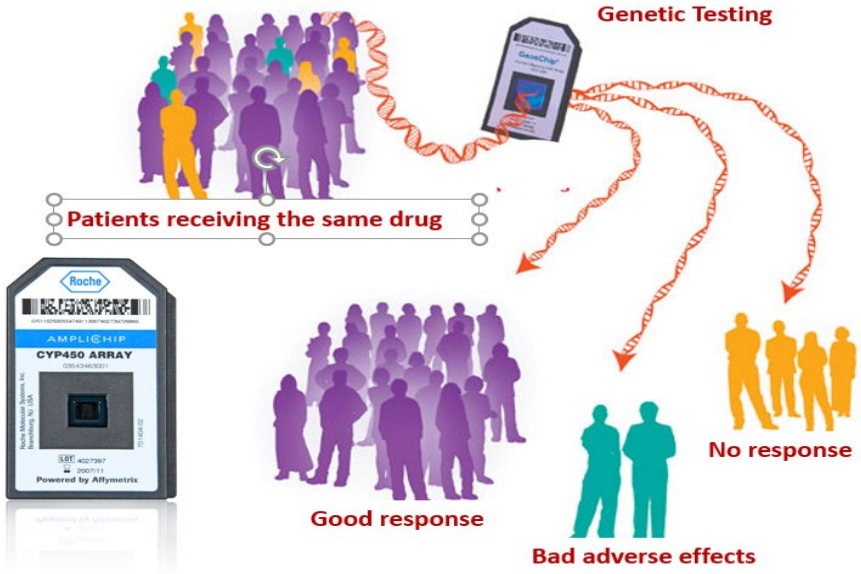


Rank of Labeling Sections

**** Data acquired on Oct . 25, 2016***

Application in Pharmacogenomics
(Personalized Medicine)

- Pharmacogenomics (PGx) is a field of research that studies the relationship between drug response and genetic makeup of an individual/population.
- Patients Respond Differently to the Same Drug Treatment
- **Right Drug, Right Dose, Right Patient (Precision Medicine)**

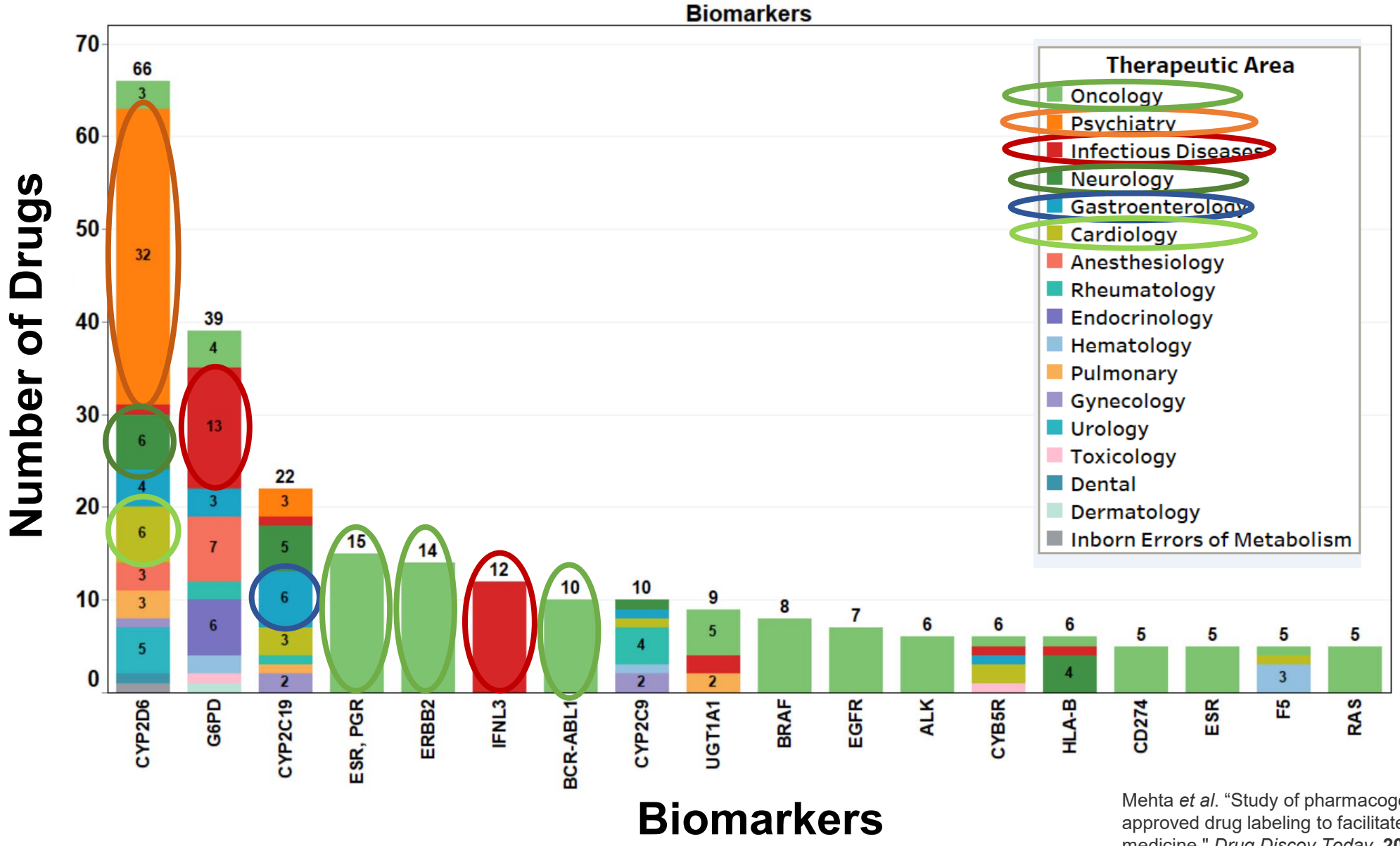


Example: VITRAKVI (Larotrectinib, initially approved in 2018) is a kinase inhibitor indicated for the treatment of adult and pediatric patients with certain solid tumors that have a neurotrophic receptor tyrosine kinase (NTRK) gene fusion (FDA Companion Diagnostic).

FULL PRESCRIBING INFORMATION: CONTENTS*

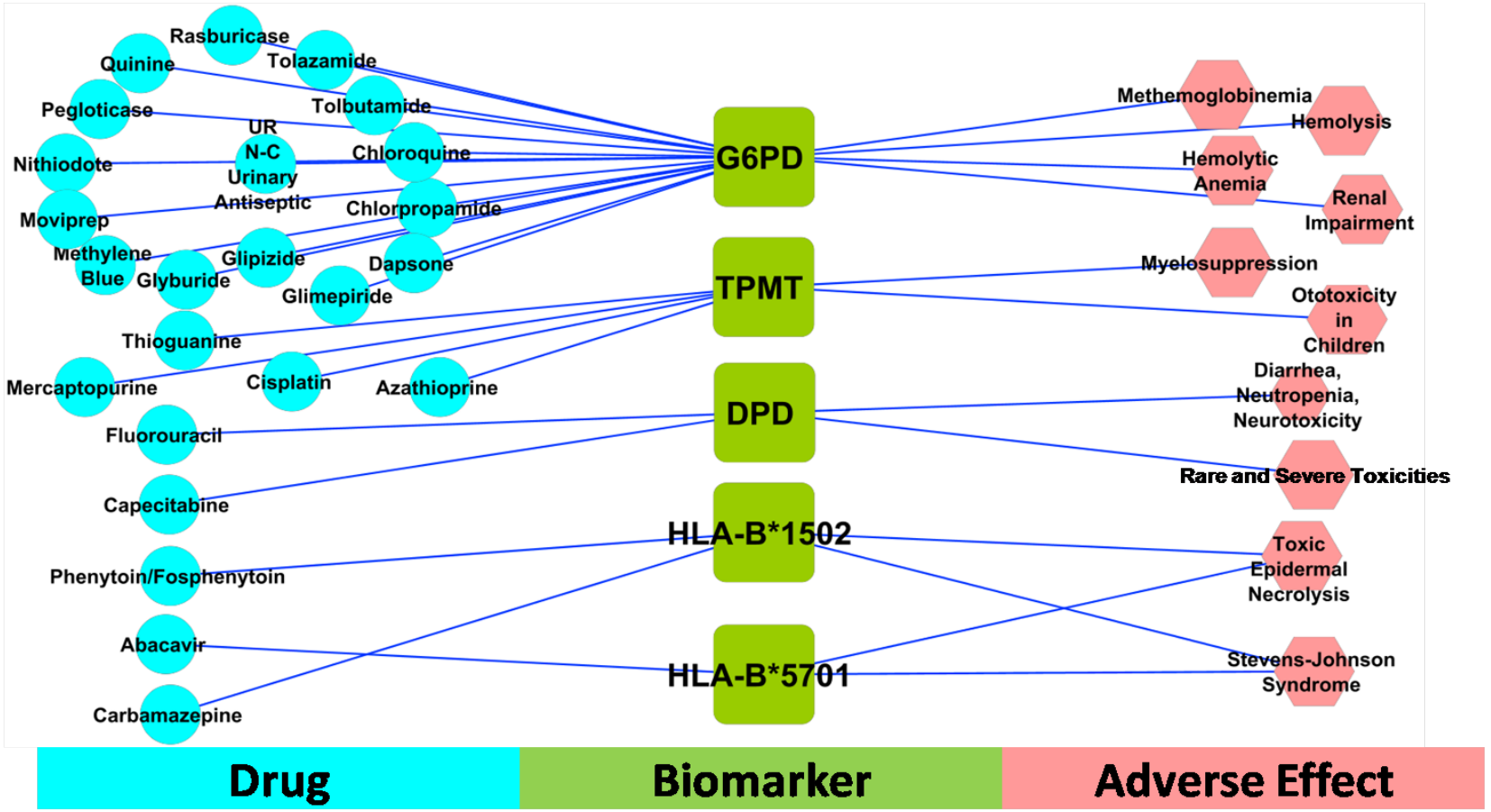
* Sections or subsections omitted from the full prescribing information are not listed.

PGx Biomarkers with Therapeutic Class



Mehta *et al*. "Study of pharmacogenomic information in FDA-approved drug labeling to facilitate application of precision medicine." *Drug Discov Today*. **2020**, 25(5):813-820. Abstract.

PGx Biomarkers for Adverse Effects



Patients who carry the HLA-B*5701 allele are at a higher risk for experiencing a hypersensitivity reaction (HR) to Abacavir®.

Fang *et al*. "FDA drug labeling: rich resources to facilitate precision medicine, drug safety, and regulatory science." *Drug Discov Today*. **2016**, 21(10):1566-1570. Abstract.

Take-Home Messages

FDALabel Applications: pharmaceutical companies for drug development, researchers for study of efficacy and drug safety, FDA for drug review

- Prescription drug labeling contains a summary of the essential scientific information needed for the safe and effective use of the drug.
- **FDALabel** is a powerful web-based database tool that allows flexible and customizable searches of human prescription drug, biological, and over-the-counter (OTC) labeling documents.
- Using **FDALabel**, information can be retrieved from drug labeling sections such as Indication and Usage, Boxed Warnings, Warning and Precautions, Adverse Reactions, and Patient Subpopulations.
- **FDALabel** is publicly available for healthcare professionals, patients, and researchers to support and advance public health.

Demo - Access FDALabel Database

FDALabel Home Page: https://www.fda.gov/fdalabeltool

FDALabel Tool Launch:
https://nctr-crs.fda.gov/fdalabel/ui/search

User Support:
Contact NCTRBioinformaticsSupport@fda.hhs.gov or
Hong Fang at Hong.Fang@fda.hhs.gov

U.S. FOOD & DRUG ADMINISTRATION

Thank you!