Cracking the Code for Clinical Pharmacology-Related Prescription Drug Labeling

Industry Perspective

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Nov 1-2, 2017

SCIENCE FOR LIFE-CHANGING IMPACT

Disclaimer

The opinions expressed in this presentation are solely those of the presenter and should not be construed to reflect the views of Pfizer or as official or unofficial FDA position.

Agenda

- Provide industry perspective on interpretation of the FDA's Clinical Pharmacology guidance.
- Describe the internal and external challenges/issues in implementing the guidance.

Clinical Pharmacology Content

Clinical pharmacology information can be presented in several sections of the US PI based on the PLR reorganization:

- Highlights
- Dosage and Administration (**Section 2**)
- Contraindications (**Section 4**), Warnings and Precautions (**Section 5**), Adverse Reactions (**Section 6**), Patient Counseling Information (**Section 17**)
- Drug Interactions (**Section 7**)
- Specific Populations (**Section 8**)
- Clinical Pharmacology (**Section 12**)

Clinical Pharmacology Section 12

12. CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

12.2 Pharmacodynamics

Cardiac Electrophysiology

12.3 Pharmacokinetics

Absorption

Food Effect

Distribution

Elimination

Metabolism

Excretion

Specific Populations

Geriatric Patients

Pediatric Patients

Male and Female Patients

Racial or Ethnic Groups

Patients with Renal Impairment

Patients with Hepatic Impairment

Pregnant Women

Drug Interaction Studies

12.4 Microbiology

12.5 Pharmacogenomics

Where We Don't Want To Go….

"Our reorganization is finally completed. Our old disorganized system has been replaced by our new disorganized system."

FDA's Guidance Documents

Clinical Pharmacology Section of Labeling for Human Prescription Drug and Biological Products — Content and Format

Guidance for Industry

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

December 2016
Labeling

Drug Interaction Studies — Study Design, Data Analysis, Implications for Dosing, and Labeling Recommendations

DRAFT GUIDANCE

This guidance document is being distributed for comment purposes only.

Comments and suggestions regarding this draft document should be submitted within 90 days of publication in the *Federal Register* of the notice announcing the availability of the draft guidance. Submit comments to the Division of Dockets Management (HFA-305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852. All comments should be identified with the docket number listed in the notice of availability that publishes in the *Federal Register*.

For questions regarding this draft document contact (CDER) Shiew-Mei Huang, 301-796-1541, or Lei Zhang, 301-796-1635.

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

February 2012
Clinical Pharmacology

FDA Guidance: Clinical Pharmacology: Format

The approach that best ensures clarity and understanding for the healthcare provider should be used.

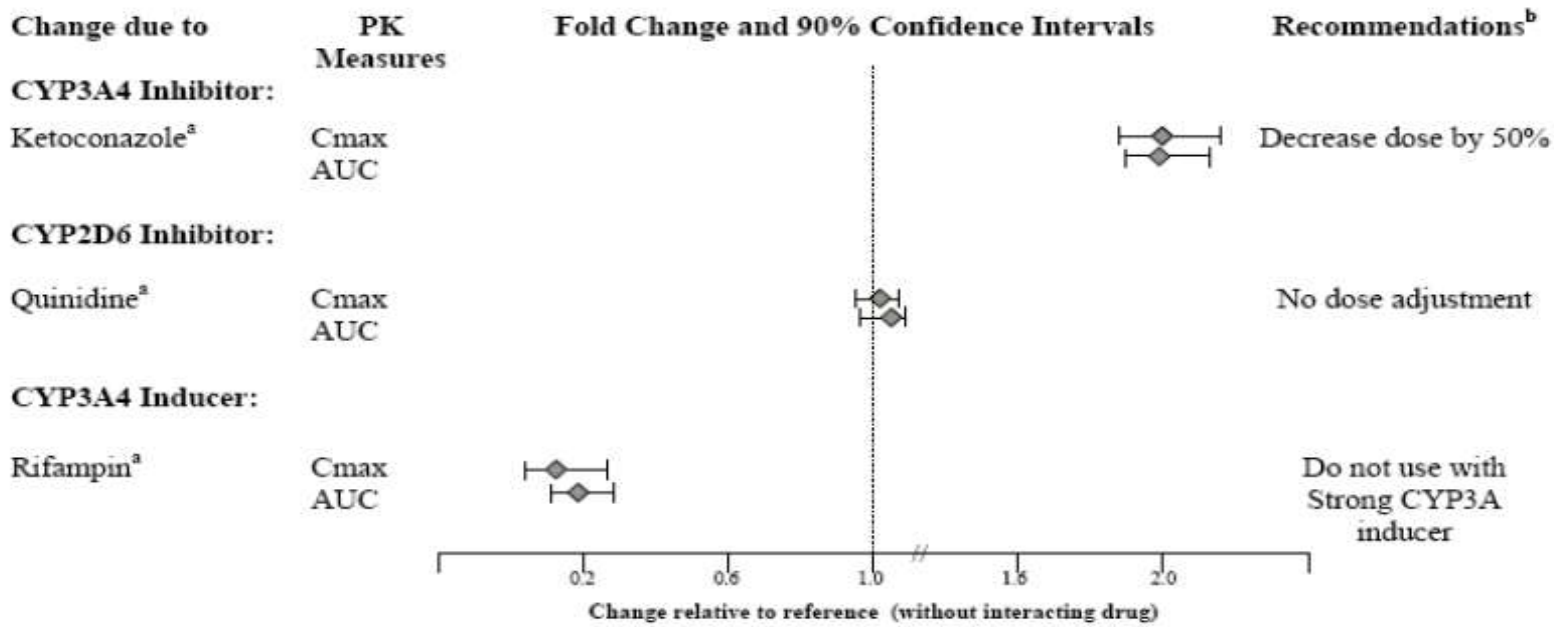
For example, general PK (e.g., linearity, accumulation, exposure parameters), absorption, distribution, and elimination information may be organized into a tabular format in lieu of text.

In addition, tables can be useful if it is important to highlight specific values or other data. Figures may be useful to show trends and presence or absence of specific phenomena, especially when absolute data values are not critical to interpretation (e.g., for some drug interactions), or to explain relationships between independent and dependent variables and time-related phenomena (e.g., exposure-response relationships, concentration-time profiles, PD endpoint dynamics). Tables and figures should be self-explanatory, clearly labeled, nonrepetitive, and consistently formatted.

FDA Guidance: Drug Interactions: Format

In the PHARMACOKINETICS subsection, a forest plot is a useful tool for presenting changes in pharmacokinetic exposure measures caused by various intrinsic and extrinsic factors such as drug interactions, hepatic impairment, and renal impairment (see Figure 8 below). The forest plot should display the fold-change in key pharmacokinetic measures such as geometric mean AUC and geometric mean C_{max} along with the 90% confidence intervals. Such graphs should clearly state the reference arm (or identify it in text accompanying the figure) and can include the doses of studied drugs, if relevant. Separate plots can display the effect of others on the labeled drug, effects of the drug on other drugs, and the effects of impaired hepatic or renal function.

Figure 8. The Effect of Various CYP Inhibitors on a Hypothetical Drug's PK as Displayed as 90% Confidence Interval of Geometric Mean AUC and C_{max} Ratios.



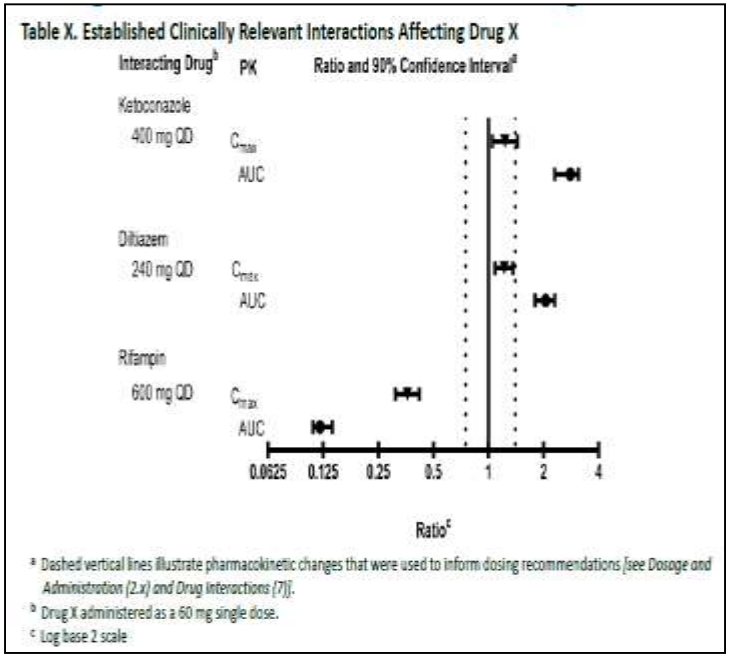
Challenges/Issues: Industry Perspective

- Forest plots are being used more commonly in the labels and they can be very helpful in presenting complex Clinical Pharmacology data.
- It may be helpful to make an effort to ensure the numbers either in the form of point estimate and 90% CI for the geometric mean ratio or percent increase or decrease in C_{max} and AUC being also presented in addition to the visual display.

Table X. Established Clinically Relevant Interactions Affecting Drugoxide

Concomitant Drug (Dosage)	Drugoxide Dosage	Ratio (90% CI) of Exposure Measures of Drugoxide Combination/No Combination [minimum to maximum][a]	
		C_{max}	AUC
Ketoconazole (400 mg once daily)	60 mg single dose	1.2 (1.1, 1.4) [0.9 to 1.9]	2.8 (2.3, 3.1) [1.9 to 4.2]
Diltiazem (240 mg once daily)		1.2 (1.1, 1.4) [0.5 to 2.9]	2.1 (1.8, 2.3) [0.9 to 3.8]
Rifampin (600 mg once daily)		0.36 (0.31, 0.42) [0.26 to 0.55]	0.12 (0.11, 0.14) [0.08 to 0.16]

[a] *[see Dosage and Administration (2.x) and Drug Interactions (7)]*

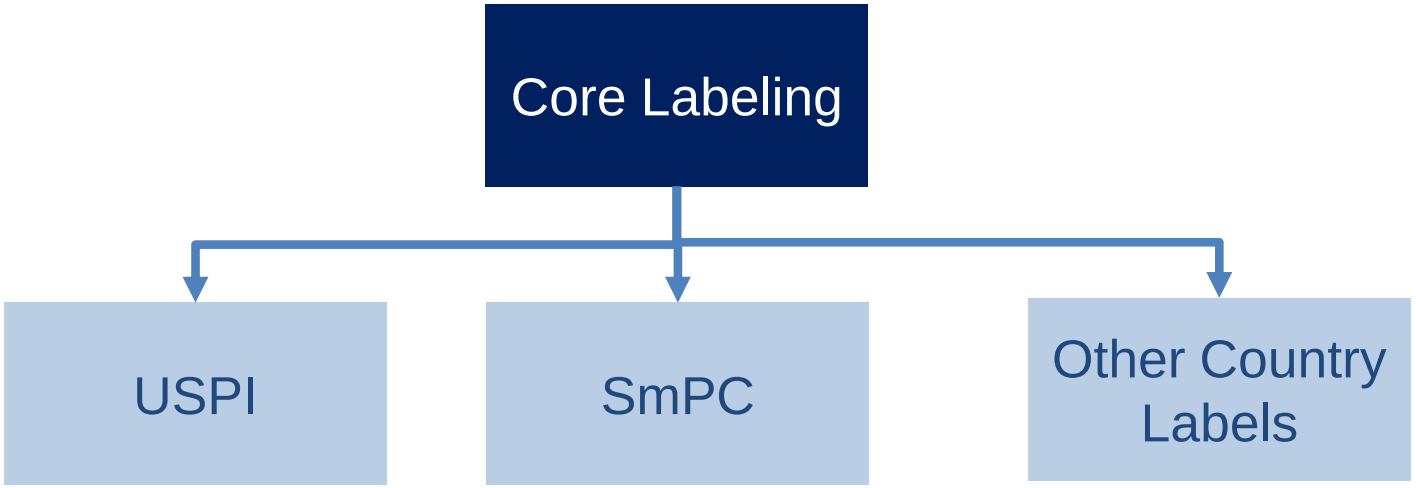


Illustrations from the FDA presentation

Challenges/Issues: Industry Perspective

Internal Implementation Challenges

1. Industry frequently needs to work on their core labeling (core datasheet), USPI and EU SmPC in parallel before a major submission in these countries
   - Need to consider their company position and the FDA and EMA requirements for every section of the label.
2. Subject Matter Experts (SMEs) within labeling teams, may miss-interpret what content goes to what section of the USPI.



Challenges/Issues: Industry Perspective

Internal Implementation Challenges

3. Same supportive studies being submitted as part of the package to HAs but different information will be presented in the US and EU.
   - One example is as simple as defining the fasting state for interactions with food.

USPI

Take Product X at least 1 hour before or 2 hours after a meal.

SmPC

This medicinal product should be taken without food. Food should not be consumed for at least 3 hours before and at least 1 hour after taking this medicinal product (see sections 4.5 and 5.2).

Challenges/Issues: Industry perspective

Internal Implementation Challenges

Another example is with Cardiac Electrophysiology:

- USPI only presented increases from baseline from a clinical study, and SmPC presented both increases from baseline and PK exposure response

USPI

Cardiac Electrophysiology

In a randomized clinical study in patients with relapsed or refractory ALL, increases in QTcF of ≥ 60 msec from baseline were measured in 4/162 patients (3%) in the BESPONSA arm and 3/124 patients (2%) in the Investigator's choice of chemotherapy arm. Increases in QTcF of > 500 msec were observed in none of the patients in the BESPONSA arm and 1/124 patients (1%) in the Investigator's choice of chemotherapy arm. Central tendency analysis of the QTcF interval changes from baseline showed that the highest mean (upper bound of the 2-sided 90% CI) for QTcF was 15.3 (21.1) msec, which was observed at Cycle 4/Day 1/1 hour in the BESPONSA arm *[see Warnings and Precautions (5.5)]*.

SmPC

Cardiac electrophysiology

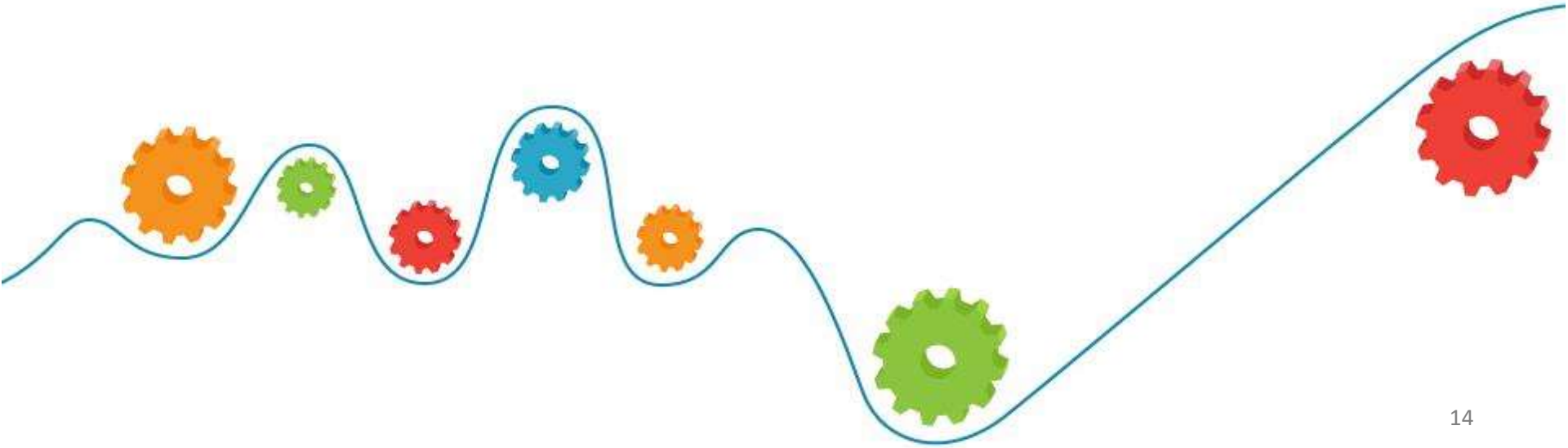
Based on a pharmacokinetic exposure-response analysis in 250 patients with relapsed or refractory ALL or other haematological malignancies who received ……., the median QTcF increased by 2.53 milliseconds (msec) from baseline (97.5th percentile: 4.92 msec) at the average C_{max} estimated for patients with relapsed or refractory ALL (371 ng/mL) and by 3.87 msec from baseline (97.5th percentile: 7.54 msec) at a 1.5 times higher average C_{max} (569 ng/mL).

In a randomised clinical study in patients with relapsed or refractory ALL (Study 1), increases in QTcF of ≥ 60 msec from baseline were measured in 4/162 (3%) patients in the inotuzumab ozogamicin arm and 3/124 (2%) in the Investigator's choice of chemotherapy arm.

Challenges/Issues: Industry Perspective

External Implementation Challenges

1. Feedback from different review divisions of the FDA and between CDER and CBER may differ at times with regards to format and content of labeling.
2. The FDA rationale for the change or the data that the FDA uses to get the numbers in the label, may not be shared with sponsors consistently.
3. Not getting enough time during labeling negotiations to understand the FDA position.



Suggestions for Future Updates to the FDA Guidance

- Provide more clarity and direction for Cardiac Electrophysiology Section (Section 12.2).
  - The central tendency findings (Change from baseline during the treatment period) versus the exposure response analysis- which one is preferred for presenting in labeling?
- More consistent use of the similar format of tables in some recent Oncology labels for interactions which helps to identify “the Clinical Impact” and also provide guidance with regards to “Prevention and Management”.

Rydapt® (midostaurin) USPI

FDA approved on April 28, 2017 for the treatment of adult patients with newly diagnosed AML.

7 DRUG INTERACTIONS

7.1 Effect of Strong Cytochrome P450 (CYP) 3A Inhibitors and Inducers

Table 6 lists the potential effects of the coadministration of strong CYP3A modulators on RYDAPT.

Table 6: Drug Interactions with RYDAPT that Affect Midostaurin

Strong CYP3A Inhibitors	
Clinical Impact	• Coadministration of RYDAPT with strong CYP3A inhibitors may increase midostaurin concentrations. The increase in midostaurin concentrations may be pronounced if strong CYP3A inhibitors are administered during the first week of RYDAPT administration *[see Clinical Pharmacology (12.3)]*. • Increased midostaurin concentrations may increase the risk of toxicity.
Prevention or Management	• Consider alternative therapies that do not strongly inhibit CYP3A activity. • Alternatively, with coadministration of RYDAPT and strong CYP3A inhibitors, monitor patients for increased risk of adverse reactions, especially during the first week of consecutive RYDAPT administration in advanced SM population, and during first week of RYDAPT administration in each cycle of chemotherapy in AML population.
Examples	Boceprevir, clarithromycin, cobicistat, conivaptan, danoprevir and ritonavir, diltiazem, elvitegravir and ritonavir, grapefruit juice[a], idelalisib, indinavir and ritonavir, itraconazole, ketoconazole, lopinavir and ritonavir, nefazodone, nelfinavir, paritaprevir and ritonavir and (ombitasvir and/or dasabuvir), posaconazole, ritonavir, saquinavir and ritonavir, tipranavir and ritonavir, troleandomycin, voriconazole
Strong CYP3A Inducers	
Clinical Impact	• Coadministration of RYDAPT with strong CYP3A inducers may decrease midostaurin concentrations *[see Clinical Pharmacology (12.3)]*. • Decreased midostaurin concentrations may reduce efficacy.
Prevention or Management	Avoid coadministration of RYDAPT with strong CYP3A4 inducers.
Examples	Carbamazepine, enzalutamide, mitotane, phenytoin, rifampin, St. John's wort[b]

[a] The effect of grapefruit juice varies widely among brands and is concentration-, dose-, and preparation-dependent. Studies have shown that it can be classified as a "strong CYP3A inhibitor" when a certain preparation was used (e.g., high dose, double strength) or as a "moderate CYP3A inhibitor" when another preparation was used (e.g., low dose, single strength).

[b] The induction potency of St. John's wort may vary widely based on preparation.

Nerlynx (neratinib) USPI

FDA approved on July 17, 2017 for the extended adjuvant treatment of early stage HER2-positive breast cancer.

7 DRUG INTERACTIONS

7.1 Effect of Other Drugs on NERLYNX

Table 7 includes drug interactions that affect the pharmacokinetics of neratinib.

Table 7: Drug Interactions that Affect Neratinib

Gastric Acid Reducing Agents		
Clinical Impact	• Concomitant use of NERLYNX with a proton pump inhibitor (PPI, lansoprazole) resulted in a decrease of neratinib C_{max} by 71% and AUC by 65% [*see Clinical Pharmacology (12.3)*]. • Concomitant use with other pH lowering agents was not studied but a decrease in neratinib AUC is also considered likely. • Decreased neratinib AUC may reduce NERLYNX activity.	
Prevention or Management	• PPIs	Avoid concomitant use [*see Dosage and Administration (2.3)*].
	• H2-receptor antagonists	Avoid concomitant use [*see Dosage and Administration (2.3)*].
	• Antacids	Separate NERLYNX dosing by 3 hours after antacids [*see Dosage and Administration (2.3)*].