UNDERSTANDING POST-MARKETING REQUIREMENTS AND COMMITMENTS FOR CYP3A-MEDIATED DRUG-DRUG INTERACTIONS: AN ANALYSIS OF FDA-APPROVED DRUGS FROM 2015 TO 2024

Jingjing Yu[1,2], Ichiko Petrie[1], Sophie Argon[1], Katie Owens[1], Isabelle Ragueneau-Majlessi[1,2]
[1]Drug Interaction Solutions, [2]Drug Interaction Science Innovation Engine, Certara

Background and Objectives

Addressing knowledge gaps at the time of a new drug approval through drug-drug interaction (DDI)-related post-marketing requirements (PMRs) and commitments (PMCs) is critical for the safe and effective use of new drug products. The objective of the present work was to review recent PMRs and PMCs related to CYP3A, the enzyme most often evaluated in post-marketing studies, to characterize the nature of the requests.

Methods

CYP3A-related PMRs, PMCs, and associated labeling recommendations were identified for small-molecule drugs approved by the US Food and Drug Administration from 2015 to 2024 using drug monographs obtained from Certara Drug Interaction Database (DIDB®, https://www.druginteractionsolutions.org/). The most recent product labels were retrieved from Drugs@FDA to assess updates of these requested studies. Drugs were categorized as CYP3A substrates, inhibitors, or inducers based on the PMR and PMC language.

Results

- Among 332 small-molecule drugs approved from 2015 to 2024, 51 drugs (15%) had CYP3A-related PMRs and PMCs, comprising 92 studies from 53 PMRs and 39 PMCs. **(Figure 1)**
- Approximately 70% of the drugs were oncology treatments, including 25 kinase inhibitors. **(Figure 2)**
- As substrates, 37 drugs had 66 requests, including 26 studies with inhibitors (all PMRs) and 40 studies with inducers (32 PMCs + 8 PMRs); 20 of these studies had the option to be performed using physiologically based pharmacokinetic (PBPK) modeling. **(Table 1)**
- As precipitants, 25 drugs had 26 requests, including 7 studies as inhibitors (all PMRs), 9 as inducers (5 PMRs + 4 PMCs), and 10 as combined inhibitors and inducers (7 PMRs + 3 PMCs), with only one option for PBPK. **(Table 2**)
- PMRs and PMCs were issued to address several clinical scenarios, most commonly requesting studies with a CYP3A substrate (N = 24) and a CYP3A moderate inducer (N = 22), followed by studies with a strong inducer (N = 16). **(Tables 1 and 2)**
- Regarding label impact, 64% of requested studies involving 24 drugs had initial labeling recommendations to manage the DDI risk in the absence of evidence. **(Tables 1 and 2)**
- Nearly 60% of these PMR and PMC studies resulted in updates to the most recent drug labels. Specifically, among the 44 drugs that originally carried *avoid co-administration* labels (32 substrates, 6 inhibitors, and 6 inducers), 21 drugs (48%; 17 substrates, 2 inhibitors, and 2 inducers) had label updates. Of these, nearly half (N = 10) were downgraded to *monitoring* or *dose adjustment*, or had the restriction removed entirely, with no remaining limitations on concomitant administration. **(Tables 1 and 2)**

Table 1. Drugs as substrates with CYP3A-related PMRs and PMCs (2015-2024)

Requested Study with CYP3A Precipitant	Number of Drugs	PMR	PMC	Study Type			Original Label Recommendation (number of drugs)	Label Recommendation Update (number of drugs) [type of update, number of drugs][2]
				clinical	PBPK	clinical or PBPK		
strong inhibitor	10	11	0	9	2	0	• Contraindication (N = 1) • Avoid co-administration (N = 4) • Dose adjustment (N =2) • No recommendation (N = 3)	• No • Yes (N = 2) [details added, N = 2] • Yes (N = 1) • No
strong (dual P-gp) inhibitor	1	1	0	1	0	0	• Avoid co-administration (N = 1)	• Yes (N = 1) [downgraded, N = 1]
moderate inhibitor	8	8	0	2	5	1	• Avoid co-administration (N = 4) • No recommendation (N = 4)	• Yes (N = 2) [details added, N = 2] • Yes (N = 4)
moderate (dual P-gp) inhibitor	3	3	0	0	3	0	• Avoid co-administration (N = 1) • No recommendation (N = 2)	• Yes (N = 1) [downgraded, N = 1] • Yes (N = 1)
inhibitor potency unspecified	3	3	0	3	0	0	• Avoid co-administration (N = 2) • Dose adjustment (N = 1)	• Yes (N = 2) [downgraded, N = 2] • Yes (N = 1)
strong inducer	16	5	11	15	1	0	• Contraindication (N = 1) • Avoid co-administration (N = 9) • Dose adjustment (N = 3) • No recommendation (N = 3)	• No • Yes (N = 3) [details added, N = 2; downgraded, N = 1] • Yes (N = 2) • No
moderate inducer	20	3[2]	19	12	6	2	• Avoid co-administration (N = 10) • No recommendation (N = 10)	• Yes (N = 4) [details added, N = 2; downgraded, N =2] • Yes (N = 8)
weak inducer	1	0	1	1	0	0	• No recommendation (N = 1)	• No
inducer potency unspecified	3	1	2	3	0	0	• Avoid co-administration (N = 2) • No recommendation (N = 1)	• Yes (N = 2) [details added, N = 2] • No

[1] Includes one post-marketing clinical DDI study which was not specified whether it was a PMR or PMC.
[2] Type of update was only added for "avoid co-administration" label recommendation.

CERTARA®

- CYP3A-mediated DDIs remain a key focus post-approval, particularly for oncology drugs.
- Post-marketing studies inform labeling updates, with nearly 60% of PMR/PMC studies leading to revisions.
- Evidence-based updates expand safe treatment options and improve access for patients with comorbidities and polypharmacy.

Want to learn more?
<< Scan Here

Conclusion

This analysis highlights that CYP3A-mediated DDIs remain a significant part of post-marketing evaluation, particularly for oncology drugs. Completion of PMR and PMC studies plays a critical role in resolving residual clinical pharmacology uncertainties and informing evidence-based labeling updates after approval. Removal or downgrading of overly conservative concomitant medication restrictions can expand access to treatment options for patients with comorbidities and polypharmacy.

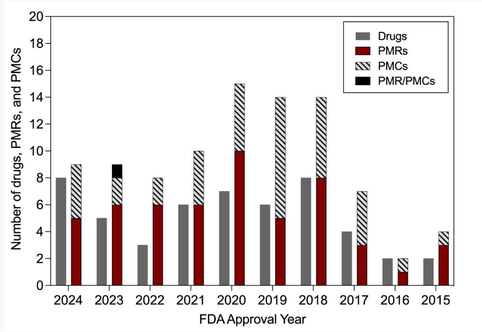

Figure 1: Number of drugs with CYP3A-related PMRs and PMCs approved from 2015 to 2024

PMR/PMCs: A post-marketing clinical DDI study was requested; however, it was not specified whether it was a PMR or PMC.

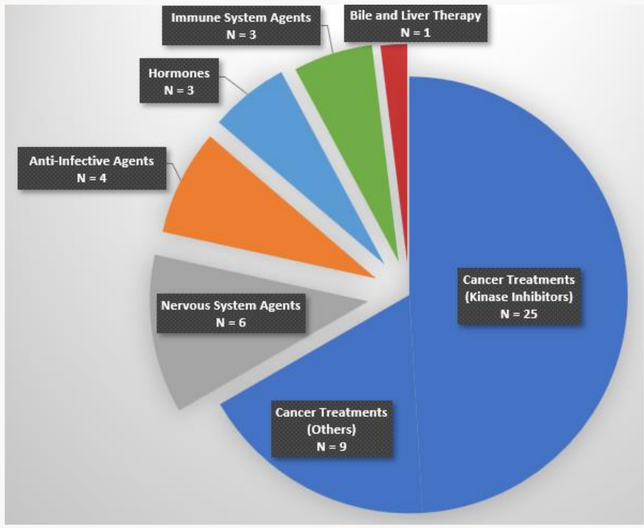

Figure 2. Therapeutic classes of drugs with CYP3A-related PMRs and PMCs approved from 2015 to 2024 (number of drugs)

Table 2. Drugs as precipitants with CYP3A-related PMRs and PMCs (2015-2024)

Requested Study with CYP3A Substrate	Number of Drugs	PMR	PMC	Study Type		Original Label Recommendation (number of drugs)	Label Recommendation Update (number of drugs) [type of update, number of drugs][1]
				clinical	PBPK		
Drugs as Inhibitors							
sensitive substrate	9	8	1	8	1	• Avoid co-administration (N = 3) • Avoid hormonal contraceptives (N = 1) • Monitor for toxicity (N = 1) • Dose adjustment (N = 2) • No recommendation (N = 3)	• Yes (N = 2) [details added, N = 1; downgraded, N = 1] • No • No • Yes (N = 1) • No
substrate sensitivity unspecified	4	4	0	4	0	• Avoid co-administration (N = 2) • No recommendation (N = 2)	• No • Yes (N = 1)
Drugs as Inducers							
sensitive substrate	8	4	4	8	0	• Avoid co-administration (N = 4) • No recommendation (N = 3)	• Yes (N = 2) [downgraded, N = 2] • Yes (N = 2)
substrate sensitivity unspecified	3	1	2	3	0	• Avoid co-administration (N = 2) • No recommendation (N = 1)	• No • No
oral contraceptives	2	2	0	2	0	• Use alternative (N = 1) • No recommendation (N = 1)	• No • No

[1] Type of update was only added for "avoid co-administration" label recommendation.