APPLICATIONS OF PBPK FOR DRUGS APPROVED BY THE US FOOD AND DRUG ADMINISTRATION IN 2023 AND 2024: A REVIEW OF DRUG LABEL CLINICAL TRIAL WAIVERS

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- The application of Physiologically Based Pharmacokinetic (PBPK) modelling in FDA NDAs was assessed across 2023 and 2024 approvals.
- A large number of label claims resulting in clinical trail waivers were observed for CYP mediated simulations, and in all cases of UGT inhibition.
- Lack of confidence in IVIVE of transporter mediated interactions highlights gaps in qualification in this field of application

Background and Objective

The reported use of Physiologically Based Pharmacokinetic (PBPK) Modelling suggests that its application in the regulatory submissions is both routine and with diverse applications with the aim of providing a mechanistic understanding of drug disposition and then applying it for clinical trail waivers[1,2]. There however remains gaps in knowledge and confidence in its use. The aim of this work was to examine the use of PBPK modelling to support novel drug therapies approval by the U.S. Food and Drug Administration across two recent years (2023 and 2024) to establish the current limitations in real world drug applications.

Methods

- U.S. Food and Drug Administration approved 55 and 50 NDAs in 2023 and 2024, respectively[2]. The clinical pharmacology reviews were accessed for each NDA and information on the application of PBPK contained within the review was assessed. Each approval was also checked against searches on The Certara Drug Interaction Solution database (CDIS, formerly known as the Washington drug interaction database, DIDB, https://www.druginteractionsolutions.org).

- The categories recorded for analyses included the therapeutic area and the specific label claims for which PBPK was applied. This included:
  - CYP-mediated DDI
  - UGT-mediated DDI
  - Other enzyme mediated DDI
  - Transporter-mediated DDI
  - Special Populations
  - Biopharmaceutics
  - Cytokine-mediated CYP suppression
  - PBPK/PD

- For each label claim, reasons for acceptance or rejection of the label claims were recorded, including software utilised, and compound files or populations utilised in the assessment.

Therapeutic Area n=31	Total Utilisng PBPK	Accepted	Not Successful
Oncology	14	10	4
Rare disease	5	3	2
Infectious disease	2	1	1
CNS	2	0	2
Cardiovascular	1	1	0
Other	7	4	3
Total	31	19	12

Table 1. Summary of Therapeutic areas for NDAs across 2023 and 2024

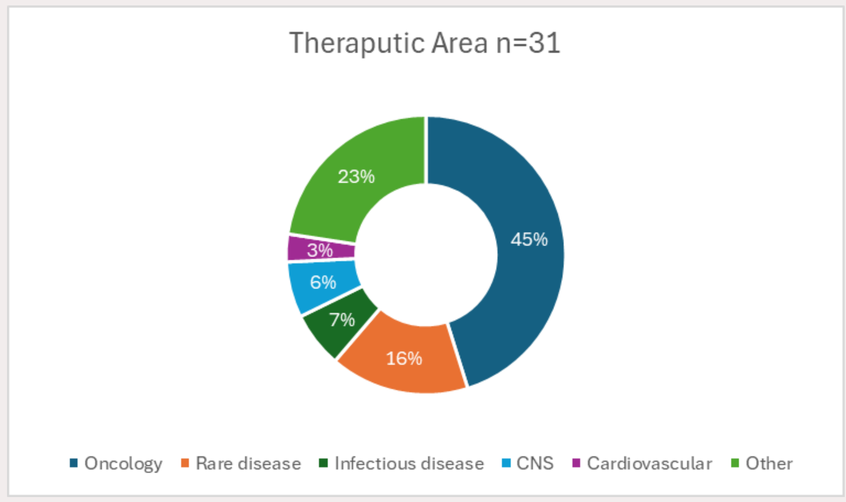

Figure 1. Summary of Therapeutic areas for NDAs across 2023 and 2024

	NDAs containing	Result, label claims, approved	Result, label claims, NOT approved	Total Label Claims
CYP-mediated DDI	21	76	36	112
UGT-mediated DDI	4	4	1	5
Other enzyme mediated DDI	0	0	0	0
Transporter-mediated DDI	6	3	6	9
Special Populations	5	4	3	7
Biopharmaceutics	1	0	1	1
Cytokine-mediated CYP suppression	0	0	2	2
PBPK/PD	1	1	1	2

Table 2. Number of accepted and rejected Label claims across applications of PBPK in NDA submissions

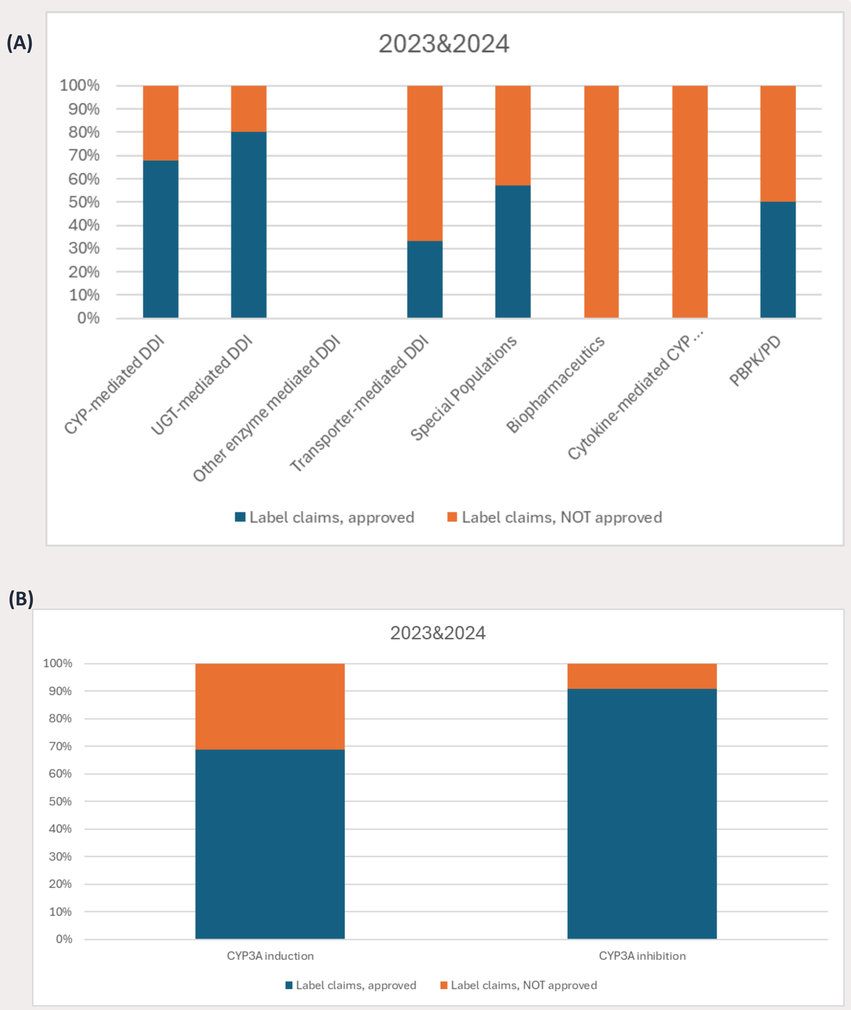

Figure 2 Summary breakdown of accepted and rejected label claims across 2023 and 2024 across PBPK applications (A), and CYP3A4 induction and inhibition (B)

Results

NDA analysis

The application of PBPK modelling was recorded in 31 (30%) of approved NDAs (20 and 11 cases for 2023 and 2024, respectively). Out of the 31 cases, 19 (61%) had an accepted PBPK model informed label claim in the final drug approval (Table 1, Figure 1).

In total 60 label claims were associated with the approved NDAs in 2023 and 2024. The overwhelming majority of these label claims were related to PBPK model simulations related to CYP-mediated DDIs accounting for 86% of total accepted claims (Figure 2a). In total, 76 of CYP-mediated DDIs sponsor claims were accepted by the reviewers (68% of all CYP-mediated DDI claims). These included 22 cases examining CYP3A4 induction and 39 cases examining CYP3A inhibition. Efavirenz and rifampicin were the most commonly used CYP3A4 inducers, whereas erythromycin and itraconazole were the most routinely used CYP3A4 inhibitors in accepted label claims. However, if the applicant's model was an inducer, these label cases were rejected even in the case of CYP3A due to uncertainty of induction parameters. Uncertainly of fm, particularly of non-CYP3A additional clearance pathways resulted in non-approval.

For CYP3A4 81% of label claims were accepted with the rejection of label claims occurring within 14 cases (Figure 2b). . Although the number of PBPK models examining UGT drug interactions was low (n=5) the acceptance of these models was high (80%) when inhibition was considered. The use of the model to examine UGT induction was not accepted. CYP and UGT metabolism were the only elimination routes for which PBPK waivers were applied.

Transporter mediated DDIs PBPK simulations were applied in 7% of the total applications and were accepted in 3 label claims. Acceptance was achieved using the BCRP substrate rosuvastatin and the P-gp substrate digoxin. However, there were rejections based on uncertainties IVIVE extrapolation of OATP1B1, MATE/OCT or BCRP inhibition.

Label claims in Specific populations

As well as DDI in healthy adults PBPK model claims were accepted in mild and moderate Cirrhosis populations for elacestrant. DDI simulations were also accepted using Cancer populations in the cases of lazertinib and vorasidenib. The impact of CYP3A4 ontogeny of exposure was accepted in paediatric populations in two drug labels (Revumenib and . vanzacaftor, tezacaftor, and deutivacaftor combination).

Conclusions

- Overall, this analysis highlights the current status of acceptance of PBPK models in clinical trial waivers.
- Given the reported trends of use of PBPK in regulatory submissions, it was relatively surprising that the number of NDAs utilizing PBPK in 2024 was low (n=11).
- Confidence in the fraction metabolized (fm) of the PBPK model compounds, particularly major non-CYP3A pathways as well as extrapolation of induction and transporter DDI highlight areas where confidence in applications of PBPK require maturation.

References

1. Sun et al., Eur J Pharm Sci. 2024 Sep 1;200:106838
2. Zhang et al., . J Clin Pharmacol. 2020 Oct;60 Suppl 1:S160-S178. Apr;42(4):107-117.
3. https://www.fda.gov/drugs/development-approval-process-drugs/novel-drug-approvals-fda

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