Assessing the risk of adverse drug reactions through *safety margin analysis*: Methodologies and applications in polypharmacy

Authors: Catherine Noban[1], Danielle Thomas[2] and Olivier Barberan[1]

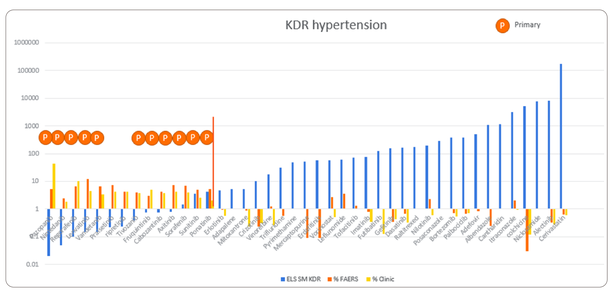
Affiliations: 1. Elsevier Life Sciences Solutions, Radarweg 29, Amsterdam 1043 NX, the Netherlands, 2. Elsevier Inc, 525 B St Suite 1800 San Diego, CA 92101

Introduction

Unexpected toxicity has become a significant obstacle to drug candidate development, accounting for 30% of drug discovery failures [1] and 3.5 million physician office visits in outpatient settings [2]. In vitro pharmacological profiling is used by most of pharmaceutical companies as a tool to detect off-target activity, used in early stage of drug discovery [3]. However, screening alone is insufficient to quantify safety risk [4].

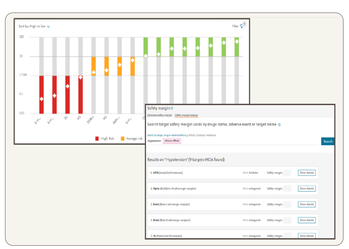
By developing a knowledgebase for many marketed drugs in terms of their clinical adverse drug reactions, therapeutic free exposure and in vitro target data for well-established off-target panels [5-7], PharmaPendium Safety Margin Tool supports the understanding of clinical exposures required to drive target effect and associated risk assessments to ensure patient safety.

Using safety margins and ADR incidence to guide drug selection: Determination of target safety assessment using statistical methods



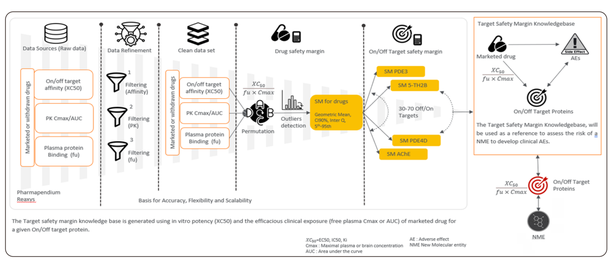
Application of safety margin concept in secondary pharmacology risk assessment

- Predict and compare safety margins across compounds to support lead selection and optimization in early stages-and optimize dosing regimen at later stages
- Troubleshooting the observed adverse effects/toxicities by providing mechanistic understanding (Polypharmacy)



Safety margin tool: Method to assess target safety margin (TSM)

- A method was developed to systematically and at large scale estimate the safety margin across a diverse range of off-targets, including GPCRs, kinases/enzymes, ion channels, and nuclear receptors, transporters.
- In vitro affinity data for well-established safety pharmacology off-target panels [5-7] for typically on-target drugs have been retrieved and refined from articles and patents. The representative drugs' associated clinical exposure data (Cmax, AUC, fu) have been selected and filtered, mainly from regulatory pharmacokinetic data to reflect their free therapeutic exposures.
- A permutation-based uncertainty analysis using refined parameters of IC_{50}/EC_{50}/Ki, Cmax/AUC and plasma binding data was then performed to estimate the individual drug Safety Margins and subsequently Target Safety Margins using different statistical approaches.



References

1. Bai C.et al. Adv. Sci., 2025; 12 (16), art. no. 2413405.
2. Howard I., et al. Sci Rep. 2022; 12 (1), 2622.
3. Valentin J.-P. et al. J Pharmacol Toxicol Methods. 2018; 93, 7-14.
4. Urban L, et al. Drug Discov. Today; 2016; 21: 8: 1232-1242.
5. Brennan R, et al Nat Rev Drug Discov. 2024; 23: 525–545.
6. Bowes J, et al. Nat Rev Drug Discov. 2012;11(12):909-922.
7. Lynch JJ 3rd, et al. J Pharmacol Toxicol Methods. 2017; 87: 108-12.
8. Sutherland, J.J. et al. Nat Commun; 2023;14, 4323.

Target coverage

The Safety Margin Tool currently includes **77 off-target data** including mechanism of action (MOA) using well-established secondary pharmacology target assessment panel [5-7] covering a broad diversity of targets:

Kinase inhibitors	ErbB, FGFR1, KDR, Kit, Lck, Src, TRK-A, VEGFR 1
Other enzyme inhibitors	Ache, Cox1, Cox2, MAO-A, PDE3A, PDE4D, MAO-B, ACE
Transporter inhibitors	BSEP, DAT, NET, SERT, VMAT2
Nuclear receptors	GR agonist, AR antagonist, PPAR-γ agonist, ER agonist, ER antagonist, PR agonist, PR antagonist
Ion channels	Blockers: Cav1.2, hERG, 5-HT3, Nav1.5, NMDA, KCNQ1/KCNE1, KATP, GABA-A Openers: GABA-A and nAChR alpha4
GPCR antagonists	5-HT1B, 5-HT2A, 5, Alpha-1A, Alpha-2A, Beta-1, Beta-2, DOR-1, MOR-1, D1, D3, H1, M1, M2, M3, A2a, AT1, D2, ETA, H2, V1A, CGRP, ETB, 5-HT2C, 5-HT7, NK-1
GPCR agonist	5-HT2B, Beta-2, KOR, MOR, 5-HT1A, 5-HT2A, CB1, CB2, D2, Alpha-2A, MT2, MC4, V1A

Methodologies tested for target safety margin (TSM) estimations

The current method using Median as TSM and an empirical 10 times the Median as a buffer zone (mid- risk) has a risk of false positive flagging. We aimed, therefore, to develop a new methodology to quantify and improve potentially the method to reduce both the risk of false positive and false negatives.

Using published data [8], **75 drugs not included in the available target cards** as positive controls and inactive results on the same drugs, several methods/models have been tested for Recall, Precision, Accuracy and Specificity:

1. Median (TSM)
2. Median (TSM)-Median*10 (Current Method)
3. Median(TSM)-Q3 (Relaxed) –with Q3 as upper boundary of Mid risk zone.
4. Q3(TSM) – Q3*10 (Conservative)- with Q3*10 as upper boundary of Mid risk zone

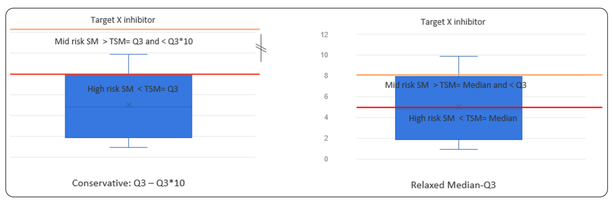
	Total	True Negative	True Positive
Drugs	75	73	65
Tagret MOA	51	48	13
Targets	44	42	12
Data points (drug safety margin)	304	224	80

Preliminary results

Models	Recall	Precision	Accuracy	Specificity
Median (TSM)	43%	85%	83%	97%
Median (TSM)*10 (Current buffer)	75%	65%	83%	85%
Median (TSM)-Q3 (Buffer relaxed)	56%	88%	87%	97%
Q3 (TSM)*10 Buffer) (Conservative)	85%	57%	79%	77%

New methodology for Target Safety Margin (TSM) estimations

- Median(TSM)-Q3 (Relaxed) –with Q3 as upper boundary of Mid risk zone.
- Q3(TSM) – Q3*10 (Conservative)- with Q3*10 as upper boundary of Mid risk zone



Conservative and relaxed assessment: Impact on drug development

Conservative assessment (Q3 – Q3*10)

- **Minimizing false negatives** (compounds incorrectly predicted as negatives "low safety risks") results in minimizing high–mid risk compounds **to go through the development**.
- Therefore, reducing the **risk of decreased productivity and higher costs** associated with allowing too many potentially unsuccessful compounds to go through the lead selection process.

Relaxed assessment (median–Q3)

- **Minimizing false positives** (compounds incorrectly predicted as positives "high/mid safety risks"), results in minimizing elimination of potentially successful compounds.
- Therefore, decreasing the **risk of eliminating promising candidates** and **associated investments/impact on business**.

Conclusion

- In the early phases of drug development, Safety Margin tool helps identify potential safety risks before they become major issues by supporting lead selection and optimization, using in vitro target and clinical free exposure data on similar marketed/withdrawn drugs.
- It also enhances the mechanistic understanding of observed adverse effects/toxicities to support further hypothesis generations and design of in vitro/in vivo experiments. The tool aims to provide insights and practical applications for improving drug safety, particularly in the context of polypharmacy for well-established off-targets.

Copyright © 2026 RELX Intellectual Properties SA. All rights reserved.
PharmaPendium, RELX Group and the RE symbol are trademarks of RELX Intellectual Properties SA, used under license.