

Shaping secondary pharmacology panels of the future: evolving target selection criteria for safety panels



We appreciate the thoughtful commentary by Maciag and Karamyan¹ on our 2024 publication ‘The state of the art in secondary pharmacology and its impact on the safety of new medicines’². In this paper, we reviewed secondary pharmacology data and profiling strategies from 18 pharmaceutical companies and recommended the implementation of an expanded core safety panel consisting of 77 diverse targets (Safety-77). The main aim of such screening panels is to identify potential human safety liabilities of novel molecules across all indications and chemotypes. To serve its purpose, the panel was balanced with respect to diversity of target families and mechanisms of toxicities, but it was also kept feasible with respect to its size.

Maciag and Karamyan highlight the underrepresentation of non-kinase enzymes in our recommended assay panels and suggest the consideration of non-kinase enzymes such as neprilysin, cathepsins, carbonic anhydrases, thromboxane A synthase and xanthine oxidase due to risks of adverse events associated with activity against these enzymes. [Studies by regulatory agencies](#) have shown that inhibition of enzymes could be implicated in adverse events and that enzymes have comparable or higher hit rates than other targets (see Related links).

Earlier panels^{3–6}, including the widely adopted Safety-44 panel³, incorporated a very limited number of enzymes, which is disproportionate to their prevalence in the pharmacological actions of drugs approved during the last decade⁷. As shown in Fig. 1a, 31 unique side-effect targets have been added to the Safety-77 panel. They primarily enrich poorly populated families such as enzymes, including kinases, proteases and bromodomain-containing proteins, but also nuclear receptors, which can affect reproductive toxicity. Consequently, the Safety-77 panel expands both target family coverage (Fig. 1b) and target organ coverage (Fig. 1c) substantially compared to the Safety-44 panel. This shift better reflects the weight of enzymes and

other target families in the drugged pharmacology space. The Safety-77 panel also expands its predictive capabilities for potential drug side effects compared to the Safety-44 panel, which has a very narrow focus on safety pharmacology organ systems specified by the ICH S7A guideline⁸. The Safety-77 panel ensures a more comprehensive assessment of potential safety risks, addressing gaps in the ICH S7A core battery and follow-up organ systems.

Continued review and refinement of the link between pharmacological targets and nonclinical and human safety liabilities is necessary to further improve preclinical safety screening. A call to rebalance the representation of enzymes and other target families in core safety panels is justified and highlights a need for a more formal approach to target selection. We recommend applying a framework of five criteria to identify core safety targets for broad safety screening:

- (1) **Human clinical translatability:** human side effects have either been clinically demonstrated by molecules with activity against the target or have a high probability of manifesting based on preclinical observations in relevant systems supported by other evidence (such as human genetic or disease association data).
- (2) **Severity:** exposure-limiting adverse effects are mechanistically explained and causally related to the target.
- (3) **Promiscuity of target–drug interactions:** unintended interaction is expected for a meaningful proportion of drug candidates ($\geq 5\%$).
- (4) **Structural diversity:** target interactions are distinct and cannot be anticipated from interactions with structurally related targets.
- (5) **Availability of a reliable, robust assay:** pharmacologically relevant drug–target interactions must be detected reproducibly.

Adoption of such a framework would help align researchers, drug developers and

regulators in the continuing improvement of safety assessment practices. Although the use of secondary pharmacology profiling is recommended in most safety-related (S) [ICH guidelines](#) (see Related links), most of the operational details are absent. Targets of concern have rarely been specified, except for cardiac ion channels in the ICH S7A and ICH S7B guidelines⁸ and the FDA guidelines for drug abuse (see Related links). Nevertheless, secondary pharmacology practice is gaining momentum. In addition to bespoke core safety target panels, specialized panels address specific target-organ risks of drug candidates, particularly in areas with highly specific but meaningful risks that are incompletely met by current core safety panels. The additional targets included in investigative, target-organ or side-effect tailored panels may not always fulfill all of the above selection criteria. Tailored panels are not limited to cardiac safety risk assessment, but are also considered highly informative, supportive data for drug abuse liability, carcinogenicity, developmental and reproductive toxicity, and seizure disorder risk assessments^{9,10}. For each of these, emphasis is placed on multiple target families; for example, activity at specific nuclear receptors involved in tumour formation, or modulation of centrally expressed ion channels for seizure development (Fig. 1d). This approach aligns with ICH and FDA guidelines and promotes innovation in panel development, data collection and analysis.

We acknowledge the need to further refine and evolve secondary pharmacology target coverage, adverse effect translatability, result contextualization, and data reporting to regulators, and we support initiatives for their harmonization. A stronger focus on human-based in vitro secondary pharmacology assessments will help to modernize drug development while adhering to [3Rs principles](#) and aligning with emerging legislation both by [FDA](#) and by the [European Commission](#) (see Related links). Collaborative efforts between the pharmaceutical industry, service and

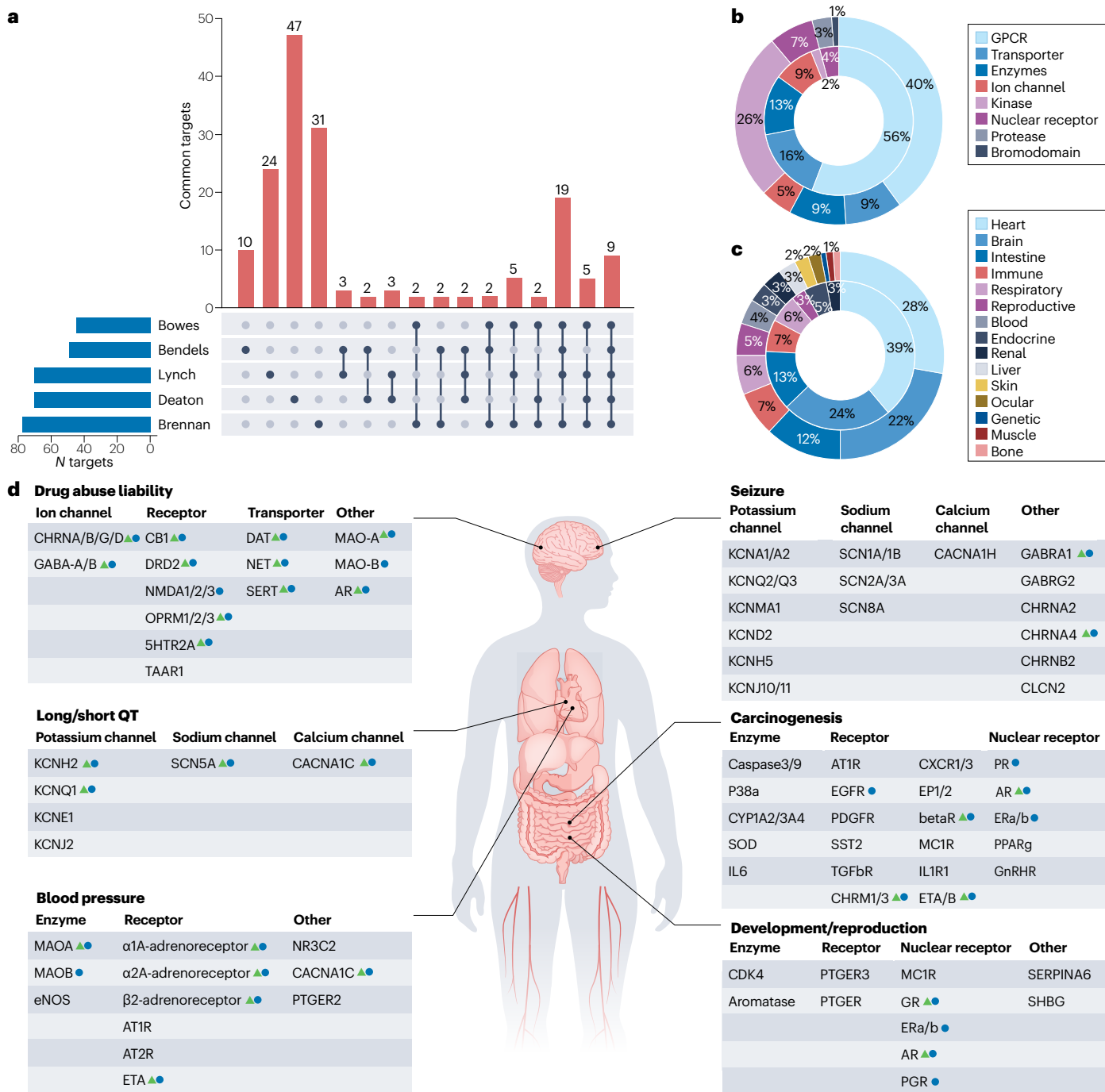


Fig. 1 | Coverage of the Safety-77 panel. **a**, The panel of 77 targets proposed by Brennan et al.² adds 31 unique targets to earlier panels. The Safety-44 panel proposed by Bowes et al.³ overlaps quantitatively by using a similar framework of target credentialing, in contrast to panels proposed by Bendels et al.⁴, Lynch et al.⁵ and Deaton et al.⁶. **b**, The Safety-77 panel (outer circle) contrasts with the Safety-44 panel (inner circle) with its much greater emphasis on kinases (26% of 77 targets compared with 2% of 44 targets), and also adds other enzymes such as proteases. **c**, While the Safety-44 panel (inner circle) targets are mostly

addressing side effects in core safety pharmacology organs as per the ICH S7A guideline (heart, brain, gastrointestinal system), the Safety-77 panel (outer circle) adopts a more diverse coverage of target organs. **d**, Safety-44 targets (green) and Safety-77 targets (blue) intersect particularly well with drug abuse potential (supportive of dedicated FDA guidance; see Related links), long/short QT effects (ICH E14/S7B) and blood pressure (see Related links), while the overlap with other specific target organ effects such as seizures, carcinogenicity (ICH S1B R2) and developmental and reproductive effects (ICH S5) is incomplete.

technology providers, academics, and regulators will be required to refine and implement this framework, to ensure the safety of new therapeutic agents.

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Competing interests

F.S. and J.-P.V. are employees of pharmaceutical companies. S.J. is an employee of Metrion Biosciences, a CRO providing screening services to pharmaceutical companies. F.S., R.J.B., S.J. and J.-P.V. may hold shares, share rights and/or stock options in pharmaceutical companies.

Related links

Assessment of Pressor Effects of Drugs Guidance for Industry | FDA: <http://www.fda.gov/media/113477/download>
Commission acts to accelerate phasing out of animal testing in response to a European Citizens' Initiative (accessed on 21 January 2025): https://ec.europa.eu/commission/presscorner/detail/en/ip_23_3993

FDA Guidance for Industry on the Assessment of Abuse Potential of Drugs: <https://www.fda.gov/media/116739/download>

H.R.7248 - FDA Modernization Act 3.0. 118th Congress (2023–2024) (accessed on 21 January 2025): <https://www.congress.gov/bills/118th-congress/house-bill/7248>

Official webpage of the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH): <https://www.ich.org/page/safety-guidelines>

The principles of the 3Rs (replacement, reduction and refinement): <https://www.nc3rs.org.uk/who-we-are/3rs>
The Translational Value of Secondary Pharmacology Binding Assays for Nonclinical Findings: <https://www.fda.gov/media/168854/download>