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Safety differentiation: emerging competitive edge in drug development

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With increasing expectations to provide evidence of drug efficacy, safety, and cost-effectiveness, best-in-class drugs are a major value driver for the pharmaceutical industry. Superior safety is a key differentiation criterion that could be achieved through better risk:benefit profiles, safety margins, fewer contraindications, and improved patient compliance. To accomplish this, comparative safety assessments using innovative and adaptive nonclinical and clinical outcome-based approaches should be undertaken, and continuous strategic adjustments must be made as the risk:benefit profiles evolve. Key success criteria include scientific expertise and integration between all disciplines during the full extent of the drug development process.

Differentiation is a key value driver

The competitive landscape of pharmaceuticals is more crowded than ever before. Approximately 60% of a specific drug target in active preclinical and clinical phases is being pursued by more than one company, whereas 88% of validated targets (for which at least one drug is already approved) is being pursued by multiple companies [1]. In addition to fierce competition, drug development is also becoming more challenging, with increasing requirements from health authorities and mounting pressure from payers and pricing governance to demonstrate the unique value of each new drug. For these reasons, there has been much debate about how pharma can continue to thrive, and whether a first or best-in-class strategy will lead to success. An analysis by The Boston Consulting Group in 2013 suggested that the first-in-class drug candidates have a higher value than the best-in-class [2], whereas a follow-up analysis by McKinsey in 2014 showed that context makes a significant difference [3]. Yet, an older analysis by Booth and Zemmel, in 2003 [4], showed that first-in-class drugs have not created more value than their follow-on counterparts because they are able to differentiate themselves through improved drug development strategies.

There is no doubt that a first-in-class drug can be of high value if there are no existing therapies for the disease it intends to treat. In this case, superiority in efficacy and safety over placebo are the only differentiation requirements. However, often there is a standard of care (SoC) available to which the test compounds has to show superiority to convince regulators and payers [5]. Furthermore, the value might also be hampered by high development costs for validating a novel target. By contrast, follow-on drugs have the downside of limitations in the patent space and fierce competition in the market, but have the potential upside of an easier and less resource intensive development path because they can leverage knowledge of the predecessors. Moreover, the path to best-in-class can also boost innovation, leading to improved preclinical risk mitigation and quicker development times. Thus, a key value driver in the pharmaceutical industry is not only whether the drug is potential first-in-class, but also how well the drug

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might be differentiated from existing therapies. In this review, we highlight the safety differentiation concept by providing examples from post-marketing evidence and possible development approaches. Although our intent is not to describe drug development in breadth and depth, we aim to trigger future discussions and analysis on this topic by the pharmaceutical community.

Safety-driven differentiation

The concept of differentiation through efficacy or convenience is well established in the clinical setting, but safety is also a key advantage for patients, and the need for safety-driven differentiation is particularly gaining traction with the increasing number and complexity of new therapies. There are several historical examples where safety was the dominant driver for differentiation within the same drug class, comprising drugs with similar mechanism of action with or without a similar chemical structure. A drastic example with major differences in safety is the thiazolidinedione class of compounds developed for treatment of type 2 diabetes mellitus. Despite their common mechanism of action and closely related chemical structures, their receptor-binding affinities and, consequently, their unique safety profiles differ [6]. Troglitazone was withdrawn from the market because hepatotoxicity, whereas rosiglitazone was withdrawn from some markets because of cardio- and cerebrovascular events, and pioglitazone has been associated with increased incidences of bladder cancer, although the causal relationship remains controversial [7]. Although these thiazolidinediones have different serious adverse drug reactions (ADRs), no alternative emerged from this chemical class with a cleaner safety profile. However, this is not always the case, as demonstrated by the structurally similar Cox-2 inhibitors rofecoxib and celecoxib, where the former was removed from the market because of cardiovascular risk, whereas the latter has been demonstrated to be safe in the same patient population [8,9]. The original intent to develop first-in-class selective Cox-2 inhibitors was their expected improved gastrointestinal (GI) and renal safety profile compared with nonselective Cox enzyme inhibitors. Indeed, a recent major safety comparison study of patients with osteoarthritis and rheumatoid arthritis (RA) showed that celecoxib results in fewer GI and renal safety liabilities compared with the nonselective and structurally different Cox-1/2 inhibitor ibuprofen [10].

Another example of safety differentiation by chemical modifications are amiodarone [approved by the US Food and Drug Administration (FDA) in 1962] and its chemical derivative, dronedarone (approved in 2009), both developed for the treatment of atrial fibrillation. Whereas amiodarone is more efficacious and more toxic, dronedarone is less efficacious but safer and, thus, is used as a first-line therapy with the exception of patients with decompensated chronic heart failure, structural heart disease, permanent atrial fibrillation, and not receiving digoxin [11,12]. The improved safety of dronedarone is largely attributed to avoiding iodine moieties that are present in amiodarone and responsible for toxic effects on the thyroid, lung, liver, and skin. Importantly, however, dronedarone does not have a clean cardiac safety profile, as reflected by the narrow target patient population described above [13]. Finally, an example of a minimal chemistry change for improved safety profile is the newly approved deutetrabenazine developed for the treatment of Huntington's chorea. In this case, the only change from the predecessor tetrabenazine is the replacement of hydrogen with deuterium. The use of the 'heavier hydrogen isotope', deuterium, makes the chemical bond breaking during metabolism slower and, thus, provides a dosing advantage and improved safety profile [14]. Taken together, the examples demonstrate that first-in-class drugs could carry the danger of unexpected adverse events, and that the development of safer alternatives is not straight forward with regards to either chemistry or target selection. A drug class comprising the same mechanism of action, but with different or similar chemical structures, can result in large safety differentiation opportunities either in terms of different, or in mitigation of the same organ toxicities.

Whereas liver and heart are the most frequently reported target organs of drug-induced toxicities post marketing, the nervous system has shown to be particularly challenging as a target for development of efficacious and safe drugs [15–17]. In terms of safety differentiation challenges for drugs in neurology, the crux is often related to target specificity and/or to enable preferential delivery to either the peripheral or central nervous system (CNS) [18,19]. The first generation of antihistamine drugs acting on the H1 receptors are associated with several CNS adverse effects, such as sedation, coordination issues, dizziness, inability to concentrate, and paradoxical reactions in children and older patients [20]. An important determinant of these effects is related to the high level of CNS penetration, poor receptor selectivity, involving antimuscarinic, anti-α-adrenergic, antiserotonin effects, as well as serotoninergic transmission [20,21]. However, by reducing their ability to cross the blood–brain barrier (BBB), second-generation antihistamines are devoid of significant CNS adverse effects [20]. Another example are the tricyclic antidepressants (tCAs), which have in general been replaced by the selective serotonin reuptake receptor inhibitors (SSRIs) as first-line treatment for depression, because of improved safety profiles [22]. Although both of these drug classes must pass the BBB to act on their respective therapeutical targets, tCAs bind additional targets affecting sodium, cholinergic, adrenergic, and histamine signaling, which are associated with their serious adverse effects and narrow safety margin in overdose and require titration upon start of treatment situation [22]. However, the benefit:risk ratio depends on the indication it intends to treat, and tCAs are, for instance, often considered as first-line treatment for neuropathic pain because of their additional pain-modulating effects and lack of better alternatives [23]. The crucial question is whether it is possible to develop effective drugs for the treatment of chronic neuropathic pain that are devoid of CNS adverse effects, such as sedation and addiction, thereby also curbing the opioid crisis. Indeed, there are recent advances with the discovery of so-called 'biased-agonists' of micro-opioid receptor (MOR) that lack adverse effects, such as constipation and respiratory depression, as demonstrated in mice [24]; however, these might not necessarily prevent abuse potential. By contrast, a novel opioid, BU08028 (University of Bath), which shows a similar binding profile to MOR as buprenorphine, but with improved efficacy at the nociceptin opioid peptide (NOP) receptor, which blocks addictive effects, has shown promising nonclinical development with a lack of abuse potential in nonhuman primates [25]. Finally, but importantly, recent research has also demonstrated

that the peripheral nervous system might have a more important role in pain sensation than previously thought, thereby opening the door for the development of new peripherally acting therapeutics devoid of CNS adverse effects [26–28]. Although many of the novel targets for human analgesic intervention remain hypothetical, they fuel the pharmaceutical pipeline with alternative therapeutic options that require, as seen with the above examples, thorough pharmacodynamics (PD) and pharmacokinetics (PK) evaluation for balanced efficacy and safety.

Other examples of safety differentiation opportunities include the importance of understanding drug–drug interactions (DDI), vulnerable patient populations, as well as comorbidities of SoC adverse effects and disease. The risk for DDI might be higher in geriatrics because of the larger number of drugs often used, and patients who are critically ill in intensive care units because complexity of pharmacotherapy combined with disease severity [29]. With regards to potential comorbidities of SoC adverse effects and disease, rheumatoid arthritis (RA) might serve as an important example. RA is associated with increased risk of infection, cardiovascular events, and GI ulcers and cancer [30], and many of the current therapies for RA have safety liabilities that can exacerbate these complications [31]. For instance, the disease-modifying therapies comprising biologics (currently mostly anti-TNFs administered intravenously) increase the risk of severe infections because of immunosuppression that can persist long after treatment has been stopped. Glucocorticoids are associated with increased blood pressure, elevated cholesterol levels, and hyperglycemia, whereas the nonsteroidal anti-inflammatory drugs have an increased risk of GI ulcers and cardiovascular risk. Hence, there is an overlap between some of the comorbidities and the therapies, which can be challenging when evaluating the risk:benefit ratio. However, there are several exciting opportunities in the field of RA. The subcutaneously administered IL-6 antibody, sarilumab, developed by Sanofi/Regeneron and approved for RA in 2017, might offer advantages to the SoC, although some adverse effects of immunosuppression have been shown [32]. The oral small-molecule JAK-3 inhibitor, tofacitinib, developed for RA by Pfizer and approved in 2012, also shows immunosuppressive effects [33]. However, it has a significant advantage in the clinical management of RA because the immune system recovers more rapidly after stopping the treatment compared with the intravenously or subcutaneously administered biologic, anti-TNF-α. Thus, not surprisingly, further oral JAK inhibitors are currently in development [34]. The JAK1-2 inhibitor, baricitinib, developed by Incyte/Eli Lilly, recently received approval in Europe, although is pending in the USA. The JAK-1 inhibitors, filgotinib, developed by Galapagos, and upadacitinib, developed by AbbVie, as well as the JAK-3 inhibitor, peficitinib, developed by Astellas, are also in clinical Phase 3 development. Thus, safer therapeutic alternatives, with hopefully fewer comorbidities, are on the horizon for RA.

Drug development approaches

The first challenge in a drug development program is to identify relevant therapeutic targets, which requires a thorough understanding of the molecular pathways of the disease and the relevance of the target to human physiology and safety. As a start, a hypothesis of the role of the target in pharmacology and safety is created. Thereafter, a target validation process ensues, where benefit and limitations in safety and efficacy are explored and compared with other target alternatives. To this end, access to human tissue, stem cell biology, genome editing, and phenotypic screening are some of the many crucial elements. However, pharmacovigilance of drugs developed for the same target or indication is also key, to guide target selection and safety differentiation testing strategies as early as possible.

Great progress has been made in the ever-growing portfolio of different modalities as well as novel approaches in drug delivery systems. Perhaps especially noteworthy are the few gene therapies that have recently successfully completed pivotal trials without major safety concerns [35]. For gene therapies using viral delivery, the route of administration (systemic versus local) and the tissue selectivity (tropism of the capsid) are often more important for safety, as opposed to potential genotoxicity or immunogenicity, which are rare [36,37]. The CAR-T cell therapy methods, where the patient's own T cells are genetically engineered to target cancer cells, are also emerging, currently comprising the CD19-directed CAR-T cell therapy Kymriah (Novartis) for B cell acute lymphoblastic leukemia and nonHodgkin lymphoma, and Yescarta (Kite Pharma/Gilead Sciences) for the treatment of B cell lymphomas [38]. Expansion of this technology into other cancers is awaited, provided safety challenges, such as 'on-target off-tumor activity' and incidences of cytokine release syndrome, can be mitigated [39,40]. Antibody therapeutics can have superior safety compared with small molecules because of their high selectivity, low off-target binding, and lack of intrinsic biochemical toxicity. However, the disadvantage is that the route of administration generally has to be parenteral instead of oral because of the low stability of proteins in the stomach, low absorption in the intestine, as well as limitations in reaching intracellular targets. Consequently, biologics might require parenteral administration, which might also confer safety risks (i.e., infections and topical reactions) as well as inconveniencies and, thus, patient compliance issues. In contrast, low molecular weight (LMW) compounds show superiority in terms of amenability for oral delivery, potential broad tissue distribution, and access to intracellular targets. Therefore, LMWs might be the preferred modality despite their potential downside of risk for off-target engagement or generation of toxic metabolites. A recent successful example is Amicus' oral LMW, migalastat (approved in 2016) for the treatment of Fabry disease, which is deemed easier to tolerate and to have fewer adverse effects than the preceding marketed enzyme replacement therapies given intravenously [41,42]. Fabry disease is a form of lysosomal storage disease caused by mutations in α-galactosidase A (α-GalA), an enzyme that is important for processing sphingolipids and the dysfunction of which leads to systemic vasculopathy among other morbidities [41]. Interestingly, the LMW, migalastat, works as a pharmacological chaperone by binding to faulty α-GalA, thereby shifting its folding towards proper conformation. However, recent advances in improving the delivery of biologics have also been made by, for example, improvements in protein-engineering and delivery systems that enhance protein stability and absorption [43]. Tiziana Life Sciences' oral anti-CD3 antibody, which is in clinical Phase 2a for nonalcoholic steatohepatitis (NASH), stands out as a unique example in the crowd of small molecules that are pursued for the same indication [44]. Should it work, it would not only be a breakthrough for treating the disease, but also a game

changer for oral antibody treatment of diseases in general. Breakthroughs in the delivery of biologics across the BBB have also been achieved by use of a 'molecular Trojan horse technology', in which the biologics are fused to a monoclonal antibody (mAb), which binds to an endogenous BBB transporter and thereby acts as a Trojan horse to deliver the biological pharmaceutical across the barrier [45]. Last but not least, in recent years, progress has been made in pulmonary drug delivery. Whereas an advantage for respiratory drugs is direct delivery to the target, pulmonary delivery can also have benefits over oral delivery for the treatment of systemic diseases by avoiding first-pass metabolism and potentially reducing adverse effects [46,47].

The first line of safety assessments might start during the lead optimization phase. These assessments comprise *in vitro*-based evaluations of absorption, distribution, metabolism, and excretion (ADME), pharmacokinetics (PK), selectivity, and off-target pharmacological assays for small molecules, and *in silico* tools of structural alerts. These assays require small amounts of compound and are relatively fast and inexpensive, thus being excellent for the direct comparison of competitive contenders. The tools are also evolving and updated based on real-world evidence, as perhaps particularly well illustrated for the off-target pharmacology assays [48,49]. For example, the second-generation antihistamine, terfenadine, was discovered to cause cardiac arrhythmias because of hERG inhibition, whereas its structurally related major metabolite fexofenadine did not show this off-target effect [50]. This, among other examples, subsequently triggered the development of preclinical secondary pharmacology profiling for off-targets associated with serious ADRs, such as ventricular arrhythmias [49,51], as also recognized by the FDA [52]. Currently, secondary pharmacology profiling is routinely performed by pharmaceutical companies during the early development phase, generally comprising an initial smaller panel followed by a full panel of up to 60 targets comprising G-protein-coupled receptors (GPCRs), kinases, proteases, nuclear receptors, enzymes, ion channels, and transporters [48,53]. To this end, an understanding of the predictive power and the usefulness of the assays is crucial, as is their continuous validation by the pharmaceutical community [54,55].

Based on the accumulated data from the in initial *in vitro*-based evaluations, *in silico* tools to assess quantitative structure–activity relationships (QSARs) might be developed to speed up the deselection or refinement of compounds. An example for the use of QSAR is the development of ranitidine (approved in 1981), a histamine H2 receptor antagonist for decreasing stomach acid production. By help of QSAR modeling, the imidazole ring of the predecessor cimetidine (approved 1976) was modified and an improved safety profile and higher efficacy were achieved for ranitidine [56,57]. Stereoselectivity of molecules is also an important consideration, because production of a single enantiomer might have the advantage of enabling lower dose, simpler dose–response relationships, and lower toxicity [58]. However, creating a single enantiomer is not always straight forward, as demonstrated for thalidomide, a drug that was introduced in 1957 as a sedative and antinausea agent but withdrawn from the market because of teratogenicity. Given that thalidomide comprised a racemic mixture, attempts to develop a single enantiomer were made in the hope that it might remove its teratogenic risk. However, this was shown to be difficult because of chiral interconversion [58]. However, stabilization of the chiral center with deuterium was achieved for a thalidomide analog (CC-122), which is currently in clinical Phase 1 and 2 development by Celgene for various cancers [59]. Although it is unknown whether stereoselectivity could reduce the teratogenicity risk, there might be new opportunities for thalidomide on the horizon, because a mechanistic link (degradation of SALL4) to its teratogenicity was recently discovered [60].

Another element during the optimization phase includes considerations to develop prodrugs for enhancing drug delivery, PK, decrease toxicity, or to target the drug to specific cells or tissues [61]. With regards to the latter, prodrugs that depend on cytochrome P450 systems for activation have shown to be a versatile approach for targeting drug activation to the liver, tumors, or hypoxic tissues [61]. In the case where CNS effects are to be avoided, then structural modification to limit brain concentrations might also be pursued [18]. Improvement of metabolic stability and prediction of human major, specific, or potentially toxic metabolites are also important components of the optimization phase [62]. Human *in vivo* ADME studies are typically conducted during the later phases (Phase 2–3) of clinical development, and identification of metabolites not adequately evaluated for safety in the preclinical toxicology program could be a costly surprise. In this case, alternative preclinical species might be needed for further evaluation and, in the worst case, halt the development program. Last but not least, a crucial element of the optimization phase is to translate the identified safety hazards into human safety risk in correlation with the predicted exposure [63]. In absence of clinical data, PK information obtained from animal models is essential. However, use of exploratory clinical trials and/or P0 trials for obtaining better insights into PK and ADME properties might also be considered. Moreover, although prediction of the clinical therapeutic index (or safety margin) should be performed at an early stage, it needs to be continuously readjusted as new *in vitro* and *in vivo* data emerge and put into context of the benefit:risk evaluation of the intended indication [63].

Exploratory sophisticated nonclinical tools might also provide additional guidance for mechanistic insights into toxicities. To this end, multiple consortiums that include industries, academia, and regulators are ongoing [i.e., Innovative Medicines Initiative (IMI) and Predictive Safety Testing Consortiums (PSTC)], which aim to develop and evaluate various technologies, including *in silico*, biomarkers, and *in vitro* systems and their use in integrated risk assessment. Noteworthy are the achievements with human stem cells. Using inducible pluripotent stem cell technology, large quantities of any human specialized cell type can be generated from a patient's skin sample, thereby opening many avenues for new drug testing strategies. For instance, safety and efficacy in the context of human genetic diversity and disease-relevant genes could be explored, also opening opportunities for personalized medicine. Moreover, combined with recent progress in microphysiological systems (MPS), enhanced preclinical to clinical translation could be achieved [64]. Use of MPS can also enable improved culture longevity, which is key for assessing chronic toxicities, where exposures of low-abundance metabolites over longer time periods, as well as adaptive changes, might have a role. Although their use for safety prediction can be debated, anchorage to *in vivo* data can provide confidence. For instance, cross-species compar-

isons using *in vitro* gut organoids from rat, dog, and human enabled progression of a bromodomain-containing protein 4 (BRD4) inhibitor (AZD5153 by AstraZeneca) by demonstrating that GI toxicity in dogs was not relevant to human. Translation of these data to the clinic was supported by using OTX015, a competitor compound developed by Merck, which is known to result in GI toxicity in rats but not in humans [65,66]. Alongside the routine *in vivo* toxicology studies, *in vivo* head-to-head comparison of competitor compounds can be considered. However, an ethical consideration to reduce the use of animals is imperative, and must be evaluated in relation to the potential clinical safety gained. Noteworthy, however, comparative assessments using short-duration *in vivo* studies and/or humanized animal models with improved translatability to human could help to reduce the drug development attrition rate, thereby also reducing overall animal use.

Lack of direct clinical trial comparisons of drugs makes it difficult to compare drugs according to their efficacy and safety. Indirect comparisons can be performed, but are often challenging because trials can differ in design. The types of outcome measure have also changed over time, recently also including health-related quality of life (HRQoL) and patient assessments of satisfaction. Comparisons can also be further complicated when combination treatments are used (i.e., for the purpose of obtaining additive beneficial effects and/or to lower the dosing regimens for avoiding adverse effects). Thus, direct head-to-head clinical trials might be essential for truly differentiating comparators. However, traditional randomized clinical trials (RCTs) following specific protocols with prespecified treatment arms for a fixed period of time are time-consuming. Accordingly, innovative adaptive clinical trial designs that provide flexibility to adjust trial characteristics based on interim safety and efficacy results, are becoming increasingly popular [67]. For example, modifications of the trial hypothesis, dose, investigational drug, cocktail of drugs, patient sample size or patient selection criteria, end points, and exploratory biomarkers can be made as the trial evolves [68]. By tailoring treatments based on interim clinical readouts and using breakthrough technological innovations, timelines are accelerated, and the probability of success is improved. Integrated research platforms with a single master protocol can be used, enabling testing of multiple drugs compared with a common placebo group, as well as collaborations across academia and industry [69]. A particularly successful example are the I-Spy 1-2 trials, which tested a range of drugs for breast cancer and delivered six drug candidates for further testing in clinical Phase 3 in record time [70]. By using adaptive trial design, the time required to identify the most effective drug candidates for different tumor subtypes was reduced. Other examples include adaptive trials run by the Global Alzheimer's Platform (GAP) and the European Prevention of Alzheimer's Dementia (EPAD) consortium [71]. Adaptive trials can include interim analyses of whether the treatment slows cognitive decline, and the possibility to adapt the treatments based on biomarker readouts, such as lowering amyloid β (Aβ) for an antiamyloid drug or lowering tau for a tau-based drug. Adaptive clinical trial designs are also actively explored by industry in their efforts to develop treatments for NASH, an indication that might require a cocktail of drugs and, thus, a series of combinatory evaluations [72]. Although adaptive trials are not new, they are not yet widely used, and are mostly referenced in the context of efficacy rather than safety. However, to this end, efficacy can also be directly related to safety, because noncompliance or inability to push a drug to a fully efficacious dose can result from suboptimal safety profiles. Moreover, adaptive trials do provide a broad potential for the exploration of safety differentiation. For example, head-to-head comparator trials can be adapted based on adverse event rates, patient withdrawal rates, discontinuation of therapy, need for intervention, and so on. Additionally, individualized risk assessments that rely on patient-specific factors as well as disease–drug interactions can also be explored. To this end, significant efforts are ongoing to develop improved predictive safety biomarkers [73], companion safety diagnostics [74], and pharmacogenetic readouts for patient safety [75], which has also been recognized by the health authorities [76]. Thus, it is not unconceivable that genetic testing will be an important future tool for personalized safety and, consequently, fundamental to differentiations strategies.

Once large amounts of clinical data become available, additional nonclinical studies might be incorrectly perceived by lay audiences to be of limited value. This perception might derive from the fact that many of the unexpected drug-induced toxicities in humans have not shown clear predictive signals during preclinical development, so why should further preclinical assessments help [77]? However, the inability to precisely predict human toxicity is not necessarily because of a lack of human-relevant models. In fact, analysis of concordance between preclinical and clinical safety observations has demonstrated high predictive power [78]. It is rather the issue that a lack of preclinical findings does not necessarily imply a lower risk to humans. This is because it is impossible to test for all imaginable risk scenarios related to individual susceptibilities. However, once clinical data are available, the establishment of tailor-made models that recapitulate the findings observed in humans can be made. Such knowledge-driven refinement of nonclinical models provides a valuable strategy for retrospective analysis of toxicity mechanisms, and can also be used effectively to enhance the predictive value of preclinical safety assessments going forward. It is to this end that the use of nonclinical models could provide an opportunity for gaining competitive advantage in contrast to large, lengthy, expensive, and difficult to fully controlled clinical studies. For example, nonclinical studies can offer greater flexibility, the ability to control variables, and thereby eliminate potential confounding factors. This can facilitate the demonstration of toxic mechanisms, guide the design of targeted clinical trials, or influence the drug label or practice of healthcare professionals. However, such impact can only be achieved if the translatability of the nonclinical model is validated by clinical data. Thus, to develop useful nonclinical models, meticulous prospective and retrospective clinical data collection of the affected individuals needs to be performed. This practice of 'reverse translation' is not an easy endeavor because it requires performing impromptu additional sample collections and *ex vivo* laboratory investigations, requiring available expertise and resources. Although this might appear to involve formidable efforts, it is the scientifically correct way forward for improving the predictability of nonclinical models, which in turn will lead to the development of safer drugs.

Although science governs the drug development process, identification of a well-differentiated value proposition and implemen-

tation of a commercial strategy is also imperative. To facilitate this integration, many drug developers use a key strategic document named the target product profile (TPP), a concept initially introduced by FDA. Its content is structured according to the labeling concept and includes a summary on, for example, product characteristics, indication and use, nonclinical and clinical development results, and plans. However, it also describes key safety and efficacy features as well as competitive positioning, which helps in identifying the key value proposition. To this end, alignment with market-access strategies, including information on key stakeholders (e.g., regulatory bodies and payers, target populations, product prescription strategy, and patient use) are crucial. Lastly, but importantly, a concerted dialog between research and development and market access expertise is key and should be initiated during the early phases of drug development, helping to guide researchers to take the best choices among the various possible safety differentiation opportunities (Fig. 1).

Concluding remarks: key to success

Successful drugs will be those that demonstrate their value to all stakeholders and do so early during development. Patients, physicians, and payers must be convinced that the new drug provides improvement in the quality of life and reduces socioeconomic burdens associated with disease or comorbidities compared with existing therapies. In a changing environment of increasing competition, it is also possible that the patient perspectives of safety and tolerability might influence payers and, thus, how a product penetrates the marketplace. Thus, the drug development focus must go beyond efficacy and include a holistic assessment of patient outcomes where patient safety is more than just minimizing adverse effects. Improved safety could include the mitigation of adverse effects, more efficacious doses, longer therapeutic duration, broader co-treatment opportunities, fewer contraindications, treatment of high-risk patient groups, such as pregnant women, children, older patients, or polymorbid patients, as well as a safer and more convenient treatment regimens leading to improved patient compliance.

An organizational structure where scientific expertise is combined with efficient business-driven decisions is essential. Safety assessment is a holistic approach starting during the early phase of drug discovery to aid the selection of molecules that show disease relevant efficacy at the desired exposure. Although ADME and PK methods are available during the early phase and can be applied effectively, safety assessment often starts relatively late, and this gap should be closed. Comparative safety assessment needs to be an integrated exercise by all key disciplinary experts during the full extent of the drug development and the preclinical and clinical and market access interfaces should be strengthened. Disciplines need to cooperate and integrate knowledge to enable risk:benefit decision-making. This assessment needs to start at the beginning of any drug discovery project, and continuously be adjusted during the development as new information from internal and competitor data emerges [79,80]. Approaches might include the use of innovative nonclinical models with improved translation to humans, adding readouts outside the standard guidelines and/or optimizing clinical trial designs [68,81]. Postmarketing pharmacovigilance will likely also become increasingly important, not only for regulatory obligations, but also for competitive safety differentiation opportunities [9,82]. In fact, companies might already have an advantage in their marketed therapies that could be exploited, or it might contribute to shape the development of their follow-on drugs. Importantly, these opportunities might not only fuel pharmaceutical development, but also ultimately provide safer drugs and, thus, improve patient care.

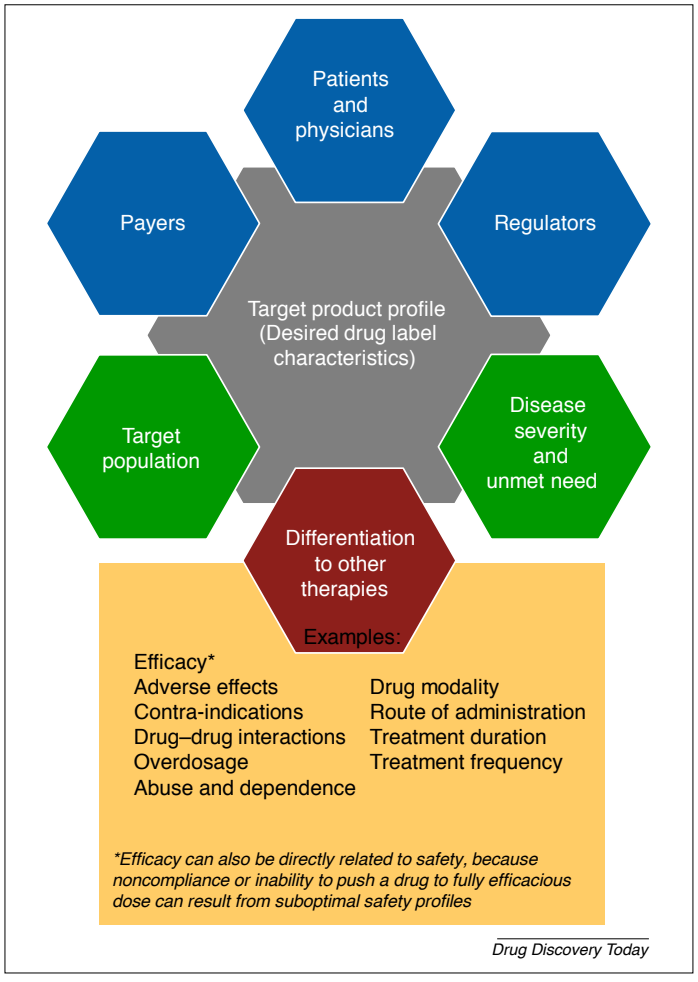

FIGURE 1

Differentiation to other therapies (red) is an integral part of the drug developer's target product profile (gray). A concerted dialog between research and development (R&D) and market access expertise on key stakeholders (blue), unmet need, and target population (green) is key to guide researchers to take the best choices among the various possible safety differentiation challenges and opportunities (yellow).

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