Safety differentiation: emerging competitive edge in drug development

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Teaser:

Safety driven differentiation of pharmaceuticals is gaining traction with the increasing number and complexity of new therapies.

Abstract

With increasing expectations to provide evidence of drugs 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 may 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 non-clinical 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. About 60% of a specific drug target in active pre-clinical and clinical phase are being pursued by more than one company, while the vast majority (88%) of validated targets (for which at least one drug is already approved) are being pursued by multiple companies [1]. In addition to fierce competition, drug development is also getting 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 a lot of debate on 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 suggests that the first-in-class drug candidates have a higher value than the best-in-class [2], while a follow-up analysis by McKinsey in 2014 showed that context makes a significant difference [3]. Yet another 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 as 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 in order to convince regulators and payers [5]. Furthermore, the value may also be hampered by high development costs for validating a novel target. On the other hand, 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 as 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 pharmaceutical industry is not solely whether the drug is potential first-in-class, but also how well the drug may be differentiated from existing therapies. In this review, we highlight the safety differentiation concept by providing examples from post marketing evidences and possible development approaches. While the intent with this review is not to describe drug development in breadth and depth, we hope to trigger future discussions and analysis on this topic by the pharmaceutical community.

Safety driven differentiation

The concept of differentiation through efficacy or convenience are 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 similar chemical structure. A drastic example with major differences in safety is the thiazolidinedione class of compounds developed for treatment of type-2 diabetes. In spite of 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 due to hepatotoxicity, while rosiglitazone was withdrawn from some markets due to cardio- and cerebro-vascular events, and pioglitazone has been associated with increased incidences of bladder cancer although the causal relationship remains controversial [7]. While 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 (Vioxx) and celecoxib (Celebrex), where the former was removed from the market due to cardiovascular risk, while 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 and renal safety profile in comparison to non-selective Cox enzyme inhibitors. Indeed, a recent major safety comparison study of osteoarthritis and rheumatoid arthritis patient populations has shown that Celebrex results

in less gastrointestinal and renal safety liabilities as compared to the non-selective and structurally different Cox-2 inhibitor ibuprofen[10]. Another example of safety differentiation by chemical modifications are amiodarone (approved by the FDA in 1962) and its chemical derivative, dronedarone (approved in 2009), both developed for treatment of atrial fibrillation. While 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 gland, lung, liver and skin. Importantly however, dronedarone does not have a clean cardiac safety profile, as reflected by the narrow target patient population as described above [13]. Finally, an example of a minimal chemistry change for improved safety profile is the newly approved deutetrabenazine (Austedo) developed for treatment of Huntington's chorea. In this case, the only change from the predecessor tetrabenazine (Xenazine) is the replacement of hydrogen to 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 could carry the danger of unexpected adverse events, and that development of safer alternatives is not straight forward with regards to neither 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.

While 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 anti-histamine drugs acting on the H1 receptors are associated with several CNS side effects such as sedation, coordination issues, dizziness, inability to concentrate and paradoxical reactions in children and the elderly [20]. An important determinant of these effects is related to high level of CNS penetration, poor receptor selectivity, involving anti-muscarinic, anti-α-adrenergic, anti-serotonin effects, as well as serotoninergic transmission [20,21].. However, by reducing their

ability to cross the blood brain barrier (BBB), the second-generation anti-histamines are devoid of significant CNS side effects [20]. Another example are the tri-cyclic anti-depressants (tCAs) which have in general been replaced by the selective serotonine re-uptake receptor inhibitors (SSRIs) as first-line treatment for depression due to improved safety profile[22]. While both of these drug classes must pass the BBB to act on their respective therapeutical targets, the 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 depends on the indication it intends to treat, and tCAs are for instance often considered as first-line treatment for neuropathic pain due to additional pain-modulating effects and lack of better alternatives [23]. The crucial question is whether it is possible to develop effective drugs for treatment of chronic neuropathic pain that are devoid of CNS side 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 side-effects such as constipation and respiratory depression as demonstrated in mice [24], however, these may not necessarily prevent abuse potential. On the other hand, 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 a promising non-clinical development with lack of abuse potential in non-human primates [25]. Finally, but importantly, recent research has also demonstrated that the peripheral nervous system might play a much more important role in pain sensation than previously thought, thereby opening the door for development of new peripherally acting therapeutics devoid of CNS side effects [26-28]. While many of the novel targets for human analgesic intervention remain hypothetical, they fuel the pharmaceutical pipeline with alternative therapeutical options which require, as seen with the above examples, – thorough pharmacodynamics and pharmacokinetic evaluation for balanced efficacy and safety.

Other examples of safety differentiation opportunities is the importance of understanding drug-drug interactions (DDI), vulnerable patient populations, as well as co-morbidities of SoC side effects and disease. The risk for DDI may be higher in geriatrics due to a larger number of medications, and critically ill patients in intensive care units due to complexity of pharmacotherapy combined with disease severity [29]. With regards to potential co-morbidities of SoC side effects and disease, rheumatoid arthritis (RA) may serve as an important example. RA is associated with

increased risk of infections, cardiovascular events, and gastro-intestinal ulcers and cancer [30], and many of the current therapies for RA have safety liabilities that may exacerbate these complications [31]. For instance, the disease modifying therapies comprising biologics (currently mostly anti-TNF administered intravenously) increase the risk of severe infections due to immunosuppression that can persist long after treatment has been stopped. Glucocorticoids are associated with increased blood pressure, elevated cholesterol levels, and hyperglycemia, while the non-steroidal anti-inflammatory drugs have an increased risk of gastro-intestinal ulcers and cardiovascular risk. Hence, there is an overlap between some of the co-morbidities and the therapies which can be challenging when evaluating the risk-benefit ratio. There are, however, 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, may offer advantages to the SoC although some side 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 as the immune-system recovers more rapidly after stopping the treatment as compared to the intravenously or subcutaneously administered biologic, anti-TNF-alpha. Thus, not surprisingly, further oral JAK inhibitors are currently in development [34]. The JAK1-2 inhibitor, baricitinib, developed by Incyte/Eli Lilly, has received approval in Europe while pending in U.S. 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 less co-morbidities, 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 target's relevance tohuman physiology and safety. As a start, a hypothesis of the target's role in pharmacological and safety is created. Thereafter, a target validation process ensues where benefit and limitations in safety and efficacy are explored and compared to 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, in order to guide target selection and safety differentiation testing strategies.

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 consisting of the CD19-directed CAR-T cell therapy Kymriah (Novartis) for B-cell acute lymphoblastic leukemia and non-Hodgkin lymphoma, and Yescarta (Kite Pharma/Gilead Sciences) for 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 to small molecules due to 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 due to low stability of proteins in the stomach, low absorption in the intestines, as well as limitations in reaching intracellular targets. Consequently, biologics may require parenteral administration, which may also confer safety risks (i.e infections) as well as inconveniencies and thus patient compliance issues. In contrast, LMW show superiority in terms of amenability for oral delivery, potential broad tissue distribution and access to intracellular targets. Therefore, LMW may be the preferred modality in spite of their potential downside of risk for off-target binding or generation of toxic metabolites. A recent successful example is Amicus' oral LMW, migalastat, (approved 2016) for treatment of Fabry disease which is deemed easier to tolerate and to have fewer side 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 whose dysfunction leads to systemic vasculopathy among other morbidities [42]. Interestingly, the LMW, migalastat, works as a pharmacological chaperone by binding to faulty α-GalA, thereby shifting its folding towards proper conformation. Recent

advances in improving delivery of biologics have, however, also been made by i.e improvement of protein-engineering and delivery systems that enhance protein stability and absorption have however made progress [43]. Tiziana Life Sciences' oral anti-CD3 antibody, which is in clinical Ph2a for non-alcoholic 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 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 mAb which binds to an endogenous BBB transporter and thereby acts as a Trojan horse to deliver the biological pharmaceutical across the barrier [45]. Finally, but noteworthy is also the progress made in pulmonary drug delivery. While the advantage for respiratory drugs is the direct delivery to the target, pulmonary delivery can also have benefits over oral delivery for treatment of systemic diseases as i.e first-pass metabolism is avoided and potentially fewer side effects may be achieved [46,47].

The first line of safety assessments may start during the lead optimization phase. These assessments comprise *in vitro*-based evaluations of absorption, distribution, metabolism and excretion (ADME), pharmacokinetic (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 excellent for 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 development of the second generation anti-histamine, terfenadine was discovered to cause cardiac arrhythmias due to hERG inhibition, while its structurally related major metabolite fexofenadine (Allegra) 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 US Food and Drug Administration (FDA) [52]. Today, secondary pharmacology profiling is routinely performed by pharmaceutical companies in the early development phase, generally consisting of 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 critical, as is their continuous validation by the pharmaceutical community [54,55].

Based on the accumulated data from the in initial vitro-based evaluations, in silico tools to assess quantitative structure activity relationship (QSAR) may be developed to speed up the de-selection or refinement of compounds. An example for 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 a better safety profile and higher efficacy were achieved for ranitidine [56,57]. Steroselectivity of molecules is also an important consideration, as production of a single enantiomer may have the advantage of enabling lower dose, simpler dose-response relationship 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 anti-nausea agent but withdrawn from the market due to teratogenicity. As thalidomide consists of 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 due to chiral inter-conversion [58]. Stabilization of the chiral center with deuterium has however been achieved for a thalidomide analogue (CC-122), which is currently in clinical phase 1 and 2 development by Celgene for various cancers [59]. While it's unknown whether stereoselectivity could reduce the teratogenicity risk, there may however be new opportunities for thalidomide on the horizon, as a mechanistic link (degradation of SALL4) to its teratogenicity was recently discovered [60]. Another element during the optimization phase includes considerations to develop pro-drugs for enhancing drug delivery, pharmacokinetics, decrease toxicity, or to target the drug to specific cells or tissues [61]. With regards to the latter, pro-drugs that depend on cytochrome P450 systems for activation have shown to be a versatile approach for targeting drug activation to the liver, tumors or to hypoxic tissues [61]. In the case where CNS-effects are to be avoided then structural modification to limit brain concentrations may 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 pre-clinical species may be needed for further evaluation, and in worst-case put the development program to a halt. Finally, but importantly, 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 / P0 trials for obtaining a better insight into PK and ADME properties may also be considered. Moreover, while prediction of clinical therapeutic index (or safety margin) should be performed at early stage, it needs to be continuously re-adjusted 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 *in vitro* tools may also provide additional guidance for mechanistic insights of toxicities. Particularly noteworthy are the achievements in human stem cells. Using the inducible pluripotent stem cell technology, large quantities of any human specialized cell type may 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 may be explored, also opening opportunities for personalized medicine. Moreover, combined with the recent progress in microphysiological systems (MPS), enhanced preclinical to clinical translation may 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, as well as adaptive changes may play a role. Although their use for safety prediction may be debated, anchorage to *in vivo* data can provide confidence. For instance, cross-species comparison 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 gastrointestinal (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 with 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 though, comparative assessments using short duration *in vivo* studies and/or humanized animal models with improved translatability to human may help to reduce the drug development attrition rate, thereby also reducing the overall animal use.

Lack of direct clinical trial comparisons of drugs makes it difficult to contrast medications according to efficacy and safety. Indirect comparisons may be performed, but are often challenging as trials may differ in design. The types of outcome measures have also changed over time, recently also including health related quality of life (HRQoL) and patient assessments of satisfaction.

Comparisons may 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 side effects. Thus, direct head-to-head clinical trials may be essential for truly differentiating comparators. However, traditional randomized clinical trials (RCTs) following specific protocols with pre-specified 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 may 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 may be used, enabling testing of multiple drugs compared to a common placebo group, but also collaborations across academia and industry [69]. A particularly successful example are the I-Spy 1-2 trials that 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 were achieved. 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 may i.e include interim analyses on whether the treatment slows cognitive decline, and the possibility to adapt the treatments based on biomarker readouts such as lowering Aβ for an anti-amyloid 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 may 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. To this end it should however be noted that efficacy can also be directly related to safety, as noncompliance or inability to push a drug to fully efficacious dose can be to due suboptimal safety profiles. Moreover, adaptive trials do provide a broad potential for exploration of safety differentiation. For example, head-to-head comparator trials may be adapted based on adverse event rates, patient withdrawal rates, discontinuation of therapy, need for intervention etc. Additionaly, individualized risk assessments that rely on patient-specific factors as well as disease-drug interactions may 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 non-clinical studies may be incorrectly perceived by lay audiences to be of limited value. This perception may 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 pre-clinical assessments help [77] ?. However, the inability of precise prediction of human toxicity is not necessarily due to 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 lack of preclinical findings does not necessarily imply a lower risk to humans. This is because it is simply impossible to test for all imaginable risk scenarios related to individual susceptibilities. Once clinical data is available, however, the establishment of tailor-made models that recapitulate the findings observed in humans can be made. Such knowledge-driven refinement of non-clinical models provides a valuable strategy for retrospective analysis of toxicity mechanisms, and can also be effectively used to enhance the predictive value of preclinical safety assessments going forward. It is to this end that the use of non-clinical models may provide a great opportunity for gaining competitive advantage in contrast to large, lengthy, expensive and difficult to fully controlled clinical studies. For example, non-clinical 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. Such impact can, however, only be achieved if the translatability of the non-clinical model is validated by clinical data. Thus, to develop useful non-clinical 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 as it requires performing impromptu additional sample collections and *ex vivo* laboratory investigations, requiring available expertise and resources. While all of this may seem to involve formidable efforts, it is the scientifically correct way forward for improving the predictability of non-clinical models, which in turn will lead to the development of safer drugs.

While science governs the drug development process, identification of a well differentiated value proposition and implementation 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 i.e product characteristics, indication and use, non-clinical 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 dialogue between R&D and market access expertise is key and should be initiated in the early phases of drug development, helping to guide the researchers to take the best choices among the various possible safety differentiation opportunities (Figure 1).

Key to success

Successful drugs will be those that demonstrate their value to all stakeholders and do so early in development. Patients, physicians and payers must be convinced that the new drug provides improvement in quality of lives and reduces socio-economic burdens associated with disease or co-morbidities as compared to existing therapies. In a changing environment of increasing competition, it is also possible that the patient perspectives of safety and tolerability may have influence on payers, and thus on 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 much more than just minimizing side-effects. Improved safety may include mitigation of side effects, more efficacious doses, longer therapeutic duration, broader co-treatment opportunities, fewer contraindications, treatment of high risk patient groups such as pregnant women, children, geriatric patients, or poly-morbid 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 at 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 in 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 pre-clinical and clinical interface should be strengthened. Disciplines need to cooperate and integrate knowledge in order 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 emerge [79,80]. Approaches may include use of innovative non-clinical models with improved translation to humans, adding readouts outside the standard guidelines and/or optimizing clinical trial designs [68,81]. Post-marketing pharmacovigilance will likely also become increasingly important, not only for regulatory obligations, but also for competitive safety differentiation opportunities [9,82]. In fact, companies may already have an advantage in their marketed therapies that could be exploited, or it may contribute to shape the development of their follow-on drugs. Importantly, these opportunities may not only fuel pharmaceutical development, but ultimately provide safer drugs and thus improve patient care.

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