Meeting the demands of regulatory requirements: the significance of ADME

“ADME will continue to play an active and expanding role in drug discovery and development, particularly in helping improve the accuracy and precision of PK/PD model predictions…”

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When I began my career in the mid-1980s as a pharmacokineticist in the pharmaceutical industry, we scientists dedicated to the study of absorption, distribution, metabolism and excretion (ADME) were relegated mostly to a characterization role – defining bioavailability, protein binding, metabolic pathways, and so on, for new molecular entities (NMEs) in development. Drug discovery was oriented toward identifying lead candidates with the highest target activity, irrespective of their physicochemical or pharmacokinetic (PK) properties. It should have come as no surprise that poor ADME was cited in 1997 as the reason for attrition of 40% of drug candidates during development [1]. This helped spawn a renaissance in drug discovery that witnessed ADME, abetted by crucial enabling technologies such as LC–MS/MS, emerge as an indispensable contributor to the process [101]. Since the early 2000s, the myopic focus on pharmacologic potency at the expense of all other properties has yielded to the merits of co-optimizing pharmacologic and ADME/PK performance, bolstering a mindset that only ‘druggable’ molecules should progress into development. As a result, compound attrition due to poor ADME properties plummeted – from 40% of failures in 1997 to a mere 10% in 2004 [2]. ADME science has come of age and continues to flourish as a core component of the discovery and development process.

Where do we go from here? The screenplay for Act II, it appears, will be written by the challenges facing the pharmaceutical industry, and several are looming.

Financial constraints & regulatory hurdles
The cost of drug development is skyrocketing, and productivity is not. One group reported that it costs approximately US$1.3 billion to develop a drug, while others have provided estimates ranging from $1.7 to 11 billion [3,4,102]. In an attempt to keep pace, the pharmaceutical industry, on balance, has continued to increase its R&D investment. Yet, even in the face of increased R&D spending, the annual number of new drug applications has been declining [103]. How could this be? On closer inspection, R&D expenditures, while increasing, began to plateau in the mid-2000s [104], no doubt in part to a flurry of corporate consolidations. Big pharma depends on blockbusters to remain viable. To compensate for the vagaries of market competition and revenues lost to patent expiries, large pharmaceutical companies are forced to enrich their pipelines by subsuming other entities, resulting in a net reduction in total R&D budget across the industry. Moreover, only those drugs with lifetime sales in the top 20% of marketed pharmaceuticals will recoup the R&D expenditures required to get them to market [105]. Consequently, the portion of NMEs dropped from development due to ‘market considerations’ soared from 5% in 1991 to 20% in 2004 [2].

It takes longer than ever to bring an NME to market. This is a natural extension of the hurdles sponsors must surmount in a regulatory environment that is demanding more expansive submissions with higher scientific quality. Is it any wonder that drug development costs are escalating and submissions and approvals are dwindling?

While the US FDA and its backers have stated categorically that regulatory scientific standards have not become more stringent, industry watchers counter that the decline in drug approvals is due to a risk-averse culture at the FDA, and to agency standards that are ‘requiring a margin of safety and a reduced margin of error’ that is...
burdensome. It is not possible to discern which of these positions most accurately reflects reality in the ‘quality’ controversy. However, the fact that strident debate is being waged suggests that the issue has import.

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Many in the industry would agree. Some, anticipating severe regulatory standards, are taking it upon themselves to raise the bar for their development candidates. In my consulting practice I have seen a surprising increase in the number of small pharma clients needlessly insisting that non-clinical ADME studies be performed according to Good Laboratory Practice (GLP) guidelines. The perception is that GLP means ‘better’. Insofar as GLPs dictate strict documentation and quality assurance oversight, there is a kernel of truth in this belief. In reality, however, GLP adherence provides only a marginal enhancement in quality above a study conducted ‘in the spirit of GLP’, that is, ‘GLP without the extra paperwork’.

Such mindsets are fueled by our own collective paranoia, coupled with a general lack of clarity on agency expectations. It is understandable. A small pharmaceutical company with very few eggs in their development basket can ill afford to risk their NME not measuring up to the arduous regulatory constraints they perceive. The fate of the company depends on bullet-proof regulatory submissions, and this also often spawns added studies (quantity) to strengthen the package.

Generally, the need for increased ‘quantity’ can be likened to the gauntlet we face at airport security. Shoes and liquids are scrutinized because bad things related to these items almost happened. Now consider that hERG channel screening is embedded in virtually all discovery programs and that a thorough human QTc study must be contemplated for every drug in clinical development. Why? Because bad things related to cardiac conduction abnormalities did happen. Patients died from fatal arrhythmias when CYP3A4 substrates with the potential to elicit QT prolongation were taken with potent CYP3A4 enzyme inhibitors. The history of drug withdrawals is replete with similar examples.

The demands for quality and quantity are merely two edges of the same sword. In fact most of the requirements for additional work to support a filing have emanated from a need to ensure some added element of quality. For example, we are now required to demonstrate the integrity of bioanalytical methods by performing incurred sample reanalyses. This requirement itself is not particularly onerous, but is just one of many that add to the overall quantity of work necessary to bring an NME to regulatory filing.

The intent of these additional requirements is laudable. They foster confidence that we understand the character of our drug and help ensure that it will be used as safely and effectively as possible. However, they do add to timelines and expenses.

So we are being asked to do more, to do it better, and to do it with less. How do we rationalize the continued, let alone expanding, role of ADME in this regulatory and financial environment? A better question may be, how could we not rationalize it?

The significance of ADME: Act II

The probability of an NME making it to market is depressingly low. Impressive ADME success rates belie the fact that the overall NME attrition rate from Phase I through approval is still 90% [2]. The primary driver has simply shifted from ADME to pharmacology. Remarkably, a recent analysis found that 66% of development failures in Phase III were due to insufficient efficacy [5]. Given that these compounds had pharmacologic activity favorable enough to justify progression into Phase III, we are left with the uncomfortable realization that in many of these cases the lack of efficacy was at least partly due to deficiencies in PK, or more accurately PK/pharmacodynamic (PK/PD), performance. This is where ADME science can make new inroads toward optimizing drug discovery and development.

Advanced PK/PD strategies and ever more sophisticated modeling tools are required to account for the complex biological variables that contribute to disease progression and the response to pharmacologic intervention. Quantitative and Systems Pharmacology (QSP) will have tremendous impact on this front. QSP – the marriage of PK/PD and systems biology – involves integrating input from all key disciplines to characterize the interaction of a drug with the physiological system, linking information at various levels of biological complexity, while investigating its interplay with a vast array of biochemical networks [108]. Ultimately, the value of QSP will manifest itself in improved...
development decisions, driven by more refined predictions across all phases of discovery and development.

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To engender greater confidence in our predictions of human drug performance and enable us to address efficacy issues earlier in the development process we must focus as much on the precision of our predictions as on their accuracy. Myriad biological factors determine how a drug behaves in any individual. A radical improvement in drug development decision making can be realized with enhanced PK/PD predictions that account for the diversity that defines the human population. This effort can be assisted by quantitative (probabilistic) risk analysis. The value of this instrument, which is a technique for quantifying uncertainty, stems from its ability to evaluate potential risk factors (e.g., in a PK/PD analysis), and derive a probability of success to guide scientific strategy decisions [6].

A solid, comprehensive ADME package with sound PK/PD underpinnings can support more aggressive transitions into Phase I, allowing important go/no-go decisions based on proof-of-principle to be made with confidence as quickly and as early as possible, streamlining the research process, improving development efficiency and timelines, and reducing attrition.

Thus, it seems clear that ADME will continue to play an active and expanding role in drug discovery and development, particularly in helping to improve the accuracy and precision of PK/PD model predictions to improve decision making and help address the key challenges we face in our quest to bring new therapeutic interventions to bear on unmet medical needs.

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