New regulatory strategies to address unmet clinical needs

Accelerating the development and regulatory approval of drug products targeted at unmet clinical needs has been the focus of several recent worldwide initiatives. In Europe, the ‘medicines adaptive pathways to patients’ (MAPPs) project is a prospectively planned, adaptive approach in bringing new drugs rapidly to the market, involving ongoing dialogue with the European Medicines Agency (EMA). Adaptive licensing (AL; another term for MAPPs) strives to maximise the potential positive effects of new drugs on patient health by ‘balancing timely access for patients with the need to provide adequate evolving information on benefits and harms.’ AL strives towards a ‘life-cycle’ approach of assessment and subsequent licensing of new medicines, aligned with a staged approach to collecting supporting evidence.

The US Food and Drug Administration’s (FDA) breakthrough therapy designation (BTD) is an expedited drug development approach, allowing the agency, under the Safety and Innovation Act (FDASIA), to support priority review of new chemical entities (NCE), if the NCE offers significant safety or efficacy advantages over existing licensed medicines for patients with serious or life-threatening diseases. A BTD can be proposed for a NCE if “it is a drug which is intended alone or in combination with one or more other drugs to treat a serious or life threatening disease or condition.” Meanwhile, the Japanese Ministry of Health, Labour and Welfare is to start reviewing proposals for an accelerated authorisation scheme under the new Sakigake early access pathway. It is envisaged that this could cut regulatory approval times for innovative therapies in Japan by half.

The rapid development and approval of Avycaz (ceftazidime and avibactam; Allergan) exemplifies this approach. Avycaz is a fixed-dose combination containing an established cephalosporin, ceftazidime and the novel beta-lactamase inhibitor, avibactam. Avycaz was designated as a ‘qualified infectious disease product’, a designation given to novel anti-infective products aimed at treating serious or life-threatening infections under the Generating Antibiotic Incentives Now (GAIN) provisions, as part of the FDA Safety and Innovation Act. Of particular note was the fact that the efficacy of Avycaz was supported in part by the findings of the efficacy and safety of ceftazidime for the treatment of complicated intra-abdominal infections (cIAI) and complicated urinary tract infections (cUTI). Tellingly, Avycaz was only studied in two Phase II trials in cIAI and cUTI and neither Phase II studies were required to show superiority versus active comparators. Similarly, in one of their ‘retrospective case studies’, the EMA identified a fixed dose combination containing ceftazidime and avibactam as an alternative to the comparators, with only Phase II studies, to show safety and efficacy in Phase II studies.

However, none of the AL guidelines give any meaningful chemistry, manufacturing and controls (CMC) guidance. Obviously, quality, efficacy and patient safety cannot be compromised, but new regulatory approaches will be required to allow early access to medicines. This will involve ongoing interaction with the regulators, as the totality of the CMC knowledge cannot be the same as with a data rich, Quality by Design approach - at least not at file. A ‘staged approach’ will be required, where the initial ‘CMC-light’ submission is continuously augmented post-submission and the desired state is reached several years post-filing. An example of such an approach could embrace commercial pack selection. Here Accelerated Stability Assessment Protocol, and Moisture Vapour Transmission Rates approaches could be used to identify the most appropriate pack configuration, including key variables such as desiccant, tablet count and container wall thickness. If confirmatory stability studies were on the critical path to file, they would be deferred. Instead, during the set down of the registration stability studies, the proposed pack(s), together with back-up contingencies (which would be more protective with increased costs) can be set down and data-driven decision making can be used to finalise the commercial pack selection. A decision tree based on a predictive in silico stability model could then be used to allocate an 18-24 month shelf-life based on six months data from both the accelerated and long-term studies. Data to fully support this shelf-life decision would then be provided post-filing using a ‘staged approach’.

Typically, meaningful commercial shelf-lives can only usually be assigned based on 12 months of real-time data. Hence, this proposed approach would save at least six months on the filing date. In conclusion, AL offers the promise of faster access to quality medicines, but the devil will undoubtedly be in the detail.

References
1. Pilot project on adaptive licensing. EMA/254350/2012. 19th March 2014