## MARKET ACCESS INSIGHT: DISEASE HETEROGENEITY

# ***Dr Michael Murphy**, chief medical and scientific officer, and **Claire Riches**, vice president project management, WCT: discuss rarity, disease heterogeneity, and a mandate to demonstrate value*

THE HEALTHCARE environment is a mosaic of providers and intermediaries delivering healthcare, regulatory and government institutions influencing patient access to therapy, and diseases which vary in prevalence, chronicity, and extent of healthcare utilisation. Data required for informed healthcare decisions for novel pharmaceutical interventions vary appreciably with the audience, the therapeutic area, and the magnitude of the unmet clinical need. Demonstrating evidence-based value in the course of clinical development can support adoption by providers, influence the extent of coverage provided, and ultimately dictate patient access. Development of products for orphan indications provides a prototype for program innovation illustrating that improved patient outcomes may be demonstrated with reduced downstream cost while acknowledging the relationships between diverse stakeholders.

### EXCEPTIONAL RESEARCH AND DEVELOPMENT INTEREST

The 1983 US Orphan Drug Act and subsequent acts in the United States and internationally provided an impetus for orphan drug development, emphasising an important unmet need and created an economically viable strategy for pharmaceutical research.[1] Approximately 400 drugs for patients with rare diseases in the US exist. With more than 7,000 rare diseases recognised, advances in genetics may further subdivide common illnesses into genetically distinct disorders. A disproportionate number of new molecular entities approved for marketing increasingly address orphan indications as the pathophysiology of illnesses become more targetable, and both research and commercial incentives are significant. For example, orphan indications provide an impetus for research and clinical development: fast tracking, tax credits, research and development grants, and potentially shorter development timelines.

Even with the absence of novel chemical or biological entities, recycling older products toward orphan indications affords an avenue of new profitability. Compounds developed for one orphan indication can expand into other clinical areas, or can benefit from off-label use (at least 20% of prescriptions in the US).

Characterised by premium pricing, blockbuster status within a seven-year market exclusivity period has been achieved by a number of brand-name drugs with orphan designations.[2] Commercially related drivers for reimbursement, exclusivity, marketing cost, and uptake yield fiscal and economic incentives which outpace the investments required.

### APPROVED, NOT ACCESSIBLE

An inflection point has been reached for orphan drug pricing, however prompting increased scrutiny of orphan drug utilisation for products with expenditures of approximately $50,000/patient/year.[3] Restriction of coverage to only approved indications and increases in the financial burden of patients through cost-sharing mechanisms have resulted.

Additionally, across international settings, more emphasis may be placed on equity versus market dynamics, yielding very different guidance impacting patient access and thus the type and amount of data that must be provided at the time of market application. Notable inconsistencies in the evaluation of orphan drug submissions exist within the European Union regarding the importance given to cost-effectiveness or cost utility analyses.[4] Attempts to remediate concerns through estimations of cost burden are variably successful due to complex disease phenotypes, and patient subgroups and outliers within those groups significantly influencing estimates. Re-evaluations of utility during a product's life cycle also are required if there are concerns regarding rare adverse events with longer-term use. Challenges are accentuated by development programs for orphan diseases based on a few studies and surrogate markers rather than clinical outcomes, which can be used to estimate utilisation and cost.[5]

### BEGINNING WITH THE END IN MIND

A program of observational and interventional research can be mutually reinforcing within orphan disease drug development. For example, the literature describing burden of illness may be limited for an orphan disease. An observational study, including a retrospective cohort trial, provides a platform of information upon which utility of a novel product can be based. The very restricted sample size imposed by orphan targets also invites the use of historical data that can be used in lieu of concurrent control information in restricted circumstances.

Finally, an opportunity to provide long-term safety and other outcome information is afforded by creation of a drug registry begun at initiation of Phase 1, an attractive initiative which permits interim data from the registry to inform registration, while longer-term assessments are possible if post-marketing commitments arise.

Although the regulatory submission data for non-interventional studies may be characterised by longer complex authorisations given the lack of international consensus, non-interventional and interventional studies differ in important dimensions which affect the complexities to trial operations required. For example, interventional clinical trials follow good clinical practices (GCPs) when most studies classified under the umbrella of 'non-interventional' can adhere to good pharmacoepidemiology practice (GPP) – a proactive, operational adaptation of GCP with much fewer detail and comprehensive attention to procedures required than GCP.[6] Notable related operational sequelae

include modest site honoraria, limited data collection and source data verification, and the use of various electronic acquisition methods which reduce cost.

## LIFECYCLE MANAGEMENT

Orphan drug candidates represent an ideal program for creation of a name-based or cohort compassionate-use program later developed into a global Expanded Access Program (EAP), acknowledging that these programs may compete with ongoing clinical trials for accrual, or prevent enrolled patients to be treated with commercial drug. For example, EAPs are considered the equivalent of clinical trials in many countries, and the Sponsor must continue to freely provide access even with commercialisation.

However, these data provide context for the initial claims and offer insights for new indications, in a classic illustration of drug lifecycle management. Post-marketing efforts for orphan diseases can also exploit techniques used to assure quality improvement initiatives used in other therapeutic areas post-marketing such as a) administrative claims data for hypothesis generation; b) step wedge designs for sequential rollout of a quality initiatives across tertiary care centers specialising in orphan disease management; c) time-series designs to judge the impact of newly introduced therapy in the context of secular trends in care; and d) controlled and uncontrolled before/after studies which can evaluate outcomes before and after introduction of new initiatives within a geographical region.[7]

Finally, observational and interventional research in tandem result in regulatory and peer-reviewed publications facilitating health technologies assessments and other evaluation of 'value' resulting in clinician adoption, payer coverage, fair pricing, and enhanced patient access. P


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She says that in the case of Yervoy, NICE just needed to find a path forward. "So that's a good example for me that NICE wants to do the right thing," Mercier says. "It could have turned the other way and then maybe we'd be having a different conversation, but overall I'm really impressed with that, because I think that's a good step forward not just for BMS, but for other organisations as well."

## UK STILL A 'CHALLENGING MARKET'

"Now, having said all of that, I would tell you that access in the UK is still very challenging," Mercier admits.

But it's not just about NICE, she argues, it's also about how market access is seen in the UK.

She says: "When I began my job as general manager in the UK, here people were saying 'Oh, it's an early launch market' and that this was a positive thing. But I was challenging my team saying you're not an early launch market – you get an early price, but not an early launch because the NHS won't pay for it until it's been appraised by NICE, and then put onto a formulary, all of which can take up to a year.

"So there's a disconnect between an early price versus early access, which are two very different things, and I think people are confusing the two.

So I think there is an opportunity to bridge that gap and there are different ways of doing it."

So despite the help NICE were willing to give with Yervoy, she still believes that "there is need of an overall reform of NICE", adding that this is 'around the corner'.

"We just need to partner together to make sure we get the right outcome for patients. It might take a couple of years, and I don't think it will be immediate, but if there is intent on bothsides, you can make it work."

She points to the European Medicines Agency as one body that HTAs such as NICE can look to for guidance.

**"We just need to partner together to make sure we get the right outcome for patients"**

**Johanna Mercier**

*General manager, Bristol-Myers Squibb UK/Ireland*

"The EMA is moving pretty quickly forward with filings with Phase II data only, or with real world data.

They are really trying to progress with these new ways of gathering data.

We in the UK and elsewhere just need to make sure that our reimbursement processes are falling in line with that, because at the moment there can be a real disconnect.

And I think what happened with Yervoy first-line is a good example where they want to go." P