CRA Insights: Life Sciences

CRA Charles River Associates

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CRA Roundtable

Opportunities and Challenges in Rare Diseases

Introduction

As part of Charles River Associates' issues leadership initiative to challenge industry thinking on rare diseases, we assembled a panel of CRA experts with a range of experience and expertise – strategy, market access, policy and litigation – to discuss the opportunities and challenges posed by the latest therapeutic breakthroughs in conditions that, according to the European Union definition, affect fewer than one in 2,000 people.

Panellists

Gregory Bell

Greg Bell is the global leader of CRA's Life Sciences Practice. As a strategy consultant, he focuses on the economics of competitive strategy, working with firms to develop sustainable advantages. During the last 25 years, he has led many consulting assignments across multiple disease areas, covering launch strategy, product positioning, market access, pricing and contracting, channel strategy, therapeutic category strategy, business model assessment and development, competitor response, and lifecycle management. Dr. Bell also testifies frequently as an expert witness in life sciences litigation disputes.

Kevin Brubacher

Kevin Brubacher has 25 years of pharmaceutical and biotech commercialization experience and has led cross-functional marketing and commercial teams during the development and launch of pharmaceutical products. His expertise includes global commercial planning and market strategy, analytics, market simulation, lifecycle management, launch planning, and competitive gaming. His time in the pharmaceutical industry spans multiple senior global strategic marketing and sales roles with a focus on orphan, immunology, and cardiovascular therapies in the US, Canada, and Europe.

Ned Kitfield

Ned Kitfield has extensive experience providing commercial decision support for large and small biotech, pharmaceutical, and healthcare companies. While Ned has worked across a broad spectrum of therapeutic categories, he brings special insight into rare and ultra-rare diseases. His expertise includes everything from commercialization strategy to advanced analytics and primary market research designed for these often-overlooked rare spaces.

Cécile Matthews

Cécile Matthews has 20 years of experience in strategy consulting in life sciences. Her areas of expertise include pricing, reimbursement, and market access. Throughout her career as a consultant, Cécile has provided her clients operating in rare diseases with strategic insights on issues such as early access, leveraging patient involvement, strategies to address uncertainty of evidence and global pricing and market access.

Tim Wilsdon

Tim Wilsdon is responsible for leading global policy work for CRA in the life sciences industry. During the last 20 years, he has worked on many high-profile policy focused projects, including studies for the European Commission, the pharmaceutical industry (through PhRMA, EFPIA, EuropaBio and IFPMA) and many individual companies on how pharmaceutical markets, including those for rare disease, could be reformed to work more efficiently. This includes studies for EFPIA and EuropaBio on the impact of Orphan Medicines regulation.

Moderator

Neil Turner

The roundtable was moderated by Neil Turner, who leads CRA's life sciences practice in marketing, issues leadership and knowledge management. He has almost 30 years' experience in the pharmaceutical sector, specialising in delivering publications, communications and consulting solutions, including in rare diseases.

Special thanks

Bhavesh Patel, Charlotte Poon and Lalitha Ramkumar for coordinating the roundtable.

Current landscape in rare diseases

Neil Turner: In your experience helping clients in rare diseases, what do you think are the main challenges?

Cécile Matthews: The most difficult thing to get right is evidence development. Conducting a clinical trial for a rare disease can be very challenging. First, there are fewer patients, so recruitment takes longer and trial size is necessarily smaller. Second, demonstrating cost-effectiveness in a single-arm trial without an active comparator, which is often the case in rare diseases because of the lack of treatment options, is a further hurdle. In simple terms, it is impossible to demonstrate improvement in quality of life if you do not have a comparator. In such cases, companies often end up using registry or longitudinal data and try to match those patients to their trial patients. And, finally, convincing payers of an unmet need can be a problem because of the lack of published literature on the rare disease being targeted.

Another key to success is the task of setting an optimal price. The challenge here is defining value and developing strong evidence that will identify unmet needs and support successful health technology assessments. In rare and orphan diseases, the challenge is often compounded by a lack of epidemiological data, gaps in the literature, and payers' unfamiliarity with the condition. Added to the fact that products for rare and orphan diseases are often first to market with no direct price comparator, the challenge of setting an optimal price is even more important to driving commercial success.

Driven by many of the same factors, a clear and robust program of value communication is another essential for a successful launch in rare diseases. Patient advocacy can be a particularly important tool for demonstrating value in rare disease. Further, relative to more mainstream therapy areas, payers need educating on the specific disease and the attendant issues around evidence generation such as low patient numbers and lack of data. Finally, these messages need to be tailored effectively, likely emphasizing different issues from those relevant for more mainstream therapy areas.

Kevin Brubacher: The regulatory pathway for a lot of orphan drugs is murky. By virtue of being rare, there is a lack of robust clinical data: typically, there is just one pivotal trial and, in the United States, an accelerated path to FDA discussion through approaches such as priority review, breakthrough designation, accelerated approval and fast track. This combination of immature evidence and earlier conversations with regulators inevitably leads to a lot of difficult questions about the product at both the FDA and the EMA, as well as HTA agencies.

Duchenne muscular dystrophy (DMD) is a case in point. The current therapies target sub-populations of the patients based on their specific mutation. This makes trial sizes very small and difficult for European HTA agencies to square the data with what they would ideally like to see – even though there is a clear unmet need. If you always must give HTA assessors exactly the data they need, orphan drugs would never make it to market as there are not enough patients. It leaves clients deliberating over whether to enter a market or not, which is sometimes the case in European countries and Canada. This tends to be less of a problem in the US.

A further challenge is price. A lot of my work is in cell and gene therapy where there isn't an established model for pricing and payment because payers and policymakers are still adjusting to the arrival of these potentially game-changing new therapies. For example, are manufacturers going to have to follow all patients in one-to-one registries to track their progress on a long-term basis? And how will payments be spread – over five years, ten years, or 20 years? Moreover, what will the landscape look like in a few years' time with 30-50 gene therapies on the market? And how will the US system deal with the movement of patients from plan to plan?

Clearly, there is a great amount of uncertainty among our clients over the challenges posed by cell and gene therapies compared with the traditional value proposition approach to justifying a price. In the end, this might well come back to the fundamental question of placing a value on human life and the level of improvement in quality of life justifiable at a price tag that can run into millions of dollars.

Tim Wilsdon: One of the biggest challenges in Europe, big enough to keep our global clients awake at night, is the threat to orphan medicine regulation. The concern is that the new European Commission, which took office in November 2019, will either change directly orphan medicine regulation, or indirectly by reforming broader pharma regulation in ways that impact rare diseases. Of significant concern is the period of market exclusivity for medicines treating rare diseases and pediatrics which has been the subject of some conjecture over recent years in Brussels. Nobody quite knows the direction the new Commission will take but there are a range of different ways the incentives could be targeted or made conditional. In contrast, despite recent controversy over drug prices and the Trump blueprint in the US, the Orphan Drug Act of 1983 is seen as successful and has come under less scrutiny than its European equivalent.

Underlying this challenge is concern about the price of orphan medicines, with policymakers and payers believing that prices are unjustifiable and unaffordable for healthcare systems facing multiple spending pressures. Even with the significant benefits that orphan and pediatric medicines regulation has delivered – we have worked with the European trade association, EFPIA [European Federation of Pharmaceutical Industries and Associations] and EuropaBio on documenting these – many have concluded that the Commission will change the regulation of these medicines. Indeed, the train may already have left the station and it will be industry's response that helps shape the future policy environment.

Ned Kitfield: The commercial landscape isn't like it was 10 years ago when the big companies were all looking to launch products that were first-to-market and to leverage this competitive advantage for as long as possible. In Hunter Syndrome, for example, Takeda had the only product for many years. The current problem is that the 'easy to treat diseases' are now very crowded; it's getting harder to secure a return on investment with fewer patients and more intense competition in some of these categories.

Greg Bell: Our clients face three main challenges from a rare disease perspective. First, there are approval issues associated with small clinical trials. These issues are compounded if you're talking about a curative product, which may address a significant proportion of the patient population just by being approved. Second, there are significant issues around market access, specifically relating to funding, reimbursement and how to carry out longer term

monitoring and payment over time. Finally, there is the combined problem of patient finding and tracking – how to help physicians identify patients, move them onto treatment and maintain them in compliance.

Future landscape in rare diseases

Neil Turner: How do you see the landscape in rare diseases evolving over the next five years?

Ned Kitfield: The rare disease space will become increasingly crowded. There are going to be many more commercial launches over the coming years in innovative treatment areas like gene therapies. This is going to make life difficult for payers as companies seek millions of dollars for their new treatments and we will see a rise in innovative contracting to facilitate access. One effect of this will be to bring commercialization and market access closer together. The two disciplines will need to become more integrated to manage strategically in areas such as patient finding, diagnosis and maintaining therapy. For smaller patient populations, the importance of building relationships with key opinion leaders and other stakeholders will only increase. It is therefore vital to keep hold of talent as relationships in rare diseases are often cultivated by a single person over an extended period; losing that person could be a major blow.

Kevin Brubacher: In the US, there is a lot of discussion about whether there should be a reinsurance market for rare diseases to spread the risk. Many of our clients believe this will be the case but it remains to be seen where this discussion ends up. In the short term, our clients must focus on the commercial priority of getting their products launched as quickly as possible while negotiating the best access with, as we've seen, limited evidence. A key factor here will be how manufacturers partner with PAGs [patient access groups] and health authorities to enable, guide and facilitate these difficult discussions.

In a recent highly publicized case, the parents of a nine-month old Belgian baby with spinal muscular atrophy (SMA) crowd-funded €1.9m to cover the cost of life-saving treatment with Novartis' Zolgensma. The gene therapy has not been approved for use in Europe but has in the US. While novel and well-meaning – almost one million Belgians responded to the appeal – crowdfunding is not a long-term societal solution for access to breakthrough therapies for patients unfortunate enough to suffer from rare and previously untreatable conditions.

Greg Bell: The development of potential treatments for rare diseases has benefited from the industry's strong emphasis on scientific and clinical innovation. Commercialization of these therapies, however, has suffered from stagnation with respect to commercial innovation. The business model to support the scaled commercialization of multiple new products for rare diseases still needs to be developed. In many respects, the necessary commercial infrastructure to effectively manufacture, distribute and market these new products does not exist. The industry's tried-and-true model of commercialization, based on improvements in small molecules and mass market indications, is not well-suited to step-changes and cures in rare diseases with high unmet need. The commercial model will need to evolve over the next five years, particularly with respect to marketing strategies based on sales reps and traditional distribution channels.

Tim Wilsdon: One recurring theme will be the uncertainty over how HTA responds to rare diseases. This appears to be evolving in three different ways. The first is what we might call the 'German approach' where RWE [real-world evidence] is required for medicines that lack the kind of robust evidence that HTA agencies are used to working with. Second, there are medicines addressing diseases for which the justification of unmet need is so clear that they can live without the same level of evidence, as pioneered by NICE [National Institute for Health and Care Excellence] guidance for Highly Specialised Technology [HST] in the UK. Although only applied to a small number of medicines each year, NICE has shown considerable flexibility in the assessment of drugs for ultra-rare diseases. Finally, there are countries that question the meaning of the orphan status of some medicines and will treat these as any other product. In all three cases it will be interesting to see how events unfold, not least to see whether consensus develops, or countries diverge further in their treatment of orphan medicines. Historically, HTA has been an area of national prerogative but in recent years we have seen the development of cross-country collaborations which also could have implications for this debate.

Cécile Matthews: In the past, payers paid relatively little attention to rare diseases because patient numbers and overall spending were both low. Much of payers' attention was focused on escalating costs in therapeutic areas like oncology. But with oncology prices plateauing and industry increasingly identifying unmet needs in rare diseases, prices will come under closer scrutiny. It will no longer be enough for payers that a new therapy targets a small patient population. As a result, industry will need to develop more holistic approaches incorporating the views of PAGs and including elements such as registry data and longitudinal research. Compelling evidence that demonstrates real value will be key to managing higher prices.

In a further development, there is significant scope to improve early access programs, both from the perspective of the healthcare system itself and their utilization by manufacturers. In this respect, we have already seen improvements in the French ATU system (*Autorisation Temporaire d'Utilisation*, Authorization for Temporary Use) which was previously reserved for first indications but has now been extended to cover indication expansions.

With the rise in expensive new therapies in rare diseases, there will also be much further discussion – there has been plenty already – about alternative payment models. It is unlikely, for example, that biosimilars are going to free up sufficient resources to fund the new technologies coming to market. Despite their reluctance to implement innovative payment models, payers are going to have to find new solutions and industry can help provide some of the answers. It remains unclear what direction these discussions will take but payers will seek innovative methods of managing, mitigating, and sharing the costs of the many new products coming to market, particularly in high-profile cell and gene therapies.

CRA experience in rare diseases

Neil Turner: What experience does CRA bring to rare diseases?

Kevin Brubacher: The only thing rarer than rare disease patients are rare disease commercialization experts. Rare diseases are a significant aspect of our offering at CRA, spanning commercial strategy and planning, pipeline development and opportunity assessments, tactical planning, pricing and market access, patient-finding, KOL [key opinion leader] identification and development planning, and real-world evidence strategies, among other services. CRA is typically brought in to ensure rare disease commercialization preparation is in line with shareholder expectations for excellence in market performance.

Tim Wilsdon: We have worked on a lot of orphan medicines for a variety of clients from 'Big Pharma' to focused rare disease companies. We've helped clients assess the value of national rare disease plans and the importance of different incentives given their portfolio. These efforts have led to work developing scenarios regarding how the incentive regime could change and how best to prepare for this.

Greg Bell: In many projects, the fact that we are dealing with a rare disease has been central to our approach. For example, we worked with one company to design and implement a patient tracking tool to identify where the patients are and follow them over time – such is the long-term value of each individual patient in rare and ultra-rare diseases. Accordingly, we are developing a platform that rare disease companies will be able to use to bring some discipline to their patient finding and tracking initiatives. This type of patient-specific marketing has not been considered appropriate for products with much larger indications but advances in digital marketing are starting to bring some patient-specific rare disease commercialization strategies and tactics into broader use.

Cécile Matthews: We support two main client groups in rare diseases. The first is 'Big Pharma' where we help cross-functional teams adapt their approaches in the rare disease space. In a recent example, we helped a client develop a detailed pricing, market access and evidence plan for a pediatric orphan indication in which the epidemiological data was patchy, there was little in the literature and no price comparator – all typical challenges in rare disease. We are also helping the same client bring together inconsistent registry and claims data into a comprehensive patient journey for the US and Europe. In addition, we work with smaller clients and start-ups that do not have the internal infrastructure to see a product for a rare disease through the market access process. For example, we partnered with a start-up with a non-oncology asset in an ultra-rare disease. Here it was more of a long-term partnership – becoming part of the team – thinking through the value proposition early in development and building an evidence plan to support the strategy. We have since moved on to implementation and are currently helping the team with mock payer negotiations.

Ned Kitfield: Typical commercial strategy projects in rare diseases include building a forecast model, conjoint analysis, and developing roadmaps and playbooks – not dissimilar to other projects. The big difference, however, is finding the patients in the first place, which has certainly been the case on a recent patient journey project for a drug for an ultra-rare disease in phase 3. The same is true of an opportunity assessment for a gene therapy which involves

tracking patients across multiple countries and includes segmentation, patient flow, war gaming and competitive simulation.

Takeaway messages in rare diseases

Neil Turner: If you were to give your clients in rare diseases one piece of advice, what would it be?

Greg Bell: Tried and tested approaches to commercialization are not going to work in rare diseases. The standard commercial model on which the industry has been based for many years does not fit the profile of the new generation of potentially curative treatments. Pharma companies with rare disease pipelines need to be reconsidering their commercial models to optimize the opportunities presented by their new products in rare diseases.

Ned Kitfield: Start identifying the patients as early as possible because they are much more difficult to find in rare diseases than in therapeutic areas with higher prevalence and incidence. For example, for the launch of Kalydeco, Vertex partnered with a PAG and achieved a 90% share six months after launch.

Cécile Matthews: Start your planning early and focus on the evidence. For example, what should your clinical trial look like to demonstrate value? What will you need to show in your HTA dossiers? And what can you learn from previous launches in rare diseases? Payer negotiations will be tough, and demonstrations of value and evidence will be even tougher, so take maximum advantage of early access schemes, patient registries and relationships with PAGs to create a compelling value story that highlights and addresses unmet need.

Tim Wilsdon: From a government affairs and policy perspective, it is often a debate about whether the industry is focusing only on commercial returns or putting the patient first and being willing to work with payers on innovative solutions. It is useful to work with, and listen to, other stakeholders like PAGs, ensuring that unmet need is well understood, and that programs exist to ensure patients have access to new therapies as early as possible The important thing is to be able to explain the challenges facing the assessment of medicines for rare diseases and how companies can work with policymakers, payers and other stakeholders to address their concerns.

Kevin Brubacher: I would advise two things. First, find the patients. In rare diseases, estimates on the numbers of patients are theoretical at best. When setting up initial commercial planning, finding the patients is the first key to connecting them to care. Unfortunately, there is no simple dataset or off-the-shelf method of finding patients, and this is complicated by the specific nature of the rare disease. Second, I advise clients to pay at least equal attention to the future payer landscape and allow for payer consultation early in the clinical development process, versus the traditional approach of focusing almost exclusively on the scientific community. While both are important, I'd suggest as much as 75% of the initial effort needs to go into the payer landscape and 25% into the scientific community.

About CRA and the Life Sciences Practice

The Life Sciences Practice works with leading biotech, medical device, and pharmaceutical companies; law firms; regulatory agencies; and national and international industry associations. We provide the analytical expertise and industry experience needed to address the industry's toughest issues. We have a reputation for rigorous and innovative analysis, careful attention to detail, and the ability to work effectively as part of a wider team of advisers. To learn more, visit **crai.com/lifesciences**.

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