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KEY CONSIDERATIONS FOR RARE DISEASE DUE DILIGENCE

The Growing Rare Disease Market

Asking the Right Questions

CLINICAL AND R&D

FORECASTING AND VALUATION

STRATEGY AND COMMERCIALIZATION

Moving Forward

PUBLISHED JUNE 2021

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THE GROWING RARE DISEASE MARKET

Despite the name, rare diseases aren't rare. The number of people living with rare diseases is sizable, estimated at 25-30 million people in the US alone.[1] With as many as 7,000 rare diseases in existence, these complex diseases present a significant growth opportunity for pharmaceutical companies.[2] Approximately 95% of rare diseases have no approved treatments.[3] The acquisition of rare disease assets offers the opportunity for pharmaceutical companies to grow in a market projected to be $217 Billion worldwide by 2024, comprising over 18% of all prescription sales.[4]

ASKING THE RIGHT QUESTIONS

Commercial due diligence is the foundation of any successful acquisition. Due to the unique nature of rare diseases, pharmaceutical companies interested in entering or expanding within the space must include additional considerations in their due diligence process. Business development teams often evaluate deals across three dimensions:

1 

Clinical and R&D

Clinical Trial Efficiencies and Inefficiencies | Patient Finding

2 

Forecasting and Valuation

Market Sizing | Pricing and Market Access

3 

Strategy and Commercialization

Commercial Synergy | Degree of Integration | Lifecycle Management | Patient Community

[1] *https://rarediseases.info.nih.gov/diseases/pages/31/faqs-about-rare-diseases*
[2] *https://rarediseases.info.nih.gov/diseases/pages/31/faqs-about-rare-diseases*
[3] *https://www.phrma.org/en/Media/Progress-in-Fighting-Rare-Diseases*
[4] *EvaluatePharma Orphan Drug Report 2020 https://www.evaluate.com/media/2741/download*

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Clinical and R&D

When evaluating the clinical and R&D costs and feasibility for a rare disease asset, there are several considerations that require additional attention during diligence:

Clinical Trial Efficiencies and Inefficiencies

- **How long will clinical trial recruitment take?** While clinical trials for rare diseases have lower sample size requirements vs. other diseases, the limited number of potential enrollees and geographic dispersion could result in longer recruiting periods and lower retention. Periodically, some rare disease trials will enroll quickly due to small study size requirements, pent-up demand, and strong advocacy and support groups to enable participant identification

- **How will orphan regulations influence the timeline?** The EMA and FDA support innovative trial designs and analyses that are intended to help companies overcome the challenges of conducting rare disease trials.[5] In addition, the FDA's programs designated for Priority Review, Breakthrough Therapy, Accelerated Approval, and Fast Track can reduce a drug's time to market by several years in some cases

- **Will clinical trial size negatively impact revenues?** When considering gene therapies and curative treatments for ultra-rare diseases, overcommitting to the number of patients for a clinical trial could negatively impact long-term revenues if the study design requires enrollment from a meaningful proportion of the addressable patient population. For other non-curative treatments treating chronic illness, there is no negative impact on revenue

Patient Finding

- **Is a "test and treat" model required?** Companion diagnostics (CDx) and other "test and treat" models can make approval more likely. Historically, therapies that use biomarkers for inclusion or exclusion criteria are three times more likely to be approved[6]

- **How are patients getting diagnosed and referred?** Breaking down the steps in the diagnosis process enables a clear view into any gaps in diagnosis and could inform site selection. In addition, developing a deep understanding of diagnosis and referral gaps could point to underreported prevalence or opportunities for disease education and market development

The FDA's programs designated for Priority Review, Breakthrough Therapy, Accelerated Approval, and Fast Track can reduce a drug's time to market by several years

[5] *https://www.fda.gov/media/131882/download*
[6] *https://invivo.pharmaintelligence.informa.com/IV005045/Companion-Diagnostics-The-Expanding-Reach-Of-Personalized-Medicine*

Forecasting and Valuation

While BD teams should follow their standard processes for forecasting and valuation, there are additional considerations to pay special attention to regarding forecasting:

Market Sizing

- **Is the market size accurate?** Due to a lack of awareness around some rare diseases, many patients go undiagnosed, which, if not accounted for, could impact the accuracy of a forecast that could fail to capture diagnosis growth potential. Patients are also frequently misdiagnosed, having to see multiple specialists before getting an accurate diagnosis, if they have access to those specialists at all. Many rare diseases do not have International Classification of Disease (ICD-10) codes, which is a major barrier in determining market size accurately, as well as tracking disease information

- **How many doctors treat the disease?** Many of these diseases have a small set of specialists who treat them at Centers of Excellence for the disease. Understanding these healthcare providers' patient volumes can be critical in sizing the market and determining go-to-market requirements and costs

- **What is the growth potential?** Though the market size for a rare disease is small by definition, companies can investigate several avenues for market growth and development, like raising awareness or creating venues for increased and early diagnosis. For example, Spark Therapeutics sponsored a free genetic testing program for RPE65 mutations to identify candidates for LUXTURNA, their gene therapy for inherited retinal disease[7]

- **What is the treatment protocol?** Treatment protocols will impact a variety of factors, including market size, price, and revenue recognition. Singular lifetime curative treatments decrease the eligible patient population after reaching patients with the treatment.[8] For chronic treatments, medication adherence can vary dramatically based on treatment protocols and available support programs

- **Are alternative market sizing approaches needed?** Taking a traditional top-down, epidemiology-based modeling approach requires an accurate estimate of the target patient population. For many rare diseases with diagnosis gaps, it may be more accurate to build the forecast based on a better-quantified starting point, such as the known number of treating physicians

[7] *https://informaconnect.com/gene-therapy-diagnostic-testing/*
[8] *https://www.soa.org/globalassets/assets/files/resources/research-report/2018/evaluating-payment-models.pdf*

Forecasting and Valuation (cont.)

Pricing and Market Access

- **What pricing models optimize access and revenue?** While the average cost of a rare disease treatment per patient in 2019 was $32,000, some treatments cost over $500,000 per patient per year.[9] With such a broad spectrum in pricing, payers are increasingly demanding alternative payment models. For costlier, potentially curative treatments, like gene therapy, many payers are seeking pay-per-performance models or annuity payments models, to spread the sum owed out over regular payments. Alternative payments models can increase access, but drive higher administrative burden and uncertainty relating to rebates and net pricing

- **What access and assistance programs are needed?** Due to the high prices associated with most rare disease treatments, access and affordability often become adoption hurdles. Patient assistance programs are essential tools to increase access. Rare disease treatments typically require higher levels of patient assistance, from case management support to financial assistance via coupon, direct discounts, and more. Alternative pre-approval paths, like Managed Access programs, allow those who cannot enroll in a clinical trial to access life-saving and life-altering treatments. Novartis' Zolgensma, a gene therapy for children with spinal muscular atrophy (SMA), costs $2.1 Million for the one-time treatment and provides a unique assistance model example. Novartis's global Managed Access Program allocates 100 free doses annually to eligible patients[10]

- **What is the competition within the space?** Although rare diseases have historically been less competitive, rare disease development programs are increasing dramatically. In 2020, the FDA received 753 new requests for orphan designation, a 41% increase from 2019.[11] The emerging competitive landscape can create even more challenging access for new treatments. Additionally, large pharmaceutical companies, such as Johnson & Johnson and Pfizer, are forecasted to make up 8 out of 10 of the top orphan drug companies in 2024.[12] The increase of large pharma in the rare disease space could have major implications on pricing and market access; these companies have the resources and experience to negotiate access and manage the increased complexity

While the average cost of a rare disease treatment per patient in 2019 was $32,000, some treatments cost over $500,000 per patient per year

[9] *https://rarediseases.org/wp-content/uploads/2021/03/orphan-drugs-in-the-united-states-NRD-2020.pdf*
[10] *https://www.novartis.com/news/novartis-gene-therapies-recommits-global-managed-access-program-2021*
[11] *https://www.fda.gov/industry/orphan-products-development-events/fda-rare-disease-day-2021*
[12] *EvaluatePharma Orphan Drug Report 2020 https://www.evaluate.com/media/2741/download*

Strategy and Commercialization

Perhaps the most vital aspect of rare disease due diligence is determining if an asset is a strategic fit for your company. There are four strategic perspectives BD teams must consider:

Commercial Synergy

- **Are you overestimating your commercial synergies?** Companies cannot assume that sales relationships focused on more common diseases will carry through to rare diseases treated by the same medical specialty, given the very specialized treatment of many rare diseases

- **How will you customize your go-to-market strategy?** For any rare disease, the go-to-market (GTM) strategy must be hyper-customized given the small patient population, highly specialized community of healthcare providers treating the condition, and often restricted referral pathways. A successful rare disease GTM strategy requires tailored medical, access, patient advocacy, and marketing capabilities that acquiring companies may not be equipped with. BD teams should evaluate internally and prepare to build out those capabilities if needed

Degree of Integration

- **How much can the businesses integrate?** Integrations can range from an acquired company fully integrating into the acquiring company to an acquired company being left as an operating company. Ipsen's over $1 Billion acquisition of Clementina Pharmaceuticals to boost their rare disease offerings showcases a full integration, absorbing the company.[13] Johnson & Johnson's $30 Billion acquisition of Actelion and incorporation into their portfolio with Janssen showcases another degree of integration. Prior to the acquisition, Actelion spun out its R&D function into a Swiss biopharmaceutical company called R&D New Co., which is now Idorisa.[14] Roche's $4.8 Billion acquisition of Spark Therapeutics is on the other side of the spectrum, with Spark continuing its operations as an independent company following the deal.[15] When assessing an asset, BD teams must consider what can and cannot be integrated between companies. Back-office operations, like Human Resources and Finance, are usually easier to integrate, while more specialized departments, like R&D and manufacturing, can be harder to integrate

[13] *https://www.ipsen.com/press-releases/ipsen-to-acquire-clementia-pharmaceuticals-to-significantly-boost-rare-disease-portfolio/*
[14] *https://www.jnj.com/media-center/press-releases/johnson-johnson-to-acquire-actelion*
[15] *https://sparktx.com/press_releases/spark-therapeutics-enters-into-definitive-merger-agreement-with-roche/*

Strategy and Commercialization (cont.)

Lifecycle Management

- **Can the treatment expand into other populations?** Single indications in the rare disease space often carry modest commercial potential, so rare disease companies typically pursue multiple, related indications to maximize platform value. Companies can utilize the additional pathways created by the FDA's expanded access programs to reach a wider market. After a successful phase 2 clinical trial, a treatment can gain expanded access.[16] Alexion Pharmaceuticals' Ultomiris was initially approved in 2018 for adults with paroxysmal nocturnal hemoglobinuria (PHN) and has since expanded into atypical hemolytic uremic syndrome (aHUS).[17] Alexion is pursuing several other rare indications with Ultomiris, including generalized Myasthenia Gravis (gMG), amyotrophic lateral sclerosis (ALS), and Neuromyelitis Optica Spectrum Disorder (NMOSD), as well as severe COVID-19.[18] The extensive lifecycle management plan drove significant deal value in the recent AstraZeneca acquisition of the company[19]

- **Can the treatment expand within the indication?** Most diseases have subtypes, and there is no cap on the number of subtypes companies can seek approval for when one is a rare disease.[20] Gaining additional orphan status for each subtype of an indication can create a larger base of exclusivity

- **Can you be first to market?** Within the rare disease market, generics, biosimilars, and novel entrants are less common due to the small market sizes.[21] This lack of competition allows a singular company to reach more patients and raises barriers for new companies considering entering the space

- **Do new capabilities create additional synergies?** In developing and commercializing a rare disease treatment, companies often need to build out new manufacturing and technological capabilities. Considering the market size and treatment type, companies must evaluate if they can leverage the new technology and capabilities for other indications or therapies

Patient Community

- **How influential are key organizations and community leaders?** Tapping into an identified support group, like patient or caregiver advocacy groups or disease specialists, that is seeking better care for patients could result in more advocacy for the treatment and a higher success rate in the long term

- **How friendly or adversarial do you expect the patient community to be with the treatment?** With rare diseases, companies could face advocacy groups more protective of a vulnerable patient population. Genentech's Hemlibra, a self-administered for all patients with hemophilia A, provides an example of a company positively engaging with the patient community, focusing on patient transparency through outreach and creating a patient website in response to community feedback that offered a high amount of detail[22]

- **Are there any ethical questions associated with the treatment of the disease?** Companies evaluating any potential rare disease assets may encounter more potential ethical challenges with treatment. One such question could come from patient demographics; around two-thirds of people diagnosed with rare diseases are children.[23] Treating children with rare diseases could pose ethical challenges around diagnostic techniques and clinical trial design

[16] *Journal of Rare Diseases Research & Treatment https://bit.ly/3vKOsDP*
[17] *https://ir.alexion.com/news-releases/news-release-details/alexion-announces-fda-approval-ultomirisr-ravulizumab-cwvz*
[18] *https://alexion.com/our-research/pipeline*
[19] *https://www.fiercepharma.com/pharma/astrazeneca-pushes-closer-to-ceo-s-40b-revenue-goal-39b-alexion-acquisition*
[20] *https://www.kellogg.northwestern.edu/faculty/garthwaite/htm/2018_NBER_IPE.pdf*
[21] *https://www.kellogg.northwestern.edu/faculty/garthwaite/htm/2018_NBER_IPE.pdf*
[22] *https://www.mmm-online.com/home/channel/features/4-rare-disease-campaigns-that-conquered-challenges-around-marketing-these-conditions/*
[23] *https://rarediseases.org/wp-content/uploads/2019/01/RDD-FAQ-2019.pdf*

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MOVING FORWARD

The rapid growth of the rare disease therapy market is a chance for companies to meet the needs of underserved patient population. When considering acquiring rare disease assets, thorough due diligence enables strategic choices and lays the groundwork for a smooth transition. Kx Advisors acts as a partner to guide your BD team through the rare disease due diligence process, from regulatory landscaping to synergy valuation. Our team can help you discern the most profitable market segments, setting your company up for long-term acquisition success.

ABOUT Kx

For more than 30 years, Kx Advisors (operating as Kaiser Associates' healthcare practice) has provided strategy consulting services to help healthcare executives achieve critical business growth goals. With a highly collaborative approach they have developed pragmatic solutions for leading pharmaceutical, biotechnology, medical device, health IT, and digital health clients, with data-driven insights to give those clients the tools to compete and win across the healthcare industry.

ABOUT THE AUTHORS

Dan O'Neill

Dan is a Managing Partner at Kx Advisors, based in Washington, DC.

You may contact him by email at dan.oneill@kxadvisors.com

Bob Serrano

Bob is a Managing Partner at Kx Advisors, based in Washington, DC.

You may contact him by email at bob.serrano@kxadvisors.com

Special thanks to Jenna Riffell, Abby Rohman, and Sean Vander Linde for their contributions to this piece

Design and Graphics by Kelly Martin Design

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