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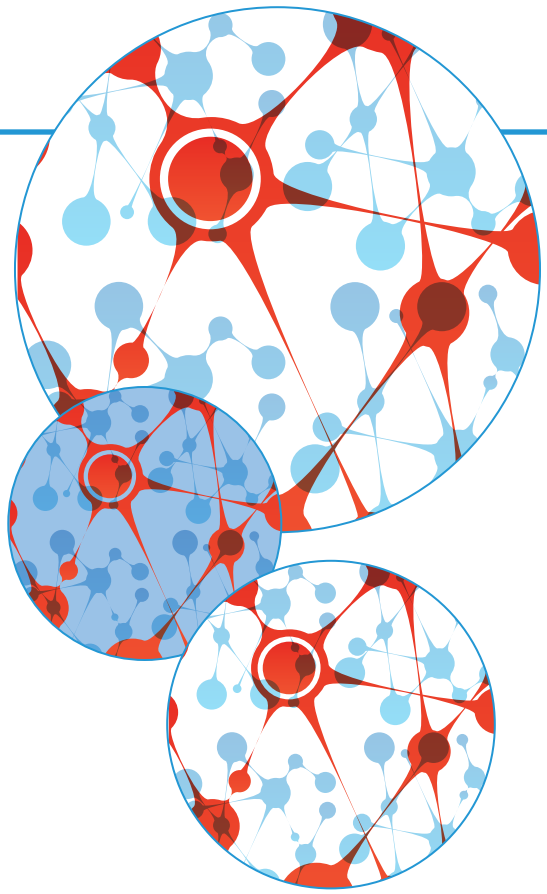

Orphans Should Live Alone

For larger organizations with interests in rare diseases, we believe it is necessary to maintain a separation from the rest of the company in order to keep the culture needed for successful product commercialization. Easier said than done.

BY ALAIN J. GILBERT, ANNE-SOPHIE DEMANGE AND MARK RATNER

- The organization and culture of a rare disease specialist company or program is distinct from that of a traditional pharma or biotech. Commercial success is driven by a patient-centric model focused on access and interactions with KOLs and less on selling features and benefits.
- An ability to connect with rare disease patient communities and physicians at the level of senior management is paramount, giving an advantage to companies of small size: it is the kind of representation a large company cannot afford for a relatively small product line.
- With size and diversity of markets often comes more rigidity and standardization of practices. Many more processes are in place at large firms and decision-making is often dominated by a committee structure. That makes alignment with a successful rare disease model difficult.
- It may be easier for larger firms to acquire ultra-rare disease firms after they have become successful, as Sanofi did with Genzyme – initially leaving it alone to preserve the benefit of the asset.
- We therefore believe orphan drug franchises should live alone – at least until they reach a level of maturity to withstand structural organizational pressures.

Two recent events have brought into relief important considerations around the business models for developing and selling drugs for rare (ultra-orphan) diseases. **Shire PLC**'s latest acquisition, of **Baxalta Inc.**, will create a specialist rare disease firm of unprecedented size, raising the question of whether the effectiveness of individual programs that by definition are targeted to very small patient populations can maintain their identity and integrity within the organizational structure. **Sanofi**'s decision to more fully integrate its **Genzyme Corp.** into the larger organization as the **Sanofi Genzyme** specialty care business unit similarly calls into question whether the move will remove some of the independence that is widely acknowledged as being critical to the successful development of rare disease drugs. Sanofi completed its acquisition of Genzyme in February 2011.

CULTURE CLASHES TO CONSIDER

Large, established pharmaceutical firms have shown interest in drugs for ultra-orphan diseases, either through R&D or licensing/acquisition. Shire and Sanofi can argue a degree of success. Much of the Shire organization has been centered on ultra-orphan markets since its takeover of **Transkaryotic Therapies Inc.** (TKT) in 2005, which brought it into the lysosomal storage disease therapy area, where it still competes with Sanofi Genzyme. Among big pharmas, **Pfizer Inc.** and **GlaxoSmithKline PLC** have initiated rare disease programs but do not have much to show for them today. Pure-play rare disease specialists including **Biomarin Pharmaceutical Inc.**, **Alexion Pharmaceuticals Inc.** and **Ultragenyx Pharmaceutical Inc.** have emerged, using a combination of internal R&D and in-licensing/M&A to build a portfolio. We believe the distinct culture and development structure needed for a successful rare disease business, especially when weighed against the ability of such assets to drive topline growth in a large firm, argues against conglomerating them inside a traditionally structured pharmaceutical business.

There are general differences between small biotechs and traditional established pharmaceutical firms. In a small company, management is usually dedicated to the disease space it is serving – a therapy area often represents most of or the entire business, which means having to worry less about maximizing ROI across a variety of opportunities in a portfolio. Smaller companies are often bolder, acting with greater flexibility and risk tolerance.

The contrast between large and small is sharpest in the rare disease space, where com-

mercial success is driven by a business model focused on patient access, building relationships with key opinion leaders (KOLs) and establishing new clinical development, regulatory and market access pathways – and less on selling features and benefits of a drug.

Having a patient-focused process is the only way to sell drugs for rare diseases effectively: the nature of these diseases and the unknowns around diagnosing and treating them mandate finding the patient population that needs treatment, educating them to what a drug does, getting them on therapy quickly and helping with country to country reimbursement – a very different model, for example, than having developed an interesting blood pressure medication and selling it into a huge space with millions of patients using a large sales force where the key factors are marketing and competition. Success in a small disease space is also oriented around a physician to physician relationship – making sure KOLs know you, that clinical investigators and physicians trust the company and providing a high level of education. The interaction is more collegial, rather than having a sales and marketing group target physicians.

It is a white glove approach to the patients that includes working with advocacy groups, understanding the natural history of a disease, making sure the organization works closely with the advocacy community to educate it about the product, helping to identify patients and recruit them for trials, and making sure that they understand the purpose of a trial. Physician-sponsored studies to learn about a drug in the post-approval setting are similarly more important than in other areas. The entire process builds a company's credibility as an entity trying to advance the science and not just sell a drug. So physicians become more interested: they participate actively in the clinical development plan, best represent patients' needs and are more loyal to the drug developer.

The approach is also more integrated than what you see in a large company. A big pharma will have thousands of researchers, so from the company perspective, there is often a different level of need to seek out academics for their expertise. In a small company, however, such outreach is needed for expertise and access to patients. "The exchange helps a company get a better sense of what patients are looking for," says John Maraganore, PhD, CEO of **Alnylam Pharmaceuticals Inc.**, whose lead program is in the rare genetic disorder transthyretin-mediated amyloidosis (ATTR). "It is a high impact part of developing drugs in this space."

The patient voice is a more important part of the regulatory process than ever, making the model even more partnership driven. With FDASIA, the FDA safety and drug development program introduced in 2012, a company has to be even more certain it has strong advocates that can help discuss the need for a rare disease drug to FDA. Most small rare disease companies could not do this alone: they need the support of patient advocacy groups and to have physicians and researchers in the field working with them to be able to bring new technologies to market. The interaction is driven more by relationships than by common commercial practices. (*See sidebar, "DMD In The Spotlight."*)

Building those relationships can be a badge of distinction: a large part of being patient centric is having direct interaction with patient communities, particularly at meetings. "It's one example of how impactful small size and senior representation can be on how well the company can do," Maraganore says. A large pharma is not likely to send such a senior contingent.

"We invite patients to come in and talk about their experience and make that available to all employees, who come with great interest to see how what they are working on can make a difference in people's lives," Maraganore says. "In our scale and size it is something very distinct and part of our culture, which is harder to achieve in a larger company."

Unlike some others in the rare disease space, Alnylam also has programs targeting broader indications in metabolic and infectious diseases. "The risk for us is as we get bigger and expand our portfolio beyond the rare disease space, as we grow in size, maintaining a patient-centric culture will become harder," Maraganore says. "As you grow, you have to introduce processes to scale. But there are good examples of companies that have done it well." For this reason, Alnylam was comfortable partnering with Sanofi Genzyme on its ATTR program, a deal later expanded to include other genetic diseases.

Several issues can stand in the way of a larger organization's ability to execute with the flexibility and creativity that mark successful rare disease franchises. With size come more rigid and standardized practices and a decision-making process often dominated by a committee structure. In a small company, nobody is there to bless decisions: executives have to be comfortable making decisions very quickly based on the information at hand and enjoy the larger responsible role they have to take on. In many ways, a rare disease company is doing things no one has done before, especially getting a first-in-class drug approved in a new indication. There is no pathway, no roadmap.

Legal corporate compliance policies at big pharma instituted across the board, often as a result of issues raised by off-label marketing, may not allow for direct interaction with patients at meetings and other settings. It is hard to imagine a company that feels that as a matter of corporate risk they cannot closely interact with patients or patient groups as part of how they do drug development aligning with a patient-centric mentality.

When orphan drugs and broader specialty drugs have been combined, "at some point, the way of working was totally transformed," says Anny Bedard, former vice president, Asia Pacific for Shire and now an advisor to early-stage companies developing drugs for orphan diseases. The metrics are simpler and more direct in a rare disease business: the focus is squarely on what is needed to make sure patients get the drug they need when they need it. "It's a different conversation that occurs," she says. "My experience has been that it works better when this culture is kept isolated and not diluted into another bigger, broader culture."

When creating a rare disease business unit within a large established pharmaceutical company, the functions that would be supporting that business unit need to have a biotechnology mind-set. "I spent 25 years in big pharma and when I moved to the rare disease space I had to relearn everything I knew, especially when it comes to clinical development, market characterization and access and the interaction with patients," says Francois Nader, MD, former CEO of

DMD IN THE SPOTLIGHT

The FDA draft guidance for Duchenne's muscular dystrophy drug development, which advocacy groups tried to push through to make sure the agency understood the complications of getting some of these drugs approved, is a good example of stakeholder interaction in the rare disease space. FDA asked Parent Project Muscular Dystrophy to start putting a draft together. A number of people, not only patient advocates but experts in dystrophin, imaging, clinical outcome measures and natural history, and then a variety of companies, including **Sarepta Therapeutics Inc.**, Prosensa Therapeutics (now part of **BioMarin Pharmaceutical Inc.**), **Shire PLC** and **PTC Therapeutics Inc.**, were involved. Having academics and multiple companies working in a precompetitive space full of development unknowns is something that is not typical for a large company to do.

As part of the process, Sarepta allowed **Summit Therapeutics PLC**, a company working on utrophin regulation, to use its protocol for collecting muscle samples. So much is unknown in the rare disease space that companies will work together to try to come up with a new way of looking at a disease and potentially new endpoints, to help ensure that their drugs will be reviewed and approved quickly. They are trying to standardize the way they do things and in some ways standardize the way they do the same tests. The DMD patient community pointed out that companies will even conduct the six-minute walk test slightly differently.

Despite the guidance, FDA rejected Biomarin's application, canceled Sarepta's advisory committee meeting and delayed completion of its review of Sarepta's drug until May 2016. (*See "BioMarin's Drisapersen 'Compete Response' Shows FDA Flexibility Still Limited"* — "The Pink Sheet" DAILY, *January 14, 2016 and "Sarepta's Duchenne Treatment Likely Making Progress At FDA"* — "The Pink Sheet" DAILY, *February 8, 2016.*) Both companies are forging ahead, but in light of these developments, it will be interesting to see how motivated **Pfizer Inc.** and **GlaxoSmithKline PLC** will be to continue their DMD drug development plans.

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NPS Pharmaceuticals Inc., which Shire acquired in 2015. "It is not how big pharma is usually structured." This may be especially true in R&D and regulatory, which are charged with designing and implementing the clinical trials. "Probably the key factor could be as simple or as complex as determining a clinically meaningful endpoint," Nader says.

"Some of the companies spend too much time on the bench without knowing how it will change someone's life," adds Rogerio Vivaldi, MD, chief commercial officer of retinal gene therapy developer **Spark Therapeutics Inc.** and former head of the rare disease business at Genzyme. "I think there is still a big separation in terms of transferring the research [into commercial]," he says. **Aegerion Pharmaceuticals Inc.**'s *Myalept* (metreleptin) is a good example. Originally thought of as a potential blockbuster diabetes drug, it passed through several hands, eventually finding its niche as a treatment for the complications of leptin deficiency in patients with generalized lipodystrophy. (*See "Repurposing Leptin (Part 2): It Really Is A One-In-A-Million Drug"* — The RPM Report, *December 2013.*) Aegerion acquired it from **AstraZeneca PLC** in 2014.

To be successful, a big pharma should carve out a niche for a rare disease business that is in many ways protected from the rest of the company. Because the development requirements are so unlike the organizational and tactical elements of commercializing drugs for large indications, it should be isolated. And that requires a commitment from senior management. GSK, for example, has not shown that commitment at the senior level to support its rare disease efforts. Pfizer launched an orphan and genetic diseases research unit in 2010, bolstering it with the acquisition of **FoldRx Pharmaceuticals Inc.** But it failed to secure US approval for FoldRx's tafamadis for transthyretin familial amyloid polyneuropathy, and internal support now appears problematic.

The best model has been one in which a rare disease company is acquired and more or less left alone to interact with the customer. "Where it has gone poorly is where they have tried to build it from scratch," Vivaldi says.

The **Children's Hospital of Philadelphia** was a founding partner and the sole initial investor in Spark. This could be a model for hospitals and other academic institutions to look at in rare diseases, says Spark CEO Jeffrey Marrazzo, especially as funding from the **National Institutes of Health** is tighter now.

The very fact of a disease being rare often allows for trials that are highly concentrated and focused, and in many cases less costly than for more common diseases. "Because of that, you have and will see hospitals carry the ball farther down the road," Marrazzo says – especially for technologies that are five to 10 years away from commercialization, where the interest of the investment community or corporate partners may be less. Spark does have an agreement with Pfizer for development of its hemophilia B gene therapy, SPK-FIX. Pfizer has been marketing the recombinant Factor IX *BeneFix* for hemophilia B since the mid-1990s. But competition has increased in that indication. "They were looking at how to maintain their leadership position and leapfrog some new recombinant proteins," Marrazzo says. Indeed, investing for the long term may be one strategy that makes sense for big pharma in rare diseases.

Exhibit 1

Acquisitions By Selected Rare Disease Specialists

COMPANY/ COMPANY ACQUIRED (DATE ANNOUNCED)	POTENTIAL ACQUISITION VALUE ($)	MAJOR ASSET(S) ACQUIRED
SHIRE (EXCLUDES PROGRAMS IN OPTHTHALMOLOGY AND RENAL DISEASES)		
Baxalta (Jan. 2016)	32bn	Recently approved antihemophilia factors Adynovate and Obizur, also Vonvendi for Gaucher's disease, along with a portfolio of other protein drugs in hematology, immunology and oncology. Over 50 programs that address rare diseases.
Dyax (Nov. 2015)	5.5bn	DX-2930, a long-acting plasma kallikrein inhibitor in Phase III testing, which would compete with Shire's Cinryze, its second-biggest drug, in hereditary angioedema. Also Kalbitor for treating acute attacks of HAE.
NPS Pharma (Jan. 2015)	4.9bn	Gattex for short bowel syndrome and Natpara for hypoparathyroidism.
ViroPharma (Nov. 2013)	3.3bn	Cinryze.
BIOMARIN		
Prosensa (Nov. 2014)	851m	Drisapersen for Duchenne's muscular dystrophy.
Zacharon (Jan. 2013)	144m	Small molecules for lysosomal storage disorders.
ZyStor (Aug. 2010)	115m	Reveglucosidase for Pompe disease.
Huxley (Oct. 2009)	58.5m	Firdapse for Lambert-Eaton myasthenic syndrome.
ALEXION		
Synageva BioPharma (May 2015)	8.56bn	Kanuma for lysosomal acid lipase deficiency.
Enobia (Dec. 2011)	1.08bn	Strensiq for hypophosphatasia.

SOURCE: *Strategic Transactions*

WHERE IS THE LEVERAGE?

A key consideration of acquisitions generally is the degree of leverage and efficiencies of scale gained in combining organizations. In the rare disease space an acquirer offers few advantages in this regard, assuming the acquired firm has established domain expertise in its core therapeutic area. That is, unless an acquirer already is immersed in rare diseases. "As you build capabilities you begin to see connections to adjacent therapeutic areas," says Mark Enyedy, head of corporate development at Shire. This is particularly the cases in medical affairs, where experience with natural history – especially bringing the first therapeutic to an area – is key, as well as with registries, diagnostics, patient management and market access. "Once you have a basic understanding of managing small populations, that experience can be extrapolated from one rare disease area to another," he says.

That said, execution still requires focus and a dedicated force. When it first launched *Firazyr* (icatibant), its first product for hereditary angioedema (HAE), Shire tried in some markets to leverage the sales force by selling it with the existing lysosomal storage disease portfolio, adding the HAE product to the bag. It didn't work.

Since its 2005 acquisition of TKT, Shire has been an aggressive acquirer. It recently bolstered its franchise in HAE (which originated with its takeover of **Jerini AG** in 2008) with the additions of **Dyax Corp.** and **ViroPharma Inc.** and with Baxalta, added a core franchise in hemophilia along with assets in immunology and oncology. (*See Exhibit 1.*) With the acquisition of Viropharma, Shire created a fully-dedicated HAE team supporting both Firazyr and Viropharma's C1 esterase inhibitor, *Cinryze*. The model was different with NPS, however. There, Shire added the NPS portfolio to its existing GI business and integrated its centralized patient management capabilities to support NPS's products *Gattex* (teduglutide) for short bowel syndrome and *Natpara* (parathyroid hormone) for hypoparathyroidism.

"As you continue to optimize the rare disease business model to enhance the level of service and care for patients, it creates the opportunity to maintain that level of focus, notwithstanding the increase in size," Enyedy says.

The creativity applied to designing a development pathway can transfer across rare disease areas. There was a significant cross-fertilization between the different therapeutic areas – GI and endocrinology – within NPS, for example. "On the surface,

Exhibit 2

Competitive Areas In Rare Diseases (Commercial Competition)

DISEASE AREA	MAJOR COMMERCIAL DRUGS (NON-EXHAUSTIVE LIST)				ADVANCED PIPELINE DRUGS (NON-EXHAUSTIVE LIST)	
	COMPOUND 1	COMPOUND 2	COMPOUND 3	COMPOUND 4	COMPOUND 1	COMPOUND 2
Fabry disease Genetic disorder	Fabrazyme (Genzyme) agalsidase beta **Marketed**	Replagal (Shire) agalsidase alfa **Marketed**			Galafold (Amicus) migalastat **Pre-reg**	
Gaucher's disease Genetic disorder	Cerezyme (Genzyme) imiglucerase **Marketed**	Cerdelga (Genzyme) eliglustat **Marketed**	Vpriv (Shire) velaglucerase alfa **Marketed**	Zavesca (Actelion) miglustat **Marketed**	Oral glucocerebrosidase (Protalix BioTherapeutics) **Phase II**	
Pulmonary arterial hypertension (PAH) Cardiovascular	Revatio (Pfizer) sildenafil **Marketed**	Tracleer (Actelion) bosentan **Marketed**	Remodulin (United Therapeutics) treprostinil **Marketed**	Volibris (GSK/ Gilead) ambrisentan **Marketed**	Uptravi (Actelion) selexipag **Pre-reg**	Tadalafil (Eli Lilly) **Phase III**
Hereditary angioedema (HAE) Immunology	Cinryze and Firazyr (Shire) C1 esterase inhibitor and icatibant **Marketed**	Ruconest (Pharming Group) C1 esterase inhibitor **Marketed**	Berinert (CSL Behring) C1 esterase inhibitor **Marketed**	Danatrol (generic) (Sanofi) danazol **Marketed**	DX-2930 (Dyax now Shire) **Entering Phase III**	Avoralstat (BioCryst Pharmaceuticals) **Phase III**

SOURCES: *Biomedtracker;* Company reports

there were limited common denominators but the same team did both. In retrospect, if it would not have been the same team, the challenges would have been magnified," says Nader. It's not the "what," but the "how," which lends itself to commonalities in a big way, he says. How a team approaches the regulatory path, how to address the importance of an end of Phase II meeting with FDA or the structure of an NDA are uniquely important within the context a rare disease application.

Despite the novelty involved in establishing a commercialization pathway for an ultra-orphan product, competencies may be applied to multiple programs. The infrastructure cost of building a commercial organization is much the same across one product or three, says Nader, with further leverage gained if a company is in multiple geographic regions. "One general manager, one head of market access, one head of medical in a given geography can certainly absorb more than one product," he says.

Although a common development perspective exists across ultra-orphan disease indications, it differs from that within companies focusing on large indications. For the latter, precedents exist that can be referred to and lessons extracted that provide benchmarks for new development plans. "You have something to rely on," Nader says. That's not the case in the rare disease space. "You have to be innovative but at the same time creative in a way that would be accepted by the regulators and eventually lead to a product approval," he says.

We do have a word of caution in this regard, however. Sometimes a small company's boldness can backfire. It might make sense to power a clinical trial for a rare disease drug based on the small number of patients' prevalence. However, the data generated has to be sufficient for approval and also to demonstrate the value the drug brings to the health care system. Having the input of an experienced rare diseases strategic advisor can be very helpful, especially when planning for a global launch.

THE EFFECT OF COMPETITION

Increasingly, competition has become an added consideration in the rare disease space. "I think we are just at the beginning of a market situation where competition for indication and competition for products will be a meaningful segment of the market," Nader says. "I would certainly spend quite a bit of time studying the market dynamics

Exhibit 3

Competitive Areas In Rare Diseases (Competition Anticipated)

DISEASE AREA	COMMERCIAL DRUGS	PIPELINE DRUGS (NON-EXHAUSTIVE LIST)		
		COMPOUND 1	COMPOUND 2	COMPOUND 3
Paroxysmal nocturnal hemoglobinuria (PNH) Hematologic disorder	Soliris (Alexion) eculizumab **Marketed**	ALN-CC5 (Alnylam) **Phase II**	ALXN-1210 (Alexion) **Phase II**	Tesidolumab (Novartis) **Phase II**
Mucopolysaccharidosis II (MPS II or Hunter syndrome) Metabolic disorder	Elaprase (Shire/Genzyme) idursulfase **Marketed**	Odiparcil (Inventiva) **Phase II**	FT-1050 (Fate Therapeutics) **Phase I**	
Pompe disease Metabolic disorder	Myozyme (Genzyme) alglucosidase alfa **Marketed**	Reveglucosidase alfa (Biomarin) **Phase III**	GZ-402666 (Genzyme) **Phase III**	Alglucosidase alfa + duvoglustat (Amicus) **Phase II**
Phenyketonuria (PKU) Metabolic disorder	Kuvan (Merck/Biomarin) sapropterin **Marketed**	Pegvaliase (Biomarin) **Phase III**		
Familial lipoprotein lipase deficiency/ familial chylomicronemia syndrome Genetic disorders	Glybera (Chiesi/UniQure) alipogene tiparvovec **Marketed**	Volanesorsen (Ionis Pharma) **Phase III**	CAT-2003 (Catabasis) **Phase II**	
Familial amyloid cardiomyopathy Metabolic disorder	**N/A**	Revusiran (Genzyme/Alnylam) **Phase III**	Tolcapone (SOM Innovation) **Phase II**	
Duchenne's muscular dystrophy Genetic disorder	Translarna (PTC Therapeutics) ataluren **EMA Conditional Approval**	Kyndrisa (Biomarin) drisapersen **US: Rejected by FDA** **EU: Pre-reg**	Eteplirsen (Sarepta) **Pre-reg**	Domagrozumab (Pfizer) **Phase II**

SOURCES: *Biomedtracker;* Company reports

given how quickly competition is evolving nowadays, as there will be more and more pressure on pricing."

A lack of competition makes access and pricing more straightforward. And while a dedicated infrastructure to get access to the patients is needed, it does not have to be large and the overall NPV may be significantly more interesting, with products commanding value for longer than in other areas. We do not favor maintaining rare disease and large indication programs under the same roof; even if getting into the more competitive markets like Gaucher's or Fabry or HAE requires a little bit more of those skill sets of big pharma. "You need to shift the thinking of the solo blank space," says Bedard. "You need that and to make sure you have those competitive skill sets you typically find in big pharma."

New entrants needing to establish their credentials as companies recognized and committed to the rare disease space can more easily do so when the competition is limited or non-existent. Coming for the first time with the fourth product in the disease makes it hard to stand out and to establish relationships with the rare disease communities and organizations. Yet despite tremendous unmet need – with 7,000 rare diseases, only a few hundred have treatments – competition is attracted to some of the more established markets. (*See Exhibits 2 and 3.*)

Competitors may struggle because patients have an allegiance to the product that has allowed them to get control of their disease. So switching happens slowly – a factor bound to be magnified with the introduction of biosimilars for rare diseases. (*See "The Birth Of An Orphan Biosimilar Market" — this issue.*) "I think many of the new entrants see it as financially a way of perhaps getting a quick return, but there is nothing quick about the rare disease business," says

David Meeker, MD, executive vice president and head of Sanofi Genzyme. "You have to commit, do the hard work of working with communities, patient by patient, trying to improve outcomes. That's not something competitors are often willing to do." Plus, some of the largest areas of growth are in developing markets – early heath care systems where there is little infrastructure.

"The work that is required to support it is laborious," Meeker says. Operating margins are not what people think, and when that reality hits, they are "more sensible" about getting into a price war, he says, because giving a 5% to 10% discount to get a few more patients is not that significant. "The market force dynamics that drive significant pricing shifts in other areas are not in play here," he says.

THIS IS NOT FOR EVERYONE

Companies that fail in rare diseases – and they can be large or small – often miss the highly personal nature of the area. "Your proximity to the communities and your ability to connect with that aspect is infinitely greater and the expectations of the community as a result of that are different," says Meeker. "We are 20 years later in the area of Gaucher's disease and the level of disease awareness is still low," he says. Sanofi Genzyme is still diagnosing as many Gaucher's patients now as Genzyme did in the beginning.

Although Genzyme's presence in the disease has transformed the community, giving a patient a better chance of being diagnosed and getting an appropriate treatment, the company is still a long way from getting it right. "There are parts of the disease we don't treat well, parts of the world that can't access therapy in the same way that others can access it, and even in the best most sophisticated health care systems these patients are still missed," he says. The question for us is: does that prolonged time frame jibe with a big pharma's expectations for growth?

The R&D elements of the former Genzyme may now be more closely integrated with the global elements of Sanofi. That could be good: according to one partner, there previously may have been more uncertainty or ambiguity regarding who the key stakeholders were on the R&D side in the model that existed, when Genzyme had its own R&D autonomy from the rest of the organization. Instead of having to navigate through many people within the old organization to get key decisions made on trial design or budget, now the process may be more streamlined.

We agree that because Sanofi Genzyme had already been successful at the commercial level, it was easier for Sanofi to initially leave it alone and then integrate it, de-risking losing the benefit of the asset. It may be that the new set-up will not cause distractions because Sanofi has long viewed the rare disease space as one of the growth drivers for the company. On the other hand, it adds unrelated infrastructure that takes away from the pure-play nature of the rare disease business and could dilute the commitment-driven culture through absorption or departure – as has happened, for example, with **Roche**'s **Genentech Inc.** unit over time. (Note that while Meeker remains at the helm of Sanofi Genzyme, several executives including Vivaldi, Enyedy and Edward Kaye, MD, chief medical officer and interim CEO at **Sarepta Therapeutics Inc.**, which is applying an RNAi technology platform to the development of treatments for various forms of Duchenne's muscular dystrophy, were key members of the Genzyme team who departed post acquisition.)

In the 1990s, the big culture issue was around how to incorporate large-molecule drug development programs into an organization focused on developing small molecules, because of the differences in clinical development and manufacturing. That affected some parts of the organization. In the rare disease space, it's not only a few pieces of the organization, but from R&D all the way down to distribution, getting the drug into the hands of patients and sustaining them in terms of the service that they need. Rare disease drug development may be transformational in nature, but it does not have the range of opportunity biological drugs offered, which forced the pharmaceutical culture to embrace them.

Rightly, rare disease franchises are too valuable to ignore. Their development is important to patients and they represent a potential opportunity for innovation. But we also believe they are not for everyone, given the distinctive processes and practices needed to be successful. Certainly, a broad-based traditional pharmaceutical firm should leave these orphans alone – at least until they reach a level of maturity to be able to withstand structural organizational pressures. IV

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