Putnam
Inizio Advisory

WHITEPAPER

Biotech Path Archetypes from Pre-Clinical Stage to Commercial Success

AUTHORED BY

Mariah Hanley, PhD, Principal, Boston

RESEARCH CONTRIBUTORS

Regan Szalay, Senior Associate Consultant

Avninder Srivastava (Director), Shruti Sharma, Shruti Goyal, Ankit Srivastava

Introduction

Putnam has supported commercial and new product planning teams at pharmaceutical and biotech companies for over 30 years. In that time, many companies in the sector have transformed from relatively small pre-clinical or clinical-stage companies to large commercial organizations with several approved assets across global markets. With careful planning, there is an opportunity for biopharma companies to not only be successful with their first commercial launches but to parlay into continued future success as an independent company with a portfolio of assets for multiple indications.

In this piece, we review the paths of five prominent biotech companies, each of which took a different path to establish itself as a successful commercial-stage organization. When looking at this history collectively, two archetypes emerge, distinguished by initial company focus (Figure 1):

- **Archetype 1: Therapeutic Area Specialists**
  - Those that focus on a key disease or set of closely related diseases.
- **Archetype 2: Technological Approach Specialists**
  - Those that have a specific technology platform with the potential to leverage to develop therapeutics for a range of disease areas (which may or may not be closely related).

The paths of each of these archetypes offer different advantages but also common potential headwinds that may require careful strategic considerations to overcome. The following sections will 1) define each archetype; 2) provide a historical overview of select examples of companies fitting the archetype; and 3) detail likely strategic considerations unique to that archetype for emerging biotech companies envisioning a similar path to longer-term commercial success. Finally, we will provide an example of a company that does not neatly fit into one of these archetypes but instead adopted a blended approach and will detail approaches to developing a strategic roadmap that capitalizes on the advantages offered by each of the two primary archetypes simultaneously.

FIGURE 1: BIOTECHNOLOGY COMPANY ARCHETYPES & COMMON CHARACTERISTICS

Therapeutic Area Specialists

Focus on developing therapies for a specific disease or closely related set of diseases

- A core condition focus, with multiple associated assets (in development or commercialized)
- Multiple pipeline assets in clear condition adjacencies to the core indication, with obvious potential for commercial synergies (e.g., similar treater type)
- Pipeline assets do not necessarily leverage similar technology and may have been acquired or licensed from other companies

Technological Approach Specialists

Aim to apply the same technology to develop therapies for many different conditions

- Company founding idea is based on a technology with therapeutic potential
- Company leadership often has strong ties to academic research institutions
- Technology could theoretically be applied to treat or prevent a range of potential diseases, which may not be related to each another
- Pipeline assets all share common technological underpinnings

Archetype 1: Therapeutic Area Specialists

Therapeutic area specialists are those who have a clear focus on a specific disease vertical (e.g., neurology, oncology, etc.). Indicators of this archetype include:

- 2+ commercial launches and/or pipeline assets in an indication
- Pipeline assets in clear condition adjacencies to the core indication, with obvious potential for commercial synergies (e.g., similar treater type)
- Pipeline assets do not necessarily leverage similar technology and may have been acquired or licensed from other companies

Biogen

Biogen is a prime example of a biotech company that has focused on a therapeutic area from the outset, with an early eye towards being a leader in multiple sclerosis (MS) and neurology more broadly. Biogen's first commercial therapy was Avonex (interferon beta-1a), approved by the FDA for relapsing forms of MS in 1996 (Figure 2).[1]

MS Before Biogen

MS is a progressive neurological condition where patients experience a range of symptoms including gait difficulties, numbness/tingling throughout the body, muscle spasms, and general weakness.[2] MS is a leading cause of disability in young adults[3] and patient quality of life can be considerably impacted. The life expectancy of MS patients has risen over the years (in part because of therapies developed by Biogen[4]), but there was (and still is not) a cure for MS available.

At the time of Avonex's launch, only one other indicated branded therapy for MS (Betaseron, marketed by Chiron & Berlex, now Bayer). Betaseron (interferon beta-1a) was the first disease-modifying therapeutic for MS, receiving accelerated approval from the FDA in 1993. Clinical trial data showed patients on Betaseron achieved a 31% reduction in annual exacerbation rate relative to placebo ($p = 0.0001$), with 2-year data available. However, the FDA label contained notable safety warnings for depression and suicide, as there was one suicide and four attempts among the 372 study patients over a two-year period.[5] Label warnings also note the potential for hepatic injury given observed neutropenia and abnormal liver enzymes.[5]

In addition to Betaseron, off-label corticosteroids (e.g., oral prednisone, IV methylprednisolone), immunosuppressants (e.g., methotrexate, azathioprine), and other non-pharmacological strategies were available to manage MS patients, especially in instances of acute MS exacerbations. However, these treatments only help manage symptoms and are also associated with adverse events, including a high risk of infection, gastric disturbance, and other potential complications.[3]

Collectively, this meant that, prior to the 1996 launch of Avonex, there was a high degree of unmet need for novel, more efficacious, and safer / more tolerable MS therapeutics for the roughly ~200k MS patients with relapsing forms in the US[6] (with ~85% of MS patients being relapsing-remitting,[7] corresponding to ~900k today[8]).

How Avonex Formed a Foundation for Biogen's MS Franchise

Critical to the success of Avonex was the pivotal clinical trial design and outcomes achieved, which engendered positive reactions from both regulatory bodies as well as physicians and patients. The pivotal Phase III trial measured time to sustained disability progression of at least 1 point on the Kurtzke Expanded Disability Status Scale (EDSS) for at least six months as the primary endpoint.[9] This is a widely accepted disability scale that assesses the following functional central venous system components of MS patients: pyramidal, cerebellar, brainstem, sensory, bowel/bladder, visual, and cerebral. These components collectively represent virtually all aspects of neurological impairment seen in MS patients.[10]

Avonex demonstrated statistical significance on the primary endpoint in the pivotal phase III trial ($p=0.02$), with 78% of patients receiving Avonex experiencing no sustained disability progression compared to 65% of patients who received placebo.[11] A follow-up trial assessing Avonex use in patients at high risk for developing clinically definite MS also showed that the time to second relapse was significantly delayed in Avonex-treated patients compared to placebo ($p=0.0002$). In this trial, 79% of patients receiving Avonex were relapse-free compared to 61% of placebo-treated patients.[11]

Beyond the achievement of statistical significance, the specific endpoint measure selected helped build a case that Avonex had the ability to meaningfully meet the high unmet need for MS patients. The Avonex data and subsequent FDA approval were received with great enthusiasm, with a ~54% jump in Biogen stock price between the day before the announcement of pivotal trial results and the day after FDA approval.[12]

The data package generated also led to the FDA granting orphan drug exclusivity to Biogen's Avonex (ending in 2003) over Betaseron[13], effectively providing Avonex with exclusive marketing rights for this class of therapies for MS. Chiron & Berlex (now Bayer) filed a lawsuit claiming Avonex's orphan designation violated the orphan drug exclusivity rights given to Betaseron at launch. However, the FDA upheld the decision, citing clinical trial data suggesting that the use of Avonex results in slower progression of the disease, results in fewer adverse reactions (in particular, flu-like symptoms and injection site reactions), and has more convenient, less frequent dosing than Betaseron, despite the lack of a direct head-to-head trial.[14]

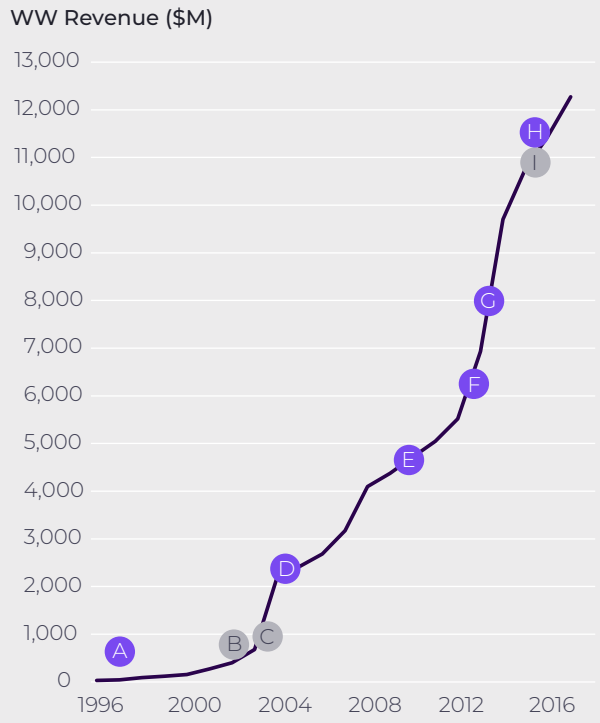
Ultimately, Avonex achieved a peak annual US revenue of ~$2 billion in 2014.[15] As recently as 2009 (prior to availability of other novel therapies for MS), Avonex was the top prescribed treatment for MS in the world16. This commercial success was achieved despite treating notably fewer patients than the total addressable market, with Biogen estimating ~135,000 patients on therapy as of 2009.[16] This suggests that, while Avonex met a critical therapeutic unmet need for MS patients, pricing flexibility was also a key factor to commercial success. The lack of strong competition, high unmet need, and a relatively small number of patients likely enabled this pricing flexibility while not attracting undue payer attention and management beyond the labeled indication.[17,18,19]

Building on the Avonex Foundation

Biogen then built on the experience and relationships gained as part of the Avonex launch to launch several sequential products that improved on Avonex's efficacy. These included Tysabri (approved in 2004 for relapsing forms of multiple sclerosis, which demonstrated a 42% reduction in risk of disability progression relative to placebo ($p<0.001$) and a 67% reduction in the rate of clinical relapses over two years ($p<0.001$)[20], and Tecfidera (approved in 2013 for relapsing forms of multiple sclerosis, with demonstrated reduction of proportion of patients who relapsed at two years by 56% vs placebo ($p= 0.0037$).[21]

Biogen was able to capitalize on the pre-existing physician and patient relationships as a trusted supplier of critical MS therapies while enhancing the clinical value of their offerings and providing multiple options for patient and provider selection. As a result of this strategy, Biogen's MS franchise products collectively achieved ~$9.1 billion in US revenue in 2017 (total 2017 worldwide revenue across all assets was >$12 billion, Figure 2).[22] This strong revenue stream enabled them to achieve longer-term success as an independent company, with capital to expand beyond MS into other neurological indications (e.g., Spinraza for SMA23, in partnership with Ionis and Aduhelm / Leqembi for Alzheimer's, in partnership with Eisai[24,25]), which also aimed to capitalize on their commercial expertise in neurology. The initial therapeutic area focus enabled Biogen both a strong commercial start as well as the opportunity to further build on that success (Figure 2).

FIGURE 2: BIOGEN WORLDWIDE REVENUE AND US LAUNCH YEARS OF KEY PRODUCTS, 1996-2017



	First Year of launch (US)	Product Name	Indication
A	1996	**Avonex**	Relapsing multiple sclerosis
B	2002 (sold to Cell Therapeutics in 2007)	**Zevalin**	NHL
C	2003 (sold to Astellas in 2006)	**Amevive**	Plaque psoriasis
D	2004	**Tysabri**	Relapsing multiple sclerosis, Crohn's Disease (2008)
E	2010	**Ampyra**	Multiple sclerosis (improve walking)
F	2013	**Tecfidera**	Relapsing multiple sclerosis
H	2016	**Zinbryta**	Relapsing multiple sclerosis
I	2016	**Spinraza**	Spinal muscular atrophy

Relating to MS Non-MS Disease Area

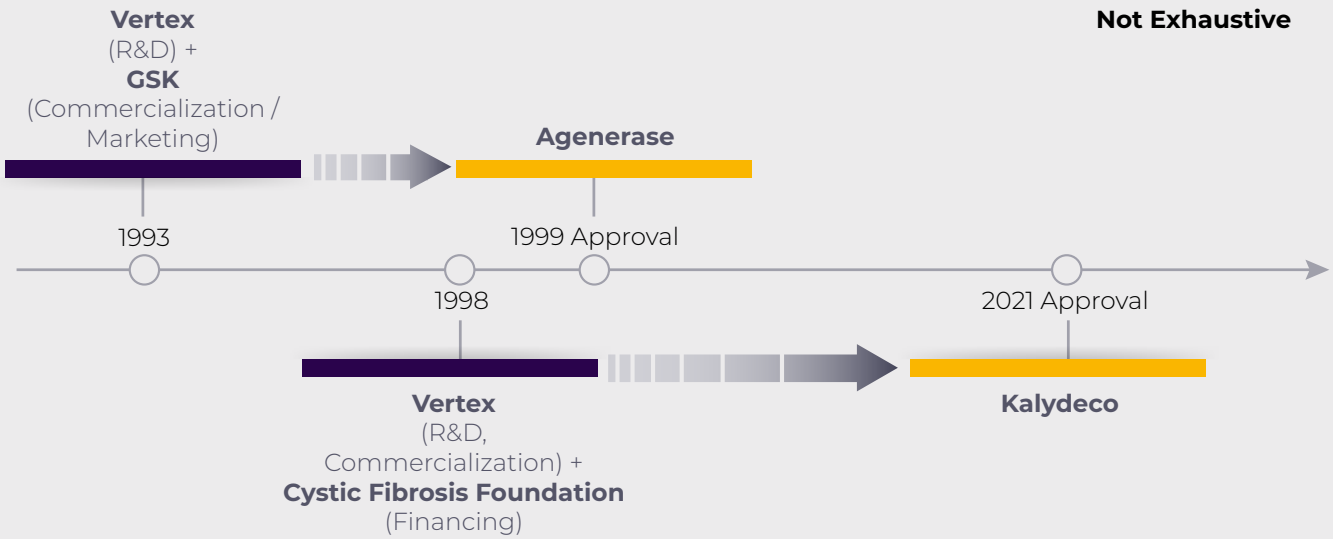
Vertex

Another prominent example of a Therapeutic Area Specialist is Vertex. This company had an early focus on two key therapeutic areas, infectious viral disease treatments, and cystic fibrosis, the latter of which arguably became their signature area.

Vertex's Initial Commercial Forays: Infectious Viral Diseases

Vertex was initially focused on developing therapies for infectious viral diseases.[26] Beginning in 1993, they collaborated with Glaxo Wellcome (now GlaxoSmithKline, GSK) to develop protease inhibitors for the treatment of those infected with HIV, resulting in the approval of Agenerase in 1999 for the treatment of HIV-1 infection (Figure 3).[27,28]

FIGURE 3: KEY VERTEX PARTNERSHIPS AND RESULTING COMMERCIALIZED THERAPIES



Despite the high unmet needs of patients with HIV, Agenerase was only one of several approved options in this class, presenting a notable commercial challenge. Agenerase also suffered from unfavorable indirect clinical comparison with Lexviva, another protease inhibitor and a pro-drug of the same active compound as Agenerase. Lexviva is thought to achieve higher blood concentrations of the active compound, amprenavir, with a lower dose of medication relative to Agenerase.[29] Vertex's overall company revenue in 2006 prior to the discontinuation of production of Agenerase in 2007 was only ~$216 million (Figure 4), hinting at the magnitude of these commercial challenges and the importance of considering competitor pipelines when selecting a lead indication or asset.[30]

Vertex's second infectious disease therapy, for hepatitis C, was more successful. Hepatitis C Virus (HCV) is a viral liver infection affecting ~71 million people globally as of 2015.[31] Hepatitis C infection can be acute or chronic, with about half of hepatitis C patients experiencing chronic manifestations with potential for longer-term liver cirrhosis or liver cancer.[32] Before 2011, HCV was treated with injectable interferon-alpha alongside antiviral drugs like ribavirin (RBV).[33]

In 2011, two protease inhibitors specifically targeting HCV were approved by the FDA, one of which was Vertex's Incivek. Incivek led to significant improvement in sustained virologic response (SVR) in HCV genotype 1 patients when used in conjunction with interferon-alpha and ribavirin (69% to 75% SVR vs 44% with PegIntron/RBV, $p<0.0001$).[34,35] On the basis of these results, combined with the unmet need, Incivek had an exceptionally fast uptake, capturing $1.56 billion in its first-year post-approval (Figure 4).[36]

However, Incivek's blockbuster status was short-lived. Demand plummeted ~3 years after launch with the approval of Gilead's Sovaldi, which cures 90% of HCV patients after a 12-week treatment course without the need for interferon. As a result, Vertex discontinued production of Incivek.[37] While the commercial availability of Incivek was quite brief, it likely played an important role in sustaining Vertex, enabling continued development of what eventually became their core multi-asset cystic fibrosis (CF) franchise.

Initial Steps in Cystic Fibrosis

Vertex had initiated a collaboration with the Cystic Fibrosis Foundation in 1998, with a longer-term vision to develop CF therapeutics in addition to those for infectious diseases (Figure 3).[38] CF is a progressive inherited genetic disorder that results in severe organ damage, significant respiratory symptoms, and (prior to approval of Vertex's disease-modifying therapies), notably reduced lifespan relative to an unaffected population.[39] As a result, although rare (<100k patients worldwide at the time of approval of Vertex's first therapy in 2012), there was considerable therapeutic unmet need.[40]

Vertex's first approved therapy to slow or halt the progression of CF was Kalydeco, approved by the FDA in 2012. Although novel, only ~4% of CF patients have specific mutations responsive to Kalydeco. Despite this very small addressable patient population, Kalydeco attained >$1 billion in revenue at its peak (2018).[15] As Dr. Janet Woodcock, the director of the Center for Drug Evaluation and Research at the FDA opined, "This is a breakthrough therapy for the cystic fibrosis community because current therapies only treat the symptoms of this genetic disease."[41]

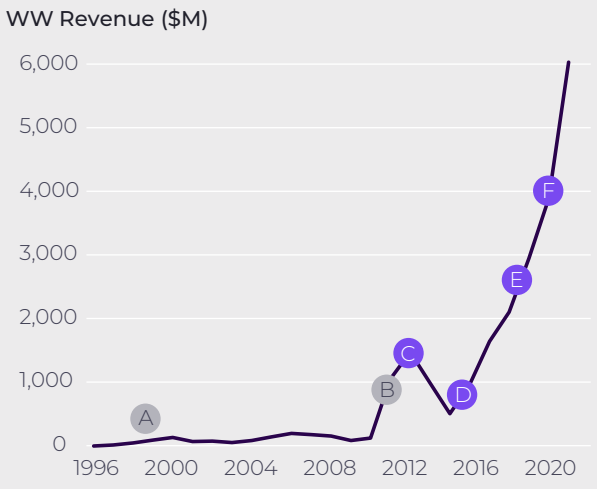
Building a Cystic Fibrosis Franchise

Vertex had longer-term plans to use Kalydeco as an entry point for a broader CF portfolio strategy to serve patients who did not have the potential to benefit from Kalydeco. Prior to Kalydeco's launch, Vertex was already developing additional CF therapies. In 2015, they launched Orkambi[42], followed by Symdeko (2018)[43] and Trikafta (2019)[44], which combined provide a disease-modifying treatment option for over 90% of CF patients.

From the launch of their first CF drug, Kalydeco, to their most recent launch, Trikafta, Vertex's valuation has increased substantially, supported by a CF franchise total of >$17 billion in revenue in 2022[45] and a strong upward revenue trajectory (Figure 4).[46] Vertex continues to prioritize development in the CF space, with several other small molecule therapies as well as undisclosed mRNA / gene therapies under exploration in additional to other pipeline assets in other disease areas.[47]

The focus on two therapeutic areas from the early stages of the company was a critical de-risking strategy for Vertex. Without the infectious disease therapies, it may have been considerably more difficult for them to develop the CF therapies as quickly, and without the CF therapies, Vertex would have had a significant gap in revenue after Incivek discontinuation.

FIGURE 4: VERTEX WORLDWIDE REVENUE & US LAUNCH YEARS OF KEY PRODUCTS, 1996-2020



	First Year of launch (US)	Product Name	Indication
A	1999	**Agenerase**	HIV-1 infection (with anti retroviral agents) (Infectious disease)
B	2011 (Discontinued in 2014)	**Incivek**	Chronic hepatitis C (CHC) (Infectious disease)
C	2012	**Kalydeco**	Cystic fibrosis (CF)
D	2015	**Orkambi**	Cystic fibrosis (CF)
E	2018	**Symdeko**	Cystic fibrosis (CF)
F	2019	**Trikafta**	Cystic fibrosis (CF)

Relating to CF Relating to Infectious Disease

Other Therapeutic Area Specialist Examples

Other companies have pursued a similar strategy of initial therapeutic area focus. For instance, Alexion has had several successful launches, including strong commercial performers Soliris (2007) and Ultomiris (2018), both indicated for paroxysmal nocturnal hemoglobinuria (PNH)48, with additional marketed products for hypophosphatasia, neurofibromatosis type 1, and lysosomal acid lipase deficiency, with a total collective revenue of almost $7.1 billion in 2022 (following acquisition of Alexion by AstraZeneca in 2021).[49] In rare genetic diseases, BioMarin first focused on varieties of mucopolysaccharidosis, first Aldurazyme (2003) to treat mucopolysaccharidosis I (MPS I) and subsequently Vimizim (2014), indicated for MPS IV.[50] Other rare genetic disease areas where BioMarin has expanded include phenylketonuria (PKU) and hemophilia A, bringing in a total combined revenue across all marketed therapies of close to $2.1 billion in 2022.[51]

The Common Therapeutic Area Specialist Focus on Rare Disease

It is notable that many of these companies have focused on rare diseases. Rare diseases offer several key advantages for smaller companies in terms of ease of commercialization, including (typically) lower competitive intensity and a more centralized treatment paradigm, resulting in a need for a relatively smaller sales force, (often) higher unmet need and resulting strong demand with lower effort required on the manufacturer's part, and finally, (frequently) lower payer scrutiny or resulting access challenges (in the US, at least) that also require time and effort to overcome (Figure 5). As a result, targeting rare disease vs larger indications may offer a smaller company greater chances of commercial success.

FIGURE 5: WHY THERAPEUTIC AREA SPECIALISTS OFTEN PURSUE RARE DISEASES

Rare diseases often have one or more attractive characteristics...

...that can offer several advantages for smaller biotech companies:

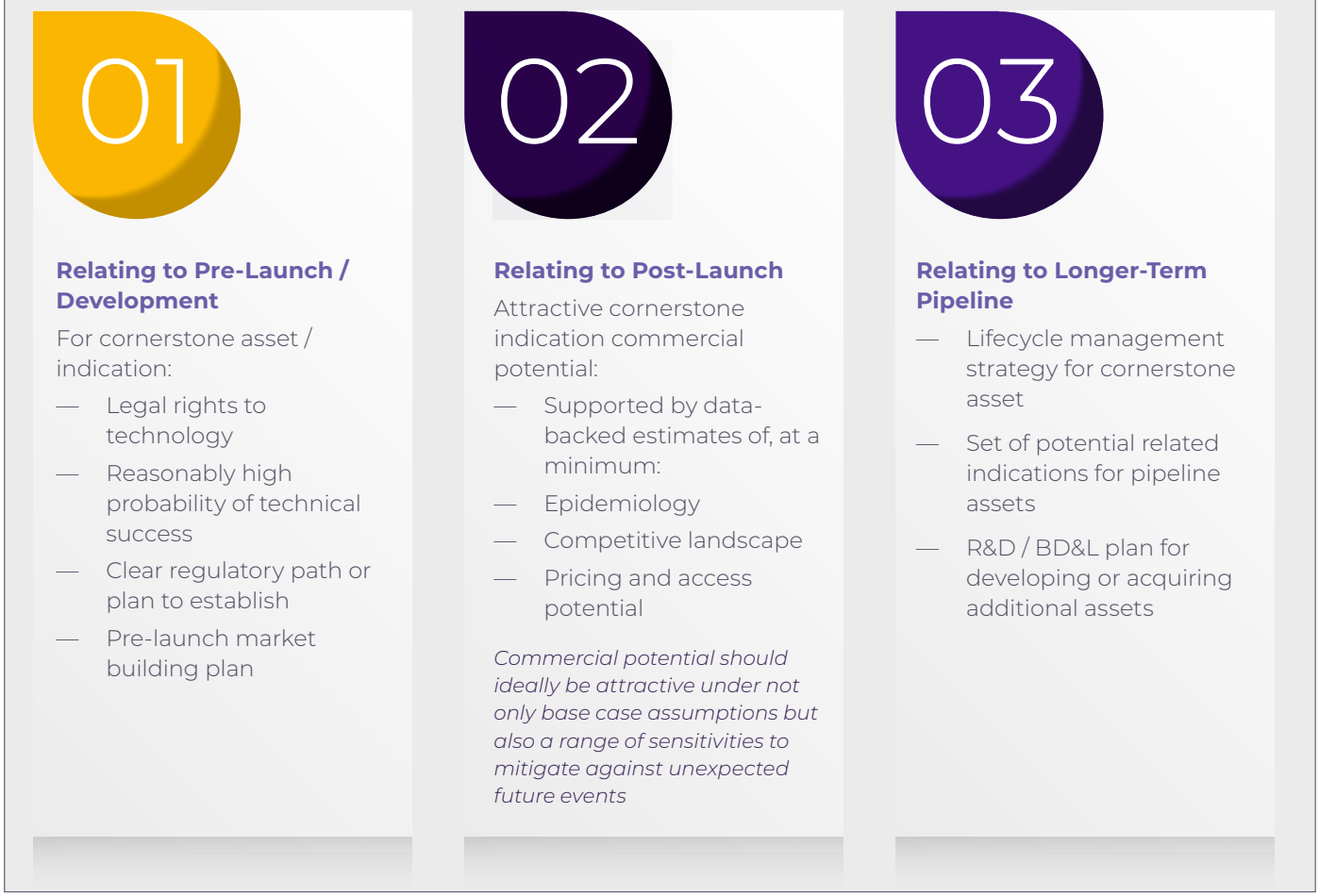
- Smaller sales force needs given treatment centralization
- Strong demand even without strong sales efforts as a result of high unmet needs
- Lower risk of pricing and access-related challenges

Key Areas for Therapeutic Area Specialist Confidence and Potential Risks

Regardless of the target therapeutic area, many elements will be critical for a biotech to ensure if pursuing a Therapeutic Area Specialist approach (Figure 6), including but not limited to:

- Identification of an indication with high unmet need (i.e., a cornerstone indication).
- Availability of internal therapeutic technology to address that need.
- Commercially attractive number of patients (i.e., likely not ultra-ultra-rare).
- High confidence in probability of technical, clinical trial, and regulatory success of the cornerstone asset.
- Low competitive threat through and beyond the likely time of launch.
- Confidence and interest in ability to do pre-launch market building for cornerstone indication.
- A set of potential related indications to enable construction of a pipeline that would capitalize on potential developmental and / or commercial synergies (ideally, both).

FIGURE 6: CRITICAL THERAPEUTIC AREA SPECIALIST AREAS OF CONFIDENCE



A key risk of this strategy is that it may require an all-in commitment to that cornerstone indication and associated asset rather than diversifying resources across multiple indications or assets. As a result, this strategy may be best for companies with very strong pre-clinical / early phase I/II data relative to the current therapeutic options available to patients as well as high confidence in the attractiveness of the commercial opportunity. Indications for which there is an opportunity to do pre-launch market building and a lack of strong competition from other recently launched branded assets will also likely be more amenable to this strategy; as for a first launch achieving fast therapy uptake post approval is particularly critical to ensure a solid revenue stream to support any ongoing and future pipeline development efforts.

Therapeutic Area Specialist Partnership Considerations

Should a company be faced with the need to devote a large portion of resources to lead asset development and commercialization, another potential option is to carefully consider strategic partnerships, as the example of Vertex and the Cystic Fibrosis Foundation collaboration demonstrated. Partnerships with other pharmaceutical or biotech companies can be beneficial from a financial standpoint (as will be demonstrated in the Technological Approach Specialists section). However, for Therapeutic Area Specialists, there is a risk of the partner company capitalizing on the expertise that would be gained in a co-commercialization scenario and becoming a future competitor in the same or adjacent therapeutic areas. As a result, partnerships with other external bodies (such as patient advocacy groups or academic institutions), if available, maybe a more advisable path for companies aiming to be a leader in a specific therapeutic area (Figure 7).

Example Key Strategic Questions for Therapeutic Area Specialists

To maximize chances of success as a Therapeutic Area Specialist, for the first commercialized asset/indication companies should proactively 1) ensure they have sufficient knowledge to be confident about the disease area in question and 2) deeply pressure test the clinical and technical success potential for the asset. Critical strategic questions to consider almost certainly include (Figure 8):

FIGURE 7: MODELS OF THERAPEUTIC AREA SPECIALIST PARTNERSHIPS

Commercial Partner

- ⊕ Can assist with ex-US / ex-EU commercialization
- ⊖ Reduces expected future revenue & ability to develop pipeline assets
- ⊖ Can lead to significant inefficiencies, as organizations need to align on commercialization strategy & perspectives may differ

Works best when partners have exclusive rights in specific markets vs splitting rights to a market

Funding Partner

- ⊕ Can help supply resources to develop assets
- ⊕ Expectations of commercial-stage collaboration are likely limited

Works best when partner either:

- Has altruistic motivations to support development of new therapies
- Is invested in partner company success (not only therapy success)

Research and Technology Partner

- ⊕ Often essential for therapeutic area specialists to supply pipeline assets
- ⊕ Expectations of commercial-stage collaboration are likely limited

Works best when partner is willing to hand over full commercial rights & decision-making power in exchange for milestone payments

What is the commercial potential of the lead indication assuming full achievement of the target product profile?

- What global markets are expected to support the majority of the opportunity?
- What is the size of the realistically addressable population in these markets?
- How high is the expected patient/physician demand in these markets?
- What is the pricing potential in these markets?

What are potential barriers to realization of that commercial potential (e.g., market development, competition, access)?

- Is the company equipped to overcome those barriers? If not, what additional resources may be required, and when should those resources be obtained or developed relative to launch?
- Are there any potential clinical development or pre-launch market-building strategies that can be used to minimize expected commercialization barriers in advance?

What are potential uncertainties that could affect the size of the opportunity?

- What are potential uncertainties in current best-available epidemiological estimates that could represent a risk to the estimated size of the opportunity?
- Are there any potential competitors that could emerge, particularly with an opportunity to develop and commercialize an asset more quickly?
- How much risk is there of downward pricing pressure or access-related challenges, particularly with an evolving level of US government involvement in drug pricing?

What is the potential downside if full clinical success is not realized (i.e., target product profile is not achieved)?

- Are there any backup strategies to continue development of the asset?
- Are there any backup strategies with other assets? To what extent should resources be put towards maintaining and developing backup strategies vs focusing on the lead asset/indication?

FIGURE 8: KEY QUESTIONS FOR ASPIRING THERAPEUTIC AREA SPECIALISTS

Of course, specifics of strategic questions and relative emphasis / need for rigorous exploration and validation will vary by lead indication/asset, with a need to carefully consider company-specific strategic imperatives. As such, a custom approach is recommended to ensure comprehensive coverage of the full set of nuances unique to the individual situation.

Companies focusing on a specific therapeutic area likely have a clear vision of which indication(s) to pursue; however, more challenging but perhaps more commonly, an emerging biotech company has a foundational technological platform and then needs to select an indication(s) for which the technology is applicable. Such companies form the second archetype identified: the Technological Approach Specialists.

Archetype 2: Technological Approach Specialists

Many biotech companies have a core focus on a specific technology (e.g., RNAi, CAR-T, mRNA, etc.), rather than a specific disease area / vertical. This is a common occurrence, given many biotech companies emerge to build on technology licensed from academic institutions. Indicators of this company archetype include:

— Company founding idea is based on a therapeutic technology.

— Company leadership often has strong ties to academic research institutions.

— Technology could theoretically be applied to treat or prevent a range of potential diseases, which may not be related to each other.

— Pipeline assets all share common technological underpinnings.

One of the challenges these companies face, however, is transitioning from a focus on developing the technology itself to a focus on identifying a path to successfully commercialize that technology. Alnylam and Ionis both have a foundational technology focus. However, Alnylam has built up capabilities to serve as the lead commercialization partner and largely retained rights to most assets, including those more advanced, while Ionis has instead tended to license commercial rights for its assets to other companies until very recently.

Alnylam

Alnylam was founded in 2002 and launched their first product in 2018, Onpattro (patisiran), a RNAi therapy indicated for polyneuropathy of hereditary transthyretin-mediated amyloidosis in adults (Figure 9).[52]

Alnylam's First RNAi Therapy: Onpattro

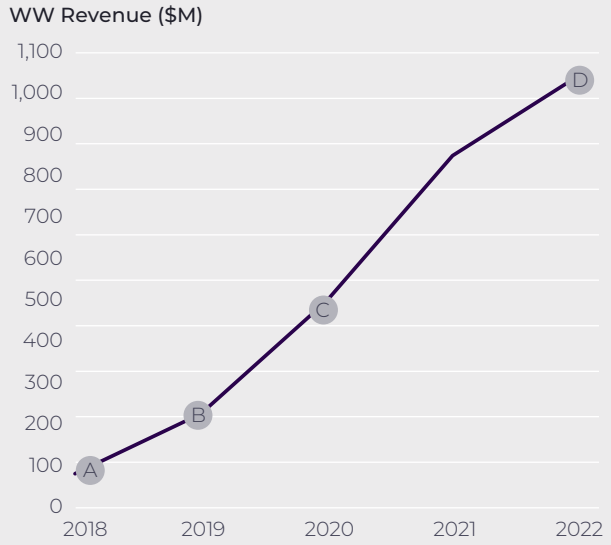
Polyneuropathy of hereditary transthyretin-mediated amyloidosis (hATTR) is a rare disease, an autosomal dominant neurodegenerative condition, affecting an estimated ~50,000 adults worldwide as of 2017.[53] It is caused by a mutation in the transthyretin (TTR) gene. The abnormal TTR causes destabilization of the normal tetramer formation, leading to dissociation/misfolding and the formation of amyloid fibrils. TTR is deposited especially in the peripheral nervous system, leading to sensory and motor polyneuropathy. Symptoms include paresthesia, pain, weakness, and autonomic dysfunction. Without a liver transplant, the condition is fatal, typically within a decade.[53]

Prior to the availability of Onpattro (patisiran), there were very few treatment options for polyneuropathy of hATTR. Early-stage patients were typically treated with liver transplantation to reduce TTR, which is primarily produced by the liver. However, outcomes were very variable based on several factors, including the patient's age, the severity of the disease at the time of the transplant, and the TTR mutation.[54]

Onpattro's pivotal Phase III trial measured change from baseline to month 18 in the modified Neuropathy Impairment Score +7 (mNIS+7). In the version used in the trial, it objectively measures deficits in cranial nerve function, muscle strength and reflexes, postural blood pressure, quantitative sensory testing, and peripheral nerve electrophysiology. Onpattro demonstrated statistical significance on the primary endpoint ($p<0.001$), with patients showing an average change from baseline to month 18 of -6.0 compared to 28.0 for patients who received a placebo.[55]

Onpattro was positively received by the medical community, with over 750 patients worldwide receiving commercial Onpattro (and over 1,000 total patients, including those that participated in clinical trials) by 2019.[56] 44% of US new starts were prescribed by cardiologists, 38% by neurologists, and the remainder from other specialties, suggesting a robust commercial sales force with the ability to call on multiple different physician specialties that are involved in the treatment of this complex rare disease.[56]

FIGURE 9: ALNYLAM WORLDWIDE REVENUE & US LAUNCH YEARS OF KEY PRODUCTS, 2018-2022



	First Year of launch (US)	Product Name	Indication
A	2018	**Onpattro**	Polyneuropathy of hereditary transthyretin-mediated amyloidosis
B	2019	**Givlaari**	Acute Hepatic Porphyria (AHP)
C	2020	**Oxlumo**	Primary hyperoxaluria type 1 (PH1)
D	2022	**Amvuttra**	Polyneuropathy of hereditary transthyretin-mediated amyloidosis

Access was also likely another factor in the success of this first therapy. Alnylam rapidly secured favorable access for Onpattro, with over 90% of US lives across commercial, Medicare, Medicaid, and other governmental payer categories enrolled in a plan with an established access policy and 10 definitive value-based agreements in place by 2019.[57] Additionally, the therapy received favorable outcomes in HTA evaluations across the EU, including France and Germany.[57] As with Biogen's MS therapies, favorable access was likely engendered by the high unmet need and strong clinical trial outcomes.

In combination, this led to a relatively successful launch of Onpattro, with 2022 worldwide sales of $435M and revenue forecasted to be as high as $1,083M by 2026.[58] However, these results would likely not have been possible without two critical partnerships Alnylam established with Ionis and Genzyme early in Onpattro development.

Role of Partnerships in Alnylam's Early Stages

Alnylam formed a partnership with Ionis Pharmaceuticals (formerly Isis Pharmaceuticals) in 2004.[59] Ionis was (and continues to be) a leading manufacturer focused on novel therapeutics targeting RNA. This partnership enabled Alnylam access to Ionis' manufacturing facilities and to license elements of Ionis' patent estate relating to antisense mechanisms and oligonucleotide chemistry. In exchange, Alnylam provided a $5 million technology access fee, participation in fees for Alnylam's partnering programs, and downstream milestone and royalty payments. Additionally, Alnylam invested a $10 million minority equity stake in Ionis.[59]

Alnylam's alliance with Genzyme, established in 2012, was also important.[60] It enabled Alnylam, at the time a relatively small biotech without a global commercial footprint, to gain support for ex-US sales. The preliminary alliance was limited to Japan and other Asia-Pacific countries, in which hATTR is disproportionately prevalent, in exchange for milestone payments and tiered royalties. Agreement expansion increased Genzyme's ex-US commercialization rights and stake in Alnylam in exchange for further R&D funding.

In 2018, the manufacturers restructured their RNAi therapeutics alliance, with Alnylam regaining global development and commercialization rights to its investigational RNAi therapeutics programs for the treatment of ATTR amyloidosis, including Onpattro (patisiran).[60] Genzyme (now Sanofi) would receive royalties from those products. Genzyme (Sanofi) obtained global development and commercialization rights to an investigational RNAi therapeutic in development for the treatment of people with hemophilia A and B, fitusiran with royalties payable to Alnylam. In 2019, Alnylam and Sanofi agreed to conclude the research and option phase of the companies' 2014 RNAi therapeutic alliance in rare genetic diseases. The terms for patisiran, vutrisiran, and fitusiran continued unchanged.[60]

This early partnership with Genzyme likely allowed Alnylam to access critical capital and revenue streams from ex-US sales even though they did not yet have the internal capabilities to support ex-US commercialization independently, but once those capabilities were established, also provided an opening for Alnylam to independently commercialize future therapies.

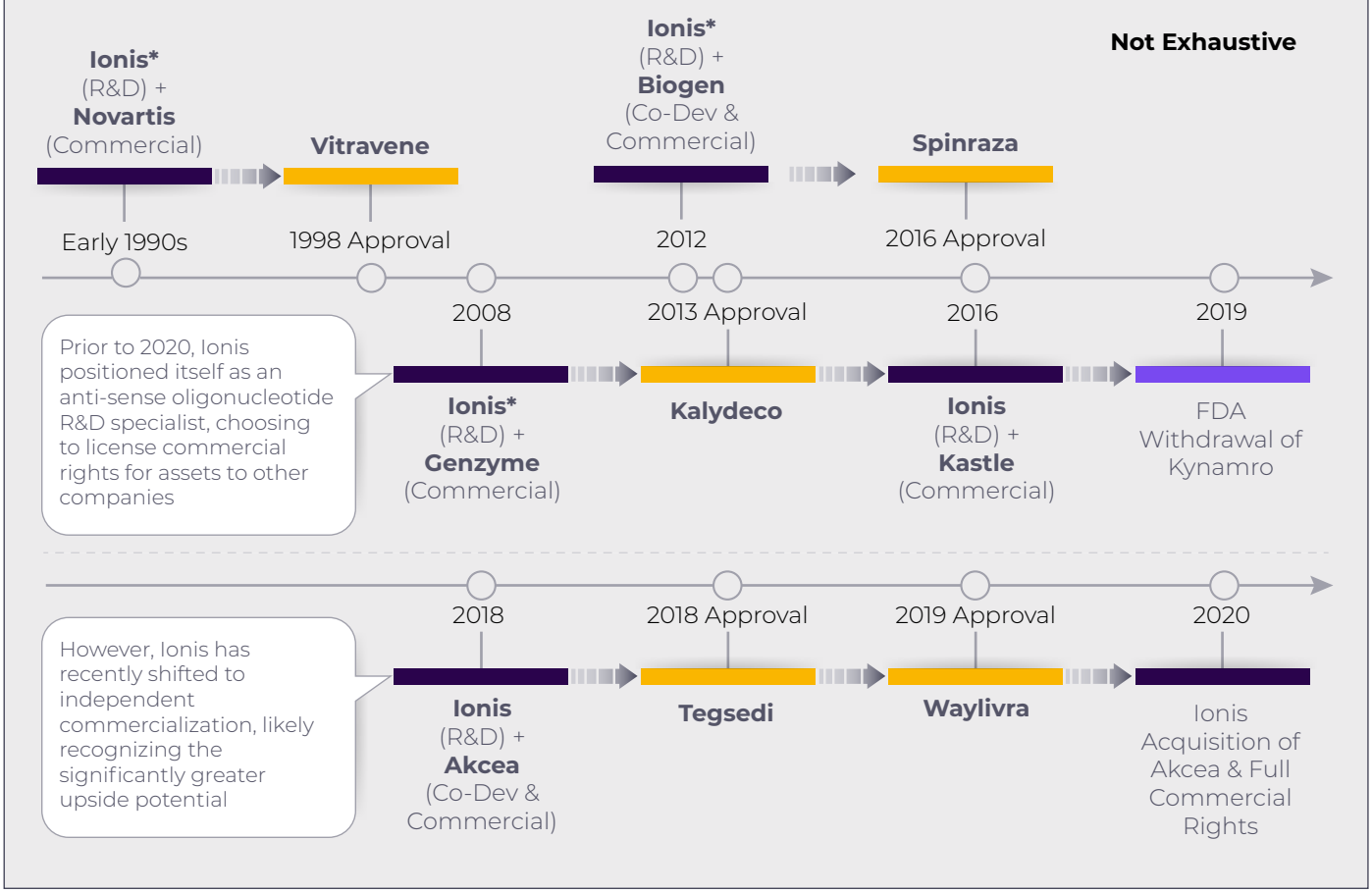
Alnylam's Subsequent Commercialized RNAi Therapies & Longer-Term Pipeline

Subsequently, Alnylam built on the success of Onpattro, with several RNAi therapy launches shortly after: Givlaari (givosiran) in 2019, Oxlumo (lumasiran) in 2020, and Amvuttra (vutrisiran) in 2022, establishing themselves as a RNAi industry leader (Figure 9).[52] This was likely possible both as a result of having a strong technology platform with the potential to meet prominent unmet needs in underserved conditions with low competitive threat, but also as a result of thoughtful, considered indication selection for their lead asset and strategic partnerships that complemented internal Alnylam skills and resources. Although this meant that Alnylam did not retain full commercial rights to all lead assets, it enabled the creation of a strong revenue stream to enable the creation and development of a more robust clinical-stage pipeline (10+ discrete assets as of Q4 2023).[61]

Ionis

In contrast, Ionis has historically positioned itself as an R&D specialist that partners with others for commercialization rather than also building internal commercialization capabilities (Figure 10). Ionis (previously Isis) was founded in 1989 to develop antisense oligonucleotide (ASO) therapeutics, which are single-stranded RNAs that bind to target mRNA to influence protein expression.[62]

FIGURE 10: KEY IONIS PARTNERSHIPS AND RESULTING COMMERCIALIZED THERAPIES



The First FDA-Approved ASO Therapy: Vitravene

Vitravene was Ionis's first therapy that was FDA approved in 1998 for the treatment of cytomegalovirus retinitis (CMVR), co-developed and licensed by Novartis[63]. CMVR is a viral infection of the eye, most commonly occurring in people who are immunocompromised, causing blurred vision and blindness, with potential for retinal detachment.[64] CMVR is particularly common in patients with acquired immunodeficiency syndrome (AIDS), estimated to affect ~21-44% of AIDS patients in 1996.[65] In Phase III clinical trials, median first progression to disease was 71 days with immediate treatment with Vitravene vs 13 days for treatment deferred until CMVR lesions occurred (p=0.0001). Progression occurred in 44% of immediate treaters vs 70% of those deferred, with no cases of retinal detachment in the treated population.[66]

The approval of Vitravene intended to address a high unmet need for AIDS patients. However, the commercial success of Vitravene was limited, primarily as a result of the emergence of anti-retroviral agents in the late 1990s that significantly brought down the incidence of AIDS and the corresponding incidence of CMVR in HIV-positive patients. As a result, Novartis discontinued Vitravene production in 2001.[67]

In retrospect, likely one of the greatest benefits of Vitravene to Ionis was to establish the promise and potential of ASOs as a novel therapeutic modality, which Ionis used to secure sufficient investment to continue development of other ASO candidates. The next FDA-approved ASO Ionis developed was Kynamro.

Ionis-Genzyme Partnership Leading to Kynamro Approval

In 2008, Ionis partnered with Genzyme to develop and commercialize Kynamro for the treatment of familial hypercholesterolemia (FH).[68] FH is an inherited disorder that affects the way cholesterol is processed, notably increasing the risk for heart disease and heart attack.[69] It is estimated that FH is present in about 1 in every 250 people, and if detected and treated early can reduce the risk of heart disease in these patients by 80%.[70] Although FH is a highly common autosomal dominant genetic disease[71], homozygous FH (HoFH) is very rare, affecting only about one in a million people worldwide. HoFH is extremely aggressive, and if untreated, can result in heart attacks in adolescents.[72]

Prior to Kynamro approval, HoFH was commonly treated with high doses of statins and lifestyle/dietary changes and, if severe, LDL apheresis.[71] In a Phase III clinical trial, patients treated with Kynamro experienced a 25% reduction in LDL-cholesterol at week 26 vs 3% in the placebo group ($p<0.001$).[73] These results were used to support a successful application for FDA approval for the treatment of HoFH, approved in 2013.

However, in January 2016, Ionis reclaimed rights to Kynamro from Genzyme, with Sarah Boyce (Chief Business Officer of Ionis) publicly signaling disappointment in Genzyme's efforts to market Kynamro.[74] Shortly thereafter, in May 2016, Ionis sold global rights to Kastle Therapeutics to develop and commercialize Kynamro worldwide.[75] However, for reasons undisclosed, withdrawal of Kynamro's FDA approval was filed in August 2019[76], and Kastle Therapeutics no longer appears to be active as a company. The challenges experienced with Kynamro commercialization highlight the potential risks for a Technological Approach Specialist biotech of relying long-term on more established companies for sales and commercialization vs developing in-house sales capabilities.

Spinraza: An Ionis and ASO Success Story

Ionis's first major success was Spinraza, the first disease-modifying therapy for spinal muscular atrophy (SMA) approved by the FDA in 2016.[77] In 2012, Ionis and Biogen entered a collaboration agreement to develop and commercialize Spinraza. Ionis received an initial payment of $29 million with up to $49 million in payments associated with clinical development of Spinraza pre-licensure.78 Biogen then had the option to license Spinraza (which they did in 2016 for $75 million), giving Biogen global development, commercialization, and regulatory responsibilities.[78]

SMA is a genetic disease that damages specialized nerve cells throughout the spinal cord and brain[79], affecting ~1 out of every 10,000 people worldwide. SMA severely affects the quality of life of patients, affecting the ability to swallow, breathe, walk, etc., often from birth. Without disease-modifying treatment, SMA can also cause premature death in those with more severe variants of the disease.[80]

Treatment for SMA before Spinraza was mostly supportive and targeted towards specific symptoms, with the goal of providing respiratory assistance and nutritional aid. However, the approval of Spinraza, as the first therapy with the potential to modify the disease trajectory, revolutionized SAM treatment.[81] In phase III clinical trials, a much larger proportion of infants with SMA treated with Spinraza (51%) showed improvement in motor milestones vs the placebo group (0%, $p<0.0001$).[82]

The availability of Spinraza was greeted with great enthusiasm by both clinicians and caregivers as a therapy with significant potential to meet critical unmet needs in a condition with high morbidity/mortality risk. The director of the Division of Neurology Products in the FDA's Center for Drug Evaluation and Research stated, "There has been a long-standing need for a treatment for spinal muscular atrophy, the most common genetic cause of death in infants, and a disease that can affect people at any stage of life… we could not be more pleased to have the first approved treatment for this debilitating disease".[83]

In its first year of availability, Spinraza generated ~$880 million in revenue worldwide, growing to over $2 billion in 2019.[15] The launch of Spinraza was obviously a great success and has undoubtedly saved lives. However, it also represents something of a cautionary tale for Technological Approach Specialists, as many of the accolades and financial benefits of marketing such a groundbreaking therapy have accrued to Biogen as the lead marketing company, not Ionis, who initially developed the therapy and underlying technology.

The Evolving Ionis Approach to Partnerships

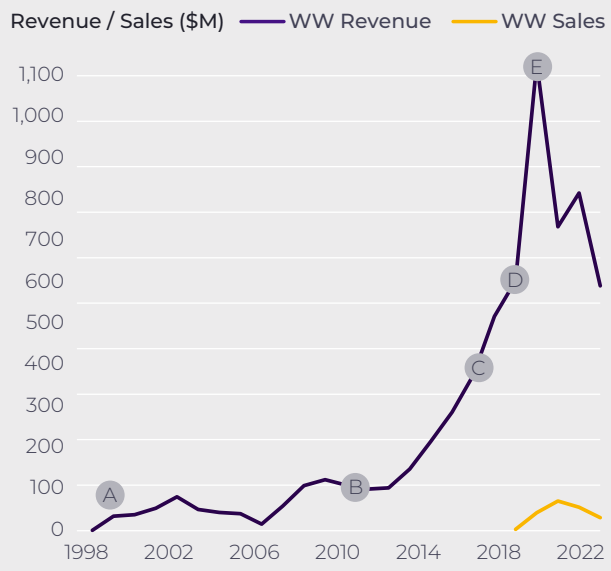
Ionis has partnered not only with Biogen but also with many other manufacturers, including GSK, AstraZeneca, and Roche.[84] Partnerships also have not been limited to large established companies; Ionis partnered with Akcea, resulting in approved therapies like Tegsedi for the treatment of polyneuropathy of hereditary transthyretin-mediated amyloidosis (hATTR) and Waylivra for the treatment of familial chylomicronemia syndrome (FCS) in the EU.[85,86] Ionis gradually acquired increasing stake Akcea, resulting in a full acquisition in 2020 (Figure 10). Ionis described this transaction as "a key step in the evolution of Ionis' business strategy".[87]

This evolution is notable, as Ionis has historically prioritized resources on building a broad and diverse platform using the ASO technology rather than using resources to develop a strong sales force to support assets post-commercialization. In contrast to Alnylam, which has selectively used partnerships to ensure sufficient resources to grow into an organization capable of independently supporting approved assets, Ionis has relied strongly on partnerships (Figure 10).

The recently completed acquisition of Akcea likely indicates a shift in focus to post-approval sales and marketing to have greater control over value capture for commercial-phase assets while still maintaining a robust and diverse pipeline. In fact, in Fall 2023, Ionis announced results from a Phase 3 trial of a next-generation therapy for FCS, olezarsen, and signaled plans to independently commercialize the therapy if approved by the FDA.[88]

As the revenue trajectory for Ionis shows, some commercialization rights can result in a higher market capitalization and revenue stream vs an exclusive focus on technology development (Figure 11). The example of Ionis highlights the value of having a differentiated technology platform that can lead to innovative therapies but also the risks of remaining heavily focused on clinical development of those therapies vs a balanced approach that also considers how to maximize post-approval sales that accrue to developing company. A thoughtful partnership strategy can help preserve the opportunity to capture the value of the R&D investment (Figure 12).

FIGURE 11: IONIS WORLDWIDE REVENUE & US LAUNCH YEARS OF KEY PRODUCTS, 1998-2022



	First Year of launch (US)	Product Name	Indication
A	1998 (Discontinued in 2004)	**Vitravene**	CMV (Cytomegalovirus) retinitis in AIDS patients
B	2013	**Kynamro**	Homozygous familial hypercholesterolemia (HoFH)
C	2016	**Spinraza**	Spinal muscular atrophy
D	2018	**Tegsedi**	Polyneuropathy of hereditary transthyretin-mediated amyloidosis (hATTR)
E	2019 (EU only)	**Waylivra**	Familial chylomicronemia syndrome (FCS)

Other Examples of Technological Approach Specialists

A technology-focused approach is not limited to RNA- or ASO-focused platforms. Examples abound; for instance, Seagen has focused on antibody-drug conjugate (ADC) development.[89] Key products include Adectris (2011) for the treatment of Hodgkin's Lymphoma and anaplastic large cell lymphoma (ALCL) and Padcev (2019) for the treatment of bladder cancer, with a total company revenue of ~$2B in 2022.[90] Pfizer is planning to acquire the company for $43B, which is the largest biopharma transaction in the past three years,[91] once again highlighting the potential of a Technological Approach Specialist path in building company value.

Key Areas of Technological Approach Specialist Confidence

For a company to achieve success as a commercial-stage Technological Approach Specialist, it is critical that the value the technology offers aligns with a particular unmet need in an indication with reasonable commercial potential (i.e., an indication with a reasonably sized addressable population and relatively low competitive intensity), and ideally multiple such indications.

While it is important for a company to believe in the value their technology can offer patients and to be able to message on that value to investors, it is similarly important for a company to have a clear and compelling story for investors and potential partner companies about how ultimately the technology will support an attractive revenue stream. Of course, these are not mutually exclusive, but it is also important to recognize that the ability to meet a high therapeutic unmet need may not necessarily automatically translate into a commercially successful product.

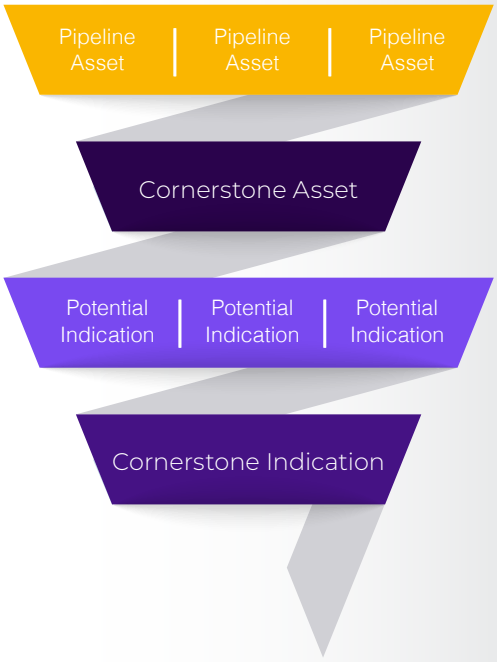
FIGURE 12: COMPARATIVE REVENUE TRAJECTORIES OF BIOGEN, ALNYLAM, AND IONIS

Example Key Strategic Questions for Therapeutic Area Specialists

The foundation of an attractive commercial story will be selecting a compelling cornerstone asset and indication (Figure 13). To ensure sufficient depth of understanding of the commercial potential to communicate that story, it will be important to evaluate a series of questions to establish a strong factual base and rationale for indication selection, including:

- What is the comprehensive set of indications for which the technology has potential to affect symptoms and/or disease course?
- Of these, which is the clinical impact of the technology likely to be superior to that offered by currently available therapeutics?
- Is there patient need for the benefit the technology can deliver?
- Is this need likely to persist until the anticipated year of launch (i.e., are there any other competitors with later-stage assets in development with similar or greater clinical potential)?
- How does the expected development timeline and probability of technical success vary across potential indications?
- What are potential back-up indications in the event that the technology is not as successful in the lead indication as currently anticipated (either developmentally or commercially)?

FIGURE 13: PATH TO LEAD INDICATION IDENTIFICATION FOR TECHNOLOGICAL APPROACH SPECIALISTS



- Which asset is most **advanced** in development?
- Which asset has the most **favorable safety & PK/PD** profile? Do any offer more or less advantageous **routes of administration**?

What is the comprehensive set of indications for which the asset has the potential to affect symptoms or disease course?

- Of these, for which is the **clinical impact of the asset likely to be superior** to that offered by currently available therapeutics?
- Is there **patient need** for the benefit the technology can deliver? Will this **need persist** given known competition?
- How does the expected development **timeline and probability of technical success** vary across potential indications?

- This framework is high-level and illustrative
- The optimal indication selection framework will vary from company to company depending on specific corporate strategic imperatives and guiding principles

Furthermore, it will also be important for Technological Approach Specialists to carefully consider the potential role partnerships can serve in the achievement of strategic objectives, considering:

- How long is the current cash runway expected to extend? Are there other income streams that will need to be considered to extend the runway until the time of launch of a key asset?
- What is the desired and feasible prioritization of building internal capabilities to support a commercial-phase asset vs investing in the pipeline?
  - Are there unique lead indication characteristics that would make developing a sales force more expensive or time-consuming (e.g., highly competitive landscape, a high number of call points, etc.)?
  - Is there potential for longer-term commercial force synergies with other pipeline assets / other planned indications?
  - Is the commercial opportunity particularly high in specific global markets that require more effort for commercialization and/or local manufacturer presence?

Future Prominent Technological Approach Specialists

Not surprisingly, many emerging biotech companies have a technology-focused platform today. A recent prominent example is Moderna, with its mRNA technology platform that was successfully leveraged to develop Spikevax to protect against COVID-19. With close to $40B in revenue since the approval of Spikevax, Moderna is now actively deploying resources to advance the development of a number of other vaccine assets against the respiratory syncytial virus (RSV), cytomegalovirus (CMV), and influenza, as well as other targets.92,93 To date, however, all pipeline assets are leveraging similar mRNA technology as Spikevax. It will be interesting to observe how Moderna continues to evolve as a company with additional commercialized assets and at what point, if any, they begin pursuing therapeutics with a different technological basis.

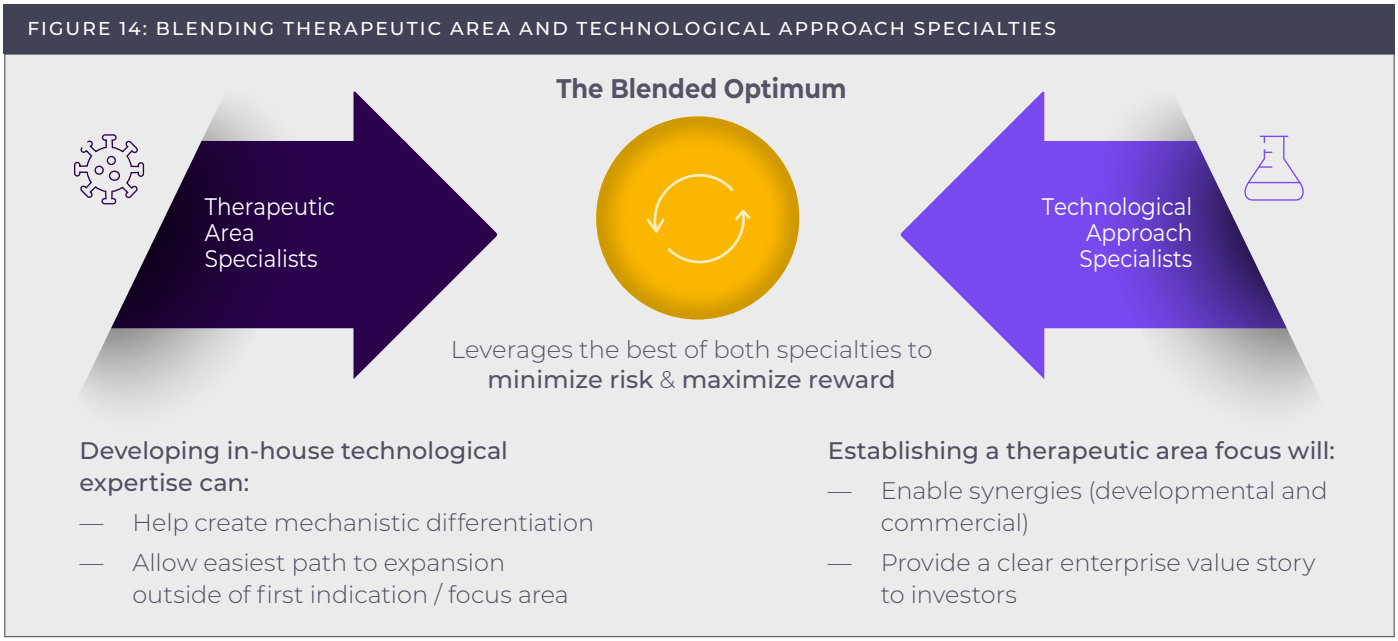
Of course, very few companies can expect a similar stratospheric rise to Moderna, particularly if they maintain a singular focus. To surmount this challenge, the best strategy is likely to take a combination approach that takes advantage of the best of both of the two primary archetypes outlined in this review.

The Blended Optimum: Capitalizing on the Best of The Therapeutic Area and Approach Specialist Approaches

Combining considerations from both strategies previously described can help minimize risk and maximize reward, regardless of the nature of foundational company expertise (Figure 14):

- **For initial Therapeutic Area Specialists**, developing in-house expertise in a specific technology can help 1) create mechanistic differentiation in the area of focus, particularly in the face of any competition, and 2) allow the easiest path to expansion opportunities outside of the area of focus.
- **For initial Technological Approach Specialists**, having a clear primary therapeutic area focus will enable potential developmental and future commercial synergies and help provide a clear and compelling value story to investors.

FIGURE 14: BLENDING THERAPEUTIC AREA AND TECHNOLOGICAL APPROACH SPECIALTIES



Celgene

As an example, Celgene had specific internal technological and developmental capabilities that they used to commercialize several early therapies for a wide variety of disease areas, but also quickly established a long-term vision to drive towards what eventually became their signature multiple myeloma franchise. By leveraging both elements, Celgene was able to commercialize several therapies in diverse therapeutic areas quickly and then use the proceeds to support in-depth research efforts for the multiple myeloma target area.

Celgene's First Chiral Therapeutic, Thalomid

The licensure of thalidomide from Rockefeller University in 1992 was Celgene's first step.[94] Thalidomide was originally marketed as an OTC sedative and antiemetic for pregnant people in the 1950s. However, it was removed from the market in 1961 due to serious side effects, later determined to be a result of a mixture of two forms of thalidomide (molecular mirror images of each other, also known as enantiomers). Over the following decades, there were signals from work at academic institutions that the compound could potentially have positive impacts for patients with leprosy (and, specifically, erythema nodosum leprosum, ENL, a skin condition that is a complication of leprosy), AIDS, and cancer.[95,96]

Following the acquisition of the rights to thalidomide in 1992, Celgene did extensive work to demonstrate therapeutic utility and safety, ultimately leading to the approval of Thalomid in 1998 for the treatment of cutaneous manifestations of moderate to severe ENL.[97] In the years following, Celgene continued to leverage its expertise in chiral pharmaceuticals to develop safer, therapeutically equivalent, or superior formulations of major therapies but also effectively used capital raised from initial launches to support initial forays into multiple myeloma.[98]

Developing and Licensing Out an ADHD Therapy

One of the results of their work in chiral pharmaceuticals was the approval of Focalin in 2001. Focalin is the enantiomerically pure version of Ritalin, both indicated for the treatment of attention deficit hyperactivity disorder (ADHD).[99] At the time of launch, nearly 10% of children ages 6 to 11 and approximately 4% of adults had been diagnosed with ADHD.100 Although very similar to Ritalin in terms of its molecular structure, Focalin is more potent than Ritalin.[101]

Celgene elected not to be responsible for the commercialization of Focalin, instead granting the intellectual property and commercialization rights to Novartis (the manufacturer of the primary alternative, Ritalin).[102] This enabled prioritization of ongoing Thalomid / Thalomid-adjacent and other oncology-focused programs while still accruing financial rewards for Focalin development (Figure 16).

Building in MM: Distributing and Promoting Alkeran

In the 1990s, treatment for MM included high-dose chemotherapy and stem cell transplants from peripheral blood, with considerable need for superior options. To gain initial commercial experience in MM, in 2003, Celgene signed a deal with GSK to distribute and promote Alkeran, a nitrogen mustard-derived alkylating agent.103 At this time, the MM treatment landscape was rapidly evolving, with not only new alkylating agents like Alkeran but other new therapeutic classes (e.g., proteosome inhibitors).[104]

As a result of this evolving competitive landscape, Alkeran experienced only modest commercial success, but it afforded Celgene the opportunity to establish itself as a MM-experienced manufacturer. The market experience Celgene gained through Alkeran commercialization was likely part of a pre-launch strategy to support what was ultimately their signature blockbuster therapy that cemented its future success, approved in 2005: Revlimid.[105]

Celgene Takes Off in Multiple Myeloma: Revlimid

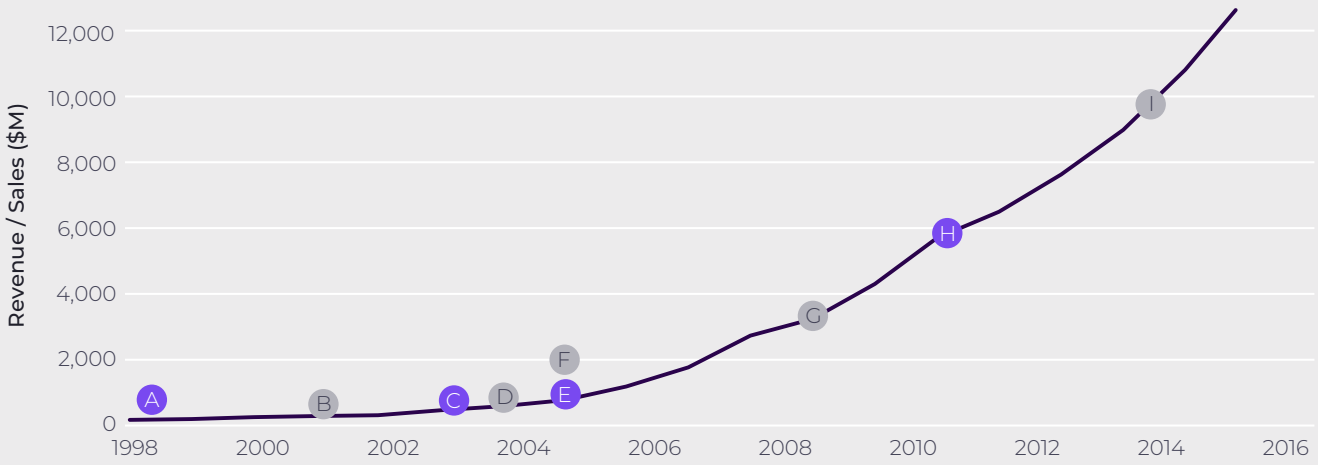
Revlimid is an immunomodulatory (IMiD) thalidomide analogue that was developed using Celgene's historical expertise in chiral small molecules. In the US, it is indicated in combination with dexamethasone for the treatment of MM patients (initially for those who have received at least one prior therapy, now for all MM patients).[105] In clinical trials, Revlimid + dexamethasone produced a slower median time to progression vs placebo combined with dexamethasone (11.1 vs 4.7 months, $p<0.001$).[106] Research also suggested Revlimid/dexamethasone was more effective and better tolerated in most newly diagnosed MM patients than Thalomid/dexamethasone.[107,108]

Within its first year, sales of Revlimid reached ~$325 million.[15] This strong start was likely enabled in part by Celgene's prior commercial experience in MM with Alkeran, in addition to the strength of the Revlimid clinical data, high unmet need, and limited in-class competition. Celgene continued to leverage these advantages to grow Revlimid revenue year-over-year, achieving close to $13 billion in 2021[109] prior to the entrance of generics (Figure 15).[110]

Revlimid's commanding commercial performance afforded Celgene the resources to develop a next-generation IMiD, Pomalyst, approved in 2013 for the treatment of MM, continuing their therapeutic area expertise.[111] However, they also leveraged their technological expertise in chiral molecules to expand into non-oncology therapeutic areas, most notably to develop Otezla, approved in 2014 for the treatment of adults with psoriatic arthritis and/or moderate to severe plaque psoriasis.[112] Both Pomalyst and Otezla eventually produced multi-billion annual revenue streams and, along with Thalomid, Revlimid, and other assets, supported a prominent acquisition of Celgene by Bristol-Myers Squibb in 2019.[113]

While Celgene ultimately became an expert in MM, it was 13 years between when they initially acquired the rights to thalidomide and attained approval of Revlimid, arguably their signature therapy. The length of this time period is notable, as many biotech companies are acquired or burn through their cash reserves in similar or shorter time periods. A likely key to their success and independent persistence was their ability to leverage their small molecule expertise and opportunistically apply it to multiple different disease areas.

FIGURE 15 : CELGENE WORLDWIDE REVENUE & US LAUNCH YEARS OF KEY PRODUCTS, 1998-2017



	First Year of launch (US)	Product Name	Indication
A*	1998	**Thalomid**	— 1998: Moderate to severe erythema nodosum leprosum (ENL) — 2006: 1L, MM (with dexamethasone)
B*	2001	**Focalin**	— Attention Deficit Hyperactivity Disorder (ADHD)
C	1964 (licensed to Celgene in 2003)	**Alkeran**	— Multiple myeloma (MM)
D*	2004	**Vidaza**	— 2004: Certain myelodysplastic syndrome (MDS) subtypes^ — 2022: 1L juvenile myelomonocytic leukemia
E*	2005	**Revlimid**	— 2005: Low- or intermediate-risk MDS — 2013: 3L, Relapsed or progressed mantle cell lymphoma (MCL) — 2015: 1L, MM (with dexamethasone)
F*	2005	**Abraxane**	— 2005: 2L+ breast cancer — 2012: 1L, NSCLC (with carboplatin) — 2013: 1L, PDAC (with gemcitabine)
G*	2009	**Istodax**	— 2L+, CTCL, prior at least one systemic therapy
H	2011	**Pomalyst**	— 2013: 3L+, MM, received prior two therapies including lenalidomide (with dexamethasone)
I*	2014	**Otezla**	— Psoriatic arthritis

Relating to MS Non-MS Disease Area

*Chiral molecule developed or optimized by Celgene, with product consisting of a single enantiomer

Requirements to Pursue a Blended Therapeutic Area Focus / Technology Specialization Approach

As the example of Celgene demonstrates, there can be great advantages to pursuing a path that combines technological expertise with a specific therapeutic area focus. However, this is arguably the most difficult strategy, as it requires (Figure 16):

— A clear therapeutic area focus (as with the Therapeutic Area Specialists).

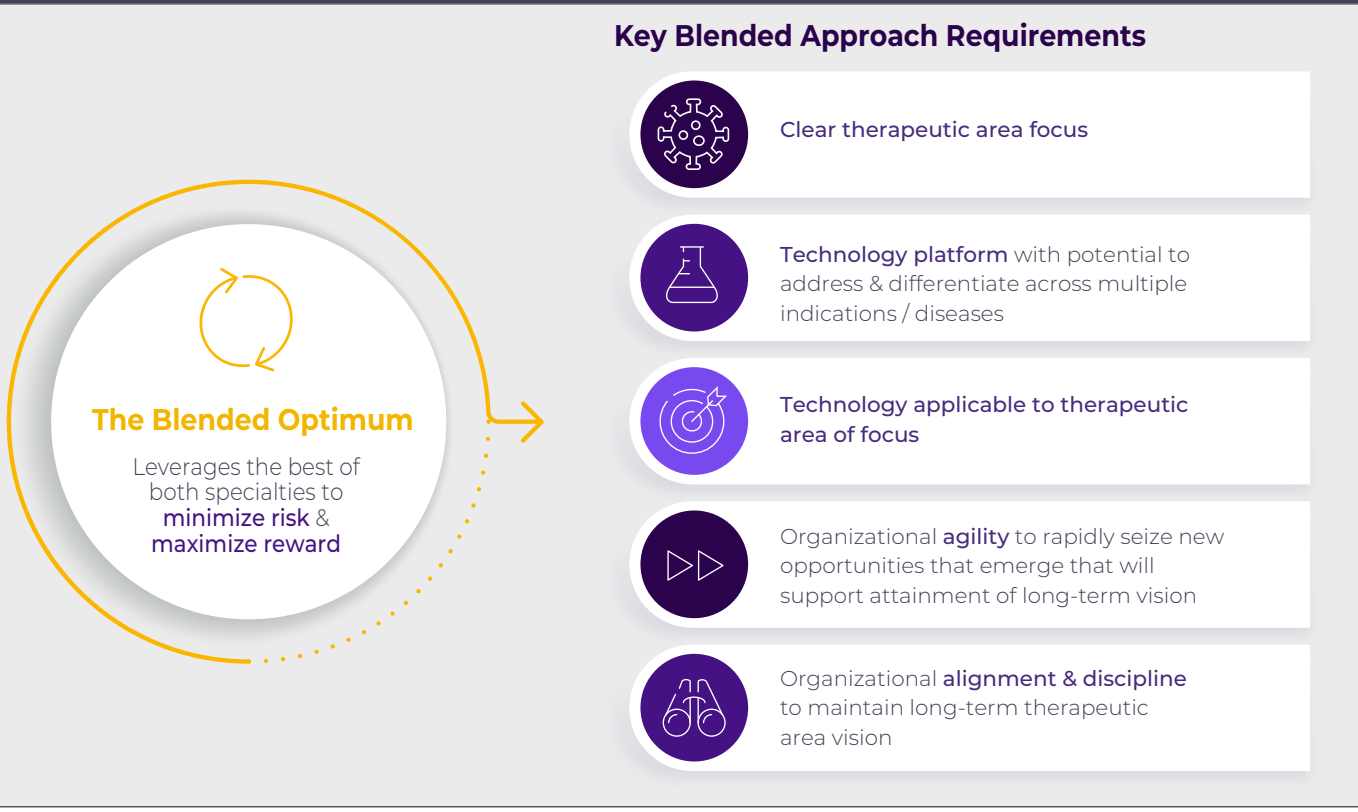
— A technology platform with the potential to address and, ideally, offer differentiated clinical value across multiple indications and disease areas (as with the Technological Approach Specialists).

— That the technology be applicable to the therapeutic area of focus.

— Organizational alignment and discipline to maintain the long-term therapeutic area target.

— Organizational agility to rapidly seize new opportunities that emerge that will support the attainment of a long-term vision.

FIGURE 16: REQUIREMENTS TO PURSUE A BLENDED APPROACH



The last two requirements can be exceedingly difficult, as they require a strong perspective and company vision years to decades in the future as well as commitment to that vision, even as other opportunities arise that seem attractive on the surface. One way to maintain this discipline is a pipeline categorization of assets into three discrete categories:

- Those central to the long-term therapeutic area focus.
- Those adjacent to the long-term therapeutic area focus.
- Those not related to the long-term therapeutic area focus, but are important for either developing company technological expertise or for capturing a low-hanging commercial opportunity.

This strategy and asset categorization can of course evolve over time, and in fact should be flexible, dynamic, and responsive to internal (e.g., trial readouts) and external market events (e.g., competitor actions). Establishing a set of categorization criteria can help maintain this longer-term discipline while also providing flexibility to optimally position the company.

Conclusion

This work has identified and detailed two primary biotech company archetypes, advantages and disadvantages of each, and key strategic questions that should be considered unique to the archetype. However, not all companies will fit neatly into one archetype, and instead, many today take a blended approach.

History suggests that there are virtually infinite paths to longer-term biotech commercial success, with every company having a unique set of considerations and strategic imperatives. It is imperative that companies carefully map out their individual path, considering the full breadth of possibilities, and then establish a flexible yet focused strategic roadmap. This is even more important in a climate of restricted funding and investment. As this work demonstrates, however, companies that carefully consider the intersection of their technology with the indication and commercial environment can have tremendous strong long-term success potential.

Sources

Figure sources include Evaluate Pharma, Biomedtracker, FDA, and Adis.

1. U.S. FDA. (2020, March). AVONEX (interferon beta-1a) injection, for intramuscular injection. Biogen Inc. https://www.accessdata.fda.gov/drugsatfda_docs/label/2021/103628s5266lbl.pdf

2. National Multiple Sclerosis Society. (2023). MS signs and symptoms. https://www.nationalmssociety.org/Symptoms-Diagnosis/MS-Symptoms

3. Olek, M. J., & Howard, J. (2023, September). Treatment of acute exacerbations of multiple sclerosis in adults. UpToDate. Last Reviewed September 2023, from https://www.uptodate.com/contents/treatment-of-acute-exacerbations-of-multiple-sclerosis-in-adults?search=multiple%20sclerosis%20treatment&source=search_result&selectedTitle=2~150&usage_type=default&display_rank=2

4. Madell, R. (2021, July 8). Multiple sclerosis prognosis and your life expectancy. Healthline. https://www.healthline.com/health/multiple-sclerosis/prognosis-and-life-expectancy

5. The Pink Sheet. (1993, July 26). Chiron/Berlex Betaseron gains first biotech accelerated approval. https://pink.pharmaintelligence.informa.com/PS023006/CHIRONBERLEX-BETASERON-GAINS-FIRST-BIOTECH-ACCELERATED-APPROVAL

6. Wallin, M. T., Culpepper, W. J., Campbell, J. D., Nelson, L. M., Langer-Gould, A., Marrie, R. A., Cutter, G. R., Kaye, W. E., Wagner, L., Tremlett, H., Buka, S. L., Dilokthornsakul, P., Topol, B., Chen, L. H., LaRocca, N. G. (2019). The prevalence of MS in the United States: A population-based estimate using health claims data. Neurology, 92(10), e1029–e1040. https://n.neurology.org/content/92/10/e1029

7. Multiple Sclerosis Centers of Excellence. (2021). Determination of multiple sclerosis subtypes. U.S. Department of Veteran Affairs. https://www.va.gov/MS/Professionals/Diagnosis/Determination_of_MS_Subtypes.asp

8. Doherty, C. (2022, August 15). Relapsing-Remitting MS Facts and Statistics: What You Need to Know. Verywell Health. https://www.verywellhealth.com/facts-about-relapsing-remitting-ms-5703612#:~:text=How%20Common%20Is%20RRMS%3F%20The%20estimated%20prevalence%20of,occurs%20in%20around%2087%25%20of%20these%20individuals.%201

9. Biomedtracker. (2023). Avonex. Pharma Intelligence UK Limited. https://www.biomedtracker.com/DrugReport.cfm?DrugID=156

10. Shirley Ryan AbilityLab. (2018, April 4). Expanded Disability Status Scale & Kurtzke Functional Systems Score. https://www.sralab.org/rehabilitation-measures/expanded-disability-status-scale-kurtzke-functional-systems-score

11. Biogen. (2023). Once a week Avonex (Interferon beta-1a). https://hcp.avonex.com/en_us/home/hcp-efficacy/hcp-pivotal-trials.html

12. Macrotrends. (2023, October 10). Biogen - 32 Year Stock Price History | BIIB . https://www.macrotrends.net/stocks/charts/BIIB/biogen/stock-price-history

13. The Pharma Letter. (1999, March 2). FDA upholds Avonex/Betaseron orphan drug status and requests more info on. https://www.thepharmaletter.com/article/fda-upholds-avonex-betaseron-orphan-drug-status-and-requests-more-info-on

14. Marshall A. Approved or Advanced Experimental MS Therapies. Nature Biotechnology, 14, 812. https://www.nature.com/articles/nbt0796-812

15. Drug Database. Revenues: Sales, by year, for certain drugs and cell therapies. https://drugdatabase.info/revenues/

16. Biogen. (2009). First Ten-Year Follow-Up Shows That Treatment with AVONEX® Leads to Long-Term Benefits in Early Multiple Sclerosis Patients. https://investors.biogen.com/news-releases/news-release-details/first-ten-year-follow-shows-treatment-avonexr-leads-long-term

17. Medical Drug Clinical Criteria. (2022, September 19). Beta interferons and glatiramer acetate for treatment of multiple sclerosis. https://www.anthem.com/ms/pharmacyinformation/Beta-Interferons-And-Glatiramer-Acetate.pdf

18. Aetna. (2023). Interferons. Last Reviewed August 30, 2023, from https://www.aetna.com/cpb/medical/data/400_499/0404.html#:~:text=Aetna%20considers%20interferon%20beta%20Avonex%20%28interferon%20beta-1a%29%20medically,who%20continue%20to%20experience%20relapse%29.%20Clinically%20isolated%20syndrome

19. United Health Care. (2023). United Healthcare Pharmacy and Clinical Pharmacy. Programs https://www.uhcprovider.com/content/dam/provider/docs/public/prior-auth/drugs-pharmacy/commercial/h-p/PA-Notification-MS.pdf

20. Biomedtracker. (2023). Tysabri. Pharma Intelligence UK Limited. https://www.biomedtracker.com/DrugReport.cfm?DrugID=158

21. Biomedtracker. (2023). Tecfidera. Pharma Intelligence UK Limited. https://www.biomedtracker.com/DrugReport.cfm?DrugID=320

22. Biogen. (2018, January 25). Biogen reports record revenues for both the full year and fourth quarter of 2017, $12.3 billion and $3.3 billion, respectively. https://investors.biogen.com/news-releases/news-release-details/biogen-reports-record-revenues-both-full-year-and-fourth-quarter

23. Biogen. (2016, December 23). U.S. FDA approves Biogen's SPINRAZA™ (nusinersen), the first treatment for spinal muscular atrophy. https://investors.biogen.com/news-releases/news-release-details/us-fda-approves-biogens-spinrazatm-nusinersen-first-treatment

24. Biomedtracker. (2023). Aduhelm. Pharma Intelligence UK Limited. https://www.biomedtracker.com/DrugReport.cfm?DrugID=18249

25. Biomedtracker. (2023). Leqembi. Pharma Intelligence UK Limited. https://www.biomedtracker.com/DrugReport.cfm?DrugID=17265

26. Vertex. (2002, December 20). Vertex Pharmaceuticals Announces Submission of NDA/MAA Filings in U.S. and Europe for GW433908 (new formulation of Agenerase [amprenavir]) for Treatment of HIV Infection [Press release]. https://www.natap.org/2002/Dec/122702_6.htm#:~:text=Vertex%27s%20first%20approved%20product%20is%20Agenerase%20%28R%29%20%28amprenavir%29%2C,cancer%2C%20autoimmune%20diseases%2C%20neurological%20disorders%20and%20genetic%20disorders

27. Biomedtracker. (2023). Agenerase. Pharma Intelligence UK Limited. https://www.biomedtracker.com/DrugReport.cfm?DrugID=239

28. U.S. FDA. (1999, April). AGENERASE. Glaxo Wellcome Inc. https://www.accessdata.fda.gov/drugsatfda_docs/label/1999/21007lbl.pdf

29. Watson S. (2022). The history of HIV treatment: Antiretroviral therapy and more. https://www.webmd.com/hiv-aids/hiv-treatment-history

30. YCharts. Vertex Pharmaceuticals Inc (VRTX). https://ycharts.com/companies/VRTX/revenues_annual

31. Elflein J. (2020, June 9). Number of people living with hepatitis C virus infection (HCV RNA positive) worldwide in 2015, by WHO region. Statista. https://www.statista.com/statistics/1121967/hepc-prevalence-global-by-region/

32. Centers for Disease Control and Prevention. (2023, April 11). Hepatitis C. https://www.cdc.gov/hepatitis/hcv/index.htm

33. Carroll, M. (2019, April 15). Then and now: The evolution of treatments for hepatitis C. Healthline. https://www.healthline.com/health/hepatitis-c/evolution-of-treatments

34. Hézode, C. (2012, February 17). Boceprevir and telaprevir for the treatment of chronic hepatitis C: Safety management in clinical practice. Liver International, 32(Suppl 1), 32–38. https://www.hal.inserm.fr/inserm-00671254v1/document----

35. Biomedtracker. (2023). Incivek. Pharma Intelligence UK Limited. https://www.biomedtracker.com/DrugReport.cfm?DrugID=47

36. Staton, T. (2014, April 22). It's official: Gilead's Sovaldi zooms past previous records with fastest-ever drug launch. Fierce Pharma. https://www.fiercepharma.com/marketing/it-s-official-gilead-s-sovaldi-zooms-past-previous-records-fastest-ever-drug-launch

37. Helfand, C. (2014, August 13). Sovaldi forces Incivek off the hep C market as Vertex calls it quits. Fierce Pharma. https://www.fiercepharma.com/sales-and-marketing/sovaldi-forces-incivek-off-hep-c-market-as-vertex-calls-it-quits

38. Vertex. (2011, April 7). Vertex and Cystic Fibrosis Foundation Therapeutics to Collaborate on Discovery and Development of New Medicines to Treat the Underlying Cause of Cystic Fibrosis [Press release]. https://investors.vrtx.com/news-releases/news-release-details/vertex-and-cystic-fibrosis-foundation-therapeutics-collaborate

39. Chalmers, S. (2021, November 23). Diseases and conditions: Cystic fibrosis. Mayo Clinic. https://www.mayoclinic.org/diseases-conditions/cystic-fibrosis/symptoms-causes/syc-20353700

40. Cystic Fibrosis Foundation. (2022, July 28). CF foundation estimates increase in CF population. https://www.cff.org/news/2022-07/cf-foundation-estimates-increase-cf-population#:~:text=The%20CF%20population%20was%20last%20estimated%20in%202012,and%20the%20Vital%20Statistics%20of%20the%20United%20States

41. Pollack, A. (2012, January 31). F.D.A. approves new cystic fibrosis drug. The New York Times. https://www.nytimes.com/2012/02/01/business/fda-approves-cystic-fibrosis-drug.html

42. Biomedtracker. (2023). Orkambi. Pharma Intelligence UK Limited. https://www.biomedtracker.com/DrugReport.cfm?DrugID=9964

43. Biomedtracker. (2023). Symdeko. Pharma Intelligence UK Limited. https://www.biomedtracker.com/DrugReport.cfm?DrugID=18177

44. Biomedtracker. (2023). Trikafta. Pharma Intelligence UK Limited. https://www.biomedtracker.com/DrugReport.cfm?DrugID=33101

45. Vertex. (2023, February 7). Vertex Reports Fourth Quarter and Full Year Financial 2022 Results [Press release]. https://investors.vrtx.com/news-releases/news-release-details/vertex-reports-fourth-quarter-and-full-year-financial-2022

46. Macrotrends. (2023, October 11). Vertex Pharmaceuticals - 32 Year Stock Price History | VRTX. https://www.macrotrends.net/stocks/charts/VRTX/vertex-pharmaceuticals/stock-price-history

47. Vertex. (2023). R&D Pipeline. https://www.vrtx.com/our-science/pipeline/

48. Biomedtracker. (2023). Alexion Pharmaceuticals Inc. Pharma Intelligence UK Limited. https://www.biomedtracker.com/companyreport.cfm?companyid=21

49. AstraZeneca. (2022). What science can do. https://www.astrazeneca.com/content/dam/az/Investor_Relations/annual-report-2022/pdf/AstraZeneca_AR_2022.pdf

50. Biomedtracker. (2023). BioMarin Pharmaceutical Inc. (BMRN). Pharma Intelligence UK Limited. https://www.biomedtracker.com/companyreport.cfm?companyid=65

51. Biomarin. (2023, February 27). BioMarin Announces Record Fourth Quarter and Full Year 2022 Total Revenues Driven by Strong Global Demand for VOXZOGO® and Steady Growth of Enzyme Business. https://investors.biomarin.com/2023-02-27-BioMarin-Announces-Record-Fourth-Quarter-and-Full-Year-2022-Total-Revenues-Driven-by-Strong-Global-Demand-for-VOXZOGO-R-and-Steady-Growth-of-Enzyme-Business

52. Alnylam. (2023). The leading RNAi therapeutics company. https://www.alnylam.com/

53. Gertz, M. A., (2017). Hereditary ATTR amyloidosis: burden of illness and diagnostic challenges. American Journal of Managed Care. 23(7 Suppl), S107–S112. https://pubmed.ncbi.nlm.nih.gov/28978215/#:~:text=Although%20the%20exact%20prevalence%20is%20difficult%20to%20determine%2C,amyloidosis%20can%20lead%20to%20significant%20disability%20and%20mortality

54. Luigetti, M., Romano, A., Paolantonio, A. D., Bisogni, G., & Sabatelli, M. (2020). Diagnosis and treatment of hereditary transthyretin amyloidosis (hATTR) polyneuropathy: Current perspectives on improving patient care. Therapeutics and Clinical Risk Management, 16, 109–123. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7041433/#:~:text=Hereditary%20transthyretin%20amyloidosis%20(hATTR)%20with,of%20different%20organs%20and%20tissues

55. Alnylam Pharmaceuticals, Inc. (2023, January). Onpattro (patisiran) lipid complex injection, for intravenous use. https://www.alnylam.com/sites/default/files/pdfs/ONPATTRO-Prescribing-Information.pdf

56. Alnylam Pharmaceuticals, Inc., (2020, January 12). Alnylam announces preliminary fourth quarter and full year 2019 global net product revenues and provides additional commercial updates. https://www.sec.gov/Archives/edgar/data/1178670/000119312520005791/d867754dex991.htm

57. Business Wire. (2019, April 30). Alnylam highlights progress on global market access for ONPATTRO (patisiran). https://www.businesswire.com/news/home/20190430006066/en/Alnylam-Highlights-Progress-on-Global-Market-Access-for-ONPATTRO-patisiran

58. Biomedtracker. (2023). Onpattro. Pharma Intelligence UK Limited. https://www.biomedtracker.com/DrugReport.cfm?DrugID=19085#ConsensusForecasts

59. Ionis. (2004, March 11). Isis Pharmaceuticals forms strategic alliance with Alnylam Pharmaceuticals in RNAi therapeutics. https://ir.ionispharma.com/news-releases/news-release-details/isis-pharmaceuticals-forms-strategic-alliance-alnylam

60. Biomedtracker. (2023). Onpattro. Pharma Intelligence UK Limited. https://www.biomedtracker.com/DrugReport.cfm?DrugID=19085#ConsensusForecasts

61. Alnylam. (2023). Our Pipeline. https://www.alnylam.com/alnylam-rnai-pipeline

62. Jarvis, L. M. (2019, May 5). Stanley Crooke on finally making sense out of antisense. Chemical & Engineering News. https://cen.acs.org/pharmaceuticals/Stanley-Crooke-finally-making-sense/97/i18

63. Alhamadani, F., Zhang, K., Parikh, R., Wu, H., Rasmussen, T. P., Bahal, R., Zhong, X.-b., Manautou, J. E., (2022, February 27). Adverse drug reactions and toxicity of the FDA-approved antisense oligonucleotide drugs. ASPET Journals. https://dmd.aspetjournals.org/content/dmd/early/2022/02/27/dmd.121.000418.full.pdf

64. Vemulakonda, G. A., (2023, April 26). What is cytomegalovirus retinitis? American Academy of Ophthalmology. https://www.aao.org/eye-health/diseases/what-is-cytomegalovirus-retinitis

65. Jacobson, M. A., (2023). Pathogenesis, clinical manifestations, and diagnosis of AIDS-related cytomegalovirus retinitis. UpToDate. Last Reviewed September 2023, from https://www.uptodate.com/contents/pathogenesis-clinical-manifestations-and-diagnosis-of-aids-related-cytomegalovirus-retinitis#!

66. Vitravene Study Group. (2002). A randomized controlled clinical trial of intravitreous fomivirsen for treatment of newly diagnosed peripheral cytomegalovirus retinitis in patients with AIDS. American Journal of Ophthalmology, 133(4), 467–474. https://pubmed.ncbi.nlm.nih.gov/11931780/

67. Bradley, C. A., (2019, November 14). First antisense drug is approved with fleeting success. Nature Portfolio. https://www.nature.com/articles/d42859-019-00080-6

68. Biomedtracker. (2023). Kynamro. Pharma Intelligence UK Limited. https://www.biomedtracker.com/DrugReport.cfm?DrugID=2110

69. Mayo Clinic. (2021, September 23). Familial hypercholesterolemia. https://www.mayoclinic.org/diseases-conditions/familial-hypercholesterolemia/symptoms-causes/syc-20353755

70. Centers for Disease Control and Prevention. (2023, June 16). Familial hypercholesterolemia. https://www.cdc.gov/genomics/disease/fh/FH.htm

71. Rosenson R. S. Familial hypercholesterolemia in adults: Treatment. UpToDate. Last Reviewed September 2023, from https://www.uptodate.com/contents/familial-hypercholesterolemia-in-adults-treatment?search=familial%20hypercholesterolemia%20treatment&source=search_result&selectedTitle=1~116&usage_type=default&display_rank=1

72. Family Heart Foundation. (2013, January 30). New HoFH drug, KYNAMRO, approved by the FDA. https://familyheart.org/new-hofh-drug-kynamro-approved-by-the-fda

73. Biomedtracker. (2023). Phase III - RADICHOL I (hoFH) (Pivotal). Pharma Intelligence UK Limited. https://www.biomedtracker.com/DrugReport.cfm?DrugID=2110

74. Fikes, B. J. (2016, January 11). Ionis takes back heart drug Kynamro. San Diego Union-Tribune. https://www.sandiegouniontribune.com/business/biotech/sdut-ionis-takes-back-kynamro-2016jan11-story.html

75. Ionis. (2016, May 3). Ionis Pharmaceuticals and Kastle Therapeutics Announce Acquisition of KYNAMRO®. https://ir.ionispharma.com/news-releases/news-release-details/ionis-pharmaceuticals-and-kastle-therapeutics-announce

76. Schiller, L. J., (2019, June 28). Liebel-Flarsheim Company LLC, et al.; Withdrawal of approval of 11 new drug applications. Federal Register. https://www.federalregister.gov/documents/2019/07/03/2019-14219/liebel-flarsheim-company-llc-et-al-withdrawal-of-approval-of-11-new-drug-applications

77. U.S. FDA. SPINRAZA (nusinersen) injection, for intrathecal use. Biogen Inc. https://www.accessdata.fda.gov/drugsatfda_docs/label/2016/209531lbl.pdf

78. Biomedtracker. (2023). Spinraza. Pharma Intelligence UK Limited. https://www.biomedtracker.com/DrugReport.cfm?DrugID=18461

79. National Institute of Neurological Disorders and Stroke. Spinal muscular atrophy. https://www.ninds.nih.gov/health-information/disorders/spinal-muscular-atrophy

80. Centers for Disease Control and Prevention. (2023, March 8). Spinal muscular atrophy (SMA). https://www.cdc.gov/nceh/dls/nsmbb_sma.html

81. Bodamer, O. A. (2023). Spinal muscular atrophy. UpToDate. Last Reviewed September 2023, from https://www.uptodate.com/contents/spinal-muscular-atrophy?search=spinal%20muscular%20atrophy%20treatment&source=search_result&selectedTitle=1~67&usage_type=default&display_rank=1

82. Biomedtracker. (2023). Spinraza. Pharma Intelligence UK Limited. https://www.biomedtracker.com/DrugReport.cfm?DrugID=18461

83. U.S. FDA. (2016, November 23). FDA approves first drug for spinal muscular atrophy. https://www.fda.gov/news-events/press-announcements/fda-approves-first-drug-spinal-muscular-atrophy

84. Ionis. (2023). The Ionis antisense pipeline. https://www.ionispharma.com/ionis-antisense-technology/antisense-pipeline/

85. U.S. FDA. (2019, October). TEGSEDI (inotersen) injection, for subcutaneous use. Akcea Therapeutics, Inc. https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/211172s004lbl.pdf

86. Ionis. (2019, May 7). Akcea and Ionis announce approval of WAYLIVRA® (volanesorsen) in the European Union. Akcea Therapeutics, Inc. https://ir.ionispharma.com/news-releases/news-release-details/akcea-and-ionis-announce-approval-waylivrar-volanesorsen

87. Ionis. (2020, October 12). Ionis Pharmaceuticals completes acquisition of Akcea Therapeutics. https://ir.ionispharma.com/news-releases/news-release-details/ionis-pharmaceuticals-completes-acquisition-akcea-therapeutics

88. Ionis. (2023, October 4). Ionis shares significant business and pipeline progress at Innovation Day, highlighting strength of capabilities from research and technology through commercialization. https://ir.ionispharma.com/news-releases/news-release-details/ionis-shares-significant-business-and-pipeline-progress

89. Seagen. (2023). Our medicines. https://www.seagen.com/medicines

90. Seagen. (2023, February 15). Seagen reports fourth quarter and full year 2022 financial results. https://investor.seagen.com/press-releases/news-details/2023/Seagen-Reports-Fourth-Quarter-and-Full-Year-2022-Financial-Results/default.aspx

91. Pfizer. (2023, March 13). Pfizer Invests $43 Billion to Battle Cancer. https://www.pfizer.com/news/press-release/press-release-detail/pfizer-invests-43-billion-battle-cancer

92. Biomedtracker. (2023). Moderna, Inc. (MRNA). Pharma Intelligence UK Limited. https://www.biomedtracker.com/companyreport.cfm?companyid=4445

93. Moderna. (2023). SPIKEVAX (COVID-19 Vaccine, mRNA) now approved! https://www.modernatx.com/research/product-pipeline

94. Terry, M. (2019, January 22). The Celgene legacy: Innovative science and price gouging. BioSpace. https://www.biospace.com/article/celgene-the-good-the-bad-and-the-ugly/

95. Stolberg, S. G. (1998, July 17). Thalidomide approved to treat leprosy, with other uses seen. The New York Times. https://www.nytimes.com/1998/07/17/us/thalidomide-approved-to-treat-leprosy-with-other-uses-seen.html

96. Data-Farber Cancer Institute. (2013, November 28). Scientists discover how thalidomide-like drugs fight cancer. https://www.dana-farber.org/newsroom/news-releases/2013/scientists-discover-how-thalidomide-like-drugs-fight-cancer

97. U.S. FDA. (1998, July 15). THALOMID (thalidomide) capsules. Celgene Corporation. https://www.accessdata.fda.gov/drugsatfda_docs/label/1998/20785lbl.pdf

98. Celgene Corporation. (1999). 1998 Annual Report. https://www.annualreports.co.uk/HostedData/AnnualReportArchive/c/NASDAQ_CELG_1998.pdf

99. U.S. FDA. (2019, November). FOCALIN® (dexmethylphenidate hydrochloride) tablets, for oral use, CII. Novartis Pharmaceuticals Corporation. https://www.accessdata.fda.gov/drugsatfda_docs/label/2021/021278s029lbl.pdf

100. SingleCare Team. (2023, February 3). ADHD statistics 2023. https://www.singlecare.com/blog/news/adhd-statistics/#:~:text=ADHD%20prevalence%20among%20adults%20was%204.4%25%20in%20the,ADHD%20will%20likely%20have%20the%20disorder%20as%20adults

101. Krull, K. R. and Chan, E. , (2023). Pharmacology of drugs used to treat attention deficit hyperactivity disorder in children and adolescents. UpToDate. Last Reviewed November 2023, from https://www.uptodate.com/contents/pharmacology-of-drugs-used-to-treat-attention-deficit-hyperactivity-disorder-in-children-and-adolescents

102. Biomedtracker. (2023). Focalin. Pharma Intelligence UK Limited. https://www.biomedtracker.com/DrugReport.cfm?DrugID=415

103. U.S. FDA. (2007, June). ALKERAN®. https://www.accessdata.fda.gov/drugsatfda_docs/label/2011/020207s017lbl.pdf

104. Kaplan, D. A. (2022). Multiple myeloma: Top 10 advances in the past 10 years. Targeted Therapies in Oncology. Targeted Therapies in Oncology, 11(4), 1–70. https://www.targetedonc.com/view/multiple-myeloma-top-10-advances-in-the-past-10-years

105. U.S. FDA. (2013, June). REVLIMID [lenalidomide] capsules, for oral use. Celgene Corporation. https://www.accessdata.fda.gov/drugsatfda_docs/label/2013/021880s034lbl.pdf

106. Biomedtracker. (2023). Revlimid. Pharma Intelligence UK Limited. https://www.biomedtracker.com/DrugReport.cfm?DrugID=398

107. Durie, B. G. M. (2019, August 1). Thalomid (thalidomide) for treatment in myeloma. International Myeloma Foundation. https://www.myeloma.org/thalomid-thalidomide#:~:text=Thalidomide%20was%20first%20used%20to%20treat%20multiple%20myeloma,Thalomid%20launched%20a%20new%20era%20of%20%22novel%20therapies.%22

108. Hadzimichalis, N. (2010, January 7). Revlimid may be more effective than thalidomide in newly diagnosed multiple myeloma. The Myeloma Beacon. https://myelomabeacon.org/news/2010/01/07/revlimid-may-be-more-effective-than-thalidomide-in-newly-diagnosed-multiple-myeloma/#:~:text=Revlimid%20May%20Be%20More%20Effective%20Than%20Thalidomide%20In,and%20professor%20of%20medicine%20at%20the%20Mayo%20Clinic%2C

109. Biomedtracker. (2023). Revlimid. Pharma Intelligence UK Limited. https://www.biomedtracker.com/DrugReport.cfm?DrugID=398

110. Durie, B. G. M. (2022, April 14). First generic Revlimid (lenalidomide) launched. International Myeloma Foundation. https://www.myeloma.org/blog/first-generic-revlimid-lenalidomide-launched#:~:text=On%20March%207%2C2022%2C%20Teva%20Pharmaceuticals%20announced%20the%20launch,interest%20and%20many%20questions%20from%20the%20myeloma%20community

111. Biomedtracker. (2023). Pomalyst. Pharma Intelligence UK Limited. https://www.biomedtracker.com/DrugReport.cfm?DrugID=399

112. U.S. FDA. (2017, June). OTEZLA® (apremilast) tablets, for oral use. Celgene Corporation. https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/205437s006lbl.pdf

113. Bristol-Myers Squibb. (2019, November 20). Bristol-Myers Squibb completes acquisition of celgene, creating a leading biopharma company. https://news.bms.com/news/corporate-financial/2019/Bristol-Myers-Squibb-Completes-Acquisition-of-Celgene-Creating-a-Leading-Biopharma-Company/default.aspx

ABOUT PUTNAM

Putnam, an Inizio Advisory company, is a leading scientific and strategic consulting partner that helps the global life science community make confident decisions, build value, and bring life-changing innovations to clinicians and patients. For more than 30 years, our rigorous, bespoke approach and globally diverse team have delivered unrivaled depth across therapeutic areas, business functions, geographic markets, healthcare sectors, and technology platforms to maximize the human impact and commercial success of client innovations.

Putnam
Inizio Advisory