Bioteching in action:

A roadmap for early planning and development

With Heart™

parexel BIOTECH

Like so many others,

I lost a beloved family member to an incurable disease. My father died of Lewy body dementia (LBD), a progressive neurological disorder with no cure. For all the patients, caregivers, and families who struggle with the heavy toll of life-threatening diseases and suffer immeasurable losses, biotech companies offer a ray of hope. These companies are an engine of innovation in drug development today working on cures for tomorrow.

Biotechs epitomize brilliant science and passionate commitment. But the journey to commercial success, including partnering and acquisition exit strategies, requires many skills. Drug development remains a complex, high-risk endeavor, especially for companies that must raise funds, fill expertise gaps, gather increasingly diverse evidence sets, and navigate a shifting global regulatory landscape. Early and sustained integration of clinical, regulatory, market access, and commercial disciplines is the surest path to approval, reimbursement, and market share. And it's the most reliable way for biotechs to bring new treatments to the patients who need them.

In this eBook, we present the Parexel Biotech perspective on five of the most significant aspects of integrated development:

- Getting the most from early interactions with health authorities
- Choosing the right expedited regulatory pathway
- Weeding out weaker assets to focus on the winners
- Designing trials that attract and retain patients
- Articulating a coherent product value story

We hope you find it helpful on your journey to commercial success.

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Executive Vice President and Global Head

Insights

Early advice from regulators and payers can shorten time to market

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In 2020, biopharmaceutical firms with fewer than 500 employees developed 47% (25/53) of the novel drugs approved by the FDA. As this data shows, biotech companies are a significant source of innovation. With limited resources, these companies often value guidance on engaging with regulators and health technology assessment (HTA) agencies to avoid pitfalls and delays in the drug development process.

Pursuing meetings with regulators and HTA officials is an excellent way for smaller companies to get the advice they need to increase their success rate and shorten the time to market. But companies must adequately prepare for these engagements and act on the feedback to mitigate risk and reap the benefits of streamlined regulatory processes, market exclusivity, and financial incentives. ›››

Here are five ways to leverage these interactions:

1 Seek advice at the right time, in the right places.

The US and EU have well-established frameworks for which products and companies qualify for early regulatory interactions (Table 1). However, it's critical to schedule the meeting during the right stage of development to reap the full benefit. For example, an INitial Targeted Engagement for Regulatory Advice on CBER producTs (INTERACT) meeting with staff at the FDA's Center for Biologics Evaluation and Research (CBER) is brief, non-burdensome, and free. It is beneficial for companies developing a new class of drugs or novel platform technology. But if you schedule the meeting too early or too late in development, it won't be as helpful. The best time to consult with CBER is after you've gathered preliminary data from animal and proof of concept (POC) in vitro studies but before you start definitive preclinical studies. At that point, regulators can help you avoid performing unnecessary preclinical work, such as a large study in non-human primates that CBER doesn't consider relevant. But if you're so far into the process that you're ready to submit an IND, it's too late to act on their recommendations.

In the EU, the EMA's Innovation Task Force (ITF) briefing meetings offer companies with a qualifying product or technology a chance for "informal scientific brainstorming discussions" with agency experts. ITF briefing meetings are intended to help clarify questions about the path to market for innovative medicines, new technologies, and borderline products at a much earlier stage of development than when formal Scientific Advice (SA) is typically sought. These briefings can be especially helpful for small companies and academic researchers who seek technical and regulatory advice early in development.

In the EU, for products that fulfill the criteria for accelerated assessment, it is best to apply for Priority Medicines scheme (PRIME) designation immediately after completing exploratory clinical studies. That's because PRIME products can benefit from EMA interactions during later development and may be eligible for accelerated assessment during the Marketing Authorization Application (MAA) review process.

Companies seeking to launch new treatments in Europe need to decide which HTA bodies to approach. The HTA landscape in Europe encompasses more than 50 different agencies in 27 EU member states at the national, regional, and local levels. To be eligible for meetings with HTA bodies, companies must be seeking guidance on the design of a pivotal trial, usually a Phase III confirmatory trial. HTA agencies don't offer advice on proof of concept or feasibility trials. Other eligibility criteria include products representing new modes of action for the target indication, products that target life-threatening or chronically debilitating diseases, and products that fill unmet medical needs.

Companies should select the HTA bodies they consult based on the rigor of the HTA process, level of market uncertainty, standard-of-care (SOC) in clinical practice, lack of precedent evaluations, and size of the patient population in that country. For example, we might advise a client to skip seeking guidance or reimbursement from Germany's G-BA, the main decision-making body of German physicians, hospitals, and health insurance funds, if very few patients in Germany have the relevant condition, but there are plenty of these patients in the UK or Portugal, for example.

2 Understand the limitations of early advice.

Although seeking early advice can help you optimize the design of a pivotal clinical trial and boost its chances of success, such advice comes with limitations. First, the advice is non-binding, which means that regulators and HTA officials can deviate from that guidance years later when they officially assess your product. Following their advice about study design doesn't guarantee that reviewers will consider your clinical data or real-world evidence (RWE) sufficient for approval or reimbursement once they examine it more closely. That will depend on the trial results, namely the strength of your safety and efficacy data.

A second drawback is that companies can only meet with a small number of regulators and HTA bodies, so the breadth of the early feedback will be limited. And early advice won't protect against market shifts that happen five to 10 years down the road. A competing product launch that changes the SOC could impact a product's viability or the relevance of the active comparator you used in your pivotal studies.

If your briefing document contains only limited substantive information or fails to seek feedback on critical issues, you may walk away with a false sense of security about your future success. Meetings that end without reaching an agreement on critical issues could result in delays and increased development costs. However, if you decide to ignore early scientific, regulatory, or HTA agency advice, knowing their concerns can help you prepare a well-documented justification for not following it, such as alternative studies and methods.

3 Write a crisp, clear briefing document.

A compelling briefing document should include everything you want advice on, including your rationale for the approach and methodology you have chosen. Your development plan needs to be supported by data, literature where relevant, and logic. It should not ask the agency to select a development plan for you.

Although the briefing document should be comprehensive, it should be succinct. Only include detailed data for issues on which you want guidance. Be sure to justify your choice of trial design and, where appropriate, explain why other more traditional approaches won't work.

Once you're in an early advice meeting, assume that everyone has read the briefing document. Don't spend half the meeting giving a lecture with slides. Instead, present a quick summary and begin asking your questions. Your objective is to explain your approach and get guidance on the most rational and efficient development plan. It's not the time to pitch your new treatment.

If you lack experience participating in these meetings, you can compensate by producing a high-quality briefing package and practicing beforehand. At Parexel Biotech, we often partner with smaller firms up to five months before an early advice meeting to conduct mock run-through presentations and question-and-response sessions.

4 Ask pointed questions.

You would never ask a house inspector, “Does the whole house look okay to you?” But you might ask, “Is the roof leaking?” Likewise, in early advice meetings, don’t ask for general opinions. Regulators and payers don’t want the responsibility of making development decisions when there are multiple options. Questions like, “Which course of action is best?” or “Which path should we take?” aren’t fruitful. Regulators don’t have the expertise or the remit to answer them.

Instead, focus on the aspects of your program that would benefit from regulatory feedback and ask questions to clarify whether your strategy is feasible. After providing a scientific basis for your decisions, discuss your approach’s pros and cons and how to mitigate specific risks. Ask questions like, “Is this sufficient?” and “Do you agree with this?” and make statements like, “We propose not doing this, and here is why.”

Before engaging with HTA bodies in Europe, do your homework on the market. Become an expert on local clinical practice—particularly the SOC, unmet need, and HTA evaluation methodology used in that market.

If you get pushback on your plan despite diligent preparation, don’t get defensive. Ask non-confrontational questions and listen carefully to the answers. Don’t agree to anything during the meeting. You should expect to hear concerns, warnings, questions, and criticisms from regulators and HTA representatives. So, thank them for their input and agree to consider their recommendations. Then use that feedback to build a better evidence generation plan to support your clinical and commercial objectives.

Table 1. Programs and mechanisms for early engagement in the US (regulatory only) and Europe (regulatory and Health Technology Assessment agencies)

Early Advice Opportunity	Year Introduced	Type and Format of Advice	Eligibility Criteria
UNITED STATES			
CDER Small Business and Industry Assistance (SBIA)	N/A	Respond to questions via phone and email; host webinars, conferences, and workshops; offer web-based learning tutorials, email updates, and electronic newsletter.	A business that has fewer than 500 employees, including employees of affiliates.
Initial Targeted Engagement for Regulatory Advice on CBER Products (INTERACT)	2018	• One informal, non-binding one-hour teleconference with CBER and/or OTAT staff • Targeted discussion of specific CMC and pharmacology/toxicology issues • Avoid unnecessary preclinical or other preparatory studies	CBER-regulated product at early stage of development AND facing unique challenges due to unknown safety profile resulting from complex manufacturing technologies, development of innovative devices, or cutting-edge testing methodologies.
Pre-IND Consultation	1988	One meeting to request advice on: • Design of non-clinical pharmacology, toxicology, and drug activity studies, including animal studies • Key CMC issues • Scope and design of Phase I trials • IND formatting • Strategies to avoid clinical holds	New product or indication prior to IND submission but after POC studies. Most useful for new or inexperienced sponsors. From 2008 to 2012, drugs that started with a pre-IND meeting had a median clinical development time of 6.4 years, versus 8.3 years for drugs that had no meeting.
End of Phase I (EOP1) Meeting	1988	Review select topics: • Pharmacokinetics and pharmacodynamics • Phase II protocol objectives and design • Other topics such as Phase III target population, pediatric studies, and adequacy of data quality measures	Any new product or indication.
CBER Advanced Technologies Team (CATT)	2019	Discussions with CBER staff, including responses to inquiries, on advanced manufacturing and testing technologies (separate from product/indication), such as: • Continuous manufacturing platforms • Unit operation and end-to-end automation • Platforms designed to support advanced analytical testing	Advanced technologies that can have a significant impact on product development OR manufacturing process and control strategies OR regulatory review. Includes manufacturing and analytical methods for products or product classes with which CBER has limited experience.
Breakthrough Therapy (BT)	2012	• Regular meetings with agency review team throughout development • Intensive guidance on efficient development plan, including non-clinical and clinical data • Senior managers and experienced review staff take part in “collaborative, cross-disciplinary” review • Project manager coordinates an efficient review of the development program and serves as scientific liaison between cross-discipline members of the review team • Potential for Priority Review and rolling submission of the marketing application	For drugs intended to treat a serious condition AND preliminary clinical evidence indicates that the drug may demonstrate “substantial” improvement over available therapy on a clinically significant endpoint. From 2012 to 2020, 41% of BT requests were granted. In 2020, 91% (21/23) of BT-designated drugs were for orphan diseases (total includes CBER-approved BT drug Tecartus, a CAR T cell therapy).
Regenerative Medicines Advanced Therapy (RMAT)	2016	• Regular meetings with agency review team throughout the development program • Intensive guidance on efficient development plan, including non-clinical and clinical data, plus discussion of potential surrogate or intermediate endpoints • Senior managers and experienced review staff take part in “collaborative, cross-disciplinary” review • Potential for accelerated approval and use of patient registry data and other real-world data in post-approval pathways	A cell or gene therapy, therapeutic tissue engineering product, or human cell and tissue product (or any combination product using such therapies or products)* AND addresses a serious or life-threatening condition AND preliminary clinical evidence shows potential to address unmet medical need for condition. From 2017 to 2020, 39% of RMAT applications were granted (58/149).

KEY TO TABLE 1 ACRONYMS:
CAT: EMA’s Committee for Advanced Therapies; CBER: FDA’s Center for Biologics Evaluation and Research; CHMP: Committee for Medicinal Products for Human Use; CMA: Conditional Marketing Authorisation; CMC: Chemistry, Manufacturing, and Controls; EMA: European Medicines Agency; EUnetHTA: European Network for Health Technology Assessment; F2F: Face-to-face; FDA: Food and Drug Administration; HTA: Health Technology Assessment; IND: Investigational New Drug; MAA: Marketing Authorisation Application; MOA: mechanism of action; NMPA: National Medical Products Administration; OTAT: Office of Tissues and Advanced Therapies; RCT: Randomized Controlled Trial; RWE: Real-world Evidence; SAWP: Scientific Advice Working Party; SME: small and medium-sized enterprises.

*Certain human gene therapies and xenogeneic cell products may also meet the definition of regenerative medicine therapy.

5 Push back as needed.

If you anticipate that an HTA body will suggest additional analyses or endpoints that could add years to your clinical trial, be prepared to push back (politely) with data. Before the meeting, research precedent decisions and gather other supporting data. If you don't think a suggested endpoint is feasible or necessary, explain another way to generate equal quality and relevance data.

In the EU, the minutes from advice sessions with regulators must be included in any future MAA, whether you're pursuing a centralized or decentralized procedure. You will need to document every engagement and justify the advice you did or didn't take, which will be of particular interest to assessors.

Early advice can create faster outcomes

Regulators want companies to succeed at demonstrating a drug's efficacy and are willing to provide early input on trial design to help achieve that objective. Likewise, HTA bodies can help companies develop smarter data-gathering and commercialization plans. By using these meetings wisely, you can get your products to the patients who need them faster.

Table 1. Continued

Early Advice Opportunity	Year Introduced	Type and Format of Advice	Eligibility Criteria
EUROPE			
Small and Medium-Sized Enterprises (SME) Office	2005	Direct assistance by phone, email, teleconference, or briefing meetings on regulatory strategy.	Enterprises with fewer than 250 employees AND either annual revenues of less than €50 million or an annual balance-sheet total of less than €43 million AND ownership structure (including partnerships or linkages) must not impact headcount or financial criteria.
Innovation Task Force (ITF)	2001	• Informal meetings to discuss scientific, technical, and regulatory issues that arise from developing innovative medicines, new technologies, and borderline products • Facilitate the exchange of information and provide guidance • Discussions led by experts from the EU Innovation Network, working parties, and committees • Meetings are free of charge and last approximately 1.5 hours	Emerging therapies OR emerging technologies OR borderline therapeutics AND at a very early stage of development (much earlier than when Scientific Advice would be sought).
Scientific Advice (SA)	2004	• Advice on the number and design of appropriate tests and studies to conduct during development—available from EMA and from EU Member State National Competent Authorities (NCAs) • EMA provides written answers to questions posed by developers (the Scientific Advice Working Party [SAWP] may invite the sponsor to meet if warranted)	It may be requested at any stage of development whether or not the medicine is eligible for the centralized authorization procedure. From 2008 to 2012, 85% of MAAs that received and followed early SA were approved, compared with only 41% that did not seek SA.
Protocol Assistance	2004	In addition to SA, developers of orphan-designated products can receive answers to questions relating to the criteria for authorization of an orphan product, such as what will demonstrate "significant" benefit in the orphan indication and what will constitute similarity or clinical superiority over other medicines.	Designated orphan medicines for rare, life-threatening, or chronically debilitating diseases. (Prevalence of condition in EU must not exceed 5 in 10,000).
EMA-EUnetHTA Parallel Consultation (1)	2017	• Parallel scientific advice on evidence generation plan from EMA and HTA bodies • Each product is assigned a SAWP Coordinator (EMA) and EUnetHTA Scientific Coordinator and Rapporteur (EUnetHTA) • Advice on "optimal" and "robust" evidence that satisfies the needs of regulators and payers • Two Early Dialogue (ED) formats are available: 1) written-only format (2.5 mos. from receipt of sponsor briefing book) and 2) F2F meeting (3.5 mos.) • Final output includes the Final CHMP Scientific Advice/Protocol Assistance Letter and the EUnetHTA Final Written Recommendation	The product addresses a life-threatening or chronically debilitating target indication AND represents a new MOA for that indication, AND there is no treatment or only unsatisfactory treatment available. Parallel consultation has an impact on pivotal trial designs: one recent study showed that after receiving EMA/HTA advice, 74% of sponsors changed the primary endpoint of their studies, and 81% changed the proposed comparator.
EUnetHTA Multi-HTA Early Dialogue (ED)	2017	Sponsor submits detailed briefing book on the development plan and gets: • Non-binding scientific advice consolidated from multiple HTA bodies (no EMA advice) • HTAs advise on which "optimal" and "strong" evidence will satisfy their needs • If HTAs cannot agree, individual HTAs answer questions separately • Two ED formats available: 1) written-only format (2.5 mos. from receipt of sponsor briefing book) and 2) F2F meeting (3.5 mos.) • The final output is the EUnetHTA Final Written Recommendation	The product addresses a life-threatening or chronically debilitating target indication AND represents a new MOA for that indication, AND there is no treatment or only unsatisfactory treatment available AND product has completed feasibility and POC studies but not entered pivotal trials (or pivotal trial designs are not yet finalized). Not all requests for multi-HTA EDs are granted.
Priority Medicines scheme (PRIME)	2016	Sponsor submits detailed briefing book on the development plan and gets: • Non-binding scientific advice consolidated from multiple HTA bodies (no EMA advice) • HTAs advise on which "optimal" and "strong" evidence will satisfy their needs • If HTAs cannot agree, individual HTAs answer questions separately • Two ED formats available: 1) written-only format (2.5 mos. from receipt of sponsor briefing book) and 2) F2F meeting (3.5 mos.) • The final output is the EUnetHTA Final Written Recommendation	Product may offer a major therapeutic advantage over existing treatments OR benefit patients without treatment options. Academics and SMEs can apply earlier based on compelling non-clinical data and safety data from initial clinical trials. As of April 2021, the cumulative success rate for SMEs and academic institutions winning PRIME designation is 19% (37/194) compared to an overall success rate of 25% for PRIME. Oncology and hematology indications dominate, and 83% of PRIME products are for rare diseases.

(1) EUnetHTA is a network of government-appointed organizations from EU countries, EU-accession countries (plus European Economic Area and European Free Trade Association countries), and relevant regional agencies and nonprofit organizations that produce or contribute to HTA in Europe.

Early planning can help you make the most of expedited regulatory pathways

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In 2020, 68% (36/53) of novel drugs approved by the FDA's Center for Drug Evaluation and Research (CDER) used one or more expedited development or review mechanisms (Table 2). Cancer drugs used an average of four per indication (Table 3). As this data shows, most companies use special regulatory mechanisms to speed drug development.

However, companies can get distracted by stockpiling expedited designations when the real prize is winning marketing approval. Accelerated programs that streamline clinical development or add business value without incurring burdensome requirements are helpful. But they are most useful for companies that have defined a target product profile (TPP) and identified a regulatory pathway. Smaller companies may struggle to tackle those tasks, though they must. Starting early and asking the following questions can help.

Table 2. Use of Expedited Mechanisms, Novel Drugs Approved by FDA's CDER in 2020[1]

57% (30/53) received Priority Review	42% (22/53) had Breakthrough Therapy designation[2]	32% (17/53) had Fast Track designation
23% (12/53) were Accelerated Approvals	58% (31/53) of NMEs in 2020 were for orphan diseases	

[1] U.S. Food and Drug Administration/Center for Drug Evaluation and Research. (2021). Advancing Health Through Innovation: New Drug Therapy Approvals 2020. Washington, DC. [Accessed 30 Mar. 2021].
[2] One CAR T cell therapy (Tecartus) approved by the FDA's Center for Biologics Evaluation and Research (CBER) in 2020 is not counted in the BT total. CBER approved five products in 2020.

1. How does this regulatory mechanism add value to my asset?

The FDA's Breakthrough Therapy (BT) designation and the EMA's Priority Medicines scheme (PRIME) are at the top of the hierarchy of expedited programs. Both allow for focused early interactions with senior regulatory staff to optimize a product's development plan, with the aim of decreasing overall time to market. A review of data on FDA-expedited programs shows the BT designation can cut more than three years from the average overall time to market.

While the premier mechanisms enable faster and more efficient development, other programs with fewer entry criteria and less intense guidance include the FDA's Fast Track (FT) designation and the EMA's Scientific Advice (SA) process (Table 4). These designations have a beneficial halo effect that can provide small and emerging companies with a public relations boost in addition to funding or partnering advantages.

For biotechs, asking two critical questions can help you determine which expedited mechanisms to pursue: 1) Will the designation give our company access to more information, meetings, or relationships with regulators that will lead to better development decisions for our product? 2) Will the designation add value to our product in the eyes of investors, stockholders, potential corporate partners, or buyers by validating our product or technology platform? For a company with constrained resources, a designation that helps raise funds is valuable.

If you are pursuing multiple designations, it is important to understand how they will act together to reduce the overall development time. More designations can mean more paperwork. For example, Accelerated Approval (AA) allows the use of a surrogate endpoint to speed market entry for drugs that fill an unmet medical need, but also imposes post-marketing requirements. Though not technically an expedited pathway, orphan drug (OD) status is a regulatory strategy that has exploded in popularity. But investment analysts and potential partners may be skeptical of companies that slice and dice patient populations to win OD status and then must run a patient registry for years after approval. Can you get approval just as quickly for a broader disease indication?

2. What are my chances of winning Breakthrough Therapy designation?

BT, the holy grail of expedited mechanisms, can change the financial reality for a smaller company overnight. Although early data suggested that larger companies were more successful at winning BT, recent results indicate that small companies have benefited equally.

Not every drug is eligible for the BT program. Smaller companies may struggle to reap the rewards if they don't have enough resources to handle the many meetings and information exchanges involved. Also, BT designation can accelerate development, necessitating a rapid scale-up of manufacturing capability and generating an expectation among investors of hitting product milestones on time.

Despite the risks, if a company believes it has a shot, applying for BT at an early stage of development is best because the business impact can be huge. The FDA wants a higher degree of confidence—meaning a durable efficacy signal—to award BT, making it more difficult for companies working on cutting-edge technologies. One approach for companies that don't get BT after a first try is to pursue FT as an interim step while waiting for more mature clinical data.

Table 3. 17 Novel cancer drugs approved in 19 indications by FDA in 2020[§]

Trade Name (generic name)/ Drug Class (Molecular Target)	FDA Mechanisms for Potentially Streamlined Clinical Development				Factors Impacting FDA Review Time				FDA IND Filing Date	FDA Approval Date	First Approved in U.S.	FDA-Approved Indication
	Fast Track	Orphan Drug	AA	BTD	Priority Review	First Cycle Review	Assessment Aid	Real-Time Oncology Review				
Ayvakit* (avapritinib) **TKI** (KIT and PDGFRα)	•	•		•	•				06/2015	01/2020	•	unresectable or metastatic PDGFRAα exon 18 mutant gastrointestinal stromal tumor—1st Line
Blenrep** (belantamab mafodotin-blmf) (2) **mAb-conjugate** (BCMA)		•	•	•	•	•	•	•	01/2014	08/2020	•	relapsed and refractory multiple myeloma—5th Line
Danyelza** (naxitamab-gqgk) **mAb** (GD2)		•	•	•	•	•	•	•	09/2017	11/2020	•	high-risk relapsed or refractory neuroblastoma in the bone or bone marrow—2nd Line
Gavreto* (pralsetinib)		•	•	•	•	•	•		08/2019	09/2020	•	metastatic RET fusion-positive non-small cell lung cancer
TKI (RET)		•	•	•	•	•	•	•	08/2019	11/2020	•	advanced or metastatic RET mutant medullary thyroid cancer
Inqovi* (decitabine and cedazuridine) (1) **NMI/CDAI**		•			•	•	•		12/2013	07/2020	•	Myelodysplastic syndromes (MDS) and chronic myelomonocytic leukemia (CMML)
Margenza** (margetuximab-cmkb) **mAb** (ERBB2)	•					•	•		2010	12/2020	•	HER2-positive breast cancer—3rd Line
Monjuvi** (tafasitamab-cxix) (2) **mAb** (CD19)	•	•	•	•	•	•	•		01/2010	07/2020	•	Relapsed or refractory diffuse large B-cell lymphoma (DLBCL) not eligible for autologous stem cell transplant
Orgovyx* (relugolix) **GnRH Receptor Antagonist**					•	•			03/2016	12/2020	(3)	Advanced prostate cancer
Pemazyre* (pemigatinib)/ **TKI** (FGFR2)		•	•	•	•	•			10/2014	04/2020	•	Advanced cholangiocarcinoma with tumors harboring FGFR2 gene fusions—2nd Line
Qinlock* (ripretinib) (1) **TKI** (KIT/PDGFRAα)	•	•		•	•	•	•		08/2015	05/2020	•	Gastrointestinal stromal tumor—4th Line
Retevmo* (selpercatanib) **TKI** (RET)		•	•	•	•	•			03/2017	05/2020	•	RET fusion-positive non-small cell lung cancer and RET-altered thyroid cancers
Sarclisa** (isatuximab-irfc) **mAb** (CD38)		•				•			12/2009	03/2020	•	Multiple myeloma—3rd Line
Tabrecta* (capmatinib) **TKI** (MET)		•	•	•	•	•			11/2012	05/2020	•	Advanced non-small cell lung cancer with a MET exon 14 skipping mutation
Tazverik* (tazemetostat) (2)		•	•			•			07/2015	01/2020	•	Metastatic or locally advanced epithelioid sarcoma not eligible for resection—1st Line
TKI (EZH2)	•		•		•	•			07/2015	06/2020	•	Relapsed or refractory follicular lymphoma with EZH2-positive tumors—3rd Line
Trodelvy** (sacituzumab-govitecan-hziy) (2) **mAb** (Trop-2)	•		•	•	•				06/2012	04/2020	•	Metastatic triple-negative breast cancer—3rd Line
Tukysa* (tucatinib) (1) **TKI** (HER2)	•	•		•	•	•		•	07/2007	04/2020	•	HER2-positive breast cancer—2nd Line
Zepzelca* (lurbinectedin) (1) Oncologic **Transcription Inhibitor**		•	•		•	•			12/2008	06/2020	•	Metastatic small cell lung cancer—2nd Line
TOTALS	**7**	**15**	**12**	**12**	**16**	**18**	**8**	**4**			**18**	
% of all 2020 indications (n=19)[§]	**37%**	**79%**	**63%**	**63%**	**84%**	**95%**	**44%**	**21%**			**95%**	

(1) Drug was reviewed under auspices of Project Orbis.
(2) First-in-class drug.
(3) Relugolix monotherapy (40 mg) has been commercialized in Japan since 2019 for treatment of symptoms associated with uterine fibroids under the brand name Relumina.

§ Totals exclude the following three cancer imaging agents approved in 2020: 1) Detectnet (Copper Cu 64 dotatate injection) – positron emission tomography (PET) imaging agent for localization of somatostatin receptor positive neuroendocrine tumors; 2) Gallium 68 PSMA-11—PET imaging of prostate-specific membrane antigen (PSMA)-positive lesions in men with prostate cancer; and 3) Cerianna (fluoroestradiol F 18)—molecular imaging agent for use in PET imaging for detection of estrogen receptor-positive lesions as an adjunct to biopsy in patients with recurrent or metastatic breast cancer. Chart also excludes CBER-approved cancer products.

*Small Molecule; **Biologic.
Drug Class Acronyms: mAb—monoclonal antibody; NMI/CDAI—nucleoside metabolic inhibitor/cytidine deaminase inhibitor; TKI—tyrosine kinase inhibitor.
Molecular Target Acronyms: BCMA: B-cell maturation antigen; CD19—cluster of differentiation 19; CD38—cluster of differentiation 38; ERBB2—erythroblastic oncogene B; EZH2—enhancer of zeste homolog 2; FGFR2 – fibroblast growth factor receptor 2; GD2—surface disialoganglioside; HER2—human epidermal growth factor receptor 2; KIT—v-kit Hardy-Zuckerman 4 feline sarcoma viral oncogene homolog; MET—mesenchymal epithelial transition factor; PDGFRα—platelet-derived growth factor receptor alpha; RET—rearranged during transfection; Trop-2: trophoblast antigen 2.
Sources: 1) U.S. Food and Drug Administration Novel Drug Approvals for 2020. Available at: https://www.fda.gov/drugs/new-drugs-fda-cders-new-molecular-entities-and-new-therapeutic-biological-products/novel-drug-approvals-2020. *Accessed Feb. 2, 2021*; and 2) U.S. Food and Drug Administration's Approved Drug Products Database (Drugs@FDA). Available at: https://www.accessdata.fda.gov/scripts/cder/daf/. *Accessed Feb. 2, 2021*.
FDA Mechanism Acronyms: AA: Accelerated Approval; BTD: Breakthrough Therapy Designation; FT: Fast Track; OD: Orphan Drug; PR: Priority Review; Project Orbis; RTOR: Real-Time Oncology Review pilot program; Assessment Aid.

3. What might the future bring for my expedited regulatory strategy?

The international regulatory environment is in constant flux, and it's essential to keep abreast of changes. For example, famed FDA cancer Czar Richard Pazdur recently observed that there are too many potentially overlapping mechanisms in the United States, particularly for cancer (Table 3), and the agency may consolidate its expedited offerings.

In 2020, the nonprofit Friends of Cancer Research analyzed the issue and prepared two reports: Modernizing Expedited Development Programs and Optimizing the Use of Accelerated Approval (AA). The first report included a proposal to bundle the application requirements for the FT and Regenerative Medicines Advanced Therapy (RMAT) designations into one pre-BT pathway. Meanwhile, the second report recommended granting the FDA increased flexibility to withdraw AAs, making the program more closely resemble the EMA's conditional marketing authorization (CMA). An April 27, 2021, ODAC meeting examined several cancer drugs that received AA but failed to demonstrate efficacy in post-marketing confirmatory trials. Companies using AA need to think through the potential ramifications of changes like this.

It's likely that the FDA will streamline its expedited offerings. Several pieces of legislation are looming that could serve as ready-made vehicles for this effort, including the 2022 FDA User Fee Reauthorization Act (PDUFA VII) and a potential sequel to the 21st Century Cures Act.

For the best chance of commercial success, pick a mechanism or a combination of mechanisms that can streamline development. That's the surest path to getting new treatments to the patients who need them.

Table 4. Comparison of FDA and EMA regulatory designations

FDA	EMA
Breakthrough Therapy Designation (BT) Intensive early interactions, regular meetings throughout development, rolling submission, and review.	**Priority Medicines Scheme (PRIME)** Intensive early interactions, regular meetings throughout development. Potential for EMA's accelerated assessment, which can shorten review time to 150 from 210 days. (In February 2021, EMA released a "draft toolbox guidance" to assist PRIME drug developers in submitting Module 3 data quality packages).
Regenerative Medicines Advanced Therapy (RMAT) All the features of BT, but for CGTs, therapeutic tissue engineering products, or combinations thereof.	
Fast Track Designation (FT) Early interactions, rolling submission, and review.	
Accelerated Approval (AA) Efficacy based on a surrogate endpoint; confirmatory studies required; products remain on the market unless data fail to confirm benefit (one study showed just 20% of AA cancer drugs confirmed survival benefit in post-market studies).	**Conditional Marketing Authorization (CMA)** Favorable benefit/risk profile established; more comprehensive data required; sponsors must renew CMA status every year (from 2006 to 2016, CMAs converted to MAs within four years on average).
Priority Review (PR) FDA reviews NDA/BLA in 6 months (10 mos. is standard).	**Accelerated Assessment** EMA reviews MAA in 150 days (210 days is standard).
	Authorization Under Exceptional Circumstances Comprehensive safety and efficacy package not possible due to a rare disease or ethical concerns.
Orphan Drug 7-year marketing exclusivity; NDA/BLA fees ($2.9 million in 2021) waived; possible research grant from FDA; protocol assistance; upon approval, tax credits up to 50% of U.S.-based trial costs.	**Orphan Drug** 10-year marketing exclusivity; MAA fees (from €296,500) waived for SMEs; Possible research grant from EMA; protocol assistance.

KEY TO TABLE 4 ACRONYMS:
BLA: Biologics License Application; CGTs: cell and gene therapies; MA: full marketing approval; MAA: Marketing Authorization Application; NDA: New Drug Application; SME: micro-, small-, or medium-sized enterprise (EMA definition).

Successful drug development starts with the patient

We asked experts in our Patient Innovation Center how biotech companies can design patient-centric trials and overcome common obstacles.

Kristina Reeder
Associate Director, Patient Innovation Center

Loren Caldwell
Patient Recruitment Manager

Aren't many biotech companies already close to the patient?

Indeed, and especially with small and emerging companies focused on a single therapeutic area, biotech companies are typically close to the patient experience. For example, if founders or primary investors have a personal or family connection to the target disease, a common scenario, it brings an emotional factor to the research.

This can be an advantage, but it can also create a false sense of security. Such companies might reason, "We don't need to worry about patient-centricity because we are already 100% focused on the patient—it's our founding principle." But even biotechs with a deep knowledge of the patient experience and medical need must do many things—such as engage early with various stakeholders—to ensure their clinical development plan is patient-centered.

What challenges do you encounter with protocol designs?

A common problem we see is trials that have more assessments and procedures than necessary. For example, we recently helped a biotech company rewrite its protocol after our team of epidemiologists and other experts looked at the schedule of assessments. When a study visit involves an invasive procedure, such as bronchoscopy or heart catheterization, you want to perform as few as possible. In this case, the original protocol called for an invasive procedure once per month for six straight months. Monthly data on that metric would not have been informative because change occurs gradually, and we were able to reduce the frequency to once every six months.

Even a six-minute walk test, an assessment that is not technically invasive and is administered at home under the right conditions, becomes tiresome for patients if it's overused. Patients' time and energy are limited resources too.

Sometimes, companies feel compelled to collect data on as many endpoints as possible as a precaution. But a protocol filled with just-in-case endpoints will put off patients, slow enrollment, and increase the dropout rate. A streamlined clinical protocol has just enough endpoints to support your strategy, but not too many. Optimal designs include

- a limited number of primary endpoints,
- a tight, relevant subset of secondary endpoints, and
- precise patient-reported outcomes (PROs).

There should be near-perfect clarity on what is collected and why.

How can decentralized trials help?

The global coronavirus pandemic catapulted the emerging field of decentralized clinical trials (DCTs) to the forefront of clinical research in a matter of months. With approaches like home nursing, telehealth, direct-to-patient (DTP) drug shipments, and mobile sensors, DCTs are making it easier for patients to participate in trials, especially for those who live far away, are too sick to travel, or are too busy.

You can make a trial more patient-centric, reducing the burden on patients by not requiring them to travel to a site for every interaction. Often trial planners theorize in meetings about what would work best for patients, but only patients know. To bring that knowledge to planning, talk with patients, caregivers, and sites, and solicit practical feedback about what they need.

How do you enroll patients from diverse backgrounds?

It is essential to include and recruit patients into a study who mirror the population it affects. Achieving inclusion and diversity in clinical trials is an industry-wide challenge that requires companies, sites, and researchers to look for ways to make it easier for patients to participate, especially underrepresented patients.

Consider how patient-centricity looks different in different countries: what works in the United States may not work in France, and what works in France may not work in Spain. Companies need to research these differences because trials that don't have sites near the patients will struggle to hit enrollment targets.

Companies can seek advice from nurses, who are experts in conducting study visits and accommodating different populations, such as the elderly and their caregivers versus toddlers and their parents. Companies can also translate trial materials into multiple languages based on the localities. Recently we heard from a study nurse that her site had missed an opportunity to enroll a patient with a rare cancer because the study documents were not translated into Mandarin Chinese, a language prevalent in that part of California. Translations in the United States should extend beyond Spanish. For example, in one New York City borough, residents speak nine different first languages, including Creole and Russian.

Sites that employ a more ethnically diverse staff are better able to enroll a more diverse patient population. We have repeatedly heard that patients prefer to be treated by people who are like them.

"A protocol filled with just-in-case endpoints will put off patients, slow enrollment, and increase the dropout rate … There should be near-perfect clarity on what is collected and why."

Getting to ‘No’ fast is more important when you are small

Skip Sands, MD
SVP, Senior Medical Officer, Americas

Drug development is a complex business. Historically, less than 8% of product candidates are reported to have made it from Phase I to market.

One effective way to mitigate risk is to weed out weak and average product candidates and focus resources on lead products and follow-ons with the best chances of success. However painful, small and emerging companies need to pause or terminate mediocre assets and reprioritize their portfolios as early as possible during development.

If warning signals are clear after you’ve spent $10 million and 10 months on a clinical trial, don’t wait until you have spent $20+ million and 18 months to cut the program. It takes near-constant vigilance to preserve resources when you are small. Here are three strategies that can help.

Invest in a comprehensive preclinical program

Vet preclinical work well. Even if you hired a crack internal team, engage an external expert to perform a gap analysis of your preclinical data program, then fill the gaps. Evaluate your preclinical work with ruthless objectivity, because you can be sure that investors and companies shopping for assets will do the same.

The money you invest in preclinical due diligence will increase your asset's value, whether you develop it yourself, partner it, or sell it. Do not put off toxicology work: The more you can get done early, the better. Perform pharmacological modeling and simulations of patient response because savvy investors and potential buyers will look for that extra step as the hallmark of a quality program.

The tools and methods for crunching numbers are better today than just 10 years ago and allow companies to predict outcomes with greater confidence and success. Choose an animal model that predicts the human response, and set aggressive goals for beneficial effects, to help identify product candidates that are more likely to induce a substantial response.

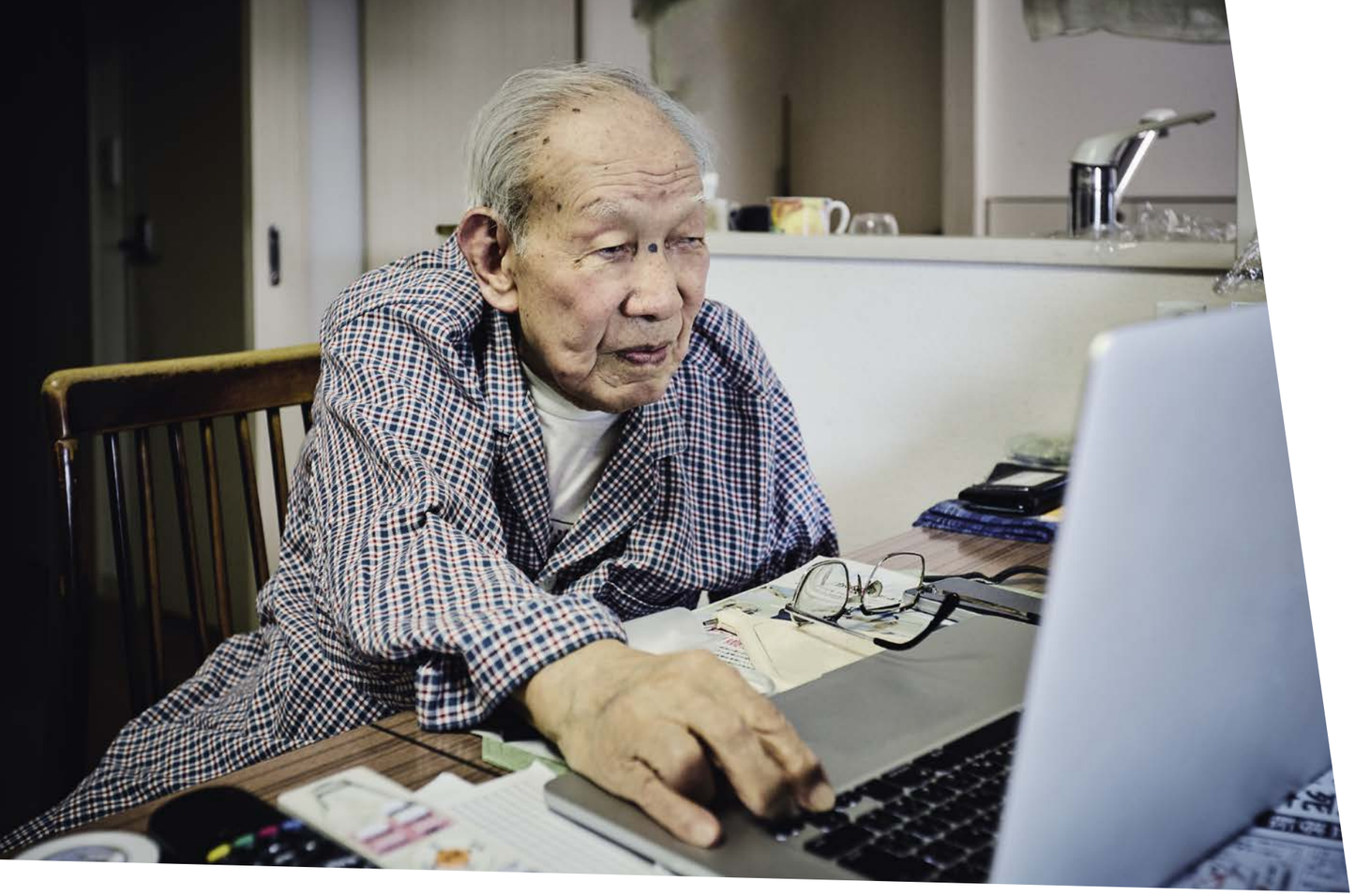
If your preclinical results don't indicate an exceptional product, you have a valuable opportunity to terminate a suboptimal asset early and invest in a better one.

Quantify the unmet need early

To understand the market for a new drug, you need to conduct literature searches, prepare a detailed competitive analysis, and interview patient advocacy groups (PAGs). PAGs understand commercial viability and can provide unique insights that cannot be gained with other methods.

Probe the data. For example, if your drug targets a solid tumor indication in which 40% of patients do not respond to the current standard of care (SOC) identify and characterize that 40%. Determine its potential revenues. Could your product give a return on investment in that slice?

If disciplined and diligent in studying the market, companies can gain an advantage. For example, plan and initiate natural history and observational studies during preclinical development, not during later-stage clinical trials.



Use innovative trial designs to pick winners (and losers)

People have talked about adaptive trials and master protocols (which include basket, umbrella, and platform trials) for years. Most of the uptake has been in oncology, but these flexible, innovative designs could make trials in other therapeutic areas more efficient and help biotech companies with strategic decision-making.

In an exploratory Phase I/II basket trial, you can test a candidate product or combination of products in patients with multiple diseases driven by the same genetic aberration or pathway. An integrated protocol can facilitate enrolling the arms independently and pooling the safety data. After reviewing efficacy signals, you can drop or pause arms that look weaker, focusing your resources on the condition for which your drug has the most powerful effects. These changes to the study don't require protocol amendments—the leading cause of clinical trial delays—because they are built into the design of a basket trial. If one arm looks promising but enrollment is slow, park that indication until you have a secure foothold in another.

Terminating products in Phase III development is the most expensive way to prune a portfolio, yet 42% of Phase III trials fail. That's a luxury biotechs can't afford. Killing an asset or indication in Phase II versus Phase III can save significant development costs and allows a company to redirect funds toward a more effective, commercially viable product.

Developing a value story that primes your product for commercial success

Holger Müller, Ph.D.
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Biotechs often have exciting science at their core. The company's culture may revolve around a groundbreaking mechanism of action, gene-editing tool, or platform technology. But translating brilliant science into a reimbursable, commercially competitive product is a multidisciplinary challenge, not just a scientific one. Articulating a coherent product value story from the start of development can help companies raise funds from investors, make smarter development decisions, gain market share, and win reimbursement.

An incomplete understanding of the unmet medical need and a lack of differentiation from competitors are two common reasons products fail commercially, according to recent research. Either problem represents a gaping hole in the product value story. However, companies small and large can mitigate the risks of an inadequate value story with three strategies:

1. Pressure test your product value proposition

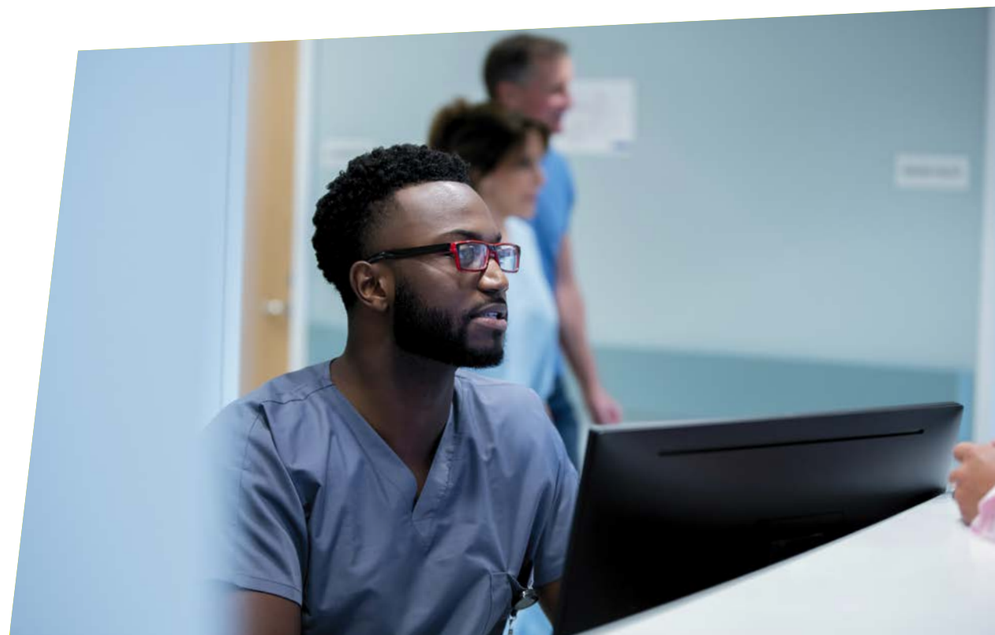
It is important not only to build a compelling value story but also to pressure test this regularly throughout development.

Companies should make sure that the value story can withstand scrutiny from all external stakeholders, including global regulators, payers, and HTA bodies. Challenge a product's value proposition early and often by seeking input from experts independent of your company and technology. And don't just examine it once or twice—inspect it continuously during development. Seeking such feedback does not have to be expensive. For example, a smaller company can get valuable insights by sitting down with practicing physicians (not just principal investigators focused on clinical research) and probing the therapeutic gaps for a condition.

If you think you can address an unmet need and capture a portion of the vast market for obesity, precisely define the target patient group most likely to benefit. Have you stratified obesity patients? At what point in disease progression does your drug enter the treatment paradigm? How does the price compare to alternatives like gastric surgery? Will insurers pay for it? Prioritize reimbursement and access in the value proposition.

Consulting with patient advocacy groups and patients (again, not just clinical trial participants) can help companies understand how to improve on the SOC with, for instance, fewer side effects or a more convenient route of administration. Companies can also meet with representatives of HTA agencies, public payers, and private insurance companies. Many national HTA bodies offer consultations for small companies and companies involved in orphan drug development at low or no cost.

"Challenge a product's value proposition early and often by seeking input from experts independent of your company and technology."



2. Elevate commercial considerations early

Early commercial planning can set your product up for success by providing a clear path to investment and revenue and avoiding unnecessary delays.

Most small and emerging companies wait until they get regulatory approval to hire a full-time chief commercial officer or similar role.

"Cross-functional decision-making should result in a value proposition supported by the data and trial outcomes that HTA agency reviewers and payers want to see, leading to a price that reflects the value of your product and captures market share from competitors."

The result is that many biotechs don't have a structure that lets them address value and access early enough.

One economical solution is to scour the globe for available commercial intelligence—you may choose to engage a consultant to do this rather than add a full-time position. Organizations, including Parexel Biotech, can help you:

- Understand past decisions of regulators and HTA agencies to understand their expectations
- Validate unmet needs and how your product will address them and construct a detailed patient care pathway
- Research the reimbursement and insurance landscape, for example, to ensure that relevant reimbursement codes exist for novel therapies or in some ultra-rare disease areas

Embed processes that elevate commercial considerations. Make successful commercialization part of your company mission statement, and make clear that it's a commitment, not just words. Place it on the agenda of every meeting, even if just for a few minutes. Ensure that every employee knows it is part of the corporate mission by including it in training.

3. Involve multiple disciplines in key decisions

Integrate scientific, clinical, regulatory, and commercial considerations from the beginning to better support development decisions.

If an HTA agency or payer will demand specific outcomes or quality of life (QOL) data to support your product value proposition, you will need to design trials that capture those data, which have regulatory implications. That's why every discipline needs to participate in decision-making.

Cross-functional decision-making should result in a value proposition supported by the data and trial outcomes that HTA agency reviewers and payers want to see, leading to a price that reflects the value of your product and captures market share from competitors. It further enables companies to manage a product's life cycle effectively, including adding new indications to the approved label, gaining approval in new countries, and partnering when warranted.

Integrated development should produce a shorter time to revenue. There will be fewer delays in achieving regulatory approval and payer reimbursement with an accurately targeted unmet need and optimized trial design. And a data-driven, well-vetted value proposition that builds investor trust and confidence makes it easier to raise funds.

Integrated development should start at the time of asset acquisition or target identification. Ensure you have a good mix of internal talent and experience to achieve integrated development and fill gaps by seeking external help.

There is no one-size-fits-all model for how to develop a commercially successful drug, but it's possible to sidestep some of the fatal mistakes that start-ups often make. Integrating the relevant perspectives and expertise within (and without) the company, and taking commercial risks seriously, improves any small company's chances of success.

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Keeping pace with the rapidly growing biotech environment requires the expertise to anticipate and adapt to development challenges before they happen. Parexel Biotech provides the experience and guidance you need to help you reach your development goals every step of the way. No matter the project, Parexel Biotech helps you put patients first with a delivery model that is fully integrated and adaptable from the very beginning. From there, your team will walk you step-by-step through every decision, touchpoint, and milestone along your clinical development journey, helping you achieve your most important endpoint—bringing your innovation from the lab to the patients who need it most, faster.

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