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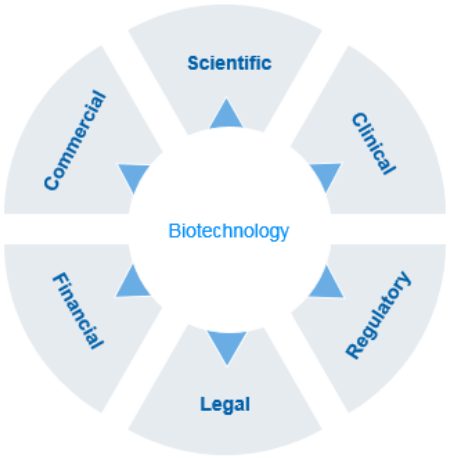
# RBC Biotechnology Primer

## How to navigate a complex space




**Given the high interest, we are releasing our RBC Biotechnology Primer as a standalone report. Our report is intended to serve as a straightforward "Biotech 101" overview explaining the fundamentals and risks of the sector, and is geared as an introduction for investors new to the space as well as healthcare specialists looking for a brief refresher and reference guide.**

**What's inside:**

- Definition of biotechnology, and where the sector fits among other therapeutics spaces
- Synopsis of the scientific and clinical development path for new drugs from discovery to approval, including typical timelines and probabilities of success through each phase
- Description of regulatory dynamics and types of drug applications and tools
- In-depth look at various market and regulatory exclusivities available to new drugs
- Summary of key financial drivers and rules of thumb
- Exploration of commercial dynamics, including competition, payer influences, drug supply chain, and pricing
- Comprehensive list of key risks to investing in the sector
- Overview of key external players and management attributes

**The RBC Biotechnology Team's knowledge and expertise spans these key areas.** Our professional experience spans scientific, clinical, legal, regulatory, financial, and commercial fields and therapeutic areas. We are here to assist you in answering questions; providing creative, objective, timely, and valuable research; and helping you make wise investment decisions.

**RBC recently launched its biotechnology research platform covering 42 biotechnology companies, and links to our recent initiations are included below.**

- Launch deck and deep dive on industry views/trends: Launching Coverage On 35 Biotech Companies: Charting A Course For 2H17 And Beyond
- Brian Abrahams, M.D.: ALDR, AVXS, BCRX, BIIB, CELG, ENTA, GLPG, GILD, IMDZ, INCY, ICPT, KPTI, MRUS, SAGE, VRTX
- Kennen, MacKay, Ph.D.: AGIO, AKBA, ALXN, AMGN, ANAB, ATNX, BIVV, BMRN, CLVS, EXEL, FPRX, OBSV, PRTA, RARX, REGN, SGEN, TSRO, XLRN
- Matthew Eckler, Ph.D.: ABEO, ONCE + DVAX, EPZM, IMGN, PBYI, PTCT, SANN-CH, SRPT

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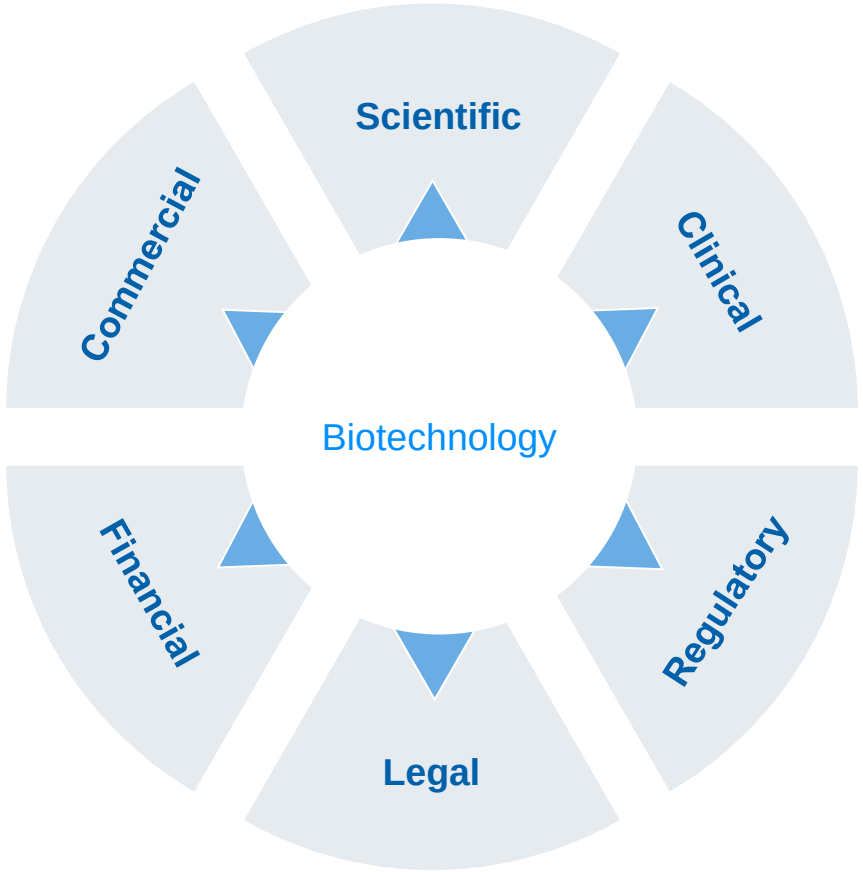
**Priced as of prior trading day's market close, EST (unless otherwise noted).**
**All values in USD unless otherwise noted.**
**For Required Conflicts Disclosures, see Page 21.**

## What is biotechnology?

- **Biotechnology**: the development of new drugs that utilize *novel and innovative* biological methods and scientific understandings to improve the human condition, usually to treat diseases of *high unmet need*
  - Biotech drugs can be classified as **biologics** (drugs manufactured using biological processes, i.e. cellular therapies, gene editing, gene therapies, antibodies, RNA, peptides – more complex and expensive) or as **small molecules** (synthetic chemical compounds that are usually easier and cheaper to manufacture)
- Biotechnology companies are usually focused on a *niche therapeutic area(s) or a specific technology platform*, and through R&D investment, are capable of achieving *high revenue growth and margins* if successful
  - Oftentimes, the entire valuation of a biotech is based upon their prospective sales growth potential – with companies not generating any revenue while they are developing a drug. This process requires an incredible amount of capital (~$1-2B/approved drug) over the course of a decade or longer, and typically ends in failure – making biotech investing a highly risky, but potentially rewarding endeavor
  - Once a biotech company successfully develops and commercializes a drug, they can be acquired by another biotech or pharma company, or, if they are larger and established, they continue to grow by investing heavily in their R&D pipelines to discover new and/or improved innovative treatments. M&A and partnerships also often take place throughout the development process
- Not to be confused with the "big pharma" and "specialty pharma" industries – though there is often overlap and blurred lines that sometimes makes it difficult to discern distinctly between the three
  - **Larger pharmaceutical** companies have much larger pipelines and significant numbers of marketed products across a *broader range of therapeutic areas*. They are usually more stable in their financial condition, which makes them less risky investments. SG&A and R&D are both significant components of operating expenses – with R&D comprising both internal development and acquisitions
    - Considering many pharmaceutical companies have acquired smaller biotechs or are developing their own biologics (whereas "pharma" was historically focused on small molecules), many pharma and biotech companies are also referred to as "biopharmas."
  - **Specialty pharmaceutical** companies are in the business of selling generic or repurposed/reformulated versions of drugs that have already been approved, and most of the upfront development costs associated with developing the drug have already been invested. Usually R&D is less of focus, with a bulk of operating expenses focused on SG&A. Specialty pharmas sell many products across a more consolidated, yet competitive space (therefore less opportunity for growth) – and unlike biotech or pharma, these products are no longer protected by patents or market exclusivity
    - Generic versions of biologics and more complex small molecules are called biosimilars and complex generics, respectively

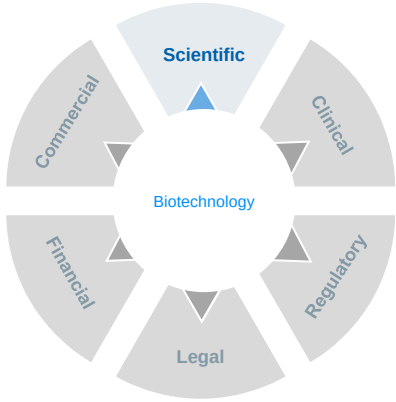
*Source: RBC Capital Markets, Company reports*

# The six elements of biotech




*Source: RBC Capital Markets, Company reports*

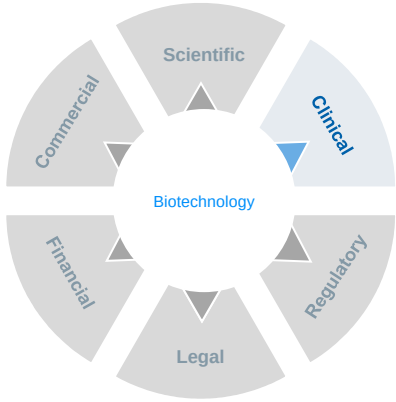
# It all begins with scientific innovation and discovery




- Basic research in the fields of chemistry and biology at private and public institutions leads to discovery of novel therapeutic agents or unique biological targets and mechanisms that can be developed to treat disease
  - Major advancements in these fields, along with interdisciplinary collaboration among physics, engineering, and computer science have permitted for a rapid increase in medical innovation – which lies at the core of biotechnology
- Through further translational and preclinical research in animal and other disease models, researchers work to better understand and characterize diseases and drugs so that they can be refined and pursued in human clinical trials
- Basic research also leads to discoveries that contribute to clinical, regulatory, and commercial aspects of drug development. For example:
  - Epidemiological research helps quantify commercial opportunity and obtain regulatory incentives, such as orphan drug status
  - Biomarkers, such as genetic identifiers, improve clinical trial design and patient stratification, which increases likelihood of trial success and identification of patients in the commercial setting
  - Disease and drug characterization allows companies to differentiate drugs from competitors and establish improved clinical trial designs with regulators

*Source: RBC Capital Markets, Company reports*

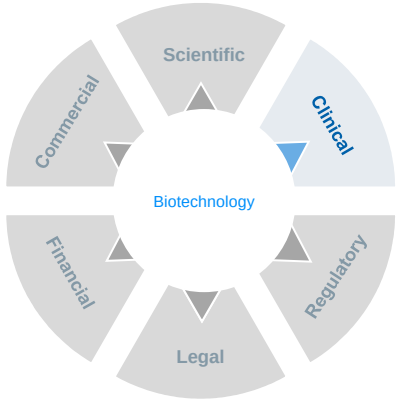
## Clinical research progresses along in three regulated phases




- Following preclinical research demonstrating that a drug is safe to animals at high doses and has potential for efficacy, a biotech is ready to begin testing their drug in humans
- Clinical testing is regulated by the Food and Drug Administration (FDA) – and the goal of clinical approval and potentially commercial differentiation is kept in mind as the drug is developed
- To begin clinical testing, a biotech must file an **Investigational New Drug (IND)** application, which outlines the general investigational plan, trial protocols, *in vitro* and *in vivo* preclinical pharmacology and toxicology data, and manufacturing details
  - Unless the FDA finds deficiencies, the IND will clear after 30 days and a biotech may begin clinical testing across the U.S.
  - An **Institutional Review Board (IRB)** and **Data and Safety Monitoring Board (DSMB)** also usually monitor protocols and patient risks of ongoing clinical trials
- Clinical trials usually progress in three phases (note these lines can be blurred, depending on the disease):
  - **Phase I**: the safety, dosing, and pharmacology of a drug is evaluated in a small group of healthy individuals
  - **Phase II**: safety and preliminary proof-of-concept for activity in a small group of diseased patients is evaluated, along with dose optimization
  - **Phase III**: safety and efficacy profile is validated in a large group of patients
- Material data from trials are presented to the public, either in a press release/call, investor conference, or medical meeting – and can be binary events with extreme upside/downside
- Medical conferences for professional societies of health practitioners and academics are often critical events for certain therapeutic sectors, given many companies and competitors present key clinical data that can be traded upon, either through abstracts released prior or at presentations or physician feedback at the meeting (e.g., ASCO, ASH, ESMO, SITC, AACR, AASLD, EASL, AAN)

*Source: RBC Capital Markets, Company reports*

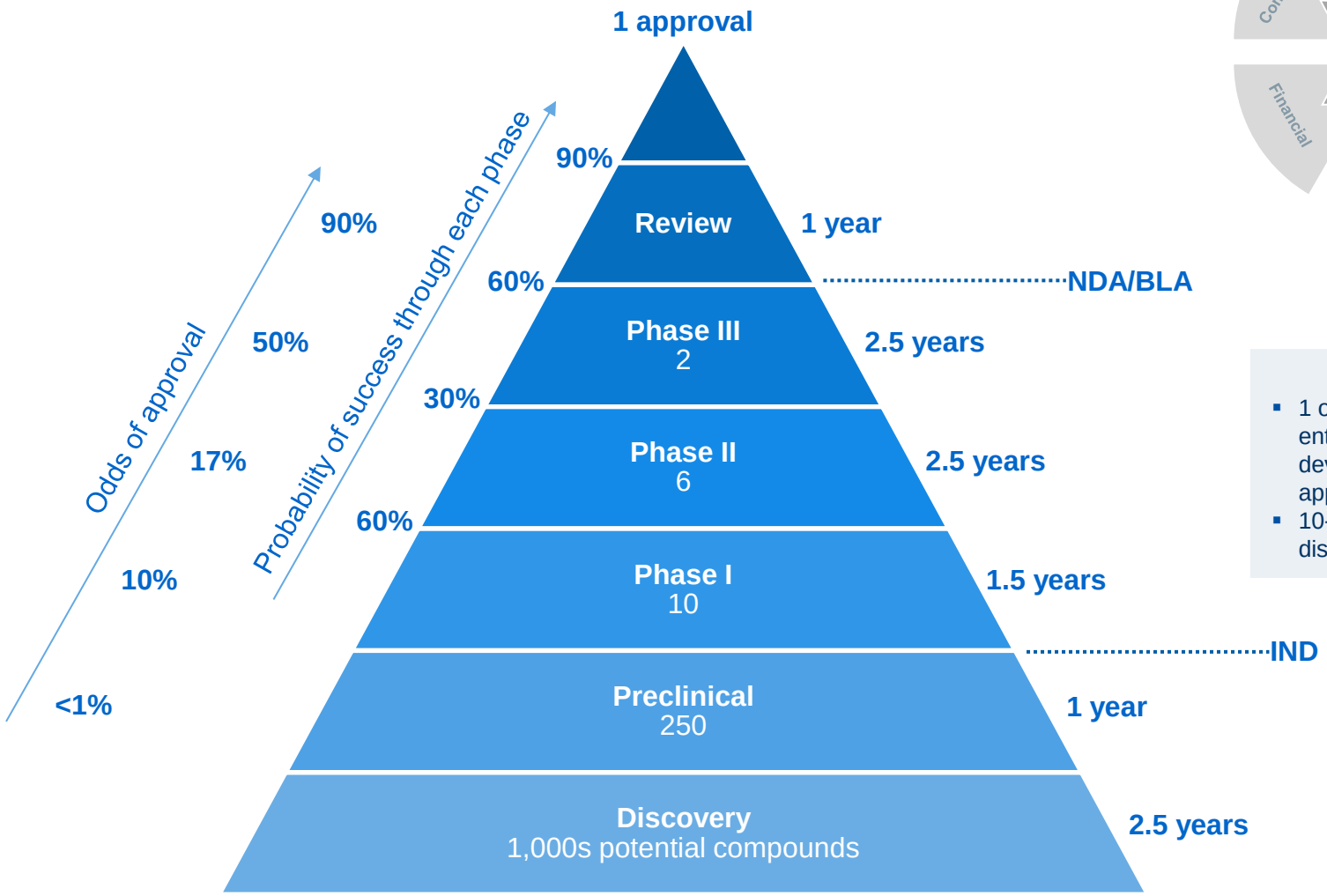
# Review of NDA/BLA by FDA is gate to approval

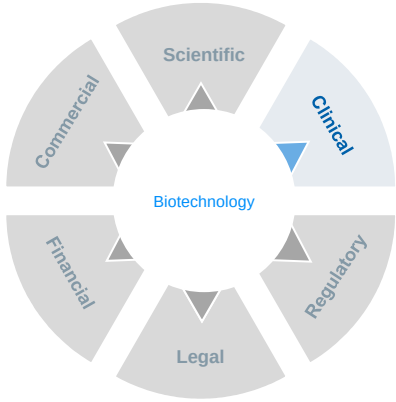



- If an agent successfully moves through all three phases, then a company can submit a **New Drug Application (NDA)** (for small molecules) or **Biologics License Application (BLA)** (for biologics) to the FDA for review
- **Standard FDA review takes ~1 year** (a 60-day period in which the FDA determines if all the required information was supplied and "accepts" the filing, and a 10-month deadline to approve/deny the application (set by **The Prescription Drug User Fee Act**, known as a **PDUFA date**)
  - Applications under "priority review" have an expedited timeline of 6 months instead of 10 (see next slide for more details), and the FDA will sometimes approve applications months before a PDUFA date, depending on the unmet need it serves/strength of the application
  - During the review process, FDA will occasionally seek independent advice from outside experts known as an **FDA Advisory Committee (AdCom) –** which can convene a public hearing to debate the risks and benefits of a drug
    - AdCom's can be highly volatile for biotech companies with a drug under review by the FDA, especially for controversial applications (limited data, questionable efficacy benefit, safety risks, etc.)
    - Given this, the FDA still has final authority and is not bound by the AdCom's determination (in fact, a number of controversial applications have been approved by the FDA even in light of an unfavorable AdCom meeting in light of high unmet needs)
- In addition to clinical data, additional activities are required for approval:
  - Additional preclinical studies examining toxicology, carcinogenicity, drug-drug interactions, cardiovascular effects, etc.
  - Manufacturing data must be provided to ensure safety and clinical quality, including periodic facility inspection
- **Phase IV**: Post-approval studies examining long-term safety and ongoing safety monitoring also remain a critical activity after approval

*Source: RBC Capital Markets, Company reports*

# Few drugs successfully make it from discovery to approval



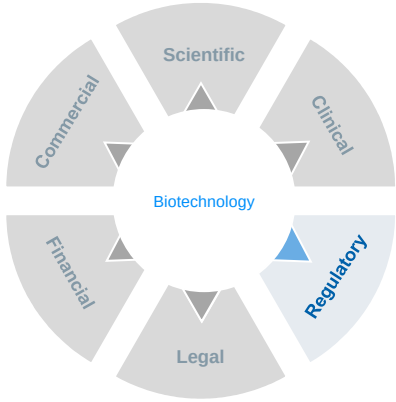




**Key figures**

- 1 out of 10 drugs entering clinical development ultimately approved
- 10-15 years from discovery to approval

*Source: RBC Capital Markets, Company reports*

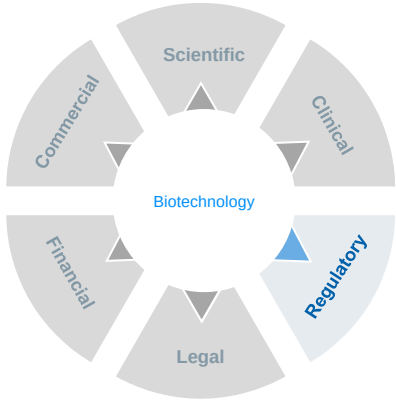
## The FDA is the biotech "gatekeeper" and is heavily involved in the drug development process during and after clinical testing and approval




- Drug development is a highly regulated industry in which a company's product must be approved by a governmental authority before it is marketed and sold
  - The FDA in the U.S., and its European counterpart, the European Medicines Agency (EMA), are responsible for carrying out these activities in which robust clinical studies demonstrating a drug's efficacy and safety are required to gain approval
  - These regulatory agencies are bestowed the authority of determining if a drug is efficacious enough to warrant approval in light of any public safety risk, i.e., is the drug safe and effective
- When reviewing whether a drug should be approved, the FDA and EMA will consider its risk/benefit profile – whether the drug's efficacy improvement upon the standard-of-care outweighs any potential safety risks
  - E.g., a drug that cures a severe disease with no available treatments may warrant some safety consequences, or a drug intended to treat a disease with multiple available therapies that incrementally improves upon standard-of-care, but has significant safety consequences may not have sufficient efficacy to gain approval
- Given the risk/benefit ratio, a pendulum exists in which regulatory agencies will shift their focus to one component of the equation over the other
  - Most recently, the FDA began shifting its attitudes of what level of efficacy vs. safety risk constitutes rationale for approval – this shift has been more favorable to drug developers and patient advocacy groups by prioritizing addressing unmet needs with innovative new treatments
- Along with clinical studies and approvals, the FDA also regulates certain market exclusivities, generic approvals, manufacturing, marketing/labelling, and safety monitoring

*Source: RBC Capital Markets, Company reports*

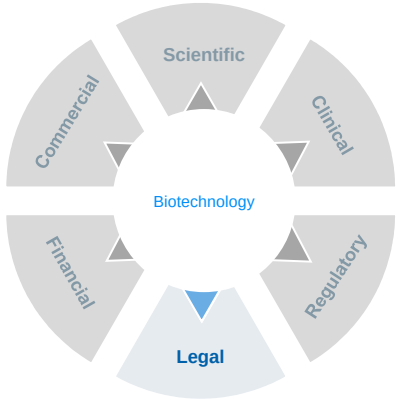
## Given the increasingly favorable regulatory environment, the FDA and EMA have incentives for the development of innovative drugs in areas of high unmet need




- The FDA/EMA provides regulatory feedback throughout the drug development process, and there are a number of additional programs for cutting-edge drugs or those that address areas of high unmet need that will increase the FDA's assistance, accelerate development timelines, and/or ease the level of scrutiny applied during review
  - **Fast Track –** Expedites FDA review *and* development for drugs addressing an unmet need in a serious condition
    - Eligible for more frequent FDA communications, accelerated approval/priority review, and/or rolling review (can submit NDA/BLA in sections rather than all at once)
  - **Breakthrough therapy –** Expedites review *and* development for drugs addressing an unmet need in a serious condition that may demonstrate a substantial improvement over current treatment
    - All Fast Track features + more FDA guidance on regulatory path
  - **Accelerated approval –** Shortens the review time to approve a drug based on a surrogate endpoint (biomarker or improvement in symptoms, often from phase II work); complete safety and efficacy still has to be proven post-approval, and if this is not demonstrated, approval may be withdrawn
  - **Orphan Drug Status** – provides exclusivity benefits and other incentives, such as more lenient review, tax credits, and reduced fees in indications that affect less than 200,000 U.S. citizens
  - **Priority Review** – FDA will complete application review within 6 months (vs. goal of 10 months for standard review, but can be shorter/longer. This "goal" date is governed under the law known as PDUFA – and lately review has been about ~1 month faster than the PDUFA date.) Priority Review can be obtained:
    - by drugs that match a certain criteria that show the drug significantly improves the safety, efficacy, treatment, diagnosis, or prevention of serious conditions
    - by using a Priority Review voucher – these can be acquired in a number of ways (either through purchase from another company or by studying certain types of indications, like tropical or orphan pediatric diseases) and can be used for any NDA/BLA
- The EMA also has analogous programs known as PRIME designation, accelerated assessment, conditional marketing authorization, and orphan drug status

*Source: RBC Capital Markets, Company reports*

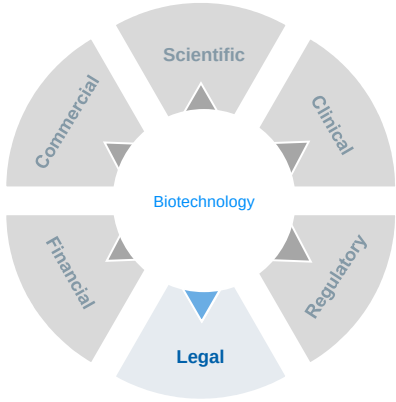
# Market exclusivity is needed to achieve high ROI and warrant investment




- Legal and regulatory exclusivity for marketed products is critical in incentivizing drug development and obtaining ROI, as once this period ends, multiple generics can begin producing a drug at a lower price and erode branded sales
- The primary modes of preventing generic entry are through patent term or regulatory exclusivity
  - Regulatory exclusivity prevents the FDA from reviewing or approving applications for **generics (small molecules)** or **biosimilars (generic biologics)**
    - Types of U.S. regulatory exclusivity include:
      - **Biologics:** 12 years from BLA approval for standard biologics
      - **New chemical entity (NCE):** 5 years for NDAs with new chemical entities
      - **New indications:** 3 years from original NDA approval for new indications in NDAs, but previously approved chemicals (seen more commonly in specialty pharma)
      - **Orphan:** 7 years from approval; applicable to both NDAs and BLAs in the specific indication submitted for that molecule
      - **Pediatric**: Adds additional 6 months to patent term and regulatory exclusivity periods as incentivizes for conducting pediatric studies
    - The EMA grants a blanket 10-year regulatory exclusivity to all biologics and small molecule drugs, with the ability to gain extension of 1 year if new indications are added within the first 8 years, or 2 years for orphan pediatric diseases

*Source: RBC Capital Markets, Company reports*

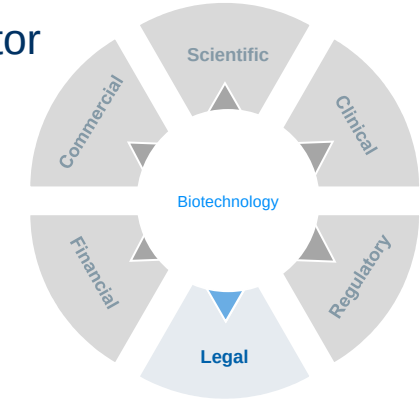
## Patents also incentivize innovation and enable ROI




- Given the high cost of development, companies that develop innovative and patentable treatments are afforded exclusivity from generics and other competitors for their specific product. This promotes better therapies by 1) ensuring a return on investment to the innovator with cheaper costs later on as generics come on board once patents and exclusivity expire, 2) encouraging competitors to develop better therapies that improve upon available technologies, and 3) promoting disclosure of information that may otherwise be kept secret
- In return for public disclosure of information and encouragement to create better drugs, companies are granted a limited “monopoly” with limited scope and timeframe
- Patents are a constitutionally afforded protections for inventions, and grant a period of exclusivity for 20 years
  - However, since drug development takes a significant amount of time after a patent is received, the period of exclusivity is typically 10-15 years, but the FDA and EMA offer patent extension that can ensure a period of 14 and 15 years of exclusivity, respectively
- The **U.S. Patent and Trademark Office (USPTO)** decides which inventions are eligible for patent protection
  - The requirements for a patent include novelty (an invention cannot have previously been invented or disclosed), utility (an invention must be useful), non-obviousness (an invention cannot be obvious in light of prior publications and patents, aka “prior art”), adequate written description (scope of invention must be adequately described, as well as how to make and use it), and it must be patent-eligible (cannot be genomic DNA or naturally-occurring)
  - A pendulum of disclosing public info and promoting innovation exists in the USPTO in which they may be more lenient or strict in which patents are granted (was strict, now becoming more lenient)
  - Patents can also protect chemical structure, formulations, methods of treatment or dosing, and manufacturing processes – theses ongoing improvements can help extend patent life

*Source: RBC Capital Markets, Company reports*

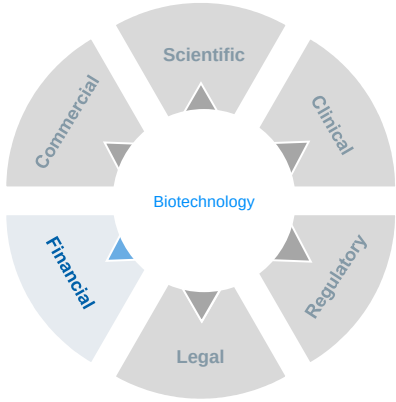
# Defending commercial position and innovation from generics and competitor therapies is also necessary




- Biotechs must defend their commercial position and innovation from generics and other branded competitor therapies that utilize their intellectual property
- The Hatch-Waxman statute governs the process for approving generic small molecules and the Biologics Price Competition and Innovation Act (BPCIA) governs biosimilar applications
  - Under Hatch-Waxman, when a competitor is ready to file a generic marketing application after regulatory exclusivity ends, the generic company files a **Paragraph IV certification** challenging any existing patents publically listed in the **FDA Orange Book**, which begins a process of patent litigation (if any patents exist) that can last for 3-5 years or more
    - Common types of generic applications include an **Abbreviated New Drug Applications (ANDA)** (for exact copies) or **505(b)(2) applications** (slightly modified chemical structure, formulation, indication, dosage, modality, etc. – often requiring some supplemental studies, but less than what is required for a full NDA)
    - The first paragraph IV filer is granted an exclusivity period of 180-days, which encourages filing – often very early on, and on all patents (which may or may not be an ultimately successful strategy)
    - Upon receipt of a paragraph IV certification, the drug manufacturer must sue the generic company within 45 days for all applicable patents, which initiates a 30-month period in which the FDA will postpone approval of a generic as companies litigate patent validity
    - If a generic is successful, they can begin marketing once they receive FDA approval, which can eventually erode nearly all of branded sales, or, if not, can wait until the patents expire
    - In certain situations, when litigation is not resolved, a generic could launch at-risk, in which they assume the litigation will be settled or work out in their favor, but they could still be liable for legal damages if not
    - Oftentimes branded and generic companies can settle and work out arrangements for a limited generic launch – sometimes referred to as pay-for-delay
- The BPCIA is a more complicated procedure involving a 180-day notice by the biosimilar applicant followed by an exchange of manufacturing information and patents to be litigated known as **"the patent dance"** – this procedure is new and much of the details are still being hashed out in court
  - Biosimilars are complicated by the fact that 1) they are more difficult and expensive to manufacture (leading to more limited price erosion for the branded therapy, once approved) and 2) they are often not identical to the branded biologic, creating a higher bar for approval for showing similar safety, efficacy, and manufacturing, but also complicating patent lawsuits
- Other mechanisms to challenge patents include administrative proceedings in the patent office, such as ***inter partes* review** (6-18 month challenge which examines novelty and obviousness in light of prior art) or ***ex parte reexamination*** (reevaluates scope of patent) – these proceedings are usually less costly, more successful, and faster for generic companies than district court litigation
- Branded therapies can also initiate lawsuits regarding technical aspects of Hatch-Waxman and BPCIA proceedings or by submitting Citizen Petitions that argue for a different standard for approval due to complexities with the drug or disease, which both also can delay approval

*Source: RBC Capital Markets, Company reports*

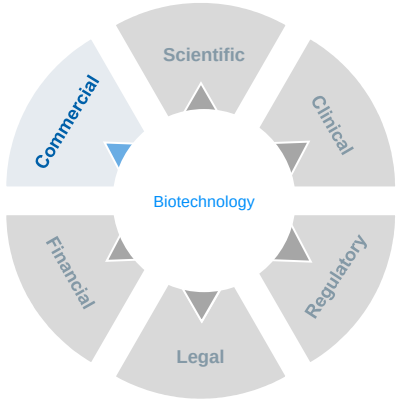
## Biotech companies are top-line driven, with increasing focus on the bottom-line as they grow




- Pre-revenue biotechs must spend a significant amount of R&D to advance their products to approval – which may be met with failure
- This requires significant capital – primarily obtained from public equity raises, but also investment from VCs or pharma companies, and/or unique debt arrangements
- Until a biotech is commercial stage, they may generate no or limited revenue
- Some revenue may be generated from milestones/upfronts from partners or royalties from collaborations on out-licensed drugs – though these usually do not contribute to growth, but provide means to advance pipeline drugs
- Top-line revenue growth is enabled once a company has a marketed product – which is usually fast, robust, and maintained for successful products
  - COGs usually comprise 3-10% of sales for small molecules and 10-15% for biologics, though can be higher for complex products, such as cellular therapies or personalized treatments
  - SG&A expenses increase as the company expands its commercial infrastructure and prepares for launch (manufacturing, sales people, marketing, etc.)
  - R&D expense is usually sustained or increases as a company works to advance additional pipeline product candidates and expand their marketed portfolio offerings
  - Tax rates often benefit from NOL carry-forwards and R&D tax credits
  - All of these aspects can be leveraged as a company grows to expand operating and net margins – but this usually isn't a focus until a biotechnology company reaches a more mature stage in launch
    - Operating margins usually range from 25-40%+ and net margins 15-30% -- which can be reinvested in pipeline development, used to buy back shares, deployed to grow the pipeline through acquisitions of new products/companies, or returned as a dividend

*Source: RBC Capital Markets, Company reports*

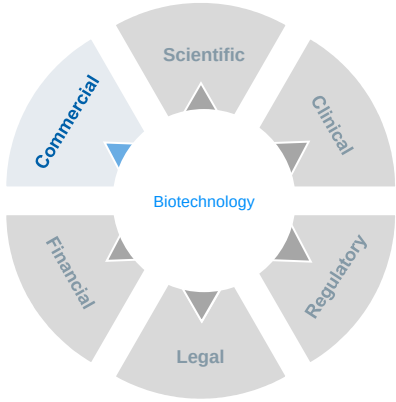
# The commercial environment in biotechnology is driven by payer dynamics and competition




- Competition in large therapeutic indications with multiple drugs emphasizes the importance of clinical differentiation, either in mode of delivery, efficacy, safety, or tolerability that offers meaningful benefit or addresses an unmet need versus standard-of-care
  - Drug pricing and payer negotiations are a complex component of commercial dynamics, and competition can give payers leverage in negotiating rebates
- Smaller indications, like orphan diseases, metabolic disease, or rare cancers, are typically sheltered from payer pressure and competition – though this has been changing in recent years, along with increased political scrutiny
  - Thus, given the lesser impact on payers' bottom-lines, limited competition to compel significant rebates, usually addressing high unmet needs (depending on profile), and need to obtain ROI, small indications usually demand high list prices ($50,000-$450,000+), whereas larger indications tend to have lower prices (though this depends on the value and pharmacoeconomic impact – such as preventing expensive surgeries or hospital stays)
- Treatments with significant benefits over available therapies, such as cures or one-time gene therapies, usually command high premiums, whereas drugs with more comparable or lesser impacts are discounted to encourage their use and adoption on payer formularies
- Being the first to launch a drug usually also helps provide substantial market entrenchment

*Source: RBC Capital Markets, Company reports*

# The biotechnology pricing environment and supply chain is complex

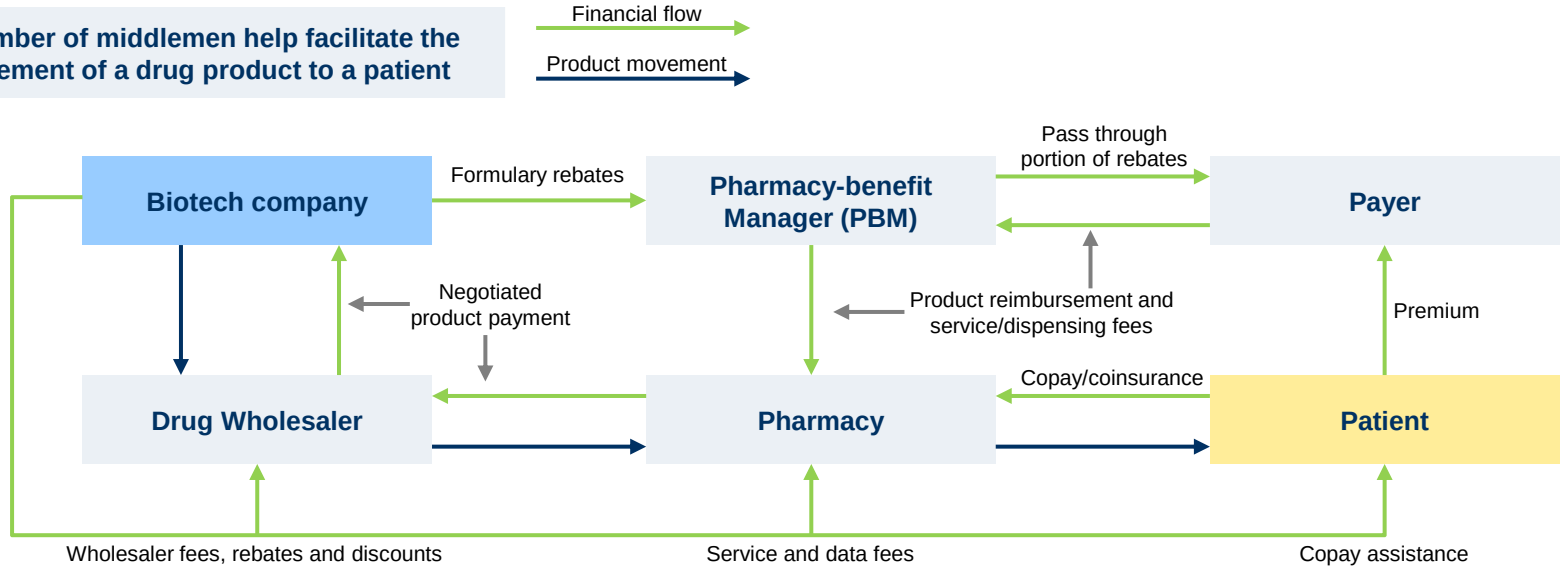



Drug pricing and payer negotiations are a complex component of commercial dynamics, and competition can give payers leverage in negotiating rebates

- Payers can be both private (Aetna, Cigna, United Health, etc.) or public (Medicare/Medicaid, England National Health Service, etc.)

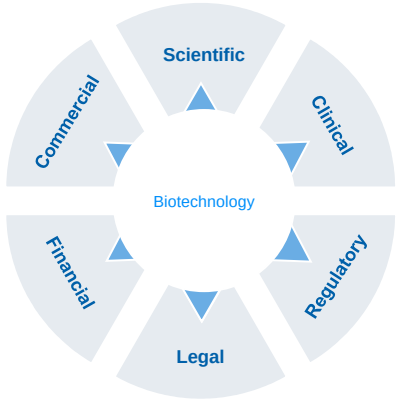
- After adjustments to a biotech drug's **list price** – the amount that the company receives after rebates, discounts, wholesaler fees and additional price concessions – the price realized by the manufacturer can be 15-25% less than the list price → though depending on the indication can be higher for unique treatments or lower for those that are not differentiated. This adjustment factor is known as the **gross/net**.
- Biotech manufactures often also provide drugs for free to patients susceptible to high prices, such as those without insurance, that cannot meet co-insurance or deductibles, or within the Medicare coverage gap for prescription drugs, as well as free treatment in clinical trials and expanded access programs for those that are ineligible to participate in clinical trials

**A number of middlemen help facilitate the movement of a drug product to a patient**




*Source: RBC Capital Markets, Company reports*

# Taken altogether, the biotech industry has significant socio-economic benefits




- **Societal**
  - Better basic understanding of life on earth and sharing of knowledge
  - Innovation that is improving our ability to live, resulting in longer, better, healthier lives
  - Curing incurable diseases and treating high unmet needs and rare diseases

- **Economic**
  - Supports economic growth and jobs across a number of other industries
    - 16% of Americans employed by the private sector of the healthcare industry – 1.6M across biotechnology
    - Makes significant contributions to economic output and growth
  - Reduce burden of more expensive standard-of-care by developing treatments that save on costs and deliver value to patients
  - Improve lost productivity among workforce

# Biotech investing is a risky endeavor that presents a unique set of risks

**Man risk** – a company can be highly dependent upon the technical knowledge and expertise of its executive team and employees, and a large degree of trust is placed in management

**Scientific risk** – incorrectly identification of disease biology, poor translatability of preclinical research, or on/off-target mechanisms may affect efficacy/safety

**Idiosyncratic risk –** random events, such as hurricanes, murders in a clinical trial, or being kicked out of a medical conference (it happens more often than you think)

**Social risk** – public perceptions of drug pricing may affect sentiment or result in backlash

**Epidemiology risk –** disease population may be smaller than expected or may be hard to identify/diagnose for treatment and clinical trial enrollment

**Competitive risk** – competition may affect sales/pricing

**Clinical risk –** efficacy/safety issue may result in clinical trial hold or failure

**Manufacturing risk** – hiccups or slow manufacturing could result in failure to meet demand

**Analysis risk –** incorrect understandings of statistics and comparators

**Pricing/payer risk** – payers may refuse to pay for a drug or limit reimbursement

**Competitive risk** – competition may create challenges in enrolling clinical trials

**Political risk** – government investigations or new legislation may affect pricing practices or regulation, resulting in large fines or settlements or changes to business practices

**Development risk –** clinical trials may need protocol changes or be poorly designed

**Liquidity risk –** stocks (small-cap biotechs) may be illiquid and difficult to trade

**Regulatory risk** – unfavorable or slow evaluation may lead to lack of approval or narrow label, and FDA may require more studies, changing/delaying regulatory path

**Financing risk** – company may need to raise additional capital, which may be dilutive, or may be unsuccessful (this includes **credit risk** from interest rate increases or default– but this is usually less of a concern with biotech)

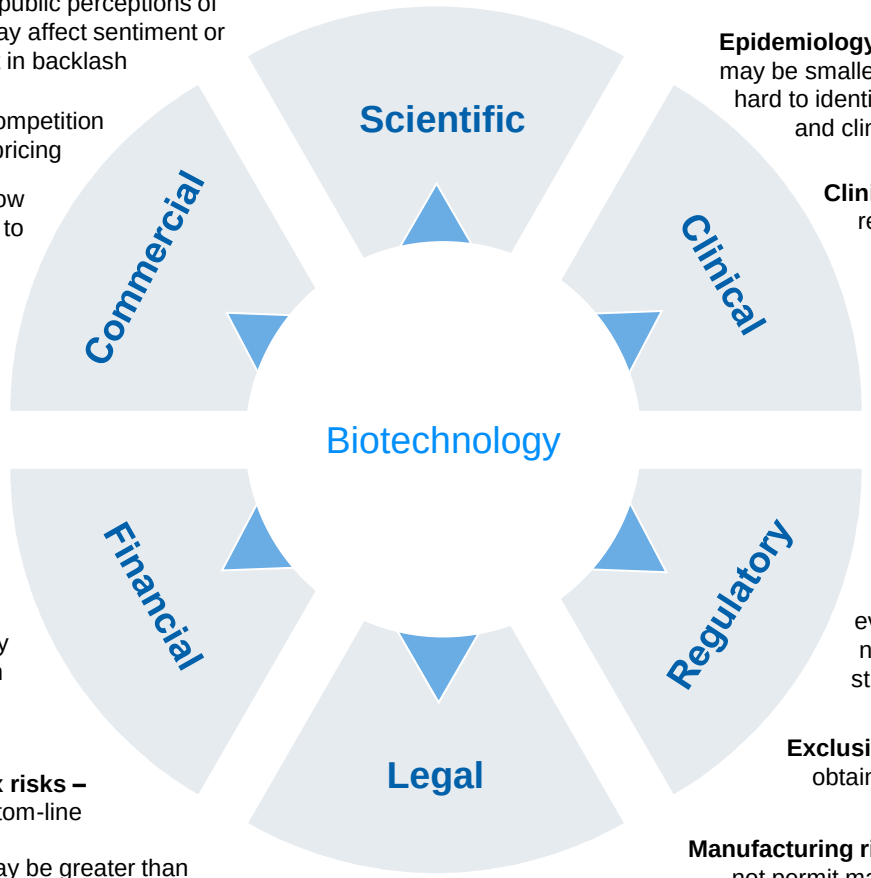
**Exclusivity risk** – loss of or failure to obtain patents/market exclusivity

**Foreign currency, accounting, and tax risks –** may unexpectedly change, affecting bottom-line

**Manufacturing risk** – the FDA may halt or not permit manufacturing of a drug

**Speculation risk** – expenses may be greater than forecasted, revenues hard to predict, and revenue-generating products may not gain approval

**Legal risk** – legal issues with generic or branded companies may result in large settlements/judgements, and may fail to block competitors, or prevent market entry



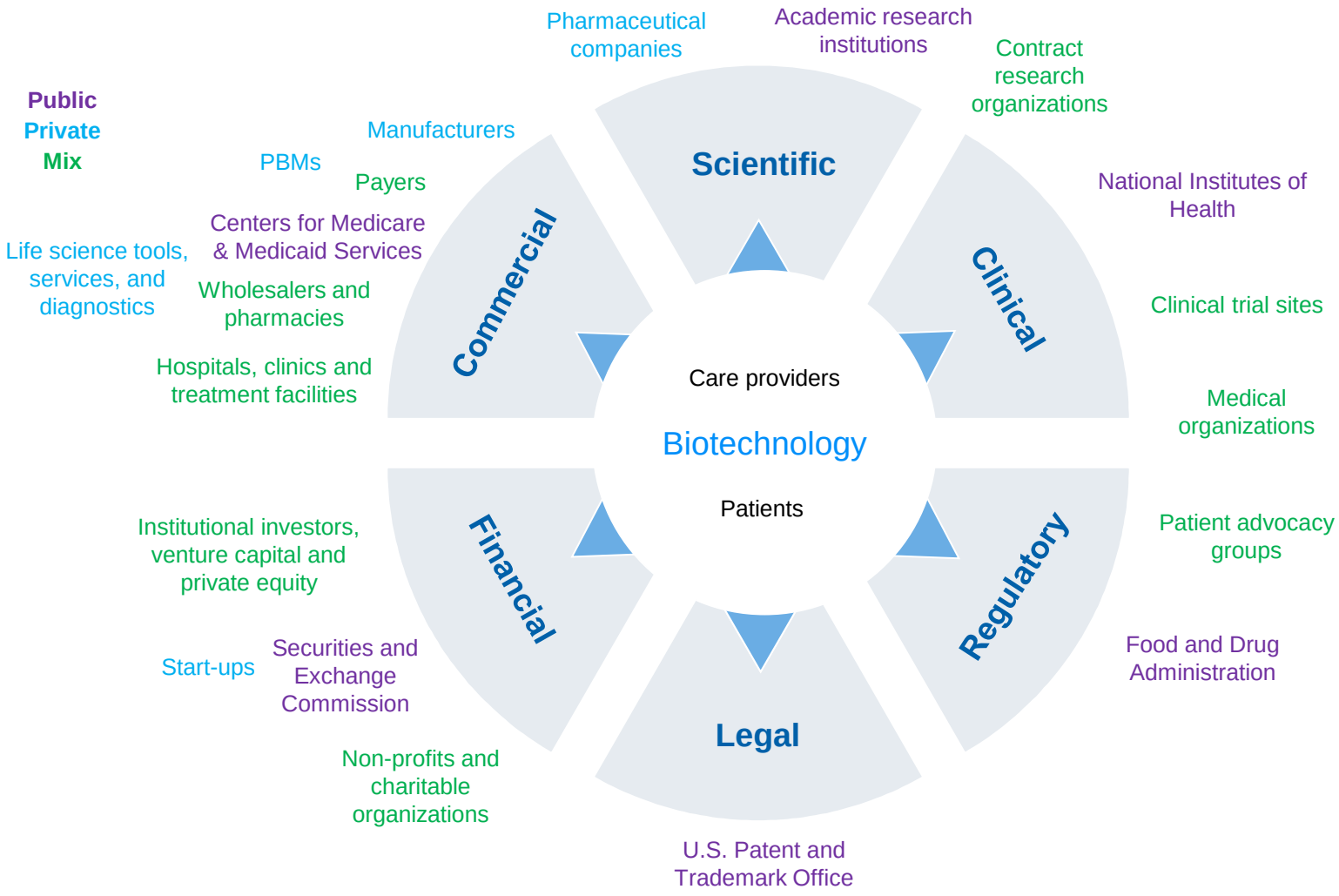

*Source: RBC Capital Markets, Company reports*

# The best risk-mitigation strategy: a skilled management team

- Given the highly-specialized nature of biotechnology, one of the most important considerations in evaluating a biotechnology company is whether their management team is skilled, trustworthy, and reputable
- Much of a company's complex activities, such as pricing negotiations, clinical trial design and evaluation, preclinical and toxicology testing, and manufacturing operations go on behind the scenes and are hard to handicap – so investors place a lot of confidence that standard procedures are being executed properly
- Since investors depend greatly on a management team's ability to efficiently and effectively design and execute a drug development plan, if an issue arises – management must also be able to communicate transparently and solve problems quickly; we believe the best teams are those who understand the science well enough to learn from their failures, and determine whether to continue developing a drug (perhaps in a slightly different population) or cut their losses and stop the program
- Given the high degree of faith in company management – investors often pay particularly close attention to management messaging and body language – and if a management team isn't careful, words can quickly be taken out of context or misconstrued
  - Meeting with management, going to company events, or attending investor conferences can be helpful in this regard, in addition to listening to company calls and data presentations (93% of communication is non-verbal)
- While it may seem obvious, some management teams are better than others, and can be a key reason why some mediocre drugs are successfully developed, while other good drugs get shelved – so, while a significant component, the drug and science are not always 100% of the story
- Perhaps one of the biggest risks in biotech is man risk – as loss of skilled drug developers, whether a key scientist or CEO, may be an integral detriment to the company's ability to succeed in the future

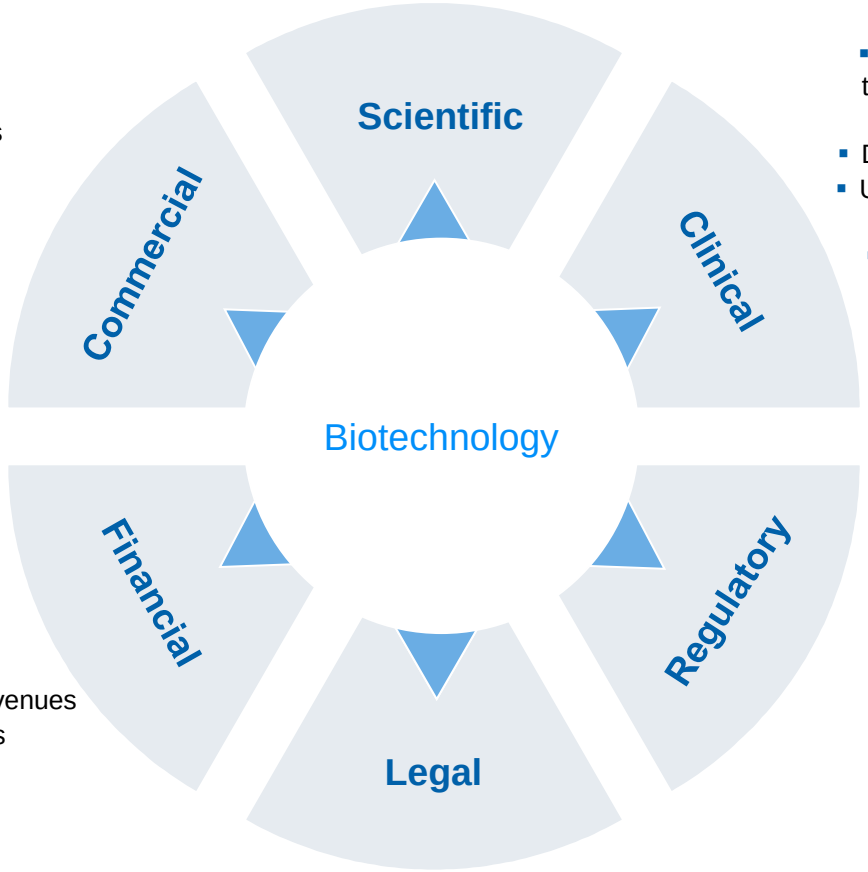
*Source: RBC Capital Markets, Company reports*

# Many players support the industry and vice-versa



# Summary: Six elements of a successful biotech

- Robust basic and translational drug research
  - Conduct preclinical testing and file IND
    - Disease characterization
  - Identify potential biomarkers for screening
    - Validate epidemiology




- Demonstrate PK/PD, safety, efficacy, tolerability, and differentiation in Phase I, II, and III
- Design and conduct optimal clinical trials
- Use biomarkers to increase probability of success
- Prepare manufacturing and conduct toxicology studies
- Phase IV post-approval safety studies/monitoring

- Determine development path
- Identify opportunities for expedited timelines
- Submit NDA/BLA to FDA for review of risk/benefit

- Obtain patents and exclusivity
- Protect IP with litigation

- Raise capital
- Achieve high-growth revenues
- Maximize margins
- Minimize taxes

- Identify key market opportunities
- Negotiate with payers to determine drug pricing
- Beat competition
- Manufacture drug
- Sell and market approved drug

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