The Drug Development Overview: Implications for Angel Investing

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Disclosure

- Represents opinions of presenter
- Not intended as investment advice or for investment decision-making
- Does not fully address risks or information related to drug development investments
- Individual opportunities may have vastly different considerations
- All of the information is gathered from public domain and source is not always referenced

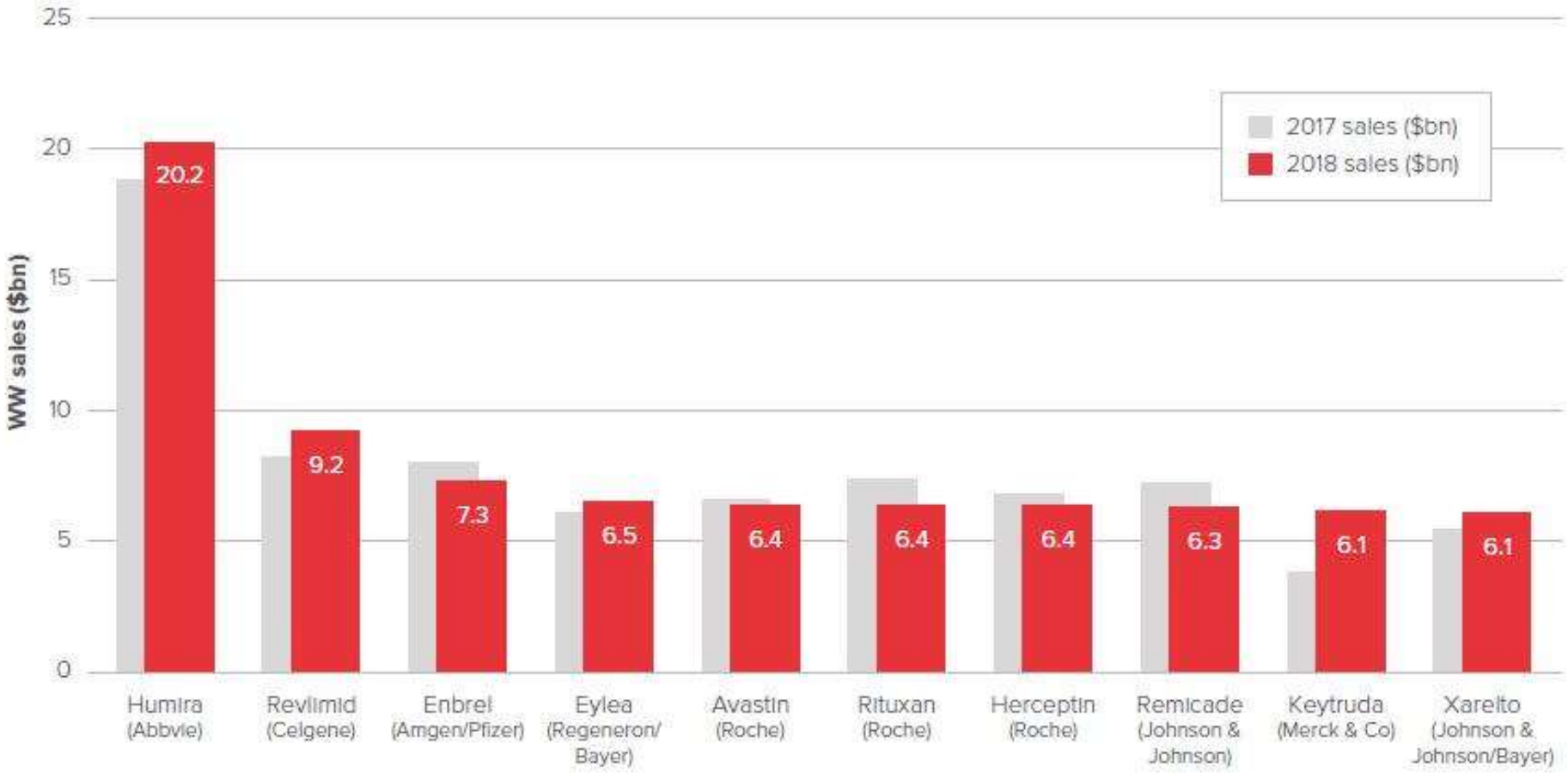
Pharmaceutical Industry Motivation

- Treat and cure diseases
- Save / improve lives
- Advance science and healthcare

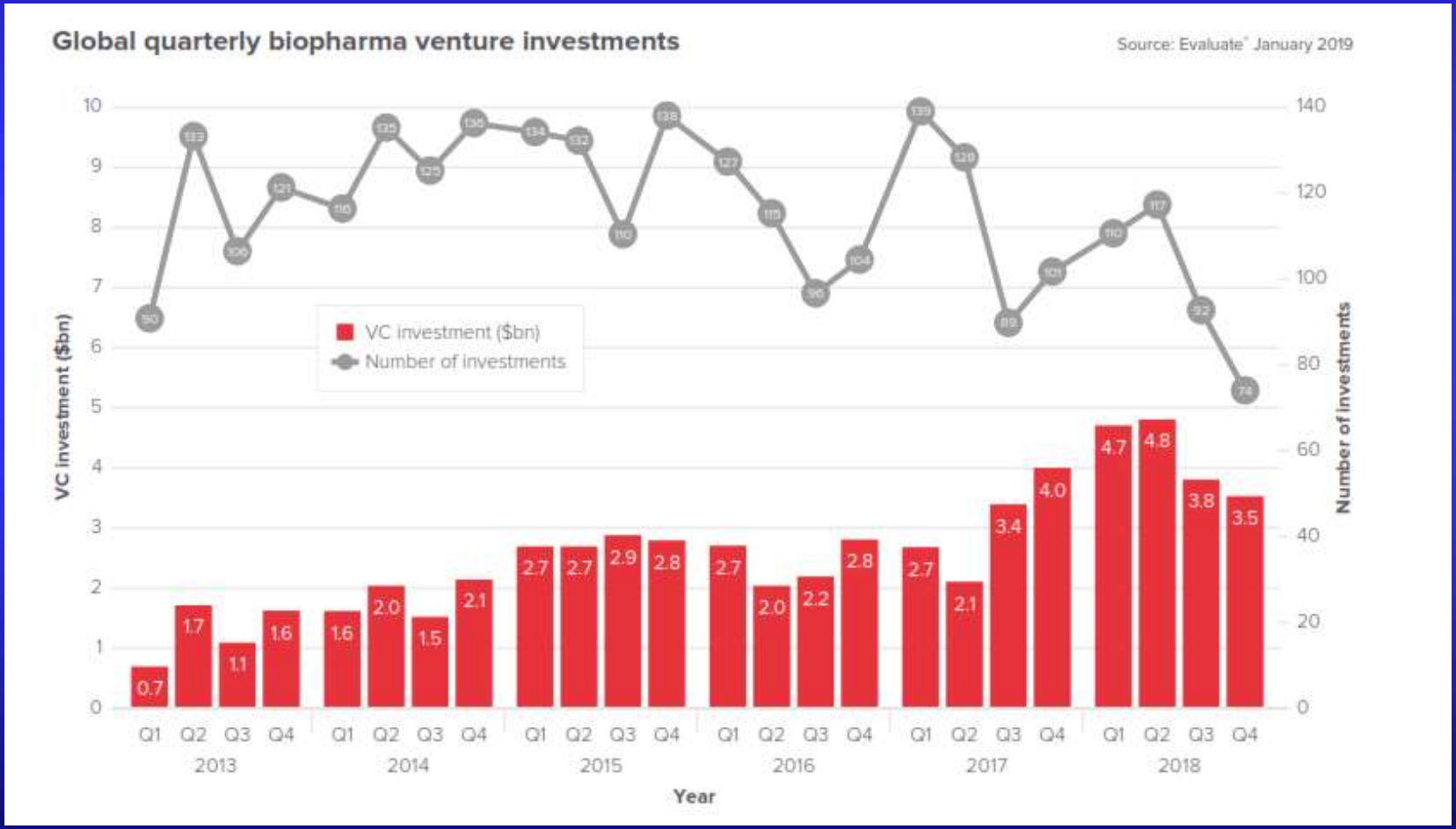
However, pharma companies are for-profit organizations and have a responsibility to its shareholders

Top 10 drugs by 2018 sales ($bn)

Source: EvaluatePharma® 15 November 2017



Biotech: Active Area for VC investing



Venture-Backed Biopharma Sector Returns

- **Biopharma returns for investors:**
  - **Are higher if investments are made in earlier rounds**
  - **Are higher at an IPO exit (vs. M&A exit)**
  - **Have been highest for the specialty pharma subsector**
- **Biopharma returns at IPO**

Biopharma Subsectors	First Round	Second Round	Later Stage
Biopharma	**7.8x**	**4.7x**	**2.0x**
Drug Delivery / Drug Dev Tech	3.6x	2.3x	1.3x
Specialty Pharmaceuticals	7.9x	6.4x	2.6x

- **Biopharma returns at M&A**

Biopharma Subsectors	First Round	Second Rnd	Later Stage
Biopharma	**6.5x**	**3.1x**	**1.2x**
Drug Delivery / Drug Dev Tech	3.4x	1.6x	0.8x
Specialty Pharmaceuticals	5.2x	3.6x	2.3x

Source: VentureSource. For venture-backed companies that went public from 2004-2006.

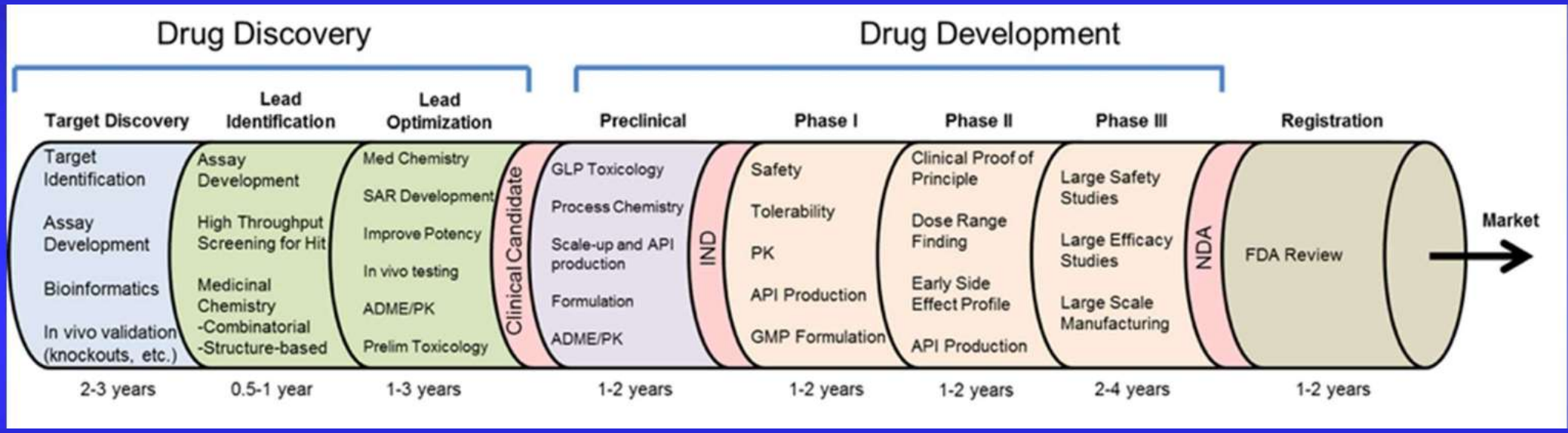
Key Areas in Drug Development

- Discovery
- Nonclinical (i.e. animal studies)
- Chemistry, Manufacturing and Controls (CMC)
- Clinical Development (clinical trials)

Key Regulatory Milestones

- IND = Investigational New Drug
  - An IND application to the FDA requests permission to embark on clinical trials
- NDA = New Drug Application
  - Requests marketing approval from the FDA

Drug Development: Process / Timeline / Cost



- Process takes 10-17 years for each drug
- Requires ~10,000 molecules in drug discovery/preclinical to get 5 molecules in clinical trials and 1 new drug approved
- Costs: Drug Discovery & Preclinical: ~$335 million; Clinical: ~467 million

Discovery

- Target identification
- Assay development
- Lead identification
  - High throughput screening
- Lead optimization
  - Chemistry, potency, disposition, prelim toxicology
- Preclinical testing

Chemistry, Manufacturing & Controls (CMC)

- Chemistry (synthesis, purification, scale-up)
- Analytical (chemical structure and activity, excipients, purity and stability)
- Pharmaceutical (dosage form, route of administration, packaging and labeling)
- Good Manufacturing Practice (GMP):
  - Guidelines related to manufacturing practices and specifications
  - Focus on impurities
  - Necessary to ensure quality of drug product (finished dosage form) and drug substance (bulk ingredients)

Adapted from presentation by R. Nolan, PhD (Calvert Research Institute, 2006)

Nonclinical

- Testing in laboratory (in vitro) and in animal models (in vivo) to assess safety and efficacy
- Objectives:
  - To develop the pharmacological profile
  - To determine the acute toxicity in at least 2 animal species
  - To assess toxicity with studies ranging from 2 weeks to several months
- Good Laboratory Practice (GLP):
  - Guidelines related to studies in animal models
  - To ensure the quality and integrity of data by establishing basic standards for the conduct and reporting of nonclinical safety studies

Adapted from presentation by R. Nolan, PhD (Calvert Research Institute, 2006)

Clinical Development

- Submission of the IND
- Conduct of Clinical Studies
  - Phase 1
  - Phase 2
  - Phase 3
  - Phase 4 (post-marketing studies)

Adapted from presentation by R. Nolan, PhD (Calvert Research Institute, 2006)

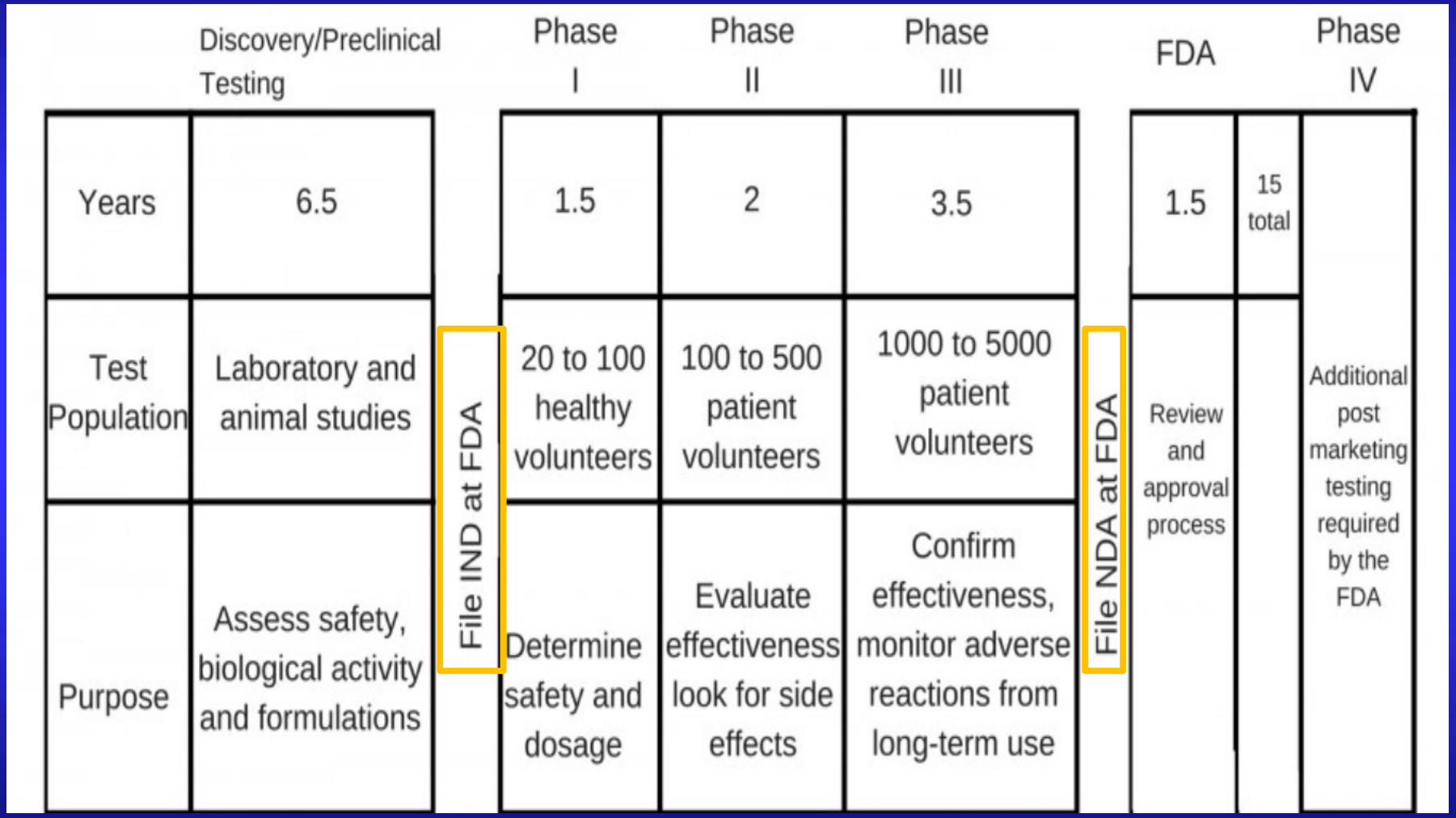
Selected Regulatory Pathways to Approval

	505(b)(1)	505(b)2	505(j)
Approval path	NDA	NDA	ANDA
Drug	New Chemical Entity (NCE)	Re-purposes previously approved drug.	Strives to be identical to currently available drug
Data	• Studies conducted by sponsor • Extensive studies needed: pre-clinical studies in multiple species; clinical studies to characterize drug, drug disposition, clinical safety and efficacy; manufacturing and quality	Hybrid between 505(b)(1) and 505(J) References much of the data previously conducted for the drug	Limited data requirements: Typically, a bioequivalence study (i.e. demonstrating similar blood levels relative reference drug)
Time / Cost	~ 10 years / ~1 billion	~4-6 years / ~10-50M	~1 year / ~1-2M
Probability of success	Low (improves through development phase)	High	Very high

Angel investment implications:

- Assess risk/reward since timeline and probability of success differ
- Generics may have a very high probability of success but may have a limited market potential
- NCE risk is high early on and investment needed is high

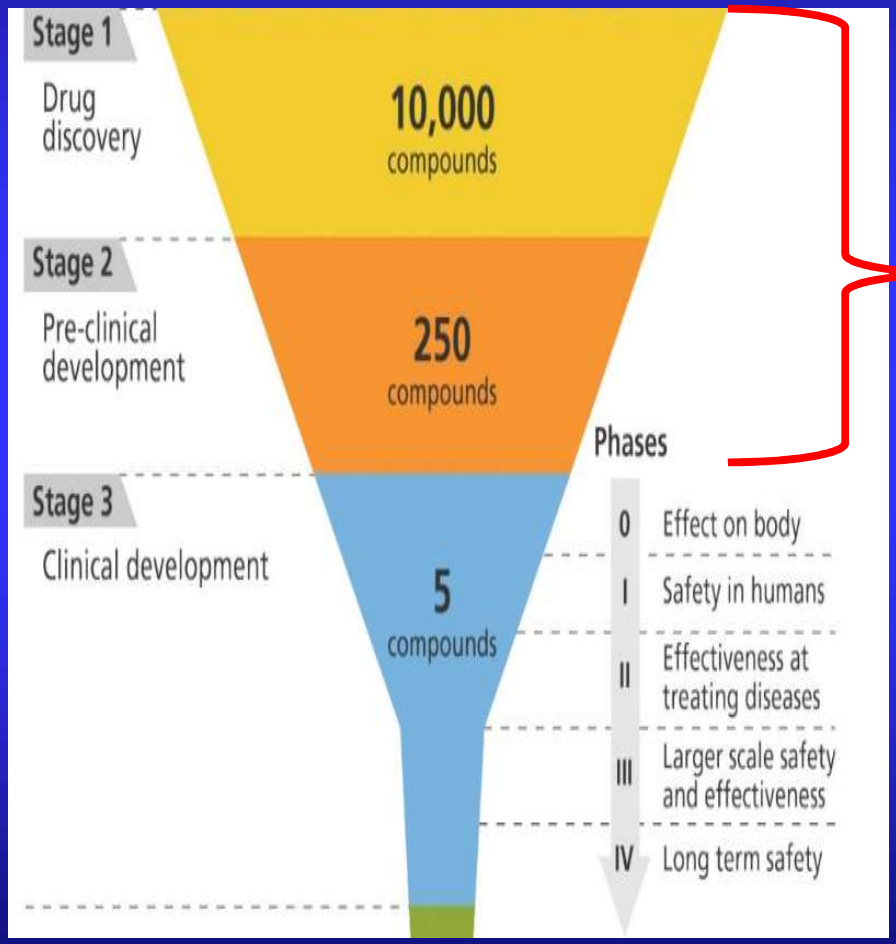
Drug Development Overview



	Discovery/Preclinical Testing		Phase I	Phase II	Phase III		FDA		Phase IV
Years	6.5		1.5	2	3.5		1.5	15 total	
Test Population	Laboratory and animal studies	File IND at FDA	20 to 100 healthy volunteers	100 to 500 patient volunteers	1000 to 5000 patient volunteers	File NDA at FDA	Review and approval process		Additional post marketing testing required by the FDA
Purpose	Assess safety, biological activity and formulations		Determine safety and dosage	Evaluate effectiveness look for side effects	Confirm effectiveness, monitor adverse reactions from long-term use				

Source: Pharmaceutical Research and Manufacturers of America, www.phrma.com

Development Stage and Implications for Angel Investing

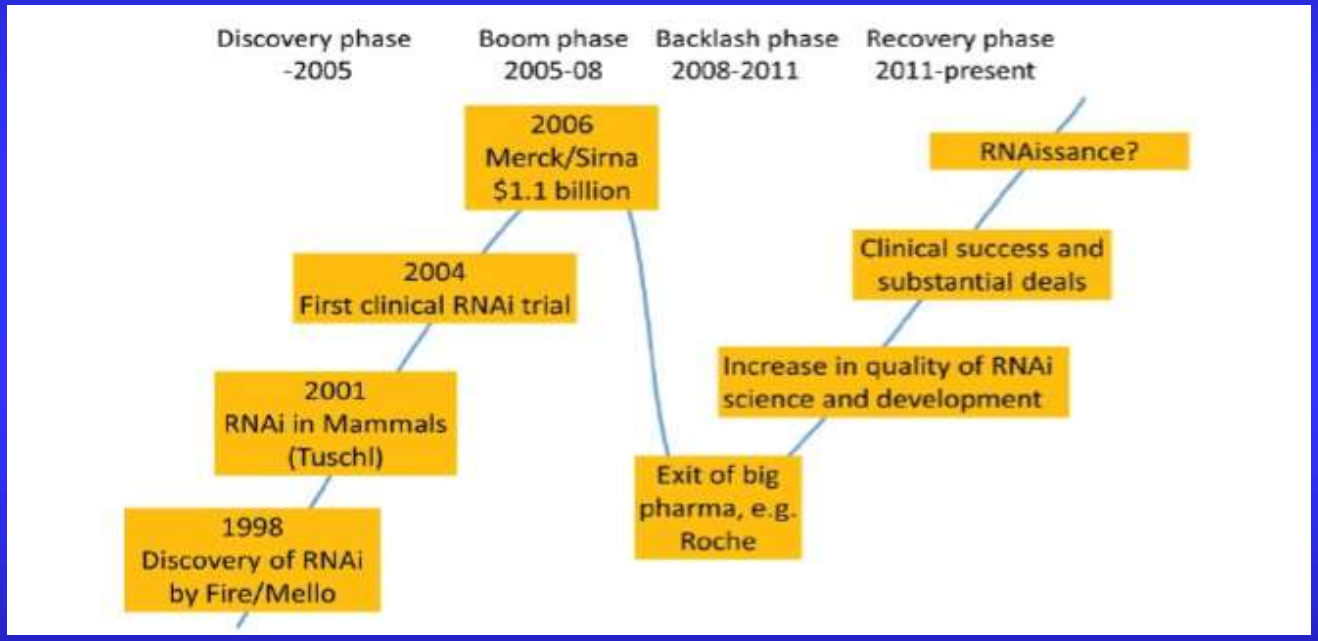


- High attrition
- Timeframe ~6.5 years
- Technology has to be compelling to provide opportunities for partnering or exits

Figure adapted from epharmacology.hubpages.com

New Technologies /Investment Challenges

RNAi therapeutics



First RNAi drug approval: August 12, 2018

Patisaran (manufacturer Alnylam) for polyneuropathy due to hereditary transthyretin-mediated amyloidosis (hATTR) in adult patients

Figure adapted from alliedacademics.org

CAR T-CELL THERAPIES: A BRIEF HISTORY

1993	First CAR T-cell developed by Dr. Zelig Eshhar
1996	The first CAR T-cell clinical trial began in 1996 in patients with ovarian cancer
2010-11	Phase 1 clinical trial of CAR T-cells in chronic lymphoid leukemia, two of the three patients achieved complete remission
2012	Emily Whitehead became the first paediatric patient to be treated with CAR T-cell therapy in acute lymphoblastic leukemia (ALL). Highly medialised, her remission helped re-energise a line of underestimated research
2017	The FDA approved the first CAR T-cell therapy, Kymriah®
2017	The FDA approved the second CAR T-cell therapy, Yescarta®
2018	The EMA to approve the first CAR T-cell therapy in Europe

ECL European Alliance for Responsible R&D and Affordable Medicines

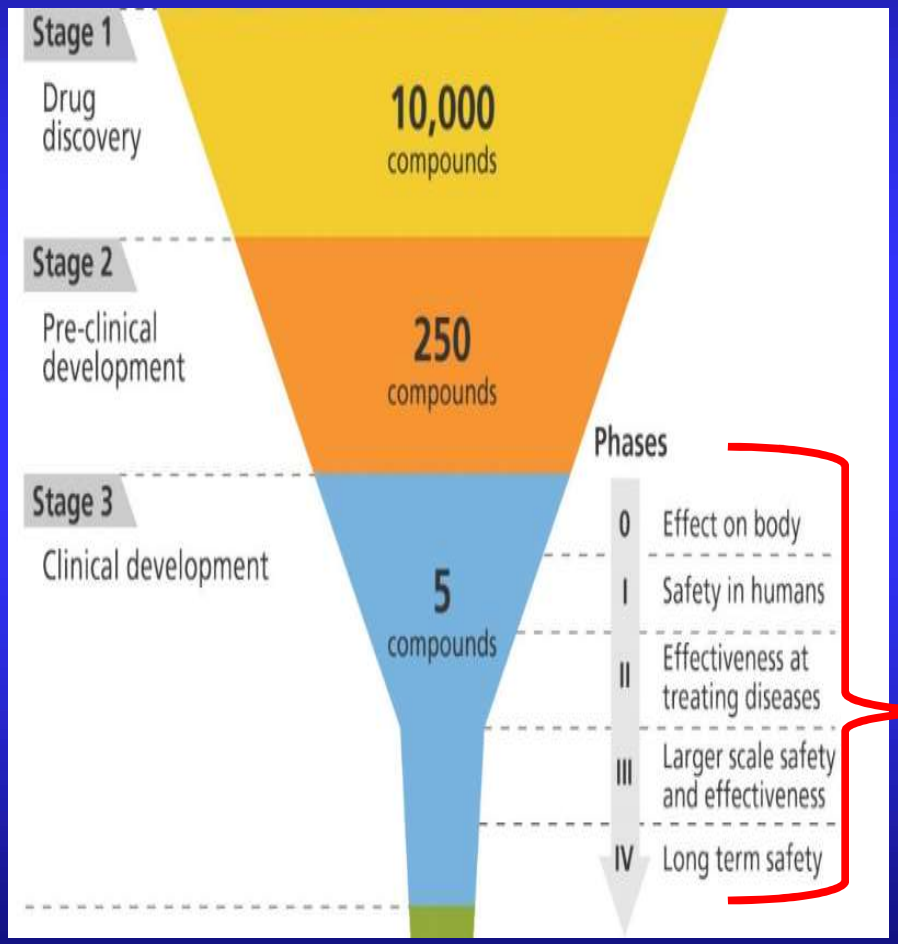
CAR T –Cell Deals

- 2012, 3 deals
- 2015, 35 deals
- Between 2012 and Septembre 2016, the deals worth at least:
  - $2 billion in disclosed upfront payments
  - $4 billion in milestones, royalties…
- August 2017, Gilead's Kite Pharma acquisition for $11,9 billion

ECL Association of European Cancer Leagues
Access to Medicines Task Force

European Alliance for Responsible R&D and Affordable Medicines

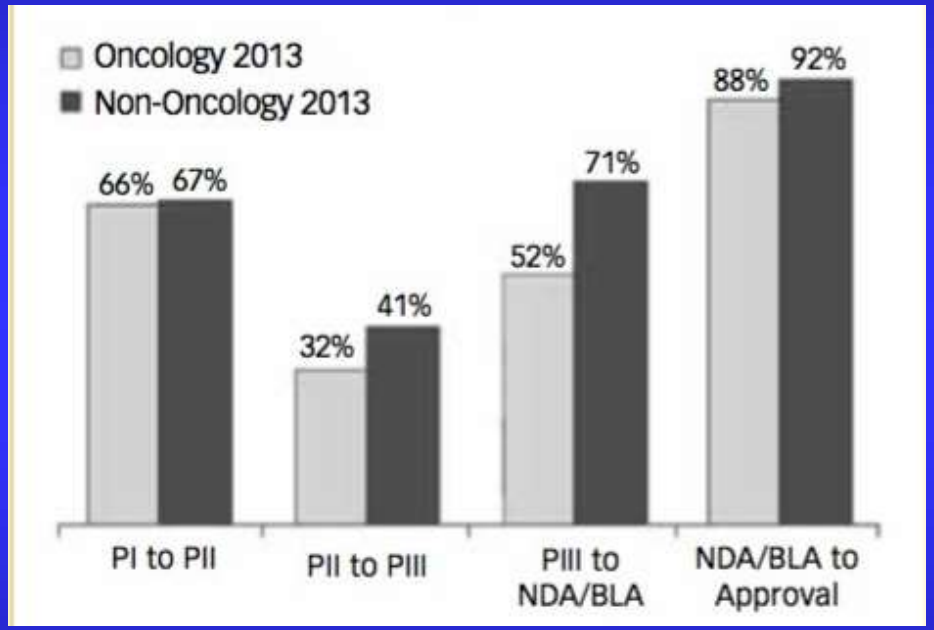
Development Stage and Implications for Angel Investing



- Much lower attrition than earlier stage
- Each "Phase" offers opportunities for partnering / exit
- Earlier Phases have shorter timeframes (1 – 2 years)
- Probability of success increases with advancing Phase
- Investment needs increase with advancing Phase

Figure adapted from epharmacology.hubpages.com

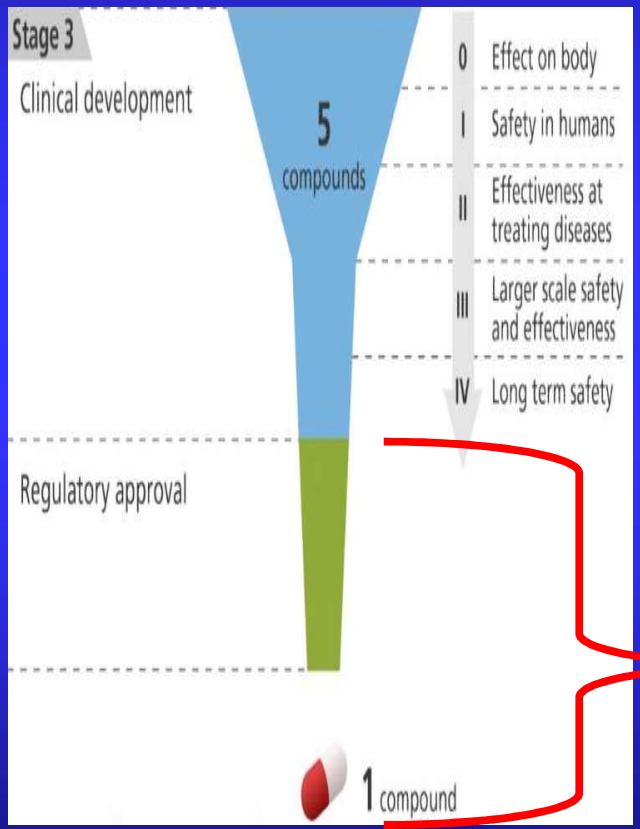
Success Rates by Phase of Development



Note: PII success rates are underestimated since many PII trials are "exploratory" trials

Figure adapted from appliedclinicaltrials.com

Development Stage and Implications for Angel Investing



- Limited opportunities for angel investing
- Most companies are public or partnered

Figure adapted from epharmacology.hubpages.com

Summary

- Drug development is the engine that delivers therapies for the future
- Offers an opportunity for investment coupled with advancing human health and well-being
- It is a long process with inherent risks but specific stages/phases of development and specific opportunities permit balancing investment risk and timeframe for meaningful return

BACK-UP

A Few Acronyms

- https://www.fda.gov/AboutFDA/FDAAcronymsAbbreviations/default.htm
- https://weekly.biotechprimer.com/100-drug-development-acronyms/

Resources

- https://www.fda.gov/ForPatients/Approvals/Drugs/default.htm
- https://drug-dev.com/fda-update-the-fdas-new-drug-approval-process-development-premarket-applications/
- https://www.fda.gov/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/default.htm
- http://www.fdareview.org/issues/the-drug-development-and-approval-process/