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Clinical Drug Development

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Clinical Drug Development

Discovery

Development

General Use

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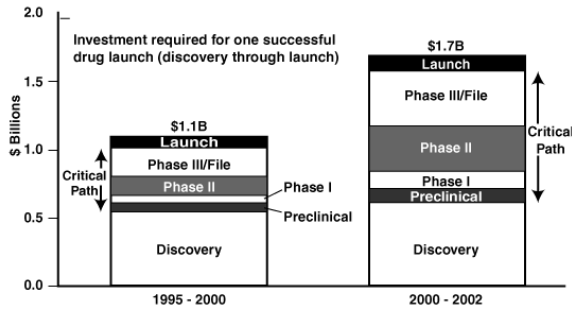
Long and Costly

- 10 years from Discovery to Market
- NZ\$3,000,000,000 per drug (at least)
- 9 out of 10 that are tested in humans do not reach market
- Patent Protection Very Important to Drug Developers

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Increased Cost in Phases II and III



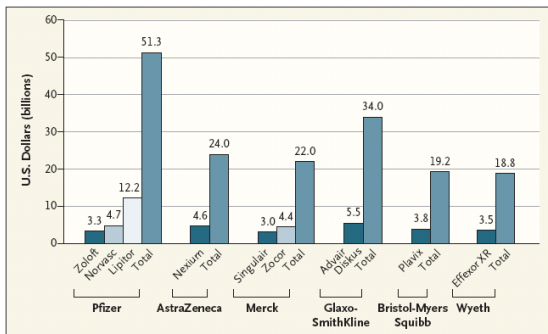
SOURCE: Windhover's In Vivo: The Business & Medicine Report, Bain drug economics model, 2003

<http://www.fda.gov/oc/initiatives/criticalpath/whitepaper.pdf> March 2004

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Blockbusters



Sales of Blockbuster Drugs in 2005 as a Portion of the Total Revenues of Pharmaceutical Companies.

Cutler DM. The Demise of the Blockbuster? N Engl J Med. 2007 March 29, 2007;356(13):1292-3.

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Zoloft=sertraline (selective serotonin reuptake inhibitor)
 Norvasc=amlodipine (calcium channel blocker)
 Lipitor=atorvastatin (HMG CoA reductase inhibitor)
 Nexium=esomeprazole (S-enantiomer of omeprazole; proton pump inhibitor)
 Singulair=montelukast (leukotriene antagonist)
 Zocor=simvastatin (HMG CoA reductase inhibitor)
 Advair=fluticasone (anti-inflammatory steroid) and salmeterol (beta2-agonist) (Diskus is blister pack)
 Plavix=clopidogrel (platelet aggregation inhibitor)
 Effexor=venlafaxine (selective noradrenaline reuptake inhibitor) (XR=extended release)

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World Wide Sales 2016

Rank	Product	Active Ingredient	Main Indications	Company	2016 Revenue (USD millions/year)
1	Humira	Adalimumab	Immunology (Organ Transplant, Arthritis etc.)	AbbVie Inc.	16,078
2	Harvoni	Ledipasvir/sosbuvir	Infectious Diseases (HIV, Hepatitis etc.)	Gilead Sciences	9,081
3	Enbrel	Etanercept	Immunology (Organ Transplant, Arthritis etc.)	AmgenPfizer	8,875
4	Remicade	Infliximab	Immunology (Organ Transplant, Arthritis etc.)	Johnson & JohnsonMerck & Co.	8,234
5	MabtheraRituxan	Rituximab	Oncology	Roche	7,227
6	Revlimid	Lenalidomide	Oncology	Celgene	6,974
7	Avastin	Bevacizumab	Oncology	Roche	6,715
8	Herceptin	Trastuzumab	Oncology	Roche	6,714
9	Lantus	Insulin glargine	Diabetes	Sanofi	6,057
10	PrevnarPrevenar 13	Pneumococcal 7-Valent Conjugate	Anti-bacterial	Pfizer Inc.	5,718

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https://en.wikipedia.org/wiki/List_of_largest_selling_pharmaceutical_products

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Phases of Drug Development

- Phase 0
 - » Predictions for Humans
- Phase 1
 - » Tolerability
- Phase 2
 - » Effectiveness
- Phase 3
 - » Safety
- Phase 4
 - » Post Marketing

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Biomarker/Surrogate/Outcome

- **Biomarker**
 - » Readily measurable marker of response
e.g. EEG response to anaesthetic induction agent
- **Surrogate**
 - » Biomarker used for Regulatory Approval
e.g. Reduction in HIV viral load
- **Outcome**
 - » How the patient functions/feels/survives
e.g. sex/pain/death

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Learn and Confirm

- Learn
 - » Exploration of the unknown
 - » Develop hypothesis/model
- Confirm
 - » Develop confidence
 - » Test hypothesis/model

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Phase 0 [Non-Clinical] Predictions for Humans

- Data from non-human animals
- Probable mechanism of action
- Likely effective concentrations
- Major routes of elimination
- Oral Absorption properties

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Phase 1 Tolerability

- Start with very small doses
- Slow increase
- Stop when adverse effects noted
- Learn
 - » Single and multiple dose PK
 - » Adverse effect PD?

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CFR - Code of Federal Regulations Title 21

FDA regulations

<https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcr/CFRSearch.cfm?fr=312.21> state:

(a) *Phase 1.* (1) Phase 1 includes the initial introduction of an investigational new drug into humans. Phase 1 studies are typically closely monitored and may be conducted in patients or normal volunteer subjects. These studies are designed to determine the metabolism and pharmacologic actions of the drug in humans, the side effects associated with increasing doses, and, if possible, to gain early evidence on effectiveness. During Phase 1, sufficient information about the drug's pharmacokinetics and pharmacological effects should be obtained to permit the design of well-controlled, scientifically valid, Phase 2 studies. The total number of subjects and patients included in Phase 1 studies varies with the drug, but is generally in the range of 20 to 80.

(2) Phase 1 studies also include studies of drug metabolism, structure-activity relationships, and mechanism of action in humans, as well as studies in which investigational drugs are used as research tools to explore biological phenomena or disease processes.

However, a more widely used objective is to determine the maximum tolerated dose ("side effects associated with increasing doses").

<p>Slide 12</p>	<h2 style="text-align: center; color: red;">Phase 2 Effectiveness</h2> <ul style="list-style-type: none"> • Phase 2A <ul style="list-style-type: none"> » “Proof of Concept” » YES/NO decision point • Phase 2B <ul style="list-style-type: none"> » Learn Dose response curve » Learn effective doses » Learn target concentration <p style="font-size: small; margin-top: 10px;">©NHG Holford, 2017. All rights reserved.</p>	<p>CFR - Code of Federal Regulations Title 21 FDA regulations https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?fr=312.21 state:</p> <p>(b) <i>Phase 2.</i> Phase 2 includes the controlled clinical studies conducted to evaluate the effectiveness of the drug for a particular indication or indications in patients with the disease or condition under study and to determine the common short-term side effects and risks associated with the drug. Phase 2 studies are typically well controlled, closely monitored, and conducted in a relatively small number of patients, usually involving no more than several hundred subjects.</p>
<p>Slide 13</p>	<h2 style="text-align: center; color: red;">Phase III Safety</h2> <ul style="list-style-type: none"> • “Safety” <ul style="list-style-type: none"> » Learn Adverse effects in target population • Confirm effective dose(s) <ul style="list-style-type: none"> » “Method Effectiveness”? • Learn PD of Surrogate/Outcome • Learn PK and PD covariates <ul style="list-style-type: none"> » Age, Sex, Other Drugs... <p style="font-size: small; margin-top: 10px;">©NHG Holford, 2017. All rights reserved.</p>	<p>FCFR - Code of Federal Regulations Title 21 DA Regulations https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?fr=312.21.</p> <p>(c) <i>Phase 3.</i> Phase 3 studies are expanded controlled and uncontrolled trials. They are performed after preliminary evidence suggesting effectiveness of the drug has been obtained, and are intended to gather the additional information about effectiveness and safety that is needed to evaluate the overall benefit-risk relationship of the drug and to provide an adequate basis for physician labeling. Phase 3 studies usually include from several hundred to several thousand subjects.</p> <p>The common belief by drug developers and clinical researchers is that the major objective is to determine “Efficacy of an experimental therapy”. This confuses “efficacy” (a pharmacological term equivalent to Emax) and “effectiveness” which determines if the treatment has a useful therapeutic benefit. The word “efficacy” is not used in FDA regulations.</p> <p>This information for patients misuses the word “efficacy” http://www.fda.gov/ForPatients/Approvals/Drugs/ucm405622.htm#Clinical_Research_Phase_Studies</p>

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Phase 4 Post-Marketing

- Confirm effective dose(s)
- Confirm common adverse events
- Learn uncommon adverse events
- Learn "Use Effectiveness"
- Learn Pharmacoeconomics

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Alternative Medicines

- Herbal/Traditional Medicines
 - » Digoxin, morphine, aspirin, quinine
 - » Gossipol, artemesin, taxol
- Patent Protection Unlikely
 - » Uneconomic for full Drug Development
- Health Foods/Nutraceuticals
 - » No Claims No Testing No Good?
 - » St John's Wort -> Cardiac transplant rejection
 - » Black Cohosh -> Liver failure requiring transplant
 - » Bracken fern -> Carcinogenic
 - » 'Natural treatment' contains sildenafil et al.

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"If its an alternative medicine then its not a medicine that is known to be safe and effective"

<http://thinking-is-dangerous.blogspot.com/2008/01/complimentary-and-alternative-medicine.html> (alternative medicine humbug)

<http://pharmacy.otago.ac.nz/rongoa/pages/rahurahu.htm/> (carcinogenic bracken)

<http://www.msnbc.msn.com/id/31088175/> (contaminants in 'natural' products)

<http://www.ncbi.nlm.nih.gov/pubmed/16006928> ('natural viagra')

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World Wide Sales 2010

Rank	Drug (brand name) use	2010 \$millions	1-year growth (%)
	All drugs (USA)	3995.2	1.16%
1	hydrocodone/acetaminophen (Vicodin) pain	131.2	2.34%
2	simvastatin (Zocor) high cholesterol	94.1	12.29%
3	lisinopril high blood pressure	87.4	5.56%
4	levothyroxine sodium (Synthroid) hypothyroid	70.5	6.82%
5	amlodipine besylate (Norvasc) high blood pressure.	57.2	11.50%
6	omeprazole (Prilosec) acid reflux	53.4	17.62%
7	azithromycin (Zithromax) antibiotic	52.6	-2.23%
8	amoxicillin antibiotic	52.3	-0.19%
9	metformin HCL (Glucophage) diabetes	48.3	9.03%
10	hydrochlorothiazide high blood pressure	47.8	-0.21%
11	alprazolam (Xanax) anxiety	46.3	5.47%
12	atorvastatin (Lipitor) high cholesterol	45.3	-12.38%
13	furosemide high blood pressure	43.4	-0.23%
14	metoprolol tartrate (Lopressor) high blood pressure	38.9	-5.35%
15	zolpidem tartrate (Ambien) insomnia	38.0	8.26%
16	atenolol high blood pressure	36.3	-7.63%
17	sertraline HCL (Zoloft) depression	35.7	4.39%
18	metoprolol succinate (Toprol) blood pressure	33.0	22.68%
19	citalopram (Celexa) depression	32.1	18.45%
20	warfarin sodium (Coumadin) blood thinner	32.0	1.27%
21	oxycodone/acetaminophen pain	31.9	5.63%
22	ibuprofen pain	31.1	2.64%
23	clopidogrel (Plavix) heart disease	29.5	-1.34%
24	gabapentin (Neurontin)	29.3	15.35%
25	montelukast (Singulair) allergies	28.7	0.35%

<http://www.forbes.com/sites/mathewherper/2011/04/19/americas-most-popular-drugs/>

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World Wide Sales 2011

Drug	Trade name	Indication	Company	Sales: (\$billion/year)
Atorvastatin	Lipitor	hypercholesterolemia	Pfizer	12.5
Clopidogrel	Plavix	atherosclerosis	Bristol-Myers Squibb Sanofi	9.1
Fluticasone/salmeterol	Seretide	asthma	GlaxoSmithKline	8.7
Esomeprazole	Nexium	acid reflux disease	AstraZeneca	8.3
Rosuvastatin	Crestor	hypercholesterolemia	AstraZeneca	7.4
Quetiapine	Seroquel	bipolar disorder schizophrenia	AstraZeneca	7.2
Adalimumab	Humira	rheumatoid arthritis	Abbott	6.6
Etanercept	Enbrel	rheumatoid arthritis	Amgen Pfizer	6.5
Infliximab	Remicade	Crohn's disease rheumatoid arthritis	Johnson & Johnson	6.4
Olanzapine	Zyprexa	schizophrenia	Eli Lilly	6.2

*Sales are for the 12 months preceding June 30, 2011.

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Found on
<http://en.wikipedia.org/wiki/Pharmaceutical>
24 Sep 2012

7. "Before the Storm". *Chemical & Engineering News* **89** (49): 12–18. 2011.

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World Wide Sales 2012

Leading product growth drivers 2012-2011 (\$m)			
Brand name	Indication	Generic name	2012.11 sales growth
Lantus	Diabetes	insulin glargine	1409
Humira	Autoimmune	adalimumab	1333
Januvia/janumet	Diabetes	sitagliptin	1058
Cymbalta	Depression	duloxetine	833
Eylea	Macular degeneration	afibercept	813
Rituxan	Non-Hodgkin's lymphoma	rituximab	770
Gilenya	Multiple sclerosis	fingolimod	701
Herceptin	HER2+ breast cancer	trastuzumab	697
Zytiga	Prostate cancer	abiraterone	660
Victoza	Diabetes	liraglutide	634
Enbrel	Autoimmune	etanercept	606
Nevlimid	Multiple myeloma	lenalidomide	559
Novo rapid	Diabetes	insulin aspart	522
Avastin	Cancer (various)	bevacizumab	518
Lyrica	Neuropathic pain	pregabalin	465
Xgeva	Bone metastases	denosumab	397
Levemir	Diabetes	insulin detemir	380
Afinitor	Cancer (various)	everolimus	354
Lucentis	Macular degeneration	ranibizumab	348
Soliris	Paroxysmal nocturnal hemoglobinuria	eculizumab	348 (f)

Source: Company reported information

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