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Drug Innovation and Longevity

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Introduction

- Drug innovation is central to longevity gains for many diseases
  - Includes infectious diseases (vaccines & antibiotics) and cardiovascular diseases (statins)
  - Clinical trials for many drugs have demonstrated longevity gains so causality is present
- Conversely, Alzheimer's shows what happens when drug innovation is absent
- USA is central to any analysis of drug innovation
  - 1/3 of world pharma sales and 1/2 of world pharma profits
- This presentation will analyse key drug innovation in the US pharma market to
  - Show its broad impact on longevity trends in recent decades
  - Develop some thoughts on likely longevity impact over the next 20-30 years
- This presentation does not seek to quantify in mathematical terms the correlation/causality between drug innovation and longevity

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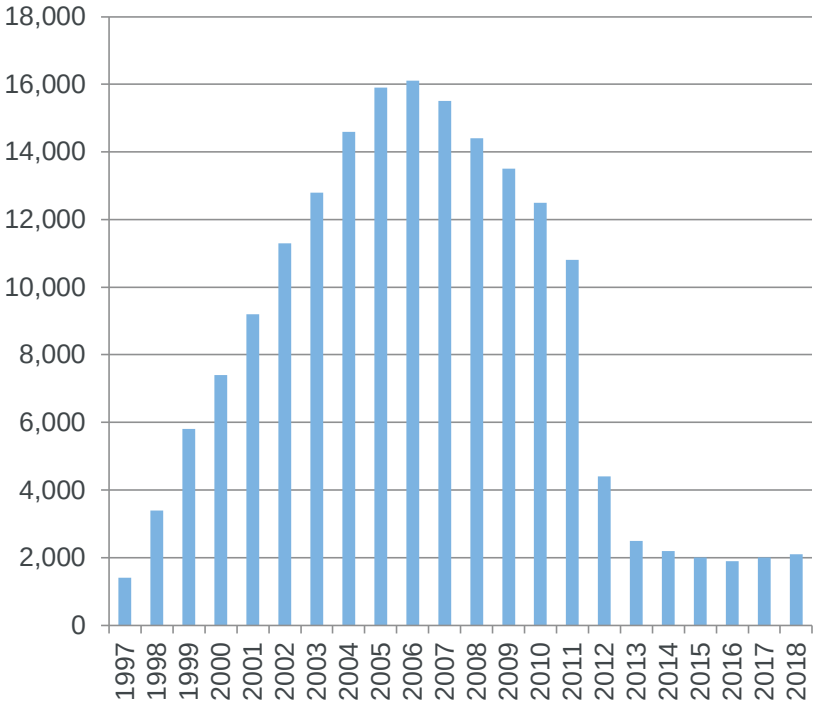
Lipitor Worldwide Sales History (Inflation Adjusted $m)



- Like life insurance, drugs are sold – not bought!
- Pharma industry uses year of peak sales (2006 here) to describe a drug's success
- Downwards drift from 2006-2011 reflects introduction of generics for older statins
- Lipitor went off patent in late 2011
- 2,000+ US salesforce used to sell to US GP's - drugs sold to specialists/ hospitals require much smaller sales forces (minimising new business strain)

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USA Major CV Drug Approvals (1987 – 2019)

Year Approved	US Brand Name(s)	Cardiovascular Drug Class(es)	Peak Sales? $bn (CPI adj.)	Cardiovascular Illness Indications
1987	Norvasc	Calcium Channel	6.1	High blood pressure & coronary heart disease
1987	Mevacor	Statin	2.2	High cholesterol
1989 (Bio.)	Epogen/Procrit	EPO	9.2	Anaemia (kidney failure, cancer treatment & surgery)
1991	Pravachol	Statin	3.9	High cholesterol
1991	Zocor	Statin	7.0	High cholesterol
1992	Toprol-XL	Beta-1	2.3	High blood pressure, heart failure & angina
1993	Lovenox	Heparin	3.6	Blood clots (inc. surgery procedures)
1995	Cozaar/Hyzaar	ARB	4.1	High blood pressure & stroke prevention
1996	Lipitor	Statin	16.1	High cholesterol
1997	Diovan/Exforge	ARB	8.1	High blood pressure, heart failure & heart attack
1997	Avapro	ARB	3.4	High blood pressure
1997	Plavix	Anti-Platelet	11.0	Blood clots (inc. post stent surgery procedures)
2001 (Bio.)	Aranesp	EPO	5.2	Anaemia (kidney failure & cancer treatment)
2002	Benicar	ARB	3.2	High blood pressure
2002	Zetia/Vytorin	Cholesterol Absorption	4.0	High cholesterol
2003	Crestor	Statin	6.1	High cholesterol
2011	Xarelto	Factor Xa	6.2 (Not Yet)	Heart beat, blood clots & hip/knee surgery
2012	Eliquis	Factor Xa	6.5 (Not Yet)	Heart beat, blood clots & hip/knee surgery
2015	Entresto	Neprilysin / ARB	1.4 (Not Yet)	Heart failure

Cardiovascular Drug Innovation

- 1987 to 2003 was a golden era for CV drug innovation
  - 16 major drugs launched from 8 different drug classes
  - EPO class included as kidney disease leads to significant knock-on CV disease
  - Plavix enabled safer and broader use of key parallel innovation of cardiac stent devices
- 2004 to now has been notably disappointing in CV drug innovation
  - Just 3 major drugs launched from 2 different drug classes
- Timing of end of golden era in 2003 and sharp fall-off in CV longevity gains beginning this decade can be very credibly linked by the following two factors
  - Several drug classes require multi-year use (e.g. statins) before benefits seen
  - Multi-year wait before peak sales are reached

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Why has CV drug innovation declined so much?

- A victim of its own success
  - In US market, non-‘biologic’ generics are often 90%+ cheaper than the original drug
  - Uneconomic to develop new CV drugs with only moderate benefits over these generics
  - Recent, successful ‘Factor Xa’ drug class offers substantive benefits over generic warfarin
  - Same issue has stifled innovation in antibiotics and depression-related illnesses
- Key innovation trend from 1990’s onwards in developing new ‘biologic’ drugs hasn’t really benefited CV space
  - Conversely, autoimmune, cancer, diabetes and ‘rare’ diseases have been big beneficiaries

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Why has CV drug innovation declined so much? (cont.)

- Strides in understanding and analysing genetics have not benefited CV space
  - CV diseases are heavily influenced by environmental factors
  - Conversely, cancer and ‘rare’ diseases have been big beneficiaries
- Strides in understanding and harnessing immune system have not benefited CV space
  - Immune system is a second order factor in CV diseases
  - Conversely, cancer and autoimmune diseases have been big beneficiaries
- More broadly, economic attractiveness of developing new CV drugs has waned in comparison to ‘rare’ diseases, cancer & autoimmune diseases
- ALL THESE ISSUES ARE STRUCTURAL AND LONG-TERM

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USA Major Cancer Drug Approvals (1987-2019)

Year Approved	US Brand Name(s)	Cancer Drug Class(es)	Peak Sales? $bn (CPI adj.)	Main Cancer Type Indications
1992	Taxol	Microtubules	2.3	Lung, Breast & Ovarian
1995	Arimidex	Estrogen Synthesis	2.3	Breast
1996	Taxotere	Microtubules	3.6	Breast, Lung, Prostrate, Stomach & Head/Neck
1997 (Bio.)	Rituxan	CD20	6.1	Blood
1998 (Bio.)	Herceptin	HER2	7.2	Breast & Stomach
2001	Gleevec	BCR-Abl	5.1	Blood & Stomach
2002 (Bio.)	Neulasta	G-CSF	5.0	Cancer Drug Treatments (Side Effects Only)
2002	Eloxatine	Platinum	2.7	Bowel
2003	Velcade	26S	2.8	Blood
2004	Alimta	Folate	3.0	Lung
2004 (Bio.)	Avastin	VEGF	7.1	Lung, Bowel, Brain, Breast, Kidney, Cervical & Ovarian
2005	Revlimid	T-Cell / NK-Cell	9.8 (Not Yet)	Blood
2006	Sprycel	BCR-Abl	2.1	Blood
2010 (Bio.)	Xgeva	RANKL	1.9 (Not Yet)	Bone (Symptoms Only)

USA Major Cancer Drug Approvals cont. (1987-2019)

Year Approved	US Brand Name(s)	Cancer Drug Class(es)	Peak Sales? $bn (CPI adj.)	Main Cancer Type Indications
2011	Zytiga	Androgen Synthesis	3.5	Prostrate
2011 (Bio.)	Yervoy	Checkpoint (CTLA-4)	1.5 (Not Yet)	Skin, Kidney & Bowel
2011	Jakafi	JAK1 / JAK2	2.4 (Not Yet)	Blood
2012 (Bio.)	Perjeta	HER2 / HER3	2.8 (Not Yet)	Breast
2012	Xtandi	Androgen Blocker	3.0 (Not Yet)	Prostrate
2013	Pomalyst	T-Cell / NK-Cell	2.1 (Not Yet)	Blood
2013	Imbruvica	BTK	4.5 (Not Yet)	Blood
2014 (Bio.)	Keytruda	Checkpoint (PD-1)	7.3 (Not Yet)	Lung, Skin, Bladder, Bowel, Cervical, Liver & Blood
2014 (Bio.)	Opdivo	Checkpoint (PD-1)	6.8 (Not Yet)	Lung, Skin, Kidney, Bladder, Bowel, Liver & Blood
2015	Ibrance	CDK 4&6	4.2 (Not Yet)	Breast
2015	Tagrisso	EGFR T790M	2.5 (Not Yet)	Lung
2015 (Bio.)	Darzalex	CD38	2.1 (Not Yet)	Blood
2016 (Bio.)	Tecentriq	Checkpoint (PD-L1)	1.3 (Not Yet)	Lung & Bladder
2017 (Bio.)	Imfinzi	Checkpoint (PD-L1)	1.2 (Not Yet)	Lung & Bladder

Why has strong cancer drug innovation only led to relatively moderate longevity gains (unlike CV)?

- Most cancer drugs only work on one or a few different cancer types
  - 22 out of 28 approved drugs on previous slides treated just one or two cancer types
  - Conversely, c. 30% of UK population is thought to have high blood pressure
  - Conversely, NICE guidelines suggest all men aged 70+ would benefit from taking statins
- 9 out of 28 drugs are for blood cancers (only 8% of UK cancer deaths)
  - Many blood cancers are immune system related and this is now better understood
  - Drugs don't have to wipe out the blood cancer (unlike with tumours) as reducing the volume of cancerous cells in the bloodstream to manageable levels is sufficient
  - Above point means the drugs MUST be taken permanently => long-term 'annuity' sales and very strong pricing power (tumour treatments are mainly short term)

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Why has strong cancer drug innovation only led to relatively moderate longevity gains (unlike CV)? cont.

- Many cancer drugs only provide modest incremental longevity gains
  - Take the example of NSCLC (85% of lung cancers) and advances in the US front-line (disease stages IIIb-IV) standard of care over the past two decades

Year Approved	Standard of Care Drug Combination	Median Survival
1998	Taxol & Platinol	c. 10 months
2006	Avastin (Bio.) & Taxol & Paraplatin	c. 12 months
2018	Keytruda (Bio.) & Taxol & Paraplatin	c. 16 months

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USA Major Lung Diseases* Drug Approvals (1987-2019)

Year Approved	US Brand Name(s)	Lung Diseases Drug Class(es)	Peak Sales? $bn (CPI adj.)	Illness Indications
1998	Singulair	Leukotriene	6.2	Asthma (Symptoms) & Allergies
2000	Advair	ICS / LABA	9.3	COPD (Symptoms) & Asthma (Symptoms)
2003	Xolair (Bio.)	Immunoglobin E	3.0 (Not Yet)	Severe Asthma (Symptoms) & Urtarcia
2004	Spiriva	LAMA	4.2	COPD (Symptoms) & Asthma (Symptoms)
2006	Symbicort	ICS / LABA	4.1	COPD (Symptoms) & Asthma (Symptoms)
2010	Prevnar 13	Preventative Vaccine	6.7	Pneumonia
2012	Kalydeco/Orkambi/Symdeko	F508del/G551D	3.1 (Not Yet)	Cystic Fibrosis
2017	Trelegy	ICS / LABA / LAMA	0.5 (Not Yet)	COPD (Symptoms)

* Excluding lung cancer diseases

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Lung Diseases Major Drug Approval Comments

- Only Prevnar 13 and the cystic fibrosis drugs (probably) improve longevity
  - Longevity gains here have been largely due to falling smoking rates (especially COPD)
- Like CV, biologic drugs have had only a moderate impact on this disease area
- The strong sales success of the cystic fibrosis drugs highlights the commercial attractiveness of ‘rare’ diseases to drug developers
- It is noteworthy no influenza vaccine makes this list
  - New influenza vaccines launched over this time have offered only minor efficacy gains
- The future for disease-modifying drug innovation here appears mediocre
  - In particular, a ‘universal’ influenza vaccine looks 10+ years away at best
  - The best hopes are potential vaccines for RSV (‘flu-like virus) and COPD

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USA Major Alzheimer's Drug Approvals (1987-2019)

Year Approved	US Brand Name(s)	Alzheimer's Drug Class(es)	Peak Sales? $bn (CPI adj.)	Alzheimer's Stage
1996	Aricept	Acetylcholinesterase	4.6	Mild, Moderate & Severe (Symptoms Only)
2003	Namenda	NMDA	2.2	Moderate & Severe (Symptoms Only)

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Alzheimer's: Pivotal Clinical Trial Results for Disease-Modifying Candidate Drugs (2010-2019)

Alzheimer's Hypothesis	Drug Name	Year Started	Year Reported	Trial(s) Failure Reason	Alzheimer's Disease Stage(s)
Unclear	Dimebon	2008	2010	Efficacy	Mild, Moderate & Severe
Amyloid	Semagacestat	2008	2011	Safety (Stopped Early)	Mild & Moderate
Amyloid	Bapineuzumab (Bio.)	2007	2012	Efficacy	Mild & Moderate
Amyloid	Solanezumab (Bio.)	2009	2012	Efficacy	Mild & Moderate
Tau	LMTX	2013	2016	Efficacy	Mild & Moderate
Amyloid	Solanezumab (Bio.)	2013	2017	Efficacy	Mild
Amyloid	Verubecestat	2013	2018	Efficacy (Stopped Early)	Prodromal*, Mild & Moderate
Amyloid & Inflammation	Azeliragon	2015	2018	Efficacy (Stopped Early)	Mild
Amyloid & Inflammation	Albutein 20% (Bio.)	2012	2018	Efficacy	Mild & Moderate
Amyloid	Atabecestat	2015	2018	Safety (Stopped Early)	Prodromal*
Amyloid	Lanabecestat	2014	2018	Efficacy (Stopped Early)	Prodromal* & Mild
Amyloid	Crenezumab (Bio.)	2016	2019	Efficacy (Stopped Early)	Prodromal* & Mild
Amyloid	Aducanumab (Bio.)	2015	2019	Efficacy (Stopped Early)	Prodromal* & Mild

* Prodromal = some cognitive issues but not yet serious enough to diagnose Alzheimer's

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Alzheimer's: Pivotal Clinical Trials Underway for Disease-Modifying Candidate Drugs (as of May 2019)

Alzheimer's Hypothesis	Drug Name	Year Started	Year Likely to Report	Drug Developer(s)*	Alzheimer's Disease Stage(s)
Inflammation	Masitinib	2012	2019	AB Sciences	Mild & Moderate
Glutamate	Troriluzole	2018	2020	Biohaven	Mild & Moderate
Neuroprotective	Anavex 2-73	2018	2021	Anavex	Prodromal & Mild
Amyloid	Elenbecestat	2016	2021	Biogen & Eisai	Prodromal & Mild
Tau	LMTX	2018	2021	TauRx	Prodromal & Mild
Amyloid & Inflammation	ALZT-OP1	2015	2021	AZTherapies	Prodromal & Mild
Periodontitis	COR388	2019	2022	Cortexyme	Mild & Moderate
Amyloid	AGB101	2019	2022	AgeneBio	Prodromal
Amyloid	Gantenerumab (Bio.)	2017	2022	Roche	Prodromal & Mild
Amyloid	BAN2401 (Bio.)	2019	2024	Eisai & Biogen	Prodromal & Mild
Amyloid	CNP520 & CAD106 (Bio.)	2015	2024	Novartis	Prodromal
Amyloid	CNP520	2017	2024	Novartis & Amgen	Prodromal

* Only included trials with commercial developers - excluded govt. funded trials

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Observations on completed & active Alzheimer's trials

- The 'amyloid' hypothesis's many failures have severely eroded its credibility
- A fairly clear trend towards only testing in Alzheimer's earlier stages
- Personal thoughts on the active trials
  - The probability of success for any of the 7 'amyloid' trials is minimal
  - I would not regard Masitinib, Trorizulole or Anavex 2-73 as being credible drugs
  - The 'Tau' hypothesis is now probably the lead explanation for Alzheimer's - so the LMTX trial could be seen as credible (but its failure in two prior pivotal trials counts against it)
  - The novel 'Periodontitis' hypothesis is intriguing and the COR388 trial is worth watching
- I personally would regard the chances of all these active trials delivering at least one clear-cut efficacy success with acceptable safety as < 1/3

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A future successful Alzheimer's drug likely to be surprisingly slow to impact on longevity

Simplified scenario : In mid 2027, a commercial developer's drug cures Alzheimer's (prodromal stage only) in a pivotal trial with acceptable safety

Timeline	Scenario Milestone	Comment
2027 (Mid)	Trial results announced	As per above simplified scenario
2028 (Start)	Submit drug for approval	US and EU regulators require several million of pages of documentation for approval
2029 (Start)	Regulators approve	Approval processes take c.1 year to fully complete
2029 (Mid)	Drug available through NHS	NHS/NICE will haggle over price (developer could want £30k-£50k p.a. per patient!)
2034 (Mid)	Drug reaches UK peak sales	An assumed 5 years is relatively quick for a new drug to reach peak sales
2037	First impact on UK mortality	Assumes (very simplistically) prodromal Alzheimer's has a life expectancy of 8 years
2042	Peak impact on UK mortality	=> Takes 15 years from drug success announcement to peak UK mortality impact

ALSO … current diagnosis methods for prodromal Alzheimer's are fairly unreliable, expensive, time-consuming and often invasive. The scenario implicitly assumes there's a prior or parallel breakthrough innovation in diagnosing Alzheimer's.
ALSO … current expectations are a new drug will slow down Alzheimer's progression – not outright cure it. Therefore, the longevity gain may only be a few years per patient.

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Thoughts on Future Drug Innovation and Longevity Impact Over Next 20-30 Years

- Heart drug innovation likely to remain muted – perhaps one new drug class every 5-10 years
- Current industry focus on ‘rare’ diseases, cancer and autoimmune likely to further intensify
- There are risks the very strong investment in cancer drug research will show declining productivity
  - Current focus on immunotherapies may be excessive - e.g. 6 approved PD-(L)1 drugs to date & several potential new immunotherapy drug classes have recently disappointed in trials
  - No new major cancer drug classes approved since 2015 could represent the start of a trend
- Alzheimer’s likely to remain unproductive & any advance would take over a decade to affect longevity
- Lung disease also likely to be mediocre for disease-modifying drug innovation
- OVERALL, THE RISKS ARE TOWARDS A FURTHER, MODERATE WEAKENING OF DRUG INNOVATION’S CONTRIBUTION TO FUTURE LONGEVITY GAINS

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Questions

Comments

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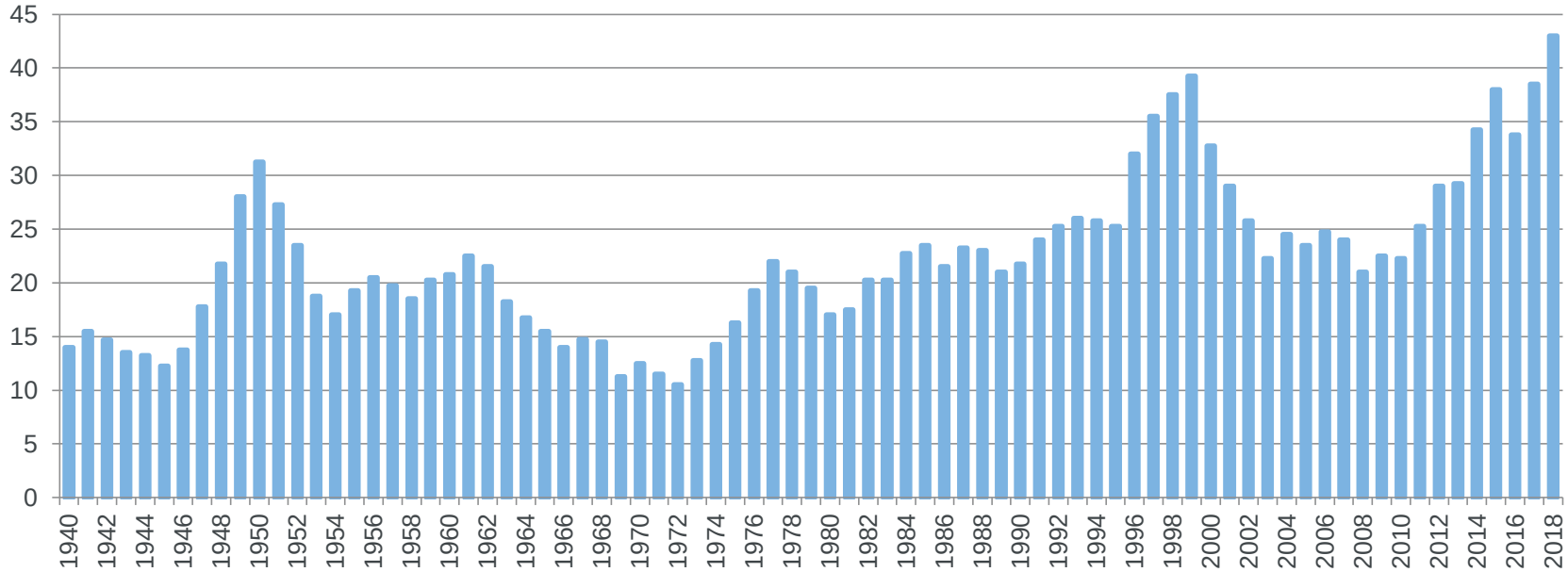
Appendix A – History of USA New Drug Approvals

4 June 2019

USA ‘New’* Drug Approval History(4 year rolling average)



* Vertical axis refers to averaged number of ‘new’ drugs approved by US regulators

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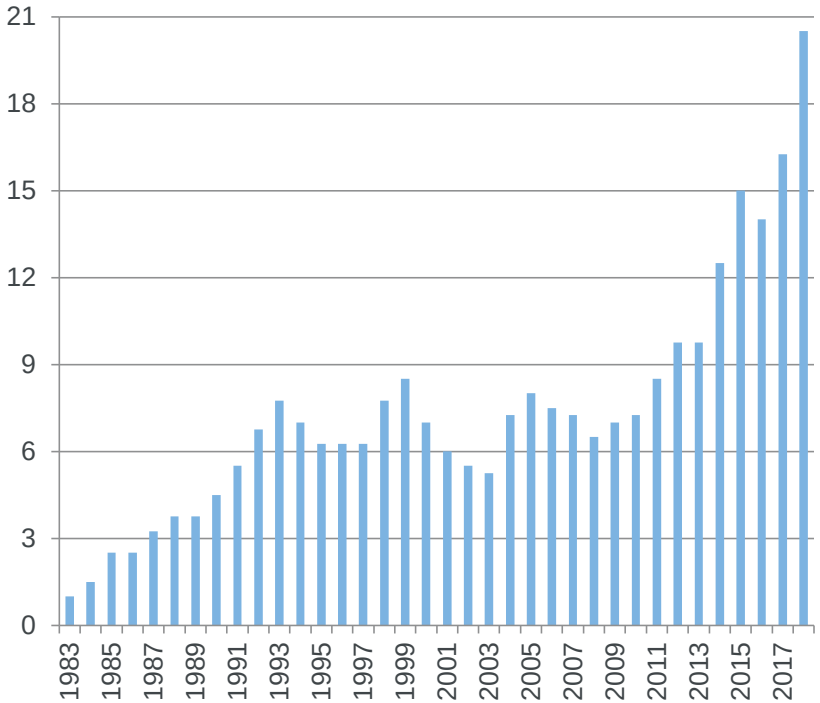
1983 Orphan Act Drug Approvals(4 year rolling average)



- ‘Rare’ (or orphan) diseases suffer from market failure – i.e. science may exist to develop drugs but heavy fixed R&D costs not covered by small market
- US 1983 Orphan Act deregulated their drug development – so cutting R&D costs
- From mid 1990’s, US insurers allowed ‘rare’ disease drugs increasingly higher pricing
- In current decade, feedback loop has set in – noticeably skewing industry investment
- By definition, trivial population longevity gains from ‘rare’ diseases

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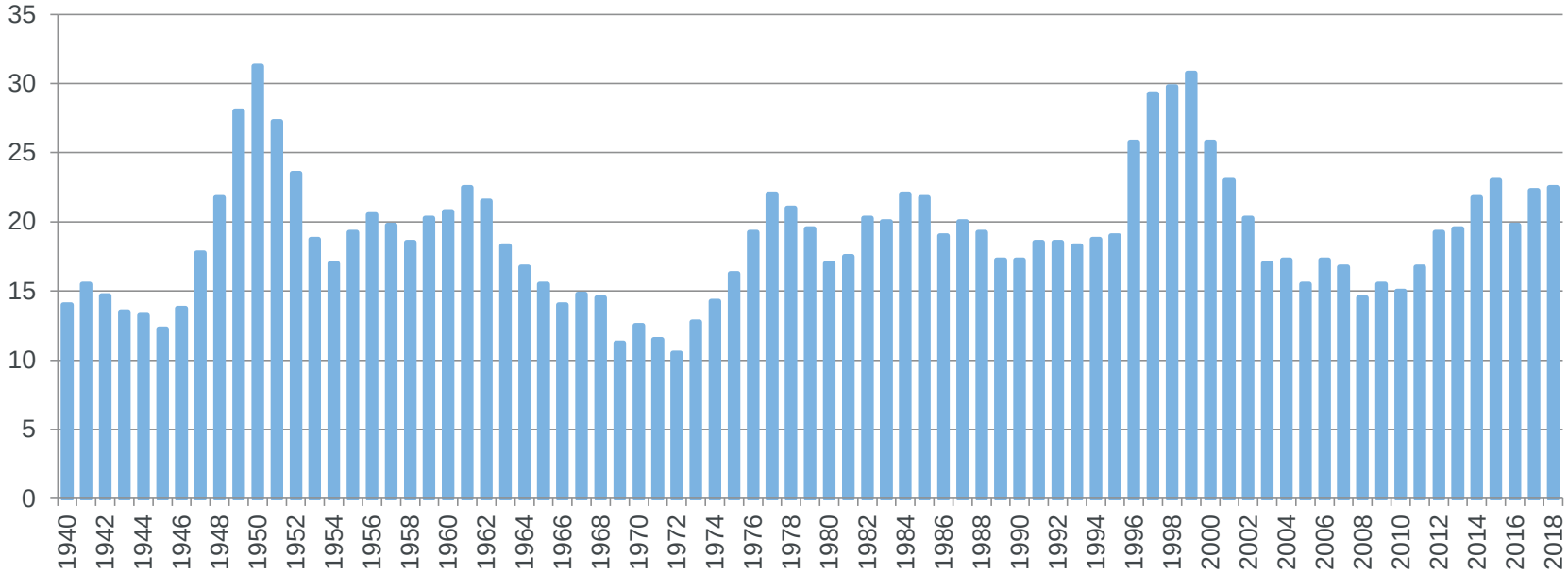
USA ‘New’ Drug Approvals (excluding 1983 Orphan Act)



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USA ‘New’ Drug Approvals (ex. Orphan Act) comments

- The low levels of new drug approvals from the 1960’s to the late 1970’s coincides with a period of relatively mediocre longevity gains at older ages
- President Nixon’s National Cancer Act 1971 was key in structuring and substantially increasing long-term federal funding for medical science research
- The ‘surge’ in approvals from the mid 1990’s to the early 2000’s is key
  - A surge in cancer, diabetes and autoimmune approvals began in the mid 1990’s and continues right up to the current era – influenced by advances in biologic drugs
  - It coincides with the peak period for CV approvals and both ended at the same time
  - It also coincides with important symptom-relieving approvals in COPD and Alzheimer’s
- The more recent moderate approval rebound is influenced by 12 new Hepatitis C drug approvals from 2014 to 2017

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Appendix B – Type 2 Diabetes

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USA Major Type 2 Diabetes Drug Approvals (1987-2019)

Year Approved	US Brand Name(s)	Diabetes Drug Class(es)	Peak Sales? $bn (CPI adj.)	Treatment Line*
1996	HumaLog/HumaLog Mix (Bio.)	Fast-Acting Insulin	3.0	4th Line
1999	Actos	Glitazone	5.4	2nd Line
2000	Lantus (Bio.)	Long-Acting Insulin	7.5	3rd Line
2000	NovoLog/NovoLog Mix (Bio.)	Fast-Acting Insulin	5.0	4th Line
2001	Avandia	Glitazone	3.8	2nd Line
2005	Levemir (Bio.)	Long-Acting Insulin	2.9	3rd Line
2006	Januvia/Janumet	DPP-4	6.5	2nd Line
2010	Victoza (Bio.)	GLP-1	3.9	2nd Line / 3rd Line
2014	Trulicity (Bio.)	GLP-1	3.2 (Not Yet)	2nd Line / 3rd Line
2014	Jardiance/Glyxambi/Synjardy	SGLT2	1.7 (Not Yet)	2nd Line
2015	Tresiba/Ryzodeg/Xultophy (Bio.)	Long-Acting Insulin	1.7 (Not Yet)	3rd Line
2017	Ozempic (Bio.)	GLP-1	0.9 (Not Yet)	2nd Line / 3rd Line

*As the disease gradually worsens, higher line treatments are required to minimise harm to the patient. Generic metformin is the established 1st Line treatment.

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Type 2 Diabetes Major Drug Approval Comments

- Diabetes does not directly lead to significant mortality – but is a significant cause of CV disease, cancer, kidney disease, dementia & blindness
  - c.10% of NHS spending goes on managing diabetes
- In contrast to CV, biologics have had a major impact on this disease area
- In contrast to CV, there has been consistent innovation since the mid 1990's
  - the launch of 3rd/4th line drugs in 1996-2000 could be seen as the most important period
- Concern has been expressed about rising diabetes levels in many countries
  - The scale of diabetes drug innovation has, to date, mitigated some (or maybe even the majority) of this negative longevity driver

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Appendix C – Autoimmune Disease Drugs

4 June 2019

USA Major Autoimmune* Drug Approvals (1987-2019)

Year Approved	US Brand Name(s)	Autoimmune Drug Class(es)	Peak Sales? $bn (CPI adj.)	Main Autoimmune Indications
1993	Betaseron (Bio.)	Interferon	2.0	Multiple Sclerosis
1996	Avonex / Plegridy (Bio.)	Interferon	3.3	Multiple Sclerosis
1997	Copaxone (Bio.)	Th2	4.5	Multiple Sclerosis
1998	Remicade (Bio.)	TNF	8.7	Arthritis, Ulcerative Colitis, Crohn's
1998	Enbrel (Bio.)	TNF	9.4	Arthritis, Psoriasis
2002	Rebif (Bio.)	Interferon	2.5	Multiple Sclerosis
2002	Humira (Bio.)	TNF	20.2 (Not Yet)	Arthritis, Psoriasis, Ulcerative Colitis, Crohn's
2004	Tysabri (Bio.)	Alpha-4 Integrin	2.1	Multiple Sclerosis, Crohn's
2005	Orencia (Bio.)	CD80 & CD86	2.7 (Not Yet)	Arthritis
2009	Simponi (Bio.)	TNF	2.9 (Not Yet	Arthritis, Ulcerative Colitis
2009	Stelara (Bio.)	IL-12 & IL-23	5.2 (Not Yet)	Psoriasis, Arthritis, Crohn's
2010	Actemra (Bio.)	IL-6	2.1 (Not Yet)	Arthritis, Arteritis

* Excluding Type 1 Diabetes & Asthma (Inhaler Drugs)

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USA Major Autoimmune Drug Approvals cont. (1987-2019)

Year Approved	US Brand Name(s)	Autoimmune Drug Class(es)	Peak Sales? $bn (CPI adj.)	Main Autoimmune Indications
2010	Gilenya	S1P1	3.4 (Not Yet)	Multiple Sclerosis
2011	Soliris (Bio.)	C5	3.6 (Not Yet)	PNH, aHUS, Myasthenia Gravis
2012	Aubagio	DHODH	2.0 (Not Yet)	Multiple Sclerosis
2012	Xeljanz	JAK	1.7 (Not Yet)	Arthritis, Ulcerative Colitis
2013	Tecfidera	NRF2	4.3	Multiple Sclerosis, Psoriasis
2014	Entyvio (Bio.)	Alpha-4-Beta-7	2.5 (Not Yet)	Ulcerative Colitis, Crohn's
2015	Cosentyx (Bio.)	IL-17A	2.9 (Not Yet)	Arthritis, Psoriasis
2016	Taltz (Bio.)	IL-17A	1.0 (Not Yet)	Psoriasis
2017	Dupixent (Bio.)	IL-4	1.5 (Not Yet)	Eczema, Asthma
2017	Tremfya (Bio.)	IL-23	0.9 (Not Yet)	Psoriasis
2017	Ocrevus (Bio.)	CD20	2.3 (Not Yet)	Multiple Sclerosis (inc. Primary Progressive)

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Autoimmune Major Drug Approval Comments

- In sharp contrast to CV, biologics have been pivotal in this disease area
- In contrast to CV, there has been consistent innovation since the mid 1990's
- These drugs often provide strong quality of life benefits – allowing high pricing
- They are also mainly prescribed by specialist doctors – allowing a much smaller sales force than (say) CV drugs prescribed mainly by GP's
- Soliris only treats 3 'rare' diseases but costs c.$500k per year per US patient
- 2 drug classes (JAK and CD20) are also important in treating blood cancers
- 4 drugs came from the same TNF drug class – including Humira, the world's largest ever selling drug

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Appendix D – Why has Alzheimer's drug development been so disappointing?

4 June 2019

To address this question, multiple attributes of Alzheimer's are compared to AIDS (where drug development has been highly successful)

Attribute 1	***Age Of Patients At Diagnosis***
Alzheimer's	c.95% of Alzheimer's patients are diagnosed over age 65. At those ages, frailty and multiple co-morbidities are common. Both these issues mean potential Alzheimer's drugs should have moderate side effect profiles or else elderly patients will struggle to take them over extended periods of time.
AIDS	The clear majority of diagnosed AIDS patients are young to middle aged and typically have few serious co-morbidities. Accordingly, potential AIDS drugs can look to trade off greater effectiveness (typically by increasing the drug dose) against some additional side effects caused by the higher dose.
Attribute 2	***Understanding Cause of Disease***
Alzheimer's	To this day, the underlying root causes of Alzheimer's have not been identified. Suspicion to date has focussed on amyloid – which form hall-mark 'plaques' in patients' brains. This 'amyloid' hypothesis has formed the basis of most potential drugs tested over the past decade. Serial trial failures have now convinced most drug developers the amyloid hypothesis is defective. However, there is no clear-cut leading alternative hypothesis, with the 'tau' hypothesis probably now attracting the most attention.
AIDS	AIDS was first observed in the US in 1981. HIV was identified as the underlying root cause in 1984. The first AIDS drug was approved in 1987. The first highly effective AIDS drug combination was approved in 1995. AIDS is like a case study in where the relatively quick identification of the underlying cause of the disease laid the foundation for an impressive cycle of successful drug innovation.

Attribute 3	***Animal Disease Models***
Alzheimer's	Testing potential drugs on suitable animal disease models can give huge insights into a drug's potential safety and efficacy (or otherwise) before the risk and expense of testing it in humans begins. For instance, pigs are a highly effective animal model for drug research into diabetes. However, human beings are to date the only animals documented to suffer from Alzheimer's. Therefore, there is no effective animal model for Alzheimer's. Genetically modified mice have been developed that show some Alzheimer's like symptoms – but this animal model has proved highly inaccurate to date in identifying promising drugs to test in humans.
AIDS	HIV originated from the SIV virus that affects primates. Therefore, SIV infected primates (particularly macaques) are very effective models for AIDS drug research. Genetically modified mice with humanised immune systems have also been shown to be effective animal models.
Attribute 4	***Tissue Models***
Alzheimer's	For any disease, having an extract of human tissue affected by the disease in question can give huge insights into how the disease starts, how it progresses and whether any drugs in development can affect it. Clearly, using an extracted live human brain as a tissue model for Alzheimer's is both technically unfeasible and ethically unacceptable. Researchers do use individual human brain cells in their work but, to date, these cells have not shown themselves to be predictive in highlighting potentially promising drugs for further development.
AIDS	It is very straightforward to extract human blood and tissue samples infected with the HIV virus and see whether potential drug candidates are effective at disabling or killing the virus.

Attribute 5	***Disease Diagnosis***
Alzheimer's	There is no reliable laboratory test to diagnose Alzheimer's. Traditionally, multiple cognitive-related questionnaires and the opinion of a trained clinician were required for diagnosis. Such an approach is time-consuming and open to significant rates of misdiagnosis. Recently, a brain PET scan combined with an injected radioactive tracer can show whether amyloid plaques (a hallmark of Alzheimer's) are present. However, this test costs $3,000-$4,000 (in the USA), is invasive and isn't definitive (as you can have amyloid plaques without any cognitive problems). In addition, it is only when people start having cognitive problems (for instance, memory issues) does it become practical to commence the diagnosis process. However, it has recently become clear that such so-called 'early stage' Alzheimer's patients are in fact likely to have had the disease for about two decades. That means such newly diagnosed patients are actually at a relatively advanced stage of the underlying disease. It is a reasonable rule of thumb that diagnosing a disease at an advanced stage of its progression makes it more difficult for a medical intervention to be meaningfully successful.
AIDS	The first AIDS test was approved by the FDA in 1985. Subsequent generations of approved tests were progressively more accurate, faster and cheaper. The ubiquity and cost-effectiveness of modern AIDS testing means many patients in practice are diagnosed at an early stage without yet showing any signs of the disease. Even if diagnosis occurs when symptoms are evident, AIDS drugs can usually restore normal immune system functioning without lasting harm to the patient.

Attribute 6	***Length of Clinical Trials***
Alzheimer's	Due to the gradual progression of the disease and the indirect and inexact methods of measuring such progression (through cognitive-related questionnaires and tests), clinical trials for potentially disease-modifying Alzheimer's drugs often require the trial patients to be assessed over an 18 month or even longer duration. For reference, two pivotal trials under way at the time of writing require patients to be assessed over 5 years. This means it takes several years to run Alzheimer's trials and this significantly slows down the rate of progress in understanding the disease and finding a disease-modifying drug. In addition, the lengthy duration of Alzheimer's trials encourages drug developers to skip past standard mid-stage clinical trials (that look for signals of efficacy) and jump straight to expensive, high-profile pivotal trials. This issue has likely contributed to the alarming run of high-profile failures in pivotal Alzheimer's trials over the past decade.
AIDS	AIDS clinical trials were allowed by US regulators from the early 1990's to use surrogate markers to assess whether potential drugs were working – i.e. they did not have to show patients were, for instance, living longer but could instead just show whether key biological markers were changing in a manner consistent with the disease going into a remission-like state. These biological markers can show decisive changes in as little as one week of taking a potential drug and such short trial durations are frequently used for early stage human trials – so allowing quick clinical trial progress. US regulators currently require the final, pivotal AIDS clinical trials to be run for 48 weeks duration to ensure the potential drug works for sustained periods of time and to demonstrate its safety profile is acceptable.

Attribute 6	***Cost of Clinical Trials***
Alzheimer's	As already discussed, pivotal Alzheimer's trials often need to monitor trial participants for a lengthy 18 months or longer. In addition, such pivotal trials typically enrol 1,250-2,000 participants to be able to statistically demonstrate - to the required regulatory standard - the potential drug is working. On top of this, the recruitment process for Alzheimer's trials is often quite slow by general clinical trial standards in terms of attracting appropriate patients (e.g. ones with few potentially confounding co-morbidities) and the moderate number of specialist Alzheimer's clinical trial sites (e.g. there isn't - at the time of writing - a single Alzheimer's trial recruiting for patients in the Republic of Ireland). One 2014 academic paper estimated the nominal cash cost of developing a disease-modifying Alzheimer's drug to be c.$400m – but the full economic cost (allowing for the cost of capital and plausible trial failure rates) to be $5.7bn. The lengthy nature of Alzheimer's drug development has another cost dimension – patents. The time taken from first synthesising a novel Alzheimer's drug compound in a laboratory until regulatory approval is of the order of 13 years. Such a long development time heavily eats into the fixed patent life the drug developer has to generate an economic return before generic competitors enter the market.
AIDS	In contrast, AIDS trials have a shorter patient monitoring period, are smaller in size (typically 500-1,000 patients for a pivotal trial), recruitment is much quicker and there is a much wider selection of suitable clinical trial sites to choose from. In addition, much higher clinical trial success rates significantly lower the full economic costs of developing an AIDS drug. Quicker development timelines also means drug developers have longer remaining patent lives to generate an economic return.

Attribute 7	*Accessing the Disease*
Alzheimer's	It is important that drugs – taken either orally or by injection – can reach their way in high concentrations to the site of the disease in question. Alzheimer's presents a major problem in this regard. The brain is surrounded by a blood-brain barrier (BBB) whose function is to heavily filter the blood and fluids that access the brain. In practice, this BBB prevents nearly all potential drug designs from accessing the brain. The only other organ to have a similar BBB is the eye – this explains why eye pain-killing or anti-inflammatory drugs must be taken by eye drops rather than the typical oral or injection methods for such medicines. This issue significantly complicates developing viable drug designs that will (a) successfully act on the brain component the Alzheimer's research scientists are targeting and (b) also cross the BBB at a sufficiently high concentration to be medically viable.
AIDS	AIDS is both very straightforward and virtually impossible to access. When the HIV virus is actively operating in the bloodstream (where it seeks out immune cells to replicate itself and so ends up heavily degrading the immune system over time) it is ideally located for oral drugs - since ingested drugs are released directly into the bloodstream through the stomach lining. However, the HIV virus can also exist in a resting, or latent, state inside immune cells for many years. Currently available drug designs cannot access this latent form of the virus located inside immune cells. This is why there has been such success in developing drugs that force AIDS back into a near-remission like state but yet there has been, to date, complete failure to fully eliminate HIV from the body and so produce a permanent, long-term cure.