How Pfizer Made History

Pfizer today
“Breakthroughs that change patients’ lives”
- #1 pharmaceutical company in the world by revenue in 2023
- Pfizer has made over 40 acquisitions as of 2023

- $44 Billion
- 36
- >185
- 83

Revenue in 2023 (as of October 31, 2023) Manufacturing sites worldwide Countries where we sell our products Projects in our pipeline (as of October 31, 2023)

~83,000
7

Employees globally Products with sales greater than $1B in 2023 (as of October 31, 2023)

CEO: Albert Bourla

Main R&D sites:
Andover, MA
Boulder, CO
Cambridge, MA
Groton, CT
La Jolla, CA
Pearl River, NY
Sandwich, UK
St. Louis, MO

Therapeutic areas: rare disease, internal medicine, inflammation & immunology, vaccines, oncology, anti-infectives

Pfizer products you may recognize:
Medicines & vaccines

Consumer healthcare products

Topics Covered:
1. Pfizer over the years — key events & acquisitions
2. A glimpse into Pfizer’s portfolio — discovery & syntheses of notable drugs

https://www.pfizer.com/
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Christine T. Chong

1. Early history ("manufacturing chemists")

1849: Cousins Charles Pfizer (chemist) and Charles F. Erhart (confectionist) founded Charles Pfizer & Co. in Brooklyn, NY.

Their first product was a preparation of santonin (antiparasitic for intestinal worms), a common ailment in the 19th century.

The bitter compound (typically ingested 3 times/day for several days) was dispersed in a toffee-flavored sugar-cream cone, which became an immediate success!

1919: Pfizer chemist James Currie and assistant Jasper Kane pioneered the mass production of citric acid from sugar through mold fermentation

This frees Pfizer from dependence on the citrus market (supply shortage due to WWI).

By 1929, 5.9 million pounds of citric acid was produced without using any lemon juice, lime juice, or citrate derivative.

By 1939, Pfizer succeeded so well that a pound of citric acid, which had cost $1.25 in 1919, tumbled to 20¢.

Pfizer was recognized as a leader in fermentation technology.

1941: Pfizer’s expertise in deep-tank fermentation was applied to the mass production of penicillin to treat Allied soldiers fighting in WWII.

Pfizer becomes the world’s largest producer of penicillin.

Pfizer earns the Army-Navy “E” Award on April 17, 1943.

The first total synthesis was not accomplished until 1957 by Sheehan at MIT.

2. A shift towards pharmaceutical research & global expansion

1950: Oxytetracycline (Terramycin®), the result of Pfizer’s first discovery program, was launched

In search for new antibiotics, shortly after the Lederle discovery of aureomycin, Pfizer isolates oxytetracycline from a soil sample collected on the grounds of a factory owned by Pfizer!

A collaboration with R. B. Woodward enabled the structural determination of oxytetracycline. (JACS 1953, 75, 5455; JACS 1963, 85, 851; JACS 1965, 87, 134)

For more info, see The Tetracyclines (Lin, 2005)

1951: Major international expansion

Pfizer establishes operations in Belgium, Brazil, Canada, Cuba, England, Mexico, Panama, and Puerto Rico.

1967: Doxycycline (Vibramycin®)

Pfizer’s first once-a day broad-spectrum antibiotic was introduced and becomes a top seller.

1972: Pfizer crosses the billion-dollar sales threshold

Recognizing that the ability to discover and develop innovative medicines was the key to growth, Chairman Ed Pratt raises the company’s R&D budget from 5% to 15-20% of sales.

1976-1989: Launch of prazosin HCl (Minipress®), glipizide (Glucotrol®), ampicillin/sulbactam (Unasyn®), nifedipine (Procardia® XL)

1980: Piroxicam (Feldene®), Pfizer’s first product to reach $1 billion USD in sales (one of the largest-selling anti-inflammatory agents in the world)

https://www.pfizer.com/; “The Founder of Pfizer was an Immigrant, Too” (Forbes, 2020)
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3. Major acquisitions & further discoveries

1990-1992: Rollout of major medicines, including antifungal
Diflucan® & antidepressant Zoloft®

1996: Pfizer entered into a co-marketing agreement with Warner-Lambert to sell
atorvastatin (Lipitor®), receiving half the profits of the drug.

1998: Sildenafil (Viagra®) — breakthrough treatment for erectile dysfunction

1999: Pfizer’s 150th anniversary

Recognized for its success in drug discovery & development, Forbes® magazine
names Pfizer “Company of the Year”.

2000: Pfizer/Warner-Lambert merger ($90 billion)

With the acquisition of Warner-Lambert, the combined group had 8 products with
greater than $1 billion in global sales. The merger created the 2nd largest
pharmaceutical company in the world, with research staff of 12,000. Pfizer gained
leadership position in the areas of cardiovascular, lipid control drugs, CNS, and
infectious diseases. A host of consumer brands (e.g. Halls cough drops, antihistamine
Benadryl, decongestant Sudafed, Listerine mouthwash), as well as the blockbuster
drug Lipitor®, were added to the Pfizer portfolio.

2003: Pfizer/Pharmacia merger ($60 billion)

Pfizer gained control of Pharmacia’s blockbuster arthritis drug Celebrex®. The
combined group became the #1 drug maker in annual sales ($46 billion), with an added
portfolio of leading drugs for impotence, high cholesterol, arthritis, glaucoma, and
depression. The company now had 12 blockbuster products.

2009: Pfizer/Wyeth merger ($68 billion)

The acquisition of Wyeth enhanced Pfizer’s portfolio in areas such as Alzheimer’s
disease, inflammation, oncology, pain, and psychosis, and made Pfizer a top-tier player
in biotherapeutics and vaccines. The merger was expected to help shorten the major
gap in revenue in 2011 when Lipitor® started facing US generic competition. Pfizer now
had 17 products with more than $1 billion each in annual revenue.

2014: Pfizer/Baxter merger ($635 million)

Pfizer acquires Baxter’s marketed vaccines, which included NeisVac-C
(meningitis vaccine) and FSME-IMMUN/TicoVac (prevention of tick-borne encephalitis). A portion of Baxter’s vaccine-manufacturing
facility in Austria was also obtained.

2015: Pfizer/Hospira merger ($15.2 billion)

Pfizer became a leading provider of global sterile injectables through the acquisition of
Hospira.

4. Entering a new era — a shift from “commerce to science”

2014: Pfizer/BioNTech COVID-19 vaccine (Comirnaty®)

Pfizer-BioNTech COVID-19 vaccine (Comirnaty®)

Phase 3 clinical trials for the COVID-19 vaccine commenced in July 2020. Shortly after
in December, the vaccine was authorized by the FDA for emergency use. The vaccine
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2016: Pfizer/BioNTech COVID-19 vaccine (Comirnaty®)

The oral COVID-19 treatment went from an idea to the first clinical test in 12 months!
Paxlovid® received Emergency Use Authorization by the FDA in 2021, and obtained full
FDA approval in May 2023.

2020-2021: Pfizer’s multifront approach to combat the
COVID-19 pandemic

COVID-19 was declared a pandemic in the US on March 11, 2020.

2021: Pfizer’s major rebranding

2022: Pfizer acquired multiple companies

Arena Pharmaceuticals, ReViral, Biohaven Pharmaceutical Holding Company Ltd.,
Global Blood Therapeutics, Inc.

2024: 175th anniversary of Pfizer

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Sildenafil (Viagra®) — the “blue pill”
- Launched in 1998 as the first oral treatment for erectile dysfunction
- Generated > $1.7 billion of revenue in 2002
- Selective inhibitor of cyclic guanosine monophosphate (cGMP)-specific phosphodiesterase type 5 (PDE5)
- Initially developed for hypertension & angina. Although clinical trials were disappointing, patients reported penile erections as a side effect.

PDE5 inhibitors on the market:

Discovery route:

Process route:

Crystal Faraday Award for Green Chemical Technology by the Institute of Chemical Engineers

See: Chemistry of Sex (Bi, 2020)
Atorvastatin (Lipitor®)
- launched in 1996 (initially co-marketed with Warner-Lambert, later acquired by Pfizer in 2000)
- the world’s best selling drug of all time ($130 billion during its 14 years on the market)
- WHO Model List of Essential Medicines
- reduces the risk of cardiovascular disease by lowering total & low-density lopoprotein (LDL) cholesterol
- inhibitor of HMG-CoA reductase (HMGR), the rate-limiting enzyme in cholesterol biosynthesis
- first totally synthetic HMGR inhibitor to be developed and marketed as a single enantiomer

**Fun fact:** atorvastatin should not be taken with grapefruit juice!

Bergamottin & DHB inactivate CYP3A4, inhibiting the presystemic degradation of statins and thus increasing their systemic bioavailability.

Progress in Medicinal Chemistry, v. 1, Ch. 1 (Roth, 2002); Contemporary Drug Synthesis, Ch. 9 (Li, 2004); J. Med. Chem. 1991, 34, 357-366
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**Enantioselective discovery route via a chiral auxiliary:**

gram scale, but linear route, multiple low-temperature reactions, relatively low yields in the final steps

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**Process route:**

common intermediate for other HMGR inhibitors

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Progress in Medicinal Chemistry, v. 1, Ch. 1 (Roth, 2002); Contemporary Drug Synthesis, Ch. 9 (Li, 2004)
Nirmatrelvir/ritonavir (Paxlovid®)
- oral COVID-19 antiviral treatment (inhibitor of the 3CL protease of SARS-CoV-2)
- received Emergency Use Authorization in Dec 2021, and full FDA approval in May 2023
- reduced the risk of hospitalization or death from COVID-19 by 88% if given within 5 days of the onset of symptoms
- project led by medicinal chemist Dafydd Owen, went from an idea to the first clinical test in a person in 12 months!
- co-packaged with ritonavir (slows metabolism of nirmatrelvir via CYP3A4 inhibition)

Discovery route:
1. **NH3, MeOH, 98%**  
2. **HCl, IPA, quant.**

Key structural modifications to increase the oral bioavailability of PF-00835231:
1. Replacement of the α-hydroxymethyl ketone with an alternative covalent-reactive group to Cys
   - The nitrile group was chosen over the benzothiazol-2-yl ketone moiety due to its greater solubility, scalability, and relative resistance towards epimerization.
2. Removal of the leucine NH bond
   - Replacement with a cyclic amino acid, but led to lost of critical contact to Gln
3. Replacement of the indole with a trifluoroacetamide
   - Interaction with Gln was restored
   - Excellent ability to permeate the gut barrier in assays

**How Pfizer Scientists transformed an old drug lead into a COVID-19 antiviral** (c&en, Halford, 2022); *Science* 2021, 374, 1586-1593
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Existing routes to bicyclic [3.1.0] proline 1:

route A

route B

route C

- ethyl chrysanthematate

- long lead time
- supply shortage
- aggressive timeline

route C was initially pursued, but:

- [Co] (15 mol %)
  Zn, I₂, THF;
  MTBE, HCl (aq.)

310 kg

1.3 eq.

[Co] (15 mol %)

1 step

5 steps

1 step

5 steps

1 step

4-5 steps

desymmetrization via amine-oxidase

Process route:

HCl, THF;

MTBE

HCl

205 kg (avg)

73% over 2 steps

the Na salt displayed
superior slurry behavior & bulk density than the Li salt

TEA, THF/H₂O;
NaOH, THF/H₂O

300-780 kg scale

88-94% yield

In spite of the supply chain issues faced during the COVID-19 pandemic & aggressive time constraints, this effective synthetic strategy enabled Pfizer chemists to scale up from the first milligrams to over 10 kg in only 8 months!

ethyl chrysanthematate

EDCI, HOPO, TEA;
NaCl, H₂O

TFAA, NMM, iPrOAc;
MTBE

80% over 2 steps

Nirmatrelvir-MTBE

iPrOAc heptane

94%

Nirmatrelvir

MsCl, TEA, iPrOAc;
citric acid, H₂O;
heptane

140-440 kg scale

75-90%

TEA, THF/H₂O;
NaOH, THF/H₂O

300-780 kg scale

88-94% yield

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Fluconazole (Diflucan®)

- Antifungal (available as a single-dose tablet or intravenously) used to treat fungal or yeast infections of the vagina, mouth, throat, esophagus, etc.
- Approved by the FDA in 1990
- WHO Model List of Essential Medicines
- Inhibitor of the fungal C-14 demethylase in the ergosterol biosynthesis pathway. Ergosterol is essential for the fluidity of the fungal membrane.

Available antifungal agents at the time:

- Promotes the loss of vital ions of the fungal cell by binding to ergosterol in the cell membrane
- Unfortunately also has an affinity for the mammalian sterol cholesterol, leading to lack of selectivity & numerous adverse side effects
- Slow intravenous infusion was required
- Typically used as a last resort

- Good oral bioavailability
- Only active against a limited range of fungi
- Resistance frequently arose during long-term treatment

A safe, convenient (effective both orally & intravenously) antifungal agent was needed for life-threatening infections.

Pfizer initiated their discovery program for fluconazole in 1978 at Sandwich, Kent (UK).

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**Piroxicam (Feldene®)**
- one of the largest-selling prescription anti-inflammatory medicines in the world
- Pfizer’s first product to reach a total of $1 billion in sales
- project began in 1962 at Pfizer, and was FDA approved by 1979
- non-selective COX inhibitor possessing both analgesic and antipyreric properties
- prevents production of endogenous prostaglandins which are involved in the mediation of pain, stiffness, tenderness, and swelling

**Other arthritis therapies available or in development at the time:**

- carboxylic acids were known to be rapidly metabolized & excreted
- multiple daily doses (3 to 6 a day) were necessary to maintain control of the pain and swelling, resulting in poor compliance
- high daily doses (e.g. up to 16 g of aspirin) may be required, increasing potential for toxicity due to heavy load on GI tract, liver, and kidneys

_Pfizer sought after a structurally novel compound which arthritis patients could safely use over long periods of time for their chronic disease._

**Other notable drugs by Pfizer that are not covered today:**

- **apixaban (Eliquis®)** anticoagulant
- **pregabalin (Lyrica®)** for neuropathic pain
- **celecoxib (Celebrex®)** nonsteroidal anti-inflammatory drug
- **sertraline (Zoloft®)** antidepressant

**Key takeaways**
1. From manufacturing to discovery
2. Expansion through acquisition