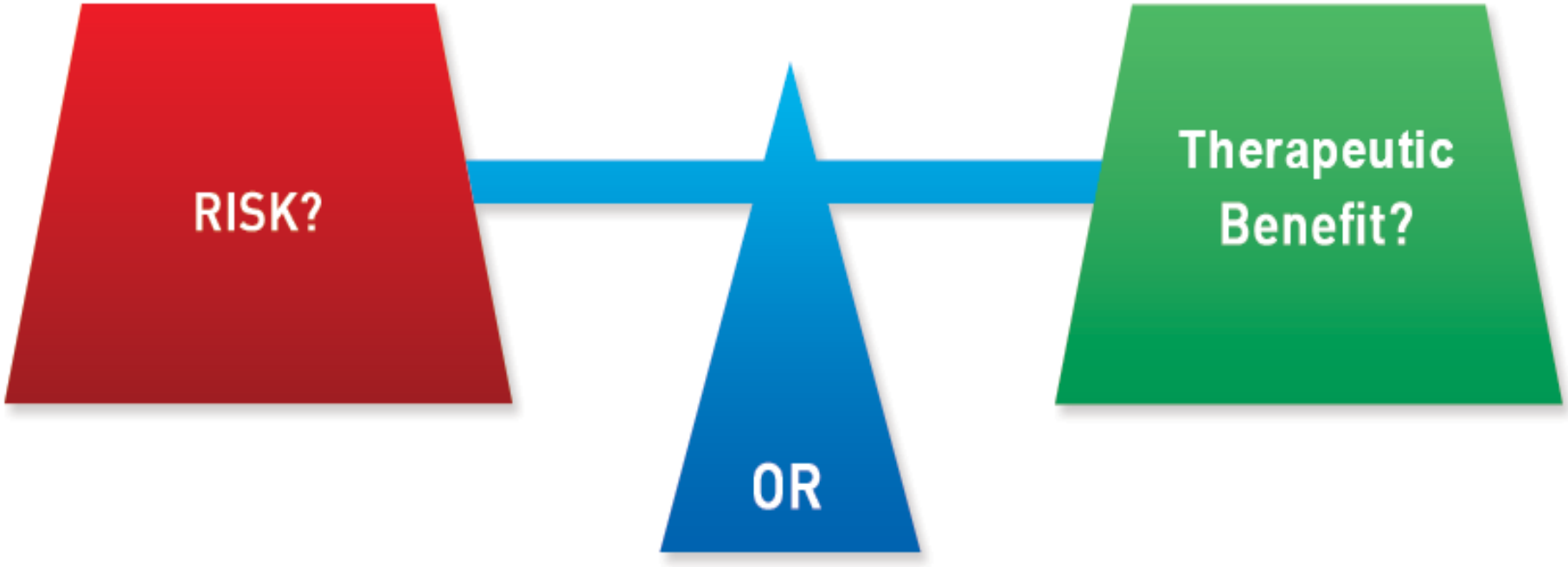
Pharmaceutical Quality Control(1)

المراقبة الدوائية

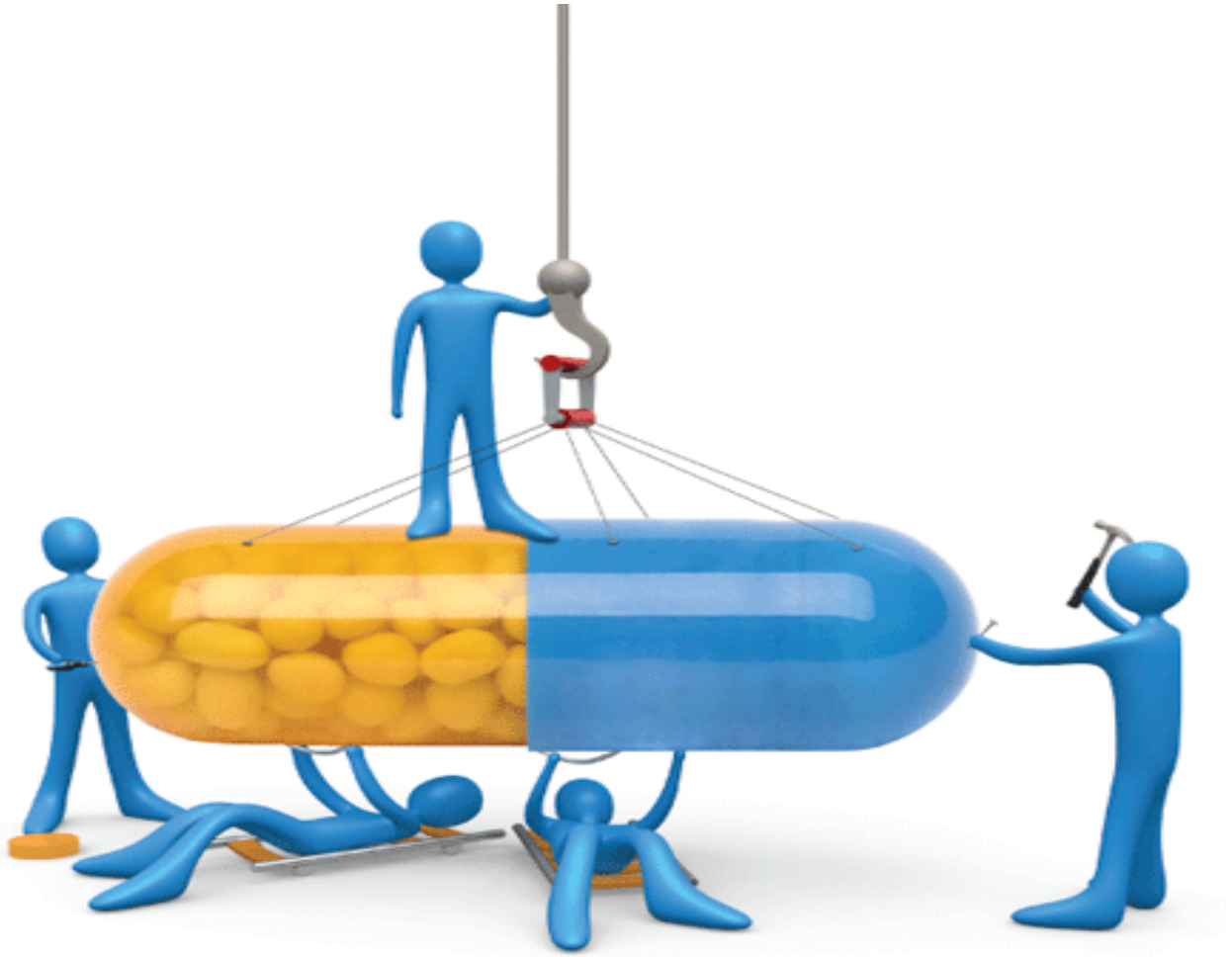
Prof.Dr.M.Amer Al-Mardini

The Drug



Safe And Effective

Quality




QUALITY
SAFETY
EFFICACY

الفعالية: Efficacy, Effectiveness

قابلية دواء ما للسيطرة على المرض أو الشفاء منه

- **المأمونية، الأمان Safety**

الخلو النسبي relative freedom من الآثار الضارة harmful effects التي قد تصيب الشخص بشكل مباشر أو غير مباشر جراء تناول رشيد للدواء

- **الجودة Quality**

توافق Conformance المادّة أَو المُنتَج مع المواصفات أَو المعايير المحددة مسبقاً pre-established specifications or

واقع الأدوية في العالم

الأدوية المبتكرة " المحمية"

Brand-Name Drugs

الأدوية الجنيسة Generics

الأدوية المصنوعة بامتياز
بيع الحقوق كلياً أو جزئياً

Brand name drug الدواء ذو العلامة التجارية

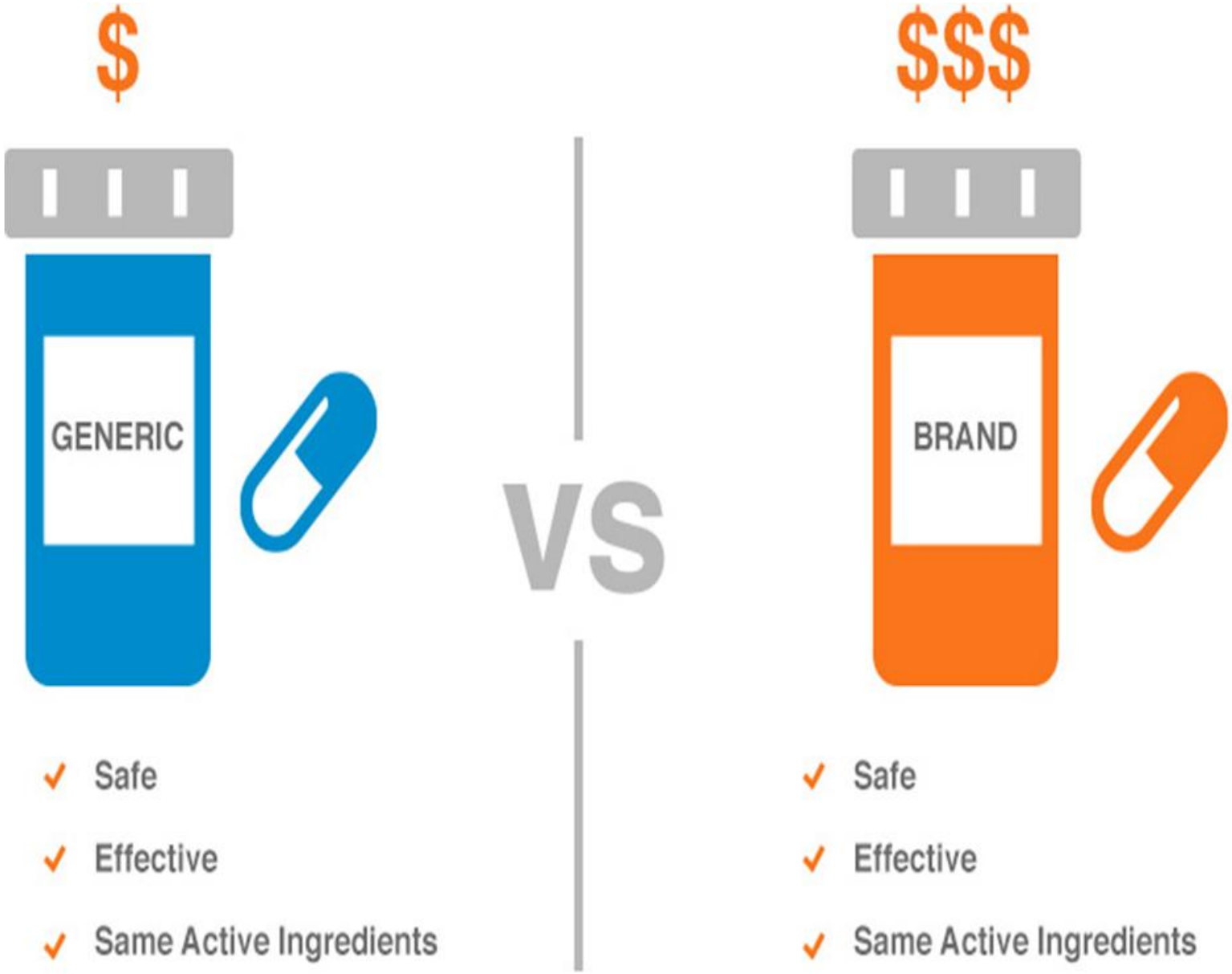
A brand name drug is an innovator drug that holds a patent to prevent other manufacturers from copying and is usually available from a single source or one manufacturer

دواء مُبتكرٍ يَحْملُ الحماية لبراءة الاختراع منعاً لشركات أخرى من نَسْخه، وعادة ما يكون هذا الدواء متوفراً مِنْ مصدر وحيد أو من شركة وحيدة

Generic drug الدواء الجنيس

A generic drug is a copy of a brand name drug. It is the same medicine with the same active ingredients as the brand name drug, but usually made by another company at a less expensive cost

دواء منسوخ من دواء ذي علامة تجارية بالمادة الفعالة نفسها لكن عادة ما يكون مصنعاً من قبل شركة أخرى بسعر أخفض


$
GENERIC
VS
$$$
BRAND
✓ Safe
✓ Effective
✓ Same Active Ingredients
✓ Safe
✓ Effective
✓ Same Active Ingredients

تطوير دواء جديد

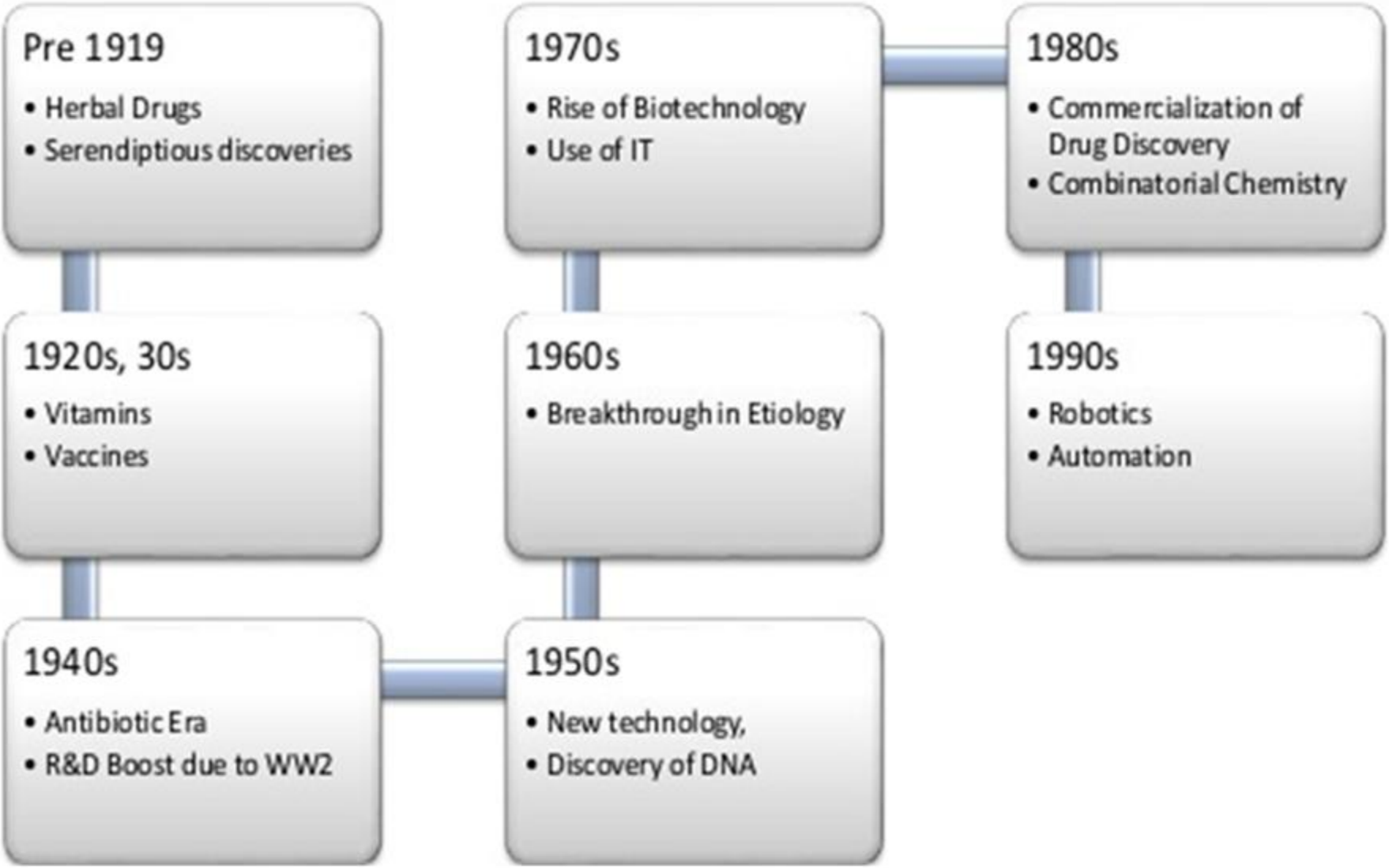
New Drug Development


Research

Research and Development

- *Before a new drug can be marketed, there are a number of lengthy processes that must be gone through, which may be loosely combined under the heading of research and development (R&D)*
- *قبل أن يدخل دواء جديد إلى السوق هناك العديد مِنْ العملياتِ الطويلةِ التي يجب المرور بها، التي يمكن إدماجها تحت عنوان البحث والتطويرِ*
- *The processes take somewhere between eight and ten years to complete for a completely new molecule*
- *تستغرقُ هذه العملياتُ تقريباً ما بين ثمان وعشْر سَنَوات لتأخذ جزيئة جديدة مكانها بين الأدوية*

History of Drug Discovery



The changed context of drug discovery and development

The 1800s:

- natural sources
- limited possibilities
- prepared by individuals
- small scale
- not purified, standardized or tested
- limited administration
- no controls
- no idea of mechanisms

The changed context of drug discovery and development

The 1900s:

- synthetic source
- unlimited possibilities
- prepared by companies
- massive scale
- highly purified, standardized and tested
- world-wide administration
- tight legislative control
- mechanisms partly understood

DRUG SOURCES

Plant / Vegetable Sources:

The oldest natural source. Even now some drugs are obtained from the plant source.

Drugs can be obtained from all parts of the plants:

- **Leaves:**

1. Digitalis Purpurea	Digitoxin and Digoxin	cardiac glycosides.
2. Eucalyptus	oil of Eucalyptus	cough syrup.
3. Tobacco	nicotine.	
4. Atropa belladonna	atropine.	

Flowers:

1. Poppy papaver somniferum	morphine (opoid)
2. Vinca rosea	vincristine and vinblastine
3. Rose	rose water used as tonic.

Seeds:

1. Nux Vomica	strychnine, which is a CNS stimulant.
2. Castor oil	castor oil.
3. Calabar beans	Physostigmine, which is a cholinomimetic

Fruits:

1. Senna pod	anthracine purgative (used in constipation)
2. Calabar beans physostigmine	cholinomimetic agent.

Roots:

1. Ipecacuanha root Emetine,	used to induce vomiting as in accidental poisoning. It also has amoebicidal properties.	
2. Rauwolfia serpentina	reserpine, a hypotensive agent.	

Bark:

1. Cinchona bark	quinine and quinidine,	antimalarial
2. Atropa belladonna	atropine,	anticholinergic.

Stem:

1. Chondrodendron tomentosum gives tuboqurarine, which is skeletal muscle relaxant used in general anesthesia.

Animal Sources

Various organs & tissue of animals are used as source of drug.

Active principles of animal drugs are proteins, oils, fat, enzymes and hormones.

- Pancreas ..... Insulin
- Cod liver ..... Cod liver oil (contains Vit A & D)
- Urine of pregnant ..... hCG
- Sheep thyroid..... Thyroxin
- Animal Blood..... Vaccines

Mineral & Earth Sources

Many drugs are mineral substances & their compounds.

Metals:

- Iron is used in treatment of iron deficiency anemia.
- Mercurial salts are used in Syphilis.
- Zinc is used as zinc supplement. Zinc oxide paste is used in wounds and in eczema.
- Gold salts are used in the treatment of rheumatoid arthritis.

Non - metallic element:

- Iodine is antiseptic. Iodine supplements are also used.

Miscellaneous: Flourine, Selenium

Semisynthetic

When the nucleus of drug obtained from natural source is retained but the chemical structure is altered, we call it semi-synthetic.

Complex molecules

Expensive and for impure natural compound

E.g. 6-aminopencillanic acid (fungus), semi-synthetic human insulin (pork insulin)

Synthetic

When the nucleus of the drug from natural source as well as its chemical structure is altered, we call it synthetic.Pharmaceutical laboratory

Organic or inorganic or combination of organic and inorganic compounds

>90% drugs

E.g. Antipyretics, sulphonamides, antihistamines, anticonvulsants, anti anxiety etc

Microorganisms

Penicillium notatum is a fungus which gives penicillin.

Actinobacteria give Streptomycin.

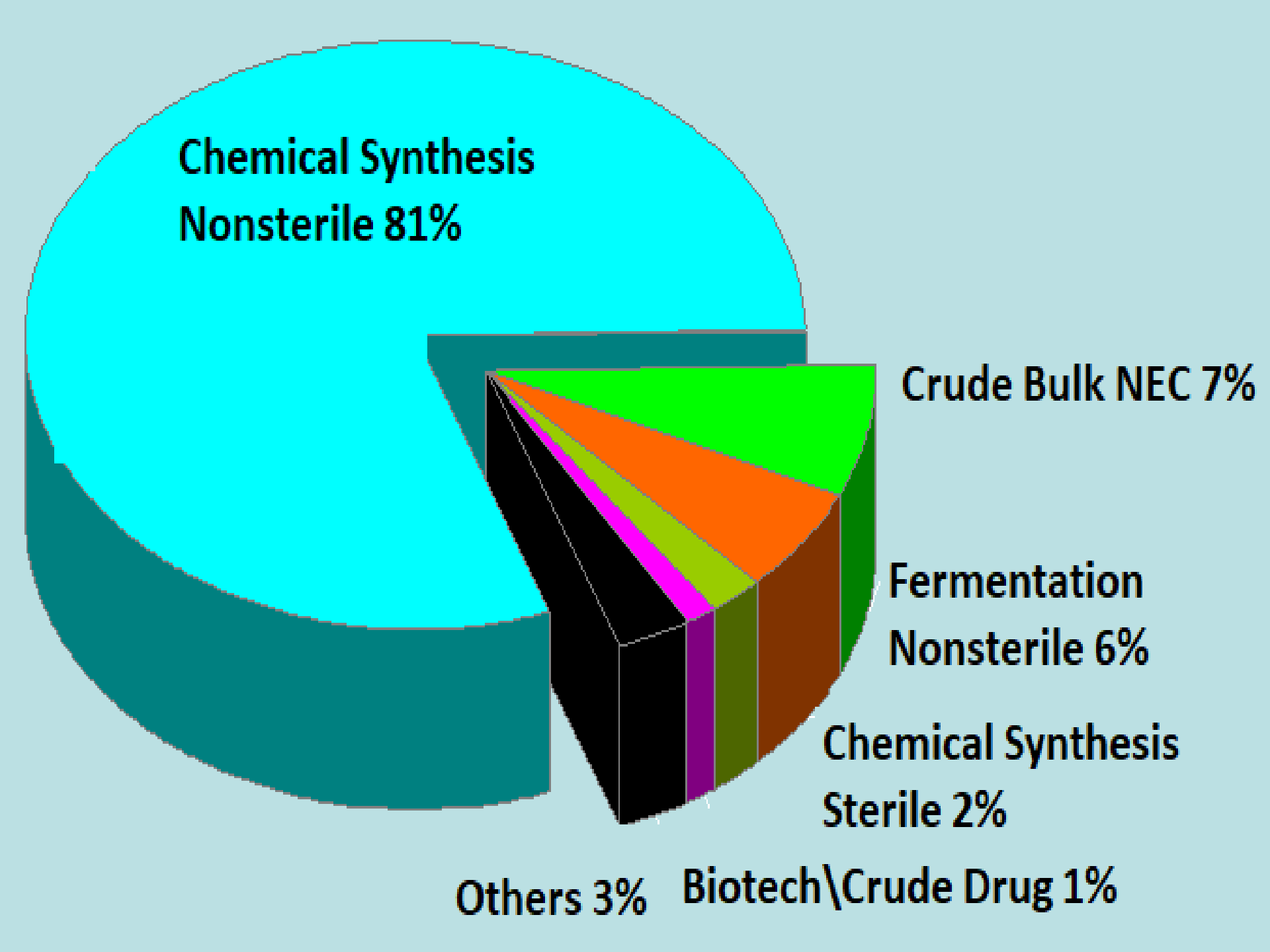
Aminoglycosides such as gentamicin and tobramycin are obtained from streptomycis and micromonosporas.

Recombinant DNA Technology / Genetic engineering

1. The new technique for preparing certain drugs e.g. Human insulin insulin analogs , Erythropoietin.
2. Human Insulin & insulin analogs may be prepared by inserting human or modified pro-insulin gene into E-coli or yeast & treating the extracted pro-insulin to form the insulin or insulin analogs.
3. Advantages:
   - Mass production.
   - Cost effective
   - Less immunological reactions.

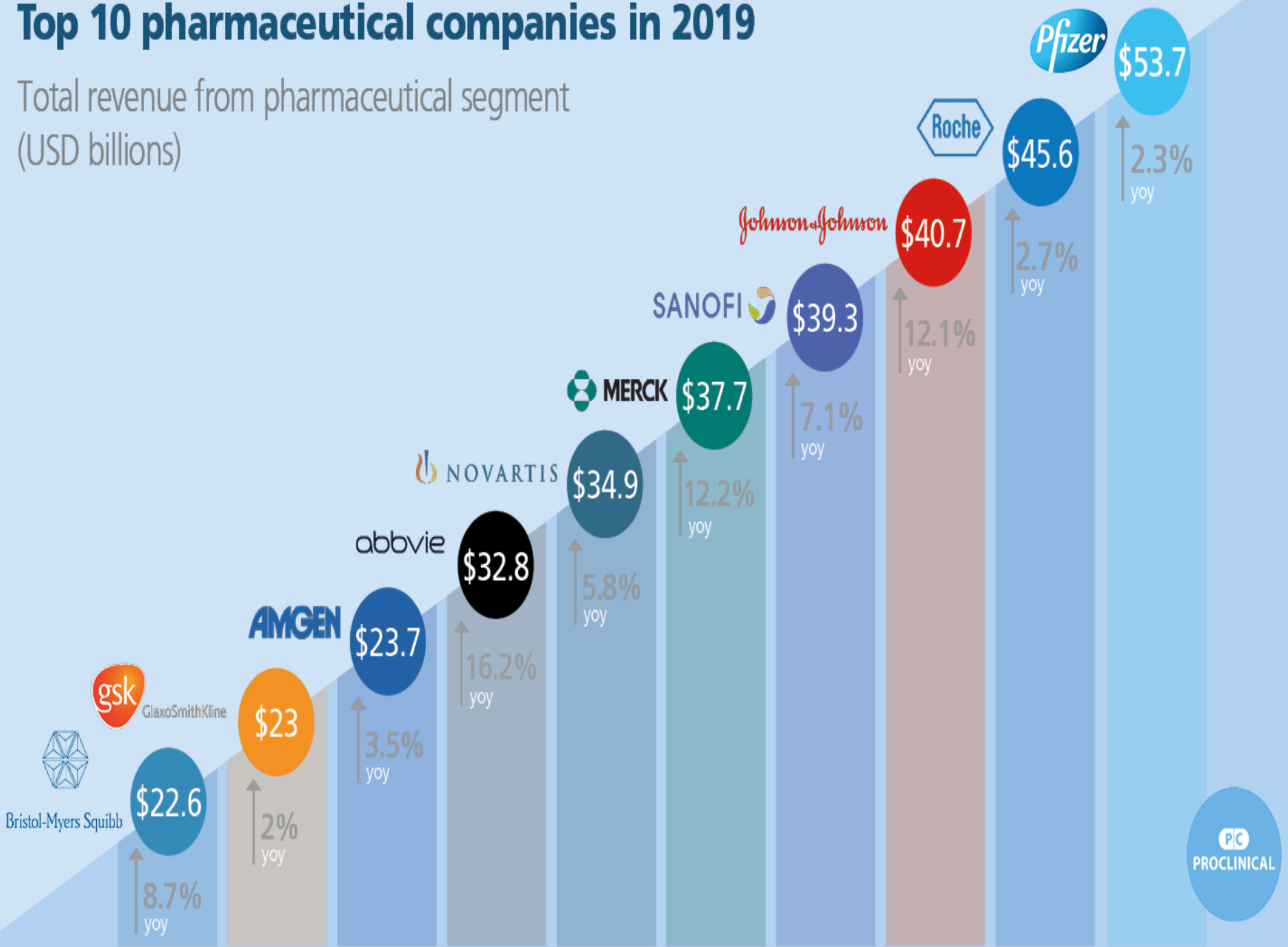
Approaches to Drug Discovery

- **Historical**: cinchona (quinine) & willow barks (aspirin)
- **Study disease process**: Parkinson's disease (L-dopa)
- **Develop Drugs to natural compound**: beta-adrenoceptors (propranolol), H2-receptors (cimetidine)
- **Design to fit known structurally identified biological site**: angiotensin-converting enzyme inhibitors
- **By chance** :(serendipidy); random screening (HTS): penicillin; dimenhydramate; pethidine
- **Genomics**: identification of receptors; gene therapy; recombinant materials


Chemical Synthesis
Nonsterile 81%
Crude Bulk NEC 7%
Fermentation
Nonsterile 6%
Chemical Synthesis
Sterile 2%
Biotech\Crude Drug 1%
Others 3%

Top 10 pharmaceutical companies in 2019

Total revenue from pharmaceutical segment
(USD billions)



PC PROCLINICAL

Top 10 Best Selling Drugs 2003 - 2005

	2003		2004		2005	
S.No	Products	Sales (USDbn)	Products	Sales (USDbn)	Products	Sales (USDbn)
1	Lipitor	9.23	Lipitor	10.86	Lipitor	12.19
2	Zocor	5.00	Plavix	5.64	Plavix	6.21
3	Ogastro/Prevacid	4.71	Zocor	5.20	Seretide/Advair	5.34
4	Norvasc	4.34	Advair,seretide	4.74	Norvasc	4.71
5	Zyprexa	4.28	Norvasc	4.46	Nexium	4.63
6	Plavix	4.13	Zyprexa	4.42	Zocor	4.40
7	Erypo (Eprex/Procrit)	3.98	Prevacid, Ogastro	4.14	Zyprexa	4.20
8	Seretide/Advair	3.94	Nexium	3.88	Prevacid/Ogastro	4.00
9	Nexium	3.30	Erypo(Eprex, Procrit)	3.59	Pravachol	3.82
10	Zoloft	3.12	Risperdal	3.05	Diovan/Co-Diovan	3.70
Top 10 drugs		46.03	Top 10 drugs	49.99	Top 10 drugs	53.2
Share of the top 10 drugs to the total market		9.36%	Share of the top 10 drugs to the total market	9.09%	Share of the top 10 drugs to the total market	9.13%

1 Humira® (adalimumab)

AbbVie
2018 Sales: **$19.936 billion**
2017 Sales: **$18.427 billion**
CHANGE ▲ **8.2%**

2 Eliquis® (apixaban)

Bristol-Myers Squibb and **Pfizer**
2018 Sales: **$9.872 billion**
($6.438B BMS + $3.434B Pfizer)*
2017 Sales: **$7.395 billion**
($4.872B BMS + $2.523B Pfizer)*
CHANGE ▲ **33.5%**

* Pfizer figures for Eliquis consist of "alliance revenues" reflecting products co-developed with partner companies, as well as direct sales in some regions of the world.

3 Revlimid® (lenalidomide)

Celgene
2018 Sales: **$9.685 billion**
2017 Sales: **$8.187 billion**
CHANGE ▲ **18.3%**

4 Opdivo® (nivolumed))

Bristol-Myers Squibb and **Ono Pharmaceutical**
2018 Sales: **$7.570 billion**
($6.735B BMS + $835M [¥92.5B] Ono)
2017 Sales: **$5.763 billion**
($4.948B BMS + $815M [¥90.2B] Ono)
CHANGE ▲ **31.4%**

5 EG-1962 (nimodipine microparticles)

Merck & Co.
2018 Sales: **$7.171 billion**
2017 Sales: **$3.809 billion**
CHANGE ▲ **88.3%**

6 Enbrel® (etanercept)

Amgen and **Pfizer**
2018 Sales: **$7.126 billion**
($5.014B Amgen + $2.112B Pfizer)*
2017 Sales: **$7.885B**
($5.433B Amgen + $2.452B Pfizer)*
CHANGE ▼ **–9.6%**

* Pfizer markets Enbrel outside the United States and Canada, where the treatment is marketed by Amgen.

7 Herceptin® (trastuzumab)

Roche (Genentech)
2018 sales: **$6.981 billion**
(CHF 6.982 billion)
2017 sales: **$7.013 billion**
(CHF 7.014 billion)
CHANGE ▼ **–0.5%**

8 Avastin® (bevacizumab)

Roche (Genentech)
2018 Sales: **$6.847 billion**
(CHF 6.849 billion)
2017 Sales: **$6.686 billion**
(CHF 6.688 billion)
CHANGE ▲ **2.4%**

9 Rituxan® (rituximab)

Roche (Genentech) and **Biogen***
2018 Sales: **$6.750 billion**
[CHF 6.752 billion]*
2017 Sales: **$7.298 billion**
[CHF 7.300 billion]*
CHANGE ▼ **–7.5%**

* Figures do not include U.S. pre-tax profits generated by Biogen, which are disclosed only in combination with profits from Gazyva® (obinutuzumab). Biogen reported Rituxan-Gazyva pre-tax profits of $1.432 billion for 2018, and $1.316 billion for 2017.

10 Xarelto® (rivaroxaban)

Bayer and **Johnson & Johnson**
2018 Sales: **$6.589 billion**
($4.112B [€3.631B] Bayer + $2.477B J&J)
2017 Sales: **$6.234 billion**
($3.734B [€3.298B] Bayer + $2.50B J&J)
CHANGE ▲ **5.8%**

11 Eylea® (aflibercept)

Bayer and
Regeneron Pharmaceuticals
2018 Sales: **$6.551 billion**
($2.474B Bayer + $4.077B Regeneron)
2017 Sales: **$5.830 billion**
($2.128B Bayer + $3.702B Regeneron)
CHANGE ▲ **12.4%**

12 Remicade® (infliximab)

Johnson & Johnson and
Merck & Co.
2018 Sales: **$5.908 billion**
($5.326B J&J + $0.582B Merck)
2017 Sales: **$7.152 billion**
($6.315 billion J&J + $0.837B Merck)
CHANGE ▼ **–17.4%**

13 Prevnar 13®/Prevenar 13®

(Pneumococcal 13-valent Conjugate Vaccine [Diphtheria CRM_{197} Protein])
Pfizer
2018 Sales: **$5.802 billion**
2017 Sales: **$5.601 billion**
CHANGE ▲ **3.6%**

14 Stelara® (ustekinumab)

Janssen Biotech (Johnson & Johnson)
2018 Sales: **$5.156 billion**
2017 Sales: **$4.011 billion**
CHANGE ▲ **28.5%**

15 Lyrica® (pregabaliln)

Pfizer
2018 Sales: **$4.970 billion***
2017 Sales: **$5.065 billion***
CHANGE ▼ **–1.9%**

* Pfizer lists separately the Lyrica revenues generated in all of Europe, Russia, Turkey, Israel, and Central Asia countries ($347 million in 2018, $553 million in 2017). Those revenues are listed by Pfizer's "Essential Health" operating segment, while its "Innovative Health" segment records Lyrica revenues generated elsewhere in the world, including the United States ($4.622 billion in 2018, $4.511 billion in 2017).

Drug Approval Process

- All countries have some form of government agency (a health authority or board of health) that has responsibility for overseeing the country's requirements for approving new drugs. e.g.
  - Food and Drug Administration (FDA), USA
- The different stages in the drug approval process are :
  - Stage 1: Preclinical Research
  - Stage 2: Clinical Research
    - Phase I
    - Phase II
    - Phase III
    - Phase IV
  - Stage 3: Review and Approval
  - Stage 4: Marketing

Preclinical Research

Chemical Characterization

Synthesis, Structure:

(MS, NMR, IR, Elementary analysis, UV/VIS, etc..)

purity, isomers, pKa, stability, solubility, salts, assay

Specifications:

1. Identification Tests (IR,UV/VIS, Chromatography, color tests ,etc..)
2. Purity Tests
3. Assay

Battery of Tests at Preclinical Stage of Development

Test parameter	Typical test procedures
1. Identity	Infrared spectroscopy Melting point
2. Structural elucidation	Mass spectroscopy Nuclear magnetic resonance
3. Assay of active parent compound	Chromatographic procedure Titration
4. Related substances (impurities)	Chromatography (HPLC/GLC/TLC)
5. Inorganic impurities	Residue on ignition Heavy metals
6. Residual solvents	GLC
7. Moisture content	Karl Fischer titration
8. pH in solution	pH measurement

in vitro/ in vivo

- When a new chemical entity (NCE) is discovered, it is initially subjected to a number of pre-clinical research activities
- First of all, it is tested both in **vitro and in vivo**

Preclinical Testing
(in vitro)

- *Studies are done in vitro with **cell cultures** and **isolated tissues***
- *Researchers evaluate the new compound for it's:*

1. *Pharmacologic effects*
   (Potential effectiveness)
2. *Toxicological effects*

   (Potential side effects it may cause)

Preclinical Testing *(in vivo)* in Animals

- *Done in at least **two species of animals***
  - *One rodent*
  - *One non-rodent species*

Preclinical Testing *(in vivo)* **in Animals**

- Acute pharmacological profile
- LD50 (***The dose which kills 50% of animals tested***)
- Binding data for many receptors
- Dose-effect relationships
- Tests for different activities (e.g. CNS, GI tract)…

Toxicology Studies

- *There are very few drugs that can be said to cause no adverse reaction at all*
- *A judgment has to be made as to whether the benefits of a drug outweigh the potential side effects*
- *There are a number of different types of toxicological studies that must be carried out, depending on the type of drug:*

-***Acute toxicity***: *carried out over two weeks in three to four species to determine the maximum tolerated dose*

-***Subacute toxicity***: *carried out over six months in two species*

-***Chronic toxicity***: *carried out over a maximum of 12 months in rats and one other species to see if there are any adverse effects resulting from repeated daily doses*

- ***Reproductive toxicity***: *carried out over a maximum of nine months in two species to identify any adverse effects on fertility and reproductive abilities*

- ***Mutagenic toxicity***: *carried out over 18–24 months under both in vitro and in vivo conditions*

- *This stage of the R & D cycle can take several years and will need to be completed before a company can obtain approval to carry out clinical studies*

Chemical Development

- الاصطناع نصف الصناعي من فئة الغرام الى الكيلوغرام
- معدات وتقانات جديدة ومحلات اقتصادية
- مواصفات جديدة
- وجبات بأرقام وشهادات تحليل
- عمليات تنقية لاحقة
- انتقاء الوجبة المرجعية(Reference Standard)

Pre-formulation studies

- *Pre-formulation studies need to be carried out in order to determine the physicochemical characteristics of the molecule and thus the most appropriate dosage forms that can be used. Studies will include some or all of the following:*

- ***Spectroscopy**: to identify a basic analytical method*
- ***Solubility**: in relation to liquid dosage forms and to identify the most appropriate salt to work with*
- ***Melting point**: to determine crystalline solubility*
- ***Assay development**: using more sophisticated equipment and related to drug stability studies*
- ***Stability**: in both liquid and solid dosage forms*
- ***Microscopy**: to identify particle size and crystal formation*
- ***Powder flow and compression properties**: in relation to dry product dosage forms*
- ***Excipient compatibility**: to ensure that the final dosage form will perform correctly*

Formulation Studies
Product Development

- *The most appropriate dosage form can be determined, based on such factors as the purpose for which the drug is intended and the physicochemical characteristics of the chemical entity*
- *DRUG +Additive: filler, lubricant, coating, stabilizer, color, binder, disintegrator*
- *Dosage form: capsule, tablet, injection, other?*

  Manipulate duration/profile: e.g. sustained release
- ***Research Dosage Forms***

  Biopharmaceutical studies

  Stability Testing

Process Development

- *نقل من المخابر الى وحدة الصناعة التجريبية*
- *ترتيب عملية الانتاج*
- *تحرير عمليات الانتاج والمراقبة*
  (اضبارة الانتاج ،المراقبة،...)

Packaging Development

- تصميم العبوة،اختيار جملة الوعاء/الغطاء الملائمة للمنتج
- تحرير مواصفات العبوة المناسبة وطرائق اختبارها

Biopharmaceutical Studies

- *As part of the process of finalizing the dosage form, it is necessary to carry out biopharmaceutical studies in order to ensure that the drug reaches the part of the body where it is required, and is maintained at the right concentration for the right period of time.*
- *This includes identification of the appropriate dosage levels and frequency*

Biopharmaceutical Studies

- *These studies relate to four stages, called ADME for short:* ***ADME***

1. ***Absorption****: how the drug enters the body and reaches the bloodstream*
2. ***Distribution****: how the drug travels through the body*
3. ***Metabolism****: the way in which the drug is changed by the body*
4. ***Elimination****: how the drug leaves the body*

- *The amount of drug that reaches the bloodstream and the speed at which it takes place is called its* ***bioavailability****.*
- *Bioavailability is generally measured by means of phrmokinetic plasma studies of drug concentration against time.*

Stability Studies

- *Pre-clinical studies of the final dosage form will extend to include stability studies relating to the primary and secondary packaging materials that are planned to be used*
- *These studies examine the physical, chemical or microbiological deterioration of the drug over time in order to determine the appropriate shelf life that can be guaranteed*

Stability Studies

- *Since stability or rather, lack of stability, is something that develops over time, it could take years to complete these studies if they were all conducted under a 'real-time' basis*
- *As an alternative to this, accelerated stability studies can be used, in which the packs are exposed to extremes of conditions such as heat, light and moisture*
- *Results thus obtained can then be converted to equivalents for ambient conditions*

Clinical Studies

- *Assuming that the pre-clinical studies, particularly the toxicological tests, have produced acceptable results, the company will seek permission from the appropriate regulatory body to carry out clinical studies*
- *The extent of the trials will depend on the nature of the drug and its proposed application*
- *The trials are generally carried out in a number of stages*
- *The experimental drug is studied in humans*

Clinical Trials

- *First consideration is the protection of the rights, safety and well-being of the study subject*
- *Clinical trials are carefully designed and controlled experiments to test its safety and to determine effectiveness*

التجارب السريرية
الخطوط العامة

- البدء بمجموعة قليلة من المتطوعين الأصحاء
- ازدياد عدد المتطوعين بازدياد أمان الدواء
- تنوع المتطوعين حسب نوع الاختبار
- دراسة الأمان،السمية ،التأثيرات الفارماكولوجية، الأعراض الجانبية،الحمل،الرضاعة،الشيوخ...
- تقييم النتائج من قبل فرق مختصة
- معاملة النتائج احصائياً
- اطلاع السلطات الصحية الحكومية والعمل تحت اشرافها

Clinical Trials

- *Professional team oversees these studies includes: pharmaceutical company, physician investigators, regulatory authorities, and committees that review safety and ethics of clinical trial*
- *Pharmaceutical companies that sponsor experimental drugs devote great amount of time to clinical testing*
- *Four general phases of clinical research as follows:*

1. ***Phase I***
2. ***Phase II***
3. ***Phase III***
4. ***Phase IV***

Clinical Trials

Phase I (volunteers)

Phase II (patients)

Phase III (large scale & multi-centre)

Phase IV (post registration monitoring)

Phase I Studies

- *How drug affects body of healthy individual?*
- *How person's body processes, responds to, and affected by drug?*
- *Low doses and high doses of drug usually studied*
- *By the end of Phase I, as a result, the safe dosage range in volunteers may be known*
- *This information will determine whether the drug proceeds to Phase II*

Phase I Studies

- ***Description:***
  - *Establishes safety and toxicity in humans*
  - *Short term (up to 1 month)*
  - *Few healthy volunteers not taking other medicines (20 – 80)*
- ***Evaluates:***
  - *Pharmacodynamics (physiologic effects)*
  - *Pharmacokinetics*
  - *Bioavailability*
  - *Bioequivalance*
  - *Dose proportionality*
  - *Metabolism*

Phase II Studies

- ***Description***
  - *Well-defined subject eligibility criteria*
  - *Controlled comparisons with either placebo or active control [sugar pill (placebo), or perhaps between new drug and existing drug]*
  - *Short-medium duration (weeks to months long)*
  - *Larger number of subjects (100-300)*
  - *Establishes effectiveness of drug for a specific population and disease*
- ***First to use subjects with the disease or condition*** *(not healthy volunteers)*

Phase II Studies

- ***Evaluates:***
  - *Safety in patients*
  - *Efficacy/pharmacologic effects*
  - *Pharmacokinetics (single and multi dose optional)*
  - *Bioavailability*
  - *Drug-disease interactions*
  - *Drug-drug interactions*
  - *Efficacy at different doses*

  Information collected in Phase II studies will determine whether the drug proceeds to Phase III

Phase III Studies

Description

- *Broader patient eligibility criteria than in Phase II studies (two or three treatment groups)*
- *Larger number of patients are studied (hundreds to thousands of subjects)*
- *Longer duration (months to years)*

Phase III Studies

- ***Evaluates***
  - *Efficacy and safety evaluation in population subgroups*
  - *Dosing intervals*
  - *Drug-drug interactions*
  - *Drug-disease interactions*
  - *Risk/benefit information*
- *The information from Phase III forms the basis for most of the drug's initial labeling, which will guide physicians on how to use the drug*

Information Contained in a Typical Specification for a Synthetic Small Molecule

Test	Analytical procedures	Acceptance criteria
Identity	Infrared spectroscopy	Conforms to standard
	Melting point	Melting range
Structural elucidation	Nuclear magnetic resonance Mass spectroscopy	Conforms to standard
Assay (parent molecule)	HPLC/GLC	97.0–102.0%
	Titration	98.0–102.0%
Related substances (impurities)	HPLC/GLC	Total impurities less than 2.0%
		Single individual impurities less than 1.5%
		Known impurity X less than 1.0%
Inorganic impurities	Residue on ignition/ sulfated ash	Less than 500 ppm
Residual solvents	GLC	Solvent X less than 0.50% Solvent Y less than 0.20% Solvent Z less than 0.05%
Moisture content	Karl Fischer titration	Less than 0.5%
pH of 1% solution	pH measurement	4.60–5.00

National Authority Review and Approval

- *After Phase III, pharmaceutical company prepares reports of all studies conducted on drug and submits reports to NA in a New Drug Application (NDA)*
- *NA then reviews information in NDA to determine if drug is safe and effective for its intended use*
- *Occasionally, NA will ask experts for their opinion of drug; this occurs at advisory committee meetings*
- *These meetings are usually open to the public*
- *If NA determines that drug is safe and effective, the drug will be approved*

NA Clinical Hold

- *NA can stop the study from proceeding or stop a trial that has started for many reasons*

  (safety, disclosing accurately the risks of the study..)

Phase IV Studies

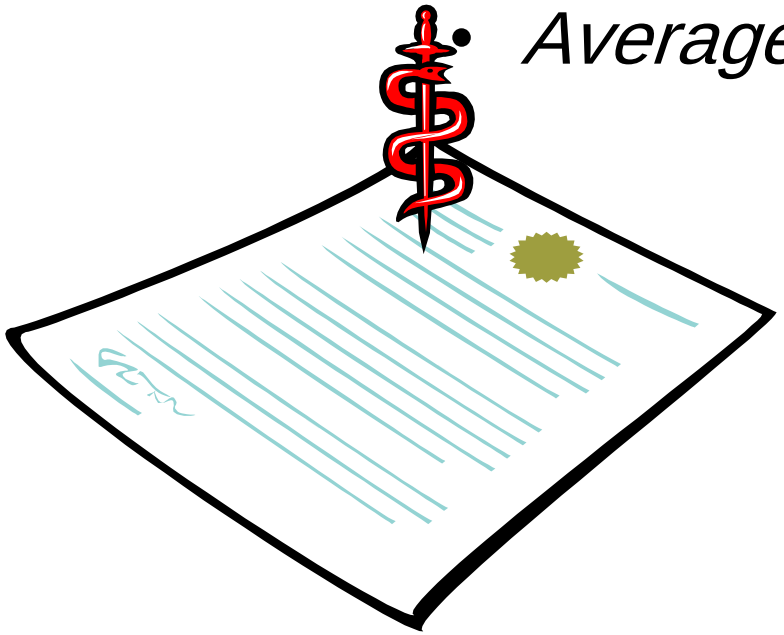
- *Conducted after a drug is approved*
- *Companies often conduct Phase IV studies to more fully understand how their drug compares to other drugs*

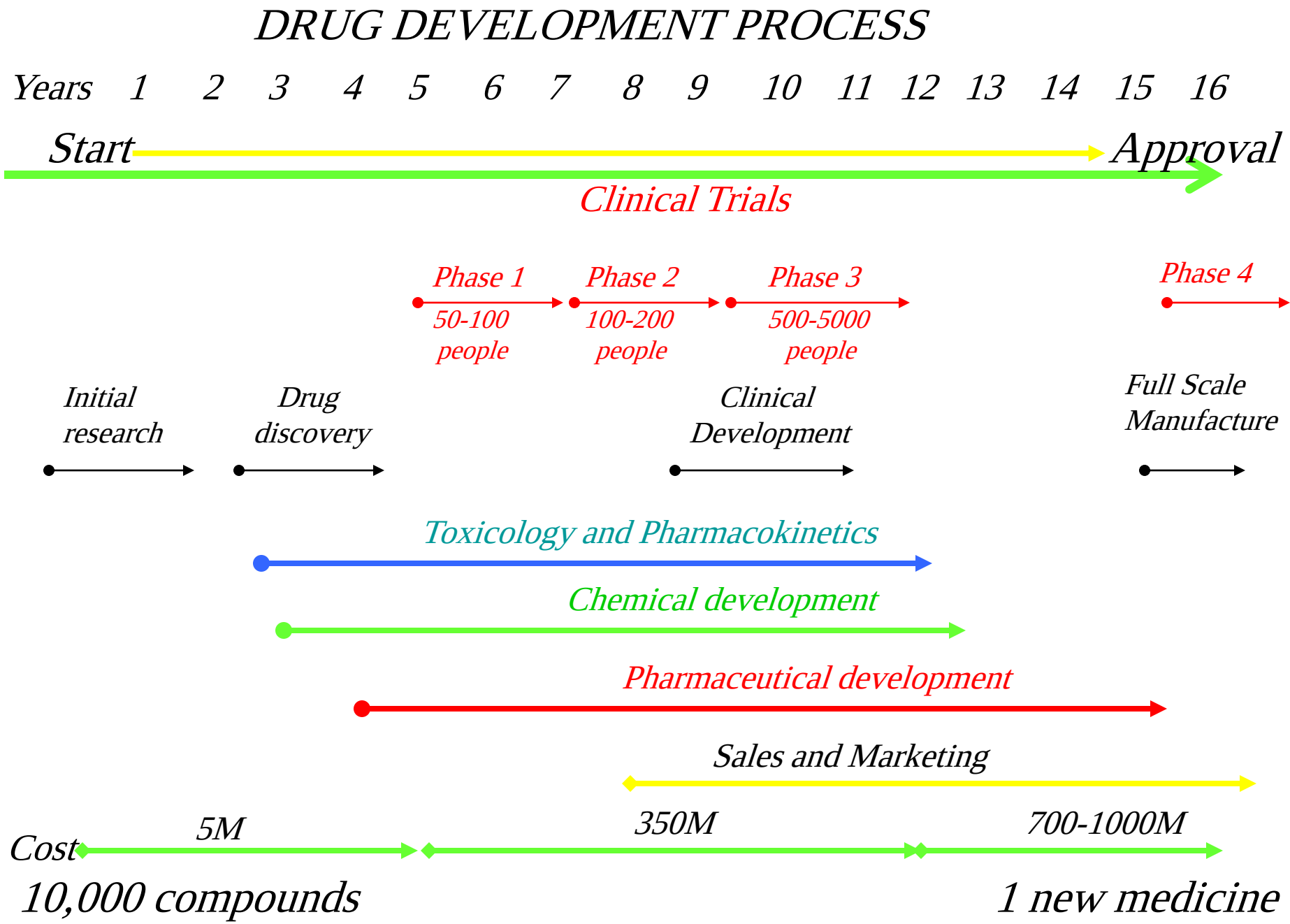
Phase IV Studies

- ***Description***
  - *Post-marketing studies*
  - *May involve additional age or ethnic groups*
  - *Monitors continued safety in large groups*
- ***Evaluates***
  - *Adverse events*
  - *Other efficacy data*
  - *Epidemiologic date*

New Drug Application (NDA)

- *Contains all scientific information company collected*
- *Typically runs 100,000 pages or more in length*
- *Average NA review time :30 months*



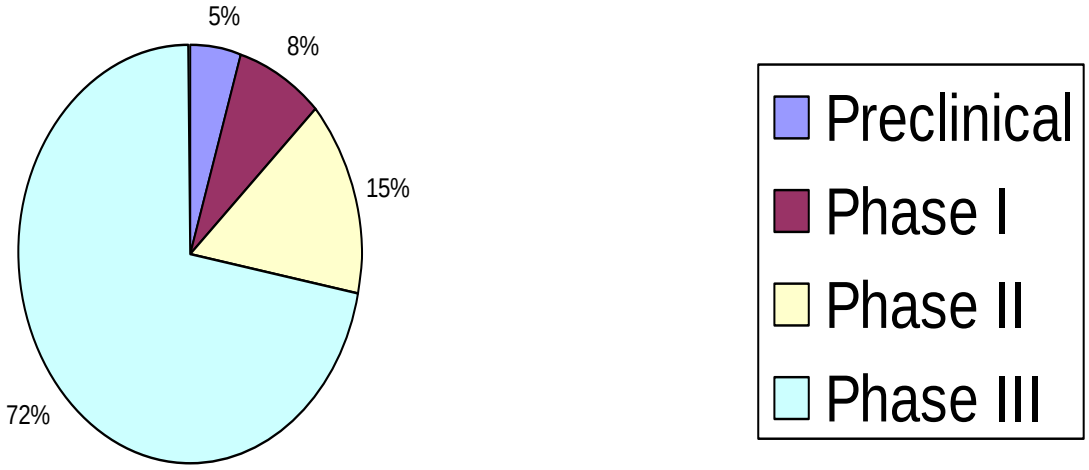

DRUG DEVELOPMENT PROCESS
Years 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16
Start
Approval
Clinical Trials
Phase 1
50-100 people
Phase 2
100-200 people
Phase 3
500-5000 people
Phase 4
Initial research
Drug discovery
Clinical Development
Full Scale Manufacture
Toxicology and Pharmacokinetics
Chemical development
Pharmaceutical development
Sales and Marketing
Cost
5M
350M
700-1000M
10,000 compounds
1 new medicine

Cost of Developing New Drugs

- *It costs **$1000,000,000***

  to develop one new medication from the laboratory to FDA approval

Breakdown of Total Costs by Clinical Development Phase



USA

Food and Drug Administration

FDA

U.S. agency, part of the Department of Health and Human Services, responsible for regulating clinical research and approval of marketing permits for food, drugs, medical devices and cosmetics in the U.S.

Japan

National Institute of Health Sciences

国立医薬品食品衛生研究所

National Institute of Health Sciences

Pharmaceuticals and Medical Devices Evaluation Center

EU

The European Agency for the Evaluation of the Medicinal Products (EMEA)

Manufacturing

- *المراقبة الحكومية للوجبات الاولى*
- *الانتاج الروتيني والمراقبة داخل المعمل*
- *المراقبة الدورية والعشوائية الحكومية*