رحلة الدواء من الفكرة إلى رف الصيدلية

New drugs: development & evaluation

تقييم

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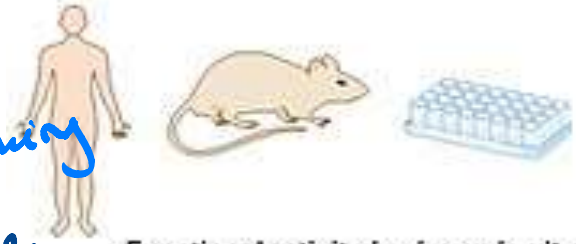
Scientific methods of drug discovery

old

دواء لمرض

Forward pharmacology approach



time consuming
costly
expensive

Functional activity *in vivo* or *in vitro* (e.g., of extracts or natural products)

Lead compounds

Target identification

تحديد المرض

resent

مرض ← دواء

Reverse pharmacology approach

توفير الوقت والمال والجهد

Identification of promising target proteins

Screening for compounds interacting with the target protein

Functional activity *in vivo*

•Developing new, innovative drugs takes time – a very long time and a lot of money (2 billion dollars).

• On average, the journey from discovery to market takes 12 years, however, in newer areas of medicine, like gene therapy, it can take up to 30 years.

• 1 in 5000 new compounds are approved as pharmaceutical drugs by regulatory agencies like the Food and Drug Administration (FDA) in the US or the European Medicines Agency (EMA) in the EU.

وكالة

Phases of a "typical" project, aimed at producing a marketable drug for a specific clinical need

DRUG DISCOVERY	PRECLINICAL DEVELOPMENT	CLINICAL DEVELOPMENT			REGULATORY APPROVAL	PHASE IV
• Target selection • Search for the lead compound • Optimization of the lead compound • Assessment of pharmacological characteristics	• Pharmacokinetics • Short-term toxicology • Formulation • Large-scale synthesis	Phase I Pharmacokinetics, tolerability, side effects in healthy volunteers 20-80 persons	Phase II Small-scale trials in patients to assess efficacy and dose. Long-term toxicology studies 100-300 persons	Phase III Large-scale controlled clinical trials 1000 (large scale)	Comprehensive data is submitted and reviewed by regulatory authorities	Post-marketing surveillance
2-5 years	1-5 years	5-7 years			1-2 years	
100 projects	20 compounds	10	5	2	1.2	1
Candidate drug						
Compound in development						
				Referral to the Health Registration Committee		
				Drug approved for marketing		

This table only shows the activities in each phase, but the details of each vary greatly according to the type of drug being developed

candidate drugs:- drug discovery + preclinical

development:- Discovery + priclinical + phase I+II of clinical

Health car committee :- phase III & Regulatory approval

drug appoved for marketing :- phase-III + IV + Regulatory approval

which Phase exclude women of childbearing age? phase-I

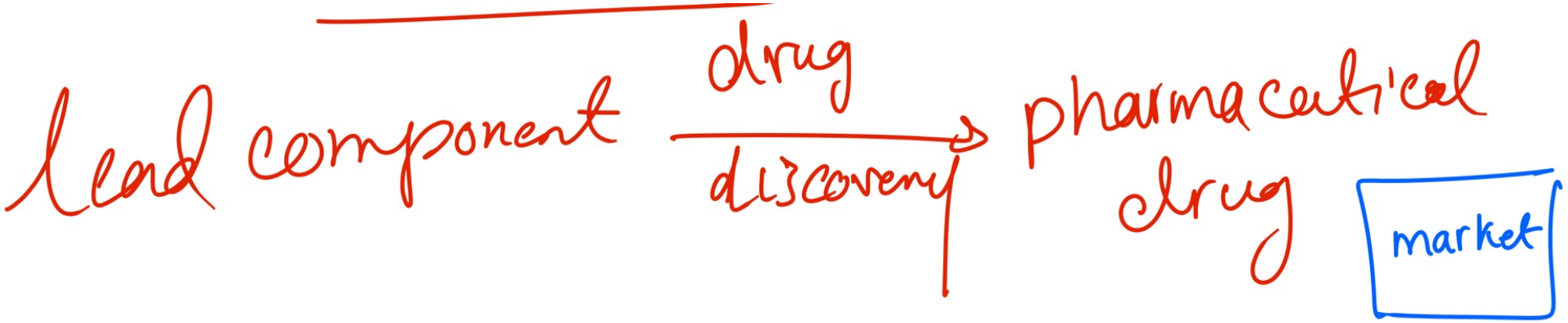
price negotiation may in way or another depend on healthcare system

rare conditions ⟶ phase IV

Drug development

- **Drug development** is the process of bringing a new pharmaceutical drug to the market once a lead compound has been identified through the process of drug discovery.

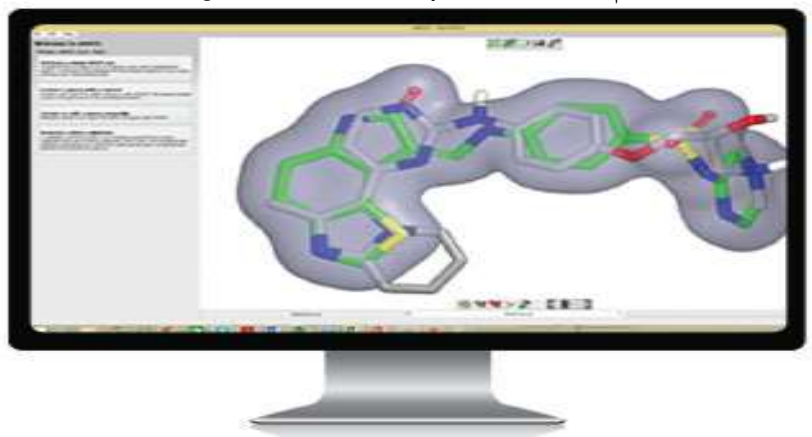
الدواء الذي في الصيدلية: جاهز ومغلف



1. Drug Discovery

- The discovery stage starts with research and development in a labs.
- Researchers identify target molecules – such as genes, proteins or enzymes that plays a significant role in a disease.
- This is followed by so-called *in silico* – computational – testing performed on hundreds – sometimes thousands – of chemical or biological compounds (hits) to evaluate their effects on the disease.
- Leads: chemical or biological compounds with increased activity at a chosen target (potency) and reduced activity against unrelated targets (specificity)

evaluate | ɪˈvaljʊeɪt | transitive verb
‹property, something's worth› قَدَّرَ something's effectiveness, a patient› ; (US)› قَيَّمَ •



= تحسينة ثاني

•Lead optimization:

•to identify one or two drug candidates (lead مرشح) suitable for further investigation by:

•High-throughput screening (HTS) is one of the newest techniques used in drug design applied by robots, detectors and software .

2. Preclinical research

- The discovery phase is followed by a pre-clinical research phase, where the lead compounds are tested both *in vitro* and *in vivo* – experimental models (cell cultures and animal studies).
- Once fully characterized, the most promising compounds become lead candidates.
- The most important aspect of preclinical research is the safety tests to ensure that the candidate is not toxic before it can go through clinical studies in humans.

الشرح:

هذا النص يصف المراحل الأولى من عملية تطوير الأدوية، وهي:

1. **مرحلة الاكتشاف والمرحلة قبل السريرية**: تستغرق هذه المرحلة وقتًا طويلاً (4-7 سنوات) وتتضمن البحث الأولي وتجارب المختبر.
2. **طلب إجراء الدراسات السريرية**: بعد نجاح الاختبارات الأولية، يتقدم الباحثون بطلب لإجراء تجارب على البشر.
3. **الإجراءات التنظيمية**: يتم تقديم الطلب إما كـ IND في الولايات المتحدة أو CTA في الاتحاد الأوروبي.
4. **مراجعة السلطات**: تقوم الهيئات التنظيمية بمراجعة البيانات واتخاذ قرار بشأن الموافقة على إجراء الدراسات السريرية.

- The discovery phase and the preclinical phase can take 4-7 years.
- After completion of the preclinical tests, developers will apply for permission to proceed with clinical – in-human – studies.
- This is done either through an *Investigational New Drug (IND)* application in the US or a *Clinical Trial Application* (*CTA*) in the EU.
- The respective regulator authority then examines all available data and decides whether to approve the clinical studies.

نطلب منهم الموافقة على اجراء تجارب على البشر

إما قبول الطلب أو رفض الطلب أو التعديل عليه ← لحد الآن إنت حر فيك ٥٠٠ مليون دولار

3. Clinical development

- **Phase I – safety** and toxicity and effectivity
- Following regulatory approval and approval from ethics committees, the first clinical study, a phase I study – which constitutes the first study in humans, is initiated.
- Here, the candidate is generally tested on 20 to 80 healthy volunteers with the aim of determining whether the candidate behaves in the same way in the human body as the preclinical studies have indicated.

- The safety profile – or toxicity – of the substance is again the main focus, but this time in humans.
- In phase I: a safe dose, how the drug is absorbed, and how long it is active in the body are tested.
- For safety reasons, phase I clinical trials tend to exclude women of childbearing age.
- A phase I study takes up to one year to perform

- **Phase II – Proof-of-Concept**

efficacy

- With positive safety results from phase I, drug developers can apply for permission to take the next clinical development step – phase II.
- In this phase, the candidate is most often evaluated in 100 to 300 patients diagnosed with the disease that the candidate is intended to treat.

Small scale

- Efficacy and safety are tested; minimum and maximum dosages of the drug are determined for use in the next phase of development.
- Phase II typically takes up to two years.

side effect إلي بتظهر ← تتسجل في وسيبة الدواء

- **Phase III – regulatory evidence**
- In the case of positive safety and efficacy data from phase II, the next step is phase III. يعني خلصت من المرحلتين السابقتين بـ امان وفاعلية
- This is the last step in the evaluation of a drug before requesting market approval from pharmaceutical regulators.
- The number of patients enrolled in a phase III study is usually at least 1000 – this ensures that enough data is obtained to show that the drug is safe for humans and has the intended clinical efficacy.

•In the phase III study: researchers document and report any side effects experienced by patients.
• The patients need to be exposed to the drug for long periods of time in order to make sure those side effects are properly assessed.
•Any side effects noted at this stage are listed in the package leaflet of the final product.
•Phase III takes an average 1-4 years.

Market approval & launch

طلب ترخيص جديد

for marketing

- **the drug registration process**
- With good results from phases I-III, an application for market approval is submitted, called *New Drug Application* (NDA)*/*Biologics License Application* (BLA) in the US and *Marketing Authorization Application* (MAA) in the EU.
- These can include hundreds of thousands of pages of documentation summarizing all collected data from the discovery phase onwards, and where the principal investigator argues for approval with the FDA and/or EMA

- عملية تسجيل الدواء
- مع الحصول على نتائج جيدة من المرحلتين الأولى إلى الثالثة، يتم تقديم طلب للحصول على الموافقة على التسويق، يُسمى طلب دواء جديد *(NDA)**/طلب ترخيص منتجات بيولوجية *(BLA)* في الولايات المتحدة، وطلب ترخيص تسويقي *(MAA)* في الاتحاد الأوروبي.
- يمكن أن تتضمن هذه الوثائق مئات الآلاف من الصفحات التي تلخص جميع البيانات التي تم جمعها من مرحلة الاكتشاف فصاعدًا، حيث يجادل الباحث الرئيسي للحصول على الموافقة من إدارة الغذاء والدواء *(FDA)* و/أو وكالة الأدوية الأوروبية *(EMA)*.

•Preparing the application documentation can take several months, followed by about 6-10 months for the authorities to process the application.

- **Market launch**
- If the regulatory authorities approve an application, the candidate – or medicine as it is now called – is ready for market launch.
- At this point, price negotiations begin between the principal and the potential buyers (government agencies or insurance companies, depending on the healthcare system).
- The price negotiation process can differ greatly from country to country.

Phase IV studies – monitoring marketing and safety

•In some cases, regulatory authorities require follow-up phase IV studies after a drug has received market approval.

• This is done by collecting data from clinical practice: real care units that treat patients.

•The aim is to increase pharmacovigilance.

•Phase IV studies evaluate whether the drug is interacts with other substances, any additional side effects.

•This is especially important for: drugs for complex medical conditions, drugs for the treatment of pregnant women.

•Additionally, phase IV studies may be relevant for drugs that will treat rare conditions, which had a limited number of patients in phases I-III.

هذه الفقرة تتحدث عن أهمية دراسات المرحلة الرابعة (**Phase IV**) في تطوير الأدوية ، وتحديداً في الحالات التالية :

• **الأدوية التي تعالج الحالات النادرة** : حيث تكون دراسات المرحلة الرابعة مهمة للأدوية التي تستهدف علاج الأمراض النادرة .

• **محدودية عدد المرضى في المراحل السابقة** : عندما يكون هناك عدد محدود من المرضى في المراحل الأولى والثانية والثالثة من التجارب السريرية .

الهدف من هذه الدراسات هو جمع المزيد من البيانات حول فعالية وسلامة الدواء بعد طرحه في السوق ، خاصة عندما يكون عدد المرضى في المراحل السابقة محدوداً بسبب ندرة الحالة المرضية .

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Thank you