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Some Important Facts in Manufacturing of New Drugs

Siniša Franjić | Faculty of Medicine, Josip Juraj Strossmayer University of Osijek, Republic of Croatia, Europe

Abstract

Every new drug which is put on the market has several phases in its creation. Most important of these phases are laboratory testing, animal experimentation, clinical trials, and economic analysis. In each of these phases, there are certain issues without which elaboration the new drug cannot be put on the market. The emphasis in this paper is precisely on these specific issues.

Keywords

Drug; Pharmacology; Manufacturing; Economy

Introduction

The development of a new drug usually begins with the discovery or synthesis of a potential new drug compound or the elucidation of a new drug target [1]. After a new drug molecule is synthesized or extracted from a natural source, subsequent steps seek an understanding of the drug's interactions with its biologic targets. Repeated application of this approach leads to the synthesis of related compounds with increased efficacy, potency, and selectivity. In the United States, the safety and efficacy of drugs must be established before marketing can be legally carried out. In addition to *in vitro* studies, relevant biologic effects, drug metabolism, pharmacokinetic profiles, and relative safety of the drug must be characterized *in vivo* in animals before human drug trials can be started. With regulatory approval, human testing may then go forward (usually in three phases) before the drug is considered for approval for general use. The fourth phase of data gathering and safety monitoring is becoming increasingly important and follows after approval for marketing. Once approved, the great majority of drugs become available for use by any appropriately licensed practitioner. Highly toxic drugs that are nevertheless considered valuable in lethal diseases may be approved for restricted use by practitioners who have undergone special training in their use and who maintain detailed records.

The interactions between a drug and the body are conveniently divided into two classes. The actions of the drug on the body are termed pharmacodynamic processes. These properties determine the group in which the drug is classified, and they play a major role in deciding whether that group is an appropriate therapy for a particular symptom or disease. The actions of the body on the drug are called pharmacokinetic processes. Pharmacokinetic processes govern the absorption, distribution, and elimination of drugs and are of great practical importance in the choice and administration of a particular drug for a particular patient, eg., a patient with impaired renal function.

The drug is a composition that alleviates the symptoms of some disease, it prevents and heals it [2]. The structure can be of natural or synthetic origin. If taken uncontrolled, it can cause addiction. Regardless of the composition, each drug should have been effective and safe. These are the facts with which each patient should be familiar.

Systems Pharmacology

Systems pharmacology is defined as a translational science that aims to examine all the biological activities in the body related to internal exposure of a drug or drug candidate and the resultant drug responses and pharmacological activities [3]. Systems pharmacology uses both experimental approaches and computational analyses to examine and understand drug action across multiple levels including molecular, cellular, tissue, and whole organisms with consideration to the presence of several interacting pathways. The field has grown and developed rapidly because of the emergence of omics technologies and network analysis capabilities, and the increased number of computer scientists, engineers, and mathematicians involved in addressing and solving complex biological problems. In an NIH (National Institutes of Health) white paper by the Quantitative systems pharmacology (QSP) workshop group in 2011, QSP was defined as providing an integrated approach to determining and understanding mechanisms of action of drugs and drug candidates in preclinical models (*in vitro* and *in vivo*) and in patients eventually receiving the drugs. The stated goals were to create a knowledge base to facilitate the change of complex cellular networks in pre-determined ways with mono and/or combination therapies; maximize therapeutic benefit by altering the pathophysiology of the disease being treated, and

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*Corresponding author:

Dr. Siniša Franjić,
Faculty of Medicine
Josip Juraj Strossmayer, University of Osijek
Cara Hadrijana, 10/E, 31000 Osijek
Republic of Croatia, Europe
Tel: +385-31-51-28-00
Fax: +385-31-51-28-33
E-mail: sinisa.franjic@gmail.com

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minimize toxicity. Given that the mammalian signaling and regulatory pathways are complex, drug–target interactions can potentially lead to adverse effects due to the propagation of signal flow to distal effectors (off-targets) in multiple cells and tissues. However, using complex pharmacological and toxicological network analyses, both positive and negative effects can be predicted.

Economic pressures constitute a considerable threat to drug research and, specifically, to its original therapeutic objectives [4]. The growth of drug research in the industrial domains as much the result of historical development as of functional necessity. The pharmaceutical industry was a product either of diversification in the dyestuffs sector or of the efforts of a small number of pharmacies toward the end of the nineteenth century to provide drugs of standardized form and consistently high quality. The diversification of the dyestuffs producers into pharmaceutical companies followed the advances made in chemotherapy, a field that owed its conceptual and experimental origins to the selective staining of host tissue and parasites with dyestuffs. This was the starting point for new therapeutic concepts that led to the identification and the development of many antiparasitic, antimicrobial, antiviral, and oncological medicines. Technically, the "industrialization" of the pharmacies was initially driven by analytical and pharmaceutical methods. Whatever its roots, drug research – naturally – borrowed a large number of techniques from other disciplines. Chemistry, physics, pharmacology, biochemistry, and – later on – microbiology, molecular biology, toxicology, and clinical medicine became essential ingredients of successful drug research. The "innate" interdisciplinarity of drug research, the concentration of so many and such varied methods all focusing on one goal, virtually predestined its development in an industrial setting – and also made conflicts inevitable.

Economic Studies

Economic studies conducted in the United States may not transfer well to other countries [5]. Although one can argue that a chemical entity (and thus a pharmaceutical product) is the same in any country, other factors come into play that limits the generalizability of pharmacoeconomic analyses of these products. For example, immunization or screening programs are more cost-effective in countries with a higher incidence of the disease of interest. The availability (or lack thereof) of timely access to medical services can modify decision making. For example, if gastrointestinal endoscopies (used to detect stomach ulcers) are delayed or unavailable, the physician may prescribe a medication to treat ulcers without confirmation that the patient actually has an ulcer. Another factor is that a product may be licensed in some countries but not others or a generic version may be available in some countries but not others, so the alternatives chosen for comparison (current usual practice) may differ by country. Even though a small number of studies have shown that there is not a great difference in people's preferences or scores for different health states between Europeans and North Americans, the dollar value placed on outcomes, such as a quality-adjusted-life-year (QALY), by decision makers has been shown to differ by country.

Governments that finance the majority of health care in their countries are particularly motivated to extract value in return for their health care spending. This may be accomplished by adding another level of control, which might include price negotiation, price setting, or formulary management. When a country is a single payer for pharmaceuticals, it has more leverage to negotiate the price and formulary status of a medication. Some countries have developed and implemented pharmacoeconomic guidelines to aid pricing and reimbursement decisions. Others have created advisory bodies that recommend what medications should and should not be included on local and national formularies. These guidelines are a set of rules that outline the requirements and information needed from manufacturers that wish to have their product considered. The number of countries that have implemented guidelines, as well as the specific rules contained in these guidelines, change frequently. Some of these guidelines are mandatory, and others are voluntary.

Public health has always been one of society's biggest challenges [6]. There are societal pressures to ensure that adequate health care is provided for citizens. Besides access to food and housing, access to health care has remained one of the bright lines between the haves and have-nots. Religious groups, charitable organizations, and advocacy groups exist to promote health-care issues ranging from vaccinations to universal care to more research into particular diseases. If investors fund only those products or services that improve health, this is also a form of public advocacy. If the market rewards products that lead to good health, then companies whose products do not lead to better health will need to adapt by improving their product or service or will be made extinct by market forces alone. Health-care investors could create a virtuous health circle by rewarding good companies. There is a role for the capital markets to play in restructuring health care, though that role is still to be defined.

A full economic evaluation stands for a comparative analysis of costs and consequences of alternative courses of action (alternative ways of using scarce resources) [7]. Courses of action include different products (e.g., two drugs for the same therapeutic indication), different pathways (e.g., two different drug sequences), and different programs (implementing a community pharmacist diabetes management education program compared to the standard of care). In brief, two features characterize a full economic evaluation: (1) costs and consequences are simultaneously estimated and (2) to take decisions on alternative ways of using scarce resources.

Costs included in an economic evaluation analysis depend on the perspective used. The perspective may range from one of the health care payers (only health care services are included), other payers (e.g., payers of social care), the patient/family (out-of-pocket expenses, transportation costs, informal care provided by the family to patients are considered), and the society as a whole (this perspective includes also productivity lost due to temporary or permanent absence from work, premature mortality, and presenteeism, i.e., working while sick). The ideal perspective is the societal one.

Unlike the conventional terrain of macro-politics where states collide over interests of national security, pharmaceutical politics play out at a level where citizens deal with illness and health and small organizations voice demands for greater representation [8]. The "high" politics that shape relations among countries and determine governance structures at the national and international level now can be found in the "low" arenas of drug regulation and health care delivery. Power and politics are not just found at the level of nations or international agreements, but are wrapped up in seemingly innocuous pharmaceutical drugs and supposedly standardized regimes for verifying their safety and efficacy. Debates over pharmaceutical drugs in this "low" arena ultimately shape the organization of states, industry, the medical profession, and non-governmental organizations.

Pharmacogenomics

Pharmacogenomics (also known as pharmacogenetics) is a component of individualized ("personalized") medicine that addresses how genetic factors impact drug therapy, with the goal of optimizing drug therapy and ensuring maximal efficacy with minimal side effects [9]. The effect of drugs is traditionally divided into pharmacokinetics (how drugs are absorbed, distributed, metabolized, and eliminated) and pharmacodynamics (the molecular target or targets underlying the therapeutic effect). In principle, genetic variation can influence pharmacokinetics, pharmacodynamics, or both. Currently, most clinical applications of pharmacogenomics involve drug metabolism, but over time more attention will likely shift to pharmacodynamics. Many of the current pharmacogenomic clinical applications focus on the cytochrome P450 (CYP) enzymes. The sequencing of the human genome and intensive research into how genetic variation affects drug response holds the promise of altering the paradigms for medication therapy. However, current clinical applications utilizing pharmacogenomics are still rather limited. The coming years should see steady growth in this field that will allow primary care providers and other health professionals to better manage drug therapy.

Pharmacogenomics, the study of genetic factors that underlie variation in drug response, is a modern term for pharmacogenetics [10]. Pharmacogenomics implies a recognition that more than one genetic variant may contribute to variation in drug response. Historically, the field began with observations of severe adverse drug reactions in certain individuals, who were found to harbor

genetic variants in drug-metabolizing enzymes. As a scientific field, pharmacogenomics has advanced rapidly since the sequencing of the human genome. In the last decade, powerful genome wide association (GWA) studies, in which hundreds of thousands of genetic variants across the genome are tested for association with drug response, led to the discovery of many other important polymorphisms that underlie variation in both therapeutic and adverse drug response. In addition to polymorphisms in genes that encode drug-metabolizing enzymes, it is now known that polymorphisms in genes that encode transporters, human leukocyte antigen (HLA) loci, cytokines, and various other proteins are also predictive of variation in therapeutic and adverse drug responses. In addition to the new discoveries that have been made, the past decade has ushered in "precision medicine," also known as "stratified or personalized medicine," in which genetic information is used to guide drug and dosing selection for subgroups of patients or individual patients in medical practice.

Clinical Trials

Clinical trials form a fundamental part of the research, development, and licensing of new medicines [11]. Research into how the drug interacts in humans is essential to ensure that safe and effective medicines are licensed as new treatments. It is an exciting and varied role at the cutting edge of modern research with trials ranging across all therapeutic specialties. Clinical trial pharmacists are therefore required to have a broad clinical knowledge and a specialist knowledge of the regulations that clinical trials have to follow.

Drug therapy, and hence also drug research, are perceived as part and parcel of the medical – or more specifically of the doctor's – vocation [4]. The declared goal of all drug research has always been to satisfy therapeutic needs. This goal goes hand in hand with the need for effective and safe drugs and for the careful assessment of the risk/benefit relationship in the therapeutic use of drugs, particularly when the relevant side effects of the drugs in question are known. In the majority of industrialized countries, these requirements are safeguarded by detailed drug licensing provisions. There are simple professional rules for estimating the risk/benefit ratio. They require an understanding of the risks associated with the condition to be treated, a realistic assessment of other available therapeutic approaches, and knowledge of the risks entailed in the proposed treatment.

API Products

The design and construction of an active pharmaceutical ingredient (API) facilities is an extremely complex and challenging undertaking [12]. The time required to design construct and validate a facility to manufacture API products must be balanced against marketing and regulatory considerations. A firm may be required early in the drug development process to start investing in new production facilities or enhancing existing capacity so that a product can be produced for testing, and eventually for full-scale production to meet the market demand. An API manufacturer must develop a comprehensive process/facility design and construction execution strategy to ensure achievement of all regulatory, cost, and market objectives for the compound.

The successful completion of a new API process facility is a function of good engineering practices, sound construction techniques, and a well-planned and documented start-up and validation plan. Early detailed process definition enables the project team to develop a comprehensive project execution strategy. The execution strategy outlines the engineering and construction methods for the project. The start-up and validation plan ensures regulatory compliance and a smooth transition from construction to operation. Active pharmaceutical ingredient production facilities are complex, expensive to design, construct, and validate. New facilities require sophisticated processing equipment, utilities, and support functions. Careful planning and good sound engineering is critical to assure that the investment in capital is managed wisely.

At various stages of the design process, a HAZOP must be conducted on the project [12]. The purpose of this analysis is to identify any potential weakness in the design of a process facility. Weaknesses are identified as:

safety concerns (i.e., dangers to personnel)

environmental impact (i.e., chemical release)

economic impact (i.e., damage or loss of equipment or facility)

The HAZOP reviews will look at each detail of the process, examine what is happening in that stage of the process, and then question a series of "what if" potential failures. Questions such as a failure of a control, loss of power, will generate a list of possible reactions to that failure mode. The failure list is then generated from experience with similar process arrangements or from experience with this specific equipment. This potential failure is then analyzed and a determination of the risks. A failure of low risk from safety exposure or cost of damage to the facility would not generate further action by the design team. An item with a potential of extremely unsafe condition or high-cost damage would then be listed with a recommendation for additional controls or a revision to the design.

Prescribing

Physicians usually tackle clinical situations by taking a history (asking questions), performing a physical examination, obtaining selective laboratory and imaging tests, and then formulating a diagnosis [13]. The synthesis of history, physical examination, and imaging or laboratory tests is called the clinical database. After reaching a diagnosis, a treatment plan is usually initiated, and the patient is followed for a clinical response. Rational understanding of disease and plans for treatment are best acquired by learning about the normal human processes on a basic science level; likewise, being aware of how disease alters the normal physiologic processes is also best understood on a basic science level. Pharmacology and therapeutics require also the ability to tailor the correct medication to the patient's situation and awareness of the medication's adverse effect profile. Sometimes, the patient has an adverse reaction to a medication as the chief complaint, and the physician must be able to identify the medication as the culprit. An understanding of the underlying basic science allows for more rational analysis and medication choices.

Therapeutic drug monitoring (TDM) may be defined as the use of a drug or metabolite monitoring in body fluids as an aid to the management of therapy (the term therapeutic drug management is now also employed as an alternative description) [14]. Since antiquity, physicians have adjusted the dose of drugs according to the characteristics of the individual being treated and the response obtained, and this practice is easiest when the response is readily measurable, either clinically (e.g. in the case of antihypertensive drugs, analgesics or hypnotics) or with an appropriate laboratory marker (e.g. in the case of anticoagulants, hypoglycemic agents or lipid-lowering drugs). Dose adjustment is much more difficult (but no less necessary) when drug response cannot be rapidly assessed clinically (e.g. in the prophylaxis of seizures or mania), or when toxic effects cannot be detected until severe or irreversible (e.g. nephrotoxicity or ototoxicity). Provided that certain basic conditions are satisfied and appropriate analytical methods are available, the plasma concentration of a drug or metabolite may serve as an effective and clinically useful surrogate marker of response in these cases. However, it must be stressed that TDM is not simply the provision of an analytical result but a process that begins with a clinical question and continues by devising a sampling strategy to answer that question, determining one or more drug concentrations using a suitable method and interpreting the results appropriately.

Prescribing is the first step, followed by dispensing and administering the drug, in a multistep process that is successful when the right patient receives the right medication in the right amount at the right time [15]. Because it is multistep and because of the various human factors involved, prescription errors are not uncommon. Errors occur due to poor handwriting, confusion of drugs with similar names, misunderstood abbreviations, inattention, and prescriber ignorance. Furthermore, a notion embedded in all of these potential errors is the assumption that the prescriber actually wrote

the correct "thing" on the prescription. As the final point indicates, prescriber ignorance is a cause of medication error.

Conclusion

Modern medicine has done so much to treat many diseases. Taking into account the fact that medical research in technology has never been so intense as it is today, it comes to the conclusion that the development of new technologies has made it possible to detect new mechanisms for developing the disease and their treatment. The availability and use of new drugs represents the crown of scientific research involving a large number of researchers from a wide range of medicine. Each new drug testing project starts with the idea, continues with complex and expensive research and ends with its put on the market. It becomes available in pharmacies and hospitals as well as in other healthcare institutions.

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