**Review Article**

**Drug Development of Second Generation Drugs: Process and Procedures**

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**Abstract**

This paper is a literature review of the process, findings, and variations through drug development. Though drug development started at a very early time in history, it has become regulated, and the refinement process continually occurs. Research and development are fueled by funding and continuing questioning for the most safe and effective medications for worldwide use. The purpose of this paper is to further review the current literature concerning drug development, pharmacogenomics, and pharmacokinetics. Though a vast amount of research and development has occurred, it is important to continually reevaluate the current medications that are being developed and marketed and adapted to all populations of individuals as needed. Special populations of individuals have fought for further investigation and research into more appropriate medications to fit their needs. Some research has been conducted for these populations, such as pregnant and lactating women and children, but much more is needed to provide equity in drug development.

**Keywords:** Drug development; Drug efficacy; First-generation drugs; orphan conditions; Pharmacogenomics; Pharmacokinetics; Special populations; Second-generation drugs

**Drug Development**

Drug development and the legislation of drug manufacturing and marketing originates back to the early 1900s. Regulatory agencies have developed throughout the years to make drugs more effective and safer for the general population, while at the same time adapting and creating new drugs for further efficacy to treat health concerns. Research and clinical trials have continued increasing over time as well, to lead to the development of new drugs that are adapted in pharmacokinetics. These advances lead to medications being able to work better in the human body, thus, leading to production of prescription and over-the-counter drugs that are available for human consumption and healthcare use.

Drug development affects all populations of people and therefore research must be persistently conducted to determine what is most safe and effective for specific special population groups such as pregnant women and children. With the use of research, technology, and knowledge of the past and present drug development, the future of drug development appears to have promises to be exponentially enhanced than the current pharmacologic situation. One area that is not adequately represented through historical data is the special populations of patient groups such as pregnant and lactating women as well as the pediatric population. Ren, et al. [1] states that it is historically known that through drug clinical trials and testing, pregnant women have been excluded due to the moral, ethical, and legal concerns associated with this situation. This area of discussion will be addressed further in this paper as well.

**Background of Drug Development**

Throughout research, it is evident that historically, until the mid-20th century, drug development and manufacturing was widely unregulated. The Federal Food, Drug, and Cosmetic Act of 1938 set regulation of drugs into motion, therefore creating stricter guidelines for safety of drug delivery [2]. Prior to this time, there were unregulated drugs being utilized and marketed to the public. This occurred without adequate knowledge of side effects and other potential risks that may occur. Sulfa drugs were the first drugs to be regulated and marketed, therefore changing the history of treatment of bacterial infections. From 1944 through the 1990s, significant increases in research and development of drugs began to take place. Many new pharmaceutical companies were born during this time and continued to flourish with the increase in funding for clinical trials and discoveries of new molecules to make life-changing medications [2].

First-generation medications took the stage in initial regulated drug delivery and then as time and research continued, later generation and more effective and specific medications came into existence [2]. Pharmacokinetics, how drugs work through the body, and pharmacodynamics, how drugs effect the body, are the main reasoning behind further generation and development of newer medications [3]. It is important to remember that without initial first-generation drugs, such as diphenhydramine, penicillin, or haloperidol, second and third-generation drugs would never have become developed. The initial first generation drug is utilized to become the "innovator" for the development of more selective and specific drugs. Benefits of second-generation and future drugs being developed is the specificity that each one brings to the body in the way in which it acts in more selective ways and the decrease in side effects and adverse effects [2].

**Summary and Synthesis of Drug Development**

Drug development must be able to appropriately follow the process of pharmacokinetics to be effective in the body. This includes absorption, distribution, metabolism, and excretion [3]. Being able to achieve the effectiveness of the drug at its maximum capability, by using the lowest dose possible, will not only create treatment against the disease or disorder it is targeting, but minimize the amount of side effects possible [4]. Drug discovery and development involves the discovery of the drug itself, preclinical development on the use of animals as test subjects, clinical trials on humans, and then to be advanced for approval through regulatory agencies [5]. The complexity of drug development begins when a particular molecule is discovered that elicits a result that is desired, such as an effect on a cell. The initial drug discovery then begins the entire process of how drugs are developed, although this is a very lengthy and costly process. Adaptations occur to the molecule found in the drug discovery stage to make it the most effective and selective through the pharmacokinetic process. The goal during this is to avoid as many side effects as possible and produce a drug that is very specific in its action to treat a given disorder or disease [5].

For oral drug development, one aspect to take into consideration is the permeability of the intestinal lumen to be able to absorb the medication. This is the first step in the pharmacokinetic process. The molecular and chemical structure of the drug itself is important to research and investigate during the clinical trials and before it is distributed and marketed to the public. By investigating and researching these chemical structures to increase solubility and permeability in the intestinal lumen, it affects the amount of bioavailability that is created of the drug. Allowing the permeability and absorption of the drug to be increased assists in the increase in bioavailability, therefore less of a dosage needed upon administration [4].

**Summary and Synthesis of Special Population Drug Development**

Ren, et al. [1], states that between forty and sixty percent of pregnant women have comorbidities that require one or more prescription medications to treat an issue either preexisting to pregnancy or pregnancy induced. Though this is known data, most of the medications that are prescribed to pregnant or lactating women are prescribed in the "off-label" use due to the lack of testing of efficacy and safety in this population of women. Some medications that have been used for problems that occur during pregnancy have been found to have teratogenic effects on the fetus while in utero. This includes the medications used in the mid-1900s, diethylstilbestrol and thalidomide. Both medications have been found to have severe teratogenic effects on the fetus such as congenital anomalies in female fetuses and severe upper and lower limb malformations [1]. Due to these findings, the FDA categorized pregnant women in the vulnerable category for drug trials and have eliminated pregnant women from clinical trials to prevent further teratogenic effects to a fetus.

A component addressed in relation to drug development compared with pregnancy is the physiological changes that occur during pregnancy that may affect drug disposition. This creates a disruption in the normal pharmacokinetic process of absorption, distribution, metabolism, and excretion. Examples such as delayed gastric emptying, increase in blood volume, and increase in renal clearance effect all areas of the normal pharmacokinetic process. The continual complexity of pregnancy and its physiologic process of this population of patients, creates a continual need for research. As technologies advance, more research and data can be collected that will play a crucial role in safe and effective drug development for this population [1]. The other main special population that is underrepresented in drug development is the pediatric population. Many of the conditions that are described in this population of individuals are classified as "orphan conditions". These conditions present themselves as an onset during the childhood years and therefore do not have specific drug development and research directly related to treatment [6]. At times, these conditions are treated with medications aimed towards the treatment of adults and used as a trial "off-label" use. Not only in this population do researchers have to assess the age range of pediatrics, but also the cognitive and behavioral development aspect related to drug development which can be a challenge. Challenges noted, mainly with central nervous system disorders, are that due to cognitive disabilities or delay, children are not able to effectively communicate symptoms they are experiencing to then have appropriate medication treatment. This can be an impairment to drug development as well for drug or clinical trials related to this special population [6].

**Summary and Synthesis of Pharmacogenomics**

An aspect of drug development that is not frequently communicated to the general population is its relation and research related to genetics. Pharmacogenomics has begun to influence the 21st century for drug development and implementation in the clinical setting. Pharmacogenomics can affect knowledge regarding efficacy of medications that exist, or are in development stages, as well as how to decrease adverse drug reactions [7]. Research has shown that though the study of genomics related to drug efficacy could be extremely beneficial, it has not been widely used in the clinical setting. Even at times there have been specific genomic studies performed, with data to support findings, but clinical practices have not yet been adapted based on these findings [8].

Specific drugs have been studied through the Genome-Wide Association Studies (GWAS) and includes clopidogrel, pegylated-interferon, and carbamazepine [8].

The prototype drug for GWAS has been pegylated-interferon. This is the standard of practice drug used to treat chronic Hepatitis C Virus. This virus affects a significant number of people, greater than 200 million worldwide, and is the leading cause of cirrhosis and cancer of the liver [8]. This treatment, combined with ribavirin is an extremely costly medication regimen, approximately $50,000 per year. Though this has been the leading treatment, along with its extreme cost, it has been found to be effective in less than fifty percent of the population being treated. Pharmacogenomics studies are beneficial in this type of scenario due to the predetermination of whether this costly medication regimen would be effective for the patient. If it is found that their genetic makeup would not be influenced by this regimen, the healthcare team could choose to follow a different treatment plan instead of wasting financial resources of the patient with no resolve [8].

Pharmacogenomics can also benefit patients and healthcare providers by predetermining risks for adverse drug reactions. The goal of medication use is that it is safe and effective with minimal side effects or adverse drug reactions. Eliminating the unknown of trial-and-error type medication use, creates safer outcomes for all patients, especially those who could be at risk for fatal adverse reactions [8]. Through GWAS, it has been found that certain alleles of antigens that are in someone's genetic makeup can cause an increased risk for hepatotoxicity of a drug. By understanding this ahead of prescribing medications, providers can adapt their treatment plan to be less caustic to the individual. Another adverse reaction discovered through GWAS is a skin rash from carbamazepine that is commonly used but can escalate into a hypersensitivity of the medication and cause Stevens-Johnson syndrome or toxic epidermal necrolysis. Both reactions using the commonly prescribed medication for neurologic and psychiatric disorders, can create a fatal reaction for the individual [8].

**Summary and Synthesis of First and Second-Generation Drugs**

As second-generation medications have been utilized in treatments for a significant amount of time, research must continue to assess the effectiveness of these drugs. In the case of antiseizure medications, it is important to reassess the effects on pharmacodynamics in relation to treatment of epilepsy and other seizure disorders. The benefit of using the second-generation drugs as opposed to the first-generation drugs for treatment, is that these medications can cause less interactions with other medications, food, or herbal supplements that are entering the patient's body. Another reasoning behind the development of future generation drugs is due to the lack of effectiveness in treating the disorder. Examples of first-generation seizure medications include phenytoin, carbamazepine, and valproic acid, yet it has been found over time these medications become extremely ineffective in treating seizures as well as causing significant and a lengthy amount of side effects to the patient [9].

Specific populations of patients may be able to use a second-generation drug in the same grouping or classification of medication versus a first-generation drug that would be toxic to them. An example of this would be the use of psychotic medications in women who are of childbearing age or pregnant. A provider must always weigh the risk versus benefit to determine what would be most beneficial for the patient. But with antipsychotic medications, second-generation or atypical antipsychotics were developed towards the end of the 20th century to benefit those with more selective effects, and less side effects or in the case of a pregnant woman, teratogenic effects [10]. Research must continue as possibilities of new side effects emerge, such as Kulkarni, et al. [10] investigates the risk of gestational diabetes mellitus for a woman during pregnancy in concurrence with administration of second-generation atypical antipsychotic medications. Areas such as these, are not widely researched or well-known as medications are newer with less time on the market to determine these possibilities.

Pediatric populations appear to be the one population that is generalized in how drugs are developed in relation to their specific needs. Most of the time adult medications are used or adapted to an "off-label" use to meet the needs of the child, but without the appropriate testing and research to determine the risks. Researchers are realizing they can no longer rely on the historical ways of "off-label" use of adult medications due to the differences in pharmacokinetics and pharmacodynamics in the child's body. Technology may be the future of how to appropriately modify medications to be pediatric specific [11,12].

**Analysis**

Collecting and reviewing literature on drug development and its fellow components has been very informative. Comprising and analyzing many of the aspects of drug development is quite complex. Beginning with the historical evidence of drug development, the lack of regulation and testing required for regulation of safe and effective drugs did not exist until the early 20th century. Without these regulatory laws, there would not be consideration for safety in the pharmaceutical world and providers would not have evidence-based research to prove effectiveness of medications to their patients.

There is also a disconnect in several areas of drug development that should be addressed. Many of the research and data findings through clinical studies, such as in pharmacogenomics, are not being utilized in the clinical setting and may further impact the development of new generational drugs. The research behind pharmacogenomics and GWAS is extremely useful information collected, but the lack of use in the clinical setting or adjustment to our pharmaceutical companies is extremely disheartening. There needs to be a shift in healthcare related to pharmaceuticals and drug development to optimize the use of medications within the most safe, effective, and costly manner.

Understanding the significance of how pharmacokinetics and pharmacodynamics affect drug development is a crucial piece of information. Drugs that are given by mouth as their main route of administration, must have the research and modifications made to be appropriately absorbed through the gastrointestinal lumen for appropriate absorption and bioavailability to the individual. Adjusting and adapting medications from first-generation to second-generation drugs and so on, show adaptation in how drug development can become more specific to the human body and its effectiveness. By utilizing knowledge and research found from first-generation drugs with future generation drugs, healthcare can be transformed to appropriately treat diseases and disorders in the best way possible without as many side effects.

**Critical Evaluation of Sources**

The sources and scholarly articles obtained showed many strengths and weaknesses of the data related to drug development and its many components. Research found through these sources showed honesty and straightforward information that is lacking in evidence, such as minimal consideration for the pediatric and pregnant women populations. There appeared to be many research articles that showed high motivation to further continue funding and research for proper drug development in these two categories. The weaknesses of the literature sources mainly come through the lack of evidence of research findings of certain areas. In this respect, the sources themselves do not appear to be weak sources, but rather minimal number of findings available in the entirety of drug development research.

**Gaps in Research**

Upon reviewing the literature provided on drug development, there does not so much seem to be a gap in the research, but rather a lack of research in certain areas. A significant amount of information can be found in relation to first and second-generation drug developments for cardiac, seizure, and antipsychotic medications. However, this type of research and data can be seen lacking in the specific populations of pregnant and lactating women and pediatrics.

There is also a significant amount of research within pharmacogenomics, yet though these findings have been presented, there is not a significant amount of correlation to application in the clinical setting. It appears that though this process can be time consuming and at times costly, the benefits could outweigh the negative possibilities to provide individuals with the best outcome and treatment plan regarding medications that are going to affect their genetic makeup in the most positive outcome possible.

**Conclusion**

In conclusion, the findings of drug development through the literature are far from few. The world of drug development, pharmacogenomics, and pharmacokinetics are vast and evolving every day. Drug development effects the safety, efficacy, and patient outcomes. Continual research and discovery of new drugs will continue to change the future of healthcare and pharmaceutical practices. As technologies advance, pharmacogenomics and adaptations for special populations will continue to be advanced for the future of healthcare. With advocacy from all parties involved and through proper funding and investigation, new advancements of pharmacologic use to benefit these groups of individuals can prevail.

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