การพัฒนาผลิตภัณฑ์ยาใหม่โดยการปรับปรุงตัวยาสำคัญเดิมและการใช้กลยุทธ์เชิงนวัตกรรม
Development of New Drug Products by Repurposing of Non-New Chemical Entities and Using Innovative Strategies

นิพนธ์ปริทัศน์

Review Article

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บทคัดย่อ

การพัฒนาเภสัชภัณฑ์ประสบความท้าทายและปัญหาต่าง ๆ มากมาย เช่น ตัวยาสำคัญมีค่าการละลายต่ำ การปลดปล่อยน้อย การดูดซึมต่ำ ชีวประสิทธิผลต่ำ และความไม่คงตัวของตัวยา ทำให้การออกสู่ตลาดของผลิตภัณฑ์ยาใหม่ช้าลง การพัฒนาผลิตภัณฑ์ยาใหม่สามารถเร่งรัดได้และคุณภาพของเภสัชภัณฑ์ยังได้รับการประกันโดยการใช้วิธีการพัฒนาทางเภสัชกรรมที่เรียกว่า Enhanced Approach หรือการออกแบบด้านคุณภาพ การปรับปรุงตัวยาสำคัญเดิม เช่น การทำเป็นรูปแบบใหม่ของเภสัชภัณฑ์ ระบบการให้ยาแบบใหม่ ข้อบ่งใช้หรือวัตถุประสงค์ใหม่จากตัวยาสำคัญเดิมที่ได้รับการอนุมัติอยู่ก่อนแล้ว และการใช้กลยุทธ์เชิงนวัตกรรมที่มีนาโนเทคโนโลยีเป็นฐาน เช่น สูตรตำรับที่ประกอบด้วยผลึกนาโนหรือลิโพโซม สามารถใช้ในการพัฒนาผลิตภัณฑ์ยาใหม่ได้ตามการขอขึ้นทะเบียนตำรับยาใหม่ประเภท 505(b)(2) ขององค์การอาหารและยาของประเทศสหรัฐอเมริกาหรือประเภท Hybrid ขององค์การยาแห่งสหภาพยุโรป ซึ่งจะใช้ระยะเวลาในการวิจัย พัฒนา และอนุมัติสั้นกว่า สามารถลดความเสี่ยงจากการล้มเหลวของการพัฒนาเภสัชภัณฑ์ และใช้ค่าใช้จ่ายน้อยกว่า กลยุทธ์ที่ใช้ในการพัฒนาผลิตภัณฑ์ยาใหม่จะต้องดำเนินการตามข้อกำหนดทางกฎหมายเพื่อให้มั่นใจว่าเภสัชภัณฑ์มีความปลอดภัย ประสิทธิภาพ และคุณภาพ

คำสำคัญ: การปรับปรุงตัวยาสำคัญเดิม; การพัฒนายาใหม่; การพัฒนาทางเภสัชกรรม; การขอขึ้นทะเบียนตำรับยาใหม่ประเภท 505(b)(2)

Abstract

Development of pharmaceutical products has been encountering several challenges and issues such as poor solubility, inadequate release, low absorption, low bioavailability, and instability of the drugs, and thus their go-to-market launches have been delayed. A new drug product development can be expedited, and its quality can be assured by utilizing the enhanced or quality by design approach. Drug repurposing (such as new dosage form, delivery system, or indication) from already approved non-new chemical entities and nanotechnology-based innovative strategies (such as nanocrystal or liposome formulations) can also be used to develop new pharmaceutical products through the US FDA 505(b)(2) new drug application pathway or the EMA Hybrid application process which take a shorter timeline, decrease failure risks, and cost less. All strategies employed in new drug product development should fulfill the regulatory requirements to ensure its safety, efficacy, and quality.

Keywords: drug repurposing; new drug development, pharmaceutical development; US FDA 505(b)(2) New Drug Application

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Introduction

New drug products are defined as pharmaceutical products that are developed from existing drug substances or non-new chemical entities already approved for registration. New drug products are categorized as pharmaceutical products with new dosage form, new delivery, new route of administration, new combination, new strength, or new indication. Those characteristic changes of the drug products require bioavailability studies demonstrating efficacy and safety compared to those of the reference listed drug. Pharmaceutical development through the traditional process usually employs an empirical method and is considered an expensive and time-consuming process involved with a high risk of failure.[1] Using the conventional approach to drug product development, there have been major challenges with getting essential medicines from the laboratory to the patient. The development of new drugs has been challenged by the physicochemical and molecular properties of the drug molecules, especially low solubility, low permeability, or

instability issues.[2,3] Pharmaceutical product development considers all factors of physicochemical properties of drugs to overcome the challenges and develop new effective drugs.

Starting from early 2020 until present, the lessons drawn from the impact of the COVID-19 pandemic have highlighted to sponsors that the timeline for developing drug products could be expedited, and novel approaches could be employed to attain successful products within a relatively brief timeframe.[4] Other sponsors recognized the potential of modifying existing medical products through alternative methods for different or improved medical uses. For example, although the utilization of hydroxychloroquine, originally designed for addressing malaria, rheumatoid arthritis, and systemic lupus erythematosus, in the context of COVID-19 situation was initially considered hasty and potentially dangerous, its application against the SARS-CoV-2 virus received approval from the United States Food and Drug Administration (US FDA) and supported by the Council for Medical Research in India in 2020.[5] Other medicines recently noticed for the purpose of SARS-CoV-2 virus treatment were remdesivir and ursodeoxycholic acid. Remdesivir, which was originally developed for treating hepatitis C virus infection, was found to decrease the duration of hospitalization for patients with COVID-19.[6] In 2020, due to its immunomodulatory and anti-inflammatory properties, researchers proposed the inclusion of ursodeoxycholic acid in the array of medications for COVID-19 treatment. Despite its FDA-approval for dissolving gallstones and addressing primary biliary cholangitis, ursodeoxycholic acid might offer clinical advantages in managing pneumonia and lung-related edema induced by COVID-19.[7]

To date, a number of new dosage forms have been approved by the FDA to overcome the obstacles of drug physicochemical properties and improve safety and efficacy of the drugs. For instance, doxorubicin hydrochloride was developed into the PEGylated nano-liposomal injection (Doxil®) to perform targeted drug delivery into the tumor cells leading to increased safety and reduced toxicity.[8,9] Several nanotechnology approaches have been utilized and approved by the FDA, such as liposomes, polymeric nanoparticles, and nanocrystals.[10-12] Furthermore, various delivery systems have been developed to improve bioavailability of drugs including transdermal delivery[13], pulmonary delivery[14], and ocular delivery[15]. Exploring novel clinical benefits of old drugs and finding strategic pathways for their developments can offer treatment options for patients with important medical needs. These options are thought to be reasonably priced, safe, and developed in a timely manner.[16]

This review article will discuss various approaches and strategies for the development of novel pharmaceutical products through the transformation of existing drug compounds into new drug and/or applications. Novel medical products can be formulated using pre-existing compounds. These existing compounds can encompass drugs that have already gained approvals and are presently being utilized, ones that were once approved but subsequently removed from the market due to developmental shortcomings, or even older medications that were created using distinct methodologies. The focused discussions in this review are new development approaches, reprofiling strategies, and generic or similar methods. This topic seeks to analyze development and approval of new drugs from existing compounds through the 505(b)(2) new drug application approval pathway which is the process created by the US FDA for the approval of drug products that are developed from old or existing drugs with changes in formulations, active ingredients, routes of administration, indications, manufacturing processes, or whether it is changing from an Over-The-Counter drug to a prescription drug. This pathway differs from the development of generic forms of a brand which employs the Abbreviated New Drug Application (ANDA) pathway for which the new drug product is exactly equivalent to the innovator brand. The alternative to 505(b)(2) pathway in Europe is the European Medicines Agency (EMA) Hybrid application (article 10(3)), and it is known as a complex generic (similar) application by the Thai FDA.

Pharmaceutical Development Strategies

Pharmaceutical development approaches could be started by studying new drug development strategies and indications, and they combined experience strategies with both drugs and indications.[17] It was afterwards discovered that the combined strategy was most likely to achieve the market state even though it was not popular.[18] Chasing innovations in pharmaceutical product development has become important because companies need to prevent the market launch of suboptimal products while they remain competitive. It is worthwhile to note that novel development approaches using existing drugs are beneficial because they are thought to be

less expensive, timesaving, and with low risk of product failure. In as much as this strategy can be used in new clinical trials, the question remains “what are the new technologies available to be leveraged?”. An important gap in this article is the major dependence on the company’s experience with some existing drugs leaving out the ones that the company did not have any experience with.

According to the International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use (ICH), drug development strategies differ between different companies and intended products. For some companies, minimal or traditional development strategies are enough to achieve the desired quality attributes while others choose enhanced strategies. There are several enhanced approaches to develop new drug products such as using the quality by design (QbD) framework, the design of experiment (DoE) method, and various process analytical technology (PAT) tools for real-time monitoring and control of processes to improve efficiency and product quality.[19]

Traditional (Minimal) Approach

To date, numerous pharmaceutical companies still use traditional approaches for the development of new pharmaceutical products. One such traditional approach involves the utilization of One-Factor-At-A-Time (OFAT) experiments. This classic methodology, also known as the Consider One Single Factor at a Time (COST) technique, adopts an intuitive stance where individual factors are maintained for examination.[20] Each variable is manipulated independently at a time while all other variables remain constant allowing measurement of the corresponding responses. This process is reiterated for every variable being investigated. However, the OFAT approach carries certain limitations including the fact that this approach assumes disregard of potential interactions between variables and presumes minimal variability between experiments. Furthermore, the OFAT method encounters challenges such as unpredictable outcomes, an oversight of interactions, and an excessive number of experiments to be conducted leading to time-consuming endeavors and inflated costs.[21]

Enhanced Approach

Conversely, the Quality by Design (QbD) framework presents a more efficient alternative by exploring a broader experimental space with fewer trials and enabling the identification of the true optimum conditions. QbD methodology has been recommended by FDA as an approach for pharmaceutical product development. QbD is an approach that utilizes several designs of experiment to develop new products so that all factors in drug development can be controlled to produce new products in specifications. The Design of Experiments (DoE) methodology presents a systematic and cost-effective approach that offers several benefits, such as proactive data collection process that yields high-quality data and tools that enable researchers to identify critical factors and accurately quantify the impact of interactions. Notably, DoE is proficient at managing substantial experimental variations and effectively measuring experimental uncertainties. DoE excels the optimal response zone within the experimental parameters and provides comprehensive insights by statistical analysis across the entire experimental range and data-driven decision-making.[1,22,23]

QbD can be employed for complicated products that may possess heterogeneity and use diverse manufacturing processes. The elements of QbD for pharmaceutical products include characterizing the product’s quality target product profile (QTPP) which accesses quality, efficacy, and safety of the drug and then defining their critical quality attributes (CQAs), critical process parameters (CPPs), and critical material attributes (CMAs).[24] The definitions and analyses of these parameters are not considered in this review. More details of these terminologies can be found in the ICH Guideline Q8(R2) on Pharmaceutical Development.[19] The next step in QbD is creation of design and control spaces using process analytical technology (PAT) tools and multivariate analysis that can provide valuable information about product behavior, scale-up and validation of the design spaces, and finally control strategy and continuous improvement.[24] It can be seen from ICH Guideline Q8(R2) that using an enhanced strategy to drug development can expedite more innovative products. This strategy involves targeting the product profile, determining the critical quality attributes of the product, linking material attributes and process parameters to the critical quality attributes, conducting risk assessments, developing a design space, creating, and implementing a control strategy, and finally managing the product lifecycle including continual improvement. For instance, particle size and particle size distribution (PSD) of the active ingredient and excipients are important CQAs that can have an impact on safety and

efficacy and hence clinical effectiveness of the medicines. Other considerations for pharmaceutical and nanomedicine development include amorphous/crystalline state, in vitro release/dissolution, and other CQAs related to new regulatory practices.[24] Typical elements of each strategy in drug development are outlined in the "Appendix 1. Differing Approaches to Pharmaceutical Development" of the ICH Harmonised Tripatite Guideline Q8(R2) on Pharmaceutical Development.[19]

Strategic Approaches to Innovative Product Development

Innovative product development schemes can be determined on a drug or an indication that is new to the company followed by consideration of a drug and/or an indication for which the company had prior development experience as depicted in Figure 1.[18] The strategy describing any development plan that consists of a drug and an indication that are both new to the company is recognized as "a new product development strategy" with novel experience of the company. On the contrary, a drug that was not apparently new to the company but used for an indication that is new to the company is termed "a new strategy". Similarly, "a new strategy" is also termed for a drug that is new to the company with an indication that was not new to the company. There are some cases where companies have prior development experiences on both of the drug molecules and the indications. Assessing these strategies does not actually provide extensive technological insights for pharmaceutical product development. There are several strategies to develop new pharmaceutical products, such as reformulation of existing drugs, repurposing drugs, advanced drug delivery systems, personalized medicines, generic and similar approaches.

Reformulation of existing drugs of which pharmacokinetic profiles and safety in humans had been clinically confirmed and approved for uses is one of the pharmaceutical development strategies at present. At the molecular level, these old compounds are thoroughly studied, and their results are employed for development of new compounds.[25] Four steps of reformulating the existing drugs are composed of targeting and selection of existing medicines, comprehensive analysis of the mechanisms of action of targeted medicines, organic synthesis of derivatives and analysis of their actions, and drug delivery system-mediated modification of drugs.[25] Figure 2 implies that clinical effects of existing drugs whose mechanisms of action are known but not clear enough (or totally unknown) for certain indications are sorted out and differentiated into main, side, and new effects. This strategy leads to organic syntheses of their derivatives and selections of possible drug candidates obtained from those syntheses. The new drug candidate is further proceeded with an obvious pathway for delivering the drug to target tissues. Important features, such as increased potency, lower side effects, and new indications or usage in other diseases, of the selected candidate are therefore developed as a new drug.

Reprofiling (also known as repurposing or rescue or repositioning) of medicines is involved with modification and improvement of drug delivery systems to distribute drugs to the target tissues, provide new effects, or bypass/delay delivery in cases where side effects occur. Drug reprofiling steps discussed in this review stem from targeting and collection of existing medicines, extensive evaluation of the mechanisms of action of focused drugs, organic synthesis of derivatives, and drug delivery system-mediated modification of drugs. The drug delivery system (DDS) reformation is determined after the basic mechanisms of action of the drugs of interest are revealed. Nanoparticle sensitization is an important method that has been found useful for targeted drug delivery such as delivery and loading certain proteins to specific tissues. This technique is composed of a variety of materials for DDS such as nanocrystals, nano-emulsions, micelles, nanosuspensions, liposomes, polymeric nanoparticles, dendrimers, and others.[24] One of the examples of approved nanotherapeutics is fenofibrate nanocrystals (TriCor®) for the treatment of hypercholesterolemia.[24] Originally fenofibrate is a highly water insoluble compound, but it was reformulated as a nanosuspension which increased its saturation solubility and consequently enhanced bioavailability. In reviewing DDS modification through nanoparticles, it is fitting that innovative product and process development considerations are noted because they will serve as basis for further discussions. These considerations include quality target product profile, critical quality attributes, critical process parameters, etc.

In addition, Mühlebach[26] investigated development and regulation of supplement forms of innovator brands of nanomedicines that were new drugs containing nanomaterials likely to overcome challenges (e.g., the nonequivalence of pharmacokinetic or quality profiles and substitutability with a

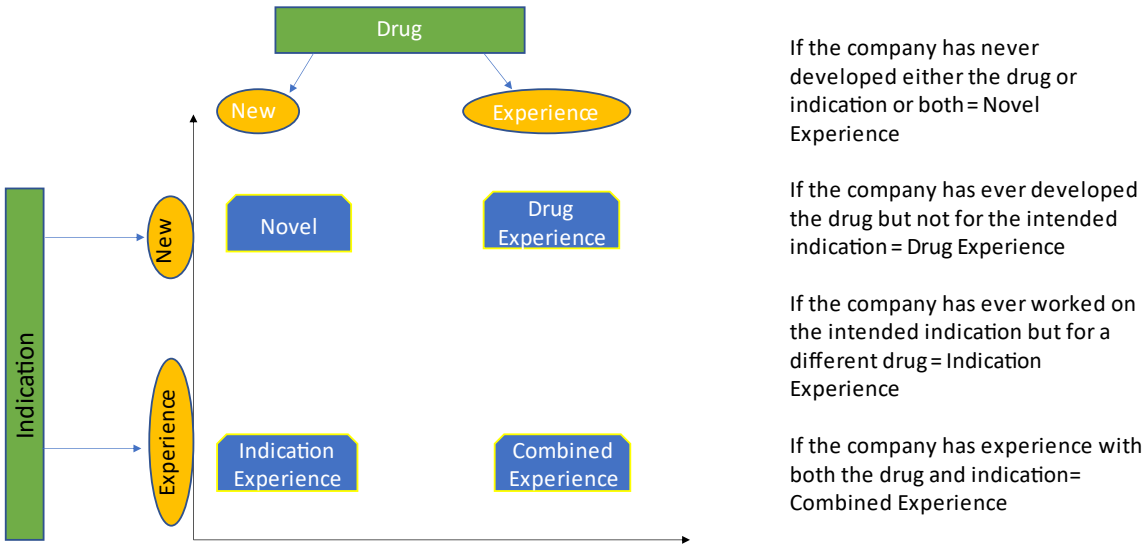

Figure 1 Categorization of product development strategies by company experience (adapted from Dahlin *et al*[18]).

different drug) of prior products that were designed and manufactured differently. In 2018, poorly soluble drugs such as ketoconazole, fenofibrate, and azithromycin were upgraded by nanocrystal technologies to enhance their solubility and hence bioavailability.[27] Subsequently, nanocrystals were presented as solutions to overcome precise solubility problems of the Biopharmaceutics Classification System (BCS) Class II and IV drugs in which active pharmaceutical ingredients in mostly oral formulations were reformed to enhance their bioavailability.[26] Mühlebach also wrote that aside formulations, complex variations of nanomedicines were used to overcome tissue barriers and for targeted delivery of compounds to increase efficacy and safety of medicines. These kinds of nanomedicines include nanoparticulate polymers, dendrimers, liposomes, and nanosuspensions. Nevertheless, drawbacks like intricacies in size, shapes, impurities, and correlations of in vivo dissolution tests make the development of these drugs and their similar forms complicated, and thus there is the need to find alternative development methods.

Moreover, since reformulation or redeveloping of old drugs is a strategy now mostly used by pharmaceutical companies to prolong the drug lifecycle and increase financial gains for the company, these new formulations are passed through advanced drug delivery techniques with the aim of either enhancing patient compliance or changing the route of administration. A new product presentation must be based on the active ingredient and required features that the marketing team will present for the development team to change. These desired features or specifications are known as target product profile (TPP)[28] and include changes in dissolution rate, dosage level, indication, etc. An example of reformulation is that of ibuprofen, a non-steroidal anti-inflammatory drug with diverse clinical benefits. It was originally developed as an immediate release tablet, but due to its gastric irritation and risk of gastric ulcer side effects, a controlled-release formulation was made to decrease its side effects.[28] Subsequently, ibuprofen was developed into various formulations (single or combination products) for different purposes such as soft gelatin capsules and fast-dissolving/orally disintegrating tablets for fast acting, sweetened suspension for children, complexation with lysine for rapid release, modified-release capsules for long acting, combination with a decongestant drug, and topical gels for local inflammatory pain of muscles. This reformulating approach not only increases the product lines but also gives physicians alternatives to conventional ibuprofen dosage form for treating various populations of patients.

The approach of reformulating or reprofiling existing drugs into new products has a number of benefits and can be utilized for boosting patient experience with novel or personalized medicines. For instance, new dosage forms such as orally disintegrating tablets and orally dispersing granules can be taken in populations who may find it difficult to swallow regular oral dosage forms. Another example is redesigning to extended-release products to reduce dosing frequency such

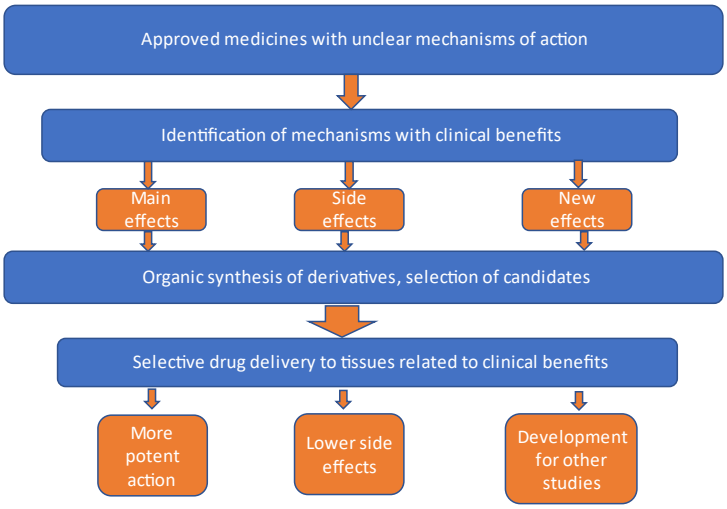

Figure 2 A schematic representation of drug reprofiling strategies (adapted from Mizushima[25]).

as Pfizer™ Xeljanz®, a drug for rheumatoid arthritis which was originally formed as twice daily 5 mg tofacitinib citrate tablets but now made into 11 mg once daily modified-release tablets. Furthermore, decreasing pill burden and increasing patient compliance can be accomplished by making a fixed-dose combination such as Glucovance® which is an antidiabetic combination of metformin and glyburide by Bristol-Myers Squibb™. Changing the route of administration of a drug can be also achieved such as transdermal delivery of methotrexate which was initially developed as tablet and injection formulations.[28]

Alternatively, the generic or similar approach to the new drug development involves crafting a wholly identical version of the original branded product once its patent protection has ended.[29] This strategy offers advantages such as reduced production expenses, shorter development timelines, decreased risk of setbacks, and improved accessibility of the drug to patients at a more budget-friendly price compared to the original brand. In general, this approach might yield a new product resembling the innovator brand with distinctions in various areas such as manufacturing process, formulation, indication, or administration route.[30] However, the generic products should be tested in order to prove bioequivalence (BE) profile with their originator or reference listed drug.

Hybrid medicinal products are drugs based upon a generic molecule but have a different indication, dosage form, strength, or route of administration from the reference listed drug, and this approval pathway is called Hybrid or 505(b)(2). In the case of nanomedicines, hybrid products are known as nanosimilars. While small molecules are clearly defined entities, complex drugs like nanomedicines exhibit significant diversity and intricate structures. These complexities are further compounded by the intricacies involved in their manufacturing processes, rendering them challenging to comprehensively characterize solely through in vitro physicochemical techniques.[26] Therefore, developing a generic product from an innovative brand is challenging since estimation of CQAs at this stage is almost invalid. Hence to create a new form of a nanodrug requires the company to follow a “similar” or hybrid approach which requires pharmaceutical equivalence and bioequivalence studies and other additional tests for a totality of evidence for the potential drug’s efficacy and safety. QbD can be used as an approach to develop new pharmaceutical products, especially innovation of nanomedicines in order to make pharmaceutical equivalence with their originator.[31-33]

Recent Innovative Strategies for Pharmaceutical Product Development

Drug Repurposing: New Indications

Drug repurposing in development of new drugs from existing compounds of which safety and efficacy was evaluated, and such products were approved by regulatory authorities. The method was based on the study of mechanisms of action at the molecular level of existing drugs, and the results were used to develop new drugs for either a new indication or a new formulation taking into cognizance of the improved safety and efficacy.[25] Numerous drugs that have been approved for another new indications can be seen in Table 1.

Table 1 Some examples of new drug indications approved from existing compounds using the repurposing strategy.

Drug	Previous Indication	New Approved Indication	References
Hydroxychloroquine	Malaria, rheumatoid arthritis, and systemic lupus erythematosus	COVID-19 related diseases	5
Aspirin	Analgesic (high dose)	Antiplatelet (low dose)	34
Sildenafil	Hypertension	Erectile dysfunction	35,36
Favipiravir	Influenza	COVID-19 related diseases	37,38
Metformin	Type II diabetes	Polycystic ovarian syndrome (PCOS)	39,40
Zidovudine	Anti-cancer	HIV/AIDS treatment	41
Minoxidil	Hypertension	Alopecia	42
Raloxifene	Osteoporosis	Breast cancer	43

Drug repurposing: new formulations using innovative drug delivery systems

Table 2 summarizes some innovative strategies that have been studied for modifying existing drugs. Taking a cue from Dahlin *et al*.[18] and Figure 1 above, the manufacturer of Panadol® product already had experiences with both drug (paracetamol) and indication (pains, headache, fever), hence developing various brands of the product was at ease. This was called “Combined Experience” (see Figure 1). The other strategies showed mainly “Drug Experience” since the new products had been developed for the same indications as the former product. Only the breviscapine-nanocrystal formulation was developed for an indication different from the original product.

Precision Medicine: Personalized Approaches in Diagnosis, Treatment, and Drug Development

Finally, precision medicine, which is also known as personalized medicine, is an approach that provides alternatives for distinctive diagnosis and treatment of diseases. According to the Center for Disease Control and Prevention in 2020[58], precision medicine can be used in treatment and management of diseases through the following examples:

- Tumor profiling which can help physicians determine the best treatment approach for targeting the cancer either using radiation therapy, chemotherapy, or even mastectomy (in case of breast cancers)
- Pharmacogenomics, a person’s genetic composition can be used to define the patient’s response to the drug product before applying drug treatment and the corresponding dosage
- Monitoring devices, like a diabetic monitoring device (an arm sensor machine) aided in manipulating insulin doses for patients hence prevent any complications.[58]

Drug development through precision medicines has possessed many benefits, especially in cancer research, due to targeted delivery which addresses the former challenges of general toxicity caused by existing medications. With precision medicine, tumor treatment can now be distinguished specifically into two methods: pathway-based targeted therapy (which selectively interrupts cancer cell duplication or survival) and artificially regulating patients' immune systems to produce response against cancer cells (immunotherapy).59 Since this review paper is more inclined at developing existing drugs, the use of pathway-based targeted therapy was more focused on. Therefore, US FDA-approved drugs that target this specific approach can then be sorted out, and opportunities for drug repurposing or development be investigated for new targets. Although this pathway looks feasible, wrong assessment of reference drug (RD) without studying its efficacy and safety in various populations of patients (not using a pharmacogenomic approach) can lead to product failure. For personalized nanomedicines (PnM), the FDA has recommended the use of quality by design strategy because PnM is meant for specific populations and this model can reduce development cost and time because it begins by the modification of an already existing nanodrug. This QbD strategy by FDA entails a constant enhancement or upgrading of the nanoproduct while obeying the necessities of the market and the limits of safety, quality, and efficacy (Figure 3). This strategy is inspired by the FDA specially for personalized nanomedicines development, since they support the design of a nanodrug with characteristics that will progress during the development process, considering the needs of different group of patients.[60]

Figure 3 Illustration of FDA-suggested Quality by Design strategy for development of nanomedicines (adapted from Fornaguera *et al*[60]).

Table 2 Some examples of innovative strategies for new drugs developed from existing compounds.

Existing Product	New Product	Innovative Strategy	Summarized Details	References
Paracetamol tablet	- Panadol fast absorption tablet - Panadol Actifast® (fast release) - Panadol Night®	- Optizorb® technology - Fast-release technology - Fixed-Dose Combination	The new disintegration technology depends on the use of super-disintegrants, such as alginic acid and calcium carbonate, providing quick, suitable, effective relief of pain and discomfort.	44
Breviscapine (BVC)	- Breviscapine-nanocrystal formulation	Nanocrystals	High pressure homogenization was used to modify BVC nanocrystals for BVS inhalation formulation resulting in high plasma concentration of the new drug.	45,46
Nimodipine (Nimotop®)	- Nimodipine-nanocrystal formulation		Nimodipine nanocrystals of various sizes were set up by a merging microprecipitation and high-pressure homogenization technique.	
Diltiazem tablet	Effervescent floating diltiazem tablet	*In vitro* buoyancy and factorial design technique	Using *in vitro* buoyancy, *in vitro* dissolution, and factorial design techniques with gel-forming Methocel® K100CR, gas-generating sodium bicarbonate, an effervescent-based floating tablet was developed to increase gastric retention time and bioavailability.	47,48
Buprenorphine tablet	Butrans® wearable buprenorphine transdermal delivery system	Transdermal delivery system	As an improvement from the tablet formulation, transdermal product improves patient experience since it was accepted as a user-friendly dosage form.	49,50
Ketotifen ocular drops	Ketotifen-contact lens formulation	Drug-device technique	Addition of ketotifen to contact lenses has achieved clinically and statistically significant reduction in mean ocular itching scores.	51-53
Hydromorphone	Exalgo® hydromorphone OROS	OROS	An advanced and patented osmotic controlled-release oral delivery system (known as OROS Push-Pull Technology®) was used to develop an extended-release, modified-release, formulation of hydromorphone and nifedipine. This increased the drug's bioavailability and improved patient compliance.	54-57
Nifedipine	Adalat®	OROS		
Doxorubicin hydrochloride	Doxil®	Liposome	Passive targeting delivery system to the tumor cells with liposomal formulation to reduce toxicity and increase safety and efficacy	8

Innovative applications of precision medicine and personalized drug delivery utilizing 3D printing

Additionally, Figure 4 below outlines different applications of PM which include three-dimensional printing (3DP), genetic sequencing, organ-on-chip, and innovative other techniques used for medicines delivery. 3D (also known as additive manufacturing) technology has become a pharmaceutical product development strategy in recent years because of its ability to deliver complex geometric forms therefore enabling the production of certain oral dosage forms. This technology is also employed in drug individualization, that is producing a particular type of drug per time, and the cost of production for a small batch is relatively low. Although the speed for manufacturing if using 3D technology is low as compared to conventional production, it is preferred in the personalized delivery of certain drugs.[61] An example of a 3D printed drug is Spritam®, a levetiracetam brand manufactured by Aprecia Pharmaceuticals for treatment of epileptic seizure.[62] The company employed a patented technology known as ZipDose™ which is a 3DP that allows the processing of high dose of active ingredients in a formulation. It loads layers of the active ingredients and other powdered excipients and binds them together with a binding liquid, the product is a very absorbent dosage form that melts once in contact with a little quantity of fluid. The benefit of Spritam® over other conventional levetiracetam brands is that it dissolves quickly in the mouth and can deliver high dose (up to 1 g) of the anti-seizure drug to the patient as and when needed. Other examples of 3DP modified drugs are Insulin controlled release skin delivery using microneedles and paracetamol oro-dispersible tablets using selective laser sintering.[62]

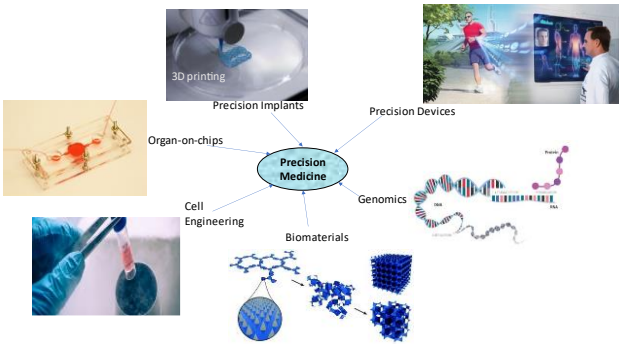

Figure 4 Diverse applications of precision medicines.

Regulatory Requirements for Pharmaceutical Product Development

The procedure of introducing novel pharmaceutical products to the market encompasses a comprehensive and methodical evaluation, aimed at ensuring the safety, efficacy, and quality for patients. Different regulations are set based on

the type of medicine and changes being made. Table 3 shows the requirements for two common approaches: the 505(b)(2) or Hybrid pathway and the Generic pathway. These ways provide plans for developing medicines and show what studies are needed to meet the regulation, including bioavailability and bioequivalence studies. This comprehensive submission requirements clarifies the essential elements and considerations necessary for achieving successful progress in the development of pharmaceutical products.

Table 3 Differences of submission requirements between 505(b)(2) (or hybrid) and generic approaches for drug development[63]

Submission Requirements	Description	Most common study requirements
505(b)(2) or Hybrid	Bioavailability (BA) studies compared with the approved Reference Listed Drug (RLD): • If the new formulation is bioequivalent to the RLD and the indication is the same, the number of subsequent studies is greatly reduced. • If they are not bioequivalent, safety and efficacy need to be established and submission requirements may include preclinical and clinical efficacy studies. Whenever possible, submitted data can include previous regulatory decisions or published research.	Formulations that are not locally acting: • Single dose comparative BA fasted • Single dose comparative BA fed-state Other studies that may be required based on case-by-case evaluation: • Preclinical toxicology studies • PK/PD, drug-drug interaction (DDI), thorough QT (TQT) studies • Multiple dose comparative BA steady-state • Clinical endpoint studies
Generic	Bioequivalence (BE) studies compared with the approved Reference Listed Drug (RLD): • Once BE is established, assessment relies on the agency's previous safety and efficacy findings reported for the RLD. • This criterion only applies when the new product and the RLD are bioequivalent and possess identical characteristics such as active ingredient, dosage form, strength, route of administration, uses.	Formulations that are not locally acting: • Single dose BE fasted • Single dose BE fed-state – if food effect is noted in a label • Steady-state BE – for EMA when there is accumulation for extended-release products Other formulations will be evaluated case-by-case: • More study designs may be required based on the drug product or applicable agency.

Regulatory Concerns for Approval of New Pharmaceutical Products from Existing Compounds

A major challenge in developing new drugs as hybrids, similar, or follow-on products is in the filing of documents for approvals. This is because some companies are unfamiliar with current regulatory processes. This unfamiliarity can lead to product failure if not clearly discussed during pre-investigational new drug (IND) meetings. Drug development regulation begins from when application for investigational new drug is submitted to the FDA for approval to initiate clinical trials, even though results of nonclinical assessments must be submitted alongside the IND application to support evidence of safety. This regulatory process extends to post-marketing investigations and subsequent pharmacovigilance, hence pharmaceutical companies need to present drug candidates of uttermost safety and efficacy characteristics and still ensure that the final drug product remains of the best quality, safety, and efficacy. Different countries have different laws, and the approval of new drugs depends upon various regulatory authorities. This review paper has shown different strategies for developing a new drug.

The US FDA approval process demands comprehensive nonclinical studies after discovery stage, followed by phases I-III clinical studies to ensure safety and efficacy. No matter the innovation or improvement done, it is only when the company successfully proves the safety and efficacy of the drug during clinical studies that the new drug application can be submitted. And if the authority is satisfied with the quality of studies done, the product will be approved for marketing purposes.[64] This process can be long and expensive, that is why the US FDA introduced abridged pathways for companies that are applying to modify existing compounds. Out of the two pathways established for this process, only the 505(b)(2) new drug application fully support the development of new drugs from existing drugs. This section 505(b)(2) of the Food, Drug, and Cosmetic Act was passed into law in 1984 under the Hatch-Waxman Amendment but it is only in the last decade that it began to gain popularity among different pharmaceutical companies, especially start-up companies. This pathway "allows for approval of a drug for which at least one of the studies was not conducted by the applicant company, therefore the company can depend on literature reference"[27] from the innovator company and FDA data about the drug product to support their own improvement. Thus, this reduces development cost and approval timeline for the new product.[65] Because the 505(b)(2) pathway depends on previous data of an already approved drug and a few necessary tests by the applicant company, the FDA continues to monitor the effects of the product long after it is released for marketing, and the product can be withdrawn at any time during this process if found deficient in quality, safety, or efficacy.

Future Perspective

To date, the company experience strategy, though simple enough for small and young pharmaceutical companies to capture, did not give in-depth analyses of the strategies suggested and did not evaluate possible technologies that could be utilized in this strategy. An exhilarating reveal was that of re-positioning of already approved or existing drugs using techniques such as nanotechnology-based platforms to produce new drug innovations with changes to formulation, dosage form, route of administration, indications among others while engaging necessary quality target profiles to ensure that the product is good enough to pass approval processes and benefit patients. As a result of the creation of considerable regulatory processes for innovative new drugs (new drugs carved out of existing, old, or already approved drugs), the generic pathway is no longer used to develop drug that has any difference from the innovator brand (also known as the reference listed drug). The preferred pathway is that of similar or hybrid application because this significantly allows major changes to be made to an existing drug while still maintaining efficacy and safety. Many companies have accepted this strategy as it is a fast and safe way to maintain a drug product line and keep a good market share.

In the future, researchers in academics and pharmaceutical companies may need to further access an expanded clinical environment and techniques for using nanotechnology in rescuing existing compounds. Personalized medicine strategy, although already in use for some treatments and procedures, is an all-encompassing methodology for repurposing existing drugs. Pharmaceutical researchers can study more in-depth questions relating to all and more of the characteristics relating to personalized medicines with state-of-the-art technologies such as artificial intelligence, machine learning, robotics, and mathematical modellings. This is attributed to the obvious positive future for this aspect of drug development.

Conclusion

Pharmaceutical product development strategies can be used to develop a new drug from an existing compound. These methods unlike the conventional development process cost less, take a shorter timeline, and decrease the risks for drug product failure while ensuring that drugs entering the market are safe, effective, and of the best quality for patient consumption. This review has compiled several strategies employed in pharmaceutical product development for creating new drugs from existing compounds, such as repurposing and reformulation to new pharmaceutical products. These approaches, combined with innovative methods of pharmaceutical development and advanced drug delivery systems, are presently crucial for developing new pharmaceutical products from existing drug compounds. The review concludes by endorsing the utilization of the 505(b)(2) new drug application route for supplemental product approval. However, it is crucial for companies to also address matters concerning intellectual property rights and market exclusivity of originators.

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