Introduction

The Thai pharmaceutical sector has been concentrating its efforts on growth aligned with the National Strategic Master Plan (2018-2037). This plan targets the improvement of the national drug system and the expansion of domestic pharmaceutical manufacturing.[1] The third national drug policy in 2011 and the 2011-2016 strategy for drug system development have emphasized the sustainable progress of the pharmaceutical industry, including biologics and herbal products, to achieve self-sufficiency.[2] The main goals include boosting the pharmaceutical sector's capabilities through research, development, and production of vaccines, medications, and biologics. Encouraging local pharmaceutical industries and services is crucial to reduce imports and increase exports.[1]

However, the research and development capacity of the Thai pharmaceutical sector is relatively limited. In the past two decades, there has been a shift from locally produced drugs to imported ones. Initially, from 1995 to 2002, the value of domestically produced drugs exceeded that of imported ones. However, afterward, the value of imported drugs surpassed domestically produced ones, indicating a decline in domestic drug stability during this period.[3]

At present, the Thai pharmaceutical manufacturing primarily focuses on generic drug production, with around 540 generic drugs approved annually, including approximately 35 new generic drugs. This happens mainly after patent expiration. Manufacturers import active pharmaceutical ingredients (APIs) and combine them with excipients to create finished products in various forms like tablets, capsules, solutions, and injections. Over the last decade, pharmaceutical manufacturers have invested in research and development, adopting new technologies to create different types of finished products.[4]

Still, the development and approval of new drug formulations in Thailand remain limited due to the unpreparedness of the pharmaceutical manufacturing sector and regulatory agencies. This is also due to the absence of clear guidelines for registering new domestically produced drugs. Research and development efforts are becoming more focused, with the Food and Drug Administration (FDA Thailand) defining seven categories of "new drugs," including new chemical entities, indications, combinations, delivery systems, routes of administration, dosage forms, and strengths. Among these, developing new chemical entities requires substantial investments, technology, and skilled personnel, which Thailand currently lacks.[4]

To support the pharmaceutical manufacturing industry's objectives, it's essential to focus on research and development of incrementally modified drugs (IMDs) that maintain the efficacy of original drugs while displaying modified properties. This can be accomplished by utilizing advanced technology platforms, ultimately promoting the self-sufficiency of the local pharmaceutical industry. Consequently, this study aims to assess the financial viability of creating a dosage form for IMDs within the local pharmaceutical manufacturing industry. The study's results will offer an investment proposal to aid policy-making and industrial investment decisions.

Research methodology

The current study utilized a mixed-methods approach, integrating a review of existing literature, surveys, and interviews to conduct the research.

Literature Review

The study gathered data by thoroughly examining available literature and pertinent documents. This review concentrated on IMDs in the form of nasal sprays, evaluating the present manufacturing capacity of nasal sprays, and crafting a tool for conducting expert interviews.

Survey

Methodology was employed to recognize and approximate expenses using the established cost frameworks, which were deduced from the research titled 'Impact of the Thai-EU Free Trade Agreement (FTA) on Intellectual Property Rights concerning the Pharmaceutical Supply Chain in Thailand.' Survey Procedure[5]:

1. Questionnaire forms containing predefined cost frameworks were distributed to 5 experts in Industrial Manufacturing and Development (IMDs).
2. These experts furnished estimated costs along with comments to enhance the credibility of the cost structure.

Interviews

Professionals and individuals possessing relevant knowledge in evaluating Thailand's manufacturing potential for IMDs were chosen using the snowball sampling method. A minimum of ten interviews were conducted, or the process continued until a point of data saturation was reached.

The investigation of this study comprised the following four key stages:

1. Selection of Incrementally Modified Drug (IMD) Types: Through a feasibility study of domestically developed incrementally modified drugs [6], the research identified nasal spray as one of the most favorable IMD types. The decision was based on data obtained from the Thai FDA, which examined trends in drug research and development using prediction market methods.

2. Creation of Investment Models: Appropriate investment models were formulated to align with the specific circumstances and capabilities of the local pharmaceutical sector.

3. Identification of Cost Structure and Cost Estimation: The cost structure was established, and the expenses linked to investments in IMDs within the manufacturing industry were approximated. A cost framework adapted from the research concerning the impact of the Thai-EU Free Trade Agreement (FTA) on Intellectual Property Rights within the Thai pharmaceutical supply chain was applied [5]. This structure encompassed various stages such as sourcing, laboratory-scale research and development, pilot batch and stability studies, non-clinical trials, clinical trials, registration, and process validation batches. Costs were estimated at each step of the drug development process leading up to the drug's market launch.

4. Financial Feasibility Analysis of IMDs: Assumptions were defined (table 1), and pertinent data regarding investment variables were gathered to evaluate the financial viability of IMDs. Following the collection of relevant variables, sensitivity analysis and scenario analysis were conducted.

Sensitivity analysis involves investigating the effects of different variables on the financial viability. The following factors are considered:

1. Growth Rate of Revenue: The annual revenue increase is impacted by the drug's characteristics and its competitiveness in the market.

2. Duration of Drug Research and Development: The complexity of the research and development process influences both the timeline and the allocated budget.

3. Investor's Acceptable Payback Period: The duration of the payback period acceptable to investors varies based on factors like the type of drug under development.

Scenario analysis [7]

Scenario 1: Perform only non-clinical trials, covering the pharmacokinetics and pharmacotoxicity aspects, followed by clinical trials in phases I to III.

In this particular situation, since the nasal spray involves a change in the administration method, additional investigations are required to assess the pharmacokinetics and pharmacotoxicity of the IMDs. Moreover, a complete clinical trial spanning from phase I to phase III remains essential to amass substantial proof concerning the nasal spray's effectiveness, safety, and potential toxicity.

Scenario 2: Carry out non-clinical trials as well as comprehensive clinical trials spanning phases I to III.

In this context, both non-clinical trials and an exhaustive clinical trial covering phases I to III are undertaken for the nasal spray. This approach is necessary due to the alteration in the administration route, and there exists inadequate preexisting data from prior medications to substantiate the development of these IMDs.

Mockup design for financial feasibility analysis

This research employs a unique model for evaluating financial feasibility. By enabling investors to derive the payback period and market growth rate according to the company's capabilities, this model offers crucial insights into the viability of pharmaceutical research and development investments. The model comprises two primary sections: a cost model for drug dosage form research and development, and a sales revenue model that computes the required revenue to achieve capital recovery within the designated payback timeframe. It provides a customizable framework allowing investors to modify variables like the payback period and market growth rate, facilitating the decision-making process when it comes to choosing and advancing potential study drugs.

Results

In the investigation of IMDs in the form of nasal sprays, it was observed that the duration for research and development spanned around 13 years. In contrast, the timeframe for new generic drugs ranged from 25 to 46 months. [5] The extended timeline in developing nasal spray formulations can be attributed to the requirement of devising new formulations and analytical techniques for both the medications and the delivery mechanisms. Moreover, specific analytical methods might not be accessible in local laboratories, leading to their creation overseas, as previously mentioned. This scenario underscores the importance of conducting non-clinical and clinical investigations to validate the effectiveness, safety, and accuracy of drug delivery to the intended target site.

Developing new drugs in the form of nasal sprays based on existing chemical compounds involves fixed costs of approximately 19.82 to 19.87 million USD (table 2), when compared to the research and development expenses for new generic drugs, which range from 0.19 to 1.13 million USD.[6] In both scenarios, a substantial portion of the cost and time associated with drug development is attributed to clinical trial studies. This is primarily due to the alteration in the method of administration, which can modify the pharmacological, pharmacokinetic, and toxicological effects of previous products. Hence, the intricacy of the study, the procedures undertaken, the sample size, and the nature of the drugs can significantly impact the research and development costs.

Investing in the advancement of novel drugs derived from existing chemical entities indeed involves substantial expenses. The analysis of feasibility takes into account the expenses linked to the development of drug formulations and presents them as the revenue that entrepreneurs must generate to attain the break-even threshold. The feasibility outcomes demonstrate that, in the context of the base case analysis with a projected payback period of 5 years, the income necessary to recuperate the invested capital spans from 3.13 to 28.14 million USD for scenario 1 and 3.13 to 28.18 million USD for scenario 2.

Additionally, it is noted that over a span of 15 years for research and development, the annual revenue required from investors would be greater compared to shorter timeframes, signifying a heightened investment level. Consequently, if entrepreneurs possess the capacity to accelerate the research and development timeline, they can curtail investment expenses and enhance the viability of drug development. In situations where there exists a substantial risk of failure in formulation and analytical method development, coupled with intricate facets of development including advanced clinical studies, the commitment to research and development could necessitate increased capital investment. In such instances, investors would need to generate augmented revenue to attain a more advanced break-even threshold.

Taking into account the payback period from an investor's perspective, it's evident that extended payback durations generally correlate with a reduced capitalization threshold. This, in turn, demands a lower annual income generation by operators as opposed to shorter payback periods. If the drug's life cycle is protracted and doesn't demand frequent updates—such as medications for chronic conditions—a longer acceptable payback period might be more appropriate. Several elements, such as the annual sales growth rate, market reception upon

launch, competitive landscape, and governmental regulations, impact the evaluation of feasibility.

Discussions

This study conducted a specialized financial feasibility analysis that was tailored to nasal spray dosage forms, distinguishing it from other financial models. The analysis encompassed the assessment of four key aspects: the overall cost for developing IMDs, the anticipated payback period, the projected growth rate, and the potential revenue that investors could generate to reach the break-even point. The cost estimation was predicated on the assumption that each business operates with its existing company and infrastructure. Additionally, specific drug-related variables were held constant, such as cost of goods sold and operational expenses, to enable a direct comparison at the dosage form level. However, it's worth noting that these variables might vary depending on the specific drug types under consideration.

The chosen methodology in this study proves to be suitable for examining the financial dimensions of new drugs or innovations, even in scenarios of limited data availability. To bolster the reliability of the constrained data, the triangulation method was adopted, enhancing the credibility and validity of the conclusions.

The examination of investment in nasal spray also unveils elevated expenses and extended timeframes when compared to new generic drugs. The primary allocation of this investment centers around conducting non-clinical and clinical investigations for registration, drug selection, and ensuring sufficient data to validate efficacy and safety.

In the first scenario, wherein pharmacology studies are unnecessary, the investment could be lower than in scenario 2, which mandates complete non-clinical and clinical trials. The costs are impacted by diverse elements like the research methodology, duration, participant count, and specific attributes of the drug. While assessing the two scenarios, minor disparities in capital requisites might arise, particularly due to non-clinical pharmacology studies entailing relatively smaller investments compared to other phases. The considerations regarding financial feasibility are also contingent on the entrepreneur's capacity to invest and generate revenue.

This study has identified key factors that can potentially impact investors' decision-making process

1. Clinical Study

The clinical study phase stands out as the most significant element in terms of drug development costs. This is primarily attributed to various factors, including the insufficiency of clinical data from reference products, the intricacies linked with studying various types of IMDs, and the inherent attributes of the drug itself, encompassing aspects like pharmacodynamics, pharmacokinetics, and toxicity. The substantial financial commitment required for this phase can exert a notable influence on investors' decision-making regarding the initiation of new drug development within the domestic pharmaceutical sector. Worth mentioning is that the median cost for conducting a new drug study hovers around 3.4 million USD for phase I, 8.6 million USD for phase II, and 21.4 million USD for phase III. These costs slightly surpass those linked to IMD studies.[8]

2. Duration of Research and Development, Including Clinical Study and Registration Process

The timeframe for research and development, encompassing clinical studies and the registration process, constitutes a pivotal factor for consideration. Given that the development of IMDs is relatively novel within the domestic industry, the extended duration of this development process can wield a significant impact on expenses, necessitating heightened investments. This prolonged duration may be attributed to the limited knowledge and experience within the domestic sector and affiliated organizations. Additionally, the time needed for conducting clinical trials and the ambiguities surrounding the registration system can collectively contribute to the overall elongated timeline. Consequently, it becomes imperative to augment the capabilities of all stakeholders involved to expedite each process's duration. Furthermore, this extended period provides increased opportunities for the development of new drugs based on existing chemical compounds.

3. Drug Selection

The process of selecting drugs for IMD development necessitates a holistic consideration of numerous factors. This evaluation should encompass not only financial implications but also patient needs, scientific and technological feasibility, as well as legal and registration feasibility. It's important to acknowledge that not every drug is suited for IMD development, and market success may not be guaranteed. Hence, the nature of the drug itself can exert a significant influence on investment decision-making. Factoring in these multifaceted dimensions is essential to ensure that selected drugs align with patient requirements, can be feasibly developed using

available scientific and technological resources, comply with relevant regulations, and possess a reasonable likelihood of achieving market acceptance.

4. Market Opportunity

Given the considerable investment required to generate adequate income for reaching the capital break-even point and achieving profitability, entrepreneurs must meticulously assess market viability and identify avenues to enhance the marketability of IMDs. It's crucial to recognize that both generic drugs and new generics have already established a foothold in the drug market. Therefore, for the successful introduction of IMDs, collaboration with governmental and relevant entities might be necessary, proposing favorable policies and regulations. Additionally, convincing payers about the significance and benefits of IMDs for patients becomes pivotal. Given the substantial capital investment involved and the need to expand the market, the industry should also set its sights on exporting these drugs. In this context, governmental support plays a vital role in fostering the stability and sustainability of the local pharmaceutical sector.

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References

1. Secretariat of the National Strategy Committee. The National strategy of THAILAND (2018 - 2037) 2016;4
2. National drug system development committee. national drug policy 2011 and national drug system development strategy 2011-2016. 2011;
3. Kessomboon N, Manomayitthikan T. Analyzed from the value of production and import of modern medicine for humans. 2019.
4. Thai drug system 2020 (2020).
5. Liangrokapart J, Kessomboon N, Sakulbumrungsil R, Akaleephan C, Poonpolsub S, Saerekul P. Impact of Thai-EU Free Trade Agreement (FTA) concerning Intellectual Property Rights on the Pharmaceutical Supply Chain in Thailand. 2013;
6. Sakulbumrungsil R, Kessomboon N, Udomaksorn K, et al. Feasibility Study of Dosage Form Drug Development for Incrementally Modified
by Domestic Pharmaceutical Industry. 2022.
7. Guideline for nonclinical and clinical evaluations of new drug products from previously approved drug substances (2019).
8. Martin L, Hutchens M, Hawkins C, Radnov A. How much do clinical trials cost? *Nature Reviews Drug Discovery*. 2017/06/01 2017;16(6):381-382. doi:10.1038/nrd.2017.70
9. Jiang J, Kong J. how did the public U.S. drugmakers' sales, expenses and profit change over time ? USC Leonard D. Schaeffer Center for Health Policy & Economics. https://healthpolicy.usc.edu/evidence-base/how-did-the-public-u-s-drugmakers-sales-expenses-and-profits-change-over-time/
10. Haacker M, Hallett TB, Atun R. On discount rates for economic evaluations in global health. *Health Policy Plan*. Feb 1 2020;35(1):107-114. doi:10.1093/heapol/czz127
11. Department of industries ministry of economic affairs royal government of Bhutan. *Feasibility analysis of drug formulation*. 2009.
12. National Institute on Aging. What Are Clinical Trials and Studies? National Institute on Aging. 2023. https://www.nia.nih.gov/health/what-are-clinical-trials-and-studies#:~:text=Clinical%20trials%20are%20research%20studies,safe%20and%20effective%20in%20people.

13. Moore TJ, Zhang H, Anderson G, Alexander GC. Estimated Costs of Pivotal Trials for Novel Therapeutic Agents Approved by the US Food and Drug Administration, 2015-2016. *JAMA Intern Med*. Nov 1 2018;178(11):1451-1457. doi:10.1001/jamainternmed.2018.3931

Table 1 Input data and assumptions for financial model and financial feasibility study

	Details	Source of data
Cost of sales	25% of revenues	Literature review,[9]
Operational expense	40% of revenues	Literature review, interview,[9]
Discounted rate	Discount rate 3%	Literature review, [10]
Interested rate	Interest rate for business is 3%	Interview
Tax rate	tax rate is 20%	Literature review, interview, [11]
Expected payback period	Payback period that investors could be accepted is 5-10 years	Interview

Table 2 The process and cost of developing IMDs in the form of a nasal spray by the domestic pharmaceutical industry

Process	**Details**[5,7]	**Cost situation 1 (Million USD)**	**Cost situation 2 (Million USD)**	**Information Source**
Sourcing	Local manufacturers choose IMD reference drugs based on marketing, user needs, sales, patents, and suitability.	0.66	0.66	Interview
R&D lab scale	The research and development unit conducts lab-scale studies to formulate nasal sprays. This entails designing a fitting analytical method for the drug, final product specs, and performance testing for the device. Challenges involve creating a consistent droplet delivery method and analytical method, sometimes requiring foreign facilities due to local limitations.			Interview
Pilot scale	After successful drug R&D, pilot batch production begins, followed by stability studies to determine shelf-life specifications. Results are reported to FDA.			Interview
Non-clinical study	Nasal spray is classified as a new route of administration. Non-clinical studies, including pharmacokinetics and toxicity, are required. Pharmacological data from the reference product can be used as a reference	0.16	0.21	
Clinical study				
-Phase I	For drugs with a new route of administration, a full clinical trial must be conducted due to changes in pharmacological,	0.86	0.86	Literature review ,Interview,[12]

Process	Details[5,7]	Cost situation 1 (Million USD)	Cost situation 2 (Million USD)	Information Source
	pharmacokinetic, and toxicological outcomes. These studies can be waived if there is sufficient supporting data.			
-Phase II		4.29	4.29	Literature review, Interview,[13]
-Phase III		12.86	12.86	
Registration	Registration of new drug formulas follows ASEAN Harmonization criteria. Application documents include administration data, product information, quality, safety, and efficacy parts. Non-clinical and clinical study data can refer to recommendations and guidelines.	0.003	0.003	Interview
Process validation batch	After obtaining FDA registration, drugs can be produced in commercial batches. Process validation and inspection results are submitted for permission to continue production and distribution.	0.99	0.99	Interview
Total		19.82	19.87	
Duration (years)		13	13	Interview