The Working Patent and Pharmaceutical Industry Development in Indonesia

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Abstract: Regulations regarding the working of pharmaceutical patents are intended to encourage invention, innovation, investment and transfer of technology. The fact is that the pharmaceutical industry is more interested in producing generic drugs than producing research drugs. The main objective to be achieved in this research is to answer predetermined problems, namely to explore and analyze the local working requirement policies, especially in the field of pharmaceutical patents linked to pharmaceutical industry development policies in order to fulfill drug availability for the public. By using analytical descriptive analysis, the findings the Indonesian pharmaceutical industry has not been able to achieve new drug discovery because there are still many obstacles, especially from the investment aspect. The national pharmaceutical industry has more interests in meeting market demand for pharmaceutical products in the context of the availability of drugs needed by the public. The development of of the pharmaceutical industry and medicinal raw materials in Indonesia is mainly constrained by technology and human resource capabilities. synthetic products produced is a lack of support from the upstream chemical industry. Potential opportunities for the development of biotechnology-based medicinal raw materials, by utilizing the wealth of biodiversity in Indonesia which is a potential resource in the pharmaceutical sector. The diversity of plants, microorganisms and marine biota is directly correlated with chemical diversity which has enormous potential for drug development.

Keywords: Working patent, Pharmaceutical industry, Intellectual Property Rights.

JEL: H75; I18; K22; K23; O34.

1. INTRODUCTION

Inventions or technological findings resulting from research and development (R&D) activities are the embryo of the emergence of patents. R&D with the ability to use technology and create innovative and patentable inventions are very important elements for the growth and development of pharmaceutical companies. Article 1 of Law No. 13 of 2016 states that, "Invention is an inventor's idea that is poured into a specific problem-solving activity in the field of technology in the form of a product or process, or the improvement and development of a product or process." Besides, the creation of pharmaceutical technology inventions (drugs) is very important to overcome public health problems, especially to cure diseases suffered by the community. The development of several types of diseases as a result of lifestyle changes and the emergence of several new tropical diseases and pandemic conditions require research efforts to produce new drug inventions that are more effective for their treatment. Drug discovery is a process that aims to identify a compound that is therapeutically useful in curing and treating disease. This process involves candidate identification, synthesis, characterization, validation, optimization, screening and testing for therapeutic efficacy. Once a compound shows its significance in these investigations, it will start the drug development process earlier for clinical trials. (Deore, AB, Dhumane JR, Wagh HV, Sonawane RB, 2019).

The company's ability to produce pharmaceutical inventions has a vital role for society, especially in maintaining health and producing drugs to treat various diseases. In the 1980s, significant developments in the field of innovative pharmaceutical inventions and successful commercialization were the discovery of insulin, recombinants, human growth hormone, interferon, tissue plasminogen activator (TPA), and erythropoietin (EPO) (Manning MC, Chou DK, Murphy BM, Payne RW, Katayama DS, 2010). The main inventors and innovators of the pharmaceutical industry can be found in five countries, namely the United States, Germany, Switzerland, the United Kingdom and France (Ariana, 2015).

The ability to conduct research that produces innovative and patentable inventions, especially related to the complexity of the technology, can be categorized as manufacturing capabilities and innovation capabilities. Drug manufacturing involves three main processes, namely drug formulation, production of bulk drugs and production of active pharmaceutical ingredients. First, drug formulation which refers to the process and packing of basic ingredientscalled bulk drugs into a form that can be consumed, such as tablets, capsules, syrups, injections, and plasters. Second, the production of bulk drugs containing therapeutic molecules in the form of powder or liquid is a more complex process because it requires a higher level of scientific and technological capabilities. Third, producing the core components of bulk drugs which are termed

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active pharmaceutical ingredients (API) is the most complicated and complex step. In each of these process activities, it is possible to produce inventions that lead to the acquisition of patents (Terstappen G, Schlüpen, C, Raggiaschi R, Gaviraghi G, 2007).

The ability to innovate, in this case, is distinguished between reengineering skills and new drug discovery skills. In general, a company starts with reengineering skills by developing a new process independently to produce bulk drugs and finally API. The ability ofreengineering skills is mostly done by pharmaceutical companies in developing countries, this is done as an investment in the development of new drug discovery capabilities. Capabilitiesin new drug discovery may take the form of integrating biotechnology and/or researchcapabilities in one or more steps of the new chemical entity (NCE) new drug discovery process.

Under the general description, patent applications in Indonesia are still dominated by innovations in the field of human needs and the field of metallurgical chemistry with claims in that class of approximately 2000 claims. Invention of pharmaceutical (chemical) products showed in pharmaceutical (chemical) patents and active drug compound patents that are submitted to DJKI until 2021, the number of invention applications is until the patent is granted. Pharmacy Patents from the 1956 applications that were later approved were granted legal protection 360 inventions (patent granted) or 18% of the total applications (DKJI, 2021). Approved domestic pharmaceutical patents 9 patents granted or 2.5% of the total number of patents granted (Table **1**).

Table 1. Invention of Compounds by Country.

Country	Application	Granted	End
United States	328	46	45
Germany	302	43	55
Japan	194	49	27
France	190	31	24
Korea, Republicof	174	66	
Switzerland	139	23	41
United Kingdom	103	15	16
Sweden	80		39
Indonesia	**74**	**9**	**4**
China	66	25	
Italy		10	7
India			

The occupancy of inventions of active compound drugs for which applications are granted until patents are granted, i.e. the number of applications approved is 7768 then those approved are given legal protection of 1481 inventions (patent granted) or 19% of the total applications. There are 231 patents granted for active medicinal compounds from domestically approved or 15.5% of the total number of patents granted. The compound invention is illustrated in the table and diagram in Table **2**.

Table 2. Occupancy of Inventions.

Country	Application	Granted	End
United States	1843	302	175
Germany	1073	152	130
Japan	1158	272	179
France	314	40	55
Korea, Republic of	197	84	
Switzerland	490	100	67
United Kingdom	359	46	51
Sweden	229		67
Indonesia	**898**	**231**	**22**
China	185	53	
Belgium			13
Luxembourg			
Netherland		41	30

Development of 50 (fifty) raw materials consisting of 1 (one) type of biotechnology, 1 (one) type of vaccine, 36 (thirty six) types of natural raw materials, and 12 (twelve) types of chemical drug raw material.

The main objective to be achieved in this research is to answer pre-determinedproblems, namely to explore and analyze local working requirements policies, especially in the field of pharmaceutical product patents linked to pharmaceutical industry development policies in order to fulfill drug availability for the public. This study uses a normative juridical method. The juridical aspect lies in the use of principles and legal principles in reviewing, especially legal principles and doctrines of intellectual property rights, especially patent law, to view and analyze the requirements for implementing patents. Meanwhile, from a normative point of view, this research is a reference used by researchers to analyze existing problems, namely the provisions of national and international legal regulations in the field of intellectual property rights law and Health law thatare enforced in Indonesia. Because it does not examine applied or implementation aspects, normative legal research is often also called "dogmatic legal research" or "dogmatic ortheoretical law research" (Abdulkadir, 2004). The analytical technique used in this research is descriptive analytical technique, which describes the applicable laws and regulations associated with legal theories and positive law enforcement practices concerning the issues discussed (Bambang, 2003). Descriptive means describing the object of research, namely The Working Patent and Pharmaceutical Industry Development in Indonesia based on existing facts, carried out systematically, chronologically and based on scientific principles. While analytical, which is associated with existing legal theories and or laws and regulations relating to the object under study.

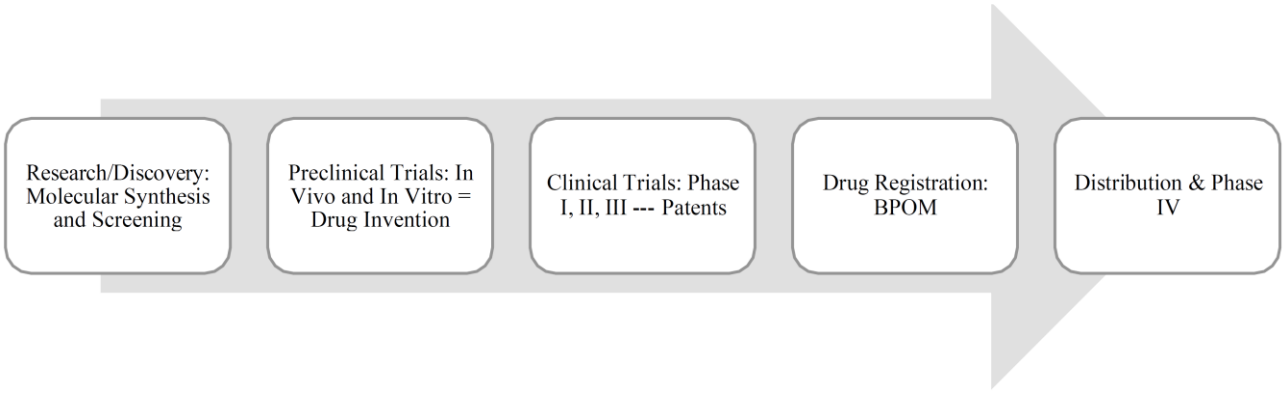

Fig. (1). Research and Development of a Pharmaceutical Intervention in Indonesia.

2. LITERATURE REVIEW: WORKING PATENT AND DEVELOPMENT OF PHARMACEUTICAL INVENTIONS

All over the world the working conditions of patents including pharmaceutical patents are to ensure that, the exclusive rights conferred by way of patents generate economic benefits for the jurisdiction grantor.(XueGaoaYiZhangb, 2022). Working patent is a requirement that can compel foreign patent recipients to place their production facilities in the jurisdiction of the patent issuer (Dixit, Pratik Prakash, 2021). This could have an impact on the flow of technology transfer from patent holders from developed economic countries to (developing) countries that apply working patent regulations.Technology transfer serves a number of developing countries' economic policy objectives, including those relating to job creation, the technology industry to economic independence . (Syahroni, Irfan Dwi, 2021) Local working will not only be considered to make a significant contribution to the technological development of developing countries, but also provide a strong means of coercion against patent holders. (Ricolfi, Marco, 2006).

While patents are seen as creating incentives for inventors to share ideas, LWR is also intended to reduce the exclusivity of patent monopolies by requiring patent holders to disseminate their inventions to the local market (Kazuyuki Motohashi, 2020). Pharmaceutical patent holders can thus impart knowledge and skills to local pharmaceutical industry players, boost economic growth, support local pharmaceutical manufacturing (Maskus, Keith E, 2019)., and promote the introduction of new pharmaceutical product innovations to local markets (Peizhen Jina Sachin Kumar Manglab Malin Songc, 2022). The working patent policy is also interpreted as a domestic provision that allows the granting of licenses when patents are not being worked on in that country (Mercurio, Bryan and Mitali Tyagi, 2010).

Broadly speaking, research and development of a pharmaceutical (drug) intervention goes through several stages. The reference for the stages of the new invention process or new chemical entity (NCE) in almost all countries in the world refers to the guidelines made by the Food and Drug Administration (FDA), including in Indonesia (Yulina, 2017). The guidelines are contained in section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act (the Act) aboutapplication is a new drug application (NDA) (CDER, 1999). The stages of the process are as follows (Ministry of Industry Republic of Indonesia, 2021).

The first is Molecular Synthesis and Screening. The development of medicinal materials can be carried out by synthesis or isolation from various sources, namely from plants, animal tissues, microbial culture, as well as by using biotechnology techniques. At this stage, various molecules or compounds that have the potential as drugs are synthesized, modified or even engineered to obtain the desired compound or drug molecule. At this stage, thousands of compounds may be potential candidates to be developed as medical treatments. However, onlya small number of compounds look promising and are subject to further study. The results of this screening procedure are referred to as main compounds, which are prime candidates for new drugs. Next, a computational compound approach (in silico) was carried out. One of them is chemical bonding of molecules. Computational chemistry approaches can be used to predictthe activity of the structure, the interactions that occur between the structure and the target molecule or between drug molecules (Hairunnisa, 2019). After obtaining the appropriate drug compound, a formula design is made so that the drug can be delivered properly to the drug target. Tablet preparations are the most popular preparations because they are easy to handle and tend to be more economical. But now, targeted drug delivery technologies are emerging in the form of inhalation, especially for respiratory tract disorders. Then an experiment was conducted to collect information about: (i) The way drugs are prescribed, distributed, metabolized and excreted; (ii) Potential benefits and mechanism of action; (iii) Best dose; (iv)the best route of drug administration (such as by mouth or injection); (v) Side effects (often referred to as toxicity.

The second is Preclinical Test. It is a test requirement for drug candidates. This test obtained information about the efficacy (pharmacological effect), pharmacokinetic profile andtoxicity of the drug candidate. Initially, preclinical testing was conducted on drug binding to receptors with isolated cell cultures or isolated organs (in vitro), then preclinical testing was carried out on intact animals (in vivo). The standard animals used are animals with certain strains of mice, rats, rabbits, guinea pigs, hamsters, dogs or some tests using primates. These animals are very instrumental in the development of drugs. Because only by using whole animals can be known whether the drug causes toxic effects at the dose of treatment or the drug is safe to use. Toxicity studies are a

potential way to evaluate: (i) Toxicity associated with acuteor chronic drug administration; (ii) Genetic defects (genotoxicity or mutagenicity); (iii) Tumorgrowth (oncogenicity or carcinogenicity); (iv) Incidence of birth defects (teratogenicity). In addition to toxicity, animal tests can study the pharmacokinetic properties of drugs including absorption, distribution, metabolism and elimination of drugs. All observations on these animals determine whether the drug candidate can be continued by testing in humans or not. Pharmacologists work together with pharmaceutical technologists in the manufacture of drug formulas, producing drug dosage forms that will be tested on humans. In addition to testing onanimals, to reduce the use of experimental animals, various in vitro tests have been developedto determine the efficacy of drugs, for example enzyme activity tests, anti-cancer tests using cell lines, antimicrobial tests on microbial seeds, antioxidant tests, anti-inflammatory tests and others. -Other to replace efficacy tests on animals.

However, not all tests can be performed in vitro. Toxicity tests are still being carried out on experimental animals, there is no other method that guarantees results that can describe toxicity in humans. In addition, this animal test is also designed with special attention to the possibility of further testing the drug in humans or clinical trials. Therefore, this preclinical trial was designed with the following considerations in mind: (i) The duration of administrationof the drug according to suspicion to humans; (ii) The age group and physical condition of theperson being addressed, with special consideration for children, pregnant women or the elderly;

Presumptive effects of the drug on humans. The results of the toxicity test cannot be usedabsolutely to prove the safety of a substance/preparation in humans, but can provide an indication of the relative toxicity and help identify toxic effects in the event of exposure to humans. The factors that determine the reliability of the in vivo toxicity test results are the selection of the test animal species, strain and number of animals, the method of administrationof the test preparation, the selection of the test dose, side effects of the test preparation, testingtechniques and procedures including the way animals are handled during the experiment. After passing the pre-clinical test, the compound or molecule of the candidate drug candidate becomes an IND (Investigational New Drug) or a new drug under research. After the drug candidate is declared to be beneficial and safe in experimental animals, it is then tested on humans (clinical trials). Tests on humans should be examined for feasibility by an ethics committee following the Declaration of Helsinki (Sukandar, 2006).

The third is Clinical Trials. Clinical trials in humans consist of 4 phases, namely:

a. Phase I, the drug candidate is tested on 25-50 healthy volunteers to see if the properties observed in experimental animals are also seen in humans. In this phase,the relationship between the dose and the effects and the pharmacokinetic profile ofthe drug in humans is determined.

b. Phase II, the drug candidate is tested on a specific patient 100-200 people, observed efficacy in the disease being treated. What is expected from a drug is to have a

c. potential effect with low or non-toxic side effects. In this phase, the development and stability test of drug dosage forms begins to be carried out.

   Phase III, involving a large group of patients about thousands of people, in which the developed drugs are compared for their effects and safety against known comparison drugs. During clinical trials, many drug candidate compounds were declared unusable. The decision to admit a new drug is given by the national regulatory agency, by attaching preclinical and clinical test document data in accordance with the proposed indication, its efficacy and safety must have been determined from the product form (tablets, capsules, etc.) that have met product requirements through quality control. In Indonesia the decision on test results is issued by the Food and Drug Supervisory Agency (BPOM), in the United States bythe FDA (Food and Drug Administration), in Canada by Health Canada, in the UKby the Medicine and Healthcare Product Regulatory Agency (MHRA), in Europeancountries others by the European Agency for the Evaluation of Medicinal Products(EMEA) and in Australia by Therapeutics Good Administration (TGA).

   Drug development is not limited to making products with new substances, but can also modify existing drug dosage forms or research new indications in addition to existing indications. Both new dosage forms and additional indications or changes in dosage in the preparation must be registered with the POM and assessed by the National Commission for Assessing Finished Drugs. The development of pharmaceutical technology and biopharmaceuticals gave birth to a new drug delivery system, especially in dosage forms such as slow-release tablets, liposomes, enteric-coated tablets, microencapsulations and others.

   Advances in DNA recombination techniques, cell culture and tissue culture have led to advances in the production of medicinal raw materials such as insulin production and others. After the drug candidate can be proven to be at least as efficacious as the existing drug and demonstrate safety for the user, the new drug is permitted to be produced by the industry as a legal drug and marketed under certain trade names and can be prescribed by doctors.

d. Phase IV after the drug is marketed, post-marketing studies are still being carried out (post-marketing surveillance) which is observed in patients with various conditions, various ages and races, these studies are carried out over a long period of time to see the therapeutic value and long-term experience in using the drug.

After the results of the phase IV study are evaluated, it is still possible for the drug to be withdrawn from the trade if it is harmful, for example, cerivastatin, an antihypercholesterolemic drug that can damage the kidneys, Enterovioform (klioquinol), an amoebic anti-dysentery drug which in the Japanese causes paralysis of the eye muscles (SMONdisease),

phenyl propanol amine which is often found in cold medicines should be reduced from 25 mg to no more than 15 mg because it can increase blood pressure and dangerous heart contractions in patients who have previously had heart disease or high blood pressure,troglitazone an antidiabetic drug in the United States withdrawn for breaking the liver.

Drugs to be circulated in the territory of Indonesia must have a distribution permit. Afterconducting a series of drug discovery and development tests. Furthermore, registration is carried out in order to support the safety of the drugs that will be developed by obtaining a registration number so that consumer safety is better maintained. Article 106 of Law Number 36 of 2009 concerning Health states that pharmaceutical preparations and medical devices canonly be circulated after obtaining a distribution permit. Marking and information on pharmaceutical preparations and medical devices must meet the requirements for objectivity and completeness and not be misleading. The pharmaceutical industry as a business actor in carrying out its business must have the obligation to provide true, clear and honest information regarding the conditions and guarantees of the drugs produced as well as to provide explanations for use, guaranteeing the quality of drugs produced and traded based on the provisions of the applicable quality standards. All of these processes are solely for the sake of ensuring the safety of the products that will be used by the public.

3. RESULTS

3.1. Pharmaceutical Patent in Indonesia

The discovery of new patentable chemotherapeutica (New Chemical Entity/NCE) drugs requires a very long road and currently tends to decline, due to the implementation of very strict conditions to be accepted, registered and allowed to circulate as drugs. This applies in European countries, the United States and other developed countries. These stringent requirements necessitate much more extensive pharmacological and safety research and are themselves very costly. The period of discovery of a new drug from the beginning when a newchemical is discovered until it becomes a new drug that is permitted to circulate takes 10 – 12years and the research cost is approximately USD 750 – 850 million (Rp. 10.5 – 11.9 trillion).In terms of costs, with a long process, finding a new drug is very expensive and requires a long-term investment, it is not surprising that the pharmaceutical industry in Indonesia generally rarely conducts research until new drugs are found and then marketed. While the results of drugdevelopment are not always as expected, depending on the efficacy, are safe and do not causeharmful side effects. As an illustration, of the 10 thousand drug candidate compounds studied, only 1 drug compound was successfully marketed and reached patients. It is this uncertainty that makes not many companies dare to invest in drug development (Priyambodo, 2014).

The ability to produce pharmaceutical inventions is highly dependent on the technological capabilities of the pharmaceutical company. In Indonesia, according to the Deputy for Science and Technology Network, Ministry of Research and Technology, the classification is divided into five types of pharmaceutical industry, namely (Ariana, 2015):

1. Pharmaceutical industry that develops from scratch, namely from basic, raw materials, and clinical trial stages.
2. Pharmaceutical industry that only develops raw materials and does not conduct clinicaltrials.
3. The pharmaceutical industry that buys raw materials that have been developed by others to clinical trials and only markets (multinational groups).
4. Pharmaceutical licensing industry that buys raw materials and in Indonesia only performs formulating (making formula), filling (filling) and packaging (packaging) so that they do not carry out activities from the beginning (basic research) to raw materials, but only follow post marketing evaluations. For example, in Indonesia currently antibiotics are bought in powder form and a certain formula is added and then they are made into capsules, tablets, or liquid drugs.
5. Manufacture of herbal ingredients that do not need to be researched and only uses traditional ingredients.

The technological capability of the pharmaceutical industry in Indonesia, in this case, is still largely limited to drug formulations, namely developing the final product by relying on its superiority or equivalence in bioavailability/bioequivalent (BA/BE) to comparator products. As an implication, in the future Indonesian national pharmaceutical companies will not be able to compete in the patented/innovative drug market segment. Moreover, the Indonesian pharmaceutical industry has not been able to achieve the discovery of new drugs because there are still many obstacles, especially from the investment aspect. It costs US$350–800 million to find a new drug (new chemical entity (NCE) and sell it on the market. The amount of R&D costs is related to the following three things: (i) Technology; (2) New, more complex active ingredients; (3) Stricter regulatory requirements in the form of preclinical trials and clinical trials. In addition, the national pharmaceutical industry is more interested in meeting market needs for pharmaceutical products that are generally needed by the community, namely the production and marketing of drugs that are off patent or hereinafter known as generic drugs (Ariana, 2015).

In addition, Indonesia's research budget originating from the APBN and non-APBN is still minimal, the research budget in Indonesia is only around 0.25% of the national gross domestic product (GDP) or around Rp. 30.8 trillion. This research budget is still lower than other ASEAN countries such as Vietnam, Thailand and Malaysia (World Bank, 2021). Indonesia's ranking in the Global Innovation Index (GII) is ranked 87 for and ranked 14 in the South East Asia, East Asia, and Oceania Region below Singapore, Malaysia, Thailand and Brunei, but in terms of Innovation performance at different income levels Indonesia, Thailand, and Malaysia entered the Upper middle-income group at level 27 (Malaysia and Thailand at level 3 and 5) with the category Performance in line with level of development (WIPO, 2021).GII is measured by how the government and companies invest to innovate by the number of publications, the budget for research and development as well as the filing of intellectual

property rights. The description of Indonesian pharmaceutical inventions can be seen in the tabulation of patent applications and the acquisition of pharmaceutical patents. The low technological capability to develop new drugs is closely correlated with the occupation of obtaining patents in the pharmaceutical sector.

Development of 50 (fifty) raw materials consisting of 1 (one) type of biotechnology, 1(one) type of vaccine, 36 (thirty six) types of natural raw materials, and 12 (twelve) types of chemical drug raw materials.

3.2. Policy of Pharmaceutical Industry

The implementation of pharmaceutical patents, especially for medicinal products, is not only required by Patent Law, but is also supported by other regulations such as regulations on industry, health, investment and technology transfer. In Indonesia, the pharmaceutical industry policy which is one of the 10 priority industries contained in the 2015-2035 National Industrial Development Master Plan (RIPIN) based on Government Regulation (PP) No. 14 of 2015 as a derivative of Law (UU) No. 3 of 2014 concerning Industry. RIPIN places the pharmaceutical industry as part of the National Long-Term Development Plan (RPJPN), one of the goals of which is to create an independent, competitive, and advanced industry and to realize the strength of the industrial structure that plays a major role as the prime mover of the economy in the future. will come.

Efforts to develop the pharmaceutical industry are carried out continuously by taking several steps towards the independence of the pharmaceutical industry. The initial step taken was the preparation of a roadmap for the development of medicinal raw materials (BBO) and traditional medicinal raw materials (BBOT) industries through the Regulation of the Minister of Health of the Republic of Indonesia Number 87 and 88 of 2013. Furthermore, with the issuance of the Presidential Instruction of the Republic of Indonesia Number 6 of 2016 concerning the Acceleration of the Development of the Pharmaceutical and Medical Devices Industry, and finally an Action Plan for the Development of the Pharmaceutical and Medical Devices Industry was made through the Regulation of the Minister of Health of the Republic of Indonesia Number 17 of 2017. Action Plan for the Development of the Pharmaceutical and Medical Devices Industry in which the development of the pharmaceutical industry is carried out in stages in 4 (four) main focus pillars for the development of pharmaceutical raw materials in the fields of Natural, Chemical (API, Biopharmaceutical and Vaccine) raw materials. The pharmaceutical industry development strategy is carried out through 68 Profile of Pharmaceuticals and Medical Devices in 2019 strengthening of resources and technology transfer.

Meanwhile, in the pharmaceutical industry sector, there is a policy of accelerating the development of the pharmaceutical industry through Presidential Instruction No. 6 of 2016 which orders 8 Ministries (Coordinating Minister for Economic Affairs, Coordinator for Human Development and Culture, Minister of Health, Minister of Finance, Minister of Research, Technology and Higher Education, Minister of Trade, Minister of Agriculture) to take steps according to their respective duties, functions and authorities to support the acceleration of the development of the pharmaceutical and medical device industry, by: (1) guarantee the availability of pharmaceutical preparations and medical devices as an effort to improve health services within the framework of the National Health Insurance; (2) increase the competitiveness of domestic and export pharmaceutical and medical device industries; (3) encourage mastery of technology and innovation in the field of pharmaceuticals and medical devices; and (4) accelerating the independence and development of production of raw materials for drugs, drugs, and medical devices to fulfill domestic and export needs as well as restoring and increasing industrial activities/utilization of industrial capacity.

The condition of pharmaceutical industry development, until 2019, 53 raw materials have been developed, consisting of 1 type of biotechnology product, 1 type of vaccine product, 39 types of natural product, and 12 types of chemical drug raw material products. In 2020-2021 it is planned to develop 34 raw materials consisting of 6 types of biopharmaceuticals, 3 types of vaccines, 13 types of natural, and 12 types of chemicals (API). In 2022-2025 it is planned to develop 47 raw materials consisting of 4 types of biopharmaceuticals, 10 types of vaccines, 17 types of natural, and 16 types of chemicals (API) (Ministry of Health Republic of Indonesia, 2019).

The growth of the Pharmaceutical industry in Indonesia is marked by the increasing number of pharmaceutical industries in Indonesia, where in the last 5 years (2015 – 2019), the domestic pharmaceutical industry has increased by 132 new industries, from a growth of 8.1 percent or increased from 210 companies in 2015 to 227 companies in 2020. Meanwhile, the drug raw material industry has also increased from 8 industries in 2016 to 14 industries in 2019.Of all these industries, they are divided into three types of companies, namely there are 167 domestic pharmaceutical industries (PMDN), 48 pharmaceutical industries originating from abroad (PMA), 8 BUMN pharmaceutical industries and 4 Indonesian National Army (TNI) pharmaceutical industries (BPOM, 2021).

Products produced from 227 pharmaceutical industries, 209 (92.1 percent) companies specifically produce chemical finished products. Seven companies (3.1 percent) produce medicinal raw materials. There are 3 companies or (1.3 percent) each that produce biological products, those that produce chemical finished products and medicinal raw materials, and those that produce medicinal raw materials and biological products. Meanwhile, there is only 1 company each or (0.4 percent) that produces finished chemical products and raw materials for drugs and radiopharmaceuticals (Christianingrum & Mujiburrahman, 2021).

A number of pharmaceutical companies are able to produce several segments of pharmaceutical products that can generally be found in Indonesia, including OTC (over the counter medicine), patented, and generics medicine (branded and unbranded). Based on Healthcare Indonesia Outlook 2016 the distribution segment of the drug is 42% geberik drugs, 40% OTC drugs and patent drugs (Lutfiyah, 2020).

The level of public consumption of drugs is increasing, from Rp. 65.9 trillion in 2016 to Rp. 88.36 trillion in 2019, and 73% of the national pharmaceutical market share is dominat-

ed by local pharmaceutical companies (Ministry of Health Republic of Indonesia. (2020a). Along with the increasing population, increasing awareness of the Indonesian people about the importance of health and the need for medicines, increasing the income of the middle class, increasing their purchasing power of medicines and health supplements, the level of consumption of pharmaceutical products is also expected to continue to increase. In the next few years, with the implementation of the National Health Insurance - Healthy Indonesia Card (JKN-KIS) which according to BPJS Director Ali Gufron on September 17, 2021, the number of JKN-KIS participants has reached 226.3 million participants or about 83.5% of the total population. population of 270 million people (Kesehatan, 2021). This program continues to be improved to reach the wider community and is targeted to provide health insurance for all Indonesian people, so that the number of JKN-KIS participants will increase from year to year, which has an influence on the growth of the pharmaceutical (drug) industry.

Despite positive growth, the concentration of pharmaceutical companies is still in the downstream sector by producing chemical finished products reaching 92.1 percent. Meanwhile, the upstream sector (companies that produce medicinal raw materials) is still below 4 percent. The consequence is that the need for medicinal raw materials is highly dependent on imports, due to limited domestic production. Data from the Ministry of Industry (2021), shows that the pharmaceutical sector still makes a very significant contribution to Indonesia's import portion. Imports of Indonesian medicinal raw materials reached 95 percent. The largest imports of medicinal raw materials came from China (60 percent), followed by India (30 percent) and European countries (10 percent).

The policy of importing pharmaceutical products to be used in Indonesia in the form of blug drugs, so that pharmaceutical products (drugs) are carried out carefully tend to be limited. Based on the Minister of Health Number 1010 of 2008 concerning Drug Registration (Articles 9-10) in conjunction with the Head Regulation (PerKa) of BPOM Number 24 of 2008 concerning Administration of Drug Registration (Articles 11-16) that imported drugs are prioritized for: (i) National health program drugs, namely government agencies administering national health programs; (ii) Newly discovered drugs consist of drugs that are still under patent protection and originator drugs, namely drugs that were first given a distribution permit in Indonesia based on complete data on efficacy, safety, and quality: and/or (iii) Drugs that are needed but cannot be produced domestically, namely drugs that require special technology and production facilities that are not owned by the Pharmaceutical Industry in Indonesia and or available technology but insufficient capacity, Drugs that are economically impossible to produce domestically Because the need is small, it can be in the form of drugs for rare diseases (Orphan Drugs) in Indonesia and drugs that are centrally produced abroad by multinational pharmaceutical industries that have pharmaceutical industries in Indonesia. Imported Drug Registration must be accompanied by justification that the said drug cannot be produced in Indonesia.

The next policy is that the registration of imported drugs must be carried out by the domestic pharmaceutical industry which obtains written approval from the foreign industry; written approval must cover technology transfer within 5 years must be able to be produced domestically (except for drugs that are still under patent protection); registration of drugs that are still protected by patents is carried out by the domestic industry holding the patent license or the domestic pharmaceutical industry appointed by the patent holder; Drug registration can be carried out by non-licensing industries, which is carried out 2 years before the expiration of patent protection; and foreign pharmaceutical industries must have a GMP certificate.

However, the import trend of the Pharmaceutical industry also increased during 2018 - 2020 in value, but decreased in volume during that period. In value, imports of the Pharmaceutical Industry increased from USD 1.52 billion in 2018 to USD 1.68 billion in 2020. Meanwhile, by volume, imports of the Pharmaceutical Industry amounted to 75.46 thousand tons in 2020, down from 75.86 thousand tons in 2018. With the value of imports rising and volume decreasing, it indicates that there is an increase in the price of pharmaceutical products, which is thought to be due to the shortage of goods during the COVID-19 pandemic, along with the increasing demand for medicines and health supplements. The largest pharmaceutical industry imports come from China, the United States, Germany, India, and France, which are indeed big players in the pharmaceutical industry in the world. Compared to exports of the Pharmaceutical Industry, Chemical Drug Products and Traditional Medicines experienced an increasing trend over a 3-year period (2018 – 2020) of 2.68%, where in 2020, the export value of the pharmaceutical industry reached USD 635.3 million from USD 602, 5 million in 2018. Meanwhile, in terms of volume, exports of the pharmaceutical industry experienced a downward trend of 7.02%, from 52.6 thousand tons in 2018 to 45.5 thousand tons in 2020. By country, the five largest export destinations for the pharmaceutical industry are all countries in Asia, namely Singapore, Japan, the Philippines, India and Thailand, with export contributions from these five countries reaching 58% of the export value of the Indonesian pharmaceutical industry to the rest of the world.

Based on the origin of FDI investment, the Netherlands is at the top with a contribution of 23.2% of FDI investment in the Pharmaceutical Industry, Chemical Medicinal Products and Traditional Medicines in 2020. Then followed by investment from Japan which contributed 19.3%, Switzerland 18.6%, South Korea, 14.2%, and the United States 10.2% (Ministry ofIndustry Republic of Indonesia, 2021). In addition to the Action Plan Policy for the Development of the Pharmaceutical and Medical Devices Industry (Ministry of Health Number 17 of 2017), 14 joint venture pharmaceutical industries have developed with the pharmaceutical industries of other countries such as the United Arab Emirates, Hong Kong, Korea, India, Germany and others. The joint venture pharmaceutical industry produces innovative products needed in health services and the production of medicinal raw materials, which are expected to realize the independence of the pharmaceutical industry (Ministry of Health Republic of Indonesia, 2019).

3.3. Invention and Innovation in Pharmaceutical Industry

The development of the pharmaceutical industry is also seen in the growth of the industry transforming from the formulation industry to a research-based industry (cumulative) with 11 industries (Ministry of Health Republic of Indonesia, 2019).

PT Biofarma as a state-owned pharmaceutical manufacturer of vaccines has R&D and production facilities for viral vaccines and bacterial vaccines; has been endorsed by the Organization of Islamic Cooperation (OIC) as a center of excellence (CoE) for the development of biotechnology and vaccines; based on the assessment of the transformation parameters already at the level of maturity transformation level 3 (consistent-designed); enable it to continue to be sustainable as a life science pharmaceutical industry.

PT. Dexa Medica as a domestic manufacturer that has carried out research and development of innovative products for traditional medicines and pharmaceutical preparations; already has an R&D infrastructure named Dexa Development Center (DDC) which conducts R&D formulations, innovative formulations and New Drug Delivery System (NDDS) as well as Dexa Laboratories of Biomolecular Science (DLBS) for R&D and production of innovative products based on biomolecular science; based on the assessment of the transformation parameters already at the level of transformation maturity level 4 (consistentimplemented); Dexa Medica and DLBS have carried out integrated research with international research centers of excellence in the pharmaceutical, biopharmaceutical, and nutraceutical fields.

PT Kalbe Farma as as a domestic manufacturer that has carried out research and development of superior research ranging from stem cells to biotechnology; Kalbe Farma has carried out R&D in the context of technology transfer and jointventures including the development of innovative and hightech products (insulin analogue, long acting EPO, EPO, rituximab and bevacizumab and transtuzumab); based on the assessment of the transformation parameters already at the level of transformation maturity level 4 (consistentimplemented); the R&D pipeline by synergizing with related stakeholders in a sustainable and systematic manner, among others, with universities UGM, ITB, UI, and Udayana.

The efforts to develop pharmaceutical production inventions and innovations to produce new drugs and generic drugs are constrained by the availability of medicinal raw materials .The problem of dependence on imported BBO is because the aspect of providing basic ingredients for raw materials from local products is still small. This is because the basic chemical industry has not yet developed to support the supply of intermediates for basic substances for drug manufacture. Dependence of some basic substance intermediates may reduce the benefits of local synthesis. The development of medicinal raw materials in Indonesia is mainly constrained by technology and human resource capabilities. The independence of medicinal raw materials is currently still very difficult to implement in Indonesia, because there are still very few medicinal raw materials, especially synthetic products (derived from chemicals) produced in Indonesia, given the lack of support from the upstream chemicalindustry. A bigger opportunity lies in the development of biotechnology-based medicinal raw materials, by utilizing Indonesia's rich biodiversity which is a potential resource in the pharmaceutical sector. Biodiversity of plants, micro-organisms and marine biota is directly correlated with chemical diversity which has enormous potential for drug development.

The problems faced in the development of medicinal raw materials include the Roadmap for the Development of Drug Raw Materials, Permenkes Number 87 of 2013: (i) Lack of basic chemical support used for the drug synthesis process as well as for the isolation, separation, purification of drugs in bioprocessed drugs; (ii) The pharmaceutical raw material industry requires a large investment with a high failure rate (uncertainty about the success of developing medicinal raw materials); (iii) The development of types of drugs and their derivatives is very fast, so that qualified research and development is needed; (iv) Lack of synergy between Academia – Business – Government (ABG); (v) The national raw material market is relatively small compared to the minimum production capacity for a single pharmaceutical raw material industry so that it will not be able to meet economies of scale. PT. Kimia Farma Sungwun Pharmacopia as foreign investor on the pharmaceutical industry for medicinal ingredients that has not developed HFC (High Function Chemistry) which has not been widely developed PMA Pharmaceutical industry for medicinal ingredients has developed HFC (High Function Chemistry) which has not been widely developed in Indonesia. Besides that, PT. Kimia Farma Sungwun Pharmacopia cooperates with Sungwun Pharmacopia Co.Ltd in South Korea in technology transfer and human resource development by sending personnel to the Sungwun Pharmacopia plant in South Korea. PT. Kimia Farma Sungwun Pharmacopia has also received an award from the Minister of Health of the Republicof Indonesia at the Domestic Health and Health Product Development Exhibition as one of the pharmaceutical industries that realizes the independence of drugs and drug raw materials in the country; based on the assessment of the transformation parameters, it is at the level of transformation maturity level 4 (consistentimplemented).

PT Kalbio Global Medika as a domestic manufacturer for the Pharmaceutical Drug and Drug Ingredients Industry that develops high-innovating products, namely Recombinant Protein Concentrates and biosimilar products, namely Bio Better Products to meet local and international market needs as well as the development of 10 (ten) molecules of biotechnology products commercially. PT. Kalbio Global Medika also invests in the development of substantial research on biosimilar products and develops human resources to develop research in collaboration with the Education Institute. PT Kalbio Global Medika has also received an award from the Minister of Health of the Republic of Indonesia at the Domestic Health and Health Product Development Exhibition as one of the pharmaceutical industries that manifests independence in drugs and drug raw materials in the country as one of the pharmaceutical industries that realizes independence in drugs and medicines. domestic medicinal raw materials; based on the assessment of the transformation parameters, it is at the level of transformation maturity level 4 (consistentimplemented).

PT. Daewoong Infion supports the transformation of the pharmaceutical industry through the development of research on high-innovating products, namely erythropoietin, EGF(Epidermal Growth Factor) and Human Pharmaceutical Industry with joint-venture between PT. Otto Pharmaceutical Industries, Indonesia with Chong Kun Dang Pharmaceuticals, SouthKorea, which developed anti-cancer drugs with a local production plan of anti-cancer drugs to meet the needs in Indonesia, where not too many pharmaceutical industries in Indonesia have developed anti-cancer drugs. Some of the products produced by PT. CKD Otto Pharmaceutical has obtained a Marketing Permit Number (NIE) and a Halal Certificate.

PT. CKD Otto Pharmaceutical: Pharmaceutical industry joint-venture between PT. Otto Pharmaceutical Industries, Indonesia with Chong Kun Dang Pharmaceuticals, South Korea, which developed anti-cancer drugs with a local production plan of anti-cancer drugs to meet the needs in Indonesia, where not too many pharmaceutical industries in Indonesia have developed anti-cancer drugs. Some of the products produced by PT. CKD Otto Pharmaceutical has obtained a Marketing Permit Number (NIE) and a Halal Certificate.

PT. Kimia Farma Plant Banjaran with the pharmaceutical industry has the largest production facility in Southeast Asia and has been equipped with production facilities connected to the internet/Internet of Things (IoT) that support industry in the industrial era 4.0. PT. Kimia Farma Plant Banjaran is also equipped with a Research and Development (RnD) laboratory as an effort to transform into a research-based industry. Pharmaceutical industry thatdevelops biological products with a focus on developing immuno-oncology products and has special funding for the development of these products. Specific funding implies that the pharmaceutical industry is committed to transforming into a research-based industry.

PT Metiska Farma as a pharmaceutical industry is committed to transforming into a research-based industry by conducting research developments on enoxaparin products which will be developed through sheep to ensure product halalness, namely as non-porcine products.

PT Combiphar Dong A as a pharmaceutical industry transfers technology in the development of biological products with the pharmaceutical company Dong A, South Korea. PT Combiphar Dong A invests in the construction of a biosimilar factory with the initial stageof producing biological products of the recombinant type of protein and has received CPOB certification from the POM Agency.

The efforts to develop pharmaceutical production inventions and innovations to produce new drugs and generic drugs are constrained by the availability of medicinal raw materials .The problem of dependence on imported BBO is because the aspect of providing basic ingredients for raw materials from local products is still small. This is because the basic chemical industry has not yet developed to support the supply of intermediates for basic substances for drug manufacture. Dependence of some basic substance intermediates may reduce the benefits of local synthesis. The development of medicinal raw materials in Indonesia is mainly constrained by technology and human resource capabilities. The independence of medicinal raw materials is currently still very difficult to implement in Indonesia, because there are still very few medicinal raw materials, especially synthetic products (derived from chemicals) produced in Indonesia, given the lack of support from the upstream chemicalindustry. A bigger opportunity lies in the development of biotechnology-based medicinal raw materials, by utilizing Indonesia's rich biodiversity which is a potential resource in the pharmaceutical sector. Biodiversity of plants, micro-organisms and marine biota is directly correlated with chemical diversity which has enormous potential for drug development.

In the field of pharmaceutical production, almost 70% of the national drug needs can be met from domestic production. But 95% of the raw materials used by the pharmaceutical industry are obtained through imports. Drug raw material components contribute 25-30% of the total cost of drug production, so intervention in this component will have an impact on drug prices. However, through coordination and cooperation between stakeholders, until 2019 the raw materials that have been developed and produced domestically are 50 (fifty) raw materials consisting of 1 (one) type of biotechnology, 1 (one) vaccine, 36 (three) twenty six) types of natural raw materials, and 12 (twelve) types of chemical drug raw materials (Ministry of Health Republic of Indonesia, 2020b).

The problems faced in the development of medicinal raw materials include the Roadmap for the Development of Drug Raw Materials, Permenkes Number 87 of 2013: (i) Lack of basic chemical support used for the drug synthesis process as well as for the isolation, separation, purification of drugs in bioprocessed drugs; (ii) The pharmaceutical raw material industry requires a large investment with a high failure rate (uncertainty about the success of developing medicinal raw materials); (iii) The development of types of drugs and their derivatives is very fast, so that qualified research and development is needed; (iv) Lack of synergy between Academia – Business – Government (ABG); (v) The national raw material market is relatively small compared to the minimum production capacity for a single pharmaceutical raw material industry so that it will not be able to meet economies of scale.

Dependence on imported BBO makes the national pharmaceutical industry unable to increase its rating status from C1 to B or A. In the categorization of the world pharmaceutical industry, Indonesia is in the C1 category, namely a country that is capable of reproducing medicinal raw materials and finished drugs. However, it has not been able to enter category B, namely countries with innovative pharmaceutical industries, which are marked by the number of drug patents produced, and category A, namely countries with the ability to mass produce finished drugs and have focused on research and development.

3.4. The Policy of Working Patent and the Development of Pharmaceutical Industry

The technological capability of the pharmaceutical industry in Indonesia is still largely limited to drug formulation, namely developing end products by relying on superiority or equality in bioavailability/bioequivalent (BA/BE) to comparator products. The Indonesian pharmaceutical industry has not been sufficiently capable of achieving new drug discoveries because there are still many obstacles to be faced,

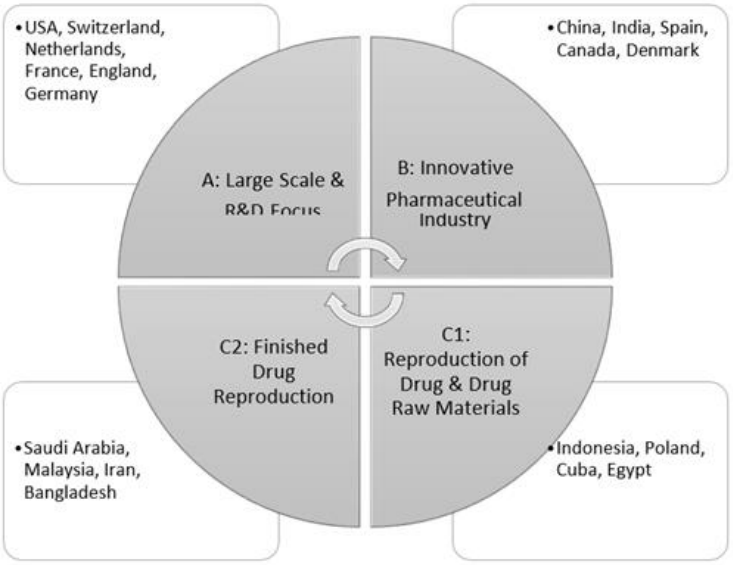

Fig. (2). The flowchart of pharmaceutical supply chain.

especially from the investment aspect of research costs and an unpromising market. Discovery of new drugs (new chemical entity -NCE) to selling them on the market requires a cost of US$ 350–800 million. The large research costs are due to: (i) Technology; (2) New, more complex active ingredients; (3) More stringent regulatory requirements in the form of preclinical trials and clinical trials. Besides that, the national pharmaceutical industry is more interested in meeting market demand for pharmaceutical products that are generally needed by the public, namely the production and marketing of drugs that are off patent or hereinafter known as generic drugs.

This condition has implications for the limited availability of innovative/patented drugs. Availability of drugs on the registered market as well as drugs available in the national drug forum-FORNAS (92% of generic drugs) for the National Health Insurance program which is dominated by generic drugs rather than new/innovative drugs with a ratio of 7:1 to innovative drugs (INDEFF, 2020). This condition has implications for the limited availability of innovative/patented drugs. Availability of drugs on the registered market as well as drugs available in the national drug forum-FORNAS (92% of generic drugs) for the National Health Insurance program which is dominated by generic drugs rather than new/innovative drugs with a ratio of 7:1 to innovative drugs (INDEFF, 2020). Based on the results of research at the United State, innovative drugs are assumed to improve the quality, life expectancy and health of citizens (Lichtenberg, 2017) and studies in 2018 in several Middle East and Africa that without the introduction of new drugs additional disability-adjusted life years (DALYs) are lost. due to medical conditions that cannot be treated (Lichtenberg, 2019).

In the future policies to further encourage drug invention and innovation or invest in the health sector are needed not only because of the cost factor, but the drivers of growth, employment, innovations and, ultimately, population health. There is a need for not only considering the therapeutic benefits that medical innovations deliver, but also on their contributions towards economic activities and general prosperity. (Claudio Schiener, Manuel Störzel, Jason Maro, Dennis Ostwald, 2021).

Government policies that provide more access to and promote generic drugs than providing access to innovative/patented drugs in Indonesia are due to: (1) the price of innovative/patented drugs is much more expensive than generic drugs; (2) the growth of the domestic pharmaceutical industry related to patent/innovative drugs is still limited; restrictions/restrictions on imported drug products including patent/innovative drugs (drugs that are still under patent protection), most of which are produced by foreign pharmaceutical companies abroad. This restriction obliges the registration of imported drugs to go through the domestic pharmaceutical industry. This policy was taken in order to protect the domestic pharmaceutical industry, which partially produces generic drugs for the benefit of serving the needs of the public's right to access cheap and affordable drugs.The wide availability of markets and access to generic drugs makes it less supportive of a research culture by pharmaceutical industry players to produce medicinal raw materials containing new active substances to be patented for pharmaceutical products.

Government policies regarding working patents in Article 20 of the Patent Law prior to amendments, especially in the field of pharmaceutical patents, are generally supported or in line with policies regarding strategic plans regarding availability, affordability, safety and independence, development and use of drugs. Implementation of the obligation to implement pharmaceutical patents in order to support policies on the availability of medicinal raw materials, more affordable patented drugs (availability and cheaper prices), higher quality and efficacious drugs, development of the pharmaceutical industry (transfer of innovative drug technology), investment and support for safe use domestically produced drugs.

Amending Article 20 of the Patent Law by substituting imports to abort the obligation to implement patents in the

country (WP) is the same as mitigating or marginalizing the main mission of accessibility policies regarding the availability and affordability of drugs. and self-sufficiency in using drugs produced in the country. Besides that, imports can hinder the development of medicinal raw materials and self-sufficiency in using domestically produced drugs.

Even though several policies to encourage the independence of pharmaceutical production have been quite successful in meeting the availability of drugs, there are still obstacles to the availability of medicinal raw materials which 90% still depend on imports. Indonesia as a country that is rich in biodiversity and supported by a culture of people consuming herbal medicine has the potential to develop raw materials for medicines/vaccines that lead to biopharmaceuticals. In this case, there needs to be a mandatory assignment policy to state-owned pharmaceutical companies (BUMN) to conduct research in collaboration with academics at universities or research grant policies for academics that must be collaborated with pharmaceutical industry players to produce inventions of medicinal raw materials or active drug compounds.

4. CONCLUSION

The technological capability of the pharmaceutical industry in Indonesia is still very limited in drug formulation, namely developing final products by relying on the superiority or bioavailability/bioequivalence (BA/BE) of comparable products. The implication is that in the future, Indonesian national pharmaceutical companies will not be able to compete in the patent/innovative drug market segment. The Indonesian pharmaceutical industry has not been able to achieve new drug discovery because there are still many obstacles, especially from the investment aspect. The national pharmaceutical industry has more interests in meeting market demand for pharmaceutical products in the context of the availability of drugs needed by the public, namely the production and marketing of off-patent drugs or so-called generic drugs.

The development of of the pharmaceutical industry and medicinal raw materials in Indonesia is mainly constrained by technology and human resource capabilities. The independence of medicinal raw materials is currently lacking, because medicinal raw materials, especially synthetic products produced in Indonesia, are still very small, and there is a lack of support from the upstream chemical industry.

Dependence on imports of medicinal raw materials and low research budgets mean that inventions in the national pharmaceutical industry have not been able to increase their ranking status from a country that is able to reproduce medicinal raw materials and finished drugs to a country with an innovative pharmaceutical industry, which is marked by the large number of drug patents produced. as well as countries with mass-producing capabilities and a focus on research and development.

Potential opportunities for the development of biotechnology-based medicinal raw materials, by utilizing the wealth of biodiversity in Indonesia which is a potential resource in the pharmaceutical sector. The diversity of plants, microorganisms and marine biota is directly correlated with chemical diversity which has enormous potential for drug development.

Government policies are needed in order to increase pharmaceutical product invention in the context of the availability of innovative drugs and the independence of the domestic pharmaceutical industry, through creating an investment-friendly climate, optimizing foreign cooperation relations, increasing research budgets, building Academic-Business-Government-Community-Innovator synergies (A-B-G-C-I). A research development facilitation policy to produce mandatory pharmaceutical product inventions is also needed towards innovation in the biopharmaceutical industry, vaccines, active pharmaceutical ingredients (API) with high-tech active chemical ingredients.

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