DENTONS HPRP

HOW GOOD MANUFACTURING AND DISTRIBUTION PRACTICES HELP ENSURE PHARMACEUTICAL QUALITY

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Indonesia was shaken by disastrous and discomforting news notably when the National Food and Drug Agency ("**NFDA**") revoked licenses for syrup-type drug production by two local pharmacy companies for violating Good Drug Manufacturing Practices (*Cara Pembuatan Obat yang Baik* or "**CPOB**"), following the temporary ban on sales of a long list of syrup-based medications consumed primarily by children under the age of five. It is now more apparent than ever that good manufacturing and distribution guidelines for pharmaceutical products are required to aid the industry in ensuring the quality and safety of pharmaceutical products, preventing patients from being exposed to substandard and falsified products, and maintaining the integrity of the distribution chain. This article will discuss how good manufacturing and distribution practices contribute to pharmaceutical quality and safety.

"EXTRAORDINARY EVENT" IN INDONESIA

A surge in acute kidney failure in children (especially <5 years old) that has resulted in tragic deaths was reportedly linked to high levels of two compounds in medicinal syrups, ethylene glycol ("**EG**") and diethylene glycol ("**DG**"), which exceeded specific guidelines by the NFDA regarding safe levels of DG and EG allowed in syrup drug products resulting in an *"extraordinary event"* in Indonesia. The NFDA has temporarily banned the sale and prescription of all syrup and liquid medications pending an investigation conducted in response to the discovery and the rise in fatalities.

Pursuant to the foregoing, the stakeholders in the medicine distribution chain (i.e., pharmaceutical companies and wholesalers as business actors) must adhere to stricter precautionary measures to maintain the quality of drugs from the manufacturing to the distribution processes to ensure that the drugs are consistently produced and controlled according to quality standards based on the guidelines and distribution permit issued by the NFDA.

Such practices and precautionary measures must be implemented based on the guidelines from NFDA, namely CPOB and Good Drug Distribution Practices (*Cara Distribusi Obat yang Baik* or "**CDOB**") in order to meet the NFDA's standards for quality and safety for consumers, including maintaining a safe level of DG and EG content in syrup drug products.

There are other main risks that could be associated with bad manufacturing and/or distribution practices such as unexpected contamination of products causing damage to health or even death; incorrect labels on containers, which could mean that patients may receive the wrong medicine; insufficient or too high levels of an active ingredient, resulting in ineffective treatment or adverse effects. As such, the CDOB and CPOB as guidelines have provided detailed, written procedures essential for each process that could affect the quality of the finished product, covering all aspects of production and distribution.

It is also worth noting that there are sanctions that can be imposed from various regulations such as (i) health law, (ii) consumer protection law, and the NFDA regulations that govern the CPOB and CDOB.

Failure to comply with the CDOB and CPOB guidelines may result in the imposition of administrative sanctions by the NFDA in the form of (a) a written warning, (b) temporary suspension of activities and/or (c) revocation of CDOB and CPOB/CPBBAOB[1] certificates.

GOOD DRUG MANUFACTURING PRACTICES

Pharmaceutical Manufacturers ("**PM**")[2] in all aspects and series of activities for the manufacturing of drugs and/or medicinal ingredients is required to apply the CPOB guidelines as set out by the NFDA Regulation Number HK.03.1.33.12.12.8195 of 2012 concerning the Implementation of Guidelines for Good Drug Manufacture as amended by NFDA Regulation Number 13 of 2018 ("**CPOB Guidelines**").

In addition to PM, (i) manufacturers that carry out the process of making radiopharmaceutical preparations and have received feedback from the competent institutions in the field of nuclear power supervision, and (ii) hospital pharmacy installations that carry out the process of manufacturing drugs for the purpose of implementing health services in the hospital concerned, are also required to apply the CPOB Guidelines.[3] For the avoidance of doubt, the term "manufacturing" in the CPOB Guidelines includes all activities receiving materials, production, repackaging, labelling, labelling reprocessing, quality control, release, storage and distribution of drugs and related controls.

In manufacturing drugs and/or medicinal ingredients, a PM must implement the CPOB Guidelines, which include the following matters:

a. Pharmaceutical industry quality system;
b. Personnel;
c. Buildings and Facilities;
d. Equipment;
e. Production;
f. Quality Control;
g. Product Complaints and Withdrawals;
h. Documentation;
i. Contracts for Manufacturing and Analysis;
j. Qualifications; and
k. Validation.

In order to prove the implementation of the CPOB Guidelines, PM is required to obtain (i) a CPOB certificate or (i) a CPBBAOB certificate, which will be issued by the Head of the NFDA.

SANCTIONS FOR VIOLATIONS OF GOOD DRUG DISTRIBUTION PRACTICES

Pertaining to the implementation of CPOB/CPBBAOB as well as the requirement for PM to have CPOB/CPBBAOB certificates, the NFDA may impose administrative sanctions on PM in accordance with CPOB Guidelines for failures to comply, in the form of:

a. Warning;
b. Strict warning;
c. Temporary suspension of activities;
d. Freezing of CPOB/CPBBAOB certificate;
e. Revocation of CPOB/CPBBAOB certificate; and
f. Recommendation for revocation of PM license.

Please see Section "***Guidelines For Follow-Up Control Of Drug And Drug Ingredients"*** for more details.

GOOD DRUG DISTRIBUTION PRACTICES

The drug distribution chain in Indonesia cannot be separated from the involvement of Pharmaceutical Wholesalers ("**PBF**"),[4] including their branches and PM for which the NFDA sets CDOB standards to guarantee the quality and safety of the drug and/or medicinal ingredients being distributed to consumers via the distribution chain. The CDOB standards for PBF including their branches and PM are provided in NFDA Regulation Number 9 of 2019 concerning Technical Guidelines for Good Drug Distribution as amended by NFDA Regulation Number 6 of 2020 ("**CDOB Guidelines**").

[1]The CPOB certificate is given for each type of medicinal preparation in accordance with the dosage form and manufacturing process carried out for some or all of the stages while the CPBBAOB certificate is issued for each type of medicinally active ingredient.

[2]Pharmaceutical Manufacturer means a business entity that has a permit from the Minister of Health to manufacture drugs or drug ingredients (Article 1 paragraph (2) of the CPOB Guidelines)

[3]Article 4 of the CPOB Guidelines

[4]A company in the form of a legal entity that has a license for the procurement, storage, distribution of drugs and/or medicinal ingredients in large quantities (Article 1 paragraph (3) of the CDOB Guidelines)

Referring to CDOB Guidelines, CDOB is the method for the distribution/supply of drugs and/or medicinal ingredients which aim to ensure their quality during distribution/supply in accordance with the requirements and purposes of their use.[5] In procuring, storing, and supplying drugs and/or drug ingredients, PBF (including their branches) must implement the CDOB technical guidelines, which include the following matters:

a. Quality management;
b. Organization, management, and human resources;
c. Building and equipment;
d. Operations;
e. Self-inspections;
f. Complaints, drugs and/or medicinal ingredients which are returned, alleged to be fake, or recalled;
g. Transportation;
h. Distribution facilities based on contract;
i. Documentation;
j. Specific provisions for medicinal ingredients,

In order to prove the implementation of the CDOB Guidelines, PBF (including their branches) are required to obtain a CDOB certificate, which will be issued by the Head of the NFDA.[6]

SANCTIONS FOR VIOLATIONS OF GOOD DRUG DISTRIBUTION PRACTICES

The NFDA may impose administrative sanctions on PBF including their branches and PM with regard to the implementation of CDOB and the possession of a CDOB certificate in accordance with the CDOB Guidelines, in the form of (a) a written warning and/or (b) a temporary suspension of activities. Ultimately, business actors that have obtained CDOB certificate but do not comply with the CDOB Guidelines may have their CDOB certificate revoked due to failures in compliance.

It should be noted that the following circumstances may result in the revocation of the CDOB certificate[7]:

a. Misconduct in the implementation of CDOB which results in the misuse of drugs and/or medicinal ingredients distribution; or
b. PBF (including their branches) deliberately committing an action which results in the CDOB not being implemented.

Please see Section "***Guidelines for Follow-Up Controls Of Drugs And Medicinal Ingredients"*** for more details.

GUIDELINES FOR FOLLOW-UP CONTROL OF DRUGS AND MEDICINAL INGREDIENTS

The procedure for imposing administrative sanctions on CPOB and CDOB is set out in NFDA Regulation Number 19 of 2020 concerning Guidelines For Follow-Up Control Of Drug And Medicinal Ingredients ("**NFDA Regulation 19/2020**"), which states that follow-ups on the results of oversight can be in the form of (i) technical guidance and/or (ii) administrative sanctions.

Administrative sanctions by NFDA may be imposed if based on NFDA's assessment, there are violations according to the following[8]:

a. Results of inspections at production facilities, distribution facilities, pharmaceutical service facilities, and Electronic System Operators *or Penyelenggara Sistem Elektronik* ("**PSE**")/Pharmacy Electronic System Operators *or Penyelenggara Sistem Elektronik Farmasi* ("**PSEF**");
b. Results of studies on safety, efficacy, and quality of drugs;
c. Results of the study of the monitoring data from production facilities, distribution facilities, pharmaceutical service facilities, and PSE/PSEF; and/or
d. Results of online monitoring of drug circulation.

Further to the above, follow-ups on the results of oversight in the form of administrative sanctions may include the following[9]:

a. Warning;
b. Strict warning;
c. Temporary suspension of activities;
d. Freezing of CPOB certificate;
e. Revocation of CPOB certificate;
f. Recommendation to freeze PM licenses;
g. Suspension of distribution permit;
h. Revocation of distribution permit;
i. Recommendation for closing or blocking of electronic systems used for online drug circulation;
j. Recommendation for revocation of pharmaceutical industry license;

[5]Article 1 paragraph (1) of the CDOB Guidelines
[6]Article 4 of the CDOB Guidelines
[7]Article 6 of the CDOB Guidelines
[8]Article 5 paragraph (5) of NFDA Regulation 19/2020
[9]Article 6 of NFDA Regulation 19/2020

k. Recommendation for revocation of license/recognition of distribution facilities;
l. Revocation of CDOB certificate;
m. Recommendation for revocation of license for pharmaceutical service facility; and/or
n. Temporary ban on distribution and/or orders for the recall of drugs or medicinal ingredients from circulation.

In light of the aforementioned, it is important for PBF including their branches and PM to have CPOB and CDOB certificates and ensure compliance with CPOB and CDOB guidelines to avoid any possible sanctions.

OVERSIGHT BY THE NFDA

Referring to Presidential Regulation Number 80 of 2017 concerning NFDA ("**PR 80/2017**"), in carrying out the task of controlling drugs and food, NFDA carries out functions including (a) preparation and determination of norms, standards, procedures, and criteria in the field of Oversight Before Circulation and Oversight During Circulation and (b) implementation of Oversight Before Circulation and Oversight During Circulation.[10]

It is clear that pursuant to PR 80/2017 that NFDA is only in charge of monitoring and setting standards before the drug is released on the market, while the obligation to ensure that the quality of raw materials of production until distribution is meeting both CPOB and CDOB guidelines rests with the PM. For the avoidance of doubt, the underlined definitions above have the following meanings:

a. Oversight Before Circulation means the oversight of drugs and food before being circulated as a preventive measure to ensure that drugs and food in circulation meet the standards and requirements for safety, efficacy/benefits, and product quality.
b. Oversight During Circulation means the oversight of drugs and food during circulation to ensure that drugs and food in circulation meet the standards and requirements for safety, efficacy/benefits, and product quality as well as law enforcement actions.

Notwithstanding the above, PR 80/2017 asserts that the authority of the NFDA in overseeing drugs and food is limited to[11]:

a. Issuing distribution permits and certificates in accordance with standards and requirements for safety, efficacy/benefit and quality, as well as drug and food testing in accordance with the provisions of laws and regulations;
b. Implementing intelligence and investigations in the field of drug and food control in accordance with the provisions of the legislation; and
c. Imposing administrative sanctions in accordance with the provisions of laws and regulations.

The occurrence of this *"extraordinary event"* resulting in kidney failure and death in children may indicate that there is still a gap in oversight that has not been addressed by the NFDA, which may have fatal consequences for consumers. Referring to Article 61 paragraph (1) of NFDA Regulation Number 24 of 2017 concerning Criteria and Procedures for Drug Registration as lastly amended by NFDA Regulation Number 13 of 2021, a drug distribution permit holder is required to monitor the efficacy, safety, and quality of the drugs during circulation and report the results to the NFDA. As such, the NFDA only oversees permitted contamination levels at the pre-market stage or on medicinal ingredients prior to the issuance of the distribution permit while the oversight of finished and distributed products by the NFDA has not been regulated yet.

RIGHTS AND OBLIGATIONS OF CONSUMERS AND BUSINESS ACTORS

Given the circumstances underlying the *"extraordinary event",* it is essential to consider the rights and obligations of consumers and business actors in addressing the situation. Referring to Law Number 8 of 1999 concerning Consumer Protection ("**Consumer Protection Law**"), the rights of the consumer encompass, among others (a) the right to comfort, security, and safety in consuming goods and/or services, (b) the right to correct, clear, and honest information regarding the condition and guarantee of goods and/or services, (c) the right to have their opinions and complaints be heard regarding the goods and/or services they used, (d) the right to obtain advocacy, protection, and efforts to settle consumer protection disputes appropriately and (f) the right to obtain compensation, indemnity and/or replacement if the goods and/or services received are not in accordance with the agreement or not as they should be.

In addition to the above, business actors are required, among others, to (a) guarantee the quality of goods and/or services produced and/or traded in accordance with the applicable provisions on goods and/or services quality standards, and (b) compensate,

[10] Article 3 of PR 80/2017
[11] Article 4 of PR 80/2017

indemnify, and/or replace losses caused by the use, consumption, and utilization of goods and/or services traded. Article 8 of the Consumer Protection Law requires business actors not to produce and/or trade goods and/or services that, among other things, do not meet or are not in accordance with the required standards and the provisions of laws and regulations.

SANCTIONS FOR VIOLATIONS OF CONSUMER PROTECTION LAW

In addition to the foregoing, Article 62 of the Consumer Protection Law also stipulates that business actors who violate the rules outlined in Article 8 of the Consumer Protection Law, specifically on the actions of business actors that are prohibited in the production and/or trading of goods and/or services as set forth above, will be subject to a maximum sentence of 5 (five) years of imprisonment **or** a fine of IDR 2,000,000,000 (two billion Rupiah).

CONCLUSION AND THINGS TO CONSIDER

The procurement, storage, and distribution of pharmaceutical products and/or ingredients are highly regulated and must fulfil stringent safety and efficacy standards. This means that the manufacturing and distribution methods for these products are important to ensure that they reach and/or are consumed by their intended consumers in a safe and effective manner. Adoption of CPOB and CDOB guidelines throughout the supply chain will undoubtedly help to improve product traceability, accountability, and reliability.

It is essential for pharmaceutical business actors to note that CPOB and CDOB compliance must be maintained in order to comply with the applicable laws and regulations, particularly for products distributed in Indonesian territory. Following the *"extraordinary event"* in Indonesia, it is anticipated that the NFDA will strengthen its oversight of pharmaceutical business actors and products to ensure that quality is maintained throughout including by compliance with the required PBF license and CDOB certificate. Failure to comply may result in the revocation of existing business licences and/or certificates including the suspension of business activities, which may have an adverse influence on the relevant pharmaceutical manufacturer.

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