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Good Manufacturing Practices for *Halal* Pharmaceuticals

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This article presents an overview and analysis of a new national standard on *halal* pharmaceutical products, MS 2424:2012, published by Malaysia, a member of PIC/S.

In 2012, Malaysia – a member of the Pharmaceutical Inspection Co-operation Scheme (PIC/S) – became the first country in the world to develop a national standard on *halal* pharmaceutical products: Malaysian Standards MS 2424:2012.[1] With an estimated 23 percent of the world's population today being Muslims,[2] this represented another significant step toward addressing the increasing demand from muslim consumers.

Halal (لالح) is a term designating an object or action as permissible according to Islamic law; on the contrary, prohibited objects or actions are termed *haraam* (مارح).[3] Most commonly used to refer to permissible foods, for example, *halal* foods must be free from pork or pork by-products, blood and blood by-products, alcohol, and animals that are not slaughtered according to Islamic principles (the method of slaughter, termed *Dhabihah*).[4]

Although modern Muslim scholars debate whether medicines should be considered in the same class as food, most acknowledge that the principles governing the use of haraam ingredients in these products still apply. Exceptions may arise when:

1. The medicine containing *haraam* ingredients is necessary for the preservation of life of the person who takes it.
2. A knowledgeable and trustworthy Muslim physician recommends such types of medicine containing haraam ingredients as necessary for critical treatment.

In November 2012, the authors published an article on the overall requirements of *halal* pharmaceuticals[5] intended for regulatory affairs professionals. This article discusses in further detail the technical considerations when implementing Good Manufacturing Practices (GMPs) with *halal* pharmaceutical products.

Scope of *Halal* Pharmaceuticals

MS 2424:2012 is a national standard published by the Department of Standards Malaysia, Ministry of Science, Technology and Innovation (MOSTI), Malaysia. According to MS 2424:2012, *halal* pharmaceuticals are required to adhere to the following aspects of *Shariah* law. *Shariah* (also *Sharia*) law is the religious law of Islam. The *Shariah* law is primarily derived from the Quran, the religious text of Islam, and from the *Sunnah* of Prophet Muhammad, which is a collection of his specific words, habits, practices, and silent approvals.

1. They must not contain any parts or products of animals that are non-*halal* or are not slaughtered accordingly.
2. They must not contain *najs*. *Najs* (e.g., use of raw materials from swine-derived sources) according to *Shariah* law are:
   - Dogs, pigs, their descendents and derivatives
   - Products contaminated or in direct contact with items that are non-*halal*
   - Any liquid and objects discharged from the orifices of human beings or animals, such as urine, blood, vomit, pus, placenta, excrement, and sperm and ova of pigs and dogs except milk, sperm, and ova of human and other animals.
   - *Maitah* or carrion or *halal* animals that are not slaughtered according to *Shariah* law
   - *Khamar* (fermented alcohol) and food or drink which contain or is mixed with *khamar*

3. They must be safe for human use: non-poisonous, non-intoxicating, or non-hazardous to health according to prescribed dosage.
4. They cannot be prepared, processed, or manufactured using equipment contaminated with *najs* (e.g., use of equipment that has been used to process products contaminated with swine-derived materials).
5. They must not contain any human parts or derivatives that are not *halal*.
6. During preparation, processing, handling, packaging, storage, and distribution, they must be kept physically separated from any other non-*halal* products and *najs*.

Except for the third point, all other points are exclusively applicable to *halal* pharmaceutical products.

Good Manufacturing Practices (GMPs) for *Halal* Pharmaceuticals

The primary objective of GMPs for *halal* pharmaceuticals is to avoid cross-contamination of non-*halal* or *najs* premises, utilities, equipment, materials, and ingredients.

Premise, Utilities, and Equipment

There is explicit requirement for dedicated facility and equipment, as well as storage and transport hardware. Potential routes of cross-contamination during production are no different than all aseptic and non-aseptic facilities, such as direct contact, air, personnel contact, etc. Therefore, for example, a filling machine that has been used to fill products containing *najs* should not be used to fill *halal* products. At the moment, there is a lack of data on acceptable residues.

The design and location of the facilities shall consider the risk of contamination with non-*halal* materials or products. For example, the premises shall be separated and well insulated from pig farming, eateries serving pork products, and avoid the possibility of cross-contamination through air, water, sewage, personnel, and equipment. Therefore, although not explicitly stated, the utilities and HVAC shall be isolated from non-*halal* production areas as well.

Ritual Cleansing

If the premises or equipment become contaminated with *najs*, they shall be washed and cleansed according to ritual cleaning methods supervised and verified by the competent authority (see section on *Competent Authority*).

In brief, ritual cleansing requires seven washes, one of which must be water mixed with soil. The soil and water shall both be free from *najs* and contaminants, as well as *musta'mal* (i.e., soil or water that has already been used for another purpose). While some Muslim scholars debate the use of substances equivalent to soil, the exclusive use of soil as an irreplaceable ingredient is widely accepted in the *halal* manufacturing industry.

MS2424:2012 refers to food-grade soil for the purpose of *halal* cleansing, which are commercially available. For pharmaceuticals application, the soil shall be sterilized prior to use to avoid any possible microbial contamination.

The ritual cleaning is not meant to result in any chemical or biological reaction to the equipment. Therefore, following ritual cleaning, the premises or equipment shall be cleaned for production use, subject to validation. Use of commercially-available food-grade soil minimizes the risk of contamination from residual soil; however, for aseptic processes or other critical processes, the introduction of soil increases the difficulty of validation. Therefore, dedicated equipment is strongly recommended. Repeated conversion of the line to *najs* and back to *halal* products is not acceptable.

Ancillary Areas

Prayer rooms shall be available. Prayer room facilities are subject to additional requirements outside the scope of MS 2424:2012; however, examples of which include nearby ritual washing facilities, free from religiously impure objects and materials, adequate space for men and women, etc.

Where applicable, animal testing facilities shall be well isolated from other areas with a separate animal entrance and HVAC. As MS 2424:2012 addresses manufacturing and handling only, there is currently no further guidelines on the animal facilities.

Materials

All materials must be clearly defined and be *halal*. This includes all starting materials, packaging materials, and any in-process lubricants or agents that may come in contact with the product. As with any GMP, adequate documentation and procedures must be in place.

All types of plants, plant products, and their derivatives are *halal except those prohibited by competent authority*.

All land animals are *halal* except for dogs and pigs, animals with long, pointed teeth intended to kill (such as tigers, bears, cats and elephants), predatory birds (such as eagles and owls), pests and poisonous animals (such as rats, cockroaches, centipedes and snakes), animals forbidden to be killed or eaten in Islam (such as bees, woodpeckers), creatures that are considered repulsive (such as lice, flies), and farmed halal animals intentionally and continuously fed with *najs*.

All aquatic animals are *halal* except for most vertebrate amphibians (such as crocodiles, turtles, and frogs), as well as animals that live in or are fed with *najs*.

In rare cases, some products may be declared *haraam* by local authorities, but not by others. The manufacturer is advised to consult with local competent bodies.

As with food products, any animal source shall be of those slaughtered according to *Dhabihah*.

Materials of Genetically Modified (GM) Origin

Whether GM materials can be considered *halal* remains under debate around the world.[6] In December 2010, an international workshop for Islamic scholars, "Agri-biotechnology: *Shariah* Compliance," held in Penang, Malaysia, declared GM foods to be *halal* as long as the sources from which they originate from are *halal*. Muslim organizations, such as the Islamic Foundation for Ecology and Environmental Sciences of the UK, however, insisted that GM material is non-*halal*.

Materials Containing Alcohol

Alcohol for consumption is *haraam*. Nonetheless, the use of alcohol is often necessary in medicines and in some manufacturing processes. Further, in some processes, alcohol is naturally present. Some scholars have argued for a defined limit, rather than zero-tolerance. However, this view remains controversial, and for international compliance, zero-tolerance is still generally expected.

The *Fatwa* Committee of the National Council for Islamic Religious Affairs Malaysia on the issue of alcohol in foods, beverages, perfumes, and medicines held a special discussion in 2011, and issued the following guidelines on 15 July 2011:

1. Alcohol derived from wine making or the fermentation process is *haraam* and *najs*.
2. Processed products not made with the intention to produce alcohol and contain alcohol below the level of one percent v/v can be consumed.
3. Products made with the intent to produce alcohol and produced using the process of fermentation and containing any amount of alcohol or distilled alcohol are *haraam*.
4. Products containing natural alcohol, such as ripe fruits, nuts or grains, or its extract, or containing alcohol produced during the manufacturing process are not *najs* and can be consumed.
5. Products containing a flavoring or coloring containing alcohol for the purpose of stabilization can be used if the alcohol was not produced through the fermentation process. The quantity of alcohol in the final product may not be intoxicating and its level shall not exceed 0.5 percent.
6. Non-fermented alcohol (industrial alcohol) used as a solvent, processing aid, or cleaning agent is not *najs*.

Quality Control

The purchase, handling, and sourcing of chemicals, reagents, apparatus, equipment, and other items required for sampling and testing shall be made from *halal* source.

Documentation

It is important to note that all records of manufacturing and quality assurance, such as incoming inspection records, batch records, non-conformance reports, vigilance reports, and CAPA, will need to be adopted for *halal* traceability purposes.

> *For pharmaceuticals, the HAS shall further ensure that the pharmaceuticals are designed and developed in a way that comply with the requirements of halal, as well as adequate, written procedures for all halal-related operations…*

Halal Assurance System (HAS)

MS 2424:2012 requires a *Halal* Assurance System (HAS) to be implemented. The HAS is a well-established requirement in the *halal* food industry. Similar to modern quality system concepts, the HAS sets forth requirements for management policy, procedures, documentation system, training programs, internal audits, corrective action system, etc., but adds requirements for administration system, socialization program (referring to the conveyance of *halal* awareness and compliance throughout the organization and stakeholders), and internal and external communication system (referring to communication among stakeholders and religious authorities). General HAS guidelines are published by such institutions as the Indonesian Assessment Institute for Foods, Drugs, and Cosmetics under the Indonesian Council of Ulama (Lembaga Pengkajian Pangan Obat-obatan dan Kosmetika Majelis Ulama Indonesia, or LPPOM MUI).[7]

For pharmaceuticals, the HAS shall further ensure that the pharmaceuticals are designed and developed in a way that comply with the requirements of *halal*, as well as adequate, written procedures for all *halal*-related operations mentioned in this article (for example, production, quality control, and ritual cleansing).

MS 2424:2012 further requires the establishment of a *Halal Committee* within the organization, which must consist of purchasing personnel and a minimum 2/3 Muslim quorum.

Competent Authority

Besides controls and inspections required by relevant pharmaceutical regulatory bodies (in the case of Malaysia, the

National Pharmaceutical Control Bureau), *halal* products are subject to certification from Islamic competent authorities.

Countries with large Muslim populations commonly have institutionalized (sometimes nationalized) bodies designated for certification, such as the LPPOM MUI of Indonesia and JAKIM of Malaysia. In other countries, *halal* certification is granted by diverse bodies with varying degrees of mutual recognition. For example, in the UK, *halal* certification may be granted by the Halal Monitoring Committee, Halal Food Authority, and Institute of Islamic Jurisprudence, to name a few; in the US, the list includes the Islamic Food and Nutrition Council of America and Islamic Services America; in Canada, the Halal Monitoring Authority and Halal Certification Agency.

Differences Between *Kosher* and *Halal*

Kosher in Hebrew means "fit or proper for use" according to Jewish law. Similar to *halal* food, *kosher* food are subject to religious rules of slaughtering, cleaning, and acceptable source materials. While *kosher* requirements are out of the scope of MS 2424:2012, and there is currently no equivalent of MS 2424:2012 for *kosher* pharmaceuticals in the world, there are similarities from a technical perspective, although the procedural differences might be the most significant.

This article shall not endeavor to analyze the details of *kosher* requirements. The reader may refer to published sources such as Wikipedia's *Comparison of Islamic and Jewish Dietary Laws*;[8] however, some examples of major similarities include:

- Common prohibition of many animals and their derivatives, such as swine, amphibians
- Common permission of many animals, such as bovines
- Requirement for isolated premises, religious cleansing

Examples of major differences include:

- Alcohol is permitted in *kosher*
- Due to the fermentation and purification processes involved, permitted sources of gelatin and enzymes differ
- *Kosher* requires further isolation between dairy and meat products
- Religious procedures during slaughtering and cleansing

As with *halal* principles, debates exist with finer details of *kosher* principles amongst Jewish scholars. Users are always recommended to seek the advisory of competent authorities.

Conclusion

Muslims comprise a sizable portion – by some estimates, one-quarter – of the world's population today. In this article, we discussed the general technical considerations when implementing GMP with *halal* pharmaceutical products based on the world-first national standard MS 2424:2012 from Malaysia.

At the present, the manufacturing of halal pharmaceuticals is largely limited to domestic manufacturers of generic pharmaceuticals in Muslim-majority countries. The need for participation from brand-name pharmaceutical manufacturers and of major multinationals has been acknowledged by some of the original authors of MS 2424:2012 and we look forward to progress in this area.

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