

## ISTIHALAH AND ISTIHLAK: ANALYSIS ON THE MANUFACTURE PROCESSES OF PORCINE BASE MEDICINE (LOW MOLECULAR WEIGHT HEPARIN (LMWH))

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### Abstract

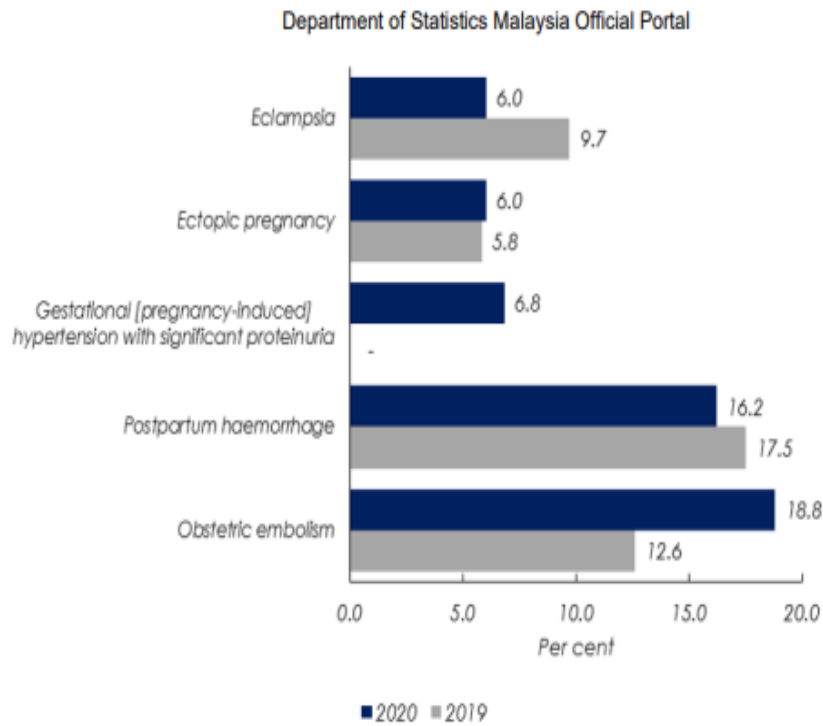
*Istihalah and istihlak are not an extraterrestrial subject and have been debated over centuries among shariah scholars. Halal Pharmaceutical had been clearly explained that must comply with shariah prerequisite to be endorsed as halal compliance medicine. However, this industry often faces unmatched medicine which able to heal deteriorated diseases such as thrombosis or embolism that require second opinion by Shariah scholars. The medicine named Low Molecular Weight Heparin (LMWH) had been imposed the fatwa on it by Malaysian National Fatwa Council (MNFC), however, some exempted conditions require this porcine base medicine for prophylaxis or therapy. This paper aims to propose istihalah and istihlak to be legal indicators through fiqh methods in the making of fatwa regarding to this notorious medicine. This paper employs qualitative methodology which using documents review method to analysis the data.*

**Keywords:** *Istihalah, Istihlak, Halal Pharmaceutical, Low Molecular Weight Heparin*

## 1. INTRODUCTION

Global Burden Diseases (GBD) study reported that venous thromboembolism (VTE) is a major contributor to mortalities and morbidities of the world (ISTH Steering Committee for World Thrombosis Day, 2014). VTE is a leading cause of maternal mortalities and morbidities in developed countries worldwide (Greer, 2015) including England (Sultan et al., 2013), Scotland (Kane et al., 2013) and Australia (Australian Institute of Health and Welfare, 2017) which has shown that thrombosis has been the direct cause of

maternal death. The similar situation is also clarified in Malaysia according to the recent statistic regarding thrombosis around pregnancy.



**Figure 1:** Five principal causes of death for maternal in 2020

As stated in the figure 1, the obstetric embolism or known as thrombosis recorded as principal death for maternal at 18.8% in 2020 followed by other causes such as postpartum haemorrhage at 17.5%, gestational (pregnancy-induced) hypertension with significant proteinuria at 6.8%, ectopic pregnancy at 6.0% and eclampsia at 6.0%.

LMWH is an anticoagulant that has been proven to be able to inhibit blood clotting and prevent it especially during pregnancy and puerperium. LMWH is prescribed to those women who are having risk factors of developing VTE. MOH (2014) published first edition of the *Training Manual for the Prevention and Treatment of Venous Thromboembolism in Pregnancy and the Puerperium* was published in 2014. A more recent guideline has since been published by MOH (2018) which mentioned that “besides recommending a standardized approach for documented VTE risk stratification, the prevention of VTE through lifestyle measures, mechanical and medical thromboprophylaxis will be discussed”.

However, MNFC officially issued a decision regarding the prohibition of LMWH (Enoxaparin Sodium) as following:

“The usage of Clexane and Fraxiparine are necessarily needed (*darurah*) upon patients to prevent blood clot formulation which could occurs immediately in chronic condition, the committee decided to impose that both types of the medicines are prohibited due to its unlawful sources in the sight of Islam as currently there is an alternative medicine called Arixtra which is lawful source extraction and its effectiveness as similar to Clexane and Fraxiparine”

(JAKIM, 2015).

In the meantime, according to MOH, the percentage of women requiring thromboprophylaxis as they were medically indicated is expected to increase further in near future. In response upon the ubiquitous implementation of LMWH as first choice in treating at-risk mothers of VTE, whereby at the same time this LMWH have gone through the additional process of removing porcine-derived ingredient, this paper is established to extend the query of the permissibility status of LMWH anticoagulant as preventive medicine which prescribed for pregnant and puerperium mothers by medical experts to preserve lives of mothers and fetuses from *fiqh* point of view instead of the benefit versus harm, necessity and tenacious need. Other *fiqh* view to justify the legal rule of this LMWH can be elaborated in another platform.

### 1.1 Definition of *Istihalah*

Literally, *istihalah* denoted from the root word *hawala* (حاول) which means change (Ibnu Manzur, 1883). *Istihalah* (استحال) comes from derivatives word *يستحيل استحال* — *استحال* in which similar meaning with *حال* means انقلب change as well as *تغير* defined as transformed to other thing (Al-Raziyy, 1986). Meanwhile, technically, *istihalah* is the term used to describe the changes that a certain substance had underwent and it is not reversible to its original condition. For instance eliminating of the impure (*najasah*) entity as well as changing the dirty thing into dust (Qal'ahjiyy, 1985).

### 1.2 Definition of *Istihlak*

Literally, *istihlak* is defined as *halaka* with *wazan fu'ul* appear as *huluk* means fall down (Ibnu Faris, 1979). The word *هالك الشيء* (*halaka al-shay'*) has relation with *istihlak al-mal* means as money that had been spend (Mu'jam al-Mustalahat wa Alfaz al-Fiqhiyyah, n.d.). In *fiqh* terminology, *istihlak* denoted a merge between physical (*'ain*) into another physical (*'ain*) that changed the original shape feature, nature and structure and is regarded as an object that undergoes physical changes specifically break down from each physical form. A drop of wine or milk, for instance, blends into water and merges together (Hammad, 2004).

### 1.3 Istihalah Process

According to the Figure 2 below, the process of *istihalah* contains three main elements, namely raw materials, conversion agents and finish products (Jamaludin et al., 2011). The process will include the interaction between raw material and conversion agent, naturally or synthetically. Finally, the finished product that had undergone the conversion process will appear in different form physically and chemically from the original material.

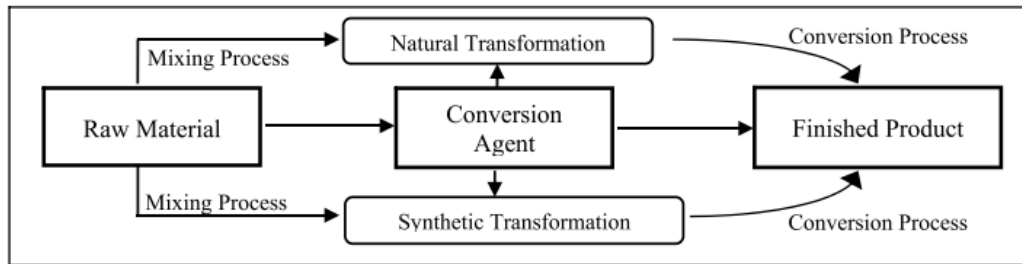


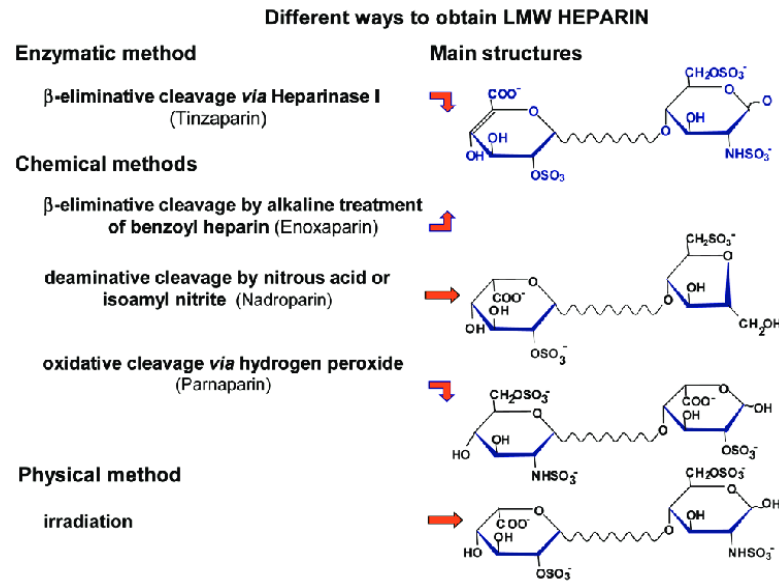
Figure 2: *Istihalah* Process (Source: (Jamaludin et al., 2011))

### 1.4 Istihlak Process

*Istihlak* is the process of assimilation and intense dilution of prohibited objects or substance in Islam, and had undergone a process of decomposition or disintegration until the original properties in the latter form are non-traceable, such as animal urination in the water, then the river is lawful for drinking or bathing in it (Farhani et al, 2014).

## 2. ANALYSIS OF LMWH THROUGH *ISTIHALAH* AND *ISTIHLAK*

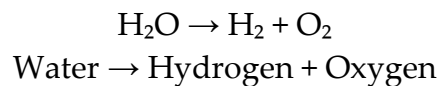
Below are the scientific ways to prove that LMWH have underwent the process of transformation (*istihalah*) and depolymerization (*istihlak*).



**Figure 3:** Different ways to obtain LMWH either with enzymatic method or chemical method or physical method and main chemical structures to each method. (Source: Torri. G &Naggi. A, 2016)

The methods of accessing LMWH from heparin are illustrated in figure 3. As indicated, eliminative cleavage by alkaline treatment of benzoyl heparin, Enoxaparin was obtained by chemical procedure. Tinzaparin is obtained by the enzymatic process of exchanging chemical structure with the chemical structure of Enoxaparin.

The depolymerization system specifically demonstrates that due to high molecular weight heparin, degraded by fractionation phase through chemical process, there are relationship to *istihlak* structure theory according to *fiqh* discipline in relation to LMWH manufacturing process. Farhani (2017) confirms this by saying that *istihlak* meant by splitting the water molecule into gas as follows:



### 3. APPLICATION OF PRODUCTS MANUFACTURED IN CURRENT PRACTICES THROUGH *ISTIHALAH*

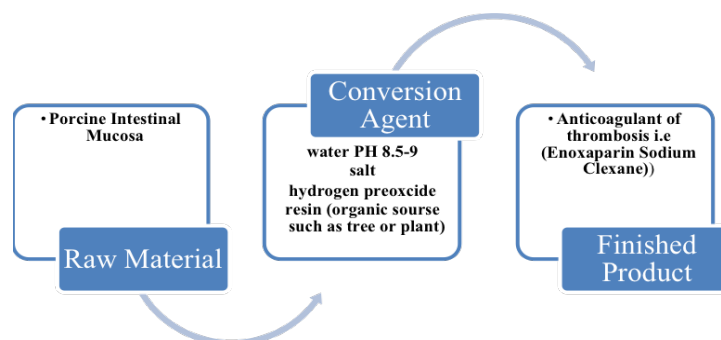
The manufacturing process of LMWH will be clarifying below as the ingredient in it is porcine intestine (Vilanova et al., 2019, Chandarajoti et al., 2016, Sanofi-Aventis, 2002)). Porcine ingredient has less side effect in virtue to its superiority in pharmacokinetic features because the natural source; biology of the animal itself, instead of chemical synthetic (Nutescu et al., 2016).

LMWH is actually produced from UFH undergoing enzymatic and cleavage process with nitrous acid and benzylation after alkaline depolymerization of UFH (Casele et al., 1999), it approved by numerous research that it offers a greater margin of safety when LMWH does not cross the placenta in any trimester (Casele, 2006). However, LMWH is not suitable for patients with kidney problems due to its renal excretion predominantly (Alshawabkeh et al., 2016).

Furthermore, LMWH usage shall be taken as precaution for those who have health problems like active gastritis or duodenal ulceration, hypersensitive to enoxaparin sodium or heparin derivatives, patient with history of heparin-induced thrombocytopenia with or without thrombosis. If there is confirmed decreasing value of platelet level after using LMWH it shall be discontinued and swapped to another choice of anticoagulant (Aventis Pharma Limited, n.d.).

Even though its superiority is guaranteed by evidence as abovementioned and mostly opted in hospitals for O&G unit, however, the porcine is persistently appears as notorious issue in Muslim countries including Malaysia as the fatwa on it also had been issued by MNFC in 2009 previously; whereby prohibited to use it owing to porcine base unless in necessarily required and prescribed by specialists. However, the condition of high risk or *darurah* remains a questioned by patients and their family members when the medicine manufactured from porcine ingredient (Irwan Mohd Subri et al., 2019, Subri et al., 2019, Zizi Azlinda, 2021).

On the important note, the researcher thought that the role of fatwa is very paramount to explain that the LMWH is actually the medicine with no residue of porcine anymore after undergone the process of *istihalah* and *istihlak* as following as an effort to pose a contemporary ijtihad regarding that issue as the principal maternal mortality in 2021 is embolism which require this LMWH as pharmacological treatment.

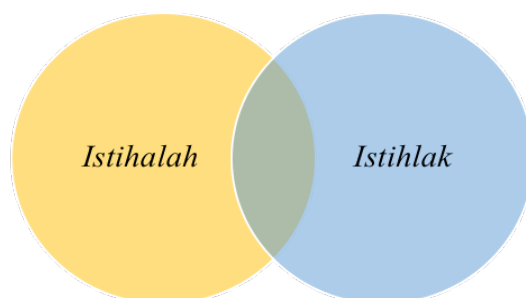


**Figure 4:** *Istihalah* structural theory of LMWH manufacture (The researcher's analysis)

Figure 4 demonstrates the structural principle of *istihalah* that uses oxidation as a conversion agent to convert from crude heparin to pure heparin resulting no porcine DNA residues. These steps are named as two chemical steps, namely oxidation and decolor treatment, to purify porcine impurities. To completely deteriorate crude heparin, precipitation later takes place.

A salt solution was centrifuged to obtain heparin pre-treatment liquid, adding hydrogen peroxide and then added to the strong base anion exchange resin column in order to change from porcine mucosal tissue and transformed into sodium, crude heparin was purified with sodium chloride dissolved in water with PH 8.5 to 9 (Method for Producing Enoxaparin Sodium by Using Crude Sodium Heparin Products, n.d.). Due to non-illegal sources engaging with this conversion agent used, herein is classified as *halal*. In turn, the researcher assumes that no residual *haram* object in the final product arising from this process, and it can be said that it is appropriate to use it.

It was found that *istihalah* and *istihlak* may be able to enlighten and answer it. Equivalently, *istihalah* is a biotransformation process, which transforming from originality crude heparin tissue to salt or sodium. According to the LMWH (Enoxaparin Sodium) manufacture process, the principle of *istihalah* can be traced at the chemical step of purification process while *istihlak* be highlighted at the process of precipitation.



**Figure 5:** The removal process of DNA porcine step formed through *istihlak* and *istihalah* process. (The researcher's illustration)

As displayed in the figure 5, the overlapping part reveals the process of purification and precipitation steps which manage to merge at the same process but in separate steps. It is clearly understood that *istihalah* in LMWH manufacturing means transformation from crude heparin into pure heparin through two chemical steps namely, oxidation and decoloring treatment. Whilst *istihlak* process can be traced at the process of precipitation in which eliminating the impurities elements from heparin completely by degrading and digestion process.

Another step of *istihlak* process occurs at the stage of depolymerization from high molecular weight into low molecular weight heparin which depolymerizing 24 polydisaccharides to be partial disaccharides. In term of chemistry discipline, Enoxaparin sodium which undergoes a complete depolymerization would lead to only simple disaccharides and its efficacious would be affected. While form *fiqh* perspective, the degradation and decomposition process can be similarly evaluated as *istihlak* concept.

Subsequently, the *istihalah* process was figured out at the step of transforming crude heparin into liquid form, which may be considered as incomplete biotransformation (*istihalah naqisah*). As far as *istihalah* is concerned here, the important element in *istihalah* requirement is called as conversion agent namely hydrogen peroxide which was added to strong base anion exchange resin column (*Method for Producing Enoxaparin Sodium by Using Crude Sodium Heparin Products*, no date.). It plays a vital role. Then, after going through the converging process, the DNA is eliminated during precipitation step in turn, and immediately indicates that *istihalah tammah* had undertaken the process. The term in science can be explained in *fiqh* term as follows:

Oxidation & Decoloring → sodium chloride, water, hydrogen peroxide and resin (*istihalah*)

Precipitation → Eliminate porcine DNA (*istihalah* and *istihlak*)

In general, purification process posed a pivotal step in determining the legal rule status of LMWH, either can be argued as *istihalah tammah* or vice versa particularly when referring to the DNA removal step. Without this purification process, LMWH merely can be regarded as *istihalah naqisah* which opposed to *istihalah tammah* from *fiqh* point of view. On the hand, *istihalah naqisah* in this case is translated as a transformation process from crude heparin into drug substance, yet still having residual of porcine DNA. Consequently, it will affect the Islamic law of the subject matter and its implementation.

The pure heparin sodium produced after the step of precipitation as shown in the flow chart reveals the Enoxaparin manufacturing process. The mucosa tissue from porcine intestine was initially in solid form has changed into liquid at oxidation step. Oxidation step was carried out after salt hydrolysis formed. Due to that, the researcher can relate that the transformation of the physical mucosa tissue of porcine began when oxidation step taken place.

To date, there are two certificates from accredited laboratories by JAKIM confirmed that there has been no residual of porcine trace or element found in



Enoxaparin sodium which represented as LMWH group in this research. The first certificate issued in 2015 carried out by TPM Biotex laboratory and most recent certificate in 2019 performed in UKM Unipex laboratory. TPM Biotex laboratory released the result of percentage of nucleotide impurities as well as protein impurities remains in that LMWH while UKM Unipex mentioned that Enoxaparin Sodium (Clexane) has no residual porcine DNA only without further details mentioned.

The researcher attempts to compare this study case of LMWH to the theory of *istihalah* category of *istihalah* that classified by Mohammad Aizat, (2009) in his research that, *istihalah* process that underwent by LMWH manufacturing is considered as *istihalah sahihah* supported by some examples such as a pig drown in a salt lake and decay in to and transformed into a new form namely salt. The same instance forwarded by Mohammad Aizat, 2009 is *jallalah* animal which must be quarantined to ensure it is occupied as halal edible animal.

Throughout this analysis, the most obvious finding to emerge from the analysis is that the discovery of DNA code in products is prime significant to impose on Islamic law of any products as emphasized by Izhar Ariff (2015) either halal or haram even though porcine protein and nucleotide impurities still exist in LMWH. It is interesting to note that in the determination status either *haram* or *halal*, the investigation on the subject matter is encouraged to not too bogged down in the details owing to a doctrinal of straight jacket by uncovering the widespread of prohibited or *shubhah* items which eventually may end into phases of difficulties to derive a legal rule.

The researcher's finding regarding *istihalah* might be contradicted to the stance decided by Malaysian National Fatwa Council (MNFC) in 2009. As most of the chores and interactions practiced in Malaysia adhering firmly with Shafi'ite school of thoughts, the most appropriate methodology in deriving legal rules used by Malaysia Muslim scholars which is suitable to its social and culture is the concept of *al-istishab* (Tuan Sidek & Rizwan, 2017).

Overall, the researcher views that most *fatwa* organization and prominent scholars more prone to consider *darurah* and *hajjah* principles to allow thromboprophylaxis with LMWH, rather than principle of *istihalah* and the researcher thought that the term verdict (sighah) of decision by MNFC shall be revisited to add *hajjah* situation, instead of *darurah* only.

Based on the principle of *istihalah tammah*, the researcher contemplates that it is pertinent to apply *qa'idah* of *takyif fiqhiyy* as comprehended by Islamic *fiqh*

sects, Hanafite and Maliki in pharmaceutical field even though that stance has less enthusiasm for MNFC regarding substance of LMWH's status. In addition to that matter, following *qa'idah fiqhiyyah* that held firmly by Hanafite sect which asserts that *al-aslu fi al-ashya' al-tuhur hatta yadullu al-dalil 'ala al-najasatihi* means the origin of everything is permissible until there is legal proof to indicate it is impure (Ibnu Nujaym, 1999).

Moreover, Izzat al-Ghananim (2008) also supported this thought with his data that the result of smoke/steam from burning process of filthy material is carbon dioxide (CO<sub>2</sub>) or water hydrogen (HO<sub>2</sub>). Experimental research even approved that the water itself have no residue of any manure or feces.

Hence, this research does not intend to blame the decision made by MNFC regarding *istihalah* stance because there is still relevancy due to the situation of Malaysia as Islamic country and guarded by law officially. The relevance of the stance can be observed as extreme caution (*ihtiyat*) as well-known method held firmly by Muslim Malaysian scholars. It is noteworthy that, method of *ihtiyat* is yet reliable to be implemented, concurrently blocking any evil intention towards porcine trading for commercial purpose (Mahaiyadin et al, 2017).

However, the researcher views that in this new modern era can be deemed as timely initiative for Malaysian shariah scholars to accept *istihalah tammah* as legitimate tool to impose *fatwa* in Malaysia which is aligning with current rapid change. This stance is favourable for the researcher academically with limited to merely pharmaceutical issue, not including food or cosmetic sector.

#### 4. CONCLUSION

To conclude, the implementation of *istihalah* concept in pharmaceutical sector supposedly not to create problems as highlighted above, either as commercial interest or in political turmoil because its implementation should be supported with the guideline in using medicine which undergoes *istihalah* process. In fact, this solution may solve many problems in pharmaceutical sector nowadays. This proposal may be applied temporarily till the whole Muslim world able to lead the pharmaceutical sector without any single prohibited derivatives.

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