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RESEARCH ARTICLE

PERMISSIBILITY (*HALAL*)-STATUS OF CARDIOVASCULAR MEDICATIONS IN MALAYSIA.

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Abstract

Cardiovascular medications are broadly prescribed in hospital settings around the world and inMalaysia.However, the Islamic-permissibility or (*Halal*)-status of these medicationsis still inadequate. This study was conducted to assess the *Halal*status of these medications from a scientific point of view depending on data collected from two hospitals in Malaysia. The *Halal* assessment in this study, wasbased on scrutinizing the sources of each ingredient listed in the selected medications leaflets by referring to thestandardacademic references and other references available at time. Froma total of 180 cardiovascular medicinal productsthat was assessedin this study, it was found that 7.78% of them arepermissible (*Halal* compatible), followed by 6.67% asnon-permissible (non-*Halal* compatible) , 49.44% were classified as doubtful (*Mushbooh*) and remaining 36.11% of them were considered as unknown in terms oftheir *Halal* status. Themajority of cardiovascular medications were classified as doubtful due to the principal concept of the final *Halal* status, which requires anabsolute permissibilityof all of the used ingredients, causing the presence of even one doubtful ingredient in the final formulation toalter the whole final product to be classified as doubtful. Whereas the unknown classification was attributed to unavailable information on the excipients used by the drug manufacturer, which prevented a detailed assessment of such medication.The non-permissibleclassification was related to the presence of any non-permissible ingredient in the product. In conclusion, despite this study have met part of the growing demand on identifying cardiovascular medications permissibility, further cooperation is required between the pharmaceutical manufacturers, Muslim academician and health care professionals,to achieve a goal of stretching the use of *Halal* medications for desiring patients.

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Introduction:-

Despite major breakthroughs in cardiovascular (CV)medications, cardiovascular disease (CVD) remainstheprimal cause of death and morbidity worldwide[1]. In 2012, it was attributed to an approximate 31.4% of total morbidity worldwide, accountingfor 17.5 million peoplein one year, of this population, 7.4 million people died of ischemic heart disease and 6.7 million from stroke [2].Even though CVD mortality rates are declining over the past decade, it remains the leading cause of death worldwide,due to the increase in both, age-adjusted CV mortality rates and aging of the populations[3].Such elevated mortality rates reflect a heavy burden on developing countries, for instance, in 2008, 41.39% of the Malaysian male population (aged 55-56) died of CVD, and 32.24% of Malaysians of all ages died for the same reason, making up to an approximate 25,000 CV morbidity cases per annum in Malaysia alone [4]. Surely, these numbers portrait an image for the massive amount of CV medications being prescribed in Malaysia alone and the sheer size of this market locally and internationally.

According to the Population Division of the United Nations, Department of Economic and Social Affairs [5] and The AmericanCensusBureau[6], the world's population grew from 2.5 billion in 1950 up to 7.4 billion in 2016. Accordingly, the Muslims world population has increased from 0.43 billion or 17% in 1950 up to 1.6 billion or 23% in 2016. Making Islam the second most dominant religion worldwide after 31% Christianity, with a wide demographic distribution where Muslims make up a majority of the population in 49 countries [7]. In Malaysia, the total population grew from 6.3 million in 1950 up to 31 million in 2016, with it, local Muslims percentage expanded from 50% up to 60.36%,making up a total population of 18 million Muslims, thus ranking local Muslims as a dominant population in the country[8, 9]. These data, sheds light on the pharmaceutical manufacturers' responsibilitytowards this growing population, as well asthe financial significance of this market to meet their mostpreferable demands.

The holy book ofMuslims, The Quran, has urged Muslims to seek permissible (*Halal*) wholesome foods and refrain from what is classified in several verses to be non-permissible or (*Haram*)[Quran, 2;168]. However, whenthe necessity calls for the consumption of those non-permissiblefoods, without any willful disobedience nor transgressing the due limits, such as life-threatening situations, their consumption would be deemed permissible in moderation, this flexibility towards the matter of non-permissible foods consumption isclearly stated in the Quranicverse [2:173].

Whether the reasons behind religious prohibitions of selected foods consumption arespiritual or physical, it was meant tobring certain benefits to mankind and persuade theirbelief to do good deeds toward each other.Moreover, during our modern era of research and technological advancement, some of these religious prohibitions have met their scientific justifications, such as the benefits behind prohibiting alcohol or porcine consumption that was found to weigh out the benefits of their consumption[10]. Likewise, the benefits of slaughtering animals according to the Islamic method whichproved efficient in draining out the animals blood, making it less susceptible to blood infections andbacterial contaminations, thus providing healthier meat [11-13]. Therefore, investigative research that looks intothe scientific benefits that stands behind some religiousteachings is worth the recognition.

Accordingly, Muslims are particular towards consuming permissible (*Halal*) products during their daily lives and refrain as possible from non-permissible (*Haram*) products, including foods and medications alike. In order to validate the *Halal*-status of any product in the market, the respective authorities have introduced a special *Halal* certification with a unique logo emblem obtained after the product has passed through a comprehensive assurance system to identify the *Halal*-status of such products to the Muslim consumers.

Even though *Halal* certificationswere initially intended to protect Muslim consumers by identifying *Halal* product from non-*Halal* ones, it was quickly found to be positively accepted and widely adopted among the non-Muslim population as an extra symbol of quality assurance aswell as a lifestyle choice [14].This positive acceptance was attributed because *Halal* certification not only focus on the ingredients of the product to be from a *Halal* source, but it also meticulously investigates the wholesomeness and overall sanitation and safety aspects of the product down to the used equipment and manufacturing apparatus, thus branding the *Halal*-certificate as an important market prospective for many manufacturers[15],as well as providing an advantage for *Halal*-certified products to have astronger selling edge to all consumer segments when compared to other non-certified products [15].

Nowadays, with the global expansion of the Muslim population, the Muslim consumer market has stretched by a manifold, even though most of the day-to-day market products have a well-defined *Halal*-status withrespective

Halal-certificates and unique *Halal*-logos, which are issuedaccordinglyfrom the respective Islamic bodies in each country, such as the Malaysian Department of Islamic Development (JAKIM) in Malaysia. The ever increasing demand for*Halal*-certifiedpharmaceutical productsis yet to be fulfilled, in particular, cardiovascular medications, which are one of the most widely prescribed medication worldwide and in Malaysia.Thus, this research was conducted in order to identify the *Halal*-status of 180cardiovascular medications available in a Malaysian hospital setting, as an effort to fulfill some of the demand on the *Halal* medications, as well as an attempt to positively impact both patients and doctor's decision making on the medication of use, not to mention the anticipated improvement of patient adherence and compliance to the medication, especially among the Muslim population.Thus,positively impacting the overall wellness of the community and eventually leading to a possible enhancement in *Halal*-medication marketability.

Methods:-

Data Acquiring:-

Cardiovascular medicationsconstituents and sourcedata were collected from the Drug Information Service, Department of Pharmacy atHospital Pulau Pinang and the medication database of Hospital Sungai Buloh.This study was registered under MRIC, research ID: 25639, NMRR-15-477-25639.Almost all cardiovascular medication leaflets that's currently or previously prescribed were obtained from the hospitals or its relative website. Each ingredient listed in the medication package leaflet was assessed on the *Halal* status.Consequently, the collected data were divided onto two main categories, namely; active ingredients of the drugs, which employs the therapeutic value, and the excipients, which are the substances added to enhance the final drug formulation. Each ingredient of both categories were assessed based on identifying its source,whether from plant, animal, marine, mineral or synthetic compound and also the manufacturing process involved. This was mainly based on the academic reference(Remington:The Science and Practice of Pharmacy, 2005)[16]. In case the information was not sufficient to make an assessment, other sources, reference and search engines were used, such asSigma – Aldrich, updated 2012; British Pharmaceutical Codex, 1973; British National Formulary, 2011; Pubchem and drug.com.

Categorizationof Halal-Status:-

The word *Halal* is driven from the Arabic, Quranic interpretations, standing for what is permissible to the followers of the Islamic faith. Briefly, all wholesome foods are considered permissible for consumption except for some prohibitions, namely swine's flesh, blood, carrion, animals that are not slaughtered according to Islamic laws and alcoholic drinks. Quranic verses [2:173 and 6:145] clearly classified the above exceptions as non-permissible for consumption. Thus, proteins, amino acids or fatty compounds that are originated from swine or human blood components were categorized as non-permissible. Whereas ingredients or compoundsthat are originated from animals other than swine wereclassified asnon-permissible because these animal mayhave not been slaughteredin accordance tothe Islamic method.

All ingredients and compounds that are not classified as non-permissible as mentioned above, were therefore classified as permissible (*Halal*), such as plants, marine and minerals. Ethanol was categorized as non-permissible ifit was present as part of the final product formulation of liquid and parenteral preparations. However, ethanol that is involved during the synthesis of solid preparations was considered as permissible, since the ethanol content is quickly evaporated during the heating or crystallization process of the solid preparation (figure 1). Likewise, topical preparations or applications that contain ethanol was not categorized as non-permissible, as long the product is not systemically absorbed, sincethe ethanol content in such preparationsis quickly evaporated in room temperature. However, topical applicationsthat areintended for mouth or oral mucosaluse were categorized as non-permissible because some extent of alcohol will be absorbed by the body.

Consequently, a product is classified as non-permissible, if it contains any active ingredient, excipient orcompound of a non-permissible source. Thus, in order for a product to be classified as permissible, all of its ingredients list should be from a permissible source. If the final product contains both non-permissible and doubtful (*Mushbooh*) compounds, this product is categorized as non-permissible based on the Islamic laws (figure 1). Furthermore, a doubtful classification (*Mushbooh*) is an indecisive state between *Halal* and *Haram.* This is a situation wherethe source ofany of the ingredientsis uncertain and it can be originated fromeither animal, plant, marine or mineral sources. Some examples of doubtful compounds is glycerin, glycerol and gelatin (figure 2).

Finally, a medicinal product is classified as 'unknown'when the package leaflet did not state the excipients or inactive ingredients, thusleading to an incomplete *Halal* assessment. Likewise, whenever theinformation of an

ingredient were unavailable or insufficient for *Halal* assessment, such products are classified as unknown as well.Other factors that contribute to the medicine *Halal*status, such as the overall hygiene of the used utensils, machineries, manufacturing apparatus, process and product packagingwere not put into consideration of this study since it is beyond the scope of this study, and as it is being monitored by the Drug Control Authority, Pharmacy Service, Ministry of Health, Malaysia, for every medication that is registered in Malaysia.

Statistical Analysis:-

The datawere analyzed using SPSS version 20. Descriptive analysis involving frequencies andpercentages was used to present the results of the analysis. Final assessments of the 180 cardiovascular pharmaceutical productsare shown in table formats.

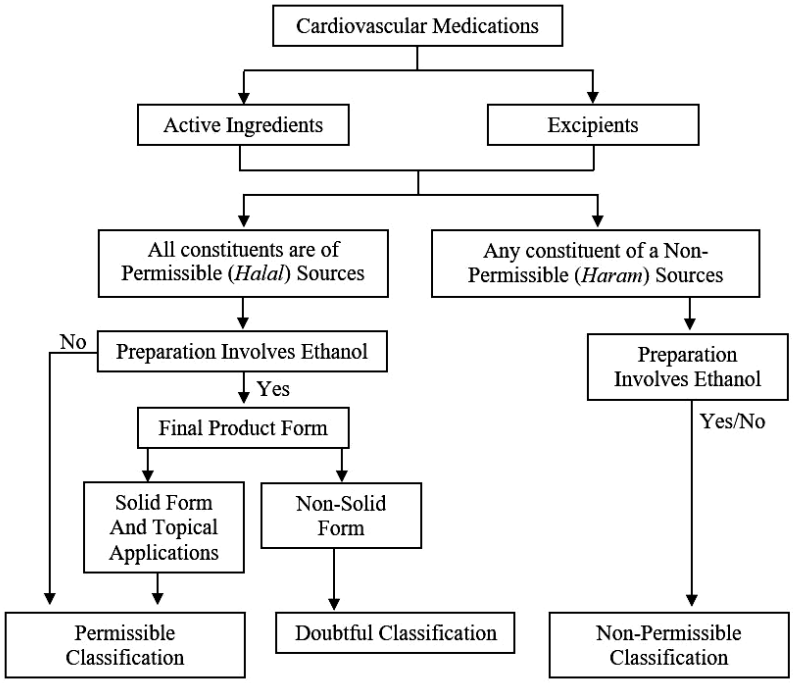
Results:-

A total number of 180 cardiovascular medications that was available at the hospitals during the period of this study were assessed for their permissible status. It was found that among the 180 medications, only 14 products 7.78% were classified as permissible(table-1), followed by 10 products 5.56% (table 2) and 91 products 50.56%, which are classified as non-permissibleand doubtful respectively. Moreover, a bulkypercentage of 36.11% of the medications was classified as unknown (table 3) or (cannot be assessed) attributed to the lack of information regarding all the constituents of those medications.

This study demonstrated that more than half of the active ingredients used in cardiovascular medications were classified as permissible, with a percentage of 72.13%, followed by 19.13% and 7.1% as doubtful (*Mashbooh*) and non-permissible respectively. Only 3 active ingredients were classified as unknown, due to the lack of sufficient information regarding theirsources. Active ingredients that were classified as non-permissible were substances such as sulodexidewhich are obtained from porcine, and blood coagulation factors that are stated to be obtained from human blood sources.

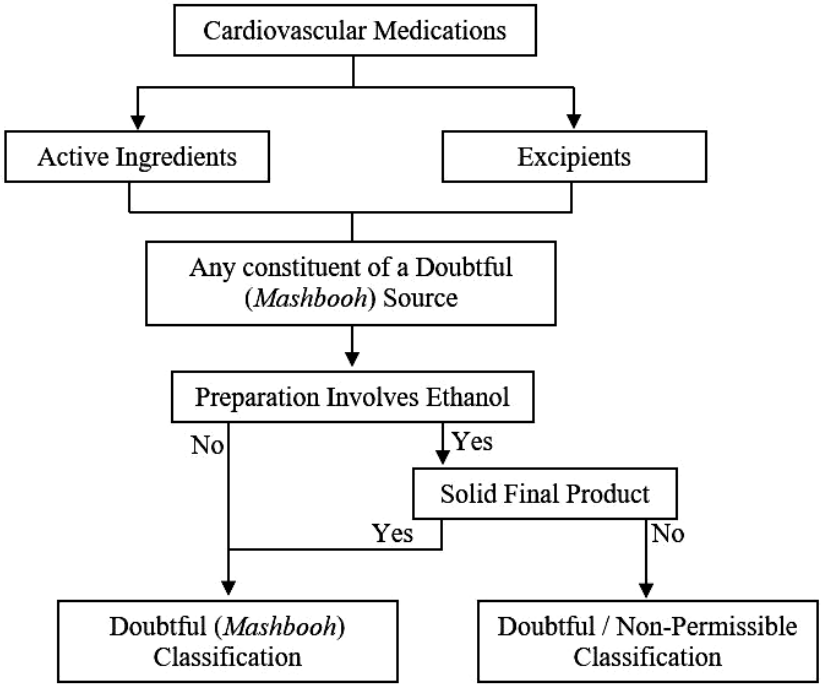
On the other hand, less than half (49.3%) of the total inactive ingredients assessed in this study was classified as permissible, followed by 25.82% and 20.66% as unknown and doubtful excipient origins respectively. Only 4.23% of the inactive ingredients were classified as non-permissible. The doubtful classification was applied when one or more doubtful constituents were involved in the drug formulation, whereasmany of the non-permissible inactive ingredients were ethanol and proteins obtained from human sources.

Figure 1:-



Flow Chart of Permissible, and Non-Permissible classification based on the constituents, note that topical applications and solid form products are classified as Permissible despite the ethanol content, that is because during the solidification process of solid products, heat is applied and most alcoholic content is evaporated, and topical applications does not permit ethanol to penetrate the system or cause any intoxication.

Figure 2:-



Flow Chart of Doubtful (*Mashbooh*) classification based on the constituents, note that final solid products might be classified as *Haram* in case one of the doubtful constituents originated from porcine.

Table 1:- List of thepermissible classifiedCVmedications.

Drug Name	Active Ingredient	Dosage Form	Status
Adenocor	Adenosine	Injection	Permissible
Aggrastat	Tirofiban HCL	Solution for dilution	Permissible
Arixtra	Fondaparinux Na	Injection	Permissible
CCMD Ephedrine	Ephedrine	Tablet	Permissible
Herbesser R100/200	Diltiazem HCL	Capsule	Permissible
Hirudoid	Heparinoids	Cream	Permissible
Isoket IV	Isosorbide dinitrate	Infusion	Permissible
Kisan	Phytomenadione	Injection	Permissible
Lingnocaine 1%	Lignocaine HCL	Injection	Permissible
Mozobil	Plerixafor	Solution for Injection	Permissible
Pradaxa	Dabigatran etexilate	Tablet	Permissible
Reparil Gel N	Aescin, Diethylamine& Salicylate	Gel	Permissible
Tambocor	Flecainide acetate	Injection	Permissible
Transamin	Tranexamic Acid	Capsule	Permissible

Table 2: - List of thenon-permissible classifiedCV medications.

Drug Name	Non-permissibleIngredient	Dosage Form	Status
Aleviate	Human coagulation factor VIII	Powder for Injection	Non-permissible
Alphanate	Von Wilebrand factor complex	Injection	Non-permissible
Alphanate SD	Coagulation factor IX	Injection	Non-permissible
Clexane	Enoxaparin	Injection	Non-permissible
Dried Factor VII Fraction, 8Y	Factor VII	Injection	Non-permissible
Gelfoam	Purified pork skin gelatin USP granulations	Injection	Non-permissible
Ilomedin	Ethanol, 96% (v/v)	Solution for infusion	Non-permissible
Innohep	Tinzaparin Na	Injection	Non-permissible
Lanoxin	10% alcohol	Injection	Non-permissible
Vessel Due F	Sulodexide	Capsule	Non-permissible

Table 3:- Final assessment of CV medications (*n*=180).

	Assessment				Total
	Permissible(%)	Non-Permissible(%)	Doubtful(%)	Unknown(%)	
Active ingredient	132 (72.13%)	13 (7.1%)	35 (19.13%)	3 (1.64%)	183 (100%)
Inactive ingredient	105 (49.3%)	9 (4.23%)	44 (20.66%)	55 (25.82%)	213 (100%)
Whole product	14 (7.78%)	10 (5.56%)	91 (50.56%)	65 (36.11%)	180 (100%)

Discussion:-

This study showed that the majority of ingredients used in the manufacturing ofcardiovascular medication are from permissible (*Halal*) sources. However, the majority of the final products fall into both doubtful andunknown classification, which is attributed to the presence of one or moredoubtful ingredient in the product. The most common inactive ingredient that were classified as doubtful and were widely used in the manufacturing of cardiovascular medications, were magnesium stearate, gelatin, lactose, tween 80, albumin, polyethylene glycol, polysorbate 80, castor oil, macrogol, triacetinand glycerol, they assist in the final production during the manufacturing process [10]. For instance,the source of fatty compounds in stearate and glycerol (glyserine) is uncertain, thus it can be obtained from plant, animal, marine or mineral. Moreover, gelatin was reported to be mostlyobtained from the partial hydrolysis of collagen originated from the skin, bones and connective tissue of animals [16], this means that gelatin may contain materials originated from animal sources which is unsure whether the animal was swine or not, and the if the animal was slaughtered according to the Islamic standards or not.

Active ingredients that were classified as non-permissible,aresulodexide and other materials that were stated to be obtained from human sources such as clotting factor VII. Likewise, Ethanol,which is used as one of the excipients in parenteral preparations. Sulodexide,a sulpfated polysaccharide complex, which is a blend of two glycosaminogens named fast – moving heparin and dermatan sulfate,which is reported to be obtained by an extraction process of porcine intestinal mucosa [17].Enoxaparin and Tinzaparin, which are two forms of low molecular weight heparin, and theyhave been reported to be obtained from porcine intestinal mucosa, as stated in the medication package leaflets[18, 19]. Human coagulation factor, Von Wilebrand factor, coagulation factor IX and Factor VII,have been reported to be obtained from blood which is categorized as a non-permissible source[20].

Medications that were classified as unknown or cannot be assessed were the once that does not have the necessary information required to be assessed. This was due to the unavailability of the complete list of inactive ingredients used to manufacture the product. The majority of medications that cannot be assessed were made by local manufacturers,fearing strong market competition from other local pharmaceutical manufacturers, they felt insecure making their full product ingredients available to the public, preferring to keep their full product information confidential in order to retain their competitive edge.However, such marketing strategy placed limitations towards this research as not all the products were able to be evaluated. In the shadow of this situation, the Ministry of Health

is advised to implement a regulation to ensure all pharmaceutical manufacturers to state the full list of all active and inactive ingredients.

In conclusion, this study serves as an accessible '*Halal*' references to fulfill part of the growing public demand on identifying *Halal* pharmaceutical products, as well as educating health care professionals and developing general public awareness about the database availability of*Halal* pharmaceutical products. Drug manufacturer are advisedto provide more information on doubtful ingredients and state a complete list of ingredients used in their formulationswhen requested by public or health care professionals, to enhance the *Halal* assessment of these medications.Therefore, pharmaceutical manufacturers, Muslim academician, government and non-government organizations and health care professionals need to work hand in hand in order to fully identify the status of the rest of the unknown or inaccessible information to fully build the cardiovascular medications-*Halal* list.

Limitations:-
Studies that attain to address the *Halal* status of pharmaceutical products are challenging, mainly due to the lack of information provided by the drug manufacturers.The assessment of the permissibility status in this study was based on the references available at time and limited to the information listed in the drugs leaflets.

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Declaration:- Authors declare no competing interests exist.

References:-

1. Wadhera, R.K., et al., *A review of low-density lipoprotein cholesterol, treatment strategies, and its impact on cardiovascular disease morbidity and mortality.* Journal of Clinical Lipidology, 2016. **10**(3): p. 472-489.
2. Organization, W.H., *World Health Organization: Health statistics and information systems. Cause-specific mortality. Glob Summ estimates for 2000-2012.* 2016.
3. Lozano, R., et al., *Global and regional mortality from 235 causes of death for 20 age groups in 1990 and 2010: a systematic analysis for the Global Burden of Disease Study 2010.* Lancet, 2012. **380**(9859): p. 2095-128.
4. (GBD), G.B.o.D., *World Health Organization (WHO). WHO Mortality Database Version*. 2014, World Health Organization (WHO).
5. Population Division, U.N., Department Of Economic And Social Affairs *World Population Prospects main page*. 2015.
6. Bureau, U.S.C., *Malaysia; Demographic data*. 2016, U.S. Census Bureau: Washington.
7. Center, P.R., *The Global Religious Landscape*. 2012, Pew Research Center: Washington, DC.
8. Kettani, H. *2010 world Muslim population.* in *proceedings of the 8th Hawaii Internafional Conference on Arts and Humanifies.* 2010.
9. Kettani, H., *World Muslim Population: 1950 – 2020.* International Journal of Environmental Science and Development (IJESD), 2010. **1**(2).
10. Sarriff, A. and H.A. Abdul Razzaq, *Exploring the halal status of cardiovascular, endocrine, and respiratory group of medications.* Malays J Med Sci, 2013. **20**(1): p. 69-75.
11. Hanzaee, K.H. and M.R. Ramezani, *Intention to halal products in the world markets.*
12. Nakyinsige, K., et al., *Bleeding Efficiency and Meat Oxidative Stability and Microbiological Quality of New Zealand White Rabbits Subjected to Halal Slaughter without Stunning and Gas Stun-killing.* Asian Australas. J. Anim. Sci, 2014. **27**(3): p. 406-413.
13. Sabow, A.B., et al., *Bleeding efficiency, microbiological quality and oxidative stability of meat from goats subjected to slaughter without stunning in comparison with different methods of pre-slaughter electrical stunning.* PloS one, 2016. **11**(4): p. e0152661.
14. Wan Rashid, W.E., et al., *The Fifth International Conference on Marketing and Retailing (5th INCOMaR) 2015Non-Muslim Consumers' Halal Food Product Acceptance Model.* Procedia Economics and Finance, 2016. **37**: p. 276-283.
15. Wan Rashid, W.E., et al., *The Fifth International Conference on Marketing and Retailing (5th INCOMaR) 2015Halal Malaysia Logo or Brand: The Hidden Gap.* Procedia Economics and Finance, 2016. **37**: p. 254-261.

16. Troy, D.B., J.P. Remington, and P. Beringer, *Remington: The Science and Practice of Pharmacy*. 2006: Lippincott Williams & Wilkins.
17. Coccheri, S. and F. Mannello, *Development and use of sulodexide in vascular diseases: implications for treatment.* Drug Des Devel Ther, 2014. **8**: p. 49-65.
18. Sanofi, *PRODUCT INFORMATION CLEXANE*. 2016, Sanofi: Australia & New Zealand. p. 22.
19. Pharma, L., *innohep® (tinzaparin sodium) Product Monograph, version 3.0* 2010, LEO Pharma Inc.: Canada. p. 34.
20. Octapharma, *Wilate PACKAGE LEAFLET: INFORMATION FOR THE USER*. 2014, Octapharma USA. p. 20.