International Journal of Chemistry, Pharmacy & Technology
Vol. 2, No.1, pp-1-11, 2017

COMPARATIVE STUDY ON CURRENT REGULATION OF MEDICAL DEVICES IN JAPAN AND RUSSIA

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Received 31-01-17; Revised/Accepted: 06-02-17

ABSTRACT

Registration of medical devices has always been a complex, time-consuming, and expensive process. All medical devices and equipment have to go through a mandatory set of tests, even though the same tests have been performed during a process. Global Harmonization Task Force defines and classifies the Medical devices on basis of risk associated with it. In this article we will study about the regulations required for both the countries to register the medical device and there comparison. As one of the largest and most affluent aging populations in the world, Japan is well known, for its standards and regulations, especially for foreign companies and manufacturers. The lack of transparency with Russia's regulatory system can confound foreign manufacturers who are used to approach countries with more established and transparent regulatory systems. The recommendation for both the authorities has discussed in the article.

Keywords: Medical Device, PMDA, RCB, Roszdravnadzor, Registration, Regulation.

INTRODUCTION

Medical Device becomes the essential requirements for the human beings. Globally Medical device market has been increasing its impact. IMDRF (International Medical Device Regulators Forum) is a voluntary group of medical devices regulatory authorities such as USFDA, whose goal is the standardization of medical device regulation across the globe. Regulators from around the world come together to build the Global Harmonization Task Force on Medical Devices (GHTF) whose objective is to encourage convergence at the global level in the evolution of regulatory systems for medical devices to facilitate trade whilst preserving the right of participating members to address the protection of public health by regulatory means considered to be most suitable. (1)

According to GHTF (Global Harmonization Task Force), 'Medical device' means any instrument, apparatus, implement, machine, appliance, implant, reagent for in vitro use, software, material or other similar material intended by the manufacturer to be used alone or in combination for human beings or for specific medical purpose(s) of :

- diagnosis, prevention, monitoring, treatment or alleviation of disease and compensation for an injury,
- investigation, replacement, modification, or support of the anatomy or physiological process,
- supporting life,
- control of conception,
- disinfection of medical devices,
- in vitro examination of specimens derived from the human body (2)

Regulatory authorities should classify devices consisting of four classes where Class A represents the lowest hazard and Class D the highest hazard according to risk. The actual classification of each device depends on the claims made by the manufacturer for its intended use and the technology it utilizes as shown in Table 1.The purpose of risk classification is to make sure that the regulatory controls applied to a medical device are proportionate to risk.(3)

Table 1: Classification of medical devices

CLASS	LEVEL	DEVICE EXAMPLES
A	Low Hazard	Bandages / tongue depressors
B	Low-moderate Hazard	Hypodermic Needles / suction equipment
C	Moderate-high Hazard	Lung ventilator / bone fixation plate
D	High Hazard	Heart valves / implantable defibrillator

JAPAN:

Japanese healthcare standards are amongst highest in the world and medical device market is largest in the globe. The most wanted devices are: Implants, CT-scans, MRI and other imaging software (4).Japan's pharmaceutical and medical device agency (PMDA) is the regulatory body responsible for reviewing medical device application. The PMDA works under Ministry of Health, labor, and Welfare (MHLW) to assess new product safety, develop comprehensive regulations and minority post-market safety. Japan medical device regulations are lead down under pharmaceutical and medical device (PMD) act. This act also called as act on securing Quality, Efficacy and safety of Pharmaceutical, Medical devices, Regenerative and Cellular therapy products, Gene therapy products and Cosmetics".(5) In PMDA act, Regenerative medical products are defined as "processed human cells that are intended to be used for:

- The reconstruction, repair or formation of structures or functions of human body
- Gene therapy
- The treatment or prevention of human diseases".

The key features of new PMD Act are:

- Manufacturing License now simplified to "registration" from "accreditation"
- Marketing Authorization Holder (MAH – the Legal manufacturer in Japan) will be responsible for QM(Quality Management) and Good Vigilance Practice (GVP)
- Medical devices and pharmaceuticals sections in separate chapters
- All Class II devices' design control activities will be covered in the quality management system audit (Article 30-36, 7.3)
- Some Class III devices with defined certification criteria are moved to certification scheme of 3rd party certification bodies.
- Standalone software for diagnosis etc. becomes a medical device

- Draft package insert required in the new application.
- Class IV devices will require submission to MHLW in advance (6)

CLASSIFICATION SYSTEM: Japan's classification system is based on risk level and complies with the Japanese standards as shown in Table 2. The standards define industry-wide safety and performance requirements. (7)

Table 2: The regulatory classes of a medical device in Japan

INCREASING RISK TO PATIENT

Class	Regulatory class in Japan	Product approved or certification	QMS review	Approval time	Validity period of registration
I	General Medical Devices like x-rays	Notification	Exempt	<1 Months	Does not expire
II	Controlled Medical Devices like MRIs	Approval	PMDA	7-9 months	
	Controlled Medical Devices with Certification Standards	Certification	Registered certification body	3-5 months	
III	Specially Controlled Medical Devices like In-Vitro Diagnostic Devices	Approval	PMDA	9-11 months	
	Specially Controlled Medical Devices with Certification Standards	Certification	Registered Certification Body	-	
IV	Highly Controlled Medical Devices like Pacemakers	Approval	PMDA	13-16 month	

REGULATIONS: Regulations are very strict in Japan since PMD act imposes strict rules i.e. requirements and standards on the foreign manufacturer and the documents that are published are exclusively in Japanese. An experienced regulatory partner is essential to get your product approved. Foreign manufacturers can also expect strong competition from domestic manufacturers. Japan is home to leading consumer technology companies that also design medical devices.

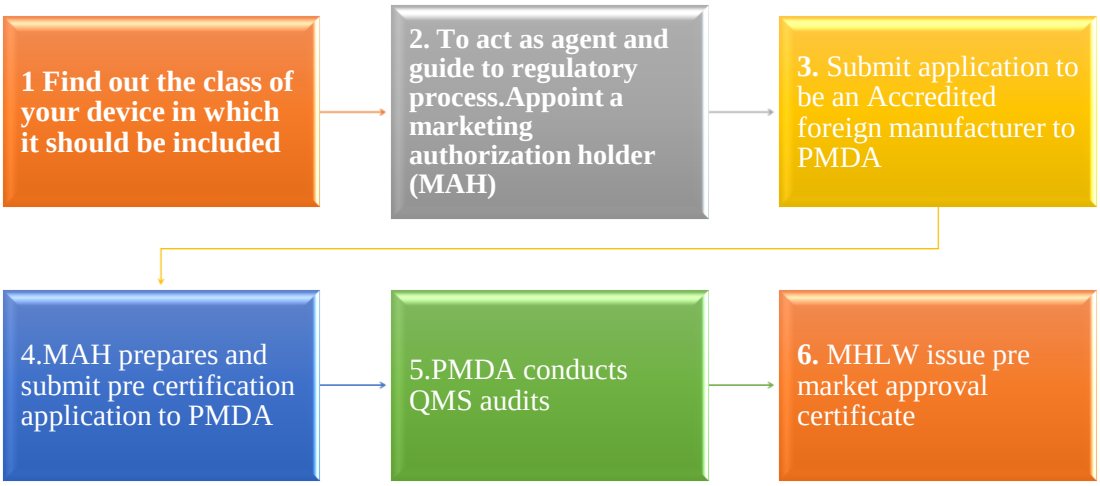
In the regulatory pathway of Japan, it is determined by device classification according to the Japan Pharmaceutical Affairs Law (PAL) and Japanese Pharmaceutical and Medical Device Act (PMD Act) which is mentioned in table 2 and further on the availability of a Japanese Medical Device Nomenclature (JMDN) code. After that applicant has to appoint Marketing Authorization Holder or designated Marketing authorization holder (MAH or D-MAH) who manages approval procedure of product in Japan.

In step 3 applicants has to submit the application for registration to the PMDA as shown in Figure: 1. more distinct registration pathways for domestic and foreign medical devices are also

components of the PMD Act. The PAL (Japan's Pharmaceutical Affairs Law) required a domestic device manufacturer to obtain a manufacturer license, while a foreign manufacturer was required to obtain foreign manufacturer accreditation (8).Under the PMD Act, a new registration system has been established requiring the following:

- Domestic manufacturers must register their manufacturing facilities with the authorities at their local prefectures
- Foreign manufacturers must register their manufacturing facilities with the PMDA

Figure: 1 Route map to get approved in the Japanese market



After that key change in the Japanese procedure is an addition of Quality Management system (QMS) compliance since earlier PMDA or registered certification bodies (RCB) conduct QMS for each manufacturer but now PMDA conducts for devices under pre-approval and RCB for devices under pre-market certification process of review. So now manufacturers of each class has to implement quality system compliant with the Pharmaceutical Affairs Law and MHLW Ordinance #169 and submit QMS Conformity Assessment Application which is Similar to ISO 13485 and US Quality System Regulation (21 CFR Part 820) Although based largely on ISO 13485:2003, MHLW Ordinance 169 does differ from ISO 13485 in some regards.

Now the applications are submitted according to the requirements to the PMDA depend on how your device is classified in the Japanese system as shown in table: 3 (9) All documents must be in Japanese.

Table 3: Applications are submitted according to the requirements to the PMDA

CLASS I	CLASS II(specifically controlled)	CLASS II(Controlled)	CLASS III(Highly Controlled)	CLASS IV(Highly Controlled)
Submit pre-market Submission to PMDA	Submit pre-market Certification Application to Registered Certification Body	Prepare Pre-market Approval Application and Supporting documents as attachment including the documents in Summary Technical Document (STED) Format and Submit To PMDA		

Now the devices require a QMS conformity assessment by PMDA or by an RCB Regulatory Authority as shown in table: 4.On-site audits are typically required for "new" devices with no existing JMDN code, Class IV devices, and those requiring clinical investigations

Table 4: QMS conformity assessment

CLASS I	CLASS II (Specified controlled)	CLASS II (Controlled)	CLASS III (Highly Controlled)	CLASS IV(Highly Controlled)
QMS Audit by PMDA	QMS Audit by RCB	QMS Audit by PMDA or Prefectural QMS Audit by RCB Regulatory Authority		

Table 5: All classes will require a QMS conformance certificate issued by PMDA or RCB

CLASS I	CLASS II	CLASS II	CLASS III	CLASS IV
Self-declaration; No Certification from PMDA	Pre-market Certification issued by RCB	Pre-market Approval Certificate Issued by MHLW; Certificate does not expire		

Japan's medical device market has long held a reputation as a complex market for foreign manufacturers to navigate, but the sheer size of the market compels many overseas firms to pursue PMDA registration. The MHLW also issued many guidance documents to further clarify the necessary steps in the registration process. During the review process, PMDA evaluates the quality, efficacy, and safety of drugs, medical devices, and cellular and tissue-based products with standards. In addition, PMDA's reviews and services consist of "consultations" which provide advice for regulatory submissions, GLP/GCP/GPSP inspections to ensure the submitted data is according to the ethical standards, and GMP/QMS/GCTP inspections is done to ensure quality management of the manufacturing facility for the product (10)

The manufacturing sites which are located outside the Japan have to obtain manufacture's registration from PMDA if the site involves any of the below-mentioned procedures:

- Design and development
- Design and development of in vitro diagnostic reagents
- Production or sterilization of Medical devices.

MAJOR CHANGES TO THE REGULATION OF JAPAN:

1. Authorities have replaced Pharmaceutical Affairs Law (PAL) with the Pharmaceutical Medical Device Act (PMDA) which will have its impact on Japanese medical device registration process.
2. The PMD Act now allows Class II as well as some Class III devices to qualify for third-party certification which will be easier for foreign manufacturers.
3. The PMD act has made changes that domestic device manufacturers will receive manufacturer licenses and that foreign manufacturers obtain foreign manufacturer.
4. The MAH now has to qualify quality system conformity assessments on a product to get the QMS certificate.
5. Draft package insert required in the new application.

6. Japan is introducing new regulation policies which can attract more applicants.

RUSSIA:

Russia is one of the European countries which is growing at the rate of 0.19% both politically and economically. Nowadays it is easy to import and register the product in its market. The president of Russian Federation establishes Federal service for surveillance in healthcare (Roszdravnadzor). Roszdravnadzor is subordinate to the Ministry of Health of the Russian federation which is guided by the Russian Federation constitution, Federation laws, and acts. Roszdravnadzor has the power to supervise and controls medical device & medicine circulation, quality & safety of medical practice etc. the federal service of surveillance in healthcare is responsible for state registration of medical devices and perfume inspections of healthcare institutions. Its other function is the regulation on Roszdravnadzor(11). Recent changes to medical device registration requirements in Russia left some areas unclear and undefined. As a result, many manufacturers benefit from the guidance of local representatives and experienced industry consultants to navigate this market.

CLASSIFICATION OF THE MEDICAL DEVICE: Classification of the device is confirmed using Roszdravnadzor Order No. 735 and Rosstandart 51609-2000. The type of the medical device is defined according to the Decree No. 4n which are classified according to EU Risked-based classification of devices as shown in Table: 6

Table 6: Classification of device is confirmed using Roszdravnadzor

INCREASING RISK TO PATIENT

CLASS	DESCRIPTION	PREMARKET REQUIREMENT	GENERAL TIME TO CLEARANCE/APPROVAL
Class I	Simple in design and have a history of safe use.	Declare conformity with the Essential Requirements.	Approval is not required.
Class II a	Devices posing relatively low risk to the human body include digestive catheters, infusion pumps, and powered wheelchairs	Manufacturers are required to submit a dossier of a relevant supporting literature (clinical and nonclinical) to substantiate safety and performance.	1 to 3 months (+ any time required for the sponsor to address any Deficiencies in the submission).
Class II b	Relatively high risk to the human body, such as technologies like respirators, dialyzers, and orthopaedic implants		-
Class III	These devices include long-term, surgically invasive devices that may endanger the Patient's life. An example is coronary stents.	Clinical studies generally are recommended for high-risk devices.	-

REGULATION: From a regulatory perspective, there are some encouraging signs of progress. Over the past couple of years, the government has released a number of guidance and regulations, clarifying elements of the registration process. For example:

- The registration application requires identifying a product nomenclature code, with the internationally recognized GMDN (Global Medical Device Nomenclature) system.
- The government's official website now lists all approved testing centers, resolving confusion on which facilities are authorized to conduct testing.
- Also, in July 2015, the government released Order 303N, simplifying the Class I medical device review process intends to provide a less cumbersome path to registration for low-risk products. (12)

The applicant has to register their devices with Roszdravnadzor (RZN), the Federal Service for Control of Healthcare and Social Development, prior to commercialization in the Russian Federation. This agency is responsible for regulating medical devices and IVDs, governs the registration procedure (including approving or rejecting applications), and is responsible for certifying testing laboratories that may perform in-country testing and clinical trials. Now medical devices in the Russian federation are regulated by Roszdravnadzor (RZN) under decree 1416 and determine class according to order 4n and GOST 31508-2012 which provides nomenclature classification code, then the applicant has to appoint Authorized representative to coordinate your medical device registration in Russia. (13) The device information is the send to an authorized test lab in Russia which then checks the in country wise testing requirements. The authorized lab in Russia checks for quality, safety, an efficacy of the product. The applicant then has to prepare registration dossier which is translated into Russian language and submit to RZN and pay fees, certificates which must be notarized. Class I devices are eligible for a simplified review process which includes Russian supplemental clinical data while for class IIa, IIb and III, RZN conducts completeness review which if accepted will be sent to expertise center for technical review and if fails RZN will review and give recommendations.

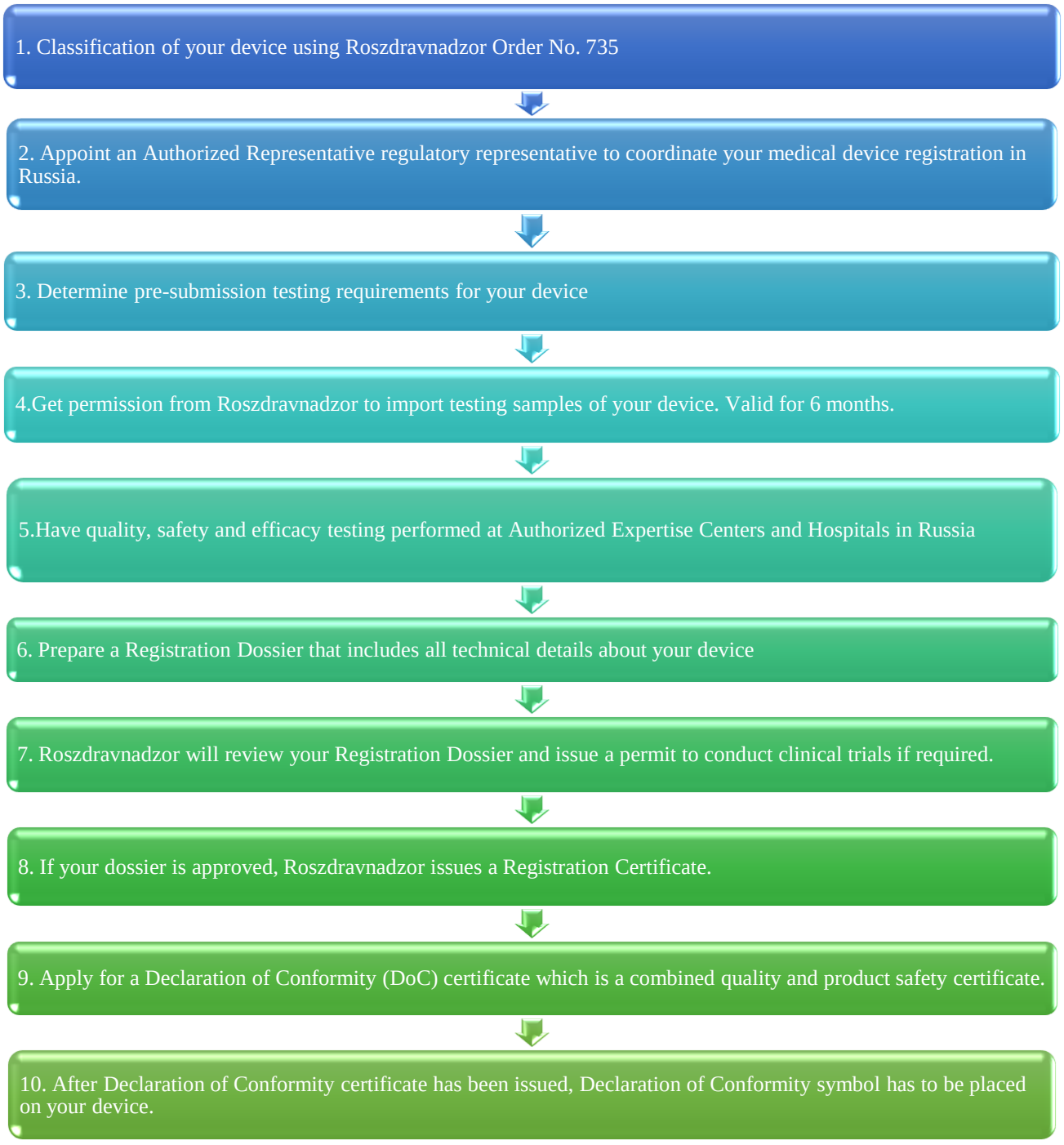
For Classes IIa, IIb, and III has to follow RZN's clinical data requirements and conduct additional testing or trials in Russia. During this time the registration is placed in "suspended" status. Submit clinical results to RZN and apply for continuation of the registration process. For all device classes: Dossier goes through Stage 2 review. If acceptable, RZN issues a Registration Certificate and lists the product in registration database on RZN's website. Registrations do not expire. For all medical device classes have to apply for Declaration of Conformity (DoC) certification which is a combination of quality and product safety certificate. Documents needed may include Registration certificate, test reports, ISO 13485 certificate, and other documents. For all device classes: After DoC certificate has been issued, the DoC symbol must be placed on your device and now authorized to market your device in Russia. The DoC certificate is valid for up to 3 years depending on the manufacturer's choice. (14)

The required documents which are needed to be submitted along with the registration application are:

1. A letter from the manufacturer describing intention to apply for registration of the product.
2. A Power of Attorney to the authorized representative (a legal entity) to conduct registration.
3. Reference material on the medical product.
4. An exact and complete description of the product and its components (if necessary).

5. A picture of the medical device
6. Advertising illustrative materials.
7. Documents on registration of the manufacturing company in the country of origin.
8. Documents on the registration of a product in the country of origin as a measurement device.
9. National or international documents describing the manufacturing process.
10. Manufacturer's operational manual in Russian and manufacturer's price list on its letterhead.

Figure 2: The medical device approval procedure



The documents described in the last four points shall be originals or notarized copies which have an Apostil from the Russian Consulate office in the country of origin (15)

MAJOR CHANGES TO THE REGULATION OF RUSSIA: Major changes are done by Russian authorities to reduce the administrative burden on companies which will start from January 2017.

1. Authorities have replaced the criteria of affiliation with control.
2. Now in the process of registration applicants have to give more detailed information about their device.
3. Authorities have introduced 'Expertise centers' who will decide whether the applicants have to conduct clinical trials for their devices and after the results they give a review on their safety.
4. Authorities have provided the requirements of authorized representative officially.
5. The authorities have included more testing requirements for devices which is an important aspect for the Russian authorities.
6. Now applicants have to show the agreement with the hospital to show where the clinical trials are taking place.
7. Applicants should have import permit for the samples which are given to RZN.
8. RZN will give the authorization of expert review of the sample submitted by the applicant.
9. The information in the registration certificate is now different.
10. It is necessary for the device applicant to designate an Authorized representative.

Table 7: Comparative analysis of Japan and Russia

S.NO	CHARACTERISTICS	JAPAN	RUSSIA
1.	Population(till January 2016)	126,890,000	146,544,710
2.	Language	Japanese	Russian
3.	Capital	Tokyo	Moscow
4.	Currency	Yen	Russian Ruble
5.	Market	Asian	European
6.	Regulatory authorities for Pre- and post-market supervision of medical devices	Japan's pharmaceutical and medical device agency (PMDA)	Federal service for surveillance in healthcare (Roszdravnadzor)
7.	Risk classification	Class I,II,III,IV	Class I,IIa,IIb,III
8.	Total healthcare spending	$469 billion	$140 billion
9.	Healthcare expenditure total (% of GDP)	10.2%	9%
10.	Size of medical device	$26 billion(USD)	$6billion(USD)
11.	Healthcare expenditure per capita	$3703 (USD)	$5939(USD)
12.	Life expectancy(male/female)	81/88 years	63/75 years
13.	Government expenditure on healthcare	84%	59.72%
14.	Private expenditure on healthcare	16%	40.28%
15.	Rank on ease of enforcing contracts globally	36	10
16.	Rank on total rate (% of commercial profit)	140	56

RECOMMENDATIONS: The following are the recommendations for the medical devices regulatory authorities of Japan and Russia:

1. The authorities should work with industry to deliver innovative medical devices to the patients of respective countries.
2. Rules establish by authorities must be clear so that companies can easily classify their products.
3. The authorities should have good communication and collaboration which is a key to success.
4. Foreign manufacturers must follow the regulations of Russian and Japan device regulations and registration requirements, such as in-country testing, clinical trials, etc.
5. Russia should improve the transparency in regulations so that it is easy for foreign manufacturers to follow the guidelines and register their products easily.
6. Post-market surveillance/vigilance should be made compulsory.
7. The procedure of Japan is very lengthy and challenging so authorities should work with industry to make it simpler for applicants.
8. The authorities should try to reduce the time period for the approval process.

CONCLUSION: Japan's medical device market is very difficult to achieve by foreign manufacturers to navigate, but it has a large sheer market which compels many overseas firms to pursue PMDA registration. The MHLW has issued many guidance documents to further clarify the necessary steps in the registration process which make it easier for companies to plan their entry to the Japanese market while Russia has made efforts to improve the medical device registration process in the last few years; it remains a challenging and ambiguous market. Companies have to carefully evaluate the risks and uncertainties of pursuing registration in this market, as the Russian regulatory environment remains unpredictable and suffers from a lack of clear published guidance, which leads to reliance on previously held practices. Since Russia is a large market that many manufacturers simply cannot ignore. Therefore, if deciding to enter the Russian market, it is important to work with a communicative and trustworthy partner and go into the process expecting that it will be challenging and lengthy.

ACKNOWLEDGEMENT

The authors are thankful to Dr. R.K Goyal (Vice chancellor) & Dr.D.P.Pathak, Offg.Registrar of Delhi Pharmaceutical Science and Research (DPSRU), New Delhi, India for providing all the facilities and encouragement to carry out the work.

CONFLICTS OF INTEREST:

The authors declare that there are no conflicts of Interest.

REFERENCES:

1. GHTF details available at: http://www.imdrf.org/about/about.asp (Assessed on 1 December 2016)
2. Despina Spanou, IMDRF Chair, 9 December 2013, "Software as a Medical Device (SaMD): Key Definitions", Available at : http://www.imdrf.org/docs/imdrf/final/technical/imdrf-tech-131209-samd-key-definitions-140901.pdf (Assessed on 3rd November 2016)
3. Dr. Kazunari Asanuma, GHTF Chair, November 2nd 2012, Title:"Principles of Medical Devices Classification", (Revision of GHTF/SG1/N15:2006).

4. Sandra Brolin, "Global Regulatory Requirements for Medical Devices", Available at: http://www.diva-portal.org/smash/get/diva2:121327/FULLTEXT01.pdfGlobal (Assessed on 6th november,2016)
5. PMDA details Available at: https://www.pmda.go.jp/english/about-pmda/index.html (Assessed on 12 december,2016)
6. PMDA available at: https://www.emergogroup.com/resources/Japan/pharmaceuticals-medical-devices-agency
7. BSI 2015 Medical Device Roadshow, "Japan Pharmaceutical & Medical Devices Act (JPMD Act)", available at: https://www.bsigroup.com/meddev/LocalFiles/en-US/Roadshow%20Resources%202015/Fall/Japan%20Pharmaceutical%20and%20Medical%20Devices%20Act%20JPMD%20Act.pdf (Assessed on 14th October,2016)
8. Michiharu Miyahara, Emergo president & CEO ,October 2016, "Overview of Japan's pharmaceutical & medical device act" available at: https://www.emergogroup.com/resources/articles/white-paper-japan-new-pharmaceutical-medical-devices-act (assessed on October 13th, 2016)
9. Japan regulatory approval process for medical devices. Available at: https://www.emergogroup.com/resources/japan-process-chart (assessed on 23rd October, 2016)
10. Japan medical device regulation available on : https://www.emergogroup.com/resources/regulations-japan (assessed on 24th october,2016)
11. Roszdravnadzor details available at : http://www.roszdravnadzor.ru/en (assessed on 19th Novemeber,2016)
12. Product registration n Russia available at : http://www.roszdravnadzor.ru/en/medproducts/registration
13. Ludmila Maksimova, March 2006, "Medical device regulatory requirement in Russia"
14. Russian approval process available at: https://www.emergogroup.com/resources/russia-process-chart
15. Russian medical device regulation available at: https://www.emergogroup.com/resources/regulations-russia (assessed on 19th Novemeber, 2016)