A Regulatory Overview of Hip and Knee Joint Replacement Devices

Anmol Wadhwa1, Sushama Talegaonkar1,* and Harvinder Popli1

1Department of Drug Regulatory Affairs, Delhi Pharmaceutical Sciences and Research University (DPSRU), New Delhi, 110017, India

Abstract: Objective: Medical device acceptance of patients has grown considerably in recent years. This has questioned the effectiveness of the current regulatory frameworks to ensure the performance, safety, and quality of new devices. This article focuses on the methodical overview on hip and knee joint replacement medical devices evaluating the procedure and proper analysis of medical device regulation in three jurisdictions i.e. the United States of America (USA), EUROPE and INDIA, exploring reforms that have been laid to stabilize and meet the requirements of existing systems, and further analyse the additional actions which should be employed to fully meet this ultimate goal.

Methods: We analysed the hip and knee joint replacement medical device regulation system through a secondary research in United States, Europe and India in compliance with the updated national regulatory authority’s legislative documents and requirements.

Results: These three regulatory systems vary in their working, organization, acceptance for their specific pre- and post-market evidence requirements, and transparency of process. The most challenging factor remains the same for the countries which are to make sure safety and effectiveness of devices, proper monitoring of its use and important compliance information readiness employing quality management system towards new findings and acceptance for the users. A case study of Johnson & Johnson ASR Implant was also studied, highlighting the major reforms required and the reforms introduced in the United States, Europe and India. Thus, quality and safety reforms are made to strengthen the premarket compliance requirements, enhancing the need of post-market regulation through proper traceability and monitoring of devices by employing the functioning medical device registry.

Conclusion: Recent reforms address the major challenges in device regulation, highlighting the need to create connecting points between the device identifier system and existing data collection tools, such as electronic health records, and maintaining effective and up to date use of registries to ensure post-market use of new and existing devices.

Keywords: Medical device, knee joint replacement, hip joint replacement, THR, TKR, pharmacological.

1. INTRODUCTION

As per the WHO, any medical intervention which can be used to diagnose, prevent, monitor, treat any disease or an injury with the help of any instrument, apparatus, machine, appliance, implant, reagent for in vitro use, software, disinfection, material or other similar or related articles, with the sole purpose of support, modify, replace, investigate and control the anatomy or of a physiological process intended by the manufacturer to be used, alone or in combination, for human beings.

Also, these intervention does not achieve its primary intended action by pharmacological, immunological or metabolic means, in or on the human body, but which may be assisted in its intended function by such means are classified under the category of “Medical devices” [1].
All of the total joint replacement medical devices which are employed as implant are also, technically referred to as “Arthroplasty Devices”.

Arthroplasty which by literal means is reforming of joint, basically by using surgical procedure where the articular surface of a musculoskeletal joint is replaced, remodelled, or realigned by osteotomy or by complete joint replacement procedure to relieve the severe pain caused damage or disease conditions and restores the function to the treated joint with more ease [2].

Joint Replacement surgery used for the following indications:

1. Bone and Joint Disorders
These further includes:
Osteoporosis (OP), Osteoarthritis (OA), Rheumatoid Arthritis, Perthes Disease (Childhood hip Disorder), Developmental dysplasia of the hip, Rotator cuff tear (RCT) that occurs as a result of trauma to one or more tendons, Traumatic arthritis - includes sports injuries, fractures, car accidents, blunt force trauma, fall, or overuse, and Failed previous joint replacement surgery [3-9].

2. Avascular Necrosis
Avascular Necrosis (AVN), also called osteonecrosis, where the surface of bone or part dies (Epiphysis – End part of long bones, such as femoral and humeral) caused by the interrupted blood supply leading into joint pain which can limit the power to perform any physical activity. Complications could embody collapse of the bone or the near joint surface [10-12].

1.1. Treatment and Complications

The treatment used for any bone disorder is usually determined by doctors based on the following factors including age, overall health, and medical history (considering diabetes mellitus, Vitamin D, malnutrition, liver disease or any mental disorder); the severity of the disease; the patient’s tolerance to specific medications, procedures, or therapies; expectations for the course of the disease; and based on patient’s opinion or preference [13, 14].

There are different forms of treatment that may include assistive devices, core decompression, bone graft, total joint replacement, and surgery [15-19].

There are further complications associated with total joint replacement therapy such as blot clots or deep vein thrombosis; infection; bleeding; loosening; mechanical wear; and failure [14].

Joint replacement surgery is employed for various categories of joints with a different approach for different circumstances, but the primary focus is on hip and knee Joint replacement.

1.2. Hip Joint Replacement

Hip replacement is a surgical procedure involving the hip ball-and-socket which is femoral head and/or the acetabulum that is substituted by artificial prosthetic material. This procedure involves prosthesis which is available in various materials including ceramic, plastic, metals, or combinations of any two. The component of prosthesis may be directly attached a to healthy bone with cement or without any such binding agent if the prosthesis is covered with hydroxyapatite (HA), a material which mimics human bone.

Total hip replacement (THR) is a cost-effective medical intervention, therefore it remains at the top of its preference list for long-term pain relief and restoration of function of diseased or damaged hips.

Hip replacement involves the use of a femoral stem, a femoral head, and an acetabular cup (Fig. 1). While a modular femoral head attaches to the stem via a taper locking mechanism, a monoblock femoral head is attached to the stem as a one-piece unit. A modular acetabular cup is com-
posed of shell that is fixed to the pelvic bone and an insert or liner that is fixed inside the shell. Conversely, a monoblock acetabular cup is a one-piece construct. The bearing surface of the joint is composed of a metal or ceramic femoral head, with the inner surface of the cup typically comprising ceramic, metal, or polyethylene (Fig. 2) with a variety of coatings like: beaded, sintered cobalt-chrome coatings on a cobalt-chrome substrate; beaded, vacuum-sintered titanium coatings on a titanium substrate; and vacuum-sintered titanium fibre mesh pads on a titanium substrate [15, 16].

Their standards conform by – ASTM standards (ASTM F1044- For shear strengths), along with their metallurgical, physical and surface analysis to maintain safety (Table 1) [22-24].

In the United States, on the basis of the material of the bearing surface, there are four types of total hip replacement (THR) devices approved. These are as following:

Table 1. ASTM standards for the hip and knee joint replacements.

<table>
<thead>
<tr>
<th>Designation</th>
<th>Title</th>
</tr>
</thead>
<tbody>
<tr>
<td>F2943 - 14</td>
<td>Standard Guide for Presentation of End User Labelling Information for Musculoskeletal Implants.</td>
</tr>
<tr>
<td>F2996 - 13</td>
<td>Standard Practice for Finite Element Analysis (FEA) of Non-Modular Metallic Orthopaedic Hip Femoral Stems.</td>
</tr>
<tr>
<td>F3140 - 17</td>
<td>Standard Test Method for Cyclic Fatigue Testing of Metal Tibial Tray Components of Unicondylar Knee Joint Replacements.</td>
</tr>
<tr>
<td>F3141 - 17a</td>
<td>Standard Guide for Total Knee Replacement Loading Profiles.</td>
</tr>
<tr>
<td>F3161 - 16</td>
<td>Standard Test Method for Finite Element Analysis (FEA) of Metallic Orthopaedic Total Knee Femoral Components under Closing Conditions.</td>
</tr>
</tbody>
</table>
Metal-on-Polyethylene: The acetabular cup of the socket is composed of metal and the socket is composed of plastic (polyethylene) or has a plastic lining.

Ceramic-on-Polyethylene: The acetabular cup is composed of ceramic and the socket is composed of plastic (polyethylene) or has a plastic lining.

Ceramic-on-Ceramic: The acetabular cup is composed of ceramic and the socket has a ceramic lining.

Ceramic-on-Metal: The acetabular cup is composed of ceramic and the socket has a metal lining [23].

Types of hip replacement devices are categorized as: cemented, cement-less, or hybrid hip replacement. In a cemented THR, the acetabular cup and prosthesis shaft are fixed to the skeleton with a self-curing bone cement, which occupies the space between the skeleton and the surface of the prosthesis. Whereas survival rates for conventional cemented, metal-on-polyethylene bearing joint replacement are impressive and appreciable as 90%, 85%, and 80% at 10, 15, and 20 years, respectively [25, 26].

In hybrid-hip replacement – one of the two components (i.e. cup or stem) is inserted without cement, the acetabulum is replaced composed of one material (polyethylene, ceramic, or metal) or a two-piece (modular) cup composed up of outer shell and a polyethylene, ceramic, or metal liner. The head of the femur is also replaced with a single-piece metal stem and head, or a modular component consisting of a metal stem (more than one piece, if available) with a metal, ceramic, or ceramicized metal head.

1.3. Knee Joint Replacement

Knee replacement is the second most common arthroplasty performed worldwide. The procedure is conducted to replace the weight-bearing surfaces of the knee joint. Total knee replacement (TKR) involves several components, including: patellar and femoral prostheses, a cruciate-sparing tibial insert, and a tibial baseplate for resurfacing.

Types of Knee Joint Replacement on the basis of body parts involved: Total Knee, Unicompartmental, and Revision Knee Replacement [13, 19, 27].

Fig. (3). Total knee replacement system [28].

Total Knee Replacement (TKR) – is suggested when all three compartments of the knee are replaced, and a prosthetic femoral head is fitted at the bottom of the resurfaced femur. On the basis of damage, femur may have to be cut off. Secondly, tibial plate is screwed on the tibial top (resurfaced), through weight-bearing metal piece. Then medical-grade flat plastic piece is placed between the tibia and tibial plate to help absorb shock and allow smooth gliding of the knee (Fig. 3). Finally, the other side of the patella facing the femur end is resurfaced and fitted with a plastic button.

Partial Knee Replacement is further categorized into Uni-compartmental, bi-compartmental, or patella-femoral process performed in when one or two respective parts are damaged. The key advantages of uni-condylar knee replacement include faster recovery, reduced post-operative pain, and lower blood loss.

Revision knee replacement involves the removal of the primary implant that would have grown into the existing bone. Once the initial prosthesis is removed, it may result in reduced bone length followed by bone graft. Thus, thicker and longer stems are used to provide stability and to compensate the weak ligaments and incremental bone loss caused.

Types of Knee Implants (On the basis of the bearing category and size variation) are further classified into fixed-bearing, mobile-bearing (Fig. 4), medial-pivot implants, gender-specific knee implants (Fig. 5), and patient-specific or customized implants.

1.4. Key Market Players

Orthopaedic market’s top 10 companies are expected to generate $41.2bn in sales, contributing over 87% of the total market revenue (Fig. 6).
1.5. Regulatory Perspective

All of the above discussed joint replacement medical devices are nationally regulated. These national regulations came together to speed up the international medical device regulatory harmonization and convergence and initiated International Medical Device Regulators Forum (IMDRF) which was conceived in February 2011 as a forum of professional regulators from around the world who have come together continuing the foundational work of the Global Harmonization Task Force on Medical Devices (GHTF) [30, 31].

The work is carried out by the various Management Committee, on rotation basis providing guidance on strategies, policies, directions, membership and activities of the Forum. The current members are: Australia, Brazil, Canada, China, Europe, Japan, Russia, Singapore, South Korea, and the United States of America.

The World Health Organization (WHO) is an Official Observer. The Asian Harmonization Working Party (AHWP), Pan American Health Organization (PAHO) and APEC LSIF Regulatory Harmonization Steering Committee are IMDRF Regional Harmonization Initiatives [30, 31].

1.6. Regulation in the United States of America

In United States of America (USA), Medical Devices are under supervision of the Food and Drug Administration (FDA), where the, Centre for Devices and Radiological Health (CDRH) within FDA is the regulatory division for medical devices regulating firms involved the manufacturing, re-packaging, re-labelling and or import of medical devices sold in the United States.

Total Joint Replacement Medical Devices products are further described on the basis of the bio-material (metal/Polymer/Ceramic), type of Joint (Hip or Knee), physiological bone involved (Hip - Constrained, Semi-Constrained; Knee - Femoro-tibial, tibial or patella with con-
strains) and method of replacement (cemented or un-cemented) and are premarket reviewed under the Office of Device Evaluation (ODE), within a dedicated Division of Orthopaedic Devices (DOD) as Joint and Fixation Devices Branch [32].

These products have been classified under the Code of Federal Regulations (CFR), Part 888 – Orthopaedic Devices, Subpart D – Prosthetic devices, Title 21, Chapter I – Food and Drug Administration with Sub-Chapters I – Medical Devices [32].

This legislation reviews medical products and classifies them on the basis of risk factors. Thus, classification becomes a major step for product approval.

Therefore, they are classified into three main categories:

- Class I – Low Risk
- Class II – Moderate Risk
- Class III – Higher Risk [33]

The regulatory pathways for obtaining marketing clearance in the USA are as follows: 510(k), Pre-Market Approval (PMA), Humanitarian device exemption (HDE) and De-Novo Approval; whereas, joint replacements are classified under Class II with the approval pathway designated under the 510(K) pre-market notification review [34].

These are the following steps of product approval:

- Step 1 – Determining device classification on the basis of: FDA classification database, using Substantial Equivalence (SE) comparison of predicate devices and valid scientific reasons for safety and efficacy to find out the approval pathway accordingly, in case of uncertainty using 513(g) we can request for classification of device from FDA.
- Step 2 – Compliance with Quality Management System which is ISO 13485:2016 (Earlier, QSR (GMP) as per FDA Quality System Regulation founded under 21 CFR Part 820).
- Step 3 – Getting a “Pre – Submission (Pre-Sub)” feedback from the FDA.
- Step 4 – In case, Clinical studies are required it is considered to apply for the related exemptions. Developing Clinical Trial protocol and conducting studies to be performed with IRB approval.
- Step 5 – Application and Fees (as per MDUFA VI) related to it are submitted [35].
- Step 6 – Facility inspection conducted for all the major suppliers involved in the design and production of device, to check their compliance with QMS guideline i.e. ISO 13485:2016 for class –II and III, whereas there is no pre- inspection for Class I but for compliance check they may conduct random inspection.

After getting approval, and listing the device, every manufacturer needs to register their company on FURLS system on FDA website in accordance with 21 CFR Part 807 – ‘Establishment registration and Device listing for manufacturers and initial importers of device’.

All the therapeutic applications of devices must be under the legislation of the federal rules of 21 CFR Part 800, 803, 806, 807, 808, 809, 810, 812, 814, 820, 821, 822, 830, 860 and 861 under the same three centers in the FDA the Centre for Drug Evaluation and Research (CDER) for drugs, the Centre for Devices and Radiological Health (CDRH) for devices, and the Centre for Biologics Evaluation and Regulation (CBER) for biologics [36].

The list of Code of Federal Regulations (CFR) Parts applicable for Hip and Knee Joint Replacement Medical Devices is given in Table 2.

1.7. Regulation in Europe

Earlier in the European Union, decentralized procedure of marketing authorization was followed as there is no single body to regulate medical devices directives, are provided in three variants of directives which regulated the safety and marketing of medical devices in Europe [37, 38].

The three directives are:

- Medical Device Directive (MDD 93/42/EEC),
- Active Implantable Medical Device Directive (AIMDD 90/42/EE).

For any device to be marketed CE marking/certification is mandatory. The notified body (regulatory arms of member states) ensures the compliance to quality and safety standards and is responsible for approving the devices for CE marking, whereas Competent Authority of the member state grants the marketing authorization.

The above mentioned Directives have undergone some major amendments in year 2017 within legislative Act [39]:


Both of the amendments are given a transition period of 3 or 5 years respectively for medical devices including Active-Implantable i.e. by Year 2020.

In order to meet legal requirements to ensure their safety and performance as intended, all of the devices in the EU have to undergo a conformity assessment. The EU Member States designate the accredited notified bodies which are responsible to conduct conformity assessments [42].

The conformity assessment is basically assessed on the basis of an audit of the manufacturer’s quality system and, depending on the device type, Technical documentation review from the manufacturer on the safety and performance of the device. After, fully complying with assessment manufacturers can place a CE (Conformité Européenne) mark on a medical device which needs to be renewed as per the national requirements.

<table>
<thead>
<tr>
<th>CFR</th>
<th>Title</th>
</tr>
</thead>
<tbody>
<tr>
<td>801</td>
<td>Labelling</td>
</tr>
<tr>
<td>803</td>
<td>Medical device reporting</td>
</tr>
<tr>
<td>806</td>
<td>Medical devices; reports of corrections and removals</td>
</tr>
<tr>
<td>807</td>
<td>Establishment registration and device listing for manufacturers and initial importers of devices</td>
</tr>
<tr>
<td>808</td>
<td>Exemptions from federal preemption of state and local medical device requirements</td>
</tr>
<tr>
<td>809</td>
<td>In vitro diagnostic products for human use</td>
</tr>
<tr>
<td>810</td>
<td>Medical device recall authority</td>
</tr>
<tr>
<td>812</td>
<td>Investigational device exemptions</td>
</tr>
<tr>
<td>814</td>
<td>Premarket approval of medical devices</td>
</tr>
<tr>
<td>820</td>
<td>Quality system regulation</td>
</tr>
<tr>
<td>821</td>
<td>Medical device tracking requirements</td>
</tr>
<tr>
<td>822</td>
<td>Post-market surveillance</td>
</tr>
<tr>
<td>830</td>
<td>Unique device identification</td>
</tr>
<tr>
<td>860</td>
<td>Medical device classification procedures</td>
</tr>
<tr>
<td>861</td>
<td>Procedures for performance standards development</td>
</tr>
<tr>
<td>888</td>
<td>Orthopaedic Devices</td>
</tr>
</tbody>
</table>
The major changes brought in by the amendments are as following:

- **Vigilance and Postmarket Surveillance (Articles 84, 85, 86, 87, 88, and 93) / EUDAMED Database (Article 33)**: this brought into a continuous evaluation and improvement cycle with continuous reviews of risk management information, along with the regular update of a public summary of clinical evaluations, safety, and performance (Fig. 7).

- **Role of Economic Operators (Articles 10, 11, 13, 14, 30) and Person Responsible for Regulatory Compliance (Article 15)**: representing a major increase in responsibilities for all stakeholders responsible for the conduct.

- **Scope and Classification of Products (Article 1, 2, 22, 23, e 51, 52, Annex VIII, IX, X, XVI)**: Strict Rules for substance-based devices and devices that use hazardous substances (Classification Rule 21 and Annex I) and New software and apps rules (Classification Rule 11).

- **Changes affecting Notified Bodies – Focusing more the Witness tests and reconciliation activities which are conducted during on-site audits to ensure that the quality management system (QMS) is working efficiently.**

- **Unique Device Identification (UDI)/Implant Card.**

- **Summary of Safety and Clinical Performance (Article 32)** — A detailed record of the safety and clinical performance check for implantable devices and for Class III devices submitted by the manufacturers in a form of summary.

- **Clinical Evaluation / Postmarket Clinical Follow-up, Clinical Investigations (Article 2, Article 55, Article 61, Annex XIV, Annex XV).**

- **Summary of Changes in Safety and Performance Requirements (Annex I)** — Directive’s Essential Requirements
were replaced by Safety and performance Requirements.

Whereas, the market authorization process remains the same as decentralized that is through notified bodies for every regional process.

1.8. Regulations in India

In India, medical devices through a specialized division called, Medical Device and Diagnostics Division, Central Drug Safety and Control Organization (CDSCO), Ministry of Health and Family Welfare is body responsible to overlook the people of India as per the Drugs & Cosmetics Act 1940.

Earlier, Notified Devices, are the only few Medical Devices and Diagnostic kits, which were regulated under Drugs and Cosmetics Act and Rules. Central Licensing Approval Authority (CLAA) with other state authorities and scheme is responsible for the purpose of Manufacture, import, sale and distribution. There is some dissonance since some medical devices were regulated as Drugs under Drugs and Cosmetics Act and Rules but are classified as devices in other countries. Thus system was inconsistent with Harmonized Standards of IMDRF.

Now, with the advent of MEDICAL DEVICES RULES 2017, which was published on 31st January 2017, and came into force since January 1st 2018 [43], some evident changes were made in India’s medical device regulations such as:

Medical devices are classified into four classes based on the risk involved & intended use of the device:

- Class A (low risk)
- Class B (low moderate risk)
- Class C (moderate high risk)
- Class D (high risk) [44]

When Class A and Class B medical devices are considered, State Licensing Authority (SLA) is the competent authority for all matters relating. SLA have the power to enforce the all the regulations regarding the sale, manufacturer, stock, and various other practices related to Class A and Class B medical devices. Class A Medical devices need not be licensed and shall remain self-regulated as per applicable standards and Import and manufacture of Class C and Class D medical devices are reviewed by the responsible Central Licensing Authority (CLA) for providing the required licenses for the. Even, irrespective of the companies intending to manufacture Class C or Class D medical devices or Class A or Class B product, applications should also be sent to the Central Licensing Authority [45-47].

Thus, as per the rules and description mentioned, all of the surgically operated total hip and knee joint replacement devices are considered under the category of either class C or D on the basis of risk to health and the applications are sent to CLA with all the following pre-requisites:

1. General information including the details of the manufacturer or import and product history of the concerned medical device.
2. Site or plant master file including the detailed information of the manufacturing site.
3. Device master file for the specific medical device.
4. Essential principles’ checklist for demonstrating conformity to the essential principles of safety and performance of the medical device [44, 47-49].

All of the processes are needed to be applied through online SUGAM portal along with the challan fees paid and tracked throughout for the purpose of review and Grant of NOC/Permission [50].

Overall, the quality of the product is maintained by following ISO 13485:2016 – Quality management system rules in Europe and India whereas, in the USA, FDA earlier needs to check the quality system Regulation as per 21 CFR Part 820 which with reforms in April, 2019 FDA [51].

After evaluating the current regulatory requirements of all the three legislation a comparative sheet of medical device regulations is prepared (Table 3).

Further, IMDRF elements of conformity assessment and responsibilities are compared for the three regulatory authorities or conformity assessment body (Table 4) [57].
Table 3. Comparative sheet of medical devices regulations in USA, Europe and India.

<table>
<thead>
<tr>
<th>Parameters</th>
<th>International Medical Device Regulatory Forum (IMDRF)</th>
<th>Countries</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Product Classification</strong></td>
<td></td>
<td>UNITED STATES of AMERICA (USA)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Class I – Low Risk</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Class II – Moderate Risk</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Class III – Higher Risk</td>
</tr>
<tr>
<td></td>
<td></td>
<td>United States (USA)</td>
</tr>
<tr>
<td><strong>Applicant Type (Total Joint Replacement Devices – Hip and Knee)</strong></td>
<td>United States (USA)</td>
<td>Class II (Knee); Class III (Hip) – as Prosthetic Device (Sub Part D) under Part 888, Orthopaedic Devices.</td>
</tr>
<tr>
<td><strong>Approval Pathways</strong></td>
<td></td>
<td>510(K) Pre-marketing Notification, PMA - Pre Market Approval, De-Novo - with no Substantial Equivalence with predicate devices.</td>
</tr>
<tr>
<td><strong>Agencies involved</strong></td>
<td></td>
<td>CDRH - Centre for Devices and Radiological Health, Department of Food and Drug Administration (FDA).</td>
</tr>
<tr>
<td><strong>Guidelines Followed</strong></td>
<td></td>
<td>21 CFR Part 800 – 861.</td>
</tr>
</tbody>
</table>

Table 3. contd…
<table>
<thead>
<tr>
<th>Parameters</th>
<th>International Medical Device Regulatory Forum (IMDRF)</th>
<th>Countries</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>UNITED STATES of AMERICA (USA)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Clinical Studies</td>
<td>-</td>
<td>Investigational Device Exemption (IDE), Humanitarian Device Exemptions (HDE).</td>
</tr>
<tr>
<td>Review Period</td>
<td>-</td>
<td>Class I - Only Notification, Class II [510(K)]- 100-150 days, Class III - 180-250 Days, De-Novo - 120 Days.</td>
</tr>
<tr>
<td>Validity of License</td>
<td>-</td>
<td>Indefinite, unless revoked or product recalled.</td>
</tr>
<tr>
<td>Labelling Requirements</td>
<td>-</td>
<td>Annual Establishment Registration is required.</td>
</tr>
<tr>
<td>Data Presentation</td>
<td>Electronic</td>
<td>Electronic</td>
</tr>
<tr>
<td>(Electronic/Paper)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Import Pathway Guideline</td>
<td>-</td>
<td>Import Program – Food and Drug Administration (FDA) [53-55].</td>
</tr>
<tr>
<td>Shelf Life of Products</td>
<td>-</td>
<td>Shelf-life and package testing as per the standard ISO 11607 [56].</td>
</tr>
</tbody>
</table>

Table 3. contd…
<table>
<thead>
<tr>
<th>Parameters</th>
<th>International Medical Device Regulatory Forum (IMDRF)</th>
<th>United States of America (USA)</th>
<th>Europe</th>
<th>India</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grouping Guidelines</td>
<td>-</td>
<td>Under the same product name or approved separately.</td>
<td>Under the same product name or approved separately.</td>
<td>In pursuance of rule 5, of the Medical Devices Rules, 2017- Grouping Guidelines for Medical Devices Applications. - Single - Family - System</td>
</tr>
</tbody>
</table>

Table 4. Conformity assessment elements and responsibility of Regulatory Authority or Conformity Assessment Body.

<table>
<thead>
<tr>
<th>Regulatory Authority or Conformity Assessment Body Responsibility</th>
<th>Conformity Assessment Element</th>
<th>International Medical Device Regulatory Forum (IMDRF)</th>
<th>Class II – 510 K application (USA - FDA)</th>
<th>Class IIb (EUROPE - NB)</th>
<th>Class - C(Knee) and Class - D(Hip) (INDIA - CDSCO)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Quality Management System</td>
<td>Verifies that a current and appropriate QMS is in place or otherwise conducts a QMS audit prior to marketing authorization.</td>
<td>Verifies that a current and appropriate QMS is in place or otherwise conducts a QMS audit prior to marketing authorization – which is done in compliance with ISO 13485:2016.</td>
<td>Verifies that a current and appropriate QMS is in place or otherwise conducts a QMS audit prior to marketing authorization. (Annexure - IX Conformity assessment based on a quality management system and assessment of the technical documentation).</td>
<td>Verifies that a current and appropriate QMS, ISO 13485:2016 is in place or otherwise conducts a QMS audit prior to marketing authorization as per the Fifth Schedule of Medical Devices Rules 2017.</td>
<td></td>
</tr>
<tr>
<td>Post-market Surveillance (PMS)</td>
<td>Satisfies that a current and appropriate adverse event reporting procedure is in place as part of the QMS.</td>
<td>Satisfies that an appropriate adverse event reporting procedure is in place as part of the QMS.</td>
<td>Satisfies that an appropriate adverse event reporting procedure is in place as part of the QMS (Annexure – III, Technical Documentation on PMS).</td>
<td>Satisfies that a current and appropriate adverse event reporting procedure is in place as part of the Seventh Schedule – with requirements for conducting Clinical Trials.</td>
<td></td>
</tr>
<tr>
<td>Registration</td>
<td>Maintains and verifies as appropriate.</td>
<td>Maintains and verifies as appropriate with F &amp; D Act.</td>
<td>Maintains and verifies with New Medical Devices Rules, 2017, to comply by 2020.</td>
<td>Maintains and verifies with updates and recent gazetted amendments by the ministry of Health, India.</td>
<td></td>
</tr>
</tbody>
</table>
Table 5. Country compliance sheet with respect to the IMDRF working item.

<table>
<thead>
<tr>
<th>S. No.</th>
<th>Focus Items of Works</th>
<th>USA</th>
<th>EUROPE</th>
<th>INDIA</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Patient Registries</td>
<td>√</td>
<td>√</td>
<td>X</td>
</tr>
<tr>
<td>2</td>
<td>Software as Medical Devices</td>
<td>√</td>
<td>√</td>
<td>X</td>
</tr>
<tr>
<td>3</td>
<td>Medical Device Single audit Program</td>
<td>√</td>
<td>√</td>
<td>X</td>
</tr>
<tr>
<td>4</td>
<td>IMDRF Recognised Standards</td>
<td>√</td>
<td>√</td>
<td>X</td>
</tr>
<tr>
<td>5</td>
<td>Roadmaps for the Implementation of UDI system</td>
<td>√</td>
<td>√</td>
<td>X</td>
</tr>
<tr>
<td>6</td>
<td>Medical Device Cyber-Security Guide</td>
<td>√</td>
<td>√</td>
<td>X</td>
</tr>
<tr>
<td>7</td>
<td>Medical Device Clinical Evaluation</td>
<td>√</td>
<td>√</td>
<td>X</td>
</tr>
<tr>
<td>8</td>
<td>Unique Device Investigation - Application Guide</td>
<td>√</td>
<td>√</td>
<td>X</td>
</tr>
<tr>
<td>9</td>
<td>Personalized Medical Devices</td>
<td>√</td>
<td>√</td>
<td>X</td>
</tr>
<tr>
<td>10</td>
<td>Standards: Improving the quality of International Medical Device for regulatory Use</td>
<td>√</td>
<td>√</td>
<td>X</td>
</tr>
<tr>
<td>11</td>
<td>Adverse Event Terminology</td>
<td>√</td>
<td>√</td>
<td>X</td>
</tr>
<tr>
<td>12</td>
<td>Regulated Product Submission</td>
<td>√</td>
<td>√</td>
<td>X</td>
</tr>
</tbody>
</table>

On all the working topics of IMDRF, a country-specific compliance sheet is prepared as an assessment to evaluate their readiness for regulatory updates (Table 5).

2. CASE STUDY

2.1. Background

Deputy International Limited (DePuy), a subsidiary of Johnson and Johnson engineered a metal-on-metal (both the prosthetic ball and socket are made of metals- cobalt & chromium) hip replacement device.

The devices were used in more than 93,000 hip replacement surgeries internationally. However, soon there were complaints about complications arising out of the implants. Many patients experienced serious adverse reactions due to metallosis (metal poisoning) and some required revision surgery to replace the ASR implant with another kind. A detailed timeline of the medical device history is presented in Fig. (8).

In case of ASR – Articular Surface Replacement both the ball and sockets are made of metal head with cobalt, chromium and molybdenum as major constituents. The conventional total hip replacement consists of a metal head with a polyethylene cup. But these joints are not durable. Over time the plastic cup wears away against the hard metal head and thus people may require a revision surgery to replace the worn out joint. However, a metal-on metal device (ASR) is more durable and is claimed to provide wide range of motion.

2.2. Root Cause of Recall

Friction between head and the cup causes wear of metal parts which results in tiny particles of metal debris. This metal debris is small enough to enter into the bloodstream. This leads to the metal poisoning with resultant tissue damage, tumour, inflammation and increased requirement of a revision surgery [59].

2.3. Issues Highlighted by the Case

2.3.1. Negligence

According to the observations of the expert committee, the CDSCO renewed J&J’s registration of its ASR products in 2009 without the knowledge of these having been recalled in Australia. This clearly highlights regulatory authority’s negligence on global developments.
2.3.2. Post-Market Follow-Up Studies

- India does not generate adequate local data on the safety of healthcare products once they are marketed and relies heavily on western regulators for signals. The post-market follow-up indicates early signs of a product being defective.

- India launched its Materiovigilance Programme only in 2015, five years after the ASR recall. It has also been alleged that the program has been progressing at a snail’s pace [61].

2.3.3. Definitional Ambiguity and Issue of Compensation

- The manufacturing, import, sale, and distribution of medical devices are regulated under the Drugs & Cosmetic Act and Rules (DCA).

- The Act presumes even a “device” to be a drug. It penalises all those who sell adulterated, spurious or sub-standard drugs. (15 devices are regulated as drugs in India).

- Critics are of the opinion that the definitional ambiguity makes it very difficult to prove that a faulty medical device amounts to a “spurious” or “adulterated” drug and thus hinders patients’ claims for compensation.

2.4. Ethical Issues Concerned

2.4.1. Doctor

Doctors in connivance with the company for monetary gains have compromised the ‘principle of beneficence’, professional integrity, and also have eroded the trust of the people from sacrosanct profession.

2.4.2. Company (Johnson and Johnson)

Absence of professional standards, avoidance of facts, varied conduct (like compensating in US
but not in India), pursuance of profits at the cost of human sufferings.

2.4.3. Government

Ill-conceived policy formulations (leading to uncontrolled globalisation) without taking into account its adverse consequences, weak and inefficient accountability standards at place, ineffective regulatory mechanisms.

2.4.4. Regulatory Authorities

Basic provisions of code of conduct disobeyed owing to carefree attitude, red-tapism, corruption, negligence and non-compassionate attitude towards beneficiaries.

2.4.5. Patients – Right

Right to healthy life, efficient medical care, right to justice and compensation, breach of trust.

2.4.6. Challenges

In order to have quality, comprehensive outcome, and observations made through data available, future legislation will also require a performance estimate within the scope of average patient care. This is supposed to address the problems associated with the Post-Marketing surveillance, and better monitoring systems along with reimbursement policies needed to be kept in mind [62].

In the new era of digitalisation, which is innovation and data-driven leading to a power shift, greater participation is required in the healthcare ecosystem along with some measures to cope up with their regulatory requirements.

This requires a higher level of reliability with regard to conclusions than is necessary for the discussion among experts.

To ensure that the future procedures can actually meet the objectives of safety improvement, a number of issues have to be dealt with:

3. Employee retention/recruiting.
4. Pricing or Profitability issues.
5. Funding/capital/credit/financing [63, 64].

All of the trends together, supported by the demographics implicate the need to focus the loops within the healthcare delivery paradigm from Fee-For-Service (FFS) to value models is expected to lead to fewer bundled payment programs for certain joint replacement and cardiac rehabilitation procedures. However, this indicates the need for value care and pilot programs to accelerate. Ultimately, lower reimbursement rates and reduced procedure volume will likely limit pricing gains for medical devices and equipment [65].

The medical device industry is encountering similar reimbursement issues globally, as the USA, EU and other jurisdictions face increasing healthcare costs, as well. A number of countries have instituted price ceilings on certain medical procedures, which could deflate the reimbursement rates of third-party payers, forcing down product prices [66].

Industry participants are required to report manufacturing costs and medical device reimbursement rates are set potentially below those figures in certain major markets like Germany, France, Japan, Taiwan, Korea, China and Brazil. Whether third-party payers consider certain devices medically reasonable or necessary for operations presents a hurdle that device makers and manufacturers must overcome in bringing their devices to market.

Improved monitoring shall include the product’s entire lifetime, which can de facto only be covered by registers. Indicators for monitoring embrace the whole treatment chain. Revision rate, the most important indicator for arthroplasty, in addition to product quality for example includes: the surgeon’s quality, the patient’s risk profile or general conditions of a healthcare system. Attribution of inferior outcome to a causer will be an essential factor as it defines at which stakeholder improvement measures can be launched. It is expected that this point will be an issue of controversial debate, particularly since responsibilities will be shared in many cases and serious legal and financial consequences may be involved [67].

Inadequate support, limited focus on innovation, unfavourable duty structures, absence of local – Quality Certification, more preference towards the ethical approach and priority to safety, quality
and efficacy combined together with improper monitoring system make the whole process more resource-intensive compared to the healthcare service provider. However, barriers to entry in the existing regulations provide a measure of relief from the competition, especially for newly developed products [45, 68, 69].

CONCLUSION

The study intends to illuminate challenging areas that need to have greater harmonization which is possible, and thus seeks practical solutions for more efficient and effective pathways for product registration.

The hope is that by studying these relationships, a useful framework for policymakers can be designed to better understand regulatory dissonance. This is the first step leading towards the creation of mechanisms to reduce its impact and improve global harmonization of indication-specific medical technologies’ development approaches.

CONSENT FOR PUBLICATION

Not applicable.

STANDARD OF REPORTING

PRISMA guidelines has been followed for this study.

FUNDING

None.

CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

ACKNOWLEDGEMENTS

Declared none.

REFERENCES


[38] Van Drongelen A, Hessels J, Geertsma R. Comparison of market authorization systems of medical devices in USA and Europe 2015; 56


