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Short Communication

Concept of Materiovigilance and Importance in AYUSH

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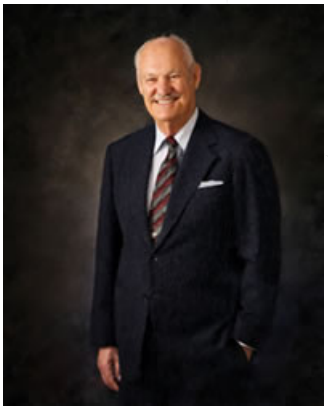
The excerpt of this paper was read as a part of invited lecture during the National Webinar on Pharmacovigilance of Ayurveda Sidhha Unani and Homeopathy (ASU & H) Drugs - AYUSHSURAKSHA 2020 through Online Zoom. It was organized by the Intermediary Pharmacovigilance Centre, National Institute of Unani Medicine, Bangalore and sponsored by the Ministry of AYUSH, Govt. of India, New Delhi on 16.9.2020.

The delivered talk was dedicated to Prof. John Autian (1924-2015), who established "Materials Science, Toxicology Laboratories", University of Tennessee Health Science Center, College of Pharmacy, Tennessee, USA. The Laboratories reached a level of national and international prominence and helped establish new federal regulations on medical devices in USA (Figure 1). In India, he delivered several talks on safety of medical devices during the annual meetings of Indian Pharmacological Society (IPSCON) and Society of Pharmacovigilance, India (SOPICON). He donated some funds to Indian Pharmacological Society for 'John Autian Travel Award' for selected young participants. SoPI in his memory organizes every year 'John Autian Oration' wherein prominent person in the field of Pharmacovigilance is invited to deliver the Oration. Prof. K. C. Singhal, an eminent Indian pharmacologist, was a good friend of Prof. John Autian and invited him in all the above academic activities.



Prof. John Autian

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INTRODUCTION

In the words of John Autian, "a large number of medical, dental, and pharmaceutical advancements have been made with the use of new plastic materials for a host of items and devices, ranging from artificial heart valves to specialized packaging systems for the storage and delivery of medication. A proper program to evaluate the toxicogenic properties of a material to be used in a medical and paramedical application must consider the end use of the device. In general test results are needed which will indicate that no toxic ingredient from a plastic will be released to tissue, the released ingredient will not produce an allergic response, and the released agent will not be teratogenic, mutagenic, or carcinogenic. For those materials that are parts of prosthetic devices that will have long-term contact with tissues and blood, consideration must also be given to the interaction of cellular components with the material. From the various tests employed, a judgment can then be made as to the benefit-to-risk ratio of the specific device or item.[1]

Medical devices vs Medicinal products

WHO has given a very comprehensive definition of medical devices. It defines as, *"Instrument, apparatus, implement, machine, appliance, implant, reagent for in vitro use, software, material or other similar or related article, intended by the manufacturer to be used, alone or in combination, for human beings, for one or more of the specific medical purpose(s) of diagnosis, prevention, monitoring, treatment or alleviation of disease, diagnosis, monitoring, treatment, alleviation of or compensation for an injury, investigation, replacement, modification, or support of the anatomy or of a physiological process, supporting or sustaining life, control of conception, disinfection of medical devices providing information by means of in vitro examination of specimens derived from the human body; and 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."* These medical devices could be simple instruments

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or mechanically complicated. They act by physical, mechanical, or thermal means and vary greatly in complexity and application.

However, medicinal products (also called pharmaceuticals) achieve their principal action by pharmacological, metabolic or immunological means and achieve its purposes through chemical action within or on the body (drug).

Although the use of medical devices benefits the patients immensely, they also carry significant potential risks. There are multiple instances where the device was recalled either due to defect or because of the significant morbidity and mortality it caused in the users.[2-4] Therefore, it is imperative to assess and ascertain the risks and benefits associated with the device at all stages of its development and uses. This can be achieved by a robust monitoring mechanism which at present is followed only in few countries.[5,6]

Post-marketing Surveillance Practice of Medical devices

Recent stride in scientific innovation substantially increased role of medical devices in health-care delivery system. More than one million medical devices are available ranging from simple low-cost bandage or tongue depressor to high cost and complex devices such as MRI machine and medical software application.[7]

Medical Devices Adverse Events (MDAE) reporting compiled by law in many countries. MDAE reporting is similar to that with medicinal products with some differences. Given the inherent difference between medicinal products and medical products, the vigilance of medical devices are also different from that of medicinal products. In contrast to voluntary reporting of AEs with medicinal products, the reporting with medical devices is negligible. MDAE reporting plays only minor role with most medical devices. Vast majority of the reports are related to medical device - defects or failures.

As described above in relation to the contribution of John Autian, US pioneered in postmarketing surveillance of medical devices by enacting FDA Modernization Act 1970 under section 522 for medical devices. Subsequently, other countries like UK, Australia, Canada and EU brought out the laws for effective surveillance of medical devices.[8]

USFDA has proposed mandatory and voluntary scheme of reporting. Medical Device Reporting regulation (21CFR 803) contains mandatory requirements for manufacturers, importer, and user's facilities to report certain adverse events and problems pertaining to use of devices on FDA Med watch form 3500A or electronically (MedWatcher mobile app). There are obligations to report by user-facilities such as hospitals and nursing homes required to report suspected medical device-related deaths to both FDA and the manufacturer (if known), and serious injuries to the FDA or to manufacturer (if unknown).

Similarly, UK Medical Devices Agency is responsible for both vigilance reporting scheme and adverse event scheme for post marketing surveillance of medical devices. Vigilance reporting scheme for manufacturers is mandatory, prescribed timeline for manufacturer to report adverse events failing which levied penalties. Adverse Event Scheme for health-care providers, hospital engineers and patients are voluntary. Health-care professionals obliged to report adverse event and expected to report it immediately.

European regulation on medical devices/ *in vitro* diagnostic medical devices oblige importers and distributors to inform manufacturers, and in certain instances the authorities, of incidents and safety issues with medical devices that have been distributed or imported in European market.

In 1993, initiative was taken to establish Global Harmonization Task Force (GHTF) by EU, USA, Japan, Australia and Canada. The aim of GHTF was to bring uniformity in regulatory system related to safety, performance, and quality of medical devices. In 2011, International Medical Device Regulators Forum (IMDRF) conceived to build on commendable work of GHTF and accelerate medical device regulatory harmonization and convergence.

The classification system was adopted in some countries to stratify the risk of failure with the different classes of devices. These classes of devices typically run on a 1-3 or 1-4 scale (GHTF). Class 1 or 2 being the least likely to cause significant harm with device failure. Example of "low risk" category includes contact lenses, while classes 3 or 4 being the most likely to cause significant harm with device failure (Table 1-4). Example of "high risk" category includes cardiac pacemakers.[9]

Table 1: TGA Classification of medical devices risk

Class	Risk	Examples
Class I	Low risk	Surgical microscopes and examination lights
Class IIa	Low to medium risk	Electrical acupunture and warming blankets
Class IIb	Medium to high risk	Infant incubators and external defibrillatos
Class III	High risk	Heparin-coated catheters and biological heart valves
Class IV	Active implantable MDs	Contraceptive IUD

Table 2: UK-MHRA classification of general medical devices

Class	Risk level	Requirements	Examples
Class I	Low risk	Premarket notification	Dressings
Class IIa	Low-medium risk	Certification by notified body	X-ray film
Class IIb	Medium-high risk	Certification by notified body	Blood bags, contact lens care
Class III	High risk	Certification by notified body	Bone cement, cardiac stents

Table 3: Medical devices are rated by their potential risk from Class I (low) to Active Implantable Medical Device (AIMD, high) - New Zealand Medicines and Medical Devices Safety Authority

AIMD	Risk	Implantable pacemaker
Class III	High	Drug eluting cardiac stents
Class IIb	Medium to High	Ventilators, orthopedic implants
Class IIa	Medium to Low	Hypodermic needles, suction equipment
Class I sterile	Low	Sterile dressings, non-medicated
Class I measuring	Low	Volumetric urine bag
Class I basic	Low	Reusable surgical instruments

Indian Medical Devices Rules 2017

Ministry of Health and Family Welfare, Government of India notified MDR 2017 with the aim to bring in highest degree of professionalism in regulating medical devices. According to MDR, devices are classified based on degree of risk associated:

Table 4: Classification of Indian Medical Devices

Class	Risk level	Examples
Class A	Low risk	
Class B	Low-moderate risk	
Class C	Moderate-high risk	
Class D	High risk	

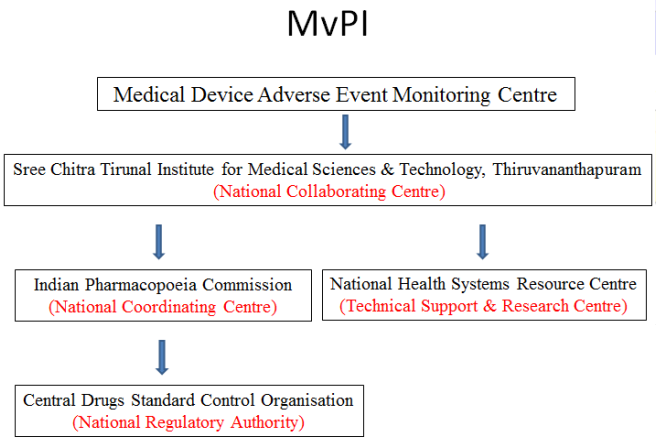
Adverse Events Reporting

The post-marketing surveillance of medical devices has been initiated in many countries, but still not as developed and robust as that of medicines. The manufacturers of medical devices required to meet risk proportionate regulatory requirements that specified in the Rules based on best international practices. As per MDR, G.S.R. 78, Chapter 4, Section 26 (ii), adverse events reporting associated with medical devices to relevant authority is mandatory and all license holders shall inform the State Licensing Authority or Central Licensing Authority, as the case may be, of the occurrence of any suspected unexpected serious adverse events and take necessary action thereon including any recall within 15 days of such event coming to the notice of License Holder.

AiMeD is an Umbrella Association of Indian Manufacturers of Medical Devices.

Materiovigilance Programme of India

The reporting to authorities and surveillance system is a grave concern. Besides the Medical Devices Rules 2017, in order to promote the culture of adverse events reporting, the Ministry of Health and Family Welfare, Government of India, approved the commencement of Materiovigilance Programme of India (MvPI) on 6 July 2015. The main aim is to monitor and assure the safety of MDs used in Indian population. Following is the structure of MvPI:



Materiovigilance refers to close monitoring of any undesirable occurrences resulting from the use of medical devices by means of having a system in place which comprises identifying, collecting, reporting, and estimating undesirable occurrences and reacting to them, or safety corrective actions after their postmarketing phase.[10,11]

Role & Responsibilities of Different Units of MvPI

MDMC collect and review completeness of MDAE, analyze failure mode effect, assess causality as per SOP, and send monthly consolidated report to NCC. As per guidance documents, 10 medical colleges are identified as MDMC. NCC receives adverse event report from MDMC and collates, analyze and perform signal detection and communicate outcome to NCC. NCC is also involved in conducting awareness program, training, and workshop on materiovigilance periodically at various zones of the country.

SCTIMST, Thiruvananthapuram functions as NCC. The main responsibility of IPC which functions as MvPI-NCC is to coordinate with all stakeholders by convening steering committee and working group meetings, to recognize new MDMCs across country, to prepare and disseminate SOP, guidance documents, training manual, and newsletter and to formulate data received from SCTIMST and recommend to the CDSCO for appropriate action.

DGCI-CDSCO: Its role is to formulate regulatory decisions and communicate to different stakeholders. As regulator, it is also incumbent upon CDSCO to join IMDRF and other international forums for exchange of postmarketing safety information. National Health System Resource Centre MoHFW, GoI, New Delhi, functions as TSRC and provide technical support to NCC for preparation of SOP, guidance documents, newsletters, and training manuals. It also helps in identifying new MDMC (12).

Objectives of MvPI

1) To track and monitor MDAE
2) To create awareness & communicate among different stakeholders mainly health-care professionals about importance of MDAE reporting & minimize risk
3) To create and recommend best practices and interventions to improve nationwide system for patient safety monitoring
4) To analyze risk–benefit ratio of MDs uses
5) To generate independent credible evidence-based data on safety of MDs
6) To emerge as a national center of excellence for Materiovigilance activities
7) To support CDSCO in decision-making process on use of MDs
8) To collaborate with other healthcare organizations and international agencies for exchange of information and data management

Goal of MvPI

- To initially enroll 10 medical colleges across four parts of India (MDMCs)
- To encourage voluntary reporting
- To expand the program to all private & public health-care delivery system
- To develop e-reporting system
- To make the reporting mandatory for device manufacturers and health-care providers

MDAEs Monitoring Centers

In order to facilitate adverse events reporting from the region, a structured programmatic approach was made by recognizing medical colleges/hospitals/other related institutions as MDMCs across the country. MDMCs are primarily responsible for monitoring and reporting adverse events within hospital to MvPI. MDMCs assigns these responsibilities to Clinician or Pharmacologist or Biomedical engineer or other healthcare professionals as Coordinator or Deputy Coordinator. MDMCs is also responsible for education and advocacy on promoting concept of MvPI as well as creating culture of adverse events reporting and to customize medical devices adverse events reporting form readily available at MDMCs. This form featured with adequate information related to the event.[13]

Concept of Materiovigilance in AYUSH

Although it is thought that it is a modern concept of monitoring and safety of medical devices, which is known Materiovigilance, however there are strong documented proof in AYUSH System of medicine. Only the need is to explore and bring forth the concept.

Devices / Equipments Used in Preparing Traditional Medicine

Kharal (Mortar and Pestle), *Hawan Dasta* (Hand-grinder) and *Sil Batta* (Grindstone) are used for making medicinal powder (Figure

2). These instruments are very critical to make compounded medicinal products into powder form (*Safoof)* as fine as possible for making medicines such as *Ma'jun*, *Khamira*, *Jawarish*, *Sharbat*, pills, etc. Mortar and pestle are made of different materials such as stone, quartz, wood, iron, brass, steel and porcelain. The stones are either of hard or soft in nature like *Sang Simaq* (Simaq Stone), *Sang Khara* (Granite Stone), *Sang Siyah* (Black Stone), *Sang Marmar* (Marble Stone) and *Sang Yashab* (Jasper Stone).[14]

Figure 2: Mortar & Pestle of different stones

Mortar and Pestle (Different Types)

In Unani Pharmacy (Saidla), if a mortar and pestle of soft stone is used for grinding hard stone-based medicines (*Hajariyat*) and jewel-based medicines (*Jawaharat*), then chances of contamination with fine pieces of soft-stones more and consequently increases the weight of powder. This is sort of adulteration of prepared drug.

Case Study: if an original weight of hard stone-based medicine was 25 grams, then after grinding by using soft stone mortar, the weight would increase the powder to 26 gm. This extra weight of one gram of soft stone is added with medicine. The extra ingredient of stone may be harmful and may lead to toxicity and mortality. So, while making powder of hard medicine, grind it by using hard stone mortar and pestle, similarly, making powder of soft medicines, there is no harm if grinded by using soft black and marble stones.

Metallic Medicinal Bowls (Magical Bowls) are often used for drug administration to enhance drug efficacy (Figure 3).. It could be religious or cultural. Different medicines are still prepared in different metallic utensils. These utensils need frequent polishing and die-casting to avoid direct contact of medicines with metal and eventually metal poisoning.

Figure 3: Metallic Medicinal Bowls (Magical Bowls)

There is a need of coordinated system of identification, collection, reporting, and analysis of any untoward occurrences associated with the use of medical devices used in AYUSH and protection of patient's health by preventing its recurrences.

Medical devices used in AYUSH need to be monitored like Modern Medical Devices. All types of adverse events related to medical devices needs to be reported. For example:

- known or unknown
- serious or non-serious
- frequent or rare
- malfunction
- deterioration in characteristics or performance
- inaccuracy in labeling or instructions

There may be modified reporting format for AYUSH medical devices as prepared by MvPI. Duly signed form can be sent to the nearest MDMC or directly to the NCC. A scanned copy of the same could be mailed as provided by NCC-PvPI. There is a need of separate helpline number as created by NCC-PvPI for documenting and reporting adverse events due to the device and finally a seamless flow of information involving various aspects and interrelationship among different stakeholders.

MvPI could empowers AYUSH hospitals/healthcare professionals other than MDMCs to participate and report MDAEs through customized paper-based reporting form (available on www.ipc.gov.in). Consumers or patients should be encouraged to report adverse events (if any) via toll free helpline i.e. 1800 180 3024. In addition, AYUSH medical devices manufacturer (cf. AiMeD), importers, etc, should be encouraged to report MDAEs or problems to MvPI. They need to inform MvPI about devices alert/recall/field safety corrective action, etc. This would also help MvPI in base line study and prompt decision making.

Suttigai Salaagai and Hijama

Thermal Cauterization (*Suttigai Salaagai*) is prepared and practiced according to Siddha text (Figure 4). If the same procedure is faulty through instrumentation, it would lead to adverse event. Similarly, there are lots of cupping (Hijama) instruments (Figure 5) used in Unani Medicine and if the same procedure is faulty through instrumentation, it would lead to adverse event.

Figure 4: *Suttigai Salaagai*

Figure 5: *Hijama* Instruments: Rubber, Glass, Cattle Horn, Bamboo (Extent at the museum of Ibn Sina Academy, Aligarh, India)

Kshar Sutra

Kshar Sutra treatment is very safe and effective if done carefully and under guidance. However, its painful if there is some procedural error in some cases. It may lead to post-surgery complications, recurrence, bleeding, pain and infection. The same procedure is harmful in grade 4 hemorrhoids and dangerous if a person is not aware.

Table 5: Proposed model of Classification of medical devices in AYUSH (Also see Figure 6)

Class	Risk level	Examples
Class A	Low risk	PPE, bandages, gloves, manual grinding instruments (mortar pestle), rubber cups in Hijama, *Shirodhara* Table
Class B	Low-moderate risk	Cupping instruments (singhi, glass / bamboo cups), Ayurveda Yantra, Electrical acupunture, warming blankets
Class C	Moderate-high risk	Kshar Sutra (a medicated cotton thread coated with Ayurvedic medicines), Moxibustion (consists of burning dried mugwort on particular points on the body)
Class D	High risk	*Suttigai Salaagai,* Needles in acupuncture (Bundestien German Needle)

Figure 6: Ayush surgical Instruments as described in Table 5

CONCLUSION

There is an upsurge in use of medical devices in recent years. No adequate measures are taken to protect patients from untoward occurrences associated with use of medical devices. MvPI is meant to analyze, scrutinize and prevent recurrence of harmful effects due to use of medical devices.

MvPI initiative and effective implementation is to ensure safety of medical devices among device users by preventing recurrence of adverse effects and reducing risk associated with use of medical devices.

The guidance document of MvPI is laid down policy guidelines, procedures and enunciated role and responsibilities of different stakeholders to enable safety data collection in systematic manner. The existing systems MvPI or PvPI are developed for synthetic medical devices and medicines and require some modifications to address specific differences for AYUSH. The COVID-19 pandemic unveiled huge challenges and risks to health workers globally and hence working in stressful environments makes health workers more prone to diagnostic errors which can lead to patient harm.

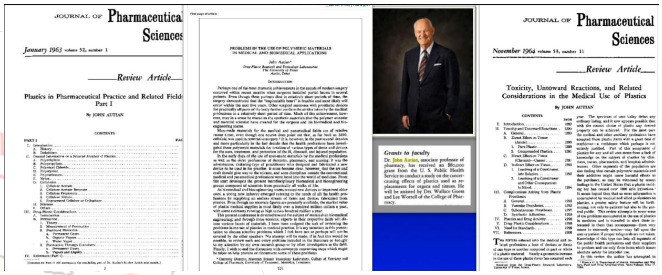


Figure 1: Collage of historical papers contributed by John Autian on medical devices

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