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EDITORIAL

Manoj K. Singh
Founding Partner

We are pleased to present this Vol. II Issue VIII of *S&A – Pharma Newsletter*. Through this Newsletter, we aim to share new or pertinent regulatory information on pharmaceutical sector within India as well as from foreign jurisdictions, based on information collated through research and appraisal of applicable statutory provisions.

In the present issue, we start with a discussion on the cognizance taken by the Ministry of Health and Family Welfare on banning the import of oxytocin and restricting its manufacturing, sales and distribution in the country apart from CDSCO's preparatory note directing State/UT regulators to sensitize respective inspectorate staff to keep strict vigil on oxytocin supply and distribution in order to curb its misuse. Going forward, this edition addresses the Health Ministry's new draft policy for Hemoglobinopathies (Thalassemia, Sickle Cell Disease and variant Hemoglobins), which covers the prevention strategy, affordable treatment measures, and empower prospective parents to exercise their right not to have a child with a serious genetic disorder and protects the rights of an affected child to have access to optimal care. The issue then, covers the MvPI's draft Guidance on Medical Devices, which is meant to provide necessary information to all the stakeholders of the country regarding the regulatory requirements, quality management systems and standards required to be followed for medical devices.

From the international arena, we talk about recent global survey reports concerning various health issues and the progress on improving health in countries. First, we discuss European Union's work programme for the next two years to better address potential problems with medicines' supply and to avoid shortages in European Union, This work programme lists out actions for regulators and industry alike to ensure the availability of medicines for the benefit of patients in the EU, and covers centrally and nationally authorized products, both for human and veterinary medicines. This article is followed by a write-up on US FDA approval to Onpattro (patisiran) infusion, which is the first FDA-approved treatment for patients with polyneuropathy caused by hATTR, a rare, debilitating and often fatal genetic disease characterized by the buildup of abnormal amyloid protein in peripheral nerves, the heart and other organs.

We wrap up this issue with US FDA's new scientific recommendations encouraging widespread innovation and development of novel medication-assisted treatment drugs for the treatment of opioid use disorder.

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Trust you enjoy reading this issue as well. Please feel free to send your valuable inputs / comments at newsletter@singhassociates.in

Thank you.

Contributors to the current issue:
Mr. Manoj K. Singh
Ms. Vijaylaxmi Rathore

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SINGH & ASSOCIATES
ADVOCATES & SOLICITORS

NEW DELHI
E-337, East of Kailash
New Delhi - 110065 INDIA

GURUGRAM
7th Floor, ABW Tower, MG Service Road
Sector 25, IFFCO Chowk, Gurugram
Haryana-122001 INDIA

MUMBAI
Unit No. 48 & 49, 4th Floor, Bajaj Bhavan,
Barrister Rajni Patel Marg, Nariman Point,
Mumbai, Maharashtra - 400021, INDIA

BENGALURU
N-304, North Block, Manipal Centre,
47, Dickenson Road
Bengaluru - 560042, INDIA

Ph : +91-11-46667000
Fax : +91-11-46667001

Email: india@singhassociates.in
Website: www.singhassociates.in

www.singhassociates.in

Managing Editor
Manoj K. Singh

Published by
Singh & Associates
Advocates and Solicitors

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Oxytocin will not be sold at retail medical shop any more

Oxytocin is a neuro-hormone and neurotransmitter normally produced by the paraventricular nucleus of the hypothalamus and is released in large amounts by the posterior pituitary gland in mammals. Oxytocin is known to induce contractions of the uterus during labour, and stimulate the ejection of milk during breastfeeding. It is also known as love-hormone as it plays a role in the female reproductive functions including sexual activity, child birth, maternal nurturing behavior along with general psychological stability. However, over time people started misusing Oxytocin by resorting to its unprescribed and frequent use for benefit/profit, for example –milch cattle are regularly injected with Oxytocin twice a day just five minutes prior to milking, for faster milk flow from the udder.

With a Central Government order banning the import of oxytocin and restricting its manufacturing, sales and distribution in the country from 1st September 2018, the Central Drug Standard Control Organization (CDSCO), as a preparatory action, has directed all its State/UT regulators to sensitize their inspectorate staff to keep a strict vigil and ensure that oxytocin is not manufactured/sold illegally to prevent its misuse in dairy and agriculture products[1].

Further, the zonal/sub zonal offices and all port offices are also directed to keep strict vigilance and ensure that oxytocin in any form/name is not imported in the country[2]. In continuance, CDSCO has asked all its State/UT regulators, zonal/sub zonal offices, and all port offices to submit action taken report in this regard to Head Quarter (CDSCO) on a quarterly basis for further necessary action.

Oxytocin, a lifesaving drug, will be regulated in the following manner after 1st September 2018:

1. Oxytocin shall not be imported in any form/any name in the country.
2. Manufacturing of Oxytocin formulations for domestic use shall be restricted to public sector companies like Karnataka Antibiotics & Pharmaceuticals Limited (KAPL) only.
3. Manufacturing of Oxytocin formulations for export purposes shall be open to both public and private sector companies.
4. Manufacturers of Active Pharmaceutical Ingredient (API) of Oxytocin shall supply the API only to the public sector manufacturers if formulations are meant for domestic use, and manufacturers may supply API to both public and private sector in case oxytocin formulations is meant for export purposes.
5. Distribution/supply of oxytocin formulations meant for domestic consumption, to be to the registered hospitals and clinics in public and private sector directly by the manufacturer. The manufacturers can also supply the formulations to the retail outlets specified by the Central Government like - Pradhan Mantri Bhartiya Janaushadhi Pariyojana(PMBJP) and Affordable Medicines and Reliable Implants for Treatment (AMRIT) etc.
6. Oxytocin in any form or name shall not be allowed to be sold through retail chemists.

The Health Ministry on August 06, 2018, held a video conference with the States/UTs on various issues relating to regulation of Oxytocin including the status of preparedness of the State Governments for implementing the amended rules in regard to manufacture, distribution and sale of Oxytocin. The video conference also assessed

1 http://cdsco.nic.in/writereaddata/Strict%20regulatory%20actions%20to%20prevent%20illegal%20manufacturing%20state.pdf

2 http://cdsco.nic.in/writereaddata/Strict%20regulatory%20actions%20to%20prevent%20illegal%20manufacturingall%20port.pdf

the stock of Oxytocin in the States to ensure that there is no shortage after restricted manufacturing and sale, through Karnataka Antibiotics & Pharmaceuticals Limited (KAPL), comes into effect from September 01, 2018.

The States have been advised to assess their requirement of the drug and to place the orders with KAPL in time or in advance for bulk procurement. The Government also asked the States to mount an awareness campaign about the government notification on restricting the manufacture and sale of Oxytocin to KAPL and asked KAPL Ltd to ensure a robust supply chain to prevent any stock outs.

KAPL on this, requested the states to place their orders in advance for bulk procurement. KAPL assured that they have the required manufacturing capacity. KAPL also assured maintenance of adequate quality of the drugs. It also assured that it shall be revising its bulk purchase pricing[3].

Apart from this, the Central Government also proposes to re-classify Oxytocin and assign it to schedule H1 of Drugs and Cosmetics Rules, 1945, as against its current placement in schedule H. Schedule H1 allows chemists to check the indiscriminate use of oxytocin in the country, and also enables them to maintain the data of the customer/prescriber for at least 3 years[4].

Note - The Delhi High Court, on August 31, 2018, suspended this ban till October 2018 while the court hears petitions opposing the ban on manufacturing, sale and distribution of oxytocin by private pharma companies.

Conclusion

The Health Ministry's order to restrict the sale of oxytocin formulation via retail chemist is seems vague, as in other way ministry proposing oxytocin under schedule H1empower chemist to control its indiscriminate use and to maintain prescriber consumer data for certain period.

3 http://pib.nic.in/newsite/PrintRelease.aspx?relid=181581

4 http://www.egazette.nic.in/WriteReadData/2018/188442.pdf

Health Ministry releases new draft policy on prevention and control of Hemoglobinopathies for public consultations

On August 07, 2018, the Ministry of Health and Family Welfare (MoHFW) released the new draft policy for Hemoglobinopathies (Thalassemia, Sickle Cell Disease and variant Hemoglobins) in India[5].

Thalassemia, and Sickle Cell diseases are two common genetic disorders that are chronic, life restricting and require long and specialized treatment. India has the largest number of children with Thalassemia major in the world – about 150,000. There are almost 42 million carriers of β- thalassemia trait, and about 10,000 to 15,000 babies with β-thalassemia major are born each year.. Hb E is variant hemoglobin that significantly contributes to the disease burden of hemoglobinopathies. The prevalence of sickle cell disease is variable, with very high percentage in many tribal communities. For sickle cell disease there are about 25, 00, 000 carriers of the gene (Hemoglobin AS), and about 1, 25,000 patients of sickle cell disease.

About Hemoglobinopathies

Hemoglobinopathies are genetic disorders with Mendelian pattern of inheritance. Genes are, therefore, the primary determinants of the disease with environmental, nutritional and infectious factors playing only a limited modifying role at best. Hemoglobinopathies are disorders with autosomal recessive inheritance and thus, have equal prevalence in males and females. Every person carries two copies of a gene, one inherited from each parent. In autosomal recessive disorders, parents are carriers. They are individuals with only one abnormal gene, the other being normal; while in the patients both copies of the gene are abnormal. Thalassemia major, Thalassemia intermedia, Sickle cell disease and Hb E, occurring singly or in combination, are the major clinical syndromes causing socio economic burden of - hemoglobinopathies in India.

Challenges in developing a plan for treatment and prevention of Hemoglobinopathies in India.

The epidemiological data is incomplete, and the precise burden of these disorders is unknown. Treatment consists mainly of giving repeated blood transfusions, bringing with it the challenges of motivating donors to give blood, and avoiding the transmission of infections such as HIV, hepatitis B and C. The excess iron that gets into the body through the blood transfusions needs to be removed by use of the expensive chelators. Bone marrow transplant as a curative treatment requires a HLA matched donor, specific infrastructure and trained doctors and nurses. The physicians need specialized training to treat the affected patients, as well as monitor and manage the complications of therapy. Treating sickle cell disease is equally challenging, especially as patients are often living in remote areas, and have poor socio-economic status. The management of pain and vaso-occlusive crises is difficult.

Recognizing the great socio-economic burden of these disorders, the government constituted a technical committee comprising of experts and representatives of parent organizations to formulate a policy on hemoglobinopathies, which aimed at informing and providing broad guidance on prevention and management of these disorders. The policy encompasses the public health goal by providing:

1. Affordable and quality care treatment to all patients with Hemoglobinopathies (affected population), and

2. Reduce the prevalence of hemoglobinopathies through carrier screening and prenatal diagnosis

5 https://mohfw.gov.in/sites/default/files/drft%20policy.pdf

1. Affordable and quality care treatment to all patients with Hemoglobinopathies

- Strengthening treatment centres in Central Government institutions and States in all districts to provide access to affordable and quality services for the management of patients with Thalassemia major by regular and safe blood transfusions and iron chelation therapy; treatment for Sickle Cell Disease with penicillin prophylaxis, immunizations and hydroxyurea, monitor for early detection of any complications, and for their optimal management to prevent morbidity and mortality.
- Setting up National/Regional Centres of Excellence as referral and training centres for hemoglobinopathies.
- Strengthening facilities for separation of blood components and blood storage.
- Initiation of newborn screening for Sickle Cell Disease where required, and institute prophylactic antibiotic therapy to improve survival rates and reduce morbidity.
- Establishing facilities for bone marrow transplants in tertiary care institutions.
- Setting-up of central Hematopoietic Stem Cell donor registry, to facilitate bone marrow transplants in, appropriately identified, patients lacking sibling donors. .

2. Reduce the prevalence of hemoglobinopathies through carrier screening and prenatal diagnosis

- Extensive awareness and education programmes in the community, schools and colleges.
- Inclusion of basic knowledge about genetics, inheritance and prevention of thalassemia major and sickle cell diseases in the school curriculum.
- Strengthening laboratories at the District level for facilitating and supporting screening and diagnosis of carriers, including extended family members of patients with thalassemia and sickle cell.
- Screening for carrier status of β-thalassemia, HbS and HbE in adolescent students in schools and colleges, to empower them to make informed decisions regarding marital and reproductive choices in future.
- Screening of pregnant women, preferably in the first trimester, for carrier status, and for those who test positive, screen their husbands and enable the at-risk couples to avail services for prenatal diagnosis to prevent the birth of an affected child.
- Strengthening facilities for prenatal diagnosis in Medical Colleges and selected tertiary care hospitals in the State.
- Screening of new born children for early detection of sickle cell disease and provide appropriate intervention followed up by counselling of families.
- Cascade screening of blood relatives of those affected with thalassemia major or sickle cell disease, as well as screen subjects in high risk communities.
- In the rural areas, 'Ashas' are envisaged to be trained to identify subjects with severe anemia which could be likely to be due to thalassemia major or sickle cell disease and counsel such patient to enable contact multipurpose worker (Female) for referral to the primary health centre for further testing and confirmation.

Research and innovation in the area of hemoglobinopathies

The policy advocates promoting research to develop innovative treatments for thalassemia major and sickle cell disease, and devise new diagnostic methods, keeping in mind the continuously evolving technology in this field. The policy also suggests requirement of international collaboration, as many countries in the West have been running successful control programs and treatment centers for hemoglobinopathies for several years. India has much to gain from their experience, so that mutual collaborations and discussions would be extremely useful for the success of the program in India. Thalassaemia International Federation (TIF) expertise may be used.

Additional aspects of treatment related issues that need to be implemented

The Policy advocates for provision of medicines, including iron chelating agents, hydroxyurea, leukocyte filters and infusion pumps free of cost to the poor patients. In line with 'Make in India' initiative, the policy advocates for promotion of manufacture of the equipment and chemicals in India, including waiver of GST and custom duties to reduce cost of treatment for the affected families The policy recommends setting up of a patient registry for thalassemia and sickle cell disease to obtain information on the number of persons affected and the number of carriers to estimate patients who require various services.

Note – This policy on hemoglobinopathies covers the prevention strategy, and empowers prospective parents to exercise their right not to have a child with a serious genetic disorder, and protects the rights of an affected child to have access to optimal care. The policy also advocates promoting research to develop innovative treatments for thalassemia major and sickle cell disease, and devise new diagnostic methods, keeping in mind the continuously evolving technology in this field.

Materiovigilance Programme of India (MvPI) issues Draft Guidance on Medical Devices

The medical device segment in India, considered Asia's fourth largest market worth approximately USD 5.5 billion and expanding at a steady pace, presents an exciting business landscape and opportunities for both domestic as well as international manufacturers/entrepreneurs. At present, India's medical device sector is dominated by multinational companies, which is evident from the fact that India relies on imports of medical devices (about 75-80% of the sales are generated by imported medical devices) for supply to its healthcare system. Over the years, many multi-nationals have set up operations in India.

On August 06, 2018, the Indian Pharmacopoeia Commission (IPC), the National Coordinating Centre (NCC) of Materiovigilance Programme of India (MvPI) released Draft Guidance Document for Medical Devices[6] to provide necessary information to all the stakeholders of the country regarding the regulatory requirements, quality management systems and standards required to be followed for medical devices. The new draft includes standards for medical devices as a Guidance Document for the benefit of the general public, patients and healthcare professionals. It will also serve as a reference manual for the licensing authority in the matters relating to medical devices. The guideline also describes post-market requirements for medical devices.

However, the nature of majority of the operations in India is to only distribute imported devices and provide support function. From this view, the purpose of this document:

- Aims to be informative in nature on medical device standards comprehensively, irrespective of usage i.e. whether on human beings and animals. Preparation of standards on medical devices nationally and internationally is an ongoing process, irrespective of regulation on same by National/State Medical Devices Regulator.
- Provide guidance to assist manufacturers, traders/distributors, importers, clinical establishments, healthcare professionals and general public on nationally-recognized medical devices standards and other regulatory requirements concerning medical devices in India.
- Serves as ready reference for medical devices standards preparation/adoptions, clinical care quality bodies, nomenclature of medical devices, claims on medical devices and validation mechanism, existence of multiple regulatory bodies on medical devices and law (ACT) directly governing medical devices in India.

Medical device Regulation in India

The Central Drugs Standard Control Organization (CDSCO) under Directorate General of Health Services in Ministry of Health and Family Welfare (MoHFW), Government of India (GoI), is the National Regulatory Authority (NRA) responsible for approval of manufacturing, import, conduct of clinical trials, laying down standards, sale and distribution of medical devices through enforcement and implementation of the Medical Devices Rules, 2017, released dated 31st January 2017 by the MoHFW. As NRA, CDSCO has the responsibility to conduct MvPI wherein, Indian Pharmacopoeia Commission functions as NCC for MvPI. MvPI is meant to enable safety data collection in a systematic manner so that regulatory decisions and recommendations on safe use of medical devices being used in India can be based on data generated here. The programme is meant to monitor medical device-associated adverse events (MDAE), create awareness among healthcare professionals about the importance of MDAE reporting in India and to monitor the benefit-risk profile of medical devices.

6 http://ipc.gov.in/images/mvpi/Guidance_Document.pdf

The draft guidance for medical device covers the regulatory approval process, classifications and grouping methodology, quality management system, labelling requirements including post marketing surveillance as draft highlights described below:

Classification of medical devices

The draft guidance describes the basic principles and parameters involved in classification of medical devices & in vitro diagnostic medical devices (hereafter referred as IVD medical device) based on the below facts:

- Classification of Medical devices based on the risk parameters as described, namely: (i) Low risk - Class A; (ii) Low moderate risk- Class B; (iii) Moderate high risk- Class C; (iv) High risk- Class D.
- Classification of Medical devices and in-vitro diagnostic medical devices based on the intended use of the device and other parameters, where the basic principle like – Medical Device's intended purpose of use, intended to be used in combination with another device, software which drives a device or influences the use of a device, and intended to be used solely or principally in a specific part of the body are considered. Moreover, the various parameters like- invasive, non-invasive, surgically invasive and implantable nature along with the medical devices incorporating medicinal products shall also be considered during classification of devices.

However, the draft also lists medical devices and IVD medical devices class wise for reference purposes.

The essential principles of medical devices

This guidance document describes fundamental design and manufacturing requirements, referred to as "Essential Principles for Safety and Performance" that, when met, indicate a medical device including IVD medical device is safe and performs to its specification. The design and manufacturing requirements in this document are grouped in categories. This section will allow manufacturers to select the design and manufacturing requirements relevant to a particular medical device, and documenting the reasons for excluding the others.

Quality management system

This is for notified medical devices and IVD medical devices (fifth schedule of Medical Devices Rules 2017) where specific requirements for a quality management system shall be used by the manufacturer for the design and development, manufacture, packaging, labelling, testing, installation and servicing of medical devices and in-vitro diagnostics. If the manufacturer does not carry out design and development activity, the same shall be recorded in the quality management system. The manufacturer shall maintain conformity with this Schedule to reflect the exclusions.

The quality management system shall be applicable to manufacturers of finished devices, In vitro diagnostics, mechanical contraceptives (condoms, intrauterine devices and tubal rings), surgical dressings, surgical bandages, surgical staplers, surgical sutures and ligatures, blood and blood components collection bags with or without anticoagulants intended for human or animal use.

Regulatory approval process of Medical Devices in India

The guidance document describes the detailed process of registration and regulatory approval for manufacture for sale/distribution of medical devices and import of medical devices. This guidance also comprises the list of application forms and required documents and fee payable for license, permission and registration certificate to manufacture or import of medical devices. The draft also cites the audit fee payable to notified bodies registered with CDSCO to carry out audit of manufacturing sites under provisions of Medical Devices Rules, 2017.

Guidance on grouping of medical devices for product registration

The guidance explains the grouping of Medical Devices for a person who applies for license to import or manufacture for sale or distribution, sell, stock or offer for sale or distribution of medical devices as specified under respective forms to the Medical Devices Rules, 2017. The applicant may group medical devices having same or similar intended uses or commonality of technology and submit in a single application. The grouping of medical devices is for the purpose of submission of single application for license to import or manufacture in the following manner:

- **Single:** A single medical device is a medical device sold as a distinct packaged entity and does not meet the criteria for family, IVD test kit, system, IVD cluster or a group. It may be sold in a range of package sizes. For example - Condoms sold in package of 3, 10 or 16, can be licensed as single medical device applications.
- **Family:** A medical device family is a collection of medical devices and each medical device is from same license holder, is of same risk classification class, has a common intended use, has the same design and manufacturing process, and have variations that are within the scope of the permissible variants. For example - Condoms that differ in colour, size and texture but are manufactured from the same material and manufacturing process and share a common intended purpose can be licensed as a Family.
- **In vitro diagnostics Test Kit:** An in-vitro diagnostics kit is a device that consists of reagents or articles which are from same license holder; intended to be used in combination to complete a specific intended purpose; sold under single proprietary test kit name; and compatible when used as a test kit. For example - Human Immunodeficiency Virus (HIV) Enzyme Linked Immunosorbent Assay (ELISA) Test Kit may contain controls, calibrators, and washing buffers. All the reagents and articles are used together to detect HIV and therefore, can be licensed as Test Kit. These reagents and articles can be supplied separately as replacement items for that particular Test Kit.
- **System:** Medical devices comprise a system, when they are from same license holder; intended to be used in combination to complete a common intended purpose; compatible when used as system; and sold under single proprietary system name. for example - a glucose monitoring system comprising of a glucose meter, test strips, control solutions and linearity solutions can be licensed as a System.
- **In vitro diagnostics cluster:** An in-vitro diagnostics cluster comprises of a number of in-vitro diagnostics reagents or articles which are from same license holder; of a common methodology; sold under single proprietary name; and compatible when used as a Test Kit.
- **Group:** A medical device Group is a collection of two or more medical devices, supplied in a single package by same license holder, which are sold under single proprietary Group name and for a common intended purpose. For example - A first aid kit consisting of medical devices such as bandages, gauzes, drapes and thermometers, when assembled together as one package, can be licensed as a Group.

Labelling of medical devices and IVD medical devices

The guidance provides the labelling instructions of medical devices which are to be printed in indelible ink on the label, on the shelf pack of the medical device or on the outer cover of the medical device and on every outer covering in which the medical device is packed, in case of small sized medical devices on which information cannot be printed legibly, shall include the information necessary for product identification and safety. Special instructions are required if:

- **Exemption of labelling requirements for export of medical devices:** the labelling exemption of such device is intentional, to follow the specific requirements of law of the country to which the device is to be

exported. However, the particulars like name of the device, the distinctive batch number or lot number or serial number, date of expiry, if any, the name and address of manufacturer, internationally recognized symbols in lieu of text, wherever required shall be adopted to meet the specific requirements of law of the country to which the device is to be exported.

- **Unique device identification of the medical device:** With effect from 1st January 2022, a medical device, approved for manufacture for sale or distribution or import, shall bear unique device identification which shall contain device identifier and production identifier.

Labelling medical device or a new in-vitro diagnostic medical device for purpose of test, evaluation, clinical investigations shall be kept in containers bearing labels, indicating the name of the product or code number, batch or lot number, serial number wherever applicable, date of manufacture, use before date, storage conditions, name and address of the manufacturer, and the purpose for which it has been manufactured.

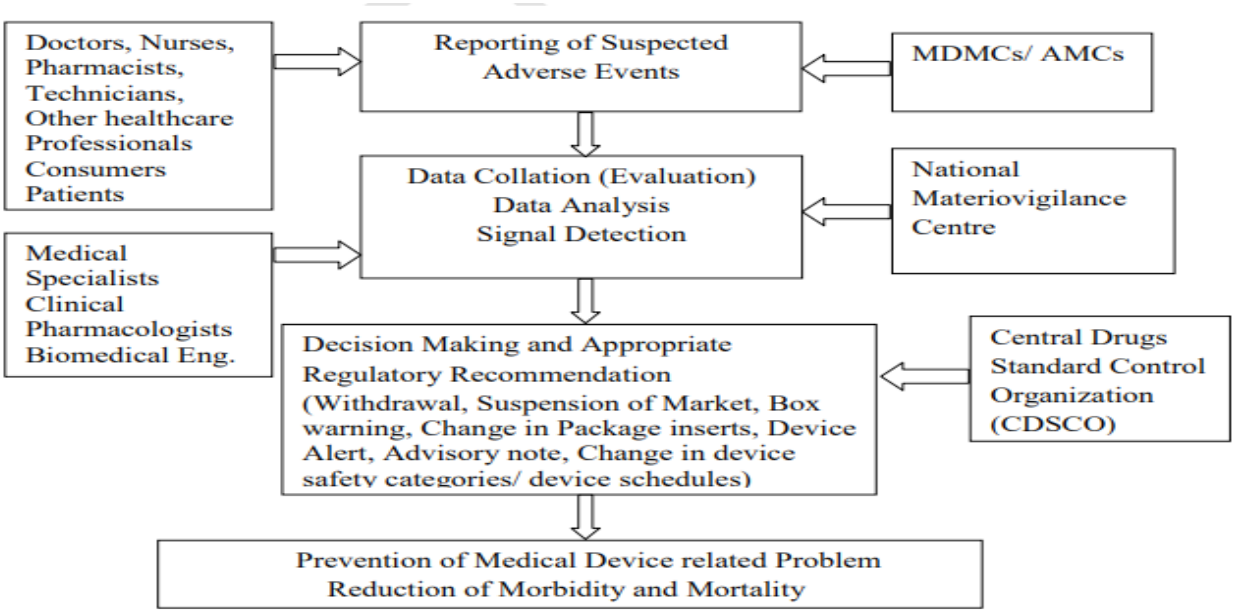
Post market vigilance and safety requirements

MvPI has been approved since July 2015, which has Indian Pharmacopoeia Commission, Ghaziabad as the NCC for the Post market vigilance of medical devices. Presently, MvPI has 10 dedicated functional Medical Device Adverse Event Monitoring Centers (MDMCs) all over the country. All the Adverse Drugs Reaction Monitoring Centres (AMCs) under Pharmacovigilance Programme of India (PvPI) have also been entrusted to report adverse events due to the use of medical devices.
Scope of MvPI is to:

- Create a nation-wide system for patient safety monitoring.
- Analyze the benefit-risk ratio of medical devices.
- Generate evidence-based information on safety of medical devices.
- Support CDSCO in the decision-making process on use of medical devices.
- Communicate the safety information on use of medical devices to various stakeholders to minimise the risk.
- Emerge as a national centre of excellence for Materiovigilance activities.
- Collaborate with other healthcare organizations for exchange of information and data management.

The adverse event reporting system of MvPI is described below[7]:

7 http://ipc.gov.in/images/mvpi/Guidance_Document.pdf



Note - Guidance document for Medical Devices is neither a regulatory nor a legal document. This document has been framed on the basis of Medical Device Rules 2017, issued by Government of India. If there are any errors or omissions found in this guidance document, readers are advised to refer to original Medical Device Rules 2017. The information contained in this document should not be a substitute for Medical Device Rules 2017.

European Union publishes work programme for improving the availability of medicines in the EU

On August 29, 2018, the task force set up by European Union (EU) regulators to better address potential problems with medicines' supply and to avoid shortages has published its work programme for the coming years 2018/20[8]. Improving the availability of human and veterinary medicines authorized in the EU is a key priority of the EU Network. The work programme lists actions for regulators and industry alike to ensure the availability of medicines for the benefit of patients in the EU. The work programme covers centrally and nationally authorised products, both for human and veterinary medicines, in the following cases:

- when medicines are authorised but not marketed (or no longer marketed);
- when medicines authorised and marketed are affected by supply-chain disruptions that directly affect their availability. Such disruptions may occur due to problems with good manufacturing practice (GMP), good clinical practice (GCP), good distribution practice (GDP) or quality defects.

The task force is a working group which has been set up by the European Medicines Agency (EMA) and the Heads of Medicines Agencies (HMA), with representatives from the European Commission and interested national competent authorities, the chairs of the Co-ordination Group for Mutual Recognition and Decentralised Procedures – Human (CMDh) and Veterinary (CMDv), the GMP/GDP Inspectors Working Group, the Working Group of Communication Professionals (WGCP) and the European Surveillance Strategy Working Group (ESS WG).
The task force will develop and coordinate actions for better prevention, identification, management of and communication on issues that can affect the availability of medicines, in order to improve continuity of supply of human and veterinary medicines across Europe. Details about groups and agreed actions are:

- Thematic working group 1 - Marketing authorisations: This group looks at ways to minimise supply disruptions and avoid shortages by facilitating authorisation and marketing of medicines using the existing regulatory framework.
- Thematic working group 2 - Supply chain disruptions: This group focuses on strategies to improve prevention and management of shortages caused by disruptions in the supply chain.
- Thematic working group 3 – Communication: This group focuses on improving timely access to up-to-date information on availability issues, for all actors within the network as well as users of medicines. The group looks at ways to enhance interactions and communication with stakeholders as well as improving collection and sharing of information between regulatory authorities and pharmaceutical industry.

Key priorities of the task force include:

- looking at ways to minimise supply disruptions and avoid shortages by facilitating approval and marketing of medicines using the existing regulatory framework (e.g. using work sharing and reduced timetables when possible);
- developing strategies to improve prevention and management of shortages caused by disruptions in the supply chain (e.g. developing guidance for companies on reporting of shortages);
- encouraging best practices within industry to prevent shortages;

8 http://www.ema.europa.eu/docs/en_GB/document_library/Work_programme/2018/08/WC500254439.pdf

- improving sharing of information and best practices among EU regulatory authorities to better coordinate actions across the EU;
- fostering collaboration with stakeholders and enhancing communication of supply problems to EU citizens[9].

Note - The task force will organize a multi-stakeholder workshop on 8-9 November 2018, to gather stakeholders' perspectives on how to address availability issues and to include their input into the deliverables of the task force. It will bring together all stakeholders impacted, including patients, consumers, healthcare professionals, industry, wholesalers/distributors, parallel distributors, academia and regulators.

9 http://www.ema.europa.eu/ema/index.jsp?curl=pages/news_and_events/news/2018/08/news_detail_003007.jsp&mid=WC0b01ac058004d5c1

USFDA approval to Onpattro; first targeted therapy to treat polyneuropathy

The U.S. Food and Drug Administration has approved Onpattro (patisiran) infusion for the treatment of peripheral nerve disease (polyneuropathy) caused by hereditary transthyretin-mediated amyloidosis (hATTR) in adult patients[10]. This is the first FDA-approved treatment for patients with polyneuropathy caused by hATTR, a rare, debilitating and often fatal genetic disease characterized by the build-up of abnormal amyloid protein in peripheral nerves, heart and other organs. It is also the first FDA approval of a new class of drugs called small interfering ribonucleic acid (siRNA) treatment.

The efficacy of Onpattro was shown in a clinical trial involving 225 patients, 148 of whom were randomly assigned to receive an Onpattro infusion once every three weeks for 18 months, and 77 of whom were randomly assigned to receive a placebo infusion at the same frequency. The patients who received Onpattro had better outcomes on measures of polyneuropathy including muscle strength, sensation (pain, temperature, and numbness), reflexes and autonomic symptoms (blood pressure, heart rate, digestion) compared to those receiving the placebo infusions. Onpattro-treated patients also scored better on assessments of walking, nutritional status and the ability to perform activities of daily living.

Approval of Onpattro was granted to Alnylam Pharmaceuticals, Inc. The FDA granted this application Fast Track, Priority Review and Breakthrough Therapy designations. Onpattro also received Orphan Drug designation.

About siRNA (Onpattro)[11]

RNA acts as a messenger within the body's cells, carrying instructions from DNA for controlling the synthesis of proteins. RNA interference is a process that occurs naturally within our cells to block how certain genes are expressed. Since its discovery in 1998, scientists have used RNA interference as a tool to investigate gene function and its involvement in health and disease. Researchers at the National Institutes of Health, for example, have used robotic technologies to introduce siRNAs into human cells to individually turn off nearly 22,000 genes. This new class of drugs, called siRNAs, work by silencing a portion of RNA involved in causing the disease. More specifically, Onpattro encases the siRNA into a lipid nanoparticle to deliver the drug directly into the liver, in an infusion treatment, to alter or halt the production of disease-causing proteins.

Onpattro is designed to interfere with RNA production of an abnormal form of the protein transthyretin (TTR). By preventing the production of TTR, the drug can help reduce the accumulation of amyloid deposits in peripheral nerves, improving symptoms and helping patients better manage the condition.

About hereditary transthyretin-mediated amyloidosis (hATTR)

Affecting about 50,000 people worldwide, hATTR is a rare condition. It is characterized by the build-up of abnormal deposits of protein fibers called amyloid in organs and tissues in the body, interfering with their normal functioning. These protein deposits most frequently occur in the peripheral nervous system, which can result in a loss of sensation, pain, or immobility in the arms, legs, hands and feet. Amyloid deposits can also affect the functioning of the heart, kidneys, eyes and gastrointestinal tract. Treatment options have generally focused on symptom management.

10 https://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm616518.htm

11 http://investors.alnylam.com/news-releases/news-release-details/alnylam-announces-first-ever-fda-approval-rnai-therapeutic

USFDA outlines new ways to encourage the development of novel medicines for the treatment of opioid use disorder

Draft guidance contains Nonbinding Recommendations for public consultations

On August 06, 2018, the U.S. Food and Drug Administration issued new scientific recommendations[12] aimed at encouraging widespread innovation and development of novel medication-assisted treatment (MAT) drugs for the treatment of opioid use disorder (OUD). The new draft guidance outlines new ways for drug developers to consider measuring and demonstrating the effectiveness and benefits of new or existing MAT products.

About MAT

MAT for opioid dependence relies on prescription drugs, including buprenorphine, methadone and naltrexone, to stabilize brain chemistry, reduce or block the euphoric effects of opioids, relieve physiological cravings, and normalize body functions. Regular adherence to MAT helps patients gain control over their use of opioids, without causing the cycle of highs and lows associated with opioid misuse or abuse. MAT, coupled with relevant social, medical and psychological services, is a highly effective treatment for OUD. Additionally, patients receiving MAT cut their risk of death from all causes in half, according to the Substance Abuse and Mental Health Services Administration.

New scientific recommendations

Clinical trials to evaluate effectiveness of MAT for the purpose of FDA approval have generally used reduction in drug-taking behavior (drug use patterns) as an endpoint. The draft guidance identifies several additional potential clinical endpoints and other outcome measures that drug developers may consider, for example:

1. Adverse Outcomes of OUD

Reductions in adverse outcomes related to OUD are desirable endpoints for a study. However, to show effects on physical or psychosocial consequences of opioid abuse, trials may need to study a large number of patients for a long period of time. This may make such studies impractical to support initial marketing approval. Nevertheless, FDA encourages sponsors to evaluate the effect of medications in development for OUD on various adverse outcomes like:

- Mortality (overall mortality or overdose mortality)
- Need for emergency medical interventions
- Hepatitis C seroconversion (the period during which antibodies develop and become detectable).

2. Change in Disease Status Using Diagnostic Criteria for OUD

Efficacy may also be measured by studying the proportion of patients who transition from meeting criteria for being diagnosed with moderate to severe OUD – based on both drug use and its impact on patient wellbeing – at baseline to being considered in remission at the end of the study.

3. Patient-Reported Outcomes

Improvements in the ability to resume work, school, or other productive activity may also demonstrate clinical benefit. Using input from patients and family members to determine the relevant symptoms/experiences

12 https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM615743.pdf

associated with OUD, the sponsor could develop an instrument to evaluate a direct effect on how patients feel or function (e.g., improvement in sleep or mood).

4. Change in Drug Use Pattern

Change in drug use pattern is the most commonly used endpoint in registration trials for drugs-in-development to treat OUD. Sponsors have used it successfully to provide support of efficacy for all approved products for the treatment of OUD. They use a variety of approaches to evaluate drug use patterns. FDA recommends that sponsors compare percent of responders, rather than group means. One method is to define a responder as a patient who reduces the use of opioids to or below a threshold known to be associated with clinical benefit. A successful trial would show either a higher percent of responders in the treatment arm (for superiority trials) or non-inferiority in the percent of responders (for active-controlled trials).

Other Outcome Measures

FDA is interested in other outcome measures that sponsors might use to demonstrate clinical benefit of medications for the treatment of OUD. There is great societal interest in assessing additional, clinically meaningful, endpoints such as reduction in hospitalizations, emergency department visits, overdose, and death as well as improvements in the ability to resume work, school, or other productive activity.

While understanding that many of these outcomes could be highly valuable, the agency recognizes that evaluating them could require larger trials than those usually conducted for marketing approval. To that end, the FDA is encouraging sponsors to discuss their plans with the agency early in the drug development process. The agency is also committed to providing assistance to sponsors interested in developing a validated measurement of patient-reported experiences, such as "craving" or "urge to use" opioids, which make it difficult for patients with OUD to sustain recovery. Patient-reported experiences could be used to complement other endpoints and help determine how a new treatment's effects on such experiences support the goal of sustained clinical response.

Note- This new draft guidance is part of the FDA's ongoing commitment to promote more widespread development, access to and adoption of MAT. As part of HHS' Five-Point Strategy to Combat the Opioid Crisis, the FDA remains committed to addressing the epidemic on all fronts, with a significant focus on decreasing exposure to opioids and preventing new addiction by taking new steps to encourage appropriate prescribing, supporting the treatment of those with OUD and promoting the development of improved as well as lower cost forms of MAT, fostering the development of novel pain treatment therapies that may not be as addictive as opioids, and opioids more resistant to abuse and misuse.

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SINGH & ASSOCIATES

FOUNDER MANOJ K SINGH

ADVOCATES & SOLICITORS

NEW DELHI
E-337, East of Kailash
New Delhi-110065, INDIA

GURUGRAM
7th Floor, ABW Tower, MG Service Road
Sector 25, IFFCO Chowk, Gurugram
Haryana-122001, INDIA

MUMBAI
Unit No. 48 & 49, 4th Floor
Bajaj Bhavan, Nariman Point
Mumbai - 400021, INDIA

BENGALURU
N-304, North Block, Manipal Centre
47, Dickenson Road
Bengaluru - 560042, INDIA

india@singhassociates.in
www.singhassociates.in