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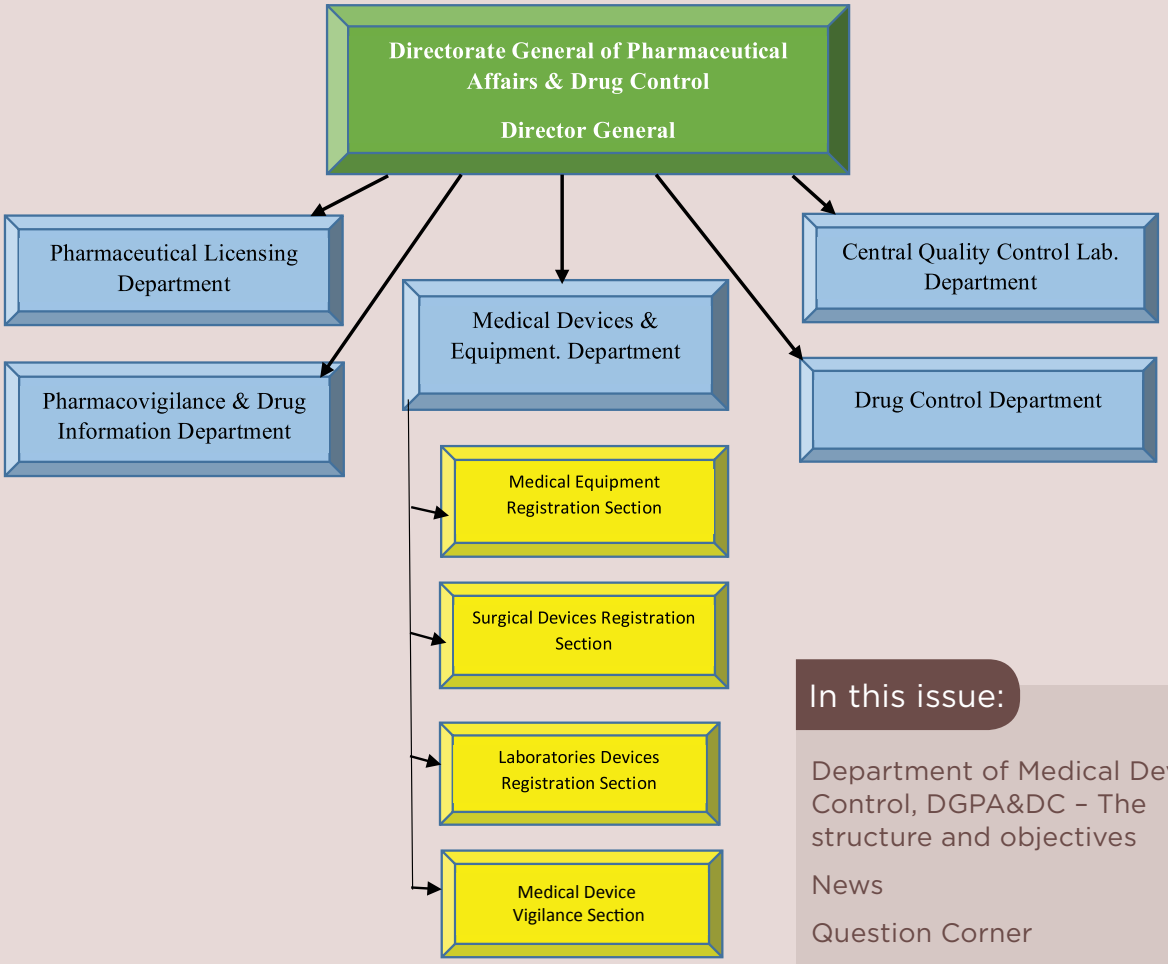
DIRECTORATE GENERAL OF PHARMACEUTICAL AFFAIRS & DRUG CONTROL (DGPA&DC)

PHARMACEUTICAL NEWSLETTER

Department of Medical Device Control, DGPA&DC – The structure and objectives:

Eng. Faiza Al Zadjali – Director of Medical Devices Control Department

Department of Medical Device Control, was added to the structure of the DGPA&DC in the year 2015, as mandated under the pharmaceutical establishment's law 35/2015. The department has 4 sections under it, which are: Medical Device Registration section, In vitro Diagnostics registration section, surgical devices section and Medical Device Vigilance section as illustrated in the figure below.



In this issue:

The main objective of the department is regulation of medical devices, which are available, and those, which are imported to the Sultanate of Oman. The measures for control of medical devices are required for pre-market, on market and post market.

It is vital here to define the term Medical device as the capacity of inclusion of the types and categories that are coming under the terminology may not be clear. A medical device is defined according to WHO and other global regulatory authorities as any 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.

  Note: Products which may be considered to be medical devices in some jurisdictions but not in others include:

- disinfection substances,
- aids for persons with disabilities,
- devices incorporating animal and/or human tissues,
- devices for in-vitro fertilization or assisted reproduction technologies

This illustrates the diversity and complexity of the medical device regulation as it includes a variety of areas. Ranging from simple cotton balls to the most complicated Magnetic Resonance Imaging machines, come in purview of medical device regulation. In addition, devices which are used for cosmetics purposes, in Vitro fertilization and contact lenses are listed under the act of medical device regulation in many countries.

The global medical device nomenclature agency has identified more than 16 categories for which medical device can be categorized, which are:

- Hospital hardware
- In vitro diagnostic devices
- Non-active implantable devices
- Ophthalmic and optical devices
- Reusable devices
- Single-use devices
- Assistive products for persons with disability
- Diagnostic and therapeutic radiation devices
- complementary therapy devices
- Biologically-derived devices
- Healthcare facility products and adaptations
- Laboratory equipment
- Medical software
- procedure packs
- other categories

Furthermore, Medical devices are classified according to their risks differently around the world, the classes are: as illustrated in the figure below:

- low risk
- low to medium
- medium to high
- high risk

Classification according to EU	Asian classification & IMDRF	US FDA Classification	Remark	example
Class 1	A	1	Low risk	Tongue depressors , wheel chairs, bandages
Class 2a	B	2	Medium to low risk	Infusion device , Blood Pressure monitors, single use catheters, contact lenses
Class 2b	C	2	Medium to high risk	Defibrillators , orthopedic implants , ventilators, external defibrillators
Class 3	D	3	High risk	Implantable Pacemakers , IUD , heart valve, absorbable sutures, stents

As stated earlier, regulation has parts that will enable control of the medical devices. According to WHO the basic level of Regulation in these parts will cover the topics according to the figure below: (From WHO model framework).

These phases are addressing the lifecycle of a medical device from design and manufacturing to the use and disposal. Regulation will take care of all three components of control throughout the lifecycle of a device.

Basic level controls and enforcement

Premarket	Placing on the market	Postmarket
• Publish law, including definition, and regulations with transition period • Establish medical device classification for regulatory purposes • Establish Essential Principles of safety and performance • Establish basis for reliance and recognition • Establish requirements for declaration of conformity • Establish requirement for manufacturers for a QMS • Establish requirements for labels and labelling • Prohibit deceptive, misleading and false advertising • Establish provisions for exceptional premarket situations	• Registration of establishments • Listing of medical devices • Import controls	• Establish a system for vigilance reporting • Require mandatory notification by the manufacturer of field safety corrective actions • Establish a procedure to withdraw unsafe medical devices from the market • Establish procedure to issue safety alerts to users • Undertake market surveillance

The department has a great deal of responsibilities and a great ambition to have good control on the medical device lifecycle to enable the provision of safe and quality made medical devices available to the public. As regulation of medicine is well established in the sultanate, Medical device regulation is taking the initial measures for its inception in the drafting of the bylaws which has reached its final stages of revision. The bylaws will cover pre market controls, on market controls and post market controls. Regulation will be gradually applied to accommodate the new changes and allow for the existing establishments to understand and develop the sense of regulation in this field.

Ministry of health has taken this very important step for the establishment of the department of medical device and for building capacities for the team, and placed it under the Directorate General of Pharmaceutical Affairs and Drug Control.

NEWS

Statement by FDA Commissioner Scott Gottlieb, M.D., on the importance of conducting proper research to prove safe and effective medical uses for the active chemicals in marijuana and its components

Over the past decade, we've seen a growing interest in the development of therapies derived from marijuana and its components. Proponents of "medical marijuana" advertised its uses for a wide number of medical conditions, such as cancer, multiple sclerosis, post-traumatic stress disorder and anxiety – just to name a few of the touted conditions. The FDA has been supportive of research in this area for many years. But marijuana is a Schedule I compound with known risks. Research to demonstrate that marijuana or its components could be safe and effective in the treatment of medical disorders should be held to the same standard as other drug compounds. And certainly it should not be held to a lower standard, as some proponents would suggest. The FDA has an active program to assist drug developers who want to investigate marijuana or its components through properly controlled clinical trials, to demonstrate the potential for safe and effective uses.

The FDA approved a purified form of the drug cannabidiol (CBD). This is one of more than 80 active chemicals in marijuana. The new product was approved to treat seizures associated with two rare, severe forms of epilepsy in patients two years of age and older.

This product approval demonstrates that advancing sound scientific research to investigate ingredients derived from marijuana can lead to important therapies. This new treatment provides new options for patients.

This is an important medical advance. But it's also important to note that this is not an approval of marijuana or all of its components. This is the approval of one specific CBD medication for a specific use. And it was based on well-controlled clinical trials evaluating the use of this compound in the treatment of a specific condition. Moreover, this is a purified form of CBD. It's being delivered to patients in a reliable dosage form and through a reproducible route of delivery to ensure that patients derive the anticipated benefits. This is how sound medical science is advanced.

This research process – from early development through preclinical and clinical research – gives us a comprehensive understanding of a new drug. That includes an understanding of whether the new product is safe and effective for treating a particular medical condition, what the proper dosage is and for what populations it is safe and effective, how the new compound could interact with other drugs, or whether the new drug has side effects or other safety concerns.

The FDA has taken several specific steps to support this research.

Drugs derived from marijuana also are eligible for several programs that are intended to facilitate and expedite development and review of new drugs that address unmet medical needs in the treatment of serious or life-threatening conditions.

The FDA will continue to support rigorous scientific research on potential medical treatments using marijuana and its components that seek to be developed through the

appropriate scientific channels. However, we remain concerned about the proliferation and illegal marketing of unapproved CBD-containing products with unproven medical claims.

The FDA, an agency within the U.S. Department of Health and Human Services, protects the public health by assuring the safety, effectiveness, and security of human and veterinary drugs, vaccines and other biological products for human use, and medical devices. The agency also is responsible for the safety and security of our nation's food supply, cosmetics, dietary supplements, products that give off electronic radiation, and for regulating tobacco products.

FDA approves novel preventive treatment for migraine

The U.S. Food and Drug Administration approved Aimovig (erenumab-aooe) for the preventive treatment of migraine in adults. The treatment is given by once-monthly self-injections. Aimovig is the first FDA-approved preventive migraine treatment in a new class of drugs that work by blocking the activity of calcitonin gene-related peptide, a molecule that is involved in migraine attacks.

"Aimovig provides patients with a novel option for reducing the number of days with migraine," said Eric Bastings, M.D., deputy director of the Division of Neurology Products in the FDA's Center for Drug Evaluation and Research. Patients often describe migraine headache pain as an intense pulsing or throbbing pain in one area of the head. Additional symptoms include nausea and/or vomiting and sensitivity to light and sound. Approximately one-third of affected individuals can predict the onset of a migraine because it is preceded by an aura – transient sensory or visual disturbances that appear as flashing lights, zig-zag lines or a temporary loss of vision. People with migraine tend to have recurring attacks triggered by a number of different factors, including stress, hormonal changes, bright or flashing lights, lack of food or sleep and diet. Migraine is three times more common in women than in men and affects more than 10 percent of people worldwide.

The effectiveness of Aimovig for the preventive treatment of migraine was evaluated in three clinical trials. The first study included 955 participants with a history of episodic migraine and compared Aimovig to placebo. Over the course of six months, Aimovig-treated patients experienced, on average, one to two fewer monthly migraine days than those on placebo. The second study included 577 patients with a history of episodic migraine and compared Aimovig to placebo. Over the course of three months, Aimovig-treated patients experienced, on average, one fewer migraine day per month than those on placebo. The third study evaluated 667 patients with a history of chronic migraine and compared Aimovig to placebo. In that study, over the course of three months, patients treated with Aimovig experienced, on average, 2 ½ fewer monthly migraine days than those receiving placebo.

The most common side effects that patients in the clinical trials reported were injection site reactions and constipation.

The FDA approved a drug that treats opioid addiction that isn't addictive itself

The Food and Drug Administration (FDA) gave final approval for a drug shown to mitigate the symptoms associated with opioid withdrawal. It's not the first treatment designed to help those

with opioid addiction, but it has a distinguishing feature: It's the first one that isn't an opioid itself, and has no addictive component.

Medications exist now to assist those trying to break their addiction to pain medications, but all of those are opioids themselves, given in gradually lower doses to mitigate the symptoms associated with addiction and withdrawal. But the problem with this is that some patients remain addicted to and dependant on opioids in the long term, even if the drugs they're receiving come under a doctor's guidance and at a much lower dose. The idea behind the newly approved medication Lucemyra is to treat those same symptoms without including an addictive component.

The active ingredients in the pill bind to cell receptors in the body that lower the production of norepinephrine. This hormone works as part of the body's fight-or-flight response, working in concert with adrenaline to increase the blood pressure, heart rate, and alertness when necessary.

While researchers don't completely understand the mechanisms involved, they believe the fight-or-flight response, also known as the autonomic nervous system, plays a key role in the development of the classical symptoms of opioid withdrawal—which include nausea, anxiety and agitation, increased heart rate, severe aches and pains, and sleeping problems. The two clinical trials (which included a total of 866 adults) that enabled Lucemyra's approval showed the drug worked to lessen the severity of those symptoms.

This new drug offers doctors a way to help severely addicted patients without switching them to another opioid, but it remains to be seen how it will fit into the existing medical toolbox.

Ref.: https://www.fda.gov

EU authorities take further action in ongoing review of sartans

Zheijiang Huahai placed under increased supervision; Aurobindo Pharma stopped from supplying irbesartan to the EU.

EU authorities are placing the Chinese company Zheijiang Huahai under increased supervision following European and US inspections which revealed weaknesses in quality management at the company's Chuannan site in Linhai, China. The inspection findings included deficiencies in the way the company investigated impurities in its valsartan products and led EU authorities to issue a statement of non-compliance with Good Manufacturing Practice (GMP), prohibiting the use of its valsartan in EU medicines. This latest action means that EU authorities will supervise the manufacture of other active substances produced by Zhejiang Huahai more closely. Authorities will monitor corrective measures being implemented by the company on a regular basis and increase the frequency of inspections of the site. In addition, marketing authorisation holders for EU medicines will be required to perform additional tests on all active substances supplied by Zhejiang Huahai. In July 2018, the detection of impurities – N-nitrosodimethylamine (NDMA) and N-nitrosodiethylamine (NDEA) – in valsartan from Zhejiang Huahai led to an EU-wide review of all valsartan medicines. The review was subsequently extended to other 'sartan' medicines when very low levels of NDEA were found in losartan made by Hetero Labs in India. Both NDMA and NDEA, which have not been found in any of Zheijiang Huahai's other products, are classified as probable human carcinogens (substances that could cause cancers). A preliminary risk assessment for NDMA in valsartan indicated that the lifetime risk of cancer is low.

Aurobindo Pharma stopped from supplying irbesartan to the EU.

Low levels of NDEA have now also been found in a third sartan, irbesartan, made by another Indian company, Aurobindo Pharma. On 8 October 2018, the European Directorate for the Quality of Medicines & HealthCare (EDQM) suspended Aurobindo Pharma's CEP effectively stopping the supply in the EU of medicines containing irbesartan from this company.

National authorities in the EU are currently considering whether to recall medicines containing Aurobindo Pharma's irbesartan from pharmacies as a precaution. The review into the presence of impurities in sartans and their potential effects in patients is ongoing. EMA will continue working with national authorities, international partners and EDQM and will provide updates as more information becomes available.

Ref. https://www.ema.europa.en

QUESTION & ANSWER

A 55 year old man experiencing heart burn for approximately 2 to 3 weeks, who came for advice from a community Pharmacist. What are the possible advices he/she can give him?

The Community Pharmacist need to make enquiries about the life style of the patient, and his medication history to look out for any triggers which could result in the heart burn, triggers could be his life style, or any purchased or prescribed medicines which are known to cause dyspepsia or heart burn, as many people experience gastric disturbances while they are on NSAIDs. The pain of esophageal spasm may resemble angina- like pain associated with ischemic heart disease. However, in ischemic heart disease, pain is usually associated with exercise and radiates to the arm and neck. He may be advised for a cardiovascular assessment if the pain and symptoms are so severe enough to impair his quality of life, to be referred for initial work up to a primary care Physician. Immediate relief from symptoms may be achieved with simple antacids which should be taken after meals.

Heart burn is a characteristic symptom of gastro esophageal reflux disease (GERD/ GORD) caused by prolonged contact of refluxed stomach contents with esophageal mucosa. Prolonged relaxation or reduced tone of the lower esophageal sphincter and increased gastric pressure are physiological variables which affect the period of time the esophageal mucosa is exposed to acid and pepsin. Certain foods, posture and medicines can affect the variables and contribute to the development of GERD. Foods with high fat content delay gastric emptying, and eating large meals at night places pressure on the lower esophageal sphincter as well as causing post prandial fullness, discomfort and bloating and belching. Eating within a couple of hours of going to bed increases the risk of refluxing stomach contents, when lying down. Wearing tight clothes and excess weight add further pressure on the stomach. Alcohol and smoking also could be a trigger for gastritis and lower the esophageal sphincter pressure. The patients should be advised on life style modifications, stressing the importance of eating smaller meals more often and reducing the fat content in the diet, losing weight, and avoiding smoking or use of alcohol.

Ref. Text book of Clinical Pharmacy Therapeutics, Edited by Roger Walker & Cate Whittlesea, Churchill Liv ingstone, Elsevier.

DGPA&DC ACTIVITIES

The 1st Medical Device Regulatory Workshop

The Ministry of Health, represented by the DGPADC organized the first Medical Devices Regulatory workshop at the Levatio Hotel Muscat, on 7th November 2018. It was held under the patronage of H.E. Dr. Mohammed bin Saif Al-Hosni, MOH Undersecretary for Health Affairs in the presence of H.E. Dr. Akjemal Magtymova, Representative of the WHO to the Sultanate.

The workshop gathered around 100 participants working in manufacturing, importing and selling the medical devices and equipment. (Engineers, Pharmacists, Technicians, Nurses). Dr. Nazeeh Al Othmany, WHO Consultant for Medical Devices along with a number of lecturers gave lectures about the relevant applicable global regulations. The lecturers touched on unifying efforts against counterfeit medical devices, the Global Medical Device Nomenclature System (GMDN) and effective quality management systems in the areas of medical devices manufacturing, safety and efficacy. Engr. Faiza Al Zadjali, Director of Medical Device Control, elaborated on the medical device regulations in Oman.

The workshop aimed at activating the Equipment and Medical Devices Control Department (EMDCD) which was developed recently in the new DGPADC structure. The EMDCD is concerned with all steps of accreditation and registration of all medical devices and equipment, as well as its trading and monitoring at all steps including manufacturing, marketing, during and post marketing according to the international standards.

The third Arab Food, Medicine and Medical device Conference

The conference was held at Sharm El Sheikh, Egypt, during 15-17 April 2018, with an aim to demonstrate the importance of governance and legislation, regulations and to ensure safety and security for food, medicine and medical devices and improve their monitoring in the Arab region.

Conference deliberations included successful experiences from Arab countries in the three sectors, applications of nanotechnology in food,

medicine and medical devices, Arabian efforts to comply with international regulations. Other topics included, clinical studies, accessibility and availability, vigilance, drug tracing, anti-fraud, conformity of medical device etc.

The Director General Dr. Mohamed Hamdan Al Rubaie, and the director of the Medical Devices Control Department, Eng. Faiza Al Zadjali participated in the conference.

Good Inspection Practices of Pharmaceutical Establishment:

DGPA&DC in collaboration with the Science Forum for Research Studies & Consultancy, carried out a two days training course about the Good Inspection Practices of Pharmaceutical Establishment (8 – 9 July 2018; Muscat Holiday Inn). The course was attended by the pharmacists and assistant pharmacist in the Directorate of Pharmaceutical Care & Drug Stores in the different governorates, who are involved in the inspection of pharmaceutical establishments in their regions. It's main

objective was to upgrade and develop their competency in the inspection area, as well as building their technical and scientific capabilities.

The main speaker for the two-day course was Pharmacist Rehab Jarar, Expert of Pharmacies, Stores, and Non-pharmaceutical Establishment Control and Inspection, Jordan Food and Drugs Administration (JFDA) who has wide experience in the field of inspection.

Lean Management Training Course

In collaboration with the Training Department in the Directorate General for Human Resources Development, a training session in Lean Management was held for 22 staff from DGPA&DC. The main objective of the training is to continuously improve the work process, purposes, and the personnel. The trained staff will use the learned tools to overcome challenges faced and find the proper solutions, using the available resources.

ISoP 2nd Middle east chapter training

Ph. Hussain Al Ramimmy, Director of Pharmacovigilance, attended the International Society for Pharmacovigilance (ISoP) Middle East chapter training, 18-19 April 2018 in Dubai. The training was made with an objective to make the participants get insight in planning and preparation for Pharmacovigilance inspection, know the processes for safety and risk communications and learn the good Pharmacovigilance from regulatory perspective.

The 3rd Global harmonization of bioequivalence requirements

The Theme of this conference, which held in May 2018 in ACDIMA, Jordan is the regulatory aspects related to bioequivalence and the objective is to discuss current international trends and updates in bioequivalence assessment, biowaivers, bioanalytics, dissolution and procedures. Dr. Nabila Al Lawati – Director of the Central Quality Control Laboratory participated in the conference. It provided a forum for pharmaceutical scientists from academia, industry and regulatory agencies to have open discussions on selected BE issues in the hope of identifying common ground and arriving at a harmonized view on these topics.

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20th International Pharmacovigilance Training Course 2018, UMC- Uppsala (Sweden)

Ms. Alia Suleiman Al Salehi, was chosen this year from Department of Pharmacovigilance & Drug Information to attend the 20th International Pharmacovigilance Training Course 2018, UMC-Uppsala (Sweden). UMC's distinctive course, established in 1993, welcomes around 30 participants to Uppsala in May each year. Participants study topics essential to effective pharmacovigilance, among them are: pharmacovigilance best practices, pharmacovigilance tools, signal detection, causality assessment and communications. This course is tailored for representatives of national pharmacovigilance centres and ministries of health but is also suitable for representatives of public health programmes and healthcare professionals from hospitals or academic settings.

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