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S&A PHARMA NEWSLETTER

EDITORIAL

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Founding Partner

The health care sector is ever evolving sector which is constantly growing and creating new milestones. In recent years the health industry has crossed over some of its previous milestones not only in terms of business but also in terms of health practice standards globally. The latest edition of our Pharma newsletter addresses progress and developments in the area of Health Research, Regulatory developments, new therapy/drug molecule/medical device approvals and public health survey reports.

The latest issue covers the tenth amendment of Drugs and Cosmetics (D&C) Rule, 2017 where the validity of drug licenses once issued, shall remain valid forever, unless suspended or cancelled by the licensing authority of India. Next we cover the draft amendment proposed to change Drugs and Cosmetics Rule, 2017 to envisage the steroids to be included in Schedule H category to control its misuse. Then we have covered three more draft amendments in D&C Act proposed by health ministry to allow import of small quantities drugs for patient's personal use with yearly review; changes in labeling of Schedule H, H1, G, K, and Schedule X drugs; and production of Oxygen 93 percent IP/USP exempted of the provision of the Chapter IV of the Act.

Then we address the European Medicines Agency (EMA) announcement that it will relocate to Amsterdam in the Netherlands post BREXIT, further we discuss important updates from American Heart Association (AHA) Scientific Sessions 2017. Then we have a write up on National Pharmaceutical Pricing Authority (NPPA) recent notification where it has fixed/revised the retail price/ceiling price of 51 formulations of schedule-I drugs under Drug Price Control Order (DPCO), 2013. Further we discuss NPPA's recent guidance for examination of new drug launch cases without prior price approval. Thereafter, we covered the First Comprehensive Estimates and Trends of Disease Burden and Risk Factor for Every State of India.

Next we address the United States Food and Drug Administration (USFDA) approval of Abilify MyCite (aripiprazole tablets with sensor) with a digital ingestion tracking system. Further we highlight CDSCO's approvals for the month November 2017.

We wrap-up this newsletter with the article on release of Eighth Edition of Indian Pharmacopoeia (IP-2018) by Indian pharmacopoeia commission (IPC) which will be effective from January 2018.

We sincerely hope that you find the articles of this newsletter interesting & enriching.

Please feel free to send your valuable inputs / comments at newsletter@singhassociates.in

Thank you.

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Contents

Central Government proposes to bring Steroids under Schedule H of the Drugs and Cosmetics Act, 1940 (23 of 1940)

On November 11, 2017 the Central Government proposed to make amendments to certain Drugs and Cosmetics Rules, in exercise of the powers conferred to it, by section 12 and section 33 of the Drugs and Cosmetics Act, 1940 (23 of 1940), in consultation with the Drugs Technical Advisory Board. The Central Government has published the draft rules, and notified to all the persons likely to be affected thereby, that the draft rules will be taken into consideration on or after the expiry of a period of forty-five days from the date on which the copies of the Gazette of India containing these draft rules are made available to the public.

Further, the proposed draft rules may be called the Drugs and Cosmetics (.....Amendment) Rules, 2017 and shall come into force on the date of their final publication in the Official Gazette.

In Drugs and Cosmetics Rules, 1945, in Schedule H, after the serial number 537, following 14 new entries, with corresponding serial numbers given below, shall be inserted:

- 538. Alclometasone
- 539. Beclomethasone
- 540. Betamethasone
- 541. Desonide
- 542. Desoximetasone
- 543. Dexamethasone
- 544. Diflorasone diacetate
- 545. Fluocinonide
- 546. Fluocinolone acetonide
- 547. Halobetasol propionate
- 548. Halometasone
- 549. Methylprednisone
- 550. Prednicarbate
- 551. Triamcinolone acetonide.[12]

These amendment/entries in schedule H were proposed after concerns were raised by the Indian Association of Dermatologists, Venereologists and Leprologists (IADVL) to the office of Drug Controller General India (DCGI) regarding-

- The adverse effects induced by rampant misuse of creams containing corticosteroids along with antibiotics and antifungals causing damage to the skin of Indian citizens.

1 http://cdsco.nic.in/writereaddata/77th%20DTAB%20Minutes%20with%20approval%20letter.pdf

2 http://www.egazette.nic.in/WriteReadData/2017/179978.pdf

- Increasing number of cases of Topical Steroid Damaged Face (TSDF) and steroid modified recalcitrant and/or extensive tinea (fungal infection of the skin known as ringworm) have come to the notice of the dermatologists.
- These creams are purchased and used by the patients without any doctor's prescription as Schedule H provided exemption for topical or external use preparations from the purview of Schedule H and H1, in the note appended to these Schedules[3].

Note- DCGI also notifies, if there are any related objections or suggestions, the matter may be addressed to the Under Secretary (Drugs), Ministry of Health and Family Welfare, Government of India within stipulated time.

3 http://www.cdsco.nic.in/writereaddata/redtab71st.pdf

BREXIT: European Medicines Agency (EMA) to relocate to Amsterdam, the Netherlands

On November 20, 2017, the European Medicines Agency (EMA) announced that it will relocate to Amsterdam in the Netherlands[4]. This decision was taken by the European Union (EU 27) Member States in the margins of the General Affairs Council (Art.50). The Agency now has just over 16 months to prepare for the move and start its operations from Amsterdam latest by March 30, 2019.

EMA must relocate due to the United Kingdom's decision to withdraw from the EU. Amsterdam was one of 19 cities from Member States who submitted an offer at the end of July 2017, to host EMA. The decision on EMA's new location follows an assessment of the bids by the European Commission and EMA. The decision marks the official start of a challenging joint relocation project that will have to be delivered within extremely tight timelines whereby the relocation has to be completed by March 30, 2019.

Effective collaboration between EMA and the Netherlands, on the basis of the commitments made in its offer to host EMA, is essential to ensure a successful move and the continuation of EMA's operations with minimal disruption.

EMA and the Netherlands will kick start their collaboration by establishing a joint governance structure to oversee and steer the relocation project. Because of its important role to safeguard public and animal health in the EU, EMA is committed to giving stakeholders and the public full visibility of the relocation project. In early December, the Agency will make available a monitoring chart on its website that will allow tracking of the progress made.

About European Medicines Agency (EMA)

Founded in 1995, the European Medicines Agency (EMA) is responsible for the scientific evaluation, supervision and safety monitoring of medicines in the EU. It currently employs nearly 900 staff members at its Headquarters in Canary Wharf, London. EMA is essential to the functioning of the single market for medicines in the EU.

Concretely, the main tasks of the EMA include:

- To facilitate development and access to medicines,
- To evaluate applications for marketing authorization,
- To monitor the safety of medicines across their lifecycle,
- To provide information to healthcare professionals and patients.

4 http://www.ema.europa.eu/ema/index.jsp?curl=pages/news_and_events/news/2017/11/news_detail_002857.jsp&mid=WC0b01ac058004d5c1

DCGI notifies the Medical Devices and In vitro Diagnostic (IVD) medical devices classification under Medical Device Rule, 2017

On November 01, 2017, the Drug Controller General India (DCGI) has notified to all stakeholders - the classification of medical devices and *in vitro* diagnostic (IVD) medical devices under the provisions of the Medical Devices Rules, 2017, for their regulation with respect to their import, manufacture, clinical investigation, sale and distribution[5]. However, the safety, quality and performance of medical devices are regulated under the provisions of the Drugs and Cosmetics Act, 1940 and rules made there under. Earlier, the Central Government, after consultation with the Drugs Technical Advisory Board (DTAB), had notified Medical Devices Rules (MDR), 2017 vide G.S.R. 78 (E) dated 31.01.2017, which are to commence from 01.01.2018.

The said notification is, in exercise of the powers conferred under sub-rule (3) of rule 4 of MDR, 2017 that "*The Central Licencing Authority shall, classify medical devices referred to in rule 2, based on the intended use of the device and other parameters specified in the First Schedule.*"

Whereas, Rule 2 of MDR, 2017 prescribes the applicability of these rules, in respect of –

I. Substances used for in vitro diagnosis and surgical dressings, surgical bandages, surgical staples, surgical sutures, ligatures, blood and blood component collection bag with or without anticoagulant covered under sub-clause (i);

II. Substances including mechanical contraceptives (condoms, intrauterine devices, tubal rings), disinfectants and insecticides notified under sub-clause (ii); and

III. devices notified from time to time under sub-clause (iv), of clause (b) of section 3 of the Drugs and Cosmetics Act, 1940 (23 of 1940)

The Central Government hereby classifies the medical devices and IVD medical devices, based on the intended use of the device and other parameters specified in the First Schedule.

In this view, the list of medical devices and *in vitro* diagnostic medical devices notified are subjected to the following parameters:

1. General intended use given against each of the devices is for guidance to the applicants who intend to furnish application for import or manufacture of medical devices under the provisions of Medical Devices Rules, 2017. However, a device may have specific intended use as specified by its manufacturer.

2. The components and accessories to a medical device or companion in vitro diagnostic medical devices have been classified separately.

3. It is also recognized that some of the medical devices or in vitro diagnostic medical devices may have dual use and they may be classified accordingly.

4. This list is dynamic and is subject to revision from time to time under the provisions of the Medical Devices Rules, 2017.

Further, the notification lists the medical devices and IVD devices with their risk classes:

5 http://www.cdsco.nic.in/writereaddata/notice%2029_6_2017.pdf

1. List A includes a total of 351 medical Devices in 16 categories with their risk class as per the provisions of Sub-rule (1) of Rule 4 of the MDR, 2017 which prescribes that "*Medical devices shall be classified on the basis of parameters specified in Part I of the First Schedule, in the following classes, namely:—*

I. *Low risk - Class A;*

II. *Low moderate risk- Class B;*

III. *Moderate high risk- Class C;*

IV. *High risk- Class D."*

2. List B includes a total of 247 in vitro diagnostics medical devices in 22 categories with their risk class as per the provisions of Sub-rule (2) of Rule 4 of the MDR, 2017 which prescribes that "*In vitro diagnostic medical devices shall be classified on the basis of parameters specified in Part II of the First Schedule, in the following classes, namely:—*

I. *Low risk - Class A;*

II. *Low moderate risk- Class B;*

III. *Moderate high risk- Class C;*

IV. *High risk- Class D."*

Note- Anticoagulant Solutions, Embolization Particles, Chitosan scaffold (for cartilage repair), Riboflavin (for Corneal Collagen cross-linking), Silicone Oil Endotamponade, Intraocular Gases and Injectable Fillers shall be regulated as drugs under the provisions of the Drugs and Cosmetics Act, and Drugs and Cosmetics Rules, 1945.

Biocon Launches KRABEVA® in India

A Biosimilar Bevacizumab for Treating Several Types of Cancer

On November 23, 2017, Biocon India's premier Biopharmaceuticals Company announced that it has launched KRABEVA®, a biosimilar Bevacizumab for the treatment of patients with metastatic colorectal cancer and other types of lung, kidney, cervical, ovarian and brain cancers, in India[6].

KRABEVA®, a monoclonal antibody (mAb) developed by Biocon, will help expand access to a world-class, high quality biosimilar Bevacizumab for cancer patients in India. It is the world´s first and only Bevacizumab with a unique ´QualCheck´ mechanism, which ensures that patients get a quality-ascertained product right up to infusion.

Bevacizumab is indicated as a first-line treatment of patients with metastatic colorectal cancer (mCRC), and is accepted as a standard treatment option in combination with chemotherapy for patients with non-small-cell lung cancer (NSLC), metastatic renal cell carcinoma or recurrent ovarian cancer.

KRABEVA® is the second key oncologic biosimilar product, from Biocon´s global biosimilars portfolio to be launched in India. It is being offered to patients at an MRP of Rs 24,000 for 100 mg / 4 ml vials and Rs 39,990 for 400 mg / 16 ml vials, making it a high quality affordable alternative to the innovator brand. In comparison, the Innovator brand for Bevacizumab marketed as Avastin® by Roche India Private Limited costs over Rs 10, 7065 for 400mg / 16ml vial.

Bevacizumab is a monoclonal antibody (mAb) targeting Vascular Endothelial Growth Factor- A (VEGF-A), a cell protein that induces growth of blood vessels that feed tumors. By blocking this protein, Bevacizumab cuts the supply of food and oxygen to the tumor, thus starving it. Bevacizumab is prescribed in the treatment of several cancers including metastatic colorectal cancer, ovarian cancer, advanced non-small-cell lung cancer, recurrent glioblastoma, cervical cancer and renal cancer. Bevacizumab was first approved by the United States Food and Drug Administration (USFDA), in February 2004[7]. It also features in the World Health Organization's (WHO) list of essential medicines[8]. The WHO list of essential medicines contains the medications considered to be most effective and safe to meet the most important needs in a health system. The list is frequently used by countries to help develop their own local lists of essential medicine.

Conclusion:

Approval and launch of a Bevacizumab biosimilar in India would provide an affordable therapy option for patients of various types of cancer.

6 https://www.biocon.com/biocon_press_releases_231117.asp

7 https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm?event=overview.process&ApplNo=125085

8 http://www.who.int/medicines/publications/essentialmedicines/EML_2015_FINAL_amended_NOV2015.pdf?ua=1

Drugs and Cosmetics (Tenth Amendment) Rules, 2017

"The licenses once issued, shall remain valid forever, unless suspended or cancelled by the licensing authority"

On October 27, 2017, the Ministry of Health and Family Welfare has published the Drugs and Cosmetics (Tenth Amendment) Rules, 2017 through official gazette, in exercise of the powers conferred by section 12 read with section 33 of the Drugs and Cosmetics (D&C) Act, 1940 (23 of 1940); further after consultation with the Drugs Technical Advisory Board has proposed the following rules to amend the Drugs and Cosmetics Rules, 1945, namely:-

Duration of licence

1) As per the amendment a various licenses once issued under Form 20, 20A, 20B, 20BB, 20F, 20G, 21, 21A, 21B, 21BB, Form 25, Form 25B, Form 25F, Form 32, Form 32A, Form 33 and Form 37; whereas loan license also issued in Form 25A shall remain valid, if licensee deposits a license retention fee referred to in sub-rule (2) before the expiry of a period of every succeeding five years from the date of its issue, unless, it is suspended or cancelled by the licensing authority.

2) The license retention fee referred to in sub-rule (1), shall be equivalent to the respective fee required for the grant of such license excluding inspection fee paid for grant of license.

3) If the license holder fails to pay license retention fee on or before the due date as referred to in sub-rule (1), he shall be liable to pay license retention fee along with a late fee calculated at the rate of two per cent of the license fee for every month or part thereof up to six months, and in the event of non-payment of such fee, the license shall be deemed to have been cancelled.

Inspection for grant of license and verification of compliance

1) Before grant of manufacturing license under Form 25, Form 25A, Form 25B, Form 25F, Form 28, Form 28A, Form 28B, Form 28D, Form 28DA, Form 32, Form 32A and Form 33, the licensing authority shall cause the establishment in which the manufacture of drugs is proposed to be conducted or being used, to be inspected jointly by the Drugs Inspectors appointed by the Central Government and the State Government under this Act who shall examine the establishment intended to be used or being used for the manufacture of drugs.

2) The premises licensed under sub-rule (1) shall be jointly inspected by Inspectors appointed by the Central Government and the State Government to verify compliance with the conditions of license, the provisions of the Act and these rules, not less than once in three years or as needed as per risk based approach."

Inspection for verification of compliance

The licensing authority shall cause inspection, by the Inspector appointed under the Act, of each premise licensed under this Part, to verify the compliance with the conditions of license and the provisions of the Act and these rules, not less than once in three years or as needed as per risk based approach.

Apart from this, a paragraph in Schedule A regarding various forms has been amended as follows:

"The license, unless sooner suspended or cancelled, shall remain valid perpetually. However, the compliance with the conditions of license and the provisions of the Drugs and Cosmetics Act, 1940 (23 of 1940) and the Drugs and

Cosmetics Rules, 1945 shall be assessed not less than once in three years or as needed as per risk based approach." Moreover, the word "Renew or Renewal or Renewed" shall be omitted from various forms of Schedule A"[9].

Note - The Drugs and Cosmetics (Tenth Amendment) Rules, 2017 is effective from March 27, 2017. However, the CDSCO has published following interim guidelines to ensure the smooth processing of applications for grant of manufacturing licenses; and for joint inspection of manufacturing premises –

1. Application for the grant of manufacturing licenses, complete in all respect as per the provisions of Drug and Cosmetic Act, 1940 and Rules, 1945 should be submitted by manufacturer to the respective State Licensing Authority.
2. The State Licensing Authority should fix a date at least seven days prior to the date of joint inspection of the manufacturing premises, in coordination with the respective zonal/ Sub-zonal offices of CDSCO.
3. In case drug inspector of CDSCO zonal/sub-zonal offices is not available on any specific date, drug inspector from CDSCO (HQ) will be deputed for the joint inspection.
4. Proper coordination between State Licensing Authorities, CDSCO HQ and Zonal/ Sub-zonal offices should be ensured for timely inspection and processing of applications.
5. In case of deficiency in the application in respect of any inspection, the joint inspection team may verify such document during the inspection and record detail of the same in the inspection report[10].

However, valuable feedback or suggestions for these guidelines will be also appreciated by CDSCO for further improvement in the implementation of the new rules.

9 http://www.cdsco.nic.in/writereaddata/GSR%201337(E)%20dated%2027_10_2017.pdf

10 http://www.cdsco.nic.in/writereaddata/library%2024.11.17.pdf

CDSCO: Drug Approvals - November 2017

The Central Drugs Standard Control Organization (CDSCO) is the Central Drug Authority for discharging functions assigned to the Central Government under the Drugs and Cosmetics Act.

Below is the list of drug approvals by the CDSCO in November 2017.

1. **Midostaurin 25 mg Capsules**: On November 09, 2017, CDSCO approved Midostaurin.
Midostaurin Capsules are indicated for use:

- In combination with standard induction and consolidation chemotherapy followed by single agent in maintenance of therapy for adult patients newly diagnosed with Acute Myeloid Leukemia (AML) who are FLT-3 Mutation positive.
- For the treatment of adult patients with Advanced Systemic Mastocycosis (Advanced SM)[11].

The approval for Midostaurin Capsules was given to Sandoz Private Limited.

At the technical advisory meeting of the Oncology & Haematology committee, at CDSCO headquarters on 18.07.2017, the committee opined that Midostaurin application of Sandoz falls under the criteria of clinical trial waiver as the said indications are conditions for which there is no therapy.

The committee also observed that the drug was granted breakthrough therapy orphan drug designation by US & EU both. Hence, the committee recommended for grant of permission to import & market the drug for the said indications with waiver of local clinical trial[12].

About Midostaurin

Midostaurin is an oral, targeted therapy, a type of treatment that interferes with certain pathways that are involved in the growth, progression and spread of cancer. Midostaurin inhibits multiple kinases, including FLT3, which help regulate many essential cell processes, interrupting cancer cells' ability to grow and multiply. Midostaurin induces cell death in leukemic cells expressing FLT3 ITD or TKD mutant receptors, or in cells overexpressing FLT3 wildtype receptors. Midostaurin also inhibits the activity of the kinase KIT (wild type and D816V mutant), inhibiting mast cell proliferation, survival and histamine release. In addition, Midostaurin inhibits several other receptor tyrosine kinases such as PDGFR alpha/ß, VEGFR2, and members of the serine/threonine kinase PKC family, inhibiting signaling of the respective growth factors in cells, resulting in growth arrest.

About Acute Myeloid Leukemia (AML)

AML is the most common acute leukemia, or blood cancer in adults; it accounts for approximately 25% of all adult leukemias worldwide, with the highest incidence rates occurring in the US, Europe and Australia. It also has the lowest survival rate amongst all adult leukemias. In AML, white blood cells are not able to mature and instead build up an accumulation of "blasts," blocking room for normal blood cells. Mutations in specific genes, such as FLT3, are found in many cases of the disease.

About Advanced Systemic Mastocycosis (ASM)

In advanced SM, the uncontrolled growth of neoplastic mast cells causes organ damage (e.g., liver dysfunction), low blood count and weight loss. People with the disease also suffer from debilitating systemic symptoms such

11 http://www.cdsco.nic.in/forms/list.aspx?lid=2034&Id=11

12 http://www.cdsco.nic.in/writereaddata/Recommendation%20Oncology_18_07_2017.pdf

as pruritus (severe itching of the skin) caused by mast cells releasing inflammatory mediators, such as histamine into the blood.

2. Tenofovir Alafenamide Fumarate bulk & 25 mg capsules: On November 10, 2017, CDSCO approved Tenofovir Alafenamide Fumarate bulk & 25 mg capsules[13].

Tenofovir Alafenamide Fumarate bulk & 25 mg capsules are indicated:

- For the treatment of chronic Hepatitis B virus infection in adults with compensated liver disease.

The approval for Tenofovir Alafenamide Fumarate bulk & 25 mg capsules was given to Mylan Labs.
Mylan Labs presented the data on the drug including data from global clinical trials conducted, in which India was a participating country. The data presented shows that Tenofovir Alafenamide and TDF are equivalent in terms of efficacy but Tenofovir Alafenamide has reduced toxicity. The data was presented on 14.06.2017 before the CDSCO's advisory committee for Antimicrobial & Antiviral drugs.

After review of the data, the committee considered the request for waiver of local clinical trial and recommended for conduct of the BE study as per the protocol submitted[14].

Tenofovir alafenamide is a nucleotide reverse transcriptase inhibitor and a prodrug of tenofovir. It was developed by Gilead Sciences for use in the treatment of HIV infection and chronic hepatitis B, and is applied in the form of tenofovir alafenamide fumarate (TAF).

3. Ceritinib150mg hard gelatin capsule: Additional indication approved

In the Subject Expert Committee (SEC) meeting of Oncology & Haematology held on 14.11.2017 – Novartis presented their proposal along with the clinical data for the proposed indication. The Committee noted that anaplastic lymphoma kinase (ALK) - positive advanced non- small cell lung cancer (NSCLC) is a serious/life threatening rare disease.

After detailed deliberation the committee recommended for approval of the proposed additional indication for Certinib:

- As a monotherapy for first-line treatment of adult patients with anaplastic lymphoma kinase (ALK)-positive advanced non- small cell lung cancer (NSCLC)[15].

4. Filgrastim/ Filgrastim Solution for Injection: Additional indications approved

In the Subject Expert Committee (SEC) meeting of Oncology & Haematology held on 14.11.2017, Intas presented their proposal for additional indications. The indications are already approved in many countries including USA & Europe. After detailed deliberation, committee recommended for approval of the following three additional indications[16] for Filgrastim.

1. For chronic use to reduce the incidence and duration of sequeale of severe neutropenia (e.g. fever, infections, oropharyngeal ulcers) in symptomatic patients with congenital neutropenia, cyclic neutropenia or idiopathic neutropenia.

13 http://www.cdsco.nic.in/forms/list.aspx?lid=2034&ld=11

14 http://www.cdsco.nic.in/writereaddata/MOM%20of%20SEC%20Antimicrobial%20and%20Antiviral%20 14_06_2017%20(Website)%20(1).pdf

15 http://cdsco.nic.in/writereaddata/Oncology%20recommendation_14_11_2017.pdf

16 http://cdsco.nic.in/writereaddata/Oncology%20recommendation_14_11_2017.pdf

2. To increase survival in patients acutely exposed to myelosuppressive doses of radiation (Hematopoietic Syndrome of Acute Radiation Syndrome).

3. For the treatment of persistent neutropenia (ANC≤1.0 x 109 /L) in patients with advanced HIV infection, in order to reduce the risk of bacterial infections when other options to manage neutropenia are inappropriate.

5. Liraglutide Injection: Additional indications approved

In the Subject Expert Committee (SEC) meeting of Endocrinology & Metabolism held on 09.11.2017, Novo Nordisk presented supportive data including clinical data for the proposed expansion of the indication of Liraglutide Injection.

The committee after detailed deliberation recommended that the indication may be expanded as follows:

- To reduce the risk of major adverse cardiovascular events in adults with Type 2 diabetes mellitus and established cardiovascular disease.

Ministry of Health (MoH) Releases 3 Draft Gazettes seeking amendments to Drug & Cosmetics Rules, 1945

On November 3, 2017, the Central Government proposing to make changes or amending the Drugs and Cosmetics Rules, 1945 in exercise of the powers conferred by sections of the Drugs and Cosmetics Act, 1940 (23 of 1940), in further consultation with the Drugs Technical Advisory Board (DTAB), has issued three separate drafts to the public, which will be taken into consideration on or after the expiry of a period of thirty days from the date of publication. The details are:

1. In the first draft Notification (S.O. G.S.R.1367 (E)), the government has proposed to substitute the existing clause 3 of Form 12B of the Drug and Cosmetic (D&C) Rule, 1945 with respect to permission of import of small quantities of drugs for personal use - allowing it till the patient requires the drug as per prescription of RMP as against the present restriction of six months from the date of issue of the permit. However, it is also proposed that the permit holder should submit the details of the drugs imported and utilized, to the licensing authorities on a yearly basis from the date specified[17].

2. In the second draft Notification (S.O. G.S.R.1368 (E), the government proposes to substitute serial number 34 under Schedule K of the D&C Rule, 1945 by including "production of Oxygen 93 percent IP in addition to Oxygen 93 percent USP for exemption of the provision of the Chapter IV of the Act. The Provision of Chapter IV of the Act and the Rule made thereunder, which requires them to be covered by manufacturing license under the rules, provided that the production facilities shall be open to inspections by an inspector appointed under the Act, who can, if necessary, take samples for test[18]"

3. In the third draft rule, the following amendments are sought vide Notification No. G.S.R.1369 (E), -

   I. It is proposed to substitute the clauses in Rule 96, in sub-rule (1), in clause (xi) D&C Rule, 1945 "In addition to the other particulars which are required to be printed or written under these rules, the label of inner most container of the following categories of drugs and every other covering in which the container is packed shall bear caution/ warning in legible black colored font size in completely red rectangular box without disturbing other conditions printed on the label under these rules, namely:- Narcotic analgesics, hypnotics, sedatives, tranquillizers, corticosteroids, hormones, hypoglycemic, antimicrobials, antiepileptic, antidepressants, anticoagulants, anti-cancer drugs and all other drugs falling under Schedules G, H, H1 and Schedule X whether covered or not in the above list".

   II. In clause (a), (b), (c), (d) and (e) of sub-rule (1) of Rule 97 of D&C Rules, 1945 indicating the manner of labeling of drugs specified in Schedule G, H, H1, and X shall be "in red and conspicuously displayed on the left top corner of the label and shall also be labeled with the following words in legible black colored font size in completely red rectangular box".

   III. In Schedule H, after Note 3 appended to the said Schedule, the following Note shall be inserted "The salts, esters, derivatives and preparations containing steroids for topical or external use are also covered by this Schedule."

   IV. In Schedule K, against serial number 27, for the entries under the column 'class of drugs' the following shall be substituted "Oral Rehydration Salts (Manufactured as per the following formula):-Composition of the formulation in terms of the amount in gm, to be dissolved in sufficient water to produce 1000 ml.

Sodium Chloride	2.6

17 http://egazette.nic.in/WriteReadData/2017/180036.pdf

18 http://egazette.nic.in/WriteReadData/2017/180051.pdf

Dextrose (anhydrous) or	13.5
Dextrose mono-hydrate	14.85
Potassium Chloride	1.5
Sodium Citrate	2.9[19]."

Note - The Health Ministry hereby requests that objections and suggestions, if any, may be addressed to the Under Secretary (Drugs), Ministry of Health and Family Welfare. Objections and suggestions which may be received from any person within the aforesaid period will be considered by the Central Government.

19 http://egazette.nic.in/WriteReadData/2017/180071.pdf

Conference Briefs from the American Heart Association (AHA) Scientific Sessions 2017

The American Heart Association (AHA) Scientific Sessions 2017, was a global event held from November 11-15, 2017 at California, USA. AHA's Scientific Sessions attracts nearly 18,000 attendees, with a global presence from more than 100 countries. In addition, two million medical professionals participate virtually in lectures and discussions about basic, translational, clinical and population science. Major landmark clinical trials and policy guidance in the domain of cardiology are presented at the AHA scientific sessions.

Some of the major clinical trials/policy statements from this year's AHA sessions are briefly discussed in this news report:

1. High blood pressure redefined for first time in 14 years: 130/80 mm Hg is the new high in the revised guideline

High blood pressure should be treated earlier with lifestyle changes and in some patients with medication – at 130/80 mm Hg rather than 140/90 mm Hg – according to the first comprehensive new high blood pressure guidelines in more than a decade. The guidelines are published by the American Heart Association (AHA) and the American College of Cardiology (ACC) for detection, prevention, management and treatment of high blood pressure[20].

As against 1 in 3 U.S. adults having high blood pressure (32 percent) with the previous definition, the new guidelines will result in nearly half of the U.S. adult population (46 percent) having high blood pressure, or hypertension.

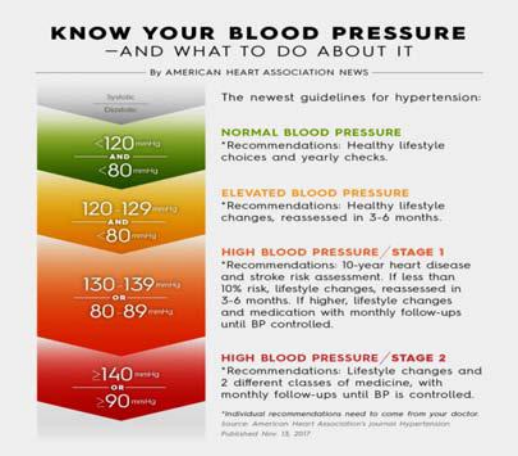
These guidelines, the first update to offer comprehensive guidance to doctors on managing adults with high blood pressure since 2003, are designed to help people address the potentially deadly condition much earlier.

The new guidelines also stress the importance of using proper technique to measure blood pressure. Blood pressure levels should be based on an average of two to three readings on at least two different occasions.

Blood pressure categories in the new guideline are:

- Normal: Less than 120/80 mm Hg;
- Elevated: Top number (systolic) between 120-129 and bottom number (diastolic) less than 80;
- Stage 1: Systolic between 130-139 or diastolic between 80-89;
- Stage 2: Systolic at least 140 or diastolic at least 90 mm Hg;
- Hypertensive crisis: Top number over 180 and/or bottom number over 120, with patients needing prompt changes in medication if there are no other indications of problems, or immediate hospitalization if there are signs of organ damage.

20 https://news.heart.org/nearly-half-u-s-adults-now-classified-high-blood-pressure-new-definitions/



Other changes in the new guideline include:

- Only prescribing medication for Stage I hypertension if a patient has already had a cardiovascular event such as a heart attack or stroke, or is at high risk of heart attack or stroke based on age, the presence of diabetes mellitus, chronic kidney disease or calculation of atherosclerotic risk (using the same risk calculator used in evaluating high cholesterol).
- Recognizing that many people will need two or more types of medications to control their blood pressure and that people may take their pills more consistently if multiple medications are combined into a single pill.
- Identifying socioeconomic status and psychosocial stress as risk factors for high blood pressure that should be considered in a patient's plan of care.

Conclusion:

The revised guideline which defines the High blood pressure as readings of 130 mm Hg and higher for the systolic blood pressure measurement or readings of 80 and higher for the diastolic measurement is a change from the old definition of 140/90 and higher, reflect complications that can occur at those lower numbers. By lowering the definition of high blood pressure, the guidelines recommend early intervention to prevent further increases in blood pressure and the complications of hypertension.

2. Quality of stent procedures consistently good across U.S. regardless of popular hospital ranking

Hospitals ranked amongst the best in Cardiology and Heart surgery by U.S. News and World Report appear no better, at performing percutaneous coronary intervention (PCI), a potentially life-saving heart procedure, than unranked hospitals, according to a preliminary research presented at the American Heart Association's Scientific Sessions 2017, a premier global exchange of the latest advances in cardiovascular science for researchers and clinicians[21].

Researchers based their comparison, of PCI results at ranked and unranked hospitals on patient information and PCI outcomes submitted to the National Cardiovascular Data Registry CathPCI. Altogether, researchers reviewed the results of 509,153 angioplasties performed between July 2014 and June 2015 at 654 hospitals (six hospitals ranked among the top 50 by U.S. News and World Report in 2015 were not included in this study because they either did not submit data to the registry or performed an insignificant number of PCIs, making comparisons difficult).

21 https://newsroom.heart.org/news/quality-of-stent-procedures-consistently-good-across-u-s-regardless-of-popular-hospital-ranking?preview=1e06

The study found that ranked and unranked hospitals had:

- similar rates of in-hospital deaths (less than 2 percent); and
- similar rates of acute kidney injury and bleeding—two of the most common complications of PCI, which can increase a patient's risk of dying, hamper recovery and lead to longer hospital stays and increased hospital costs.

Conclusion:

The study found out that there was no difference in the quality of stent procedures across the United States, irrespective of popular hospital ranking, which should come as a reassurance to the patients undergoing the percutaneous coronary intervention procedures.

3. Gobbling your food may harm your waistline and heart

People who eat slowly are less likely to become obese or develop metabolic syndrome or a cluster of heart diseases or diabetes and stroke risk factors, according to a preliminary research presented at the American Heart Association's Scientific Sessions 2017[22].

Metabolic syndrome occurs when someone has any of three risk factors that include abdominal obesity, high fasting blood sugar, high blood pressure, high triglycerides and/or low HDL cholesterol, said Japanese researchers. The researchers evaluated 642 men and 441 women, average age 51.2 years, who did not have metabolic syndrome in 2008. They divided the participants into three groups depending on how they described their usual eating speed: slow, normal or fast.

After five years, the researchers found:

- Fast eaters were more likely (11.6 percent) to have developed metabolic syndrome than normal eaters (6.5 percent) or slow eaters (2.3 percent);
- Faster eating speed was associated with more weight gain, higher blood glucose and bigger waistline.

Conclusion:

Eating more slowly may be a crucial lifestyle change to help prevent metabolic syndrome. The researchers concluded that when people eat fast they tend not to feel full and are more likely to overeat. Eating fast causes bigger glucose fluctuation, which can lead to insulin resistance.

4) Sudden cardiac death rates may be seven times higher among young people with diabetes
Children and young adults with diabetes may be seven times more likely to die from sudden cardiac death compared to children and young adults without diabetes, according to a preliminary research from Denmark presented at the American Heart Association's Scientific Sessions 2017[23].

Sudden cardiac death is defined as a sudden, unexpected death that occurs instantly or shortly after symptoms appear. It is often caused by malfunctions in the heart's electrical system. The study, which was conducted in Denmark, also found that overall, compared to those without diabetes, children and young adults, ages 1-49,

22 https://newsroom.heart.org/news/gobbling-your-food-may-harm-your-waistline-and-heart?preview=1e06

23 https://newsroom.heart.org/news/sudden-cardiac-death-rates-may-be-seven-times-higher-among-young-people-with-diabetes?preview=1e06

with diabetes were eight times more likely to die from any kind of heart disease, such as heart failure or the chronic narrowing of arteries known as atherosclerosis, compared to children and young adults without diabetes.

Young people with diabetes may be at increased risk of sudden cardiac death because of abnormalities in their blood vessels caused by the disease.

The study is one of the first to examine causes of death and cause-specific death rates among children and young adults with diabetes in a nationwide setting.

The study population consisted of all persons in Denmark age 1 to 35, in 2000-09 and age 36 to 49 in 2007-09. During the 10-year study period 14,294 deaths occurred, and the cause of death was established based on information from death certificates and autopsy reports. The Danish Register of Medicinal Product Statistics, which holds information on all prescriptions dispensed from Danish pharmacies, was used to identify persons with either Type 1 or Type 2 diabetes. Among those who died, 669 (5 percent) had diabetes, of which 471 (70 percent) had Type 1 and 198 (30 percent) had Type 2.

Conclusion:

The study shows the importance of early and continuous cardiovascular risk monitoring in children and young adults with diabetes. In the light of the results from this study, tight control and effective treatment of blood lipids, blood pressure, and blood glucose is also important among children and young persons with diabetes. Healthcare providers need to be aware that even young patients with diabetes have elevated risk of mortality and that this can mainly be explained by increased risk of sudden cardiac death.

5) Men more likely to receive bystander Cardiopulmonary Resuscitation (CPR) in public than women

Men are more likely to receive bystander CPR in public locations compared to women, and they are more likely to survive after the life-saving measure, according to a preliminary research presented at the American Heart Association's Scientific Sessions 2017[24].

CPR involves pushing on the chest, so it could make people less certain whether they can or should perform CPR in public on women.

The data for the study was compiled by the Resuscitation Outcomes Consortium, a network of regional clinical centers in the United States and Canada that study out-of-hospital treatments of cardiac arrest and trauma, where the researchers analyzed 19,331 cardiac events in the home and in public.

- The preliminary results released showed 45 percent of men received bystander CPR in public settings compared to just 39 percent of women. By the time men were discharged from the hospital, their odds of survival were 23 percent greater compared to women.
- The disparity narrowed to 35 percent of women and 36 percent of men receiving CPR when the emergencies occurred at home. There was no significant statistical difference.

According to the American Heart Association, approximately 90% of individuals who have an out-of-hospital cardiac arrest (OHCA) die; but CPR, especially if given immediately, can double or even triple the chance of survival.

Conclusion:

The study researchers concluded that these findings identify a gap in bystander CPR delivery that can help improve future messaging and training to lay responders, health care providers and dispatchers.

24 https://newsroom.heart.org/news/men-more-likely-to-receive-bystander-cpr-in-public-than-women?preview=1e06

NPPA releases Guideline for examination of 'New Drugs' launch cases without obtaining prior price approval

The National Pharmaceutical Pricing Authority (NPPA) in continuation with its previous Office Memorandum dated 17.05.2017 and 26.05.2017[25], which directed all Pharma companies and Pharma associations regarding violations of various provisions under DPCO, 2013 (including cases of New Drugs launch without obtaining prior price approval, and violation of ceiling price fixed by NPPA); has further requested all Pharma companies to submit the reasons for such violations and complete their database of IPDMS (Integrated Pharmaceutical Database Management System) at the earliest.

The cases of violations have been listed out based on the examination and analysis of market data provided by Pharmatrac. However, during the course of examination of replies submitted by various Pharma companies, it has been observed that the companies have not submitted the requisite document(s) to support their contention.

In order to bring clarity in the examination of cases of new drugs launch "without prior price approvals" (WPA) and standardization of documents to be submitted by the companies, NPPA has decided to follow a standard and uniform procedure, as described in the following guidelines:

- **WPA cases will be dropped in the following cases and the Company will be duly informed, if:**

  a) The Company produces evidence (license issued by State Drugs Controller (SDC)/ Drugs Controller General (India) (DCG(I)) and invoices and samples prior to 15th May 2013, certified by Chartered Accountant (CA) / Cost Accountant (CMA) in support of the claim that the formulation was launched before the DPCO 2013 came into effect;

  b) AIOCD-Pharmatrac data confirm that the formulation was launched prior to 15th May 2013.

  c) The company claims and produces sufficient evidence to support the claim that the formulation does not come under the definition of a "new drug" under paragraphs 2 (u) of the DPCO 2013, i.e.,

     (I) Either the Company is not an "existing manufacturer" of the scheduled formulation; or

     (II) None of the components of the formulation is under Schedule I of the DPCO, 2013 as amended from time to time.

  d) The Company claims are duly supported with sufficient evidence i.e. samples and invoices that the formulation is a scheduled formulation and the ceiling price is complied therewith and followed in accordance with provisions of the DPCO, 2013.

  e) The Company's claim that the formulation was never manufactured/ marketed by it, is confirmed by AIOCD-Pharmatrac.

  f) The Company has changed only the pack size and launched the new pack size

     I. At a price equal to or less than the pro rata price of the previous pack size, or

     II. The increase in pro rata price, if any, undertaken by the company is in conformity with the provisions of paragraphs 20 (1) of DPCO, 2013.

  The Company will be required to submit evidence (license issued by SDC/DCG(1), invoice and sample,

25 http://www.nppaindia.nic.in/order/memorandum26052017.pdf

duly certified by CA/CMA regarding the previous and the existing pack size of concerned formulation manufactured / marketed by it.

g) The Company has launched a new brand having same composition as an earlier brand, merely with a different brand name

I. At the price equal to or less than that of the earlier brand, or

II. The increase in price effected by the company is in conformity with the provisions of paragraph 20 (1) of DPCO 2013.

The Company will be required to submit evidence (license issued by SDC/DCG (I) and invoice and sample, duly certified by CA/CMA regarding the previous and the existing brand of concerned formulation manufactured / marketed by it.

h) In cases where the brand has been procured/re-launched under a different name by another Company post-DPCO 2013, keeping the same composition of the formulation concerned as in the earlier brand

I. At a price equal to or less than that of the earlier brand, or

II. The increase in price effected by the company is in conformity with the provisions of paragraph 20 (1) of DPCO 2013.

The Company will be required to submit evidence (license issued by SDC/DCG (I) and invoice/sample, certified by CA/CMA) regarding the previous and the existing brand manufactured / marketed by it.

- **Any WPA case not coming under any of the above said categories will be referred for price fixation and, after fixing the price, the concerned companies shall be liable to deposit the overcharged amount along with interest from the date of overcharge, in addition to penalty, as per provisions of paragraph 15 of the DPCO, 2013.**

- **The companies are instructed to submit complete and requisite documents as stipulated in paragraph 3 herein above. Companies are once again advised to check 'new drugs', if any, has been launched by them and obtain requisite price approval after complying with IPDMS requirements by submitting Form I prescribed in Schedule-II of DPCO, 2013, along with the documents as required by NPPA vide O.M. No. 19(78)/2014/Div.II/NPPA dated 07.02.2017 and OM No. 19(78)/2014/DP/NPPA/Div.II dated 01.05.2017, if not done earlier[26].**

26 http://www.nppaindia.nic.in/order/om_24-11-2017.pdf

European Medicines Agency (EMA): Recommends Approval of Ten medicines in its November Meeting

- Meeting highlights from the Committee for Medicinal Products for Human Use (CHMP) 6-9 November 2017
- Ten medicines recommended for approval, including two orphans

The European Medicines Agency (EMA) on November 11, 2017, announced that its Committee for Medicinal Products for Human Use (CHMP) is recommending approval of six new drugs, one biosimilar and three generic medicines in the European Union (EU)[27].

The six new drugs recommended for approval are:

1. Jorveza (Budesonide) - to treat eosinophilic esophagitis, a rare inflammatory condition of the oesophagus. This medicine was reviewed under EMA's accelerated assessment mechanism, reserved for medicines of major public health interest. Jorveza has an orphan designation.

The active substance in Jorveza - Budesonide, is a well-known glucocorticosteroid that has been authorized since many years for the treatment of autoimmune disorders such as asthma and inflammatory bowel disease in different presentations. Budesonide as inhalation spray has been used off-label in the treatment of patients with eosinophilic esophagitis and its effects on the inflamed oesophageal mucosa of these patients have been extensively described in the scientific literature[28].

The applicant for Jorveza is Dr. Falk Pharma GmbH.

2. Prevymis (Letermovir), an antiviral medicine that prevents cytomegalovirus (CMV) reactivation and disease in patients who receive immunosuppressant medicines following an allogeneic haematopoietic stem cell transplant. Prevymis has an orphan designation.

CMV is a common virus that usually causes only mild infections such as a sore throat. But after infection, the virus remains in the body in a latent state and can become active again and cause a severe disease if the body's immunity is compromised, for instance in patients who need to take medicines that prevent their body to reject a transplant. CMV disease in these patients can be life-threatening[29].

The applicant for Prevymis is Merck Sharp & Dohme Limited.

3. Ocrevus (Ocrelizumab), for the treatment of adult patients with relapsing multiple sclerosis (RMS) and early primary progressive multiple sclerosis (PPMS).

27 http://www.ema.europa.eu/ema/index.jsp?curl=pages/news_and_events/news/2017/11/news_detail_002844.jsp&mid=WC0b01ac058004d5c1

28 http://www.ema.europa.eu/ema/index.jsp?curl=pages/news_and_events/news/2017/11/news_detail_002846.jsp&mid=WC0b01ac058004d5c1

29 http://www.ema.europa.eu/ema/index.jsp?curl=pages/news_and_events/news/2017/11/news_detail_002848.jsp&mid=WC0b01ac058004d5c1

Ocrevus is the first medicine to receive positive opinion for treatment of patients with early stage of primary progressive multiple sclerosis[30].

Multiple sclerosis (MS) is a condition which affects the brain and/or spinal cord, causing a wide range of potential symptoms, including problems with vision, arm or leg movement, sensation or balance. It occurs more frequently in women than in men and is among the most common causes of neurological disability in young adults. In majority of patients (around 85%), MS begins as a relapsing, episodic disorder with gradual complete or incomplete recovery. For approximately 10% of patients with PPMS the disease is characterised by worsening neurological function from the onset of symptoms, without early relapses or remissions.

The applicant for Ocrevus is Roche.

4. Adynovi (Rurioctocog alfa pegol), received a positive opinion for the treatment and prophylaxis of bleeding in patients 12 years and above with Haemophilia A (congenital factor VIII deficiency).

Adynovi will be available as a powder and solvent for solution for injection (250 IU, 500 IU, 1000 IU and 2000 IU). The active substance of Adynovi is rurioctocog alfa pegol, a recombinant human factor VIII which replaces the missing coagulation factor VIII needed for effective haemostasis[31].

The applicant for Adynovi is Baxalta.

5. Fasenra (Benralizumab), for the treatment of severe eosinophilic asthma.

Fasenra will be available as 30-mg solution for injection in pre-filled syringes. The active substance of Fasenra is Benralizumab, an anti-eosinophil, humanised monoclonal antibody which binds to the human interleukin-5 receptor expressed on the surface of eosinophils and basophils. This leads to apoptosis of eosinophils and basophils through enhanced antibody-dependent cell-mediated cytotoxicity, and therefore, reduces eosinophilic inflammation[32].

The applicant for Fasenra is AstraZeneca.

6. Intrarosa (Prasterone), received a positive opinion for the treatment of vulvar and vaginal atrophy in postmenopausal women.

Intrarosa will be available as a 6.5 mg pessary. The active substance of Intrarosa is Prasterone, also known as Dehydroepiandrosterone (DHEA), a precursor steroid which is converted into oestrogens and androgens. The medicine increases the number of superficial and intermediate cells and decreases the number of parabasal cells in the vaginal mucosa via an oestrogen-mediated mechanism. In addition, it decreases the vaginal pH towards the normal range, thus facilitating the growth of the normal bacterial flora[33].

The applicant for Intrarosa is Endoceutics.

30 http://www.ema.europa.eu/ema/index.jsp?curl=pages/news_and_events/news/2017/11/news_detail_002847.jsp&mid=WC0b01ac058004d5c1

31 http://www.ema.europa.eu/docs/en_GB/document_library/Summary_of_opinion_-_Initial_authorisation/human/004195/WC500238103.pdf

32 http://www.ema.europa.eu/docs/en_GB/document_library/Summary_of_opinion_-_Initial_authorisation/human/004433/WC500238040.pdf

33 http://www.ema.europa.eu/docs/en_GB/document_library/Summary_of_opinion_-_Initial_authorisation/human/004138/WC500238036.pdf

Besides these six new drugs, one biosimilar medicine - Mvasi, was also recommended for approval by the Committee:

Mvasi (bevacizumab) has been recommended for the treatment of carcinoma of the colon or rectum, breast cancer, non-small cell lung cancer, renal cell cancer, epithelial ovarian, fallopian tube or primary peritoneal cancer, and carcinoma of the cervix.

Mvasi will be available as a 25 mg/ml concentrate for solution for infusion. The active substance of Mvasi is bevacizumab, a monoclonal antibody which binds to vascular endothelial growth factor (VEGF), the key driver of vasculogenesis and angiogenesis, thereby, inhibiting the binding of VEGF to its receptors on the surface of endothelial cells. Neutralising the biological activity of VEGF regresses the vascularisation of tumours, normalises remaining tumour vasculature, and inhibits the formation of new tumour vasculature, thereby inhibiting tumour growth[34].

Mvasi is a biosimilar medicinal product, similar to the reference product Avastin (bevacizumab). Data shows that Mvasi has comparable quality, safety and efficacy to Avastin.

The applicant for Mvasi is Amgen.

The agency also recommended positive opinion on approval of Three (03) generic medicines:

Darunavir Krka (darunavir) and

Darunavir Krka d.d. (darunavir): both for the treatment of human immunodeficiency virus (HIV-1) infection. Darunavir Krka will be available as film-coated tablets (400 mg, 600 mg and 800 mg). The active

substance of Darunavir Krka is darunavir, a protease inhibitor. It acts by inhibiting the HIV enzyme protease, thus preventing formation of mature virus. Darunavir KrKa must be given with a small dose of ritonavir (as a booster), which decreases the breakdown of darunavir in the liver, resulting in higher levels of darunavir in the blood[35].

Darunavir Krka d.d. will be available as film-coated tablets (400 mg, 600 mg and 800 mg). The active substance of Darunavir Krka d.d. is darunavir, a protease inhibitor. It acts by inhibiting the HIV enzyme protease, thus preventing formation of mature virus. Darunavir Krka d.d. must be given with a small dose of ritonavir or cobicistat (as a booster), which decreases the breakdown of darunavir in the liver, resulting in higher levels of darunavir in the blood[36].

Darunavir Krka, and Darunavir Krka d.d. is a generic of Prezista.

Fulvestrant Mylan (Fulvestrant), for the treatment of locally advanced or metastatic breast cancer

Fulvestrant Mylan will be available as a 250-mg solution for injection. The active substance of Fulvestrant Mylan is fulvestrant, an anti-oestrogen which attaches to the receptors for oestrogen on the surface of cells, thereby

34 http://www.ema.europa.eu/docs/en_GB/document_library/Summary_of_opinion_-_Initial_authorisation/human/004728/WC500238063.pdf

35 http://www.ema.europa.eu/docs/en_GB/document_library/Summary_of_opinion_-_Initial_authorisation/human/004273/WC500238035.pdf

36 http://www.ema.europa.eu/docs/en_GB/document_library/Summary_of_opinion_-_Initial_authorisation/human/004891/WC500238034.pdf

blocking the effects of the hormone and causing the number of oestrogen receptors to fall. As a result, the tumour cells are not stimulated to grow by oestrogen and the growth of the tumour is reduced[37].

Fulvestrant Mylan is a generic of Faslodex

Four recommendations on extensions of therapeutic indication

The Committee recommended extensions of indications for Adcetris, Genvoya, Nplate and Orkambi.

Outcome of review on Zinbryta

The CHMP concluded its review of the multiple sclerosis medicine Zinbryta (daclizumab) and confirmed further restrictions to reduce the risk of serious liver damage.

Withdrawals of applications

Applications for initial marketing authorisations for Kyomarc (bevacizumab) and Plivensia (sirukumab) have been withdrawn.

- Kyomarc was intended to be used to treat cancer of the colon or rectum, breast cancer, non-small cell lung cancer, kidney cancer, cervical cancer, and cancer of the ovary, the fallopian tube, or the peritoneum.
- Plivensia was intended to be used to treat rheumatoid arthritis.

37 http://www.ema.europa.eu/docs/en_GB/document_library/Summary_of_opinion_-_Initial_authorisation/human/004649/WC500238082.pdf

USFDA grants pre-market clearance and a CLIA waiver to common blood test

On November 6, 2017, the U.S. Food and Drug Administration (USFDA) has cleared a complete blood cell count (CBC) test (XW-100 Automated Hematology Analyzer) to Sysmex America, Inc. The XW-100 Automated Hematology Analyzer offers faster results for patients and providers based on its categorization, and can be run in more health care settings, including physicians' offices, clinics or other types of health care facilities, by a wider range of personnel (e.g. support staff).

The XW-100 Automated Hematology Analyzer is intended for use in patients ≥2 years of age who require a whole blood cell count and white blood cell differential. Test results can be used with other clinical and laboratory findings to provide early alerts for patients with serious conditions such as severe anemia (low red blood cell or hemoglobin count) and agranulocytosis (low white blood cell count), who require additional testing. However, it is not intended to diagnose or monitor patients with primary and/or secondary hematologic diseases, including oncology and critically ill patients. The device works by using a blood sample to classify and quantify 12 different blood characteristics (hematology parameters), which provides patients with a blood component profile as part of their overall health assessment.

The FDA reviewed data from a study conducted on 582 samples collected from patients ranging from 2 to 92 years of age. The study compared the XW-100 test results collected by non-medical personnel in CLIA-waived settings to a hematology analyzer in an accredited clinical laboratory. Results found that by following the manufacturer's instructions for use, accurate testing can be effectively conducted by untrained personnel.
The XW-100 Automated Hematology Analyzer was also granted a waiver under the Clinical Laboratory Improvement Amendments of 1988 (CLIA). The CLIA waiver for this device allows it to be used by a variety of non-traditional laboratory sites, including physicians' offices, clinics or other types of health care facilities with a CLIA Certificate of Waiver (CLIA-waived settings).

The CLIA certificate to a laboratory depends upon the complexity of the tests it performs. CLIA regulations describe three levels of test complexity: waived tests, moderate complexity tests and high complexity tests.

The XW-100 Automated Hematology Analyzer was originally cleared through the 510(k) pathway in 2015 for use at the patient's point-of-care. To support the use of this device in CLIA-waived settings with non-medical personnel, the analyzer provides simple instructions for operator actions when results are flagged or outside of a specified range. To further ensure accurate testing in this setting and to eliminate results that are most susceptible to inaccuracy or require additional testing, the number of hematology parameters has been reduced to 12[38].

38 https://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm583997.htm

First Comprehensive Estimates and Trends of Disease Burden and Risk Factor for Every State of India

On November 14, 2017, the India State-level Disease Burden Initiative, which is a joint initiative between the Indian Council of Medical Research (ICMR), Public Health Foundation of India (PHFI), and Institute for Health Metrics and Evaluation (IHME) in collaboration with the Ministry of Health and Family Welfare, Government of India along with experts and stakeholders associated with over 100 Indian institutions, released the first comprehensive set of state-level disease burden, risk factors estimates and trends for each state in India for informed health planning to reduce health inequalities amongst states in India. These estimates are based on analysis of all identifiable epidemiological data from India over quarter of a century[39].

The report provides the first comprehensive set of findings for the distribution of diseases and risk factors across every state of India from 1990 to 2016, utilizing all available data and in close engagement with many leading health scientists of India. Through an elaborate process all available data sources to estimate disease burden in every state and union territory of India were identified and accessed. These included censuses, vital registration, Sample Registration System, large-scale national household surveys, other population-level surveys and cohort studies, disease surveillance data, disease programme-level data, administrative records of health services, disease registries, and a wide range of other studies conducted across India. Data was included in the analysis if it met quality and inclusion criteria. The burden from 333 disease conditions and injuries and 84 risk factors were computed for each state of India as part of the Global Burden of Disease Study 2016.

In order to understand the specific disease trends amongst various states at different levels of epidemiological transition, the states were divided into groups based on the ratio of Disability Adjusted Life Years (DALYs) from infectious and associated diseases to DALYs from non-communicable diseases and injuries combined. Variations of diseases and risk factors were analyzed between groups of states and between individual states that are relevant for a more informed specific health system response in each state.

The report shows a rising burden of non-communicable diseases in all states. The percentage of most of the major non-communicable disease groups to the total disease burden has increased all over India since 1990, including cardiovascular diseases, diabetes, chronic respiratory diseases, mental health and neurological disorders, cancers, musculoskeletal disorders, and chronic kidney disease.

The Key Findings of this report are as follows:

- Life expectancy at birth improved in India from 59.7 years in 1990 to 70.3 years in 2016 for females, and from 58.3 years to 66.9 years for males. However, inequalities in life expectancy continues between states, with the same ranging from 66.8 years in Uttar Pradesh to 78.7 years in Kerala for females, and 63.6 years in Assam to 73.8 years in Kerala for males in 2016.
- Even though, the per person disease burden dropped by 36% from 1990 to 2016 in India, there was an almost two-fold difference in this rate between the states in 2016, with Assam, Uttar Pradesh, and Chhattisgarh having the highest rates, and Kerala and Goa the lowest rates.
- The under-5 mortality rate has reduced substantially from 1990 in all states, but there was a four-fold difference in this rate between the highest in Assam and Uttar Pradesh as compared to the lowest in Kerala in 2016, highlighting the vast health inequalities between the states.

39 http://icmr.nic.in/publications/India_Health_of_the_Nation's_States_Report_2017.pdf

- In 1990, 61% of the total disease burden in India was due to communicable, maternal, neonatal, and nutritional diseases; the corresponding number for which to 33% in 2016. However, the percentage of non-communicable diseases in the total disease burden rose from 30% in 1990 to 55% in 2016, and the percentage of injuries also rose from 9% to 12%.

Infectious and associated diseases, which accounted for more than half of the disease burden in most of the states in 1990, slid down to less than half in all states in 2016, though there were wide variations between the states. Kerala, Goa, and Tamil Nadu show the highest dominance of non-communicable diseases and injuries over infectious and associated diseases, whereas a similar dominance, though reflected, is relatively the lowest in Bihar, Jharkhand, Uttar Pradesh, and Rajasthan.

- The burden of most infectious and associated diseases reduced in India from 1990 to 2016, but five of the ten individual leading causes of disease burden in India in 2016 still belonged to this group:

  Diarrhoeal diseases,

  Lower respiratory infections,

  Iron-deficiency anaemia,

  Neonatal

  Preterm birth, and

  Tuberculosis.

The range of disease burden or DALY rate among the states of India was nine-fold for diarrhoeal disease, seven-fold for lower respiratory infections, and nine fold for tuberculosis in 2016, highlighting the need for titrating efforts based on the specific trends in each state.

- The contribution of most of the major non-communicable disease groups to the total disease burden has increased all over India since 1990, including cardiovascular diseases, diabetes, chronic respiratory diseases, mental health and neurological disorders, cancers, musculoskeletal disorders, and chronic kidney disease. In 2016, three of the five leading individual causes of disease burden in India were non-communicable, with ischaemic heart disease and chronic obstructive pulmonary disease as the top two causes and stroke as the fifth leading cause. The range of disease burden or DALY rate among the states in 2016 was nine-fold for ischaemic heart disease, four-fold for chronic obstructive pulmonary disease, and six-fold for stroke, and four-fold for diabetes.

- The contribution of injuries to the total disease burden has increased in most states since 1990. The highest proportion of disease burden due to injuries is in young adults. Road injuries and suicides are the leading contributors to the injury burden in India. The range of disease burden or DALY rate varied three-fold for road injuries and six-fold for suicide among the states of India in 2016.

- A group of risks including unhealthy diet, high blood pressure, high blood sugar, high cholesterol, and overweight, which mainly contribute to ischaemic heart disease, stroke and diabetes, caused about 25% of the total disease burden in India in 2016, up from about 10% in 1990. There were large variations between states in the degree to which these risks are rising.

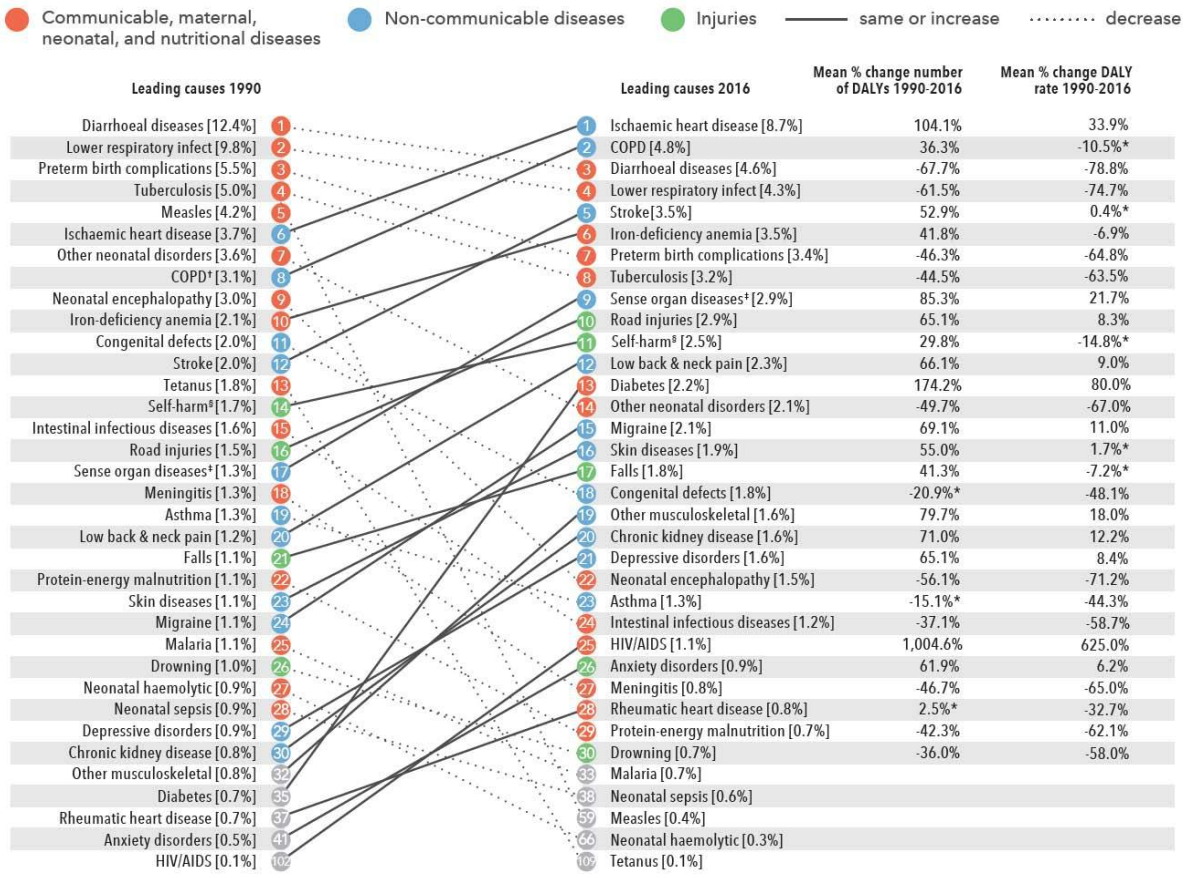
- While the disease burden due to child and maternal malnutrition has dropped in India substantially since 1990, it is still the single largest risk factor responsible for 15% of the total disease burden in India in 2016. This burden is highest in the EAG states[40] and Assam, and is higher in females than in males. The disease

40 Empowered Action Group (EAG) states: A group of eight states that receive special development effort attention from the Govern ment of India, namely, Bihar, Chhattisgarh, Jharkhand, Madhya Pradesh, Odisha, Rajasthan, Uttarakhand, and Uttar Pradesh.

burden due to child and maternal malnutrition in India was 12 times higher per person than in China in 2016. Kerala, having the lowest burden in this category, still lags behind China by 2.7 times higher risk.

- The disease burden due to unsafe water and sanitation has also reduced significantly in India, but this burden is still 40 times higher per person in India than in China. The EAG States and Assam have a particularly high burden due to this risk.
- The contribution of air pollution to disease burden has remained high in India between 1990 and 2016, with levels of exposure amongst the highest in the world. The burden of household air pollution has decreased during this period due to decreasing use of solid fuels for cooking, but that of outdoor air pollution has increased due to a variety of pollutants from power production, industry, vehicles, construction, and waste burning. The level of exposure to air pollution is highest in the EAG states.

Change in DALYs number and rate for the leading individual causes in India from 1990 to 2016



*Change not significant
The percent figure in bracket next to each cause is DALYs from that cause out of the total DALYs.

†COPD is chronic obstructive pulmonary disease.
‡Sense organ diseases includes mainly hearing and vision loss.
§Self-harm refers to suicide and the nonfatal outcomes of self-harm.

NPPA updates for the month of November on price capping of scheduled formulations

On November 23, 2017, National Pharmaceutical Pricing Authority (NPPA) has fixed/revised the retail price/ceiling price of 51 formulations of schedule-I formulations under Drug Price Control Order (DPCO), 2013. However, the price capping of the existing schedule I formulations / new drugs formulations is exclusive of goods and services tax applicable, if any. The updates on ceiling/retail prices capping are discussed point wise –

1. NPPA, by its first notification, has fixed the ceiling prices of six formulations including prices of Japanese Encephalitis and measles rubella vaccines exclusive of goods and services tax, if any. The price fixing is performed in exercise of the powers conferred by paragraphs 4, 6, 10, 11, 14, 15, 16, 17 and 18 of the Drugs (Prices Control) Order, 2013 for below formulations-

Sl. No.	**Scheduled Formulation**	**Dosage form & Strength**	**Unit**
1.	Oxaliplatin	Injection 100mg (as licensed)	Each Pack
2.	Acetylsalicylic acid	Effervescent/ Dispersible/Enteric coated Tablet 100 mg	1 Tablet
3.	Japanese Encephalitis Vaccine	4mcg to 6mcg	Each Pack
4.	Japanese Encephalitis Vaccine	up to 3mcg	Each Pack
5.	Measles Rubbela Vaccine	-	Each Pack (0.5ml)
6.	Surfactant	Suspension for intratracheal instillation (As licensed)	Per mg of Phospholipids in the pack

2. NPPA, by its second notification, has revised the ceiling prices of eight scheduled formulations after suppressing its previous notifications SO 2060(E) & S.O. 2061(E) dated June 30, 2017 as listed in the table –

Sl. No.	**Scheduled Formulation**	**Dosage form & Strength**	**Unit**
1.	Sevoflurane	Inhalation	1 ml
2.	Acetylsalicylic acid	Tablet 325mg	1 Tablet
3.	Desferrioxamine	Powder for Injection 500mg	each pack
4.	Oxaliplatin	Injection 50mg (as licensed)	Each Pack
5.	Phytomenadione (Vitamin K1)	Injection 10mg/ml	1 ML
6.	Glutaraldehyde	Solution 2%	1 ML
7.	Anti-D immunoglobulin	Injection 300mcg	Each Pack
8.	BCG vaccine	-	Each Dose

3. NPPA, by its third notification has fixed the ceiling prices of below seven formulations on the basis of procurement prices; and in exercise of the powers conferred by paragraphs 19 of the Drugs (Prices Control) Order, 2013 which makes it mandatory to fix ceiling prices of scheduled formulations -

Sl. No.	Scheduled Formulation	Dosage form & Strength	Unit
1.	Morphine	SR Tablet 30 mg	1 Tablet
2.	Alteplase	Powder for Injection 20 mg	Each Pack
3.	Alteplase	Powder for Injection 50 mg	Each Pack
4.	Gadobenate	Injection 529 mg/ml	1 ML
5.	Haemodialysis fluid	as license	1 ML
6.	Furosemide	Oral liquid 10 mg/ml	1 ML
7.	Glucose	Injection 50%	1 ml

4. NPPA, by its fourth notification, has revised the ceiling prices of below seven formulations by suppressing its notification no. S. O. 2060(E) and SO 2061(E) dated June 30, 2017, and in exercise of the powers conferred by paragraphs 19 of the Drugs (Prices Control) Order, 2013 as it is necessary to fix ceiling prices of scheduled formulations -

Sl. No.	Scheduled Formulation	Dosage form & Strength	Unit
1.	Lignocaine (A) + Adrenaline (B)	Injection 1% (A) + 1:200000 (5 mcg/ml) (B)	1 ML
2.	Calcium gluconate	Injection 100 mg/ml	1 ML
3.	Dextran-40	Injection 10%	1 ML
4.	Coagulation factor IX	Powder for Injection 600 IU	Each Pack
5.	Digoxin	Oral liquid 0.05 mg/ml	1 ML
6.	Potassium permanganate	Crystals for topical solution	1 gm
7.	Pilocarpine	Drops 4%	1 ML

5. NPPA fixed the retail price of New Drug formulations applicable only to the individual manufacturers / marketers who have applied for the same by submitting Form-I for price fixation / revision as stipulated under DPCO, 2013. For example – the retail price of each film coated tablet of Sofosbuvir & Velpatasvir has been fixed, which contains: Sofosbuvir 400mg and Velpatasvir 100mg is supplied by six odd combinations of manufacturer & marketing companies i.e. M/s Hetero Labs Ltd. is a manufacturer and M/s Abbott India Ltd is a marketing company[41].

41 http://www.nppaindia.nic.in/ceiling/press23oct17/Prices(5).pdf

6. NPPA has further notified the retail price of new Drug formulations applicable only to the individual manufacturers / marketers who have applied for the same by submitting Form-I for price fixation / revision as stipulated under DPCO, 2013 as mentioned below-

Sl. No.	Name of the Scheduled Formulation / Brand Name	Strength	Unit	Manufacturer & Marketing Company
1.	Sofosbuvir & Velpatasvir	Sofosbuvir 400mg + Velpatasvir 100mg	28 Tablets	1. M/s Dr. Reddy's Limited 2. M/s Hetro Labs Ltd.
2.	Voglibose + Metformin	Voglibose 0.2mg + Metformin 500mg	1 Tablet	M/s Lupin Ltd.
3.	Voglibose + Metformin	Voglibose 0.3mg + Metformin 500mg	1 Tablet	M/s Lupin Ltd.
4.	Voglibose + Metformin + Glimepirid	Voglibose 0.2mg + Metformin 500mg + Glimepirid 1mg	1 Tablet	1. M/s Lupin Ltd. 2. M/s Sanofi India Ltd. 3. M/s Biocon Ltd
5.	Voglibose + Metformin + Glimepirid	Voglibose 0.2mg + Metformin 500mg + Glimepirid 2mg	1 Tablet	1. M/s Lupin Ltd. 2. M/s Sanofi India Ltd. 3. M/s Biocon Ltd.
6.	Voglibose + Metformin + Glimepirid	Voglibose 0.3mg + Metformin 500mg + Glimepirid 1mg	1 Tablet	1. M/s Lupin Ltd. 2. M/s Alembic Ltd.
7.	Voglibose + Metformin + Glimepirid	Voglibose 0.3mg + Metformin 500mg + Glimepirid 2mg	1 Tablet	M/s Lupin Ltd.
8.	Diclofenac + Tramadol	Diclofenac 75mg + Tramadol 50mg	1 Tablet	M/s Alembic Ltd.

7. NPPA fixed the retail price of 1 scheduled formulation (Volitra Enzo enteric coated tablet) in implementation of review orders issued by the Department of Pharmaceuticals (DOP) under para 31 of Drugs (Prices Control) Order, 2013.

Volitra Enzo enteric coated tablet which contains: Trypsin 48mg Bromelain 90mg Rutoside Trihydrate 100mg Diclofenac Sodium 50mg manufactured by M/s Akums Drugs & Pharmaceuticals Ltd. and marketed by M/s Sun Pharmaceuticals Ind. Ltd[42].

8. NPPA fixed the retail price of two formulations in implementation of directions given in line with review orders issued by the Department of Pharmaceuticals (DOP) under para 31 of Drugs (Prices Control) Order, 2013. Hereby NPPA revise the retail price of Ceftriaxone Powder for Injection 1gm each pack and Chloroquine Tablet 150mg per tablet[43].

42 http://www.nppaindia.nic.in/ceiling/press23oct17/Prices(7).pdf

43 http://www.nppaindia.nic.in/ceiling/press23oct17/Prices(8).pdf

FDA approves pill with sensor that digitally tracks if patients have ingested their medication

On November 13, 2017, the United States Food and Drug Administration (USFDA) approved the first ever drug in the U.S. with a digital ingestion tracking system. Abilify MyCite (aripiprazole tablets with sensor) has an ingestible sensor embedded in the pill that records that the medication was taken. The product is approved for the treatment of schizophrenia, acute treatment of manic and mixed episodes associated with bipolar I disorder and for use as an add-on treatment for depression in adults[44].

The system works by sending a message from the pill's sensor to a wearable patch. The patch transmits the information to a mobile application so that patients can track the ingestion of the medication on their smart phone. Patients can also permit their caregivers and physician to access the information through a web-based portal.

Schizophrenia is a chronic, severe and disabling brain disorder. Symptoms of schizophrenia include hearing voices, believing other people are reading their minds or controlling their thoughts, and being suspicious or withdrawn. Bipolar disorder, also known as manic-depressive illness, is another brain disorder that causes unusual shifts in mood, energy, activity levels and the ability to carry out day-to-day tasks. The symptoms of bipolar disorder include alternating periods of depression and high or irritable mood, increased activity and restlessness, racing thoughts, talking fast, impulsive behavior and a decreased need for sleep.

ABILIFY MYCITE (aripiprazole tablets with sensor) is a drug-device combination product comprising of Otsuka's oral aripiprazole tablets embedded with an Ingestible Event Marker (IEM) sensor. This IEM sensor is the size of a grain of sand, and is made up of ingredients found in food. The IEM sensor gets activated when it comes in contact with stomach fluid and communicates to a wearable sensor, called the MYCITE Patch. The IEM sensor is then digested and eliminated from the body.

The ABILIFY MYCITE System includes: ABILIFY MYCITE, the MYCITE® Patch (wearable sensor); the MYCITE APP (a smartphone application); and web-based portals for healthcare providers and caregivers. The system records medication ingestion and communicates it to the patient and healthcare provider. In addition, it can collect data on activity levels, as well as self-reported rest and mood which, with patient consent, can be shared with the healthcare provider and selected members of the family and care team. The system provides an objective summary of drug ingestion over time, to help enhance collaboration with healthcare providers who treat patients with certain serious mental illnesses[45].

Abilify was first approved by the FDA in 2002 to treat schizophrenia. The ingestible sensor used in Abilify MyCite was first permitted for marketing by the FDA in 2012. The FDA granted the approval of Abilify MyCite to Otsuka Pharmaceutical Co., Ltd. The sensor technology and patch are made by Proteus Digital Health.

Conclusion:

The approval of ABILIFY MYCITE, the first digital medicine system, provides an innovative way to treat individuals with serious mental illness, and also provides valuable information about patient medication ingestion patterns, that could help physicians in better illness management and provide more personalized treatment plan to individual patients.

44 https://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm584933.htm

45 https://www.otsuka-us.com/discover/articles-1075

Health Ministry introduces Daily Drug Regimen for treatment of Tuberculosis

The Ministry of Health & Family Welfare has recently announced the launch of daily regimen for TB patients across the country, under the Revised National TB Control Programme (RNTCP). The Health Ministry has been mandating the thrice-weekly regimen for the treatment of tuberculosis (TB). However, it has now decided to change the treatment strategy for TB patients from thrice weekly to a daily drug regimen using fixed dose combinations (FDC) for treatment. This change will bring transformation in the approach and the intensity to deal with this disease which accounts for about 4.2 lakh deaths every year[46].

The daily FDC anti-TB drugs regimen will be made available to private pharmacies and to private practitioners free of cost, to dispense to TB patients who seek care in private sector. The Health Ministry will take this forward with all major hospitals, IMA, IAP and other professional medical associations to expand access to daily FDC to all TB patients.

The salient features of this treatment strategy are use of Ethambutol in continuation phase for all patients, drugs to be given daily (as against only 3 times weekly previously), fixed dose combination (FDC) tablets to be used which will reduce pill burden (as against separate 7 tablets previously), for children - child friendly formulations as dispersible tablets and use of Information Technology (IT) enabled treatment adherence support system.

The WHO Global TB Report, 2017 has reported that incidence of TB has reduced from 28.2 lakh to 27 lakh and mortality by 60 thousand over the last one year, which is a testimony of anti TB drive by the Government of India.

46 http://pib.nic.in/newsite/erelease.aspx?relid=173607

Indian Pharmacopoeia Commission (IPC) releases Eighth Edition of Indian Pharmacopoeia (IP)

The Indian Pharmacopoeia Commission (IPC) has released the Eighth Edition of Indian Pharmacopoeia (IP-2018). It was released by the Secretary, Ministry of Health & Family Welfare, Government of India[47].

The IP is an authoritative and legally enforceable book of standard of drugs manufactured/marketed in India. It is published by the Indian Pharmacopoeia Commission (IPC) on behalf of the Ministry of Health & Family Welfare, Government of India, in fulfillment of the requirements of the Drugs and Cosmetics Act, 1940 and the Rules thereunder. It intends to help in the licensing of manufacturing, inspection and distribution of medicines.

Regular publication of IP is an important mandate of IPC aimed at improving health by ensuring the quality, safety and efficacy of medicines. The Commission has been receiving significant advisory and directions from regulatory bodies and valuable inputs from industrial houses, academic institutions, national laboratories, individual scientists and others.

IP-2018 has been brought out in 4 Volumes incorporating 220 new monographs (Chemical Monographs (170), Herbal Monographs (15), Blood and Blood related products (10), Vaccines and Immunosera for Human use monographs (02), Radiopharmaceutical monographs (03), Biotechnology Derived Therapeutic Products (06), Veterinary monographs (14)), 366 revised monographs and 7 omissions.

Salient Features of IP-2018 are[48]:

Keeping in view the essential requirement for harmonization of analytical methods with those accepted internationally, steps have been taken for monitoring drug standards.

- General Chemical tests & Thin Layer Chromatography (TLC) for identification of an article have been almost eliminated; and more specific infrared, ultraviolet spectrophotometer and HPLC tests have been emphasized. The concept of relying on published infrared spectra as a basis for identification has been continued.
- The use of chromatographic methods has been extended to cope with the need for more specificity in assays and in particular, in assessing the nature and extent of impurities in ingredients and products.
- Most of the existing Assays and Related Substances Test methods have been upgraded by liquid chromatography to harmonize with other International Pharmacopoeias.
- Pyrogen test has been replaced by Bacterial Endotoxin test (BET) in parenteral preparations and other monographs.
- For ease of access to make Pharmacopoeia more user-friendly, an Index has been incorporated in Volume-I along with the already existing one in Volume-IV of IP.
- 53 New Fixed Dose Combination (FDCs) monographs have been included, out of which 25 FDC monographs are not available in any Pharmacopoeia.
- General Chapters on Volumetric Glassware, Conductivity, Dissolution test, Disintegration test, Dimensions of Hard Gelatin Capsule Shells etc. have been revised.

47 http://ipc.nic.in/index1.asp?EncHid=&lang=1&linkid=88&lid=850

48 http://ipc.nic.in/showfile.asp?lid=851&EncHid=

For Controlling the Microbial quality of the entire medicinal range, a general chapter on Maintenance, Identification, Preservation and Disposal of Microorganism has been revised.

The 170 New Chemical Monographs in IP-2018 are:

1. Abiraterone Acetate Tablets
2. Aluminium, Magnesium and Simethicone Chewable Tablets
3. Aluminium, Magnesium and Simethicone Oral Suspension
4. Ambrisentan
5. Ambrisentan Tablets
6. Amiloride and Hydrochlorothiazide Tablets
7. Amlodipine and Benazepril Hydrochloride Capsules
8. Aprepitant
9. Aprepitant Capsules
10. Armodafinil
11. Artesunate Injection
12. Atenolol and Chlorthalidone Tablets
13. Atorvastatin and Fenofibrate Tablets
14. Azelnidipine Tablets
15. Bisoprolol Fumarate
16. Bisoprolol Fumarate and Hydrochlorothiazide Tablets
17. Bosentan Monohydrate
18. Bosentan Tablets
19. Calcium and Vitamin D3 Tablets
20. Captopril and Hydrochlorothiazide Tablets
21. Carmustine
22. Carmustine Injection
23. Cefdinir
24. Cefdinir Oral Suspension
25. Cefixime Dispersible Tablets
26. Cefuroxime Axetil and Potassium Clavulanate Tablets
27. Cholecalciferol Concentrate (Powder Form)
28. Cilnidipine
29. Cilnidipine Tablets
30. Cinacalcet Hydrochloride
31. Clindamycin Palmitate Hydrochloride
32. Clindamycin Palmitate Hydrochloride Oral Suspension
33. Clonidine Hydrochloride and Chlorthalidone Tablets
34. Cyclobenzaprine Hydrochloride
35. Cyclobenzaprine Tablets
36. Dacarbazine
37. Dacarbazine Injection
38. Daclatasvir Hydrochloride
39. Dapoxetine Tablets
40. S-Dapoxetine Hydrochloride
41. S-Dapoxetine Tablets
42. Dapsone Gel
43. Darifenacin Hydrobromide
44. Darifenacin Prolonged-release Tablets
45. Darunavir Ethanolate
46. Darunavir Tablets
47. Diclofenac Diethylamine
48. Diclofenac Sodium and Paracetamol Tablets
49. Diclofenac Gel
50. Diethylene Glycol Monoethyl Ether
51. Dinoprostone
52. Dinoprostone Oral Solution
53. Diphenoxylate Hydrochloride and Atropine Sulphate Tablets
54. Dopamine Hydrochloride and Dextrose Injection
55. Dothiepin Tablets
56. Enalapril Maleate and Hydrochlorothiazide Tablets
57. Escitalopram Oxalate and Clonazepam Tablets
58. Esmolol Injection
59. Etodolac Prolonged-release Tablets
60. Folic Acid and Methylcobalamin Tablets
61. Ganciclovir
62. Ganciclovir Injection
63. Ganciclovir Oral Suspension
64. Glibenclamide and Metformin Tablets
65. Glycopyrrolate
66. Glycopyrrolate Injection
67. Glycopyrrolate Tablets
68. Hydroxyurea
69. Hydroxyurea Capsules
70. Ibuprofen and Paracetamol Tablets
71. Ibuprofen and Pseudoephedrine Hydrochloride Tablets
72. Isoflurane
73. Isotretinoin Gel
74. Latanoprost Eye Drops
75. Latanoprost and Timolol Ophthalmic Solution
76. Letrozole
77. Letrozole Tablets
78. Levetiracetam Tablets
79. Levodopa and Carbidopa Prolonged-release Tablets
80. Levofloxacin Oral Solution
81. Lignocaine
82. Lignocaine and Prilocaine Cream
83. Lignocaine Hydrochloride Topical Solution
84. Lignocaine Oral Topical Solution
85. Lorcaserin Hydrochloride Hemihydrate
86. Lorcaserin Tablets
87. Magaldrate and Simethicone Chewable Tablets
88. Magaldrate and Simethicone Oral Suspension
89. Mefenamic Acid and Dicyclomine Hydrochloride Tablets
90. Memantine Hydrochloride
91. Memantine Tablets
92. Mesna
93. Metadoxine
94. Metformin Hydrochloride Prolonged-release and Glimepiride Tablets
95. Methylcobalamin
96. Methyldopa and Hydrochlorothiazide Tablets
97. Metoprolol Succinate Prolongedrelease and Amlodipine Besilate Tablets
98. Metoprolol Tartrate and Hydrochlorothiazide Tablets
99. Montelukast Granules
100. Montelukast Sodium and Levocetirizine Hydrochloride Tablets
101. Mycophenolate Mofetil Oral Suspension
102. Mycophenolate Mofetil Tablets
103. Nadifloxacin
104. Nadifloxacin Cream
105. Nadifloxacin Gel
106. Nitroglycerin Injection
107. Norethisterone and Ethinyl Estradiol Tablets
108. Norgestimate
109. Norgestimate and Ethinyl Oestradiol Tablets
110. Ofloxacin and Ornidazole Tablets
111. Olanzapine and FluoxetineTablets
112. Olmesartan Medoxomil and Hydrochlorothiazide Tablets
113. Omeprazole and Domperidone Capsules
114. Olopatadine Hydrochloride
115. Olopatadine Ophthalmic Solution
116. Olopatadine Tablets
117. Oxaliplatin
118. Oxaliplatin Injection
119. Oxybutynin Hydrochloride
120. Oxybutynin Prolonged-release Tablets
121. Oxymetazoline Hydrochloride Nasal Solution
122. Oxymetazoline Hydrochloride
123. Paliperidone
124. Pantoprazole Gastro-resistant and Domperidone Prolonged-release Capsules
125. Paracetamol and Caffeine Tablets
126. Paroxetine Hydrochloride Hemihydrate
127. Phenylephrine Eye Drops
128. Phenylephrine Hydrochloride and Chlorpheniramine Maleate Drops
129. Phenylephrine Hydrochloride and Chlorpheniramine Maleate Syrup
130. Phytomenadione
131. Phytomenadione Injection
132. Piperacillin and Tazobactam Injection
133. Piroxicam Tablets
134. Pregabalin and Methylcobalamin Capsules
135. Prilocaine
136. Procarbazine Hydrochloride Capsules
137. Propylene Glycol Monocaprylate
138. Quinapril Hydrochloride
139. Quinapril and Hydrochlorothiazide Tablets
140. Repaglinide and Metformin Tablets
141. Risedronate Sodium Tablets
142. Ropivacaine Hydrochloride
143. Ropivacaine Injection
144. Rosuvastatin Calcium and Ezetimibe Tablets
145. Rosuvastatin and Fenofibrate Tablets
146. Sertaconazole Nitrate
147. Sertaconazole Nitrate and Beclomethasone Dipropionate Cream
148. Sodium Alendronate Trihydrate
149. Sucralfate
150. SucralfateTablets
151. Tamsulosin Hydrochloride Prolonged-release and Dutasteride Capsules
152. Tazobactam
153. Telmisartan and Amlodipine Tablets
154. Telmisartan and Hydrochlorothiazide Tablets
155. Terbinafine Hydrochloride
156. Terbinafine Cream
157. Terbinafine Tablets
158. Thioguanine
159. Thioguanine Tablets
160. Ticagrelor
161. Tobramycin and Fluorometholone Acetate Ophthalmic Suspension
162. Tobramycin Inhalation Solution
163. Trimetazidine Tablets
164. Trospium Chloride Tablets
165. Voriconazole Injection
166. Xylometazoline Hydrochloride and Sorbitol Nasal Drops
167. Zolpidem Tartrate Prolongedrelease Tablets
168. Zonisamide Capsules
169. Gentamicin Cream
170. Gentamicin Ointment

The 15 New Herbal Monographs in IP-2018 are

1. Amarbel	9. Mandarin Oil
2. Anise Oil	10. Milk Thistle
3. Belladona Dry Extract Tablets	11. Milk Thistle Dry Extract
4. Citronella Oil (Geraniol type)	12. Schisandra Dry Extract
5. Citronella Oil (Java type)	13. Schisandra Fruit
6. Green Coffee Bean Extract	14. Sweet Orange Oil
7. Horse Chestnut Dry Extract	15. Tvak
8. Juniper Oil	

The 10 New Monographs on Blood and Blood related products in IP-2018 are

1. Anti-D (IgM) monoclonal blood grouping reagent	6. Blood Grouping Reagents Anti P1
2. Blood Grouping Reagent Anti-Fy^a, Anti-Fy^b	7. Blood Grouping Reagents Anti-Lea, Anti-Leb
3. Blood Grouping Reagent Anti-Jk^a, Anti-Jk^b	8. Blood Grouping Reagents Anti-S, Anti-s
4. Blood Grouping Reagent Anti-K, Anti-k	9. Blood Grouping Lectins Anti-H
5. Blood Grouping Reagent Anti-M, Anti-N	10. Blood Grouping Lectins Anti-A1

The 6 New Monographs on Biotechnology Derived Therapeutic products in IP-2018 are

1. Follicle Stimulating Hormone Concentrated Solution	4. Interferon b-1a Injection
2. Follicle Stimulating Hormone Injection	5. Teriparatide
3. Follicle Stimulating Hormone	6. Teriparatide injection

The 2 New Monographs on Vaccines and Immunosera for Human use in IP-2018 are

1. Pneumococcal polysaccharide conjugate vaccine (Adsorbed)	2. Scorpion Venom Antiserum

The 3 New Monographs of Radiopharmaceutical in IP-2018 are

1. Gallium (^{68}Ga) Chloride solution for Radiolabelling	3. Sodium Iodide (^{123}I) Solution for Radiolabelling
2. Sodium Iodide (^{123}I) Injection (From ^{124}Xe)	

The 14 Monographs of Veterinary Non-biological IP-2018 are

1. Albendazole Veterinary Oral Powder	8. Cephalexin Veterinary Oral Powder
2. Amoxycillin Tablets	9. Enrofloxacin Injection
3. Amprolium Oral Powder	10. Marbofloxacin Injection
4. Buparvaquone	11. myo-Inositol
5. Buparvaquone Injection	12. Oxytetracycline Hydrochloride Injection
6. Cefuroxime Intramammary Infusion	13. Sodium Acid Phosphate Injection
7. Cephalexin Intrauterine Powder for Suspension	14. Trimethoprim and Sulphamethoxazole In jection

One-in-Ten medical products is substandard or falsified in developing countries: World Health Organization (WHO)

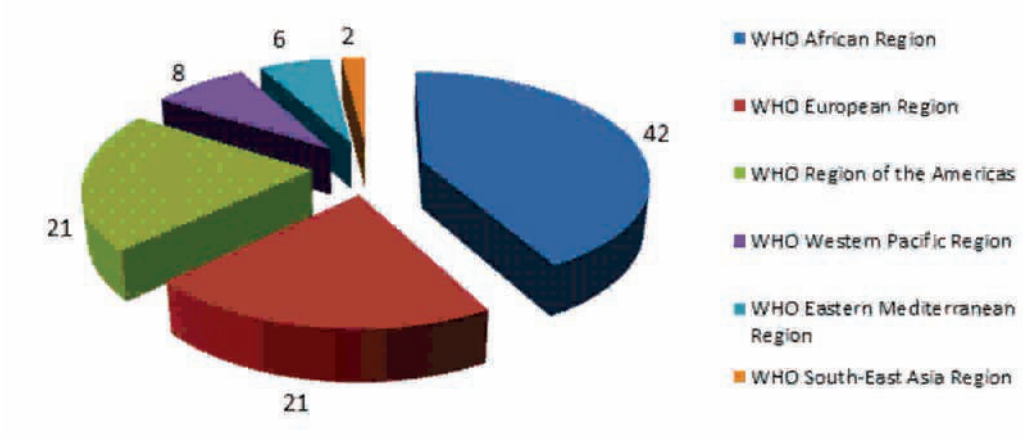
WHO urges governments to take action

An estimated 1-in-10 medical products circulating in low- and middle-income countries is either substandard or falsified, according to new research from WHO[49].

WHO said that this means that people are taking medicines that fail to treat or prevent diseases. Not only is it a waste of money for individuals and health systems that purchase these products, but substandard or falsified medical products can cause serious illness or even death.

WHO further said that since 2013 it has received 1500 reports of cases of substandard or falsified products. Of these, anti-malarials and antibiotics are the most commonly reported, followed by Lifestyle products that include products for cosmetic use, erectile dysfunction, body-building and dieting.

About 42% of the reports come from the WHO African Region, 21% from the WHO Region of the Americas, and 21% from the WHO European Region. WHO also said that this is likely just a small fraction of the total problem and many cases may be going unreported. For example, only 8% of reports of substandard or falsified products to WHO came from the WHO Western Pacific Region, 6% from the WHO Eastern Mediterranean Region, and just 2% from the WHO South-East Asia Region (Figure 1 below).



The WHO research highlights that it has received reports of substandard or falsified medical products ranging from cancer treatment to contraception. These are not confined to high-value medicines or well-known brand names but are split almost evenly between generic and patented products.

In conjunction with the first report from the Global Surveillance and Monitoring System[50], WHO has also published a research that estimates a 10.5% failure rate of all medical products used in low- and middle-income countries.

This study was based on more than 100 published research papers on medicine quality surveys done in 88 low- and middle-income countries involving 48000 samples of medicines. Lack of accurate data means that these

49 http://www.who.int/mediacentre/news/releases/2017/substandard-falsified-products/en/

50 http://www.who.int/entity/medicines/regulation/ssffc/publications/gsms-report-sf/en/index.html

estimates are just an indication of the scale of the problem. More research is needed to accurately estimate the threat posed by substandard and falsified medical products.

Based on the 10% estimates of substandard and falsified medicines, a modelling exercise developed by the University of Edinburgh estimates that 72000 to 169000 children may be dying each year from pneumonia due to substandard and falsified antibiotics. A second model developed by the London School of Hygiene and Tropical Medicine estimates that 116000 (64000 – 158000) additional deaths from malaria could be caused every year by substandard and falsified anti-malarials in sub-Saharan Africa, with a cost of US$ 38.5 million (21.4 million – 52.4 million) to patients and health providers for further care due to failure of previous treatment.

What are substandard and falsified medical products?

Substandard medical products

- Also called "out of specification", these are authorized medical products that fail to meet either their quality standards or their specifications, or both[51].

Unregistered/unlicensed medical products

- Medical products that have not undergone evaluation and/or approval by the NMRA for the market in which they are marketed/distributed or used, subject to permitted conditions under national or regional regulation and legislation.

Falsified medical products

- Medical products that deliberately/fraudulently misrepresent their identity, composition or source[3].

The Internet Gateway

WHO also reported that in some high-income countries, medical products bought over the Internet from illegal or unauthorized websites, social media platforms or smartphone applications frequently fail to meet quality standards. Online pharmacies have become increasingly popular, for example in the United States of America, the number of people buying medicines online has more than quadrupled in less than a decade[52]. The inexorable growth in online sales provides criminals with a relatively easy entry point into even the best regulated markets. Authorities around the world are working to tackle this new challenge, but it is universally recognized to be a difficult task. Modern purchasing models such as online pharmacies can easily circumvent regulatory oversight. Regulating the supply of medicines and investigating the online supply of substandard and falsified medical products is complex, often involving several countries. This can lead to jurisdictional complexities and the requirement of evidence from multiple countries.

Substandard and Falsified Medical Products: The Solution

According to the WHO report, Globalization is making it harder to regulate medical products. Many falsifiers manufacture and print packaging in different countries, shipping components to a final destination where they are assembled and distributed. Sometimes, offshore companies and bank accounts have been used to facilitate the sale of falsified medicines.

Therefore, WHO has called for serious, well-resourced efforts to tackle the issue and has summarized what needs to be done to achieve this:

51 Appendix 3 to Annex, World Health Assembly document A70/23, 2017.

52 WHO Global Surveillance and Monitoring System for substandard and falsified medical products, 2017

- PREVENT the manufacture, sale and consumption of substandard and falsified medical products;
- implement systems to DETECT any substandard or falsified products that are already in the supply chain;
- RESPOND quickly and proportionately to any incidents that are detected, in ways that safeguard patients and the supply chain, take appropriate action against those responsible, whilst not causing unnecessary shortages.

Most of these actions require the coordinated participation of a number of different actors, including national and regional governments; global organizations; the private and non-profit sectors; and civil society. Effective action also requires close collaboration between disciplines: health authorities must work with customs and law enforcement agencies; pharmacovigilance systems must link to those that track antimicrobial resistance and falsified products; pharmaceutical and logistics companies must exchange information with regulators; patient and consumer groups must interact fluently with authorities.

Conclusion

Substandard medical products reach patients when the tools and technical capacity to enforce quality standards in manufacturing, supply and distribution are limited. Falsified products, on the other hand, tend to circulate where inadequate regulation and governance are compounded by unethical practices by wholesalers, distributors, retailers and health care workers. A high proportion of cases reported to WHO occur in countries with constrained access to medical products.

WHO has called this a global problem, and calls on nations for a globally coordinated response to tackle the issue. Countries need to assess the extent of the problem at home and cooperate regionally and globally to prevent the traffic of these products and improve detection and response.

World Health Organization: New global commitment to end tuberculosis

Moscow Declaration to end Tuberculosis (TB)

The World Health Organization (WHO) organized the WHO Global Ministerial Conference in Moscow, Russia from 16-17, November 2017. The conference was attended by more than 1000 participants including Ministers and leaders from UN agencies, civil society, partners, private sector, philanthropies, academia and donors[53].

75 ministers agreed to take urgent action to end tuberculosis (TB) by 2030. The announcement came at the first WHO Global Ministerial Conference on Ending Tuberculosis in the Sustainable Development Era: A Multi-sectoral Response, which brought together delegates from 114 countries in Moscow. President Vladimir Putin of the Russian Federation opened the Conference, together with Amina J Mohammed, UN Deputy Secretary General, and Dr Tedros Adhanom Ghebreyesus, WHO Director-General.

The Moscow Declaration to End TB is a promise to increase multi-sectoral action, track progress, and build accountability. It will also inform the first UN General Assembly High-Level Meeting on TB in 2018, which will seek further commitments from heads of states.

Global efforts to combat TB have saved an estimated 53 million lives since 2000 and reduced the TB mortality rate by 37%. However, progress in many countries has stalled, global targets are off-track, and persistent gaps remain in TB care and prevention.

As a result, TB still kills more people than any other infectious disease. There are major problems associated with antimicrobial resistance, and it is the leading killer of people with HIV.

The conference resulted in collective commitment to ramp-up action on four fronts:

1. Move rapidly to achieve universal health coverage by strengthening health systems and improving access to people-centered TB prevention and care, ensuring no one is left behind.
2. Mobilize sufficient and sustainable financing through increased domestic and international investments to close gaps in implementation and research.
3. Advance research and development for new tools to diagnose, treat, and prevent TB.
4. Build accountability through a framework to track and review progress on ending TB, including multi-sectoral approaches.

Ministers also promised to minimize the risk and spread of drug resistance and do more to engage people and communities affected by, and at risk of, TB.

From India, Shri J P Nadda, Union Minister of Health and Family Welfare, reaffirmed India's commitment to eliminating TB by 2025. The Ministry of Health and Family Welfare also organized a side event at the conference on 'Ending TB: Our Promise to Our People' assisted by Global Coalition against TB to be attended by 7 MPs and other world leaders[54].

53 http://www.who.int/mediacentre/news/releases/2017/commitment-end-tuberculosis/en/

54 http://pib.nic.in/newsite/erelease.aspx?relid=173580

Speaking at the first high level plenary, Shri Nadda said that India has ended polio and will use a similar intensified effort to end TB also. The National Strategic Plan for TB elimination in India has essentially four pillars to address the major challenges for TB control - "Detect, Treat, Build and Prevent". "This plan requires a significant increase in the budget compared to previous NSP and I am happy to share with you that this plan is fully funded and most of this is through domestic resources," Shri Nadda elaborated.

Shri Nadda informed the participants that the Indian government has given top priority to address the quality of care for patients. 25% of the budget is earmarked for direct interventions in this area. This includes free diagnosis with rapid molecular tests, free treatment with best quality drugs and regimens, financial and nutritional support to patients, online TB notification systems, mobile technology based adherence monitoring system, interphase agencies for better private sector engagements, policy for transparent service purchase schemes, stronger community engagements, communication campaigns, regulatory systems to capture information on all those consuming anti-TB drugs etc.

Shri Nadda also said that India is a major manufacturer of anti-TB drugs for the world, having almost an 80% global market share. "We give only the best quality drugs to our patients, whether within the country or abroad. There is a wide scope for us to sit together and discuss seriously about promoting generic drugs for TB patients all over the world, I have no doubt that together we can make TB treatment affordable to all in the world. We owe it to the millions of TB patients and we owe it to ourselves".

The top thematic priorities of this conference based on the SDGs (Sustainable Development Goals) and the UNGA (United Nations General Assembly) high level health themes include Universal Health Coverage, Increased and Sustainable Financing and Scientific Research and Innovation.

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