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S&A PHARMA NEWSLETTER

EDITORIAL

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Founding Partner

The globalization of Healthcare offers a certain degree of exposure of foreign services, ideas, expertise and policies to a country, when it comes to global pharmaceutical industry, despite this exposure various regulatory challenges occur that can impact commercialization of services in most emerging markets. In our present newsletter we start with an article on Indian Pharmaceutical Companies approval from USFDA for their Abbreviated New Drug Applications (ANDAs) for year 2017. The year 2017 was a remarkable year for both Indian pharma industry and United States, as USFDA approved record total 847 ANDAs during 2017 which is highest number of ANDA approvals during last decade, and Indian Pharmaceutical companies bagging over 300 ANDA approvals. Then, we have an article on European Medicines Agency's - Human medicines, Highlights of its new product approvals in 2017. We go on to discuss another article discussing European Medicines Agency (EMA) Recommending Approval of seven medicines in its January Meeting.

The current edition of our Pharma newsletter also addresses; the recent regulatory developments from Health Research, new therapy Approvals worldwide, regulatory reforms in Drug labeling and recall procedures, and global health survey reports on antibiotics resistance. The current issue covers World Health Organization's pre-qualification nod to Bharat Biotech's Typbar-TCV, the first conjugate vaccine for typhoid have longer-lasting immunity than older vaccines. The next is WHO's report of Global Antimicrobial Surveillance System (GLASS) which shows increasingly high levels of antibiotic resistance worldwide, which is a grave concern for the healthcare fraternity.

Then we adress the Competition Commission of India (CCI) decision to Penalise two Chemists and Druggists Associations of Gujrat; The Chemists and Druggists Associations of Baroda (CDAB), and Federation of Gujarat State Chemists and Druggists Association (Gujarat Federation) respectively to be in contravention of the provisions of the Competition Act. Next we highlight the Central Drug Standard Control Organization (CDSCO) notice that clarifies issuance of No Objection Certificate (NOC) for issuance of Form 29 License which is used to manufacture drugs for the purposes of examination, test or analysis for biological products.

Our current issue then covers the USFDA's Breakthrough Therapy designation to Novartis's Kisqali® (Ribociclib) for initial endocrine-based treatment of pre- or peri-menopausal women with HR+/HER2- advanced or metastatic breast cancer. We also address the USFDA draft guidance for strengthening public warning and notification of product recalls, as well as the USFDA recommendation Labeling Changes for Cough and Cold Drugs Containing Opioids to Protect Children.

We wrap up this newsletter with the BREXIT Update where UK's Drug Regulator (MHRA) has issued update to pharmaceutical companies on its exit preparations from the European union.

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Thank you.

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Union Budget 2018: Budget Focuses on Healthcare

The Union Budget 2018 was presented by Finance Minister (FM) Arun Jaitey on February 01, 2018. The major announcements of Union Budget 2018 related to Health sector are being discussed in this article, the Schematic outlays of health sector budget allocation is also being described in the tables below :-

Schematic outlay of health sector budget allocation:

Ministry/Department/Scheme Name	FY 2017-18	FY 2018-19
Health & Family Welfare	**47,353** (crore)	**52,800** (crore)
Pradhan Mantri Swasthya Suraksha Yojna (PMSSY)	3,975	3,825
National AIDS and STD Control programmme	2,000	2,100
National Rural Health Mission	21,189	24,280
National Urban Health Mission	752	875
Human Resoruces for Health & Medical Education	4,025	4,225
Tertiary care programme	725	750
Rashtriya Swasthya Bima Yojana (RSBY)	1,000	2,000
AYUSH	**1,429**	**1,626**
National Ayush Mission (NAM)	441	504
Health Research	**1,500**	**1,800**

- ***Healthcare gets a big boost with announcement of National Health Protection Scheme*** – The finance minister has announced that the government will provide health insurance worth Rs 5 lakh to 10 crore poor families across India. This will be the world's largest government funded health care programme.
- ***Primary, Secondary and Tertiary healthcare:*** 1.5 lakes health and wellness centres for primary, secondary and tertiary healthcare would provide comprehensive healthcare with free diagnostics treatment. This has been given a provision of Rs 1200 crore in the budget.
- ***Tuberculosis (TB) Patients:*** The Government has, decided to allocate additional `600 crore to provide nutritional support to all TB patients at the rate of `500 per month for the duration of their treatment.
- ***Setting up 24 new Government Medical Colleges and Hospitals:*** By upgrading existing district hospitals in the country. This would ensure that there is at least 1 Medical College for every 3 Parliamentary Constituencies and at least 1 Government Medical College in each State of the country.
- ***Health and Education Cess increased by 1%:*** The existing three per cent education cess will be replaced by a four per cent "Health and Education Cess" to be levied on the tax payable. This will enable government to collect an estimated additional amount of `11,000 crores.
- ***Proposals to modify custom Duty rates:*** under indirect tax regime the changes in custom duty to address the problem of duty inversion in medical device sector, further to provide adequate protection to domestic Perfumes and toiletry industry as described below-

Items	Description	Rate of Duty	
		From	To
Medical Devices	Raw materials, parts or accessories for the manufacture of Cochlear Implants	2.5%	nil
Perfumes and toiletry preparations	Preparations for oral or dental hygiene, including denture fixative pastes and powders; yarn used to clean between the teeth (dental floss), in individual retail packages	10%	20%

- **Amendments in Import duty – First Schedule to the Customs Tariff Act, 1975:** The tariff rate of customs duty for the specified medical devices is being increased from 7.5% to 10%. The effective rate of import duty on such medical devices will, however, remain unchanged.
- ***Health insurance limit increased for senior citizen and salaried taxpayer***:

  - Raising the limit of deduction for health insurance premium and/ or medical expenditure from 30,000/- to 50,000/-, under section 80D. All senior citizens will now be able to claim benefit of deduction up to `50,000/- per annum in respect of any health insurance premium and/or any general medical expenditure incurred.
  - Raising the limit of deduction for medical expenditure in respect of certain critical illness from, 60,000/- in case of senior citizens and from 80,000/- in case of very senior citizens, to 1 lakh in respect of all senior citizens, under section 80DDB.
  - In order to provide relief to salaried taxpayers, a standard deduction of 40,000/- in lieu of the present exemption in respect of transport allowance and reimbursement of miscellaneous medical expenses.

- **Promote cultivation of medicinal/ aromatic plants:** Indian ecology supports cultivation of highly specialized medicinal and aromatic plants. India is also home to a large number of small and cottage industries that manufacture perfumes, essential oils and other associated products. To support organized cultivation and associated industry the allocation of a sum of 200 crore is purposed.

Conclusion:

The Union Budget 2018 has taken a step big leap towards achieving universal health coverage by making health care more accessible with the flagship National Health Protection Scheme initiative which should expand access to quality healthcare to the poor and under-privileged. The increase in health insurance limit should also lead to substantial boost in the healthcare insurance sector, Hospital sector should also make gains from this budget.

Bharat Biotech's typhoid vaccine gets World Health Organization (WHO) pre-qualification

On January 03, 2018, the World Health Organization (WHO) announced that it has prequalified Bharat Biotech's Typbar-TCV®[1], the first conjugate vaccine for typhoid. Typhoid conjugate vaccines (TCVs) are innovative products that have longer-lasting immunity compared to older vaccines, require fewer doses, and can be given to young children through routine childhood immunization programs. Prequalification of the vaccine by WHO means that it meets acceptable standards of quality, safety and efficacy. This makes the vaccine eligible for procurement by UN agencies like UNICEF and Gavi - the Vaccine Alliance.

In October 2017, the Strategic Advisory Group of Experts (SAGE) on immunization, which advises WHO, recommended TCV for routine use in children over 6 months of age in typhoid endemic countries. SAGE also called for the introduction of TCV to be prioritized for countries with the highest burden of typhoid disease or of antibiotic resistance to *Salmonella Typhi*, the bacterium that causes the disease. Use of this vaccine is expected to help curb the frequent use of antibiotics for treatment of presumed typhoid fever; and thereby help to slow the alarming increase in antibiotic resistance in Salmonella Typhi.

Shortly after SAGE's recommendation, Gavi Board approved US$85 million in funding for TCVs starting in 2019. Prequalification is therefore, a crucial next step needed to make TCVs available to low-income countries where they are needed most. And even in non-Gavi-supported countries, prequalification can help expedite licensure. WHO prequalification helps to ensure that vaccines used in immunization programmes are safe, effective and appropriate for countries' need. WHO's prequalification procedure consists of a transparent, scientifically sound assessment that includes reviewing the evidence, testing the consistency of each lot of manufactured vaccine, and visiting the manufacturing site.

About Typhoid

Typhoid fever is a systemic infection caused by *Salmonella Typhi*, usually through ingestion of contaminated food or water. The acute illness is characterized by prolonged fever, headache, nausea, loss of appetite, and constipation or sometimes diarrhea. Symptoms are often non-specific and clinically non-distinguishable from other febrile illnesses. However, clinical severity varies and severe cases may lead to serious complications or even death. It occurs predominantly in association with poor sanitation and lack of clean drinking water. According to recent estimates from the WHO, approximately 21 million cases and 222 000 typhoid-related deaths occur annually worldwide[2]. Typhoid fever, results in reduced school attendance, loss of work and wages, lowered pregnancy outcomes and impaired physical and cognitive development of children. In most developing countries the cost of a course of treatment for typhoid fever ranges from $50 to $5000 for outpatient and inpatient treatments[3].

Urbanization and climate change have the potential to increase the global burden of typhoid. In addition, increasing resistance to antibiotic treatment is making it easier for typhoid to spread through overcrowded populations in cities due to inadequate and/or flooded water and sanitation systems.

About Tybar TCV®

According to Bharat Biotech the manufacturer of this vaccine, Typbar TCV ® is a Typhoid VI Capsular Polysaccharide Tetanus Toxoid Conjugate vaccine. The Typhoid VI Capsular Polysaccharide Tetanus Toxoid Conjugate vaccine

1 http://www.who.int/medicines/news/2017/WHOprequalifies-breakthrough-typhoid-vaccine/en/

2 http://www.who.int/immunization/diseases/typhoid/en/

3 http://www.bharatbiotech.com/wp-content/plugins/prs/pdf/Bharat-Biotech-TypbarTCV-WHO-PQ-Press-Release-India-F.pdf

stimulates specialized T cells in the human body. Engagement of T cells by VI conjugate vaccine results in superior and longer lasting antibody response, which helps in the prevention of typhoid disease not only in adults but also in children and infants[4].

Typbar TCV® is the world's 1st clinically proven conjugate Typhoid vaccine. Further, the Typhoid Vi Capsular Polysaccharide Tetanus Toxoid Conjugate vaccine is the only approved vaccine for children and infants less than 2 years of age. During the Phase III clinical study, a single dose of Typbar TCV elicited 4-fold seroconversion rates of 98.05%, 99.17% and 92.13% in subjects between ≥6 months to 2 years, >2 to 15 years and >15 to 45 years respectively.

Typbar TCV® has been evaluated in several clinical trials, in several thousand healthy adults and children, across 21 sites in India and the United Kingdom. Active post marketing surveillance is ongoing and has been completed in more than 7000 subjects, since the vaccine was first launched in India in 2013.

Conclusion:

Enteric fever caused by *Salmonella Typhi* remains a major public health problem in various countries globally, and WHO pre-qualification of the new typhoid vaccine from an Indian manufacturer is an important event which is a true reflection of India's growing prowess in the global arena of pharmaceuticals, vaccines, and biotechnology. The WHO prequalification of this vaccine also marks an important milestone in the global effort to rid the world of typhoid fever.

4 http://www.bharatbiotech.com/products/vaccines/typbar-tcv-2/

Competition Commission of India imposes Penalty on two Chemists and Druggists Associations of Gujarat

The Competition Commission of India (CCI), an executive body under Competition Act 2002, and Competition amendment Act 2007, An Act to prohibits anti-competitive agreements, abuse of dominant position by enterprises and regulates combinations (acquisition, acquiring of control and M&A), which causes or likely to cause an appreciable adverse effect on competition within India.

On January 05, 2018 the CCI found two Chemists and Druggists Associations; The Chemists and Druggists Associations of Baroda (CDAB), and Federation of Gujarat State Chemists and Druggists Association (Gujarat Federation) respectively to be in contravention of the provisions of the Competition Act. As one of the stockiest based in Vadodara filed an information alleging that despite an earlier order of the Commission in the year 2012, CDAB, through its practices, has continued to limit and control the supply of drugs and medicines in the market by mandating 'No Objection Certificate' ('NOC'/'LOC') prior to appointment of stickiest and payment of 'Product Information Service' ('PIS') charges prior to introduction of new products in the market by pharmaceutical companies.

Investigation carried-out by the Director General ('DG') revealed involvement of the State Level Association, *i.e.* the Gujarat Federation, besides CDAB, in the alleged conduct. After detailed enquiry, the Commission has found that CDAB and the Gujarat Federation were indulging in the anti-competitive practice of insisting NOC prior to the appointment of new stockists by pharmaceutical companies. Further, the Gujarat Federation was found to be carrying on the practice of making introduction of new products in the market subject to payment of PIS charge and its approval. These practices were held to be limiting and controlling supplies of drugs/medicines in the market, in contravention of Section 3 (3) (b) read with Section 3 (1) of the Act. Further, the Commission has held office bearers of CDAB and Gujarat Federation, namely Shri V.T. Shah (President, CDAB), Shri Jashvant Patel (President, Gujarat Federation), to be responsible under Section 48 of the Act, for their involvement in the anti-competitive practices.

Accordingly, CDAB, Gujarat Federation and their office bearers have been directed to cease and desist from indulging in the aforesaid anti-competitive practices. Further, under the provisions of Section 27 of the Act, the Commission imposed a monetary penalty of Rs. 1, 08,588/- and Rs. 11, 11,549/- on CDAB and the Gujarat Federation, respectively, calculated at the rate of 10% of their respective average incomes. , Penalties of Rs. 34,048/- and Rs. 62,144/-, calculated at the rate of 10% of their respective average incomes, have also been imposed upon Shri V.T. Shah (President, CDAB) and Shri Jashvant Patel (President, Gujarat Federation).

This case is yet another example of how competitive markets and fair-play in the distribution of drugs/medicines are being compromised by persistent anti-competitive behavior of the chemist and druggist associations at the regional and state levels.

It is a serious matter that despite various orders by the Commission in similar cases and specific directions through a press notice, chemist and druggist associations have not amended their ways and continue to indulge in such anti-competitive conduct[5].

5 http://pib.nic.in/PressReleseDetail.aspx?PRID=1515612

Conclusion:

The Competition Commission of India after considering the larger public interest involved in the distribution of drugs/medicines, deprecates such a conduct and its perpetration in any form by anyone responsible, be it the Associations, Stockists/Distributors/Wholesalers/Retailers or the Pharmaceutical Companies. Given the widespread and continuing indulgence in anti-competitive practices, CCI will be keeping a close watch on the conduct by all such entities in various parts of the country and will not hesitate to take action, wherever deemed necessary.

CDSCO issues clarification regarding issuance of NOC for issuance of Form 29 License

On January 19, 2018, the Central Drug Standard Control Organization (CDSCO) has published clarification regarding issuance of No Objection Certificate (NOC) for issuing Form 29 License used to manufacture drugs for the purposes of examination, test or analysis of biological products (Vaccines 86 r-DNA products).

Form 29 is a license to manufacture drugs for the purpose of Examination Testing and Analysis. An application for a Form 29 license shall be made to the Licensing Authority appointed by the State Government for the purpose of this Part (hereafter in this Part referred to as the Licensing Authority) in Form 30 and shall be made by or countersigned by the head of the institution in which, or a director of the firm or company by which, the substance will be manufactured. A license in Form 29 shall, unless sooner cancelled, be in force for a period of one year from the date of issue, and may thereafter be renewed for periods of one year at a time[6].

However, the CDSCO on its previous notification has also clarified that "the product manufactured under Form 29 license can be exported only for the purpose of examination, test or analysis including clinical evaluation involving human subjects and not meant for commercial purposes as per Drug and Cosmetic Rules"[7].

CDSCO's further discussion with stakeholders has clarified the application process as:

- The applicants shall submit application for obtaining Form 29 license to the concerned State Licensing Authority (SLA).
- Firm shall simultaneously apply to CDSCO, HQ (Head quarter) for issuance of NOC to obtain Form 29 with the documents as mentioned in the checklist & undertaking, with a copy to concerned CDSCO, Zonal office by hard copy as well as soft copy through e-mail.
- NOC for issuance of Form 29 will be issued by this Directorate (CDSCO) within 7 working days.
- The joint inspection will be conducted based on risk based approach as per following criteria:
    a. If the seed/strain falls under BSL - III & IV, joint inspection shall be conducted in such cases. The applicant shall also inform about the BSL of the microorganisms/ strains with supporting documents while submitting the application.
    b. If seed/stain falls under BSL I & II, joint inspection may not be required, provided that the manufacturing facility is already jointly inspected earlier.
    c. The joint inspection shall be conducted for all new facilities which have never been licensed/incorporated.
- The joint inspection shall be conducted within 15 working days from the date of receipt of application wherever required, as per Sr.No. 4 above.
- In all cases, if the NOC from CDSCO, HQ is not granted within 7 working days after receipt of application, NOC will be deemed as granted.

6 http://www.cdsco.nic.in/writereaddata/GUIDANCE%20DOC.pdf

7 http://cdsco.nic.in/writereaddata/Circular%2013_12_2016(1).pdf

- The State Licensing Authority (SLA) shall issue the Form 29 License for purposes of examination, test or analysis within 03 working days from the date of receipt of NOC from CDSCO-HQ.
- In case of non-compliances observed during the joint inspection, the firm is required to submit the Corrective and Preventive action (CAPA) along with supported documents within 30 days to CDSCO, HQ for review. In case of unsatisfactory reply and/or compliance, Form 29/NOC so granted may be cancelled/ suspended.[8]

Note - The CDSCO has requested all Drug Controllers of States and Union Territories and all Zonal/Sub zonal offices to advise the concerned manufacturers situated in their jurisdiction to comply with the above pathway for obtaining NOC and license in Form 29 to manufacture drugs for the purposes of examination, test or analysis for Biological products (vaccines 86 r-DNA products).

8 http://www.cdsco.nic.in/writereaddata/FORM%2029%20NOC%20DOCUMENTS.pdf

Indian Pharmaceutical Companies: Abbreviated New Drug Application Approvals 2017

The United States Food and Drug Administration (USFDA) approved more Abbreviated New Drug Application (ANDA) in 2017 than any other year, according to its latest FY 2017 activities report[9].

An ANDA contains data which is submitted to FDA for the review and potential approval of a generic drug product. Once approved, an applicant may manufacture and market the generic drug product to provide a safe, effective, lower cost alternative to the brand-name drug it references. A generic drug product is one that is comparable to an innovator drug product in dosage form, strength, route of administration, quality, performance characteristics, and intended use[10].

The USFDA approved total 847[11] ANDA during 2017 which is the highest number of ANDA approvals during the last decade. Indian Pharmaceutical companies along with their combined global subsidiaries have received a total of 314 final ANDA amounting to 37% of total approvals from the USFDA in the year 2017.

Amongst the Indian pharmaceutical companies, the Zydus group and its subsidiaries secured 77 approvals, the highest number of ANDA approvals received in 2017. The Zydus group is followed by Aurobindo Pharma (51), Sun Pharma (22) Glenmark Pharmaceutical (18), Lupin (17), Gland Pharma (16), Alkem Laboratories (15), Macleods Pharma (15), Cipla (10) and Dr Reddy's (10).

The table below represents all final ANDA approvals by the Indian pharmaceutical companies:

Name of the Company	Number of final ANDA Approvals
ZYDUS GROUP	77
AUROBINDO PHARMA	51
SUN PHARMA GROUP	22
GLENMARK PHARMA	18
LUPIN	17
GLAND PHARMA	16
MACLEODS PHARMA	15
ALKEM LABS	15
CIPLA LTD	10
DR REDDYS	10
STRIDES PHARMA	9
ALEMBIC PHARMA	9
JUBILANT GENERICS	7
AJANTA PHARMA	6
MICRO LABS	6
UNICHEM LABS	5

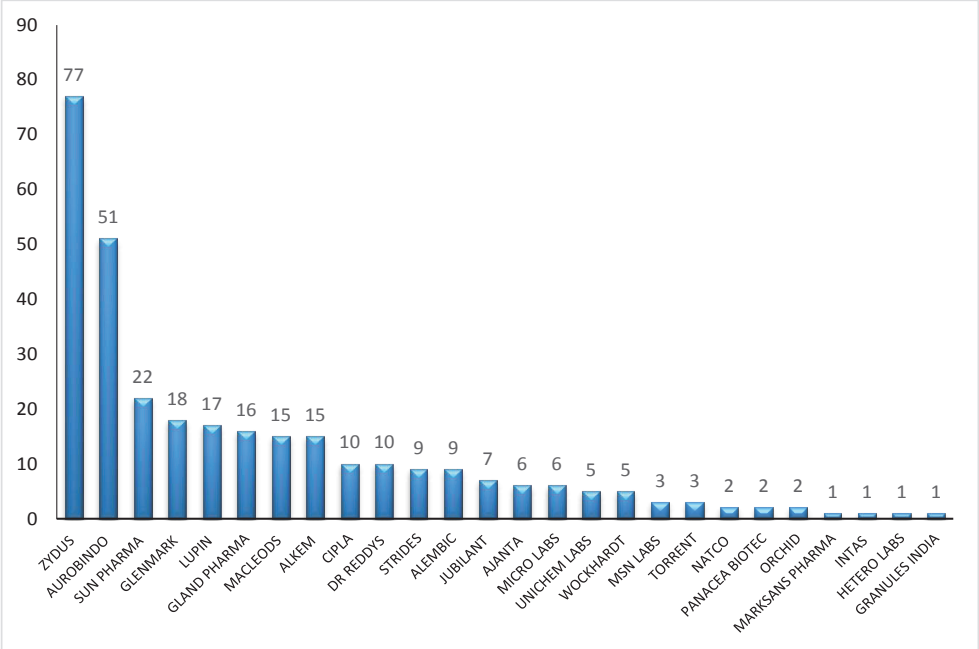
9 https://www.fda.gov/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/AbbreviatedNewDrugApplicationANDAGenerics/ucm584749.htm

10 https://www.fda.gov/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/AbbreviatedNewDrugApplicationANDAGenerics/default.htm

11 https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm

Name of the Company	Number of final ANDA Approvals
WOCKHARDT	5
MSN LABS	3
TORRENT PHARMA	3
NATCO PHARMA	2
PANACEA BIOTEC	2
ORCHID HLTHCARE	2
MARKSANS PHARMA	1
INTAS PHARMA	1
HETERO LABS	1
GRANULES INDIA	1
Total	**314**

The Graph below shows final ANDA Approvals received by the Indian Pharmaceutical Manufacturers and their subsidiaries.



Further, the FDA tentatively approved 175 applications. According to the US FDA, a tentative approval is issued to the applicant when the application is approvable prior to the expiration of any patents or exclusivities accorded to the reference listed drug product. A tentative approval does not allow the applicant to market the generic drug product and postpones the final approval until all patent/exclusivity issues have expired. First Generics are those drug products that have never been approved before as generic drug products and are new generic products to the marketplace[12].

Out of these 175 tentative approvals by the FDA[13], the Indian Pharmaceutical companies and their subsidiaries managed to secure 66 tentative approvals from the agency in 2017. The highest number of tentative approvals was secured by the Aurobindo group (11), followed by Sun Pharma (09), Zydus (08), Cipla (07), and Alembic Pharma, and Glenmark Pharma with 05 approvals each.

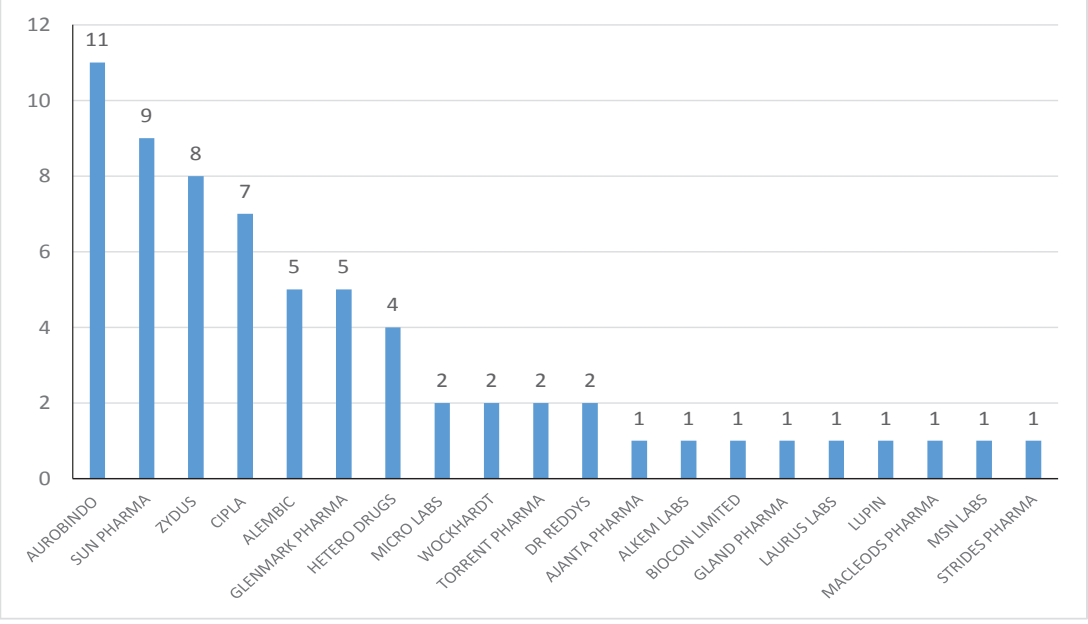
12 https://www.fda.gov/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/DrugandBiologicApprovalReports/ANDAGenericDrugApprovals/ucm050527.htm

13 https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm

The table below represents all tentative ANDA approvals by the Indian pharmaceutical companies:

Name of the Company	Number of Tentative ANDA Approvals
AUROBINDO PHARMA LTD	11
SUN PHARMA	9
ZYDUS PHARMA	8
CIPLA	7
ALEMBIC PHARMS LTD	5
GLENMARK PHARMA	5
HETERO DRUGS	4
MICRO LABS LTD	2
WOCKHARDT	2
TORRENT PHARMA	2
DR REDDYS	2
AJANTA PHARMA LTD	1
ALKEM LABS LTD	1
BIOCON LIMITED	1
GLAND PHARMA LTD	1
LAURUS LABS PRIVATE LTD	1
LUPIN LTD	1
MACLEODS PHARMS LTD	1
MSN LABS PVT LTD	1
STRIDES PHARMA	1
Total	**66**

Other Indian Pharmaceutical companies that received tentative approvals from the US FDA are Hetero, Micro labs, Wockhardt, Torrent, Dr Reddys, Ajanta pharma, Alkem labs, Biocon, Gland pharma, Laurus labs, Lupin, Macleods, MSN labs, and Strides Pharma.



Conclusion:

The Indian Pharmaceutical Manufacturers had a splendid year at US FDA where they managed to secure the highest number of final and tentative ANDA approvals from the agency. This record ANDA approvals for the Indian manufacturers should also translate into higher revenues for them once they start marketing their approved generic products in the United States.

NPPA Monthly updates for January 2018

The National Pharmaceutical Pricing Authority (NPPA), is an executive body under the Drugs (Prices Control) Order (DPCO), 2013 under the Department of Pharmaceuticals, Ministry of Chemicals and Fertilizers, Government of India. NPPA regulates drug prices and availability of medicines in the country by fixing/revising the prices of controlled bulk drugs and formulations. The NPPA's key announcements/notice of January 2018 are reviewed and described below:

1. **NPPA has fixed retail prices of 14 formulations under DPCO 2013,**
2. **NPPA has fixed/revised ceiling prices/retail prices of 33 formulations under DPCO, 2013,**
3. **NPPA has fixed/revised ceiling prices/retail prices of 06 formulations under DPCO, 2013,**
4. **NPPA partially revised format of Form – I for applications of new drug under Para 2(u) of DPCO, 2013 (effective from 09.01.2018),**
5. **NPPA publishes the status of Form-IV applications for discontinuation of scheduled medicines, &**
6. **NPPA to hold Stakeholder consultation for revising the ceiling price of Coronary Stents**

1. **NPPA fixed Retail prices of 14 formulations under DPCO 2013:** On January 01, 2018, NPPA has fixed the retail price of 14 schedule formulations, exclusive of goods and services tax, if any. The manufacturer may add goods and services tax only if they have paid it actually or it is payable to the Government on the retail price of formulations listed below:

Sl. No.	Name of the Scheduled Formulation / Brand Name	Strength	Unit
1.	Cilnidipine + Metoprolol Tablet	Each film coated Bi- Layered tablet contains: Cilnidipine 10mg, Metoprolol Succinate IP 47.5mg eq. to Metoprolol Tartrate 50mg (ER)	1 Tablet
2.	Metformin + Glimepiride + Voglibose Tablets	Each tablet contains: Metformin HCL 500mg (as sustained release form) Glimepiride 1mg Voglibose 0.3mg	1 Tablet
3	Rosuvastatin + Clopidogrel Capsule	Each Hard gelatin capsule contains: Rosuvastatin Calcium IP eq. to Rosuvastatin 20mg, Clopidogrel Bisulphate IP eq. to Clopidogrel 75mg	1 Capsule
4.	Telmisartan + Chlorthalidone Tablet (Tigatel CH 80)	Each film coated tablet contains: Telmisartan IP 80mg, Chlorthalidone IP 12.5mg	1 Tablet
5.	Rosuvastatin + Clopidogrel Capsule	Each hard gelatin capsule contains: Rosuvastatin Calcium IP eq. to Rosuvastatin 20mg (As pellets) Clopidogrel Bisulphate IP eq. to Clopidogrel 75mg (As pellets)	1 Capsule
6.	Paracetamol + Caffeine + Phenylephrine + Diphenhydramine Tablet (Sinus77)	Each uncoated tablet contains: Paracetamol-500mg Caffeine (anhydrous)-30mg Phenylephrine HCl-5mg Diphenhydramine HCl-25mg	1 Tablet
7.	Atorvastatin + Clopidogrel Capsule	Each hard gelatin capsule contains: Atorvastatin Calcium IP eq. to Atorvastatin 10mg, Clopidogrel Bisulphate IP eq. to Clopidogrel 75mg	1 Capsule
8.	Atorvastatin + Clopidogrel Capsule	Each hard gelatin capsule contains: Atorvastatin Calcium IP eq. to Atorv astatin 20mg, Clopidogrel Bisulphate IP eq. to Clopidogrel 75mg	1 Capsule
9.	Gliclazide + Metformin Tablet (Glychek M +)	Each uncoated tablet contains: Gliclazide IP 40mg, Metformin Hydrochloride IP 500mg	1 Tablet

10.	Atorvastatin + Clopidogrel Capsule (Atocor CV 20mg)	Each hard gelatin capsule contains: Atorvastatin Calcium IP eq. to Atorvastatin 20mg (As two film coated tablet each containing Atorvastatin 10mg) Clopidogrel Bisulphate IP eq. to Clopidogrel 75mg (As 2 film coated 37.5mg each tablet)	1 Capsule
11.	Atorvastatin + Clopidogrel Capsule (Avas 20 Gold)	Each capsule contains: Atorvastatin Calcium IP eq. to Atorvastatin 20mg (As film coated tablet) Clopidogrel Bisulphate IP eq. to Clopidogrel 75mg (As 2 film coated 37.5mg each tablet)	1 Capsule
12.	Atorvastatin + Clopidogrel Capsule (Astin 20 Gold)	Each capsule contains: Atorvastatin Calcium IP eq. to Atorvastatin 20mg (As film coated tablet) Clopidogrel Bisulphate IP eq. to Clopidogrel 75mg (As 2 film coated 37.5mg each tablet)	1 Capsule
13.	Rosuvastatin + Clopidogrel Capsule	Each hard gelatin capsule contains: Rosuvastatin Calcium IP eq. to Rosuvastatin 10mg, Clopidogrel Bisulphate IP eq. to Clopidogrel 75mg	1 Capsule
14.	Rosuvastatin + Clopidogrel Capsule	Each hard gelatin capsule contains: Rosuvastatin Calcium IP eq. to Rosuvastatin 20mg,	1 Capsule[1]

2. NPPA fixed/revised the ceiling price/retail price of 33 scheduled formulations: On January 16, 2018, NPPA has fixed/revised the price of 33 scheduled formulations under DPCO, 2013. The formulations used for the treatment of cancer, diabetics, hyperlipidemia including other antibiotics are:

a. NPPA revised ceiling prices of 3 scheduled formulations under para 31 of Drugs (Prices Control) Order, 2013

Sl. No.	Name of the Scheduled Formulation	Dosage form & Strength	Unit
1.	N-acetylcysteine	Sachet 200mg	1 GM
2.	Gemcitabine	Powder for Injection 200mg	Each Pack
3.	Amphotericin B - Lipid/ Liposomal	Powder for Injection 50 mg	Each Pack[2]

b. NPPA fixed retail prices of 30 formulations exclusive of goods and services tax, if any, in relation to the formulation specified in the corresponding entry in the said table –

Sl. No.	Name of the Scheduled Formulation / Brand Name	Strength	Unit
1	Glimepiride + Metformin Tablet	Each uncoated Bi- Layered tablet contains: Glimepiride IP 1mg, Metformin HCL IP 850mg (As sustained release form)	1 Tablet
2	Glimepiride + Metformin Tablet	Each uncoated Bi- Layered tablet contains: Glimepiride IP 2mg, Metformin HCL IP 850mg (As sustained release form)	1 Tablet
3	Cilnidipine + Metoprolol Tablet	Each film coated Bi- Layered tablet contains: Cilnidipine 10mg, Metoprolol Succinate IP 23.75mg eq. to Metoprolol Tartrate 25mg (ER)	1 Tablet
4	Escitalopram + Clonazepam Tablet (CENSPRAM MINI)	Each film coated tablet contains: Escitalopram Oxalate IP eq. to Esccitalopram 5mg Clonazepam IP 0.5mg	1 Tablet
5	Ceftriaxone sodium & Tazobactam Sodium Injection	Each combipack contains: Ceftriaxone sodium (sterile) eq. to anhydrous Ceftriaxone 500mg Tazobactam Sodium (sterile) eq. to anhydrous Tazobactam 62.5mg, And One FFS Ampoule containing Sterile water for injection 5ml	Each pack
6	Olmesartan + Amlodipine Tablet (Tripinom 40)	Each uncoated tablet contains: Olmesartan Medoxomil 40mg, Amlodipine Besylate eq. to Amlodipine 5mg, Hydrochlorothizide 12.5mg	Per Tablet
7	Rosuvastatin + Aspirin Capsule (Rozucorn Asp 20 Forte)	Each hard gelatin capsule contains: Rosuvastatin Calcium eq. to Rosuvastatin 20mg (As film coated tablet) Aspirin IP 150mg (as enteric coated tablet)	1 Capsule

Sl. No.	Name of the Scheduled Formulation / Brand Name	Strength	Unit
8	Rosuvastatin + Aspirin + Clopidogrel Capsule (Unistar Gold 10/75)	Each hard gelatin capsule contains: Rosuvastatin Calcium IP eq. to Rosuvastatin 10mg (As Pellets), Aspirin IP 75mg (As enteric Coated Pellets), Clopidogrel Bisulphate IP eq. to Clopidogrel 75mg (As Pellets)	1 Capsule
9	Rosuvastatin + Aspirin + Clopidogrel Capsule (Zyrova Gold 10)	Each hard gelatin capsule contains: Rosuvastatin Calcium IP eq. to Rosuvastatin 10mg (As granules), Aspirin IP 75mg (As enteric Coated Tablets), Clopidogrel Bisulphate IP eq. to Clopidogrel 75mg (As two film coated tablets)	1 Capsule
10	Rosuvastatin + Aspirin + Clopidogrel Capsule	Each hard gelatin capsule contains: Rosuvastatin Calcium IP eq. to Rosuvastatin 10mg (As granules), Aspirin IP 75mg (As enteric Coated Tablets), Clopidogrel Bisulphate IP eq. to Clopidogrel 75mg (As two film coated tablets)	1 Capsule
11	Rosuvastatin + Aspirin + Clopidogrel Capsule	Each hard gelatin capsule contains: Rosuvastatin Calcium IP eq. to Rosuvastatin 10mg (As Pellets), Aspirin IP 75mg (As enteric Coated Pellets), Clopidogrel Bisulphate IP eq. to Clopidogrel 75mg (As Pellets)	1 Capsule
12	Rosuvastatin + Aspirin + Clopidogrel Capsule	Each hard gelatin capsule contains: Rosuvastatin Calcium IP eq. to Rosuvastatin 10mg (As Pellets), Aspirin IP 75mg (As enteric Coated Pellets), Clopidogrel Bisulphate IP eq. to Clopidogrel 75mg (As Pellets)	1 Capsule
13	Rosuvastatin + Aspirin + Clopidogrel Capsule	Each hard gelatin capsule contains: Rosuvastatin Calcium IP eq. to Rosuvastatin 10mg, Aspirin IP 75mg, Clopidogrel Bisulphate IP eq. to Clopidogrel 75mg	1 Capsule
14	Rosuvastatin + Aspirin + Clopidogrel Capsule	Each hard gelatin capsule contains: Rosuvastatin Calcium IP eq. to Rosuvastatin 10mg (As film coated tablet), Aspirin IP 75mg (As Gastro – resistant tablet), Clopidogrel Bisulphate IP eq. to Clopidogrel 75mg (As film coated tablet)	1 Capsule
15	Rosuvastatin + Aspirin + Clopidogrel Capsule	Each hard gelatin capsule contains: Rosuvastatin Calcium IP eq. to Rosuvastatin 10mg, Aspirin IP 75mg, Clopidogrel Bisulphate IP eq. to Clopidogrel 75mg	1 Capsule
16	Rosuvastatin + Aspirin + Clopidogrel Capsule (Unistar Gold 20/75)	Each hard gelatin capsule contains: Rosuvastatin Calcium IP eq. to Rosuvastatin 20mg (As Pellets), Aspirin IP 75mg (As enteric Coated Pellets), Clopidogrel Bisulphate IP eq. to Clopidogrel 75mg (As Pellets)	1 Capsule
17	Rosuvastatin + Aspirin + Clopidogrel Capsule (Zyrova Gold 20)	Each hard gelatin capsule contains: Rosuvastatin Calcium IP eq. to Rosuvastatin 20mg (As granules), Aspirin IP 75mg (As enteric Coated Tablets), Clopidogrel Bisulphate IP eq. to Clopidogrel 75mg (As two film coated tablets)	1 Capsule
18	Rosuvastatin + Aspirin + Clopidogrel Capsule	Each hard gelatin capsule contains: Rosuvastatin Calcium IP eq. to Rosuvastatin 20mg (As granules), Aspirin IP 75mg (As enteric Coated Tablets), Clopidogrel Bisulphate IP eq. to Clopidogrel 75mg (As two film coated tablets)	1 Capsule
19	Rosuvastatin+Aspirin + Clopidogrel Capsule	Each hard gelatin capsule contains: Rosuvastatin Calcium IP eq. to Rosuvastatin 20mg (As Pellets), Aspirin IP 75mg (As enteric Coated Pellets), Clopidogrel Bisulphate IP eq. to Clopidogrel 75mg (As Pellets)	1 Capsule

Sl. No.	Name of the Scheduled Formulation / Brand Name	Strength	Unit
20	Rosuvastatin+Aspirin + Clopidogrel Capsule	Each hard gelatin capsule contains: Rosuvastatin Calcium IP eq. to Rosuvastatin 20mg (As Pellets), Aspirin IP 75mg (As enteric Coated Pellets), Clopidogrel Bisulphate IP eq. to Clopidogrel 75mg (As Pellets)	1 Capsule
21	Rosuvastatin+Aspirin + Clopidogrel Capsule	Each hard gelatin capsule contains: Rosuvastatin Calcium IP eq. to Rosuvastatin 20mg (As Pellets), Aspirin IP 75mg (As enteric Coated Pellets), Clopidogrel Bisulphate IP eq. to Clopidogrel 75mg (As Pellets)	1 Capsule
22	Rosuvastatin + Aspirin + Clopidogrel Capsule (Jubira Gold 20)	Each hard gelatin capsule contains: Rosuvastatin Calcium IP eq. to Rosuvastatin 20mg (As film coated tablet), Aspirin IP 75mg (As Gastro – resistant tablet), Clopidogrel Bisulphate IP eq. to Clopidogrel 75mg (As film coated tablet)	1 Capsule
23.	Rosuvastatin+Aspirin + Clopidogrel Capsule	Each hard gelatin capsule contains: Rosuvastatin Calcium IP eq. to Rosuvastatin 20mg, Aspirin IP 75mg, Clopidogrel Bisulphate IP eq. to Clopidogrel 75mg	1 Capsule
24	Rosuvastatin+Aspirin + Clopidogrel Capsule	Each hard gelatin capsule contains: Rosuvastatin Calcium IP eq. to Rosuvastatin 20mg (As film coated tablet), Aspirin IP 75mg (As enteric coated tablet), Clopidogrel Bisulphate IP eq. to Clopidogrel 75mg (As film coated tablet)	1 Capsule
25	Voglibose + Glimeperide + Metformin Tablet (Glimy MVI)	Each uncoated bilayer tablets contains: Voglibose IP 0.2mg, Glimeperide IP 1mg & Metformin Hydrochloride IP 500mg (SR)	1 Tablet
26	Voglibose + Glimeperide + Metformin Tablet (Glimy MV2)	Each uncoated bilayer tablet contains: Voglibose IP 0.2mg, Glimeperide IP 2mg & Metformin Hydrochloride IP 500mg (SR)	1 Tablet
27	Cefixime + Ofloxacin Tablet (Stancef-O plus)	Each film coated tablet contains: Cefixime Trihydrate eq. to Cefixime Anhydrous IP 200mg, Ofloxacin IP 200mg	1 Tablet
28	Trypsin + Bromelain + Rutoside + Diclofenac Tablet (Volitra Enzo)	Each enteric coated tablet contains: Trypsin BP 48mg, Bromelain 90mg, Rutoside Trihydrate BP 100mg Diclofenac Sodium IP 50mg	1 Tablet
29	Gliclazide + Metformin Tablet (GLZ MEX)	Each film coated tablet contains: Gliclazide IP 60mg (In modified release form), Metformin HCL 500mg (extended release form)	1 Tablet
30	Rosuvastatin +Clopidogrel Capsule (Turbovas C)	Each hard gelatine capsule contains:Rosuvastatin Calcium IP eq. to Rosuvastatin 10mg (as film coated tablet),Clopidogrel Bisulphate IP eq. to Clopidogrel 75mg (as 2 film coated tablet)	1 Capsule[3]

c NPPA holds its previous notification S.O. 1526(E) dated 11th May 2017 regarding the following formulations with immediate effect:

Sl. No.	Name of the Formulation
1.	Erythromycin Estolate Tablet 250mg
2.	Erythromycin Estolate Tablet 500mg
3.	Erythromycin Estolate Syrup 125 mg / 5 ml
4.	Chloroquine Phosphate Injection 40 mg / ml (64.5mg eq. to 40mg chloroquine)[4]

3. NPPA fixed/revised the ceiling prices/retail prices of 06 formulations: On January 23, 2018, NPPA has fixed the retail price of 05 Scheduled formulations under DPCO, 2013. The five formulations are used for the treatment of Hypertension, Angina, and Asthma. NPPA also revised ceiling price of 01 scheduled formulation under DPCO, 2013 as described below –

a. Retail prices of 05 formulations exclusive of goods and services tax, if any

Sl. No.	Name of the Scheduled Formulation / Brand Name	Strength	Unit
1	Olmesartan Medoxomil + Amlodipine + Hydrochlorothiazide Tablet	Each film coated tablet contains: Olmesartan Medoxomil IP 40mg Amlodipine Besylate IP eq. to Amlodipine 5mg Hydrochlorothiazide IP 12.5mg	1 Tablet
2	Olmesartan Medoxomil + Amlodipine + Hydrochlorothiazide Tablet	Each film coated tablet contains: Olmesartan Medoxomil IP 20mg Amlodipine Besylate IP eq. to Amlodipine 5mg Hydrochlorothiazide IP 12.5mg	1 Tablet
3	Tiotropium Bromide + Formoterol Fumarate + Ciclesonide Powder for Inhalation	Each capsule contains: Tiotropium (as Tiotropium Bromide Monohydrate) 18mcg Formoterol Fumarate Dihydrate 12mcg	1 Tablet
4	Isosobide Dinitrate + Hydralazine HCl tablet (Sorbitrate HF)	Each film coated tablet contains: Diluted Isosorbide Dinitrate eq. to Isosorbide Dinitrate 20mg Hydralazine Hydrochloride 37.5mg	1 Tablet
5	Olmesartan Medoxomil + Amlodipine + Tablet	Each film coated tablet contains: Olmesartan Medoxomil IP 40mg Amlodipine Besylate IP eq. to Amlodipine 5mg	1 Tablet[5]

b. Revised ceiling price of 01 scheduled formulation of Schedule -I under Drugs (Prices Control) Order, 2013.

Sl. No.	Name of the Scheduled Formulation	Doasage form Strength	Unit
1	Metronidazole	Injection 500mg/100ml	1 ML[6]

4. NPPA Partially Revised format of Form – I for applications: On January 09, 2018, NPPA via. O.M., directed all Apex Pharma organizations/Associations and drug manufacturers/ marketing companies to comply with the Partially Revised format of Form-I for fixing retail price of new drug under Para 2(u) of DPCO, 2013 with immediate effect. NPPA also requested to furnish all the information/ documents as mentioned in the O.M. for the same.

The existing Form-I was first notified via. O.M. dated 07.02.2017[14]. The joint undertaking between the manufacturer and marketer company for the new drug price fixation was later added as a request along with Form I[15]. The partially revised Form I has some added information as mentioned below, wherein the added/ revised information have been marked in bold and deleted information has been underlined –

1. Information as per Schedule-II, Form I of the DPCO, 2013-

a Name of the formulation

b Name and address of the manufacturer/importer

c Name of the Marketing Company, if any

d Composition as per label claimed and approved by Drug Control Authorities

e Drugs Control Authority Permission Number and Date (copy to be enclosed)

f Proposed date of commencement of production /import

14 http://www.nppaindia.nic.in/order/officememorandamon07022017_02.pdf

15 http://www.nppaindia.nic.in/order/memorandum01052017.pdf

g Type of formulation (Tablets/Capsules/Syrup/Injection/Ointment/Powder etc.)

h Size of packs (10's/100's/1 ml/2 m1/10 ml/5 gms/10 gms etc.)

i Therapeutic category/use of the formulation

j The Retail Price claimed for approval (with/without GST. if any) Previously- (With/without VAT/Local; Taxes, if Any)

k **Name of the scheduled drug/drugs proposed to be part of the new drug.**
Previously- Reason for submission of Application for price fixation/revision.

l **Whether NPPA has already approved price of similar drug, if yes, the name of the company, S.0, number and the date.** (Newly Added Information)

m Any other information relevant to product and its process of manufacturing/ packaging/ distribution.

2. Other information/documents to be provided under Paras (9), (20), (21) and (29) etc. of DPCO, 2013 –

a Status of Drug Category (A, B, C, D etc.) as per the Kokate Committee for Fixed Dose Combinations (FDCs).
Previously- *Status of Drug whether banned by MoH&FW or not*.

b Status of drug as per Drug Technical Advisory Board.

Previously- *Status of registration and filing necessary data online on Integrated Pharmaceutical Database Management System (IPDMS) as per the prescribed formats viz. Form II/III/IV i.e. hard copies of last forms submitted on IPDMS along with date of submission and certificate to the effect that they have filed all the requisite forms for all their formulations through IPDMS*

c Whether there is any proposal by the company to discontinue or reduce production of scheduled formulation already being manufactured by it under NLEM, 2015, which has been combined with the new drug or if the strength is proposed to be changed.

d Provide details of quarterly production, sales, etc. in the last six quarters duly certified by CA/CMA for the scheduled drug component of the proposed new drug as per Form-III of IPDMS, if being made as per above (c). *(Newly Added Information)*

e Joint undertaking between the manufacturer and marketer company for the new drug, duly attested by their respective authorized signatories (without any trade secret). (As referred from O.M. dated 01.05.2017[16])

3. The manufacturers who have already submitted their applications-

a But not compliant with these instructions may submit the remaining documents by 16.01.2018 to avoid rejection of their applications.

b No proposal for retail price fixation of new drug shall be considered unless complete in all respects as per this O.M. in future.

16 http://www.nppaindia.nic.in/order/memorandum01052017.pdf

5. NPPA publishes the status of Form-IV applications for discontinuation of scheduled medicines

National Pharmaceutical Pricing Authority (NPPA) on January 16, 2018, released the notifications where the status of Form-IV applications for discontinuation of scheduled medicines received in NPPA office till 30.12.2017 is published. Further, NPPA has directed all Apex Pharma Associations and interested Pharma Companies to refer the notification and convey response to the same as detailed below:

a. In the following cases, discontinuation requests of Companies were approved and they were asked to issue public notice, which they have issued and submitted a copy of the same to this Office. Accordingly, their discontinuation requests of scheduled formulations indicated against their name have been approved subject to conditions mentioned in column (D). Manufactures are required to follow the conditions

Sl. No.	Company Name	Brand Name of Formulation	Approval is subject to following Conditions
(A)	(B)	(C)	(D)
1	Astrazeneca Pharma India Ltd.	Novaclex TM	Company may continue to manufacture/ import and sell the formulation till June 2018. Till then, Company may follow the ceiling price fixed by NPPA and Notified from time to time and not reduce level of production by more than 25% (of previous year's production in each quarter).
2	Sanofi India Limited	Claforan Oral Suspension -30m1	Company may continue to manufacture/ import and sell the formulations for a period of six months (as already intimated to them) from the intended date of discontinuation or date of public notice, whichever is later. During this period of six months, Company may follow the ceiling price fixed by NPPA and notified from time to time and not reduce level of production by more than 25% (of previous year's production in each quarter).
3	Sanofi India Limited	Claforan 0 Tablets 200 mg	
4	Sanofi India Limited	Clavohext Suspension 228.5 mg	
5	Sanofi India Limited	Clavohext Tablet 625 mg	
6	Abbott Healthcare Pvt. Ltd.	Pedialyle200 ML	
7	Indoco Remedies	Fevorit 200 DT	
8	Indoco Remedies	Clopirad 75 tablet	
9	Indoco Remedies	Vcef-o 200 DT	
10	Baxter (India) Pvt. Ltd	Dextrose 5% (500 ml)	Company may continue to manufacture/ import and sellt h e formulations for a period of twelve months (as already intimated to them) from the intended date of discontinuation or date of public notice, whichever is later. During this period of twelve months, Company may follow the ceiling price fixed by NPPA and notified from time to time and not reduce level of production by more than 25% (of previous year's production in each quarter).
11	Baxter (India) Pvt. Ltd	Dextrose with Normal Saline 500m1	
12	Baxter (India) Pvt. Ltd	Inj. Ringer Lactate (500 ml)	
13	Baxter (India) Pvt. Ltd	Inj. 0.45% Sodium Chloride	

b In the following cases, requests of Companies for discontinuation of scheduled formulations indicated against their name, have been approved subject to conditions mentioned in column (D) and they are requested to issue public notice as per details in column (D) and provide a copy of the same to this Office immediately

Sl. No.	Company Name	Brand Name of Formulation	Approval is subject to following Conditions
(A)	(B)	(C)	(D)
1	M/s Magnet Labs Private Ltd. (Mankind)	Napilex CR 200 tablet	Company will issue a public notice in prescribed format (copy enclosed), in at least two national newspapers (one in English and one in Hindi newspaper) and provide a copy of the same to this Office immediately. Company will continue to manufacture/ import and sell the formulation for a period of 9 months from the date of public notice. During this period of 9 months, it will follow the ceiling price fixed by NPPA and notified from time to time and will not reduce level of production by more than 25% (of previous year's production in each quarter).
2	M/s Magnet Labs Pvt. Ltd.	Cope MD tablets	Company will issue a public notice in prescribed format (copy enclosed), in at least two national newspapers (one in English and one in Hindi newspaper) and provide a copy of the same to this Office immediately. Company will continue to manufacture/ import and sell the formulations for a period of 6 months from the date of public notice. During this period of 6 months, it will follow the ceiling price fixed by NPPA and notified from time to time and will not reduce level of production by more than 25% (of previous year's production in each quarter).
3	M/s Magnet Labs Pvt. Ltd.	Napilex CR 500 tablet	
4	M/s Magnet Labs Pvt. Ltd.	Tryal tablet	
5	M/s Magnet Labs Pvt. Ltd.	Eptokind 100 tablet	
6	Raptakos, Brett & Co. Ltd.	Igol(90 gm)	
7	Raptakos, Brett & Co. Ltd.	Igol(250 gm)	
8	Baxter (India) Pvt. Ltd.	Inj Normal Saline 0.9% 1000 ml	
9	Baxter (India) Pvt. Ltd.	Inj. Ringer Lactate (1000m1)	
10	Baxter (India) Pvt. Ltd.	Inj. Mannitol 20% (100 ml)	
11	Fulford (I)Ltd.	Virferon Peg 120 mcg	
12	Strassenburg Pharmaceuticals Ltd.	Parasafe Suspension	
13	LG Life Science India Pvt. Ltd.	(Venofer) 5m1 ampoule;	
14	Sanofi India Limited	Arava 10mg	
15	Sanofi India Limited	Arava 20mg	
16	A. Menarini India Pvt. Ltd.	Azcre 500 tablets	
17	A. Menarini India Pvt. Ltd.	Cropara 650 tablets	
18	A. Menarini India Pvt. Ltd.	Cropara 250 Suspension 60m1	
19	A. Menarini India Pvt. Ltd.	Reggi Syrup 30m1	
20	A. Menarini India Pvt. Ltd.	Reggi Syrup 450m1	
21	A. Menarini India Pvt. Ltd.	Reggi Tablets 500	
22	A. Menarini India Pvt. Ltd.	Reggi Tablets 25*10	
23	A. Menarini India Pvt. Ltd.	Cropara Suspension 60m1	
24	Seagull Pharmaceutical Pvt. Ltd.	Captol 650 mg Tablet	

c. In the following cases, requests of Companies in respect of scheduled formulations indicated against their name, were approved subject to conditions mentioned in column (D). These companies were also directed to issue public notice and submit a copy of the same to this Office which they

have not submitted so far. These Companies are again directed to issue public notice as per details in column (D) and provide a copy of the same to this Office immediately:

Sl. No	Company Name	Brand Name of Formulation	Approval is subject to following Conditions
(A)	(B)	(C)	(D)
1	Mankind Pvt. Ltd.	Clindatime 150 capsule	1. Company will Issue a public notice in prescribed format (copy enclosed), in at least two national newspapers (one in English and one in Hindi newspaper) and provide a copy of the same to this Office. 2. Continue to manufacture/ import and sell the formulation for a period of six months from the date of public notice. However, from the seventh month production/import may be reduced @ 15% every month for another five months and at the end of the twelfth month, it may be withdrawn completely. 3. During above mentioned period of twelve months, follow the ceiling price fixed by NPPA and notified from time to time and maintain the level of production as stated at (ii) above.
2	Astrazeneca Pharma India Ltd	Iressa TM	1. Companies will issue a public notice in prescribed format (copy enclosed), in at least two national newspapers (one in English and one in Hindi newspaper) and provide a copy of the same to this Office immediately. 2. Companies will continue to manufacture/ import and sell the formulations for a period of six months from the date of public notice. 3. During this period of six months, it will follow the ceiling price fixed by NPPA and notified from time to time and time and not reduce level of production by more than 25% (of previous year's production in each quarter).
3	Unichem Laboratories Ltd.	XT PARA Drops	
4	Panacea Biotec Ltd.	Lower A- 10	

d. In the following cases, Companies, in respect of their request for discontinuation of scheduled formulations indicated against their name have been asked certain information/explanation as indicated in column (D) to enable this office to process their requests. These companies are advised to forward the requisite information/explanation to NPPA immediately.[17]

17 http://www.nppaindia.nic.in/order/om_2018-01-18.pdf

Sl. No.	Company Name	Brand Name of Formulation	Approval held up due following information/explanation awaited from Company
(A)	(B)	(C)	(D)
1	Mylan Pharmaceuticals Pvt. Ltd.	Viread	Explanation from company for Discontinuing the formulation without consent of NPPA awaited.
2	Medopharm Pvt. Ltd.	Alworm Tablet	Explanation from company for Discontinuing the formulation without consent of NPPA and information regarding year-wise production/sale awaited from company.
3	Medopharm Pvt. Ltd.	Alworm Suspension	
4	Medopharm Pvt. Ltd.	Combet 1000	
5	Medopharm Pvt. Ltd.	Fungiban 150	
6	Medopharm Pvt. Ltd.	Jalan-20	
7	Medopharm Pvt. Ltd.	Jalan-D	
8	Medopharm Pvt. Ltd.	Medomol-25	
9	Medopharm Pvt. Ltd.	Cedomox 1.2gm Inj.	
10	Medopharm Pvt. Ltd.	Medomol Suspension	
11	Medopharm Pvt. Ltd.	Medofer xt Syrup	
12	Medopharm Pvt. Ltd.	Medofer-xt Tablet	
13	Medopharm Pvt. Ltd.	Medocid 1 gm Inj.	

6. **NPPA to hold Stakeholder consultation for revising the ceiling price of Coronary Stents:** On January 29, 2018**,** NPPA, through an office memorandum, has announced that the Authority in its meeting to be held on February 05, February 2018 (Monday), will hear all the stakeholders for revising the ceiling price of coronary stents. The stakeholders include intervention cardiologists, multinational and Indian stent manufacturers, trade associations and others.

   NPPA had fixed the ceiling prices of coronary stents vide notification dated February 13, 2017, which is valid for one year. This decision is to be revisited now in February, 2018[18].

18 http://www.nppaindia.nic.in/order/Stakeholder_consultation.pdf

High levels of antibiotic resistance found worldwide: GLASS Report

On January 29, 2018 World Health Organization (WHO) released the surveillance data of new "**Global Antimicrobial Surveillance System** (**GLASS**)" on antibiotic resistance. GLASS report reveals high levels of resistance to a number of serious bacterial infections among 500 000 people with suspected bacterial infections across 22 countries. The aim of the report is to document participation efforts and outcomes across countries, and highlight differences and constraints identified to date.

Common Resistant Bacteria

The most commonly reported resistant bacteria were - *Escherichia coli*, *Klebsiella pneumoniae*, *Staphylococcus aureus*, and *Streptococcus pneumoniae*, followed by *Salmonella spp*. The system does not include data on resistance of *Mycobacterium* tuberculosis, which causes tuberculosis (TB), as WHO has been tracking it since 1994 and providing annual updates in the Global tuberculosis report.

Among patients with suspected bloodstream infection, the proportion that had bacteria resistant to at least one of the most commonly used antibiotics ranged tremendously between different countries – from zero to 82%. For example - resistance to penicillin, the medicine used for decades worldwide to treat pneumonia – ranged from zero to 51% among reporting countries. Similarly, *E. coli* associated with urinary tract infections presented for resistance to ciprofloxacin between 8% to 65%, an antibiotic commonly used to treat this condition.

The Participating Countries

At present, 52 countries (25 high-income, 20 middle-income and 7 low-income countries) are enrolled in WHO's Global Antimicrobial Surveillance System. For the first report, 40 countries provided information about their national surveillance systems and 22 countries also provided data on levels of antibiotic resistance.

Data presented in this first GLASS report varies widely in quality and completeness. Some countries face major challenges in building their national surveillance systems like a lack of personnel, funds and infrastructure. However, WHO is supporting more countries to set up national antimicrobial resistance surveillance systems that can produce reliable, meaningful data.

The rollout of GLASS is already making a difference in many countries. For example, Kenya has enhanced the development of its national antimicrobial resistance system; Tunisia started to aggregate data on antimicrobial resistance at national level; the Republic of Korea completely revised its national surveillance system to align with the GLASS methodology, providing data of very high quality and completeness. Countries such as Afghanistan and Cambodia, that face major structural challenges, have enrolled in the system and are using the GLASS framework as an opportunity for strengthening their Antimicrobial resistance (AMR) surveillance capacities. In general, national participation in GLASS is seen as a sign of growing political commitment to support global efforts to control antimicrobial resistance.

About GLASS

In October 2015, WHO launched the Global Antimicrobial Surveillance System (GLASS) working closely with WHO Collaborating Centres and existing antimicrobial resistance surveillance networks, based on the experience of other WHO surveillance programmes. GLASS is a system that enables standardized global reporting of official national AMR data. It collaborates with existing regional and national AMR surveillance networks to produce timely and comprehensive data. It is built upon the experience gained by longstanding WHO AMR surveillance programmes like the tuberculosis (TB) surveillance at global level, and CAESAR (Central Asian and Eastern

European Surveillance of Antimicrobial Resistance) and ReLAVRA (Latin American Antimicrobial Resistance Surveillance Network) at regional levels.

GLASS is expected to perform a similar function for common bacterial pathogens like TB, Malaria, and HIV surveillance programmes of WHO. Any country, at any stage of the development of its national antimicrobial resistance surveillance system, can enroll in GLASS. Countries are encouraged to implement the surveillance standards and indicators gradually, based on their national priorities and available resources.

Conclusion:

The AMR surveillance standards established by GLASS proved to be a valuable and feasible methodology and represented a major achievement for the participating countries and GLASS, both. There is still large variability in terms of data submission, not only with respect to the types of data submitted, but also its completeness. GLASS also encourages countries to report on population data, to calculate the incidence rates and infection types globally, which eventually inform and direct mitigation strategies and interventions to control AMR in the most affected groups.

WHO revises advice on Delamanid drug usage in multidrug-resistant tuberculosis (MDR-TB) patients

On January 15, 2018, the World Health Organization's (WHO) Global Tuberculosis Programme has released a Position Statement[19] on the use of delamanid in treatment of multidrug-resistant tuberculosis (MDR-TB), following an expedited review of the phase III randomized controlled trial results by Otsuka Pharmaceutical, released at the 48th UNION World Conference on Lung Health in Mexico. Based on the results of this trial, the WHO is advising national TB programmes and other stakeholders to only add delamanid to a longer MDR-TB regimen when the regimen cannot be composed according to WHO recommendations, eg. when drug intolerability or drug resistance requires changes. When an effective and well-tolerated longer MDR-TB regimen can be otherwise composed, the addition of delamanid may not be warranted[20].

Background

Delamanid was approved for use in multidrug-resistant tuberculosis (MDR-TB) patients by the WHO in October 2014[21], by issuing an interim policy guidance on the use of this novel medicine developed by Otsuka Pharmaceutical. The interim policy guidance stated that 'delamanid may be added to a MDR-TB regimen in adult patients with pulmonary TB' conditional upon: i) careful selection of patients likely to benefit; ii) patient informed consent; iii) adherence to WHO recommendations in designing a longer MDR-TB regimen; iv) close monitoring of clinical treatment response; and v) active TB drug-safety monitoring and management (aDSM). Further in 2016, the delamanid interim policy by WHO was extended to cover children aged 6-17 years following a review of data from a six-month safety, efficacy, and pharmacokinetic trial of paediatric patients[22].

Phase III Clinical Trial of Delamanid

The purpose of this trial was to determine whether delamanid is effective in the treatment of Multidrug-resistant Tuberculosis (MDR TB) in combination with other MDR TB medications during 6 months of treatment. This trial was the first-ever MDR-TB treatment study of its kind to be completed and reported and its findings were thus much-awaited. The trial conformed to whigh scientific standards, as guided by an extensive and detailed study protocol, and with broad geographical distribution of study sites in seven countries (Estonia, Latvia, Lithuania, Republic of Moldova, Peru, the Philippines, and South Africa).

Trial participants received either delamanid or a placebo for six months, added to an optimised, longer background MDR-TB regimen designed according to WHO recommendations. Participants were randomised to receive either delamanid or placebo in a 'blinded' fashion, i.e neither they nor the treating physicians were aware of whether the medicine added to the MDR-TB regimen was active delamanid or an inactive placebo.

Trial Results

Efficacy Results

- There was no clinically relevant or statistically significant difference between the delamanid and placebo study arms in treatment success: At 30 months' follow-up, 77.1% of participants receiving delamanid achieved sustained cure versus 77.6% of participants receiving placebo.

19 http://www.who.int/tb/features_archive/WHO_statement_use_delamanid_MDR_TB/en/

20 http://www.who.int/entity/tb/publications/2018/WHOPositionStatementDelamanidUse.pdf

21 http://apps.who.int/iris/bitstream/10665/137334/1/WHO_HTM_TB_2014.23_eng.pdf

22 http://apps.who.int/iris/bitstream/10665/250614/1/9789241549899-eng.pdf

- There was no clinically-relevant or statistically significant difference in all-cause mortality between the two study arms: at 30 months' follow-up mortality was 5.3% in the delamanid group and 4.7% in the placebo group.

Safety Results

- There was no significant difference in treatment-emergent adverse events (TEAEs) between participants receiving delamanid and those receiving placebo. No new or significant drug-drug interactions between delamanid and antiretroviral (ARV) drugs were observed,

The overall, cure and mortality rates were similar in trial participants who received delamanid and in those who received the placebo on top of the optimised background MDR-TB regimen. The trial thus did not confirm the efficacy findings of earlier studies. However, no additional or new safety concerns were identified, providing reassurance of the safety of delamanid relative to many of the other second-line medicines used for MDR-TB treatment.

Study Conclusions

Delamanid in the present trial did not show any statistically significant difference in successfully curing the disease or reducing the mortality rates compared with a placebo in this Phase III human clinical trial. However, the drug was found to be safe unlike many of the other second-line medicines used for MDR-TB treatment.

WHO's revised Advise on usage of Delamanid

- WHO is advising national TB programmes and other stakeholders to add delamanid to a longer MDR-TB regimen only when the regimen cannot be composed according to WHO recommendations, eg. when drug intolerability or drug resistance requires changes. When an effective and well-tolerated longer MDR-TB regimen can be otherwise composed, the addition of delamanid may not be warranted.
- The decision to use delamanid in such regimens should be made by treating clinicians based on individual patient assessment and well-established considerations for composition of MDR-TB regimens including drug susceptibility profiles, drug intolerability and safety, risk-benefit and ethics.
- The conditions for delamanid use in individual patients remain the same, i.e. i) careful selection of patients likely to benefit; ii) patient informed consent; iii) adherence to WHO recommendations in designing a longer MDR-TB regimen; iv) close monitoring of clinical treatment response; and v) active TB drug-safety monitoring and management (aDSM).
- Use of delamanid in the shorter MDR-TB regimen under programmatic conditions is not recommended by WHO given the lack of data.
- Delamanid should be retained in country guidelines, national essential medicine lists and procurement options. MDR-TB treatment algorithms may need adjustment in view of the Trial 213 outcomes.
- Research on the role of delamanid in MDR-TB treatment should continue; particularly, its use in MDR-TB regimens compromised by drug resistance or drug intolerability should be pursued.

Delamanid in India

Delamanid in India was approved by the Central Drugs Standard Control Organization (CDSCO) India in August 2017. It has been approved for the use as part of an appropriate combination regimen for pulmonary multi-drug resistant tuberculosis (MDR-TB) in adult patients when an effective treatment regimen cannot otherwise be

composed for reasons of resistance or tolerability[23]. Further in the Subject Expert Committee (SEC) meeting, the experts of Antimicrobial and Antiviral SEC committee recommended based on the examination of the data on global clinical trials conducted and approval by EU and Japan for this drug, and risk benefit analysis, the committee recommended for waiver of local clinical trial as this drug is required as an unmet need in emergency for the treatment of MDR/XDR-TB in adult. Further, the Committee recommended for approval of the drug in the conditional access programme through Revised National Tuberculosis Control Program (RNTCP)[24].

Conclusion

The bacteria that causes tuberculosis (TB) can develop resistance to the antimicrobial drugs used to cure the disease. Multidrug-resistant TB (MDR-TB) is a form of TB that does not respond to even isoniazid and rifampicin, the 2 most powerful anti-TB drugs. MDR-TB is a complex form of disease and is difficult to treat with limited treatment option. In this scenario, results from the phase III clinical studies on Delamanid, have been hugely disappointing.

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

24 http://www.cdsco.nic.in/writereaddata/MOM%20of%20SEC%20Antimicrobial%20and%20Antiviral%2014_06_2017%20(Website)%20(1).pdf

European Medicines Agency (EMA) Recommends Approval of seven medicines in its January Meeting

The European Medicines Agency's (EMA) Committee for Medicinal Products for Human Use (CHMP) has recommended seven medicines for approval, including one orphan medicine, at its January 2018 meeting[25].

The seven new drugs recommended for approval are:

1. Hemlibra (Emicizumab) - First-in-class medicine to prevent bleeding in Haemophilia a patients with inhibitors

The EMA's CHMP has recommended granting a marketing authorization for Hemlibra (emicizumab)[26], a first-in-class medicine to prevent bleeding or reduce the frequency of bleeding episodes in patients of all ages with Haemophilia A with factor VIII inhibitors.

Haemophilia A is an inherited bleeding disorder caused by lack of a clotting protein called factor VIII and mainly affects males. Patients with Haemophilia A are usually treated with factor VIII medicines, which replace the missing clotting protein and help control and prevent bleeding. However, the body may develop inhibitors (antibodies) as a reaction to these medicines. The inhibitors reduce the effect of medicines; hence, bleeding is no longer controlled. The development of inhibitors is the most severe treatment-related complication of Haemophilia A because it makes it difficult to manage the disease. Current treatment alternatives in patients with Haemophilia A who develop inhibitors are time-consuming and often burdensome, particularly for children, and they are also not effective in all patients. There is therefore, an unmet medical need for more convenient and effective treatment option.

Hemlibra is the first monoclonal antibody to be recommended for use in patients with Haemophilia A with inhibitors - an area of medicine where no new medicines have been made available in last 20 years. It works by mimicking the coagulation function of factor VIII. The treatment is given weekly via a subcutaneous injection, making it more convenient compared to bypassing agents (medicines that bypass factor VIII), which are the current standard of care but which require frequent, prolonged administration by infusion (drip). The CHMP reviewed the application for Hemlibra under its accelerated assessment procedure, which allows the speeding up of patients' access to medicines that address unmet medical needs.

The applicant for Hemlibra is Roche.

2. Lamzede (velmanase alfa) - New enzyme replacement therapy to treat rare genetic disorder alpha-mannosidosis in children and adults

The EMA's Committee for Medicinal Products for Human Use (CHMP) recommended granting a marketing authorization in the European Union (EU) for Lamzede (velmanase alfa), a long-term enzyme replacement therapy in adults, adolescents and children with mild to moderate forms of alpha-mannosidosis[27].

Alpha-mannosidosis is a rare inherited enzyme disorder that causes cell damage through build-up of mannose-rich oligosaccharides in many organs and tissues of the body. Patients affected by the disease may have intellectual disability, liver or spleen enlargement, distinctive facial features and skeletal abnormalities. The symptoms of alpha-mannosidosis range from mild to moderate to severe. Individuals with early onset of severe symptoms and

25 http://www.ema.europa.eu/ema/index.jsp?curl=pages/news_and_events/news/2018/01/news_detail_002888.jsp&mid=WC0b01ac058004d5c1

26 http://www.ema.europa.eu/ema/index.jsp?curl=pages/news_and_events/news/2018/01/news_detail_002893.jsp&mid=WC0b01ac058004d5c1

27 http://www.ema.europa.eu/ema/index.jsp?curl=pages/news_and_events/news/2018/01/news_detail_002891.jsp&mid=WC0b01ac058004d5c1

rapid progressive disease often do not survive beyond childhood, whereas those affected with the milder forms of the disease survive into adult life. Alpha-mannosidosis is a rare disease estimated to occur in approximately 1 in 500,000 to 1 in 1,000,000 people worldwide. There is currently no cure for this disease. Patients with less severe forms of the disease are managed with supportive care including symptom management, medical and surgical treatment of complications and physical therapy. Because alpha-mannosidosis is an extremely rare disease, Lamzede was granted an orphan designation.

Lamzede is a recombinant human alpha mannosidase developed as an intravenous enzyme replacement therapy (ERT) for the treatment of alpha-mannosidosis. The objective of the treatment is to administer the medicine into the blood stream in order to replace the function of the deficient enzyme in the body. The ERT aims to normalise oligosaccharide levels in the body, to prevent progression of the disease and formation of abnormalities, as well as to improve the patient's condition.

The applicant for Lamzede is Chiesi Farmaceutici S.p.A.

3. Segluromet (Ertugliflozin / Metformin) - Treatment of type 2 diabetes

The Committee for Medicinal Products for Human Use (CHMP) adopted a positive opinion, recommending the granting of a marketing authorization for the medicinal product Segluromet, intended for the treatment of type 2 diabetes[28].

Segluromet is a fixed dose combination of ertugliflozin and metformin, two oral blood glucose lowering medicines. It will be available as film-coated tablets (containing 2.5 mg ertugliflozin/1000 mg metformin; 2.5 mg/850 mg; 7.5 mg/1000 mg; and 7.5 mg/850 mg). Ertugliflozin works by blocking a protein in the kidney called the human sodium-glucose co-transporter-2 (SGLT2). This reduces glucose re-absorption in the kidney leading to glucose excretion in the urine. Metformin works by suppressing glucose production by the liver, by decreasing intestinal absorption of glucose, and by increasing peripheral glucose uptake and utilization.

The applicant for this medicinal product is Merck Sharp & Dohme Limited.

4. Shingrix (herpes zoster vaccine (recombinant, adjuvanted)) - Prevention of Herpes zoster (HZ) and post-herpetic neuralgia (PHN), in adults 50 years of age or older

The Committee for Medicinal Products for Human Use (CHMP) adopted a positive opinion, recommending the granting of a marketing authorization for the medicinal product Shingrix, intended for prophylaxis of Herpes zoster[29].

Shingrix will be available as a powder and suspension liquid - to be made into a suspension for injection. The active substance of Shingrix is varicella zoster virus glycoprotein E antigen (VZV gE). In Shingrix, VZV gE is combined with an adjuvant (AS01B) and is designed to induce antigen-specific cellular and humoral immune responses in individuals with pre-existing immunity against varicella zoster virus.

The benefits with Shingrix are its ability to significantly decrease the incidence of Herpes zoster and consequently of post-herpetic neuralgia compared with placebo. Shingrix is indicated for prevention of herpes zoster (HZ) and post-herpetic neuralgia (PHN), in adults 50 years of age or older.

The applicant for this medicinal product is GlaxoSmithkline Biologicals SA.

28 http://www.ema.europa.eu/ema/pages/includes/document/open_document.jsp?webContentId=WC500242391

29 http://www.ema.europa.eu/ema/pages/includes/document/open_document.jsp?webContentId=WC500242399

5. Steglatro (Ertugliflozin) - Treatment of type 2 diabetes

The Committee for Medicinal Products for Human Use (CHMP) adopted a positive opinion, recommending the granting of a marketing authorization for the medicinal product Steglatro, intended for the treatment of type 2 diabetes[30].

Steglatro will be available as 5 mg and 15 mg film-coated tablets. The active substance of Steglatro is ertugliflozin, a blood glucose lowering agent. Ertugliflozin works by blocking a protein in the kidney called the human sodium-glucose co-transporter-2 (SGLT2). This reduces glucose re-absorption in the kidney leading to glucose excretion in the urine. Steglatro is indicated in adults aged 18 years and older with type 2 diabetes mellitus as an adjunct to diet and exercise to improve glycaemic control.

The applicant for this medicinal product is Merck Sharp & Dohme.

6. Steglujan (Ertugliflozin / Sitagliptin) - Treatment of type 2 diabetes

The CHMP adopted a positive opinion, recommending the granting of a marketing authorization for the medicinal product Steglujan, intended for the treatment of type 2 diabetes[31].

Steglujan is a fixed dose combination of ertugliflozin and sitagliptin, two oral blood glucose lowering medicines. It will be available as film-coated tablets (containing either 5 mg ertugliflozin and 100 mg sitagliptin, or 15 mg ertugliflozin and 100 mg sitagliptin). Ertugliflozin works by blocking a protein in the kidney called the human sodium-glucose co-transporter-2 (SGLT2). This reduces glucose re-absorption in the kidney leading to glucose excretion in the urine. Sitagliptin is a dipeptidyl peptidase 4 (DPP-4) inhibitor. DPP-4 inhibition reduces the cleavage and inactivation of the incretin hormone glucagon-like peptide 1 (GLP-1), leading to an increase in incretin levels, which in turn stimulates glucose-dependent insulin secretion and inhibits the release of glucagon. Steglujan is indicated in adults aged 18 years and older with type 2 diabetes mellitus as an adjunct to diet and exercise to improve glycaemic control.

The applicant for this medicinal product is Merck Sharp & Dohme Limited.

7. Semglee (Insulin glargine) - Treatment of diabetes

The CHMP adopted a positive opinion, recommending the granting of a marketing authorization for the medicinal product Semglee, intended for treatment of diabetes[32].

Semglee will be available as a solution for injection (100 units/ml). The active substance of Semglee is insulin glargine, a long-acting insulin analogue. Insulin glargine binds specifically to the human insulin receptor and results in the same pharmacological effects as human insulin. Semglee is a biosimilar medicinal product. It is highly similar to the reference product Lantus (insulin glargine). Semglee is indicated for Treatment of diabetes mellitus in adults, adolescents and children aged 2 years and above.

The applicant for this medicinal product is Mylan.

30 http://www.ema.europa.eu/ema/pages/includes/document/open_document.jsp?webContentId=WC500242393

31 http://www.ema.europa.eu/ema/pages/includes/document/open_document.jsp?webContentId=WC500242397

32 http://www.ema.europa.eu/ema/pages/includes/document/open_document.jsp?webContentId=WC500242403

B) Re-adoption of opinion for new medicine

Lokelma (Sodium zirconium cyclosilicate) - Treatment of Hyperkalaemia

The CHMP confirmed its previous positive opinion and recommended the granting of a marketing authorization for the medicinal product Lokelma[33]. This follows an inspection of the manufacturing site for Lokelma's active substance confirming that the site is compliant with good manufacturing practice. Lokelma is intended for the treatment of Hyperkalaemia.

Lokelma will be available as 5g and 10g powder for oral suspension. The active substance of Lokelma is sodium zirconium cyclosilicate. Sodium zirconium cyclosilicate selectively binds potassium in exchange for hydrogen and sodium cations throughout the gastrointestinal (GI) tract and reduces the concentration of free potassium in the GI lumen. This lowers serum potassium levels by drawing potassium into the GI tract and increasing faecal potassium excretion to resolve Hyperkalaemia.

The applicant for this medicinal product is AstraZeneca AB.

C) Negative opinion on new medicine

EnCyzix (enclomifene) - Treatment of hypogonadotropic hypogonadism in men

The CHMP adopted a negative opinion for EnCyzix (enclomifene). EnCyzix was expected to be used to treat hypogonadotrophic hypogonadism in men. The committee noted that although the studies showed an increase in testosterone levels with EnCyzix, they did not look at whether EnCyzix would improve symptoms such as bone strength, weight gain, impotence and libido. In addition, there is a risk of venous thromboembolism (problems due to the formation of blood clots in the veins) with the medicine. Therefore, the CHMP was of the opinion that the benefits of EnCyzix did not outweigh its risks and recommended that it be refused marketing authorization[34].

D) Recommendations on extensions of therapeutic indication

The Committee recommended three extensions of indications for Hizentra, Relvar Ellipta and Revinty Ellipta.

- **Hizentra (Human normal immunoglobulin)** - The CHMP adopted a new indication, Immunomodulatory therapy in adults, children and adolescents (0-18 years): Hizentra is indicated for the treatment of patients with chronic inflammatory demyelinating polyneuropathy (CIDP) as maintenance therapy after stabilization with IVIg[35].
- **Relvar Ellipta (Fluticasone furoate / vilanterol)** - The CHMP adopted an extension to the existing indications as follows[36]:

Asthma

Relvar Ellipta is indicated for the regular treatment of asthma in adults and adolescents aged 12 years and older where use of a combination medicinal product (long-acting beta2-agonist and inhaled corticosteroid) is appropriate:

- Patients not adequately controlled with inhaled corticosteroids and 'as needed' inhaled short acting beta2-agonists.
- Patients already adequately controlled on both inhaled corticosteroid and longacting beta2-agonist.

33 http://www.ema.europa.eu/docs/en_GB/document_library/Summary_of_opinion_-_Initial_authorisation/human/004029/WC500222241.pdf

34 http://www.ema.europa.eu/docs/en_GB/document_library/Summary_of_opinion_-_Initial_authorisation/human/004198/WC500242417.pdf

35 http://www.ema.europa.eu/docs/en_GB/document_library/Summary_of_opinion/human/002127/WC500242389.pdf

36 http://www.ema.europa.eu/docs/en_GB/document_library/Summary_of_opinion/human/002673/WC500242405.pdf

- ***COPD (Chronic Obstructive Pulmonary Disease)***
- Relvar Ellipta is indicated for the symptomatic treatment of adults with COPD with a FEV1<70% predicted normal (post-bronchodilator) with an exacerbation history despite regular bronchodilator therapy.

3) Revinty Ellipta (Fluticasone furoate / vilanterol) The CHMP adopted an extension to the existing indications as follows[37]:

Asthma

Revinty Ellipta is indicated for the regular treatment of asthma in adults and adolescents aged 12 years and older where use of a combination medicinal product (long-acting beta2-agonist and inhaled corticosteroid) is appropriate:

- Patients not adequately controlled with inhaled corticosteroids and 'as needed' inhaled short acting beta2-agonists.
- Patients already adequately controlled on both inhaled corticosteroid and longacting beta2-agonist.

COPD (Chronic Obstructive Pulmonary Disease)

Revinty Ellipta is indicated for the symptomatic treatment of adults with COPD with a FEV1<70% predicted normal (post-bronchodilator) with an exacerbation history despite regular bronchodilator therapy.

37 http://www.ema.europa.eu/docs/en_GB/document_library/Summary_of_opinion/human/002745/WC500242408.pdf

BREXIT Update: UK's Drug Regulator (MHRA) issues update to pharmaceutical companies on exit preparations

On January 16, 2018, the United Kingdom's Medicines and Healthcare products Regulatory Agency (MHRA) issued update to pharmaceutical companies on its exit preparations from the European Union (EU). It said that it will ensure minimum disruption and burden on companies as the UK exits the EU; there would be no sudden changes to the regulatory framework. The agency would also be pragmatic in establishing UK regulatory requirements and would give adequate notice and ensure that companies have sufficient time to implement any changed requirements[38].

Update on negotiations

The European Council formally agreed in December last year that sufficient progress has been made to move on to the second stage of the negotiations and adopted guidelines for the same[39]. This followed the publication of a Joint Report on progress during the first phase by the Government and the European Commission on 8 December, 2017[40]. In the context of ensuring continuity in the availability of goods placed on the market under Union law before withdrawal, the Joint Report made clear that "goods placed on the market under Union law before the withdrawal date may freely circulate on the markets of the UK and the Union, with no need for product modifications or re-labelling; be put into service where provided in Union law, and that the goods concerned should be subject to continued oversight."

Preparing for all outcomes

The agency has stated that it is aware that companies that market pharmaceuticals in the EU and UK will need to plan and make decisions prior to the UK's departure from the EU in March 2019. The agency further reiterated that UK's intention remains to secure an implementation period based on the existing structure of EU rules and regulations as quickly as possible, and to agree to a deep and special future partnership. The agency will continue to advise businesses on the basis of the UK position and will continue to work with the EMA while planning for the UK's withdrawal from the EU and future relationship.

Current regulatory relationship between UK and European network

The agency stated that it is also important to note that the UK's current regulatory relationship with the European network remains unchanged. The UK has reiterated to Member States and to the EMA on several occasions that at present:

- The UK continues to be a full member of the EU: the agency will fulfil all its responsibilities, and, in turn expect to be treated as such.
- The UK continues to bid for EMA work and expects its bids to be respected and considered on merit. There are simple, pragmatic solutions to manage the possibility of various outcomes in March 2019 - the agency, for example, was putting forward UK bids in conjunction with other Member States, in the centralised procedure, to ensure business continuity where procedures are likely to run beyond this date.
- MHRA has committed to complete all assessments under evaluation by the time the UK departs from the EU and will make assessment reports available to the network.

38 https://www.gov.uk/government/news/mhra-update-to-pharmaceutical-companies-on-exit-preparations

39 http://www.consilium.europa.eu/en/press/press-releases/2017/12/15/european-council-art-50-guidelines-for-brexit-negotiations/

40 https://www.gov.uk/government/publications/joint-report-on-progress-during-phase-1-of-negotiations-under-article-50-teu-on-the-uks-orderly-with drawal-from-the-eu

- The UK continues to carry out its Official Control Authority Batch Release (OCABR) responsibilities as part of the Official Medicines Control Laboratory (OMCL) network for human biologicals.
- The UK will continue to put candidates forward for leadership roles where appropriate and expects the committees with responsibility for electing chairs to do so on merit.

UK regulatory requirements after March 2019 in the event of no ongoing relationship with EMA networks

Companies have been asking for detail about UK legislative requirements in different scenarios. The agency has been working closely with industry associations and other stakeholders and further details on all these issues and more – both our Day One and longer-term proposals.

The UK intends to agree to a time-limited implementation period with the EU, and both parties have recognized it as important. However, should there be no implementation period, MHRA's approach would be in line with the following principles:

- The European Union (Withdrawal) Bill will convert the existing EU legislative framework into UK law at the moment of exit, so there would be no sudden changes to the UK regulatory framework.
- The agency would be pragmatic in establishing UK regulatory requirements and would give adequate notice and ensure that companies had sufficient time to implement any changed requirements.
- Wherever possible, the agency would be making use of the information it already has to complete administrative tasks for continuity of work and licenses.
- The agency has assured that it would ensure minimum disruption and burden on companies as the UK exits the EU, while building on the existing relationship between MHRA and firms.

The trade unions in the United Kingdom, the Association of the British Pharmaceutical Industry (ABPI), and UK Bioindustry Association (BIA) reacted positively to MHRA's statement and welcomed the agency's reassurance that it would take a pragmatic approach to instituting new regulatory requirements if a deal with the EU is not reached.

European Medicines Agency's - Human medicines: Highlights of 2017

On January 23, 2018, the European Medicines Agency (EMA) has published its annual report titled 'Human medicines: Highlights of 2017[41]. In the report, the EMA has published an overview of its key recommendations of 2017 regarding the authorization of new medicines and the safety monitoring of medicines.

Advances in medicines authorizations are essential for public health as they have the potential to improve treatment of diseases. In 2017, EMA recommended 92 medicines for marketing authorization. Of these, 35 had a new active substance, which has never been authorized in the European Union (EU) before. Many of these medicines represent a significant improvement in their therapeutic areas; they include medicines for children, for rare diseases and advanced therapies[42]. Amongst the 35 new active substances (NAS) that EMA recommended, 11 were new drugs and biologics to treat cancer, 05 to treat neurological disorders, 04 for infectious diseases, 04 for immunology/rheumatology, 03 for endocrinology, 02 each for Uro-nephrology, haematology, and dermatology, 01 for Pneumonology, and 01 for hepatology/gastroenterology class of drugs.

Table 1: List of New Active Substances Approved by the European Medicines Agency

Sr. No.	Medicine Approved	Therapeutic Area
1.	Axumin (Fluciclovine)	Cancer/Oncology
2.	Bavencio (Avelumab)	Cancer/Oncology
3.	Besponsa (inotuzumab ozogamicin)	Cancer/Oncology
4.	Fotivda (Tivozanib)	Cancer/Oncology
5.	Kisqali (Ribociclib)	Cancer/Oncology
6.	Lutathera (Lutetium (177Lu) oxodotreotide)	Cancer/Oncology
7.	Rydapt (Midostaurin)	Cancer/Oncology
8.	Tecentriq (Atezolizumab)	Cancer/Oncology
9.	Tookad (Padeliporfin)	Cancer/Oncology
10.	Varuby (Rolapitant)	Cancer/Oncology
11.	Zejula (Niraparib)	Cancer/Oncology
12.	Brineura (Cerliponase alfa)	Neurology
13.	Ocrevus (Ocrelizumab)	Neurology
14.	Oxervate (Recombinant human Nerve Growth factor (rhNGF))	Neurology
15.	Reagila (Cariprazine hydrochloride)	Neurology
16.	Spinraza (Nusinersen)	Neurology
17.	Maviret (Glecaprevir/pibrentasvir)	Infections
18.	Prevymis (Letermovir)	Infections

41 http://www.ema.europa.eu/ema/index.jsp?curl=pages/news_and_events/news/2018/01/news_detail_002886.jsp&mid=WC0b01ac058004d5c1

42 http://www.ema.europa.eu/docs/en_GB/document_library/Report/2018/01/WC500242079.pdf

Sr. No.	Medicine Approved	Therapeutic Area
19.	Trumenba (Meningococcal group B vaccine (recombinant, adsorbed))	Infections
20.	Vosevi (Sofosbuvir / Velpatasvir / Voxilaprevi)	Infections
21.	Kevzara (Sarilumab)	Immunology/Rheumatology
22.	Spherox (Spheroids of human autologous matrix-associated chondrocytes)	Immunology/Rheumatology
23.	Tremfya (Guselkumab)	Immunology/Rheumatology
24.	Xeljanz (Tofacitinib)	Immunology/Rheumatology
25.	Crysvita (Burosumab)	Endocrinology
26.	Ozempic (Semaglutide)	Endocrinology
27.	Xermelo (Telotristat etiprate)	Endocrinology
28.	Lokelma (Sodium zirconium cyclosilicate)	Uro-nephrology
29.	Veltassa (Patiromer sorbitex calcium)	Uro-nephrology
30.	Adynovi (Rurioctocog alfa pegol)	Haematology
31.	Refixia (Nonacog beta pegol)	Haematology
32.	Dupixent (Dupilumab)	Dermatology
33.	Kyntheum (Brodalumab)	Dermatology
34.	Alofisel (Expanded human allogeneic mesenchymal adult stem cells extracted from adipose tissue)	Hepatology/Gastroenterology
35.	Fasenra (Benralizumab)	Penumology

EMA's Special Program Approvals

EMA, in its report, also highlighted its expedited programs and incentives to bring products to market more quickly and spur development of products to treat rare diseases or other areas of high unmet medical need.

Orphan Medicines

To qualify for agency's orphan designation, a medicine must meet a number of criteria[43]:

- It must be intended for treatment, prevention or diagnosis of a disease that is life-threatening or chronically debilitating;
- The prevalence of the condition in the EU must not be more than 5 in 10,000 or it must be unlikely that marketing of the medicine would generate sufficient returns to justify the investment needed for its development;
- No satisfactory method of diagnosis, prevention or treatment of the condition concerned can be authorized, or, if such a method exists, the medicine must be of significant benefit to those affected by the condition.

In 2017, the agency approved 19 drugs in its Orphan Medicine Program, out of which 13 were New Active Substances.

Accelerated Assessment

Accelerated assessment reduces the timeframe for the EMA's Committee for Medicinal Products for Human Use (CHMP) to review a marketing authorization application. Applications may be eligible for accelerated assessment

43 http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general_content_000029.jsp

if the CHMP decides that the product is of major interest for public health and therapeutic innovation[44]. This mechanism is reserved for medicines that are able to address unmet medical needs. It allows for faster assessment of eligible medicines by EMA's scientific committees (within up to 150 days rather than up to 210 days).

In 2017, seven medicines received a recommendation for marketing authorization following an accelerated assessment out of which five were new active substances.

Conditional marketing authorizations

The EMA supports development of medicines that address unmet medical needs of patients. In the interest of public health, applicants may be granted a conditional marketing authorization for such medicines where the benefit of immediate availability outweighs the risk of less comprehensive data than normally required, based on the scope and criteria defined in relevant legislation and guidelines[45].

In 2017, three medicines received a recommendation for conditional marketing authorization out of which two were new active substances.

Approval under exceptional circumstances

Approval under exceptional circumstances is an agency's regulatory pathway that allows patients access to medicines that cannot be approved under a standard authorization as comprehensive data cannot be obtained, either because there are only very few patients with the disease, or the collection of complete information on the efficacy and safety of the medicine would be unethical, or there are gaps in the scientific knowledge. These medicines are subject to specific post-authorization obligations and monitoring[46].

In 2017, two medicines were authorized under exceptional circumstances.

Table 2: Number of Drugs Approved by EMA Special Program Approvals

Program or Designation	New Active Substances Approved	Total Approvals
Orphan Medicine	13	19
Accelerated Assessment	05	07
Conditional Marketing Authorization	02	03
Approval Under Exceptional Circumstances	01	02

New uses for existing medicines

51 extensions of indication were recommended in 2017. The extension of the use of a medicine that is already approved in a new therapeutic indication can also offer new treatment opportunities for patients.

EMA's Safety Monitoring

Once a medicine is placed on the market, EMA and the EU Member States continuously monitor the quality and the benefit/risk balance of the medicine under its authorized conditions of use. In 2017, EMA gave new safety advice to manage risks observed with a number of medicines on the market in the EU. Regulatory measures ranged from a change in the product information to the suspension or withdrawal of a medicine to even recall of a limited number of batches.

44 http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general_content_000955.jsp&mid=WC0b01ac05809f843a

45 http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general_content_000925.jsp

46 http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general_content_000925.jsp

Important new safety advice issued in 2017 included:

- Information about a potential increased risk of lower limb amputation (mostly affecting the toes) in patients taking the SGLT2 inhibitors canagliflozin, dapagliflozin and empagliflozin used for type 2 diabetes.
- Recommendations to restrict the use of some linear gadolinium agents used in MRI body scans and suspend the authorizations of others. EMA's scientific review found that small amounts of gadolinium may remain in the brain after a scan with these agents, although there is currently no evidence that these small amounts cause any harm.
- Recommendation to restrict the use of Zinbryta for treating multiple sclerosis, in view of the risk of serious liver damage in some patients.
- Recommendation to suspend marketing of paracetamol medicines designed to release the active ingredient over a long period (modified-release medicines) because of the difficulty in managing overdoses.
- New recommendation on medicines containing a combination of dienogest 2 mg and ethinylestradiol 0.03 mg which can continue to be used to treat moderate acne when certain other treatments have failed, but should only be used in women who also choose oral contraception.
- Prescription information for the antibiotic vancomycin to be changed to ensure appropriate use in the treatment of serious infections caused by Gram-positive bacteria. The recommendation aims to ensure appropriate use in the context of the fight against antimicrobial resistance.
- New contraindication for Uptravi, which must not be taken simultaneously with medicines like gemfibrozil which are strong blockers (inhibitors) of the liver enzyme CYP2C8.
- New recommendation for Symbioflor 2 to continue to be used to treat irritable bowel syndrome (IBS), but not for other functional gastrointestinal disorders. The company will provide a study on effectiveness and safety among patients with different features of IBS.
- Review of human factor VIII medicines authoriszd in the EU - EMA concluded that there is no clear evidence of a difference in the risk of inhibitor development between the two classes of factor VIII medicines. Patients should therefore continue to use their factor VIII medicines as prescribed by the doctor.
- New contraception recommendations for male patients regarding concerns that mycophenolate medicines (used to prevent rejection of transplanted organs) cause miscarriages or birth defects.
- New recommendation on injectable methylprednisolone medicines (used to treat the symptoms of severe allergic reactions) containing lactose which must not be used in patients with a known or suspected allergy to the proteins in cow's milk.

Conclusion:

In 2017, the EMA saw an increase in the number of new/novel drugs and biologics it recommended for marketing authorization. New Drugs/ Novel drugs are innovative products that serve previously unmet medical needs or otherwise significantly help to advance patient care and public health.

Hydroxyethyl-starch solutions for infusion to be suspended in the European Union

On January 12, 2018, the European Medicines Agency's Pharmacovigilance Risk Assessment Committee (PRAC) recommended the suspension of the marketing authorizations for hydroxyethyl-starch (HES) solutions for infusion across the European Union. These products are used as plasma volume replacement following acute (sudden) blood loss, where treatment with alternative products known as 'crystalloids' alone is not considered to be sufficient[47].

The review was triggered by results from two drug utilization studies indicating that HES solutions are being used in critically ill patients and even to those with sepsis and kidney injury despite restrictions introduced in 2013 to reduce the risks of kidney problems and deaths in these patient populations.

Background

In 2013, the PRAC had recommended restrictions on the use of HES solutions, including that they must no longer be used to treat critically ill patients or patients with sepsis, because of an increased risk of kidney injury and mortality seen in clinical trials. The Committee requested that further studies be carried out to verify adherence to these restrictions.

The PRAC reviewed the results from the drug utilization studies of HES solutions for infusion together with the currently available data on benefits and risks from clinical trials and observational studies and feedback received from stakeholders and experts.

Results from these studies show that the implemented restrictions have not been adhered to in practice. Non-adherence to the revised product information was reported to range from 67% - 77%, including 20 – 34% non-adherence to contraindications. On an average, across all EU Member States included in the study, 9% of patients exposed to HES solutions for infusion were critically ill, 5-8% patients had renal impairment and 3- % had sepsis. This raised serious concerns as use of medicinal products containing HES, in patient populations which are contraindicated - those who are critically ill, those with renal impairment, or with sepsis, is associated with a scientifically well-established risk for serious harm including mortality. Recent estimations of patient exposure across the EU indicate approximately 750 000 – 1.5 million patients exposed yearly[48].

Based on this review, the PRAC has concluded that the restrictions introduced in 2013 have not been sufficiently effective. The Committee explored the possibility of introducing additional measures but concluded that such measures would be ineffective or insufficient. In view of the serious risks that certain patient populations are exposed to, the PRAC has recommended suspension of the marketing authorizations for HES solutions. Alternative treatment options are available.

PRAC recommendations endorsed by CMDh

The PRAC recommendation was sent to the Coordination Group for Mutual Recognition and Decentralised Procedures–Human (CMDh) for consideration at its meeting held from January 22-25, 2018.

On January 26, 2018, the CMDh endorsed the recommendation to suspend the marketing authorizations of hydroxyethyl-starch (HES) solutions for infusion across the European Union[49]. The CMDh agreed with the PRAC

47 http://www.ema.europa.eu/ema/index.jsp?curl=pages/news_and_events/news/2018/01/news_detail_002882.jsp&mid=WC0b01ac058004d5c1

48 http://www.ema.europa.eu/docs/en_GB/document_library/Referrals_document/Hydroxyethyl_starch_107i/Procedure_started/WC500237820.pdf

49 http://www.ema.europa.eu/ema/index.jsp?curl=pages/news_and_events/news/2018/01/news_detail_002892.jsp&mid=WC0b01ac058004d5c1

recommendation that, in view of the serious risks that certain patients are exposed to, HES solutions for infusion should be suspended. Alternative treatment options are available. The CMDh position will now be sent to the European Commission, which will take an EU-wide legally binding decision.

About HES (HydroxyEthyl Starch)

HES solution for infusion is used for the management of hypovolaemia (low blood volume) caused by acute blood loss, where treatment with alternative infusion solutions known as 'crystalloids' alone is not considered to be sufficient. It is given by infusion (drip) into a vein and is used as blood volume expander to prevent shock following acute bleeding. It belongs to the class of medicines known as colloids. Besides blood products, there are two types of medicines used for plasma volume replacement: crystalloids and colloids. Colloids contain large molecules such as starch, whereas crystalloids, such as saline or Ringer's solutions, are pure electrolyte solutions.

About the Procedure

The review of HES solutions for infusion was initiated on October 17, 2017, at the request of the Swedish Medical Products Agency, under Article 107i of Directive 2001/83/EC.

Article 107i procedures:

This type of procedure is triggered when a Member State or the European Commission consider that urgent action is necessary because of a safety issue. Situations that fall under this procedure include consideration for suspension or revocation of the marketing authorization for a medicine, the prohibition of supply of a medicine or major changes to the marketing authorization such as deletion of indications, reduction of the recommended dose or new contraindications. The procedure is also applicable in case of a safety issue with a class of medicines[50].

Conclusion:

The suspension of Hydroxyethyl-Starch solutions across European Union is due to serious risks of kidney injury and death in certain patient populations. The safety recommendations from the agency will now be sent to the European Commission, which will take an EU-wide legally binding decision on this matter.

50 http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general_content_000150.jsp&mid=WC0b01ac05800240d0

Novartis's Kisqali® (Ribociclib) received FDA Breakthrough Therapy designation

On January 03, 2018, Novartis announced that Kisqali® (Ribociclib) has received US Food and Drug Administration (FDA) Breakthrough Therapy designation for initial endocrine-based treatment, in combination with tamoxifen or an aromatase inhibitor[51], for pre- or perimenopausal women with hormone-receptor positive, human epidermal growth factor receptor-2 negative (HR+/HER2-) advanced or metastatic breast cancer.

The Breakthrough Therapy designation was based on positive results of the Phase III MONALEESA-7 trial demonstrating Kisqali in combination with tamoxifen or an aromatase inhibitor as initial endocrine-based therapy showing significantly prolonged progression-free survival (PFS) compared to endocrine therapy alone (median PFS 23.8 (95% CI: 19.2 months-not reached) vs. 13.0 months (95% CI: 11.0-16.4 months); HR=0.553; 95% CI: 0.441-0.694; p<0.0001). A total of 672 women ranging from 25-58 years in age were enrolled and randomized in the trial. All treatment combinations also included goserelin. Treatment benefit with Kisqali combination therapy was consistent across the population regardless of treatment with tamoxifen or aromatase inhibitor endocrine partners, and across predefined patient subgroups[52].

MONALEESA-7 was the first Phase III trial entirely dedicated to evaluating a CDK4/6 inhibitor in premenopausal women with HR+/HER2- advanced breast cancer. The trial evaluated Kisqali in combination with oral endocrine therapies (tamoxifen or an aromatase inhibitor) and goserelin compared to oral endocrine therapy and goserelin in this patient population. In subgroup analyses of median PFS by endocrine partner, Kisqali in combination with tamoxifen and goserelin demonstrated 22.1 months median PFS compared to 11.0 months for tamoxifen and goserelin alone; Kisqali in combination with an aromatase inhibitor and goserelin demonstrated 27.5 months median PFS compared to 13.8 months for an aromatase inhibitor and goserelin alone.

No new safety signals were observed in the MONALEESA-7 trial; adverse events were generally consistent with those observed in MONALEESA-2, identified early and mostly managed through dose interruptions or reductions. Combination treatment with Kisqali was well tolerated with a discontinuation rate due to adverse events of 3.6% compared to 3.0% in patients who received endocrine therapy alone. The most common (>=5%) grade 3/4 adverse events in patients receiving Kisqali combination therapy, compared to endocrine therapy alone, were neutropenia (60.6% vs 3.6%) and leukopenia (14.3% vs 1.2%).

Premenopausal breast cancer is a biologically distinct and more aggressive disease than postmenopausal breast cancer, and it is the leading cause of cancer deaths in women 20-59 years of age[53].

According to FDA, Breakthrough Therapy designation is intended to expedite the development and review of potential new medicines that treat serious or life-threatening conditions, if the therapy has demonstrated substantial improvement over an available therapy on at least one clinically significant endpoint. The designation includes all of the Fast Track program features, as well as more intensive FDA guidance on an efficient drug development program[54].

51 https://www.novartis.com/news/media-releases/novartis-kisqalir-received-fda-breakthrough-therapy-designation-initial-endocrine-based-treatment- premenopausal-women-hrher2-advanced-breast-cancer

52 http://www.ascopost.com/News/58328

53 http://www.who.int/mediacentre/factsheets/fs334/en/

54 http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM358301.pdf

This Breakthrough Therapy designation marks the second such designation for Kisqali. The first Breakthrough Therapy designation for Kisqali was granted in August 2016 based on results of the Phase III MONALEESA-2 trial.

About Kisqali® (Ribociclib)

Kisqali is a selective cyclin-dependent kinase inhibitor, a class of drugs that helps slow the progression of cancer by inhibiting two proteins called cyclin-dependent kinase 4 and 6 (CDK4/6). These proteins, when over-active, can enable cancer cells to grow and divide quickly. Targeting CDK4/6 with enhanced precision may play a role in ensuring that cancer cells do not continue to replicate uncontrollably.

Kisqali was approved by the European Commission in August 2017, as initial endocrine-based therapy for post-menopausal women with HR+/HER2- locally advanced or metastatic breast cancer in combination with an aromatase inhibitor based on findings from the pivotal MONALEESA-2 trial.

USFDA draft guidance for strengthening public warning and notification of product recalls

The United States Food and Drug Administration (USFDA) on January 18, 2018, released a draft guidance "*Public Warning and Notification of Recalls Under 21 CFR Part 7, Subpart C*" explaining new policy steps for strengthening public warning and notification of recalled products which eventually ensure that a better, and timely information reaches to consumers. Although we often hear the most about recalled food products, this guidance covers recalls of other FDA-regulated products including drugs, medical devices and cosmetics.

According to the US Federal Regulations, **Recall** means removal or correction of such marketed product, by the manufacturer-marketer, which the FDA considers to be in violation of the laws it administers and against which the Agency would initiate legal action, e.g., seizure. Recall does not include a market withdrawal or a stock recovery[55].

The draft guidance specifically outlines the circumstances when a company should issue a public warning about a recall, describes the general timeline for companies to issue such a warning, discusses what information should be included in a public warning, and describes situations where the FDA may take action to issue its own public warning should a company's warning be deemed insufficient.

This guidance applies to voluntary recalls of products subject to FDA's jurisdiction, including any food, drug, and device intended for human or animal use, any cosmetic and biologic intended for human use, any tobacco product intended for human use, and any item subject to a quarantine regulation under part 21 Part 1240. The draft guidance does not specifically address recalls of alcohol beverage products regulated by the Federal Alcohol Administration (FAA) Act or the primary role of the Alcohol and Tobacco Tax and Trade Bureau (TTB) in seeking and monitoring recalls of such beverages.

About Public warning:

According to the draft, Public warnings are for urgent situations to alert the public that a product being recalled presents a 'serious hazard' to health, and where other means for preventing the use of a recalled product appear inadequate. A public warning is also often needed when a recalled product has been widely distributed but are likely to be classified as, or have been classified as Class I recalls, unless specific circumstances indicate that the warning would not be beneficial to the public. According to this draft guidance, following recalls present examples of serious hazards to health such that a public warning may be warranted:

- Recalls of food products initiated by a firm after receipt of consumer reports of illness or injury (including allergic reactions), where an active outbreak is associated with the product or its ingredients, or for which FDA has substantiated reports of illness or injury.
- Recalls of food products that are intended for or would more likely be consumed by vulnerable populations. Examples of vulnerable human populations include infants, toddlers, the elderly, pregnant women, and medically-compromised individuals, who may be more susceptible to foodborne hazards than healthy persons.
- Recalls of food products initiated because of manufacturing deviations where the consequences of the deviations could have significant health impacts; e.g., under processed low-acid canned foods which could result in botulism if the product is consumed.

55 https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?fr=7.3

- Recalls of food products initiated because of microbiological pathogen findings (e.g., Listeria monocytogenes, Salmonella, etc.) in environmental testing where direct food manufacturing contact surfaces are found to be contaminated.
- Recalls of animal food products which may be contaminated with low levels of drugs or unsafe food additives. Examples include pet jerky treats contaminated with antibiotics, and cat food products containing propylene glycol.
- Recalls of medical devices which may malfunction and lead to incorrect dosing of drugs or blood volumes.
- Recalls of sterile injectable drug products with particulate matter.
- Recalls of drug products associated with reports of death or other serious adverse events.

The public warning should have the information of:

- Information to help identify the recalled product including images, codes (e.g., lot number, expiration date, serial number, unique device identification (UDI) number), packaging information or brand names;
- The geographic areas and dates of distribution of the product;
- A thorough description of the product defect, health hazard involved and reason(s) for recall (e.g., product testing, environmental sampling, etc.);
- The name and contact information for the recalling firm;
- Instructions to consumers or users;
- The number and nature of any illnesses/injuries/complaints associated with the product; and
- A description of common symptoms of any illness of concern. The headline of the public warning should include the brand name, type of product, and the hazard prompting the recall (e.g., "XYZ chocolate chip cookies recalled for potential Salmonella contamination."

The draft also suggests that Public Warnings by the relevant firm and FDA should be distributed and displayed by various means, including issuing press releases to the media, sending emails to a listserv or subscription service, and posting on FDA and company websites or social media. All of these methods could be used to issue a public warning.

About Public Notification of Recalls

FDA provides public access to information on recalls by posting a listing of recalls according to their classification in the "*FDA Enforcement Report*", whether they were requested by FDA or firm-initiated, and the specific action taken by the recalling firm. The FDA Enforcement Report is designed to provide a public listing of products in the marketplace that are being recalled. Unlike with public warnings, the recalls listed in the FDA Enforcement Report are not limited to urgent situations that present serious hazards to health and are not necessarily used to alert the public about the risk or hazard of a product under recall[56].

Conclusion:

The draft guidance is a key step to enhance the recall process. It gives the industry clear direction on how to navigate and work with the FDA to make sure that recalls are communicated promptly. Ultimately, it will better empower consumers by providing timely and accurate information on recalled products. This draft guidance is

56 https://www.fda.gov/downloads/Safety/Recalls/IndustryGuidance/UCM592851.pdf

just the first in a series of policy steps FDA has planned, as part of a broader action plan to further improve the oversight of food safety and implementation of the recall process.

Note: This draft guidance contains *Nonbinding Recommendations Draft to industry and FDA staff regarding the use, content, and circumstances for issuance of public warnings and public notifications.*

The United States FDA Recommends Labeling Changes for Cough and Cold Drugs Containing Opioids to Protect Children

On January 11, 2018, the United States Food and Drug Administration (US-FDA) announced that it is requiring safety labeling changes to limit the use of prescription opioid cough and cold medicines containing codeine or hydrocodone in children younger than 18 years of age because the serious risks of these medicines outweigh their potential benefits in this population[57]. After safety labeling changes are made, these products will no longer be indicated for use to treat cough in any pediatric population and will be labeled for use only in adults aged 18 years and older. Labeling for the medications is being updated with additional safety information for adult use – including an expanded Boxed Warning, FDA's most prominent warning – notifying about the risks of misuse, abuse, addiction, overdose and death, and slowed or difficult breathing that can result from exposure to codeine or hydrocodone.

The FDA Commissioner said that given the epidemic of opioid addiction and knowing that any exposure to opioid drugs can lead to future addiction, the agency is concerned about unnecessary exposure to opioids, especially in young children.. It has become clear that the use of opioid-containing prescription medicines to treat cough and cold in children comes with serious risks that does not justify their use in this vulnerable population; making it critical to protect children from unnecessary exposure to such medicines.

In addition to limiting use in children, following a comprehensive assessment of the risks and benefits of these products, labeling for adult-only use of prescription opioid cough and cold medicines that contain codeine or hydrocodone will also include updated safety information. The new labeling will provide safety warnings on these products that are consistent with the labeling of other opioid-containing drug products, including immediate-release opioid analgesics and extended-release and long-acting opioid analgesics. Information about these required safety labeling changes are being made available to parents and health care professionals through a Drug Safety Communication.

The required safety labeling changes announced are based on an extensive review of available data and expert advice. The expanded pediatric restrictions were put in place last year[58], when the FDA required the addition of its strongest warning, called a contraindication, to the labeling of prescription codeine products alerting that codeine should not be used to treat pain or cough in children younger than 12 years due to a specific risk of ultra-rapid metabolism in certain patients. The FDA also held an expert roundtable and convened a meeting of its Pediatric Advisory Committee to look at all the risks associated with the use of codeine- or hydrocodone-containing cough and cold products in children and adolescents younger than 18 years of age. Experts indicated that although some pediatric cough symptoms do require treatment, cough due to a cold or upper respiratory infection typically does not require treatment. Moreover, the risks of using prescription opioid cough products in children of all ages generally outweigh the potential benefits.

Common side effects of opioids include drowsiness, dizziness, nausea, vomiting, constipation, shortness of breath and headache. Some products sold over-the-counter in a few states may contain codeine and may not be appropriate for young children.

Through another Drug Safety Communication[59], the agency has notified health care professionals, parents and caregivers the following:

57 https://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm592109.htm

58 https://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm553285.htm

59 https://www.fda.gov/Drugs/DrugSafety/ucm590435.htm

- **Health care professionals** should be aware that FDA is changing the age range for which prescription opioid cough and cold medicines are indicated. These products will no longer be indicated for use in children, and their use in this age group is not recommended. Health care professionals should reassure parents that cough due to a cold or upper respiratory infection is self-limited and generally does not need to be treated. For those children in whom cough treatment is necessary, alternative medicines are available. These include over-the-counter (OTC) products such as dextromethorphan, as well as prescription benzonatate products.
- **Parents and caregivers** should be aware that prescription opioid cough and cold medicines that include codeine or hydrocodone should not be used for children. Codeine and hydrocodone are narcotic medicines called opioids and may carry serious risks when used in children. It is important for parents and caregivers to understand that a cough due to a common cold often does not need medicines for treatment. If a cough medicine is prescribed, ask your child's health care professional or a pharmacist if it contains an opioid such as codeine or hydrocodone. Always read the labels on prescription bottles. If the medicine prescribed for your child contains an opioid, talk to your child's health care professional about a different, non-opioid medicine, or if you have any questions or concerns.

Codeine and hydrocodone are available in combination with other medicines, such as antihistamines and decongestants, in prescription medicines to treat coughs and symptoms associated with allergies or the common cold. Other non-opioid prescription and OTC medicines are available to treat these symptoms.

List of Prescription Cough and Cold Medicines Containing Codeine

Active Ingredient(s)
codeine, chlorpheniramine
codeine, phenylephrine, promethazine
codeine, promethazine
codeine, pseudoephedrine, tripolidine

List of Prescription Cough and Cold Medicines Containing Hydrocodone

Active Ingredient(s)
hydrocodone, guaifenesin
hydrocodone, pseudoephedrine, guaifenesin
hydrocodone, chlorpheniramine
hydrocodone, chlorpheniramine, pseudoephedrine
hydrocodone, homatropine

Conclusion:

This action of FDA is to protect patients for whom the risks of opioid products outweigh the benefits. The agency continues its ongoing efforts to reduce the scope of the epidemic of opioid addiction on several fronts, including decreasing exposure and preventing new addiction, supporting treatment for those with opioid use disorder, fostering development of novel pain therapies, and improving enforcement.

United States FDA approves new treatment for certain digestive tract cancers

On January 26, 2018, the United States Food and Drug Administration (USFDA) approved Lutathera (lutetium Lu 177 dotatate) for the treatment of a type of cancer that affects the pancreas or gastrointestinal tract called GastroEnteroPancreatic NeuroEndocrine Tumors (GEP-NETs)[60]. This is the first time a radioactive drug, or radiopharmaceutical, has been approved for the treatment of GEP-NETs. Lutathera is indicated for adult patients with somatostatin receptor-positive GEP-NETs including foregut, midgut, and hindgut neuroendocrine tumors.

GEP-NETs are a rare group of cancers with limited treatment options if initial therapy fails to keep the cancer from growing; this approval provides another treatment choice for patients with these rare cancers.

Lutathera was granted Priority Review and received Orphan Drug designation earlier; a designation which provides incentives to assist and encourage the development of drugs for rare diseases. The approval of Lutathera was supported by two studies -

- The first was a randomized, pivotal phase III clinical trial in 229 patients with a certain type of advanced somatostatin receptor-positive GEP-NET. Patients in the trial either received Lutathera with octreotide or octreotide alone. Progression-free survival was longer for patients taking Lutathera with octreotide compared to patients who received octreotide alone. This means the risk of tumor growth or patient death was lower for patients who received Lutathera with octreotide compared to that of patients who received only octreotide.
- The second study was based on data from 1,214 patients with somatostatin receptor-positive tumors, including GEP-NETS, who received Lutathera at a single site in the Netherlands. Complete or partial tumor shrinkage was reported in 16 percent of a subset of 360 patients with GEP-NETs who were evaluated for response by the FDA. Patients initially enrolled in the study received Lutathera as part of an expanded access program. Expanded access is a way for patients with serious or immediately life-threatening diseases or conditions who lack therapeutic alternatives to gain access to investigational drugs for treatment use.

The FDA had granted the approval of Lutathera to Advanced Accelerator Applications, earlier in October 2017; the Applications being acquired by the global pharmaceutical giant Novartis[61].

About GEP-NETs

GEP-NETs, rare tumors originating in the neuroendocrine cells of numerous organs, can be present in the pancreas and in different parts of the gastrointestinal tract such as the stomach, intestines, colon and rectum. It is estimated that approximately one out of 27,000 people are diagnosed with GEP-NETs per year. Some patients develop symptoms arising from the excessive production of hormones by neuroendocrine tumor cells, while others remain clinically silent for years. The estimated incidence, or rate of new cases, of NETs in the United States is approximately 6.98/100,000 per year, while the estimated prevalence for 2014, based on the National Cancer Institute's Surveillance, Epidemiology, and End Results (SEER) database, was 171,321.

60 https://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm594043.htm

61 https://www.novartis.com/news/media-releases/novartis-announces-planned-acquisition-advanced-accelerator-applications

About Lutathera

Lutathera is a first-in-class drug and the first available FDA-approved Peptide Receptor Radionuclide Therapy (PRRT), a form of treatment comprising a targeting molecule that carries a radioactive component. After binding to the receptor, the drug enters the cell allowing radiation to cause damage to the tumor cells. Lutathera is a radioactive drug that works by binding to a part of a cell called a somatostatin receptor, which may be present on certain tumors[62]. Because Lutathera emits some radioactivity, it is only used in special controlled areas and must be handled and given to patients by qualified personnel. The patient cannot leave the controlled areas until told to do so by the doctor. Before starting treatment, the doctor will have checked that the patient's tumours have somatostatin receptors on their cell surfaces. Lutathera is given by infusion (drip) into a vein. The usual treatment involves 4 infusions 8 weeks apart, but the gap between infusions can be increased to up to 16 weeks if the patient experiences severe side effects. The patient should also be given an infusion of an amino acid solution which helps protect their kidneys.

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62 https://www.novartis.com/news/media-releases/advanced-accelerator-applications-receives-fda-approval-lutatherar-treatment-gastroenteropancreatic-neuroendocrine-tumors

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