EDITORIAL

Manoj K. Singh
Founding Partner

The pharmaceuticals & health care sector is ever-evolving, constantly growing and creating new milestones whether in terms of new drugs and therapy availability, or in quality drug distribution channel; various regulatory authorities with their comprehensive updated guidelines keep regulating the healthcare and pharmaceutical industries globally.

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

In the present issue, we start with a discussion on the Central Government's draft rules on regulatory fee hike of various drug licensing activities including import licensing and manufacturing registration carried out by CDSCO, which was last updated in year 2003. Going forward, this edition addresses the CCI's first policy note "Making Markets Work for Affordable Healthcare", which lays down the key issues and recommendations concerning affordable healthcare. This issue then covers the Health Ministry's notice banning import of Antibody Detecting Rapid Diagnostic Tests for routine diagnosis of Malaria, after banning its manufacturing, sale and distribution in the country; followed by a write-up on strategic partnership between International AIDS Vaccine Initiative and Serum Institute of India, to develop and manufacture affordable and accessible monoclonal antibody products for HIV and other global health challenges.

From the international arena, we talk about recent global survey reports concerning various health issues and the progress on improving health. First, we review approvals granted in EMA's Committee for Medicinal Products for Human Use meeting in October 2018. Then we discuss a historic commitment made by global health organizations to unite for health, Coordinated by the World Health Organization, the initiative unites the work of 11 organizations, with others set to join in the next phase; followed by a note on the WHO prequalification of thermostable rotavirus vaccine, ROTASIIL® manufactured by Serum Institute of India.

We wrap up this newsletter with a write-up on United States Food and Drug Administration approval to 1) Xofluza (baloxavir marboxil) for the treatment of acute uncomplicated influenza (flu); and 2) Expanding the approved use of Gardasil 9 (Human Papillomavirus (HPV) 9-valent Vaccine, Recombinant) to women and men aged 27 through 45 years.

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

Thank you.

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

All ©Copyrights owned by Singh & Associates

S&A Pharma Newsletter
Volume II, Issue X
October 2018

SINGH & ASSOCIATES
ADVOCATES & SOLICITORS

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

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

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

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

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

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

www.singhassociates.in

Managing Editor
Manoj K. Singh

Published by
Singh & Associates
Advocates and Solicitors

Contents

Central Government to increase regulatory fee for various drug licensing activities

On October 5, 2018, the Central Government, in consultation with the Drugs Technical Advisory Board (DTAB), proposed rules to amend Drugs and Cosmetics Rules, 1945[1] (D&C Rules, 1945) with an intention to revise fee for various regulatory activities carried out by Central Drugs Standard Control Organization (CDSCO). The proposed revision comprises - the fee for issuing import licenses, manufacturing sites registration overseas and inspections of these sites therein[2].

India's registration and inspection fees for pharma product exporters are very low compared to its foreign counterparts. Since the CDSCO last updated the fee structure in 2003, a sharp fee hike was imperative as the current fee structure does not automatically alter with inflation. The proposed fee revision in D&C Rules, 1945 are described below:

Import license: The proposed amendment of Rule 24(1) of D&C Rules, 1945, demands fee hike in case of import license from INR 1,000 to INR 10,000 rupees for a single drug. Additionally -

- For each additional drug by the same importer for import license for drugs manufactured by the same manufacturer, the additional fee raised from INR 100 to INR 1,000.
- For a duplicate copy of import license if the original is defaced, damaged or lost, the application fee raised from INR 250 to INR 2,500.

Manufacturing site registration for importing medicine: The proposed amendments to Rule 24A (3) of D&C Rules, 1945, have raised the site registration fee for importing medicines to India from US$ 1,500 to US$ 10,000. The applicant has to pay the amount or its equivalent in Indian Rupees along with the application in Form 40 for the registration of a single drug meant for import into and use in India. In addition -

- For each additional drug by same manufacturer, the additional fee is raised from US$ 1,000 to US$ 5,000.
- For an inspection of the overseas manufacturing premises by licensing authority, the expenditure fee is raised from US$ 5,000 to US$ 25,000.
- For making amendment in the registration certificate or for a duplicate copy of the Registration Certificate, the application fee is raised from US$ 300 to US$ 1,800.

Application for license for examination, test or analysis: The proposed amendment to Rule 34(3) of D&C Rules, 1945, has raised the import license fee for importing medicine for examination, test or analysis from INR 100 to INR 5,000 for a single drug. In addition - for each additional drug the additional fee is raised from INR 50 to INR 2,000.

Application for license to import small quantities of new drugs by government hospitals: The proposed amendment to Rule 34A (3) of D&C Rules, 1945 has raised the application fee for license to import small quantities of new drugs by a Government Hospital or Autonomous Medical Institution for the treatment of patients from INR 100 to INR 600 for a single drug. Further, for each additional drug the additional fee is raised from INR 50 to INR 300.

Application for permission to import new drug for clinical trial and marketing: The proposed amendment to Rule 122A (1) of D&C Rules, 1945, has raised the application fee from INR 50,000 to INR 2, 50,000. Further, for a

1 http://www.cdsco.nic.in/writereaddata/Drugs&CosmeticAct.pdf

2 https://cdsco.gov.in/opencms/opencms/system/modules/CDSCO.WEB/elements/download_file_division.jsp?num_id=MjA0NA==

subsequent application by the same applicant for that drug, whether in modified dosage form or with new claims, the application fee is hiked from INR 15,000 to INR 1,00,000.

Permission to import or manufacture fixed dose combination: The proposed amendment to Rule 122D (1) of D&C Rules, 1945, has raised the application fee for permission to import or manufacture fixed dose combination of two or more drugs from INR 15,000 to INR 1, 00,000.

Note – The draft rules published via Gazette of India is available at CDSCO official website for public comments.

Competition Commission's recommendations to make Healthcare affordable and transparent

On October 24, 2018, the Competition Commission of India (CCI) released a policy note on "Making Markets Work for Affordable Healthcare" after observing information asymmetry in the pharmaceutical/healthcare sector which significantly restricts consumer choices[3]. Through the nine years of enforcement of the Competition Act, 2002 (the Act), the Competition Commission of India ('the Commission') has received 52 cases pertaining to the pharmaceutical and healthcare sector.

As the competition authority of the country, CCI felt the need for close examination and focused deliberations on these issues, which have implications on markets and on competition in this sector which is of critical importance. Now, the issues identified, and the recommendations suggested by the stakeholders have been documented in a Policy Note by the Commission titled 'Making Markets Work for Affordable Healthcare'. The key issues and recommendations are as under:

1. Role of intermediaries in drug price build-up:

One major issue that contributes to high drug prices in India is the unreasonably high trade margins. The high margins are a form of incentive and an indirect marketing tool employed by drug companies. Further, self-regulation by trade associations also contributes towards high margins as these associations control the entire drug distribution system in a manner that reduces competition.
The Commission's recommendations are as under –

- Efficient and wider public procurement and distribution of essential drugs can circumvent the challenges arising from the distribution chain, supplant suboptimal regulatory instruments such as price control and allow for access to essential medicines at lower prices.
- Electronic trading of drugs, with appropriate regulatory safeguards, could be another potent instrument for bringing in transparency and spurring price competition among platforms and among retailers, as has been witnessed in other product segments.

2. Quality perception behind proliferation of branded generics:

Worldwide, generic drugs are seen as a key competitive force against patent-expired brands marketed at monopoly prices. But in India, the pharmaceutical market is dominated by 'branded generics' which limit generic-induced price competition. The branded generic drugs enjoy a price premium owing to perceived quality assurance that comes with the brand name. Here the brand proliferation is to introduce artificial product differentiation in the market, offers no therapeutic difference, but allows firms to extract rents.

The Commission's recommendations on this are as under–

- The regulatory apparatus must address the issue of quality perception by ensuring consistent application of statutory quality control measures and better regulatory compliance.
- The practice of creating artificial product differentiation for exploitation of consumers may be addressed through a one-company-one drug-one brand name-one price policy.

3. Vertical arrangements in healthcare services:

In view of the incentive-based referral system that pervades the healthcare landscape, issuing of periodic validated data by hospitals relating to mortality rate, infection rate, number of procedures etc. could help patients make informed choice.

3 https://www.cci.gov.in/sites/default/files/press_release/PressRelease.pdf

The Commission's recommendations on this are as under –

- The regulation of in-house pharmacies of super-specialty hospitals that mandates hospitals to allow consumers to buy standardized consumables from the open market.
- All accredited diagnostic labs should meet the same quality standards in terms of infrastructure, equipment, skilled manpower etc. for getting accreditation. This will ensure the same degree of reliability and accuracy of test results across labs.
- Regulatory framework to ensure portability of patient data, treatment record and diagnostic reports between hospitals. Portability of patient data can help ensure that a patient is no longer locked into the data silos and does not bear additional cost for switching medical services and that doctors/hospitals can have timely access to patient data.

4. Regulation and competition:

Another issue is the number of regulators governing the pharmaceutical sector at the center and state level, implementation of regulations is not uniform across the country. This has resulted in multiple standards of same products and also different levels of regulatory compliance requirements.
The Commission's recommendations on this are as under –

- A mechanism may be devised under the aegis of the CDSCO to harmonize the criteria/processes followed by the state licensing authorities to ensure uniformity in interpretation and implementation.
- It is also imperative to make the approval of new drugs time-bound along with publication of detailed guidelines governing each stage of new drug approval process.

Finally, two other major issues that affect the healthcare sector and thus warrant policy response are: (i) shortage of healthcare professionals in the country owing inter alia to high cost of medical education and (ii) inadequacy in health insurance.

Note - The Policy Note is being shared with Ministry of Corporate Affairs, Ministry of Health and Family Welfare, Department of Pharmaceuticals and NITI Aayog. The Commission decided to continue to enforce antitrust rules in the pharmaceutical and healthcare sector to ensure that effective competition is not undermined in these markets.

It's also appreciable for the Commission to delineate the issues that hamper competition and make healthcare unaffordable. With these fresh recommendations it can also makes a strong case for the government to act.

After banning manufacturing, sale and distribution of Antibody Detecting Rapid Diagnostic Tests for the diagnosis of Malaria, the Health Ministry now bans its import too

On October 30, 2018, the Ministry of Health and Family Welfare (MoHFW) banned the import of Antibody Detecting Rapid Diagnostic Tests (ADRDTs) used for routine diagnosis of Malaria. The Ministry informed this decision of the Central Government, through a gazette notification G.S.R. 1074(E)[4], in exercise of the powers conferred by section 10A of the Drugs and Cosmetic Act, 1940 (23 of 1940).

Earlier, the matter was examined by an Expert Committee appointed by the Central Government, which recommended that the said drug was found to have no therapeutic justification. It has been found that there is a rampant use of Antibody Detecting Rapid Diagnostic Tests due to its low cost and free availability. Also this test raises the rate of false positive tests - very high - in the endemic areas, as patients with fever due to other reasons, who test negative by antigen detection, test positive by ADRDTs. Further, the Central Government was satisfied that it is necessary and expedient in public interest, to prohibit the use of the ADRDTs for routine diagnosis of malaria; therefore, earlier it had prohibited the manufacture for sale, sale and distribution of 'Antibody Detecting Rapid Diagnostic Tests' for routine diagnosis of malaria via S.O. 1352(E)[5].

Now, the Central Government has banned the import of ADRDTs in exercise of the powers conferred by section 10A of the Drugs and Cosmetic Act, 1940.

> ***Section 10A: Power of Central Government to prohibit import of drugs and cosmetics in public interest -*** *Without prejudice to any other provision contained in this Chapter, if the Central Government is satisfied that the use of any drug or cosmetic is likely to involve any risk to human beings or animals or that any drug does not have the therapeutic value claimed for it or contains ingredients and in such quantity for which there is no therapeutic justification and that in the public interest it is necessary or expedient so to do then, that Government may, by notification in the Official Gazette, prohibit the import of such drug or cosmetic.*

Conclusion

The government's decision to prohibit the use of Antibody Detecting Rapid Diagnostic Tests for routine diagnosis of malaria is in wider public interest owing to high degree of false positive results and its rampant usage due to its low cost and easy availability. Since other tests like Antigen Detecting Rapid Diagnostic Tests and blood smear examination, are available there would not be any problems faced for malaria diagnosis by banning the Antibody Detecting Rapid Diagnostic Tests.

4 http://www.egazette.nic.in/WriteReadData/2018/191623.pdf

5 http://www.mondaq.com/india/x/702320/Life+Sciences+Biotechnology/Ministry+Of+Health+Prohibits+Antibody+Detecting+Rapid+Diagnostic+Tests+For+Routine+Diagnosis+Of+Malaria

IAVI and SII Collaborate to Develop Affordable and Accessible Antibody Products for HIV globally

On October 22, 2018, the International AIDS Vaccine Initiative (IAVI) and Serum Institute of India (SII), the world's largest vaccine manufacturer, announced a strategic partnership to develop and manufacture affordable and accessible monoclonal antibody products for HIV and other global health challenges[6].

Serum Institute of India was founded to address the shortage of life-saving vaccines in India. Its vaccines are now in used in 170 countries. IAVI has worked in India since 2001, and partners with the Government of India on its network of clinical research centers and laboratories engaged in cutting-edge HIV research, including the Translational Health Science and Technology Institute. The collaboration between IAVI and Serum Institute brings together partners with complementary expertise and a shared public health commitment to expedite the introduction of affordable, accessible, and sustainable global health solutions, particularly in countries with the highest disease burden.

About HIV

Globally, 36.9 million people were living with HIV in 2017. The world is facing a prevention crisis with 1.8 million new infections occurring in 2017. More alarming is that certain groups are being left behind. New infections are particularly high among adolescent girls and young women in sub-Saharan Africa, people who use drugs in Eastern Europe and parts of Asia, and globally, populations of men who have sex with men, transgender people and sex workers.

HIV prevention and management

In recent years, researchers, including those at IAVI, have identified hundreds of broadly neutralizing monoclonal antibodies (bNAbs) that are both potent and broadly cross reactive against the majority of HIV variants circulating globally. Some of these bNAbs are now being explored for their potential ability to prevent, treat, and cure HIV infection. The results of the first study of the efficacy of a bNAb for prevention of HIV infection are expected within the next two years, and additional bNAb combinations are advancing towards efficacy testing. It is still unknown whether antibody prophylaxis will be effective in blocking HIV infection but defining a pathway to access at the outset will hasten the introduction of new products, should they work. There is a pressing need to develop a sustainable model to ensure that bNAb products are widely available and affordable to protect individuals at high risk of HIV infection in low-income countries where HIV incidence is highest.

IAVI and its partners are pursuing the development of optimized versions and combinations of some of the most promising bNAbs as a new HIV prevention approach. This includes working with scientific collaborators to rapidly select and optimize a combination of the most potent antibodies available. The partnership between IAVI and Serum Institute will focus on developing large-scale, low-cost manufacturing processes to produce these optimized antibodies, evaluate them in clinical trials, and, if effective, register and commercialize an antibody-based HIV prevention product globally. IAVI and Serum Institute will simultaneously define a pathway for sustainable access and delivery of these antibodies in developing countries, in collaboration with other stakeholders.

Note - The goal for this partnership is to be of broad benefit to the field and to enable the most promising antibodies to be developed in the most promising combinations to maximize chances of success. New HIV prevention methods are desperately needed, as the rate of new infections has not declined significantly in more than a decade.

6 https://www.iavi.org/newsroom/press-releases/2018/iavi-and-serum-institute-of-india-to-develop-and-manufacture-globally-affordable-and-accessible-antibody-products-for-hiv

European Medicines Agency (EMA) recommends approval of six medicines in its October meeting

The European Medicines Agency's (EMA) Committee for Medicinal Products for Human Use (CHMP) recommended six medicines for approval, including two orphan medicines, at its October 2018 meeting[7].

A) The six medicines recommended for approval are:

1. Takhzyro - for the prevention of recurrent attacks of hereditary angioedema (HAE)

On October 18, 2018, the Committee for Medicinal Products for Human Use (CHMP) adopted a positive opinion, recommending the granting of a marketing authorization for the orphan medicinal product Takhzyro, intended for the prevention of recurrent attacks of hereditary angioedema.

Takhzyro will be available as a 300-mg solution for injection. The active substance of Takhzyro is lanadelumab, a monoclonal antibody that inhibits active plasma kallikrein proteolytic activity. Increased plasma kallikrein activity leads to angioedema attacks in patients with hereditary angioedema through the proteolysis of high-molecular-weight kininogen and bradykinin. Lanadelumab provides sustained control of plasma kallikrein activity and thereby limits bradykinin generation in patients with hereditary angioedema.

The applicant for this medicinal product is Shire Pharmaceuticals Ireland Limited[8].

2. Flucelvax Tetra - for prophylaxis against influenza

On October 18, 2018, the Committee for Medicinal Products for Human Use (CHMP) adopted a positive opinion, recommending the granting of a marketing authorization for the medicinal product Flucelvax Tetra, intended for prophylaxis against influenza.

Flucelvax Tetra will be available as a suspension for injection in pre-filled syringes. The active substance of Flucelvax Tetra consists of influenza virus surface antigens (haemagglutinin and neuraminidase), inactivated and prepared in cell cultures, of 4 different influenza virus strains (two A subtypes and two B types). Flucelvax Tetra provides active immunisation against influenza virus by inducing humoral antibodies against the haemagglutinins. These antibodies neutralise influenza viruses.

The applicant for this medicinal product is Seqirus Netherlands B.V[9].

3. Namuscla - for the treatment of myotonia

On October 18, 2018, the Committee for Medicinal Products for Human Use (CHMP) adopted a positive opinion, recommending the granting of a marketing authorization for the orphan medicinal product Namuscla, intended for the treatment of myotonia in adults with certain hereditary muscle disorders.

Namuscla will be available as capsules (167 mg). The active substance of Namuscla is mexiletine which reduces skeletal muscle hyperexcitability by blocking sodium channels. The benefits with Namuscla are its ability to reduce muscle stiffness and improve quality of life in patients with non-dystrophic myotonic disorders (sodium or chloride channelopathies).
The applicant for this medicinal product is Lupin Europe GmbH[10].

7 https://www.ema.europa.eu/en/news/meeting-highlights-committee-medicinal-products-human-use-chmp-15-18-october-2018

8 https://www.ema.europa.eu/documents/smop-initial/chmp-summary-positive-opinion-takhzyro_en.pdf

9 https://www.ema.europa.eu/documents/smop-initial/chmp-summary-positive-opinion-flucelvax-tetra_en.pdf

10 https://www.ema.europa.eu/documents/smop-initial/chmp-summary-positive-opinion-namuscla_en.pdf

4. Dengvaxia - for prophylaxis against dengue disease

On October 18, 2018, the Committee for Medicinal Products for Human Use (CHMP) adopted a positive opinion, recommending the granting of a marketing authorisation for the medicinal product Dengvaxia, intended for prophylaxis against dengue disease.

Dengvaxia will be available as a powder and solvent to be made into a suspension for injection. The active substance of Dengvaxia is made of chimeric yellow fever-based live attenuated viruses, which contain 2 surface dengue proteins from each of serotypes 1 to 4 of dengue virus. Following administration, the viruses replicate locally and induce neutralizing antibodies and cell-mediated immune responses against the four dengue virus serotypes.

The applicant for this medicinal product is Sanofi Pasteur[11].

5. Bevespi Aerosphere - for the maintenance treatment of chronic obstructive pulmonary disease (COPD)

On October 18, 2018, the Committee for Medicinal Products for Human Use (CHMP) adopted a positive opinion, recommending the granting of a marketing authorization for the medicinal product Bevespi Aerosphere, intended for the maintenance treatment to relieve symptoms in adult patients with chronic obstructive pulmonary disease (COPD).

Bevespi Aerosphere is a fixed dose combination of a long-acting beta-2 receptor agonist (formoterol fumarate dihydrate) and a long-acting muscarinic antagonist (glycopyrronium). It will be available as a suspension for inhalation (7.2 micrograms / 5.0 micrograms). Formoterol and glycopyrronium relax bronchial smooth muscle helping to dilate the airways and make breathing easier. The benefit with Bevespi Aerosphere is its ability to relieve symptoms such as shortness of breath, wheezing and cough in patients with COPD.

The applicant for this medicinal product is AstraZeneca AB[12].

6. Ogivri (trastuzumab) - for the treatment of breast and gastric cancer

On October 18, 2018, the Committee for Medicinal Products for Human Use (CHMP) adopted a positive opinion, recommending the granting of a marketing authorization for the medicinal product Ogivri, intended for the treatment of breast and gastric cancer.

Ogivri will be available as a 150-mg powder for concentrate for solution for infusion. The active substance of Ogivri is trastuzumab, a monoclonal antibody that binds with high affinity and specificity to HER2 leading to the inhibition of proliferation of tumour cells that overexpress HER2. Ogivri is a biosimilar medicinal product. It is highly similar to the reference product Herceptin (trastuzumab).
The applicant for this medicinal product is MYLAN S.A.S[13].

B) CHMP recommendations on extensions of therapeutic indication

The European Medicines Agency's (EMA) Committee for Medicinal Products for Human Use (CHMP) has recommended a change to the terms of the marketing authorization for three drugs on extensions of therapeutic indication as described in table (New indications are marked in bold, and removed indications are marked in strikethrough)

11 https://www.ema.europa.eu/documents/smop-initial/chmp-summary-positive-opinion-dengvaxia_en.pdf

12 https://www.ema.europa.eu/documents/smop-initial/chmp-summary-positive-opinion-bevespi-aerosphere_en.pdf

13 https://www.ema.europa.eu/documents/smop-initial/chmp-summary-positive-opinion-ogivri_en.pdf

Sl. No.	Name of medicine	Full Indication	Marketing-authorisation holder
1	Kalydeco (ivacaftor)	Kalydeco granules are indicated for the treatment of children with cystic fibrosis (CF) aged ~~2 years~~ 12 months and older and weighing 7 kg to less than 25 kg who have one of the following gating (class III) mutations in the CFTR gene: G551D, G1244E, G1349D, G178R, G551S, S1251N, S1255P, S549N or S549R.	Vertex Pharmaceuticals[1]
2	Keytruda (pembrolizumab)	-Keytruda as monotherapy is indicated for the treatment of advanced (unresectable or metastatic) Melanoma in adults. -**Keytruda as monotherapy is indicated for the adjuvant treatment of adults with Stage IIImelanoma and lymph node involvement who have undergone complete resection**.- -Keytruda as monotherapy is indicated for the first-line treatment of metastatic non-small cell lung carcinoma (NSCLC) in adults whose tumours express PD-L1 with a ≥ 50% tumour proportion score (TPS) with no EGFR or ALK positive tumour mutations. -Keytruda, in combination with pemetrexed and platinum chemotherapy, is indicated for the first-line treatment of metastatic non-squamous NSCLC in adults whose tumours have no EGFR or ALK positive mutations. -Keytruda as monotherapy is indicated for the treatment of locally advanced or metastatic NSCLC in adults whose tumours express PD-L1 with a ≥ 1% TPS and who have received at least one prior chemotherapy regimen. Patients with EGFR or ALK positive tumour mutations should also have received targeted therapy before receiving Keytruda. -Keytruda as monotherapy is indicated for the treatment of adult patients with relapsed or refractory classical Hodgkin lymphoma (cHL) who have failed autologous stem cell transplant (ASCT) and brentuximab vedotin (BV), or who are transplant-ineligible and have failed BV. -Keytruda as monotherapy is indicated for the treatment of locally advanced or metastatic urothelial carcinoma in adults who have received prior platinum-containing chemotherapy. -Keytruda as monotherapy is indicated for the treatment of locally advanced or metastatic urothelial carcinoma in adults who are not eligible for cisplatin-containing chemotherapy and whose tumours express PD L1 with a combined positive score (CPS) ≥ 10. -Keytruda as monotherapy is indicated for the treatment of recurrent or metastatic head and neck squamous cell carcinoma (HNSCC) in adults whose tumours express PD-L1 with a ≥ 50% TPS and progressing on or after platinum-containing chemotherapy.	Merck Sharp & Dohme B.V.[2]

Sl. No.	Name of medicine	Full Indication	Marketing-authorisation holder
3	NovoSeven (eptacog alfa (activated))	NovoSeven is indicated for the treatment of bleeding episodes and for the prevention of bleeding in those undergoing surgery or invasive procedures in the following patient groups: in patients with congenital haemophilia with inhibitors to coagulation factors VIII or IX > 5 Bethesda Units (BU) in patients with congenital haemophilia who are expected to have a high anamnestic response to factor VIII or factor IX administration in patients with acquired haemophilia in patients with congenital FVII deficiency in patients with Glanzmann's thrombasthenia with ~~antibodies to GP IIb - IIIa and/or HLA, and~~ past or present refractoriness to platelet transfusions, **or where platelets are not readily available.**	Novo Nordisk A/S[3]

Note - The CHMP's assessments are based on a comprehensive scientific evaluation of data. They determine whether the medicine meets the necessary quality, safety and efficacy requirements and that it has a positive risk-benefit balance. The CHMP carries out a scientific assessment of the application and gives a recommendation on whether the medicine should be marketed or not. Once granted by the European Commission, the centralized marketing authorization is valid in all EU Member States as well as in the European Economic Area (EEA) countries Iceland, Liechtenstein and Norway.

Global health organizations make a historic commitment to unite for health

On October 16, 2018, the eleven heads of the world's leading health and development organizations signed a landmark commitment to find new ways of working together to accelerate progress towards achieving the United Nations' Sustainable Development Goals[14]. Coordinated by the World Health Organization, the initiative unites the work of 11 organizations, with others set to join in the next phase.

The organizations that have already signed up to the Global Action Plan for Healthy Lives and Well-being for All are - Gavi the Vaccine Alliance. the Global Fund to Fight AIDS, Tuberculosis and Malaria, the Global Financing Facility, UNAIDS, UNDP, UNFPA, UNICEF, Unitaid, UN Women, the World Bank and WHO. The World Food Programme has committed to join the plan in the coming months[15].

The group has agreed to develop new ways of working together to maximize resources and measure progress in a more transparent and engaging way. The first phase of the plan's development is organized under three strategic approaches - Align, Accelerate and Account.

Align - The organizations have committed to coordinate programmatic, financial and operational processes to increase collective efficiency through:

- collaborating and harmonizing processes such as for financing and procurement
- strengthening provision of essential global public goods for health
- streamlining programmatic and operational policies to seize efficiencies and synergies in our work
- aligning investment case approaches
- enhancing access through supply chain management
- harmonizing operational policies

Accelerate - They have agreed to develop common approaches and coordinate action in areas of work for which they identified seven overlapping areas where more innovative, synergistic efforts can significantly accelerate progress in global health:

1. Sustainable financing
2. Frontline health systems
3. Community and civil society engagement
4. Determinants of health
5. R&D, innovation and access
6. Data and digital health
7. Innovative programming in fragile and vulnerable states and for disease outbreak response

Account - To improve transparency and accountability to countries and development partners, the health organizations are breaking new ground by setting common milestones for nearly 50 health-related targets across 14 Sustainable Development Goals. These milestones will provide a critical checkpoint and common reference to determine where the world stands in 2023 and whether it is on track to reach the 2030 goals.

The Global Action Plan will also enhance collective action and leverage funds to address gender inequalities that act as barriers to accessing health, and to improve comprehensive quality health care for women and girls, including sexual and reproductive health services.

14 http://www.who.int/sdg/global-action-plan

15 http://www.who.int/news-room/detail/16-10-2018-global-health-organizations-commit-to-new-ways-of-working-together-for-greater-impact

WHO prequalifies a thermostable rotavirus vaccine from Serum Institute of India

On October 01, 2018, the World Health Organization has prequalified the thermostable rotavirus vaccine, ROTASIIL® manufactured by Serum Institute of India[16].The vaccine which prevents severe rotavirus-induced diarrhea in infants, provides an innovative and affordable option to the global market as it is the first rotavirus vaccine that does not require constant refrigeration and will help meet the critical public health goal of improving vaccine supply worldwide.

The vaccine will now be available for procurement by United Nations agencies and Gavi, the Vaccine Alliance for use in low- and middle-income countries. This will help accelerate availability of the vaccine in countries experiencing the highest burden of rotavirus-induced diarrhea by providing a practical and affordable option for vaccine introduction.

About ROTASIIL

ROTASIIL is Live Attenuated (Oral) pentavalent bovine vaccine indicated for active immunization of healthy infants from the age of 6 weeks for the prevention of gastroenteritis due to rotavirus infection when administered as a 3-dose series. The vaccine can last for months without refrigeration, which makes it far easier to use in remote villages with no electricity[17].

About Rotavirus

Rotaviruses are contagious virus that can cause gastroenteritis symptoms including severe watery diarrhea, vomiting, fever, and abdominal pain. Infants and young children are most likely to get the rotavirus disease. According to WHO 2004 estimates, 527 000 children aged <5 years die each year from vaccine preventable rotavirus infections; most of these children live in low-income countries. Two brands, both oral, live, attenuated rotavirus vaccines, Rotarix and RotaTeq, are available internationally; and both vaccines are considered safe and effective in preventing gastrointestinal disease[18].

Note - WHO prequalification of vaccines is a comprehensive assessment that takes place through a standardized procedure aimed at determining whether the product meets requirements for safety and efficacy in immunization programmes. The full prequalification assessment process includes the following components - Review of production process and quality control procedures; Laboratory testing; WHO site audit to manufacturing facilities with the responsible National Regulatory Authority.

16 http://www.who.int/immunization/newsroom/news_WHO_prequalifies_thermostable_rotavirus_vaccine/en/

17 https://www.seruminstitute.com/product_viral_rotasiil.php

18 http://www.who.int/immunization/topics/rotavirus/en/

USFDA approves new drug for influenza treatment after nearly 20 years

On October 24, 2018, the U.S. Food and Drug Administration approved Xofluza (baloxavir marboxil) for the treatment of acute uncomplicated influenza (flu) in patients 12 years of age and older who have been symptomatic for no more than 48 hours[19,20]. It is the first new antiviral flu treatment with a novel mechanism of action approved by the agency in nearly 20 years.

The FDA approval is based on the clinical efficacy and safety data from a phase II study conducted in Japan and phase III study (CAPSTONE-1) conducted in Japan and the U.S. in otherwise-healthy patients. A single dose of XOFLUZA significantly reduced the duration of influenza symptoms compared to placebo and demonstrated clinical efficacy which was not significantly different from that of oseltamivir with twice-daily doses administered for 5 days.

About Influenza (Flu)

Influenza (flu) is a contagious respiratory illness caused by influenza viruses. It can cause mild to severe illness. Seasonal and pandemic influenza remains a major public health concern, and novel influenza drugs that will offer significant improvement over current therapy are urgently needed. Globally, annual epidemics result in 3 to 5 million cases of severe disease, millions of hospitalizations and up to 650,000 deaths worldwide.

In the U.S., an estimated 3-11 percent of the U.S. population gets the flu each year, and it can be very serious, resulting in hospitalization or even death. In the 2017/2018 flu season, more than 900,000 people were hospitalized, and more than 80,000 people died in the U.S. Since 2010, the Center for Disease Control and Prevention (CDC) estimates that the flu has resulted in 9.2 to 35.6 million illnesses, 140,000 to 900,000 hospitalizations and 12,000 to 80,000 deaths.

About XOFLUZA (baloxavir marboxil)

XOFLUZA is a first-in-class, single-dose oral medicine with a novel mechanism of action that inhibits cap-dependent endonuclease in the polymerase acidic (PA) protein (in the United States Prescribing Information, this enzyme is stated as polymerase acidic endonuclease), an enzyme essential for viral replication. The regimen for XOFLUZA is a single-oral dose to treat uncomplicated influenza, which is different from all currently available antiviral treatments.

Note – XOFLUZA was discovered and developed by Shionogi. Shionogi and the Roche Group, which includes Genentech in the U.S., have a license and collaboration agreement to further develop and commercialize XOFLUZA globally. Under the terms of this agreement, Genentech has development and commercialization rights of XOFLUZA. In the U.S. XOFLUZA will be available across the U.S. in the coming weeks.

XOFLUZA was already approved and is now available in Japan for the treatment of influenza Types A and B in adults and pediatric patients. Shionogi also submitted an NDA for XOFLUZA in Taiwan on June 29, 2018, for the treatment of influenza in patients 12 years of age and older.

19 https://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm624226.htm

20 http://www.shionogi.co.jp/en/company/news/2018/pmrltj0000003xss-att/e_181025.pdf

USFDA approves expanded use of Gardasil 9 to include individuals from 27 to 45 years of age

On September 05, 2018, the U.S. Food and Drug Administration approved a supplemental application for Gardasil 9 (Human Papillomavirus (HPV) 9-valent Vaccine, Recombinant) expanding the approved use of the vaccine to include women and men aged 27 through 45 years. Gardasil 9 prevents certain cancers and diseases caused by the nine HPV types covered by the vaccine[21]

Gardasil, a vaccine approved by the FDA in 2006 to prevent certain cancers and diseases caused by four HPV types, is no longer distributed in the U.S. In 2014, the FDA approved Gardasil 9, which covers the same four HPV types as Gardasil, as well as an additional five HPV types. Gardasil 9 was approved for use in males and females aged 9 through 26 years.

The effectiveness of Gardasil is relevant to Gardasil 9 since the vaccines are manufactured similarly and cover four of the same HPV types. In a study in approximately 3,200 women 27 through 45 years of age, followed for an average of 3.5 years, Gardasil was 88 percent effective in the prevention of a combined endpoint of persistent infection, genital warts, vulvar and vaginal precancerous lesions, cervical precancerous lesions, and cervical cancer related to HPV types covered by the vaccine. The FDA's approval of Gardasil 9 in women 27 through 45 years of age is based on these results and new data on long term follow-up from this study.

Effectiveness of Gardasil 9 in men, 27 through 45 years of age, is inferred from the data described above in women 27 through 45 years of age, as well as efficacy data from Gardasil in younger men (16 through 26 years of age) and immunogenicity data from a clinical trial in which 150 men, 27 through 45 years of age, received a 3-dose regimen of Gardasil over 6 months.

The FDA granted approval of this supplement to the Gardasil 9 Biologics License Application to Merck, Sharp & Dohme Corp. a subsidiary of Merck & Co., Inc.

About HPV

HPV is a group of more than 150 related viruses. Each HPV virus in this large group is given a number which is called its HPV type. HPV is named for the warts (papillomas) some HPV types can cause. Some other HPV types can lead to cancer. Men and women can get cancer of mouth/ throat, and anus/rectum caused by HPV infections. Men can also get penile HPV cancer. In women, HPV infection can also cause cervical, vaginal, and vulvar HPV cancers. But there are vaccines that can prevent infection with the types of HPV that most commonly cause cancer[22]. According to the CDC, every year about 14 million Americans become infected with HPV; about 12,000 women are diagnosed with and about 4,000 women die from cervical cancer caused by certain HPV viruses. Additionally, HPV viruses are associated with several other forms of cancer affecting men and women.

About Gardasil9

Human Papillomavirus 9-valent Vaccine, recombinant is a non-infectious recombinant 9-valent vaccine prepared from the purified virus-like particles (VLPs) of the major capsid (L1) protein of HPV Types 6, 11, 16, 18, 31, 33, 45, 52, and 58. HPV only infects human beings. Animal studies with analogous animal papillomaviruses suggest that the efficacy of L1 VLP vaccines may involve the development of humoral immune responses. Efficacy of GARDASIL

21 https://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm622715.htm

22 https://www.cdc.gov/hpv/parents/whatishpv.html

9 against anogenital diseases related to the vaccine HPV types in human beings is thought to be mediated by humoral immune responses induced by the vaccine, although the exact mechanism of protection is unknown[23].

***

23 https://www.fda.gov/downloads/BiologicsBloodVaccines/Vaccines/ApprovedProducts/UCM426457.pdf

notes

notes

SINGH & ASSOCIATES

FOUNDER MANOJ K SINGH

ADVOCATES & SOLICITORS

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

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

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

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

india@singhassociates.in
www.singhassociates.in