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Vol. III, Issue IV
April 2019

S&A PHARMA NEWSLETTER

EDITORIAL

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Founding Partner

The role of a drug regulatory authority is not limited only to drug authorization, but it is also responsible for maintaining the rigor of an approval process towards patients' safety. Achieving regulation is not an easy task as it is critical to monitor the stages of therapy availability, quality drug distribution channel, reports of fake/spurious drugs, and the safety of patients or consumer. Regulatory authorities with their comprehensive updated guidelines keep regulating these challenges globally; however, extra efforts are needed from the organizations and governments to combat the challenges in tandem.

We are pleased to present this Vol. III Issue IV of S&A – Pharma Newsletter. Through this Newsletter, we aim to share recent information allied to regulatory reforms and updates from pharmaceutical sector in 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 decision made by central government to supply Buprenorphine formulations to the psychiatric clinics and hospitals in addition to the already designated de-addiction centers set up by the government. Going forward, this edition covers the Indian Council of Medical Research's license agreement with Hilleman Laboratories Pvt. Ltd., where the technology for Shigella vaccine is transferred to Hillman for further scaling up and commercialization. Going further this edition discusses the Memorandum of Understanding (MOU) signed between the Ministry of AYUSH and Council of Scientific and Industrial Research (CSIR) for cooperation in research, education and interdisciplinary sciences for promoting the traditional medicines and imparting the traditional knowledge. Next, we discuss the proposed amendment in the D&C Act to give trade of medicines a better professional recognition and making a uniform system of calling the medicine shops as 'Pharmacy'. Further this edition covers another proposed amendment in D&C Act, which suggests import license holders to mandatorily maintain the reference samples for the products, in order to check the authenticity of misbranded products any time. Lastly in the domestic news we discuss Government's proposal to amend Schedule-V of D&C Rules to revise 'free salicylic acid' content in drugs containing aspirin.

From the international arena, we talk about restriction on the use of Lemtrada imposed by EMA, while a review is ongoing; restriction will support patient safety. The edition then brings you the news on the launch of world's first malaria vaccine pilot program in Malawi followed by a discussion on a report on 'antimicrobial drug-resistance' by WHO which suggests that various stringent actions need to be taken to avert antimicrobial drug-resistance resulting in rising death rate in the future.

We wrap this edition with the United States Food and Drug Administration approval to Balversa, a first targeted therapy for adult patients with locally advanced or metastatic bladder cancer and a collaboration between USFDA and CBP for enhanced public health and safety.

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

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S&A Pharma Newsletter
Volume III, Issue IV
April 2019

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Contents

Now onwards the psychiatric clinics will receive government supply of Buprenorphine formulations in addition to the designated de-addiction centres

On March 28, 2019, the central government has amended the conditions for supply of sublingual tablets of Buprenorphine + Naloxone FDC and Buprenorphine alone. According to the notification the said formulations shall be supplied to the psychiatric clinics and hospitals in addition to the already designated de-addiction centres set up by the government/ funded by the MoHFW. The notification also requested all State/UT drug controllers to submit detailed list of centres, to which the supply of drug is made, to the office of Drug Controller General (India) periodically indicating the quantity supplied to each centre.

The sublingual tablet of Buprenorphine was first approved by the Central Drug Standard Control Organization in year 1999, followed by FDC of Buprenorphine + Naloxone in year 2008. The said approval comes with the condition that the said formulation shall only be supplied to the designated de-addiction centres set up by the government/ funded by the MoHFW and Ministry of Social Justice and Empowerment and hospital with de-addiction facilities. Subsequently, the association of Psychiatrists through their representation have asked to withdraw the restriction of supply to only the de-addiction centres by listing down various reasons like the formulation demand in the country, the limited numbers of de-addiction centres, and improper definition of de-addiction centre which limits the accessibility of said medicine to the trained psychiatrists in the country.

Thereafter, on August 08, 2018, the 38th Subject Expert Committee of Neurology & Psychiatry[1] deliberated and discussed the representation and noted that the existing conditions regarding the restriction on sale and distributions need to be modified and recommended that Buprenorphine sublingual tablets should be allowed to be supplied to psychiatric clinics, hospitals instead of earlier condition that the drug should be supplied to de-addiction centers only.

Now therefore, the Central Government after consultation with Ministry of Health And Family Welfare has amended the condition (The insertions are underlined and deletions are struckthrough) as prescribed below:

> *"The preparation shall be supplied ~~only~~ to the psychiatric clinics and hospitals in addition to the designated de-addiction centre set up by the government of India funded by the Ministry of Health and Ministry of social justice and empowerment and hospital with de-addiction facilities, and a list of centres to whom the supply of drug is made should be made to the office of DCGI periodically indicating the quantity supplied to each centre."*

Note – All State/UT drug controllers and manufacturers are directed to comply with the above conditions while granting license to the manufacturers and while suppling of said product respectively.

1 https://cdsco.gov.in/opencms/opencms/system/modules/CDSCO.WEB/elements/common_download.jsp?num_id_pk=NDM=

ICMR licenses Shigella Vaccine technology to Hilleman Laboratories

On April 23, 2019, Indian Council of Medical Research (ICMR) licensed the technology for Shigella vaccine for further scaling up and commercialisation to MSD Wellcome Trust Hilleman Laboratories Pvt Ltd.[2] Biotech Consortium India Limited (BCIL), New Delhi, executed the License Agreement with NICED on behalf of ICMR and Hilleman Labs.

The technology was developed by ICMR-National Institute of Cholera and Enteric Diseases (NICED). Shigella Vaccine in the form of heat treated/formalin killed vaccines as well as next generation vaccines including OmpA nano-formulation and OMVs (Outer Membrane Vesicles) is developed to address the need for controlling Shigella infection.

In view of no licensed Shigella vaccine and emergence of increased antimicrobial resistance, the vaccines are the only effective tool to fight against the disease. The Shigella vaccine, developed by ICMR-NICED is expected to have a huge potential and likely to benefit children living in low and middle-income settings.

The licensed Shigella vaccine candidate has been developed through support from ICMR, Okayama University, Japan and National Institute of Infectious Diseases, Japan. The translation of the licensed Shigella vaccine candidate to a market-ready product will involve a stringent pre-clinical and clinical development pathway before it reaches the market.

About Shigella

Shigellosis is an infectious disease, marked by bloody diarrhoea with or without fever caused by Shigella species with huge disease burden globally causing 125 million diarrhoeal episodes annually, around 160,000 deaths, with a third of these associated with children under five years age. Management of shigellosis includes improvement of sanitation, rehydration therapy and most essentially, antibiotic therapy. Considering the global emergence of multidrug resistance (MDR), absence of effective Shigella vaccine and one of the prioritised vaccines recommended by the WHO; developing this indigenous vaccine against shigellosis is the need of the hour and is a major breakthrough.

Note – This is the first-ever vaccine for treatment for Shigellosis. At present Shigellosis is largely treated through antibiotics globally, but the fact of antibiotic resistance and global emergence is a major concern making vaccine development the only solution for Shigellosis.

2 https://www.icmr.nic.in/sites/default/files/press_realease_files/Press_Release_Shigella_Vaccine-converted.pdf

MoU signed between Ministry of AYUSH and CSIR to promote traditional medicines

On April 22, 2019, a Memorandum of Understanding (MOU) was signed between the Ministry of AYUSH and Council of Scientific and Industrial Research (CSIR) for cooperation in research, education and interdisciplinary sciences that integrate/co-opt traditional systems of medicine and modern science[3]. Moreover, a Working Group of CSIR-AYUSH Ministry has been formed to take this cooperation forward.

Earlier, CSIR jointly with Department of AYUSH (now Ministry) had developed the Traditional Knowledge Digital Library (TKDL), a globally recognized proprietary database on Indian systems of medicine for preventing bio-piracy and misappropriation of our traditional knowledge. Apart from this, the constituent laboratories of CSIR with councils/institutes of the Ministry of AYUSH have also supported each other in the development of improved varieties and captive cultivation of the medicinal plants including rare, engendered and threatened (RET) species, Botanical Reference Standards and Pharmacopoeial standards, and Ayurgenomics, among many others.

In due cognition of the increasing demands and usage of herbal medicines and supplements worldwide, the joint endeavor of Ministry of AYUSH and CSIR, has decided to bring the organizations under an umbrella understanding for pursuing focused R&D efforts in the domain.

As per the understanding, both organizations shall jointly endeavor to pursue:

- R&D covering fundamental research; AYUSH specific diagnostic tools;
- Linking microbiome, gene expression and prakriti;
- Multi-ingredient herbal formulations, including their standardization;
- Exploring modern scientific methods for integration with traditional Indian Systems of Medicine (ISM);
- Linking disease signatures; etc.
- Furthering the collaboration in preserving and protecting traditional knowledge related to the Indian systems of healthcare, through the existing TKDL platform; and
- Development of international standardized terminologies (disease-morbidity codes) in Ayurveda, Siddha and Unani (ASU), Database on Medicinal plants, Foods, etc.

About Traditional medicine[4]

Traditional medicine (TM) includes diverse health practices, approaches, knowledge and beliefs incorporating plant- animal- and/or mineral-based medicines, spiritual therapies, manual techniques and exercises applied singularly or in combination to maintain well-being, as well as to treat, diagnose or prevent illness.

About TKDL[5]

TKDL involves documentation of the knowledge available in public domain on traditional knowledge from the existing literature related to Ayurveda, Unani and Siddha in digitized format, in five international languages which are English, French, German, Spanish and Japanese. So far, the TKDL includes more than 2 lakhs medicinal formulations using 148 books available in public domain.

3 https://www.csir.res.in/sites/default/files/Signing-of-MoU-between-CSIR-and-Ministry-of-AYUSH_1.pdf

4 http://apps.who.int/medicinedocs/pdf/s5525e/s5525e.pdf

5 http://ayush.gov.in/traditional-knowledge-digital-library

Government to amend Drugs and Cosmetics (D&C) Rules to give trade of medicines a better professional recognition

The Union Health Ministry in a recent update has come up with a plan to amend Rule 65(15)(b) and Rule 65(15)(c) of Drugs and Cosmetics (D&C) Rules where the word 'Chemists & Druggists' will be replaced with Pharmacy for uplifting the standard of pharmacy professionals in the country. This new amendment is in accordance with the international practice of calling all the medical shops selling medicines as "Pharmacy".

Earlier the Karnataka State Registered Pharmacists Association urged the Union government to remove the words "Chemists and Druggists" from Rule 65(15)(b) of the Drugs and Cosmetics Rules and replace it with "Pharmacy" in order to give trade of medicines a better professional recognition.

The said amendment was discussed in the *55th Drug Consultative Committee (DCC)* meeting held in February 2019[6]. Later, the proposal was placed before the Drug Technical Advisory Board (DTAB), where DTAB deliberated the matter and agreed to amend Rule 65(15) of the D&C Rules, 1945 and recommended that all licensees in Form 20 and Form 21 should display the word "Pharmacy".

The proposed amendment (Insertions are marked and deletions are struckthrough) in subrule 15(b) and 15(c) of Drugs and Cosmetics (D&C) Rules, 1945 prescribes that:

1. [The description —~~Chemists and Druggists~~ "Pharmacy" shall be displayed by such licensees who employ the services of a [Registered Pharmacist] but who do not maintain a —Pharmacy for compounding against prescriptions.]

2. The recent amendment will upgrade the pharmacy professionals and will create a uniform standard of calling all the medical shops dispensing drugs as pharmacy.

Conclusion

The proposed amendment that is already prevailing in other countries will upgrade the pharmacy profession and trade in country. This amendment will make a uniform system of calling all the shops selling medicines as pharmacy a practice.

6 https://cdsco.gov.in/opencms/opencms/system/modules/CDSCO.WEB/elements/common_download.jsp?num_id_pk=ODMz

Health Ministry to mandate maintaining of reference sample for the import license holder to tackle the issue of misbranded drugs

Union Health Ministry has proposed to amend Rule 26 of D&C Rules to make it mandatory the import license holder to maintain a reference sample. The current rule 26 of D&C Rules provides the provision for maintaining the reference sample for the manufacturing license. In order to keep the authenticity of the misbranded product the government has decided to include such provision for the import license holder also in order to maintain the authenticity of the misbranded product which are imported.

Earlier it was mandatory only for manufacturers to maintain reference samples under rule 74(l) of Drug and Cosmetic Rules, 1945. According to it[7]:

> *"The licensee shall maintain reference samples from each batch of the drugs manufactured by him in a quantity which is at least twice the quantity of the drug required to conduct all the tests performed on the batch. In case of drugs bearing an expiry date on the label, the reference samples shall be maintained for a period of three months beyond the date of expiry or potency. In case of drugs where no date of expiry of potency is specified on the label, the reference samples shall be maintained for a period of three years from the date of manufacture."*

However, there is no such provision for the import license holder to maintain the sample. Hence, in order to prevent this discrepancy, the Health Ministry proposed to amend the Rule 26 of the Drugs and Cosmetics Rules, 1945, where the sub rule (viii) to be incorporated under Rule 26 is prescribed as below:

> ***"The licensee shall maintain reference samples from each batch of the drugs imported by him in a quantity which is at least twice the quantity of the drug required to conduct all the tests performed on the batch. In case of drugs bearing an expiry date on the label, the reference samples shall be maintained for a period of three months beyond the date of expiry or potency. In case of drugs where no date of expiry or potency is specified on the label, the reference samples shall be maintained for a period of three years from the date of manufacture."***

In case of drugs bearing an expiry date on the label, the reference samples shall be maintained for a period of three months beyond the date of expiry or potency. In case of drugs where no date of expiry or potency is specified on the label, the reference samples shall be maintained for a period of three years from the date of manufacture.

Conclusion

Government has proposed to make a provision under Drugs and Cosmetic Rules to maintain the reference samples for the import license holders. Such provision already exists for the manufacturing license holder. Inclusion of this new provision will help in maintaining the authenticity of the misbranded or substandard drugs which was earlier not possible as the control samples of these imported drugs was not available with the import license holder.

7 https://cdsco.gov.in/opencms/opencms/system/modules/CDSCO.WEB/elements/common_download.jsp?num_id_pk=ODc5

Government to amend Schedule-V of D&C Rules to revise 'free salicylic acid' content in drugs containing aspirin

The Union Health Ministry has proposed to soon amend the Schedule-V of the Drugs and Cosmetics (D&C) Rules, 1945, in order to revise the free limit content of the salicylic acid in medicines containing aspirin. This limit is uniform throughout the globe based on pharmacopoeia standards.

The matter was discussed by the Drugs Technical Advisory Board (DTAB) at its meeting held in New Delhi recently, and it was concluded that the limit of free salicylic acid content shall be not more than 3 per cent in all medicines containing aspirin. The current provision under Schedule-V of the D&C Rules, 1945 states that all patent and proprietary medicines containing aspirin shall be subjected to free salicylic acid test and the limit of such acid shall be 0.75 per cent, except in case of soluble type aspirin in which case the limit of such acid shall be 3 per cent.

Key points of the new proposal

Aspirin and Aspirin containing FDCs are widely used formulations, and several such single ingredient, formulations and FDCs are covered under various Pharmacopoeia. The "Free Salicylic Acid" content limit specified in such Pharmacopoeia are as under:

- IP 2018: Maximum 3 per cent
- BP 2018: Maximum 3 per cent
- USP 41: Not more than 3 per cent
- USP 41: Not more than 8 per cent (for Aspirin Effervescent Tablets for Oral Solution)

DTAB deliberated the proposal and agreed to amend Schedule-V of the Drugs and Cosmetics Rules, 1945 to revise the limit of free salicylic acid content in medicines.

Note: All medicines containing aspirin shall be subjected to "Free Salicylic Acid Test", and the limit of "Free Salicylic Acid" content shall be not more than 3.0 per cent.'

EMA restricts the use of multiple sclerosis drug 'Lemtrada' while review is ongoing

On April 12, 2019, the European Medicine Agency (EMA) has temporarily restricted the use of Lemtrada (alemtuzumab), while the review is ongoing[8]. The restriction says that the drug should only be started in adults with relapsing-remitting multiple sclerosis that is highly active despite treatment with at least two disease-modifying therapies (a type of multiple sclerosis medicine) or where other disease-modifying therapies cannot be used. Patients being treated with Lemtrada who are benefitting from it may continue treatment in consultation with their doctor.

The ongoing review of Lemtrada by EMA is followed by the reports of immune-mediated conditions (caused by the body's defense system not working properly) and problems with the heart and blood vessels with the medicine, including fatal cases.

Apart from this restriction, EMA's safety committee has recommended an update on Lemtrada to inform patients and healthcare professionals about:

- Reports of immune-mediated conditions, including autoimmune hepatitis (with damage the liver) and haemophagocytic lymphohistiocytosis (overactivation of the immune system which may affect different parts of the body) occurring within 1–3 days of receiving the medicine;
- Problems with the heart and blood vessels occurring within 1–3 days of receiving the medicine, including bleeding in the lungs, heart attack, stroke, cervicocephalic arterial dissection (tears in the lining of the arteries in the head and neck);
- Severe neutropenia (low levels of neutrophils, a type of white blood cell that fights infections).
- If patient observes any of these symptoms, then doctor will examine their condition and may consider stopping Lemtrada and switching to an alternative treatment. Patients are also asked to speak with doctor if they have any questions or concerns about treatment.
- An in-depth review of Lemtrada is ongoing and further information will be provided as soon as it is available. While the review is ongoing, Lemtrada will only be prescribed to new patients if other medicines have not worked or are not suitable.
- Doctors are being informed in writing of temporary restrictions on the prescription of Lemtrada pending the conclusion of an ongoing review of the medicine and inclusion of new safety warnings in the product information of Lemtrada.
- Patients who develop signs of pathological immune activation should be evaluated immediately, and a diagnosis of haemophagocytic lymphohistiocytosis considered. Symptoms of immune activation may occur up to 4 years after the start of treatment.

About Lemtrada (alemtuzumab)

Lemtrada is a monoclonal antibody (a type of protein) that has been designed to recognise and attach to a protein called CD52 found on white blood cells of the immune system (the body's defenses). By attaching to CD52, alemtuzumab causes the white blood cells to die and be replaced, thereby reducing damaging activity of the immune system. Lemtrada is indicated to treat adults with relapsing-remitting multiple sclerosis, a disease of the nerves in which inflammation destroys the protective sheath surrounding the nerve cells.

The marketing authorization of Lemtrada was given to Sanofi Belgium in 2013.

8 https://www.ema.europa.eu/en/documents/referral/lemtrada-article-20-referral-use-multiple-sclerosis-medicine-lemtrada-restricted-while-ema-review_en.pdf

Note- EMA will now evaluate all available data on the safety concerns with the medicine and consider any additional measures necessary to protect patients and whether there should be changes in its authorized use. Further information will be provided once the review of Lemtrada is concluded.

World's first Malaria vaccine pilot program launched in Malawi

On April 23, 2019, Malawi became the first of the three countries in Africa to roll out landmark Malaria vaccine through a pilot program[9]. The vaccine, known as RTS,S will be made available to children up to 2 years of age; Ghana and Kenya will introduce the vaccine in the coming weeks.

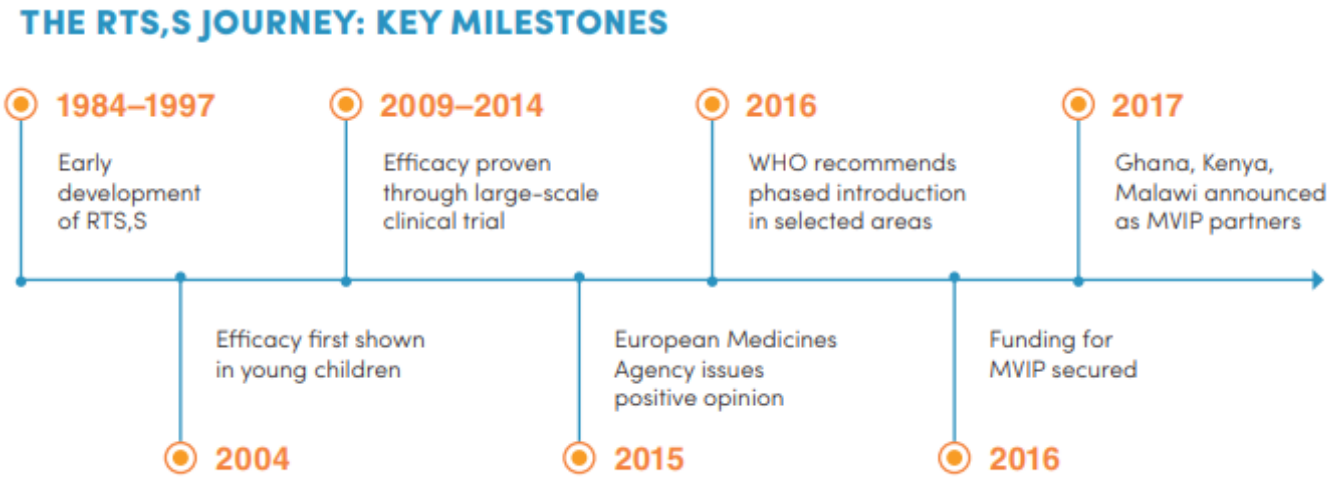
The pilot program is designed to generate evidence and experience to inform WHO policy recommendations on the broader use of the RTS,S malaria vaccine. It will look at reductions in child deaths; vaccine uptake, including whether parents bring their children on time for the four required doses; and vaccine safety in the context of routine use.

Malaria remains one of the world's leading killers, claiming the life of one child every two minutes. Most of these deaths are in Africa, where more than 250 000 children die from the disease every year. Children under 5 are at greatest risk from its life-threatening complications. Worldwide, malaria kills 435 000 people a year, most of them children.

About RTS,S Vaccine

RTS,S acts against Plasmodium falciparum, the most deadly malaria parasite globally and the most prevalent in Africa. The vaccine provides partial protection against malaria among young African children, the population most affected by the disease. Rigorous clinical testing in seven African countries has shown its potential to boost malaria prevention and save lives.

RTS,S was developed over three decades by GSK, including through a collaboration, begun in 2001, with PATH's Malaria Vaccine Initiative (PATH/MVI) and a network of African research centres[10]:



About MVIP

The Malaria Vaccine Implementation Programme (MVIP) was established by WHO to coordinate and support the introduction of the vaccine in selected areas of Africa through country-led routine immunization. The Programme

9 https://www.who.int/news-room/detail/23-04-2019-malaria-vaccine-pilot-launched-in-malawi

10 https://apps.who.int/iris/bitstream/handle/10665/272456/WHO-CDS-GMP-2018.05-eng.pdf

will evaluate the vaccine's public health impact in the context of routine use and inform policy about its potential deployment on a broader scale. Financing for the MVIP has been mobilized through an unprecedented collaboration between three major global health funding bodies - Gavi, the Vaccine Alliance, the Global Fund to Fight AIDS, Tuberculosis and Malaria, and Unitaid. WHO and GSK are providing additional in-kind contributions, and PATH's activities are also supported by the Bill & Melinda Gates Foundation.

Conclusion

The WHO-coordinated pilot programme is a collaborative effort with Ministries of Health in Ghana, Kenya and Malawi and a range of in-country and international partners, including PATH, a non-profit organization, and GSK, the vaccine developer and manufacturer, which is donating up to 10 million vaccine doses for this pilot.

The malaria vaccine pilot aims to reach about 360,000 children per year across the three countries. Ministries of Health will determine where the vaccine will be given; they will focus on areas with moderate-to-high malaria transmission, where the vaccine can have the greatest impact.

Antimicrobial resistance could cause millions of death and extreme poverty by 2030: WHO

United Nation (UN) Ad hoc Interagency Coordinating Group has recently published a report "*Antimicrobial Resistance drug-resistant diseases*" that warns that an urgent action needs to be taken at ground level to prevent a potentially disastrous antimicrobial drug-resistance crisis. As per the report, antimicrobial resistance could cause 10 million deaths each year by 2050, and can damage the economy. By 2030, antimicrobial resistance could force up to 24 million people into extreme poverty.

As per the data available at least 700,000 people die each year due to drug-resistant diseases, including 230,000 people who die from multidrug-resistant tuberculosis. Moreover, the economic and health consequences prevent the action of the crucial medicines.

The Report calls for an urgent action to:

- Prioritize national action plans to scale-up financing and capacity-building efforts;
- Put in place stronger regulatory systems and support awareness programs for responsible and prudent use of antimicrobials by professionals in human, animal and plant health;
- Invest in important research and development for new technologies to combat antimicrobial resistance;
- Urgently phase out the use of critically important antimicrobials as growth promoters in agriculture.[11]

Antimicrobial resistance must be addressed urgently, through a One Health approach involving bold, long-term commitments from governments and other stakeholders, supported by international organizations. This report demonstrates the level of commitment and coordination that will be required as we face this global challenge to public health, animal health and welfare, and food security. We must all play our part in ensuring future access to and efficacy of these essential medicines."

Conclusion

The report highlights the need for coordinated and intensive efforts to overcome antimicrobial resistance - a major barrier to the achievement of many of the UN Sustainable Development Goals, including universal health coverage, secure and safe food, sustainable farming systems and clean water and sanitation. Moreover, it says that more stringent policies need to be developed at the ground level to prevent the future generations from suffering from the hazards of antimicrobial resistance, a major cause of millions of death.

11 https://www.who.int/news-room/detail/29-04-2019-new-report-calls-for-urgent-action-to-avert-antimicrobial-resistance-crisis

FDA approves Balversa, a first targeted therapy for metastatic bladder cancer

On April 12, 2019, the U.S. Food and Drug Administration (USFDA) granted accelerated approval to Balversa (erdafitinib), a treatment for adult patients with locally advanced or metastatic bladder cancer that has a type of susceptible genetic alteration known as (fibroblast growth factor receptor) FGFR3 or FGFR2, and that has progressed during or following prior platinum-containing chemotherapy[12]. This approval represents the first personalized treatment targeting susceptible FGFR genetic alterations for patients with metastatic bladder cancer.

The approval followed by the efficacy study of Balversa included 87 patients with locally advanced or metastatic bladder cancer, with FGFR3 or FGFR2 genetic alterations, that had progressed following treatment with chemotherapy. The overall response rate in these patients was 32.2%, with 2.3% having a complete response and almost 30% having a partial response. The response lasted for an average of approximately five-and-a-half months. About a quarter of patients in the study were previously treated with anti PD-L1/PD-1 therapy, which is a standard treatment for patients with locally advanced or metastatic bladder cancer. Responses to Balversa were seen in patients who had previously not responded to anti PD-L1/PD-1 therapy.

Balversa received an Accelerated Approval and was also granted Breakthrough Therapy designation. The FDA granted the approval of Balversa to Janssen Pharmaceutical.

The FDA also approved the therascreen FGFR RGQ RT-PCR Kit, which is the first PCR-based companion diagnostic approved to detect FGFR alterations developed by QIAGEN Manchester, Ltd., for use as a companion diagnostic with Balversa for this therapeutic indication.

About Urothelial Carcinoma

Urothelial carcinoma is also known as transitional cell carcinoma, the most common type of bladder cancer. Bladder cancers are associated with genetic mutations that are present in the patient's bladder or entire urothelium (the lining of the lower urinary tract). Bladder cancer is the sixth most common cancer in the United States. Fibroblast growth factor (FGFR) alterations are present in approximately one in five patients with recurrent and refractory bladder cancer.

About Balversa (erdafitinib)[13]

BALVERSA (erdafitinib) is a once-daily, oral FGFR kinase inhibitor indicated for the treatment of adults with locally advanced or metastatic urothelial carcinoma (mUC) which has susceptible FGFR3 or FGFR2 genetic alterations and who have progressed during or following at least one line of prior platinum-containing chemotherapy, including within 12 months of neoadjuvant or adjuvant platinum-containing chemotherapy.

Note - The approval of BALVERSA for said indication is under accelerated approval based on tumor response rate. Continued approval for this indication may be contingent upon verification and description of clinical benefit in confirmatory trials. In US, BALVERSA will be commercially available through the single-source specialty pharmacy provider US Bioservices. Janssen entered into an exclusive worldwide license and collaboration agreement with Astex Pharmaceuticals to develop and commercialize BALVERSA.

12 https://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm635906.htm

13 https://www.janssen.com/balversa-erdafitinib-receives-us-fda-approval-treatment-patients-locally-advanced-or-metastatic

USFDA and CBP bolster collaboration to protect public health and safety

On April 04, 2019, an agreement was signed between the U.S. Food and Drug Administration and the U.S. Customs and Border Protection (CBP) leaders to maximize inspection and detection capabilities in order to prevent illegal and harmful products, that pose a threat to public health, from entering the U.S. through the nation's International Mail Facilities (IMFs) and Ports of Entry [14]. This agreement enables each agency to work towards:

Enhancing knowledge-transfer to increase efficiency, reduce duplication of efforts and facilitate mission responsibilities.

- Collaboration on shared laboratory space, scientific equipment and facilities, along with intellectual, historical and institutional knowledge will optimize the resources at each agency's disposal.

In 2018, FDA staff posted at the IMFs around the country examined packages from more than 180 countries. Approximately 90 percent of the packages reviewed by the FDA contained products that should not have been entering the country. Most mail arrives in an IMF without advanced or specific identifying information. The FDA uses advanced screening technology to assess the contents of these packages and to increase efficiency of the agency's overall investigational capabilities.

The FDA and CBP with this agreement will expand how information is shared between the agencies to identify trends which can target future entries. This may include general data points on frequent countries of origin, as well as specific products and volumes of packages at each location.

An additional focus of this effort will be coordinating shared space as well as increased scientific presence at high-risk/high-volume IMF locations, helping to facilitate and support real-time entry decisions and increased data sharing. Additionally, the FDA and CBP will enhance coordination around efforts to identify violative packages and develop new targeting and enforcement strategies at Ports of Entry.

Note- At present, there are nine IMF locations across the U.S., with one location each in Florida, Hawaii, Illinois, New Jersey, New York, Puerto Rico, U.S. Virgin Islands respectively and two locations in California. CBP provides security and facilitation operations at 328 Ports of Entry throughout the country.

14 https://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm635270.htm

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