EDITORIAL

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We are pleased to present this Vol. II Issue VII 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 cognizance taken by the Ministry of AYUSH in relation to the increasing numbers of misleading advertisements being reported in recent years in India; the article also describes Ministry's efforts to address these instances by informing this to respective State Regulatory Authorities for necessary action. Going forward, this edition addresses the matter of patent opposition, where a patient group living with hepatitis C infections has filed two pre-grant oppositions at Indian Patent Office against Gilead's patent application for lifesaving hepatitis C drug. The issue then, covers the CSIR-IMITECH collaborative research agreement with Zydus Cadila for development of novel drug candidates for treatment of drug-resistant infections like tuberculosis; followed by an article on United Nation Global AIDS update report 2018, which shows the major reduction in new HIV infections and AIDS-related deaths in India during the period of 2010-2017.

From the international arena, we talk about recent global survey reports concerning various health issues and also the progress on improving health in countries. First, we discuss a global tripartite self-assessment survey report on "Monitoring Global Progress on Addressing Antimicrobial Resistance", which shows countries' significant efforts in tackling antimicrobial resistance (AMR), yet serious gaps which require accelerated effort and urgent action.; followed by a global report on "Delivering Quality Health Services". The report shows that quality of care in most countries, particularly low- and middle-income countries, is suboptimal which cause increasing burden of illness and health costs globally. Next, we have a review on EMA's Committee for Medicinal Products for Human Use meeting July 2018, where the committee recommended approval of sixteen medicines, two orphan medicines in European Union (EU).

We wrap up this newsletter with write-ups on (i) United States Food and Drug Administration approval to TPOXX (tecovirimat), the first drug for treatment of smallpox and (ii) USFDA key steps to tackle the issue related to compounding of human drug products, as part of its ongoing implementation of the Drug Quality and Security Act and to advance the goals of its 2018 Compounding Policy Priorities Plan.

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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

Thank you.

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Increasing instances of misleading advertisements of products & services from AYUSH and herbal medicines

The Minister of State for the Ministry of Ayurveda, Yoga & Naturopathy, Unani, Siddha and Homoeopathy (AYUSH), in a written reply to a query from Lok Sabha, has stated that increasing number of misleading advertisements of AYUSH products are being reported in recent years[1]. Such complaints are also registered in the GAMA (Grievances against Misleading Advertisements) portal maintained by the Department of Consumer Affairs (DoCA). About 809 complaints of advertisements pertaining to AYUSH and herbal medicines/products have been received during the period from April, 2015 to March, 2018. Advertising Standards Council of India (ASCI), with whom Ministry had signed a MoU for suo moto monitoring of AYUSH advertisements appearing in print and TV media, reported 732 complaints in the period from 20th January, 2017 to 19th January, 2018[2].

Regulatory framework for AYUSH drugs

The manufacturing, sale and distribution of Ayurvedic, Siddha and Unani medicines is regulated under various provisions of Drugs and Cosmetics Act, 1940 (the 'Act') and the Drugs and cosmetic Rule, 1945. However, there is no exclusive definition for herbal medicines clinical trial in said Act and Rules thereunder. In the year 2015, the central government introduced a new category of drugs derived from herbal materials or medicinal plants called as "Phytopharmaceuticals" under Drugs and Cosmetics Rules, 1945, to provide regulatory provisions for such drugs, made from purified and standardized fraction of minimum four bio-active or phyto-chemical compounds extracted from a medicinal plant or its part. Further, The provisions of Rule 158-B of the Drugs & Cosmetics Rules, 1945 provide for pilot studies for generating proof of safety and effectiveness for grant of license to manufacture for sale certain categories of Ayurveda, Siddha and Unani drugs.

The advertising regulation of AYUSH products comes under the ambit of the Drugs and Magic Remedies (Objectionable Advertisements) Act, 1954 (the '1954 Act'), since the definition of 'drug' given in the Act covers all medicines, substances and articles other than food. For checking the veracity and for monitoring of misleading advertisements, powers are vested with the State Governments to authorize Gazetted Officers to search, seize, examine any record, register, document or any other material object related to any objectionable advertisement under the provisions of Section 8(1) of the 1954 Act.

Central Government's efforts to tackle misleading advertisement

In order to check the veracity of misleading advertisements and claims of AYUSH products, the Central Government has taken following steps-

I. State Governments have been directed for appointing Gazetted Officers under section 8 (1) of the Drugs and Magic Remedies (Objectionable Advertisements) Act, 1954 to enter, search any premises or examine or seize any record which contravenes any provisions of the Act. About 621 Gazetted Officers for this purpose are reported to have been appointed in 22 states.

II. Complaints of misleading advertisements of Ayurvedic, Siddha, Unani and Homoeopathic medicines are forwarded to the concerned State Licensing Authorities for action in accordance with the provisions of Drugs & Cosmetics Act, 1940 and Rules thereunder and Drugs & Magic Remedies (Objectionable Advertisements) Act, 1954 and Rules thereunder. Out of the 809 complaints reflected on GAMA portal, about 274 complaints have been resolved and 585 complaints forwarded to concerned state authorities for appropriate action in accordance with the legal provisions. States have reported action taken by them

1 https://www.ascionline.org/images/pdf/au1336.pdf

2 http://pib.nic.in/PressReleseDetail.aspx?PRID=1541936

against the defaulters.

III. Ministry of AYUSH signed MoU with Advertising Standards Council of India (ASCI) to undertake monitoring of the misleading AYUSH –related advertisements appearing in print and TV media and bring the instances of improper advertisements to the notice of the State Regulatory Authorities for taking necessary action. ASCI reported that 233 alleged advertisements were rectified or withdrawn by the advertisers and about 456 complaints were escalated to the State regulators for appropriate action.

IV. On the request of Ministry of AYUSH, Ministry of Information & Broadcasting issued an advisory to all media channels to ensure strict compliance of the provisions of Drugs & Cosmetics Act, 1940 and Drugs & Magic Remedies (Objectionable Advertisements) Act, 1954 in respect of AYUSH health products/drugs being advertised. TV channels have been advised to advertise only those AYUSH products, which have valid manufacturing license.

V. Provision of surveillance of AYUSH advertisements has been kept in the central scheme implemented for safety monitoring of Ayurvedic, Siddha, Unani and Homeopathy drugs under the pharma vigilance initiative.

Note: The Ministry of AYUSH, established to ensure the optimal development and propagation of AYUSH systems of health care in the country has issued State-wise/company-wise list of 407 such misleading advertising instances along with the details of 585 complaints forwarded to the respective State Regulatory Authorities for necessary action in accordance with the legal provisions in last three years.

Patient group challenges the ever-greening patent of Gilead's lifesaving hepatitis C drug

On July 09, 2018, the Delhi Network of Positive People (DNP+) filed two pre-grant oppositions at the Indian Patent Office against Gilead's patent application for hepatitis C drug under Section 25(1) of the Patent Act, 1970 (the 'Act'). The DNP+ has challenged the patent application of Gilead's sofosbuvir/velpatasvir Fixed-Dose Combination (FDC), and polymorph form of velpatasvir, a direct acting antiviral drug for the treatment of Hepatitis C Virus (HCV) infection[3].

Gilead Pharmasett, LLC (hereinafter the 'Applicant'), on November 21, 2016, filed a patent application (Application no. 201627039572) with title "*Solid Forms of an Antiviral Compound*" with 80 claims, seeking to patent a compound which is used to treat Hepatitis C. The opponent, DNP+, is a community based non-profit organization representing the needs of people leaving with HIV/AIDS and HCV. DNP+ is also a network working extensively in the area of access to medicines. In present case, the opponent's key concern is access of affordable HCV medicine, where, if patent is granted to such a product, it will influence the affordability of the drug for people not just in India but across all developing countries, since India plays a critical role in supplying affordable, quality lifesaving generic medicines to developing countries, largely because the country's patent law strikes a balance between promoting public health and access to medicines, while also protecting companies' intellectual property rights by granting patents for true innovative developments.

The grounds for opposition

The opponent filed pre-grant opposition under section (25)(1) of the Act on the following grounds:

- The invention claimed in complete specification is obvious and does not involve inventive steps, and fails under Sections 2(1)(j) and 2(1)(ja) of the Act. Therefore, the opponent is filing this pre-grant opposition for obviousness of invention under Section 25 (1)(e) of the Act.
- The invention claimed in complete specification is not an invention nor does it exhibits enhanced therapeutic efficacy required under section 3(d) of the Act. Therefore, the Opponent brings the opposition under Section 25(1) (f) - that the subject of any claim of the complete specification is not an invention within the meaning of this Act.
- The Opponent brings opposition under Section 25(1) (h) of the Act - that the Patent Applicant has failed to disclose the information required by Section 8.

Gilead already has patent for sofosbuvir (Sovaldi) in India and the company has applied for multiple patents on sofosbuvir based formulations. DNP+ aims to prevent such unmerited patent applications from being granted and encourages open competition on the combination of sofosbuvir and velpatasvir after the basic compound patents have expired or are revoked in countries excluded from Gilead's license agreements.

Velpatasvir, a direct-acting antiviral (DAA), is one of the key medicines used in combination with sofosbuvir for the oral treatment in people with all six major genotypes of hepatitis C virus. Its effectiveness as a pan-genotypic medicine makes it a key drug in the fight against hepatitis C. Access to affordable generic sources of this medicine, and its combination with sofosbuvir, are therefore, critical for all countries with a high burden of people living with Hepatitis C. Sofosbuvir/velpatasvir was launched in the United States by Gilead at over $74,000 for a 12-week regimen in 2016 but the said combination is available in India at approximately $286 per 12 weeks.[4]

3 https://www.patentoppositions.org/en/drugs/velpatasvir/patent_oppositions/5b418334d2708f0005fd8aec

4 https://www.msfindia.in/people-living-hepatitis-c-and-hiv-challenge-evergreening-patents-lifesaving-hepatitis-c-drugs-india

The opponent refers the provisions of Indian Patent Act that prevent patent ever-greening, which restricts the patentability of a host of secondary patents, i.e., new forms of known substances, new property or new use of known substances, use of known processes without showing any enhanced therapeutic efficacy, and admixtures without synergistic effect.

Note: ever-greening patent tactic to block affordable lifesaving drugs that other countries may import in the future. With these patent challenges, DNP+ hopes to prevent Gilead from gaining unmerited patent rights on sofosbuvir + velpatasvir combination. DNP+ also filed an opposition with Initiative for Medicines, Access & Knowledge (I-MAK) at IPO against the granting of a patent to AbbVie on pibrentasvir, which is in comination with Glecaprevir indicated to treat hepatitis C.

Zydus allies with CSIR- Institute of Microbial Technology (IMTECH) for development of new drugs for drug-resistant infectious diseases

On July 05, 2018, the Council of Scientific and Industrial Research (CSIR) - Institute of Microbial Technology (IMTECH), a premier microbial institute under the aegis of the Ministry of Science and Technology, Government of India, announced a collaborative research agreement with Zydus Cadila, an innovation-driven global healthcare group[5].

The partnership primarily aims to identify novel drug candidates for treatment of drug-resistant infections like tuberculosis. For this project, scientists at IMTECH will utilize their expertise and scientific knowledge in microbiology while Zydus Cadila will provide its expertise in medicinal chemistry & pharmaceutical drug development with an aim to develop new drug combinations against drug-resistant pathogens which cause severe diseases in India and across the world. A positive outcome from such collaborative efforts could define the way drug discoveries will be carried out in future in India via public-private partnerships.

CSIR-IMTECH established in 1984, is a national center for excellence in microbial sciences. IMTECH's vision is to discover and develop translational products and new drugs to address key unmet medical needs. Zydus Cadila is a fully integrated, global healthcare provider, with strengths all along the pharmaceutical value chain. With a core competence in the field of healthcare, Zydus has successfully developed novel therapies that have provided people in India an access to new and hitherto unavailable drugs.

About AMR

Antimicrobial resistance is the ability of a microorganism (like bacteria, viruses, and some parasites) to stop an antimicrobial (such as antibiotics, antivirals and anti-malarial) from working against it. As a result, standard treatments become ineffective, infections persist and may spread to others[6]. AMR is a serious threat to global public health that requires action across all government sectors and society. Emergence of Multi drug-resistant (MDR)/extremely drug-resistant (XDR) tuberculosis is a big challenge in India and across several other countries in the world.

WHO's Global Antimicrobial Surveillance System has reported Antimicrobial resistance (AMR) among 500,000 people with suspected bacterial infections across several nations. The cost of health care for patients with resistant infections is higher than care for patients with non-resistant infections due to longer duration of illness, additional tests and use of more expensive drugs. Drug resistance is a global threat and India needs sustained research & development efforts to tackle this global scourge.

About IMTech[7]

The Institute of Microbial Technology (IMTech) is one of the 37 national laboratories, 6 units and 39 outreach centers of the Council of Scientific & Industrial Research. The Institute's primary asset is a team of more than 55 highly motivated scientists. Most of them have several years of training in world renowned laboratories. These scientists have built strong peer credibility both in basic and application-oriented broad thematic areas of molecular biology and microbial genetics, cell biology and immunology, protein science and engineering, and fermentation technology and applied microbiology.

5 http://zyduscadila.com/wp-content/uploads/2018/07/Press-release-IMTECH-ZYDUS-final.pdf

6 http://www.who.int/antimicrobial-resistance/en/

7 https://www.imtech.res.in/about/about-imtech

Global AIDS response is at a precarious point: UN report

On July 18, 2018, UNAIDS released a report titled "*Miles to go—closing gaps, breaking barriers, righting injustices*[8]" as a part of global AIDS update report 2018. The report is a stark wake-up call for countries as it indicates that the global AIDS response is at a precarious point - partial success in saving lives and stopping new HIV infections is giving way to complacency. At the halfway point to the 2020 targets, the pace of progress is not matching the global ambition - for example the progress in Asia and the Pacific Region is encouraging while West and Central Africa lagging behind, as described below:

Progress in Asia and the Pacific Region

Asia and the Pacific Region have made strong inroads with their HIV response. Sustained and focused efforts to reach key populations led to significant reduction in HIV infections in Cambodia, India, Myanmar, Thailand and Vietnam between 2010 and 2017. However, epidemics are expanding in Pakistan and Philippines. on a brighter note, new HIV infections and AIDS-related deaths have significantly dropped in India during the period 2010-2017.

The vast majority of new HIV infections in Asia and the Pacific are associated with current or former members of key populations and their partners. Unprotected sex between men especially young men, is an increasingly important factor in many of the regions' HIV epidemics; epidemics among gay men and other men who have sex with men are expanding in several countries. Key populations must remain at the core of HIV prevention. HIV risk among young people within key populations is of particular concern; since 2010, new HIV infections among young people (aged 15–24 years) increased by 170% in Philippines and 29% in Pakistan.

In case of Combination HIV Prevention there has been an encouraging increase in the number of countries offering pre-exposure prophylaxis (PrEP), albeit mainly through pilot projects and at demonstration sites. By March 2018, PrEP was available on a limited basis to gay men and other men who have sex with men in China, India, Malaysia, New Zealand, Philippines, Thailand and Vietnam.

West and Central Africa lagging behind

Only 26% of children and 41% of adults living with HIV had access to treatment in western and central Africa in 2017, compared to 59% of children and 66% of adults with HIV in eastern and southern Africa. Since 2010, AIDS-related deaths have fallen by a mere 24% in western and central Africa, compared to a considerable 42% decline in eastern and southern Africa.

Nigeria has more than half (51%) of the HIV burden in the region and there has been little progress in reducing new HIV infections in recent years. New HIV infections declined by only 5% (9000) in seven years (from 179 000 to 170 000) and only one in three people living with HIV is on treatment (33%), although HIV treatment coverage has increased 24% from just two years ago.

The report further highlights the following observations:

1. HIV PREVENTION CRISIS

Global new HIV infections have declined by just 18% in the past seven years, from 2.2 million in 2010 to 1.8 million in 2017. Although this is nearly half the number of new infections compared to the peak in 1996 (3.4 million), the decline is not quick enough to reach the target of fewer than 500 000 by 2020.

8 http://www.unaids.org/sites/default/files/media_asset/miles-to-go_en.pdf

The reduction in new HIV infections has been strongest in the region most affected by HIV - eastern and southern Africa - where new HIV infections have been reduced by 30% since 2010. However, new HIV infections are rising in around 50 countries. In Eastern Europe and Central Asia the annual number of new HIV infections has doubled, and new HIV infections have increased by more than a quarter in the Middle East and North Africa over the past 20 years.

2. TREATMENT SCALE-UP SHOULD NOT BE TAKEN FOR GRANTED

Due to the impact of antiretroviral therapy roll-out, the number of AIDS-related deaths is the lowest in this century (940 000), having dropped below 1 million for the first time in 2016. Yet, the current pace of decline is not fast enough to reach the 2020 target of fewer than 500 000 AIDS-related deaths.

In just one year, an additional 2.3 million people are newly accessing treatment. This is the largest annual increase to date, bringing the total number of people on treatment to 21.7 million. Almost 60% of the 36.9 million people living with HIV were on treatment in 2017, an important achievement, but to reach the 30 million target there needs to be an annual increase of 2.8 million people, and there are indications that the rate of scale-up is slowing down.

3. KEY POPULATIONS ACCOUNT FOR ALMOST HALF OF ALL NEW HIV INFECTIONS WORLDWIDE

The report also shows that key populations are not being considered enough in HIV programming. Key populations and their sexual partners account for 47% of new HIV infections worldwide and 97% of new HIV infections in Eastern Europe and Central Asia, where one third of new HIV infections are among people who inject drugs.

Half of all sex workers in Eswatini, Lesotho, Malawi, South Africa and Zimbabwe are living with HIV. The risk of acquiring HIV is 13 times higher for female sex workers, 27 times higher among men who have sex with men, 23 times higher among people who inject drugs and 12 times higher for transgender women.

4. STIGMA AND DISCRIMINATION PERSIST

Discrimination by health-care workers, law enforcement, teachers, employers, parents, religious leaders and community members is preventing young people, people living with HIV and key populations from accessing HIV prevention, treatment and other sexual and reproductive health services.

Across 19 countries, one in five persons living with HIV responding to surveys reported being denied health care and one in five persons living with HIV avoided visiting a health facility for fear of stigma or discrimination related to their HIV status. In five of 13 countries with available data, more than 40% of people said they think that children living with HIV should not attend school with children who are HIV-negative.

However, successive surveys in Cambodia, India, Thailand and Vietnam indicate that attitudes towards people living with HIV have improved. The Avahan programme in Karnataka and other states in India remains a sterling example of the impact of combining condom programming with community empowerment and structural improvements that tackle stigma, violence and unsafe working environments.

5. NEW AGENDA NEEDED TO STOP VIOLENCE AGAINST WOMEN

In 2017, around 58% of all new HIV infections among adults over 15 years old were women and 6600 young women between the ages of 15 and 24 years became infected with HIV every week. Increased vulnerability to HIV has been linked to violence. More than one in three women worldwide have experienced physical or sexual violence, often at the hands of their intimate partners.

Criminalization also exposes sex workers to violence from clients and other sexual partners. Studies from India and the United Kingdom of Great Britain and Northern Ireland found that sex workers who had been arrested or imprisoned were more likely to be assaulted by clients than peers who had avoided arrest.

The report also included an example of Indian state of Karnataka, where advocacy work with senior police officials, sensitization workshops and the inclusion of HIV and human rights topics in pre-service curricula led to significant decrease in the arrest of female sex workers, especially during police raids. Before the interventions, half (50%) of the 4110 surveyed female sex workers said they had been arrested or detained at some point during police raids; that proportion shrank to 20% after the interventions.

A recent analysis of data from 27 European countries underscores the public health benefits of decriminalizing sex work. It found that countries that have decriminalized at least some aspects of sex work have fewer sex workers living with HIV than countries that criminalize all aspects of sex work. Predictive models based on data from Canada, India and Kenya indicate that the decriminalization of sex work could avert 33–46% of HIV infections over the course of a decade.

Note – The report shows that though there has been progress in the 90–90–90 target toward diagnosis-treatment access-suppressed viral load, only six countries - Botswana, Cambodia, Denmark, Eswatini, Namibia and the Netherlands have reached the 90–90–90 target and seven more countries are on track. However, much faster paced progress is required to achieve the global target. The largest gap is in the first 90 as observed in western and central Africa, where only 48% of people living with HIV know their status.

WHO urges countries to accelerate efforts to tackle antimicrobial resistance

On July 18, 2018, the Food and Agriculture Organization of the United Nations (FAO), the World Organization for Animal Health (OIE) and the World Health Organization (WHO) together released a survey report on "*Monitoring Global Progress on Addressing Antimicrobial Resistance*[9]". The report says that countries are taking significant steps in tackling antimicrobial resistance (AMR), but serious gaps remain and require urgent action.

Monitoring Global Progress on Addressing Antimicrobial Resistance 2018

The global tripartite self-assessment survey of country progress in addressing antimicrobial resistance (AMR) is a component of a broader approach for monitoring and evaluation of the global action plan on AMR. This report analyses the results of the second tripartite self-assessment survey. It has been developed and run by the three organizations (FAO, OIE and WHO) and reflects progress in the human, animal (terrestrial and aquatic), plant, food safety and environmental sectors.

The 2018 round of the self-assessment survey received responses from 154 countries out of 194 WHO Member States – a response rate of 79.4%. All countries' responses from both years are published in an open-access database, offering scope for in-country review with civil society and other stakeholders[10].

About AMR

Antimicrobial resistance (AMR) is a grave threat to human health and economic development. The overuse and misuse of antimicrobials in humans, animals and plants have accelerated the natural evolutionary processes which makes microbes resistant to antimicrobial treatments. Today, some infections have even been rendered untreatable by existing antimicrobials. Projections suggest that AMR is likely to exacerbate global economic inequality, with the economic costs disproportionately affecting poorer countries.

Report Highlights

The report looks at surveillance, education, monitoring and regulating consumption and use of antimicrobials in human health, animal health and production, as well as plants and the environment – as recommended in the Global Action Plan (GAP) published in 2015.

The report charts progress in 154 countries and reveals wide discrepancies. Some countries, including many European states, have been working on AMR policies in human and animal sectors for more than 4 decades. Others have only recently started to take action to contain this growing threat. Progress in developing and implementing plans is greater in high-income as compared to low-income countries but overall all countries have scope for improvement. No country reports sustained capacity at scale in all areas. Promising findings include:

- 105 countries have a surveillance system in place for reporting drug-resistant infections in human health, and 68 countries have a system for tracking consumption of antimicrobials.
- 123 countries reported that they have policies to regulate the sale of antimicrobials, including the requirement of a prescription for human use – a key measure to tackle overuse and misuse of antimicrobials.

9 http://apps.who.int/iris/bitstream/handle/10665/273128/9789241514422-eng.pdf

10 http://www.who.int/news-room/detail/18-07-2018-countries-step-up-to-tackle-antimicrobial-resistance

1. Progress towards the development of national action plans

When WHO endorsed the 2015 Global Action plan on AMR, all Member States committed to the ambitious target of developing a multisectoral national action plan within two years. By May 2017, 79 countries reported that they had a plan, and a further 50 countries having a plan under development. While the 2017 target is still unmet, the second tripartite self-assessment survey shows that progress has been sustained.

Now 93 countries (60.4%) have developed a national action plan on AMR. Among the 61 (39.6%) countries that have not yet developed a national action plan, 51 (33.1%) have a plan currently in development but 10 (6.5%) have reported no progress towards developing a national action plan. The ten respondent countries that have not yet taken any action to develop national action plans are predominantly a mix of small island states and fragile states across all regions.

2 Multi-sectoral approaches to addressing AMR

A need to establish a multi-sectoral working group was identified in the global action plan as an important facilitator of a One Health approach to addressing AMR. Where working groups have been established, they typically include representatives from human health, animal health, and food safety. Representatives from other sectors including food production, environment, and plant health are less frequently included.

The findings from this national self-assessment survey clearly show the importance of One Health approach and multi-sector working for progress in AMR. For future progress it will be important to ensure all sectors like the following, are playing their part:

Animal and food sectors

- Only 64 countries report that they follow FAO-OIE-WHO recommendations to limit the use of critically important antimicrobials for growth promotion in animal production. Of these, 39 are high-income countries, with the majority in WHO's European Region. By contrast, only 3 countries from WHO's African Region and 7 countries from the WHO Region of the Americas have taken this important step to reduce the emergence of antimicrobial resistance.

- A total of 67 countries report at least having legislation in place to control all aspects of production, licensing and distribution of antimicrobials for use in animals. But 56 either said that they had no national policy or legislation regarding the quality, safety and efficacy of antimicrobial products used in animal and plant health, and their distribution, sale or use, or that they were unable to report whether they have these policies in place.

Environment and plant sectors

- Although 78 countries have regulations in place to prevent environmental contamination generally, only 10 of them report having comprehensive systems to ensure regulatory compliance for all waste management, including regulations that limit the discharge of antimicrobial residues into the environment. This is insufficient to protect the environment from the hazards of antimicrobial production.

Human sector

- 105 countries report that they have a surveillance system in place and 68 have a system for tracking consumption of antimicrobials at national level. Whilst this is encouraging, only 61 countries have enrolled in the Global Antimicrobial Surveillance System (GLASS) with only a proportion of these submitting data to GLASS on resistance, or consumption data to WHO.

Much more progress around animal, plant and environmental surveillance is required, although steady progress is being achieved on data on antimicrobial usage in animals. Research and policy efforts to tackle AMR may be compromised without these data from both human and non-human sectors. Both axes of monitoring are needed to better understand and for informed AMR interventions and policies.

Note - As this is a self-assessment survey, it is possible that some countries reported progress in a very positive light. However, where joint external evaluations or JEEs have been held, scores have been compared and are broadly consistent with what has been reported in this survey. All countries' responses will be published in an open access database, offering scope for in-country review with civil society and other stakeholders.

Low quality healthcare is increasing the burden of illness and health costs globally: WHO report

The World Health Organization (WHO), Organization for Economic Co-operation and Development (OECD) and the World Bank have jointly prepared a report titled "***Delivering Quality Health Services – a Global Imperative for Universal Health Coverage***[11]" which was released on July 05, 2018. It shows that poor quality health services are holding back progress on improving health in countries at all income levels. The report highlights that sickness associated with poor quality health care imposes additional expenditure on families and health systems.

The report also shows that quality of care in most countries, particularly low- and middle-income countries, is suboptimal, as is revealed by the following examples.

- Adherence to clinical practice guidelines in eight low- and middle-income countries was below 50% in several instances, resulting in low-quality antenatal and child care and deficient family planning. For example, just 28 % of antenatal care, 26% of family planning services and 21% of sick-child care across these countries qualified as 'effective.'
- The Service Delivery Indicators initiative in seven low- and middle-income countries showed significant variation in provider absenteeism (14.3–44.3%), daily productivity (5.2–17.4 patients), diagnostic accuracy (34–72.2%), and, adherence to clinical guidelines (22–43.8%).
- A systematic review of 80 studies showed that suboptimal clinical practice is common in both private and public primary health care facilities in several low and middle-income countries.
- OECD's data from high- and middle-income countries show that 19–53% of women aged 50–69 years did not receive mammography screening, and that 27–73% of older adults (age 65 years and above) did not receive influenza vaccination.

The situation is worst in low and middle-income countries where 10% of hospitalized patients can expect to acquire an infection during their stay, as compared to seven percent in high income countries. This is despite hospital acquired infections being easily avoided through better hygiene, improved infection control practices and appropriate use of antimicrobials. At the same time, one in ten patients is harmed during medical treatment in high income countries.

There has been some progress in improving quality, for example in survival rates for cancer and cardiovascular disease. Even so, the broader economic and social costs of poor quality care, including long-term disability, impairment and lost productivity, are estimated to amount to trillions of dollars each year[12].

The report describes the essential role of quality in the delivery of health care services. As nations commit to achieving universal health coverage by 2030, there is a growing acknowledgement that optimal health care cannot be delivered by simply ensuring coexistence of infrastructure, medical supplies and health care providers. Improvement in health care delivery requires a deliberate focus on quality of health services, which involves providing effective, safe, people-centered care that is timely, equitable, integrated and efficient.

Building Quality Mechanisms into the Foundations of Health Care Systems

The report outlines the five foundational elements critical to delivering quality health care services are health care workers; health care facilities; medicines, devices and other technologies; information systems; and financing.

11 http://www.who.int/news-room/detail/05-07-2018-low-quality-healthcare-is-increasing-the-burden-of-illness-and-health-costs-globally

12 http://apps.who.int/iris/bitstream/handle/10665/272465/9789241513906-eng.pdf

To ensure that quality is built into the foundations of systems, governments, policy-makers, health system leaders, patients and clinicians should work together to:

- ensure a high-quality health workforce;
- ensure excellence across all health care facilities;
- ensure safe and effective use of medicines, devices and other technologies;
- ensure effective use of health information systems;
- develop financing mechanisms that support continuous quality improvement.

Call for action

The report based on the perspective of OECD, the World Bank and the WHO proposes a way forward for health policy-makers seeking to achieve the goal of access to high-quality, people-centred health services for all. High-level actions are called-for from each of the key constituencies that need to work together with a sense of urgency to enable the promise of the Sustainable Development Goals for better and safer health care to be realized.

1. **All governments should:**

- have a national quality policy and strategy;
- demonstrate accountability for delivering a safe high-quality service;
- ensure that reforms driven by the goal of universal health coverage build quality into the foundation of their care systems;
- ensure that health systems have an infrastructure of information and information technology capable of measuring and reporting the quality of care;
- close the gap between actual and achievable performance in quality;
- strengthen the partnerships between health providers and health users that drive quality in care;
- establish and sustain a professional healthcare workforce with the capacity and capability to meet the demands and needs of the population for high-quality care;
- purchase, fund and commission based on the principle of value;
- finance quality improvement research.

2. **All health systems should:**

- implement evidence-based interventions that demonstrate improvement;
- benchmark against similar systems that are delivering best performance;
- ensure that all people with a chronic disease are enabled to minimize its impact on the quality of their lives;
- promote the culture systems and practices that will reduce harm to patients;
- build resilience to enable prevention, detection and response to health security threats through focused attention on quality;
- put in place the infrastructure for learning;

- provide technical assistance and knowledge management for improvement.

3. **All citizens and patients should:**

- be empowered to actively engage in care to optimize their health status;
- play a leading role in the design of new models of care to meet the needs of the local community;
- be informed that it is their right to have access to care that meets achievable modern standards of quality;
- receive support, information and skills to manage their own long-term conditions.

4. **All health care workers should:**

- participate in quality measurement and improvement with their patients;
- embrace and practice philosophy of teamwork;
- see patients as partners in the delivery of care;
- commit themselves to providing and using data to demonstrate the effectiveness and safety of the care.

Note- While no single actor will be able to effect all these changes, an integrated approach wherein different actors work together to achieve their part will have a demonstrable effect on the quality of health care services around the world.

European Medicines Agency (EMA): Recommends approval of sixteen medicines in its July meeting

The European Medicines Agency's (EMA) Committee for Medicinal Products for Human Use (CHMP) recommended sixteen medicines for approval, including two orphan medicines, three new Biosimilars, three new generic drugs and one hybrid drug, at its July 2018 meeting[13].

A) The sixteen medicines recommended for approval are:

Sl. No.	Name of Medicine	Indicated For	Marketing-Authorisation Holder
1	Braftovi (encorafenib)	In combination with binimetinib is indicated for the treatment of adult patients with unresectable or metastatic melanoma with a BRAF V600 mutation	Pierre Fabre Medicament
2	Ilumetri (tildrakizumab)	Treatment of moderate to severe plaque psoriasis	Almirall S.A.
3	Imfinzi (durvalumab)	Treatment of non-small cell lung cancer	AstraZeneca AB
4	Mektovi (binimetinib)	In combination with encorafenib, is indicated for the treatment of adult patients with unresectable or metastatic melanoma with a BRAF V600 mutation	Pierre Fabre Medicament
5	Onpattro (patisiran)	Treatment of hereditary transthyretin-mediated (hATTR) amyloidosis in adult patients with stage 1 or stage 2 polyneuropathy (a condition in which the peripheral nerves are damaged). - hATTR amyloidosis is an inherited, rare, life-threatening disease. It is caused by mutations in the transthyretin (TTR) gene that result in misfolded TTR proteins accumulating as amyloid fibrils in multiple sites, including the nerves, heart and gastrointestinal tract. Patients with this condition usually have heart problems and symptoms such as muscle weakness in the limbs and, at later stages, inability to walk, problems affecting the stomach and the gut (leading to malnutrition), and bladder dysfunction. hATTR amyloidosis is more frequent in men than women[1].	Alnylam Netherlands B.V.
6	Slenyto (melatonin)	Treatment of insomnia in children from 2 years of age with autism spectrum disorder and Smith-Magenis syndrome (a disorder with a variety of features including intellectual disability, speech and language delay, distinctive facial features, difficulty sleeping and behavioural problems).	RAD Neurim Pharmaceuticals EEC Ltd.
7	**Symkevi (tezacaftor / ivacaftor)**	Treatment of cystic fibrosis	Vertex Pharmaceuticals (Europe) Ltd.
8	**Verzenios (abemaciclib)**	Treatment of locally advanced or metastatic breast cancer	Eli Lilly Nederland B.V.
9	**Xerava (eravacycline)**	Treatment of complicated intra-abdominal infections in adults	Tetraphase Pharmaceuticals Ireland Limited
10	**Deferiprone Lipomed (deferiprone)**	Treatment of iron overload in patients with thalassemia major	Lipomed GmbH
11	**Gefitinib Mylan (gefitinib)**	Treatment of non-small cell lung cancer	Mylan S.A.S.

13 http://www.ema.europa.eu/ema/index.jsp?curl=pages/news_and_events/news/2018/07/news_detail_002994.jsp&mid=WC0b01ac058004d5c1

Sl. No.	Name of Medicine	Indicated For	Marketing-Authorisation Holder
12	**Lenalidomide Accord (lenalidomide)**	Treatment of multiple myeloma	Accord Healthcare Limited
13	**Hulio (adalimumab)**	Treatment of certain inflammatory and autoimmune disorders	Mylan S.A.S
14	**Pelgraz (pegfilgrastim)**	Intended to reduce the duration of neutropenia and the incidence of febrile neutropenia due to chemotherapy	Accord Healthcare Limited
15	**Udenyca (pegfilgrastim)**	Intended to reduce the duration of neutropenia and the incidence of febrile neutropenia due to chemotherapy	ERA Consulting GmbH
16	Kigabeq (vigabatrin)	Treatment of infantile spasms (West's syndrome), an uncommon and severe form of epilepsy associated with a highly-resistant seizure type (epileptic spasms) and a rapid psychomotor regression, and in resistant partial epilepsy, in infants and children from 1 month to 7 years of age[2].	Orphelia Pharma SAS

B) Negative recommendations on new medicines following re-examination

The CHMP's re-examined the negative recommendation for two drugs Dexxience (betrixaban) and Eladynos (abaloparatide). The applicants requested re-examination of the Committee's negative opinions for these medicines adopted at its March 2018 meeting. After considering the grounds for these requests, the CHMP re-examined the initial opinions and confirmed its previous recommendations to refuse the granting of marketing authorizations for these medicines. The applicant for Dexxience is Portola Pharma UK Limited, and for Eladynos applicant is Radius International Ltd.

C) Twelve recommendations on extensions of therapeutic indication

The Committee recommended extensions of indication for twelve medicines - Abseamed, Binocrit, Blincyto, Darzalex, Epoetin alfa Hexal, Kalydeco, Mekinist, Nucala, Tafinlar, Xarelto and two extensions of indication for Keytruda.

D) Negative opinions on extension of therapeutic indication

The CHMP adopted a negative opinion for the use of Opdivo (nivolumab) and Yervoy (ipilimumab) in combination to treat renal cell carcinoma (kidney cancer). The Committee also adopted a negative opinion for an extension of therapeutic indication for Blincyto in patients with minimal residual disease after treatment for B-precursor acute lymphoblastic leukaemia.

E) Outcome of review on Xofigo

The CHMP recommended restricting the use of Xofigo (radium-223 dichloride) in patients who have had two previous treatments for metastatic prostate cancer or who cannot receive other treatments.
Xofigo must also not be used with the medicines Zytiga (abiraterone acetate) and the corticosteroid prednisone or prednisolone. Xofigo should not be used with other systemic cancer therapies, except for treatments to maintain reduced levels of male hormones (hormone therapy). The medicine should also not be used in patients who have no symptoms, in line with the current indication; in addition, the use of Xofigo is not recommended in patients with a low number of bone metastases called osteoblastic bone metastases[14].

F) Withdrawals of applications

Raligize (axalimogene filolisbac) - The application for an initial marketing authorisation for Raligize (axalimogene filolisbac) was withdrawn. This medicine was intended to be used for the treatment of cervical cancer.

Opdivo (nivolumab) - Application to extend the use of Opdivo (nivolumab) to the treatment of stomach cancer has been withdrawn.

14 http://www.ema.europa.eu/ema/index.jsp?curl=pages/news_and_events/news/2018/07/news_detail_002996.jsp&mid=WC0b01ac058004d5c1

Sutent (sunitinib) - Application to extend the use of Sutent (sunitinib) to treat patients at high risk of kidney cancer returning after surgery has also been withdrawn.

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 whether 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 centralised marketing authorisation is valid in all EU Member States as well as in the countries in European Economic Area namely Iceland, Liechtenstein and Norway.

USFDA approves TPOXX, the first drug for the treatment of smallpox

On July 13, 2018, the United States Food and Drug Administration (USFDA) approved TPOXX (tecovirimat), the first drug for treatment of smallpox[15]. Though the World Health Organization declared smallpox, a contagious and sometimes fatal infectious disease, eradicated in 1980, there have been longstanding concerns that smallpox could be used as a bioweapon.

The approval is based on data from 12 clinical trials of oral TPOXX in over 700 healthy human volunteers, which showed no drug-related serious adverse events. Four pivotal trials in non-human primates (NHPs) and two pivotal trials in rabbits demonstrated that TPOXX significantly reduced both mortality and viral load in NHP infected with monkeypox virus (MPXV) and in rabbits infected with rabbitpox virus[16]. TPOXX was approved under the FDA's Animal Rule, which allows efficacy findings from adequate and well-controlled animal studies to support an FDA approval when it is not feasible or ethical to conduct efficacy trials in humans.

The FDA granted approval of TPOXX to SIGA Technologies Inc. The FDA also granted Fast Track designation, priority review designations, and Orphan Drug designation to TPOXX.

TPOXX was developed in conjunction with the U.S. Department of Health and Human Services' Biomedical Advanced Research and Development Authority (BARDA). TPOXX will be available initially only through the U.S. Government's Strategic National Stockpile (SNS). SIGA has a $472 million procurement and development contract with BARDA, as part of which 2 million courses of oral TPOXX have been delivered to the SNS. Currently, there is a Request for Proposal outstanding for the maintenance of a smallpox antiviral stockpile within the SNS. SIGA intends to explore additional markets and potential indications for TPOXX in the United States and around the world.

About TPOXX (Tecovirimat)

TPOXX®, also known as tecovirimat and ST-246®, an orally administered and IV formulation antiviral drug for the treatment of human smallpox disease caused by variola virus. Tecovirimat inhibits an orthopoxviral protein that is required for the exit of enveloped virions from the infected cell; this block in virus release is sufficient to halt the spread of infection until the body's immune system can clear the virus. Tecovirimat is formulated as immediate release capsules to be taken at a dose of 600 mg twice daily with a meal for 14 days[17].

About Smallpox

Smallpox is a contagious, disfiguring and often deadly disease that has affected humans for thousands of years. Naturally-occurring smallpox was eradicated worldwide by 1980, the result of an unprecedented global immunization campaign. Samples of smallpox virus have been kept for research purposes. This has led to concerns that smallpox could someday be used as a biological warfare agent. No cure or treatment for smallpox exists. A vaccine can prevent smallpox, but the risk of the vaccine's side effects is too high to justify routine vaccination for people at low risk of exposure to the smallpox virus.

15 https://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm613496.htm

16 https://investor.siga.com/news-releases/news-release-details/us-food-and-drug-administration-approves-siga-technologies

17 https://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/Anti-InfectiveDrugsAdvisoryCommittee/UCM605890.pdf

USFDA continues taking key actions on regulating safety of compounded drugs to protect public health

On July 23, 2018, the U.S. Food and Drug Administration (USFDA) announced several actions to protect public health related to the compounding of human drug products, as part of its ongoing implementation of the *Drug Quality and Security Act* and to advance the goals of its *2018 Compounding Policy Priorities Plan*[18]. The key steps regarding its approach to bulk drug substances that are used to make compounded drugs are:

1. Risk alert and citizen petition on Cesium chloride compounding

The FDA issued a compounding risk alert to warn health care providers, compounders and patients of the dangers of using the bulk drug substance cesium chloride. Cesium chloride is sometimes used by cancer patients despite never having been proven safe and effective for any use. Serious adverse events associated with the use of Cesium chloride and other Cesium salts include abnormal heart rhythms (arrhythmias), low potassium (hypokalemia), seizures, fainting (syncope), cardiac arrest and death.

The FDA is also announcing that it intends to move Cesium chloride to category 2 under the FDA's interim policy on compounding with bulk drug substances under section 503A. Under the interim policy, a bulk drug substance placed in category 2 raises significant safety risks in compounding and is not subject to the FDA's enforcement policy on compounding with the bulk drug substance while the FDA is formally evaluating that substance for use in compounding through the rulemaking process.

2. Collaborations with universities on bulks list projects

The FDA is announcing two new research collaborations to support its goal of developing the list of bulk drug substances that can be compounded under section 503B and to help inform public for understanding of the use of bulk drug substances in compounding. The FDA is collaborating with the University of Maryland and Johns Hopkins University, two of the agency's Center of Excellence in Regulatory Science and Innovation (CERSI) partners, to gather and analyze information important for developing the list of bulk drug substances that may be used in compounding.

- The University of Maryland will be working closely with medical specialty groups and researching information about the use of drug products including certain bulk drug substances historically and in current clinical practice.
- The Johns Hopkins University will systematically study available safety and effectiveness information on certain bulk drug substances for use in compounding drug products for patients with autism spectrum disorder.

These projects will help inform the FDA's regulatory decision-making, including whether to place the evaluated substances on the list of bulk drug substances that outsourcing facilities can use in compounding under section 503B, and help promote public awareness and understanding.

3. Bulks category updates

The FDA has developed interim policies on the use of bulk drug substances in compounding while the 503A and 503B bulks lists are being developed through procedures involving notice and comment. Under these interim policies, the FDA does not intend to object to compounding with a bulk drug substance if it meets certain conditions including being nominated with adequate supporting information for the FDA to evaluate it and it

18 https://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm614281.htm

not having been identified by the agency as a substance that presents significant safety risks. The FDA is currently updating the categories of substances that are subject to its interim policies on compounding with bulk drug substances:

- Category 1 – These substances may be eligible for inclusion on the 503B bulks list, were nominated with sufficient information for FDA to evaluate them, and do not appear on any other list. FDA does not intend to take action against an outsourcing facility for compounding drugs using bulk drug substances identified in Category 1 provided that the conditions described in the guidance document are met.
- Category 2 – These are bulk drug substances that were nominated with sufficient supporting information for FDA to evaluate them, but FDA has identified significant safety risks relating to the use of these substances in compounding pending further evaluation. Drug products compounded using these substances are not eligible for the policy described for the substances in Category 1. FDA would consider taking action against an outsourcing facility for compounding drug products with this bulk drug substance under its general enforcement policies.
- Category 3 – These substances may be eligible for inclusion on the 503B bulks list but were nominated with insufficient supporting information for FDA to evaluate them. The substances are not eligible for the policy that applies to substances in Category 1. FDA would consider taking action against an outsourcing facility for compounding drug products with any of these bulk drug substances under its general enforcement policies. These bulk drug substances can be re-nominated with sufficient supporting information through Bulk Drug Substances That Can Be Used To Compound Drug Products in Accordance With Section 503B of the Federal Food, Drug, and Cosmetic (FD&C) Act; Establishment of a Public Docket[19].

The FDA designed its interim policies to avoid unnecessary disruptions to any patient treatment. During this interim period, the FDA will continue to restrict compounding of essentially copies of FDA-approved products. If the FDA encounters such compounding during an inspection or otherwise, the agency intends to take action, such as issuing a warning letter or pursuing an injunction.

4. Pharmacy Compounding Advisory Committee Meeting

To continue to seek public input on its policies around compounding, the ninth Pharmacy Compounding Advisory Committee meeting is scheduled for September 12, 2018. The committee will discuss six bulk drug substances that were nominated for use in compounding by 503A facilities: alpha lipoic acid, coenzyme Q10, creatine monohydrate, pyridoxal 5 phosphate, choline chloride and quercetin dihydrate. The FDA is dedicated towards developing the framework for evaluating bulk drug substances and will continue to update the public on the progress being made in the coming months.

Note – Compounded drugs are not FDA-approved. This means that FDA does not review these drugs to evaluate their safety, effectiveness, or quality before they reach patients. In 2012, contaminated drugs compounded by a Massachusetts pharmacy led to more than 750 cases of infection and more than 60 deaths of patients in 20 states. Since then, FDA has taken many steps and planning more in future as a part of its ongoing implementation of the Drug Quality and Security Act and to advance the goals of its 2018 Compounding Policy Priorities Plan for public safety.

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19 https://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/PharmacyCompounding/ucm614205.htm?utm_campaign=CDER%20New%207%2F24&utm_medium=email&utm_source=Eloqua&elqTrackId=1370c75f590d42738d6e6c5fb0bd48b6&elq=39ef471f20ce4bd29819bfd383f2aaa6&elqaid=4372&elqat=1&elqCampaignId=3450

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