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Vol. II, Issue VI
June 2018

S&A PHARMA NEWSLETTER

EDITORIAL

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Founding Partner

It gives us immense pleasure to present Vol. II Issue VI 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 extent and implications of Competition Commission of India's conditional approval to acquisition of Monsanto Company by Bayer in India, after reviewing its market competition in the country under Competition Act, 2002. This issue then, covers the release of special Sample Registration System report on Maternal Mortality in India 2014-2016, which suggests a significant decline in Maternal Mortality Ratio in the country since 2013; followed by an article on release of Central Tuberculosis Division's clarification on mandatory Tuberculosis notification by pharmacist/ chemist.

From the international arena, we talk about recent developments qua regulatory authorities of foreign jurisdictions. First, we discuss Strides Shasun's Rectal Artesunate capsule getting WHO pre-qualification for pre-referral management of severe malaria; followed by the launch of a new secure online portal 'IRIS' by European Medicines Agency for orphan designation for a medicine, which provides a single platform to submit and manage the information and documents related to Orphan Designation process. Next, we have a review on EMA's Committee for Medicinal Products for Human Use June 2018 meeting, where the committee recommended approval of nine medicines, including first two CAR-T cell therapies and six orphan medicines in European Union (EU). Further, we provide highlights from the World Health Organization's (WHO) released new International Classification of Diseases, which is an advance preview that will allow member countries to plan its usability and adaptability, prepare translations, and train health professionals all over the country.

We wrap up this newsletter with write-ups like (i) United States Food and Drug Administration approval to Epidiolex (cannabidiol) oral solution for the treatment of seizures associated with two rare and severe forms of epilepsy (ii) USFDA advancement on Patient-Focused Drug Development and regulatory decision-making by releasing a draft guidance for Industry, Food and Drug Administration Staff, and Other Stakeholders.

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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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S&A Pharma Newsletter
Volume II, Issue VI
June 2018

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CCI approves conditional acquisition of Monsanto by Bayer

The Competition Commission of India (CCI) is an administrative or regulatory body formed under the Competition Act 2002 (as amended vide Competition (Amendment) Act 2007, and hereinafter referred to as the 'Act"). The objective of the Act is to prohibit anti-competitive agreements, abuse of dominant position by enterprises, and to regulate combinations/merger & acquisition of enterprises likely to cause an appreciable adverse effect on market competition in the country.

On August 7, 2017, the Competition Commission of India (Commission) received a notice from Bayer Aktiengesellschaft (Bayer) in relation to its proposed acquisition of Monsanto Company (Monsanto). Bayer, the acquirer, is a German stock corporation and is a life sciences company with competencies in areas of healthcare and agriculture. The activities of Bayer are carried out in three main portfolios viz. pharmaceuticals, consumer health, and crop sciences. Monsanto is a global supplier of agricultural products like seeds, biotechnology traits, and herbicides.

CCI's decision

On June 14, 2018, CCI, based on its investigation, opined that the proposed combination is likely to have an appreciable adverse effect on competition in some markets in India but the same could be addressed by way of modifications to the proposed combination. Accordingly, the Commission approved the proposed combination under Section 31(7) of the Competition Act, 2002, subject to some remedies to be implemented by the parties[1]

Approval of acquisition with condition

The CCI has asked for divestment of the following businesses of Bayer, to an independent entity, which meets the parameters prescribed in the order of the Commission[2]:

I. Glufosinate ammonium (a non-selective herbicide); Crop traits of cotton and corn; and Hybrid seeds of vegetables,

II. Divestment of the shareholding of Monsanto in Maharashtra Hybrid Seed Company Limited (26%), to an independent entity, which meets the parameters prescribed in the order of the Commission.

In addition to the above divestment, Bayer is also bound by the following commitments for a period of 7 (seven) years from the closing of the Bayer/Monsanto transaction:

I. The resultant entity of the combination (Combined Entity) should follow a policy of broad based, non-exclusive licensing of Genetically Modified (GM) as well as non-GM traits currently commercialized in India or to be introduced in India in the future, on a fair, reasonable and non-discriminatory terms (FRAND Terms);

II. The Combined Entity to follow a policy of non-exclusive licensing of non-selective herbicides and / or their active ingredient(s) in case of launch of new GM / non-GM traits in India that restrict agricultural producers including farmers to use specific non-selective herbicide(s) being supplied only by the parties, on a fair, reasonable and non-discriminatory basis;

III. Combined entity to allow Indian users / potential licensees to access the following on FRAND Terms:

   a) Existing Indian agro-climatic data owned and used by the Combined Entity for its digital applications commercialized in India;

1 http://pib.nic.in/PressReleseDetail.aspx?PRID=1536060

2 https://www.cci.gov.in/sites/default/files/Notice_order_document/Order_14.06.2018.pdf

b) Commercialized digital farming platform(s) of the Combined Entity for supplying/selling agricultural inputs to agricultural producers in India; and

c) Digital farming applications of the Combined Entity, commercialized in India, on subscription basis. This remedy to operate for a period of 7 years from the commencement of commercialization of digital farming product(s) or digital farming platform(s), subject to a total period of 10 years from the closing of the combination.

IV. Combined Entity would also grant access to Indian agro-climatic data, free of charge to Government of India and its institution(s), to be used exclusively for public good in India.

V. Combined Entity is barred from offering its clients, farmers, distribution channels and/or its commercial partners, two or more products as a bundle which may potentially have the effect of excluding any competitor.

VI. Combined Entity is further barred from imposing, directly or indirectly, commercial dealings capable of causing exclusivity in the sales channel for supply of agricultural products.

The Commission further ensured in its order, that in case the Combined Entity offers better commercial terms to a new licensee for any of the above licenses, then it would be bound to offer, within 60 days, such similar terms to all existing licensees.

Bayer is also directed to disclose, on its Indian websites, all contact details to facilitate the implementation of remedies ordered by the Commission. The remedies ordered by the Commission will strengthen the agricultural input suppliers in India, by enabling innovation and launch of new products for the benefit of the farmers.

Note - The Bayer-Monsanto combination has already been approved by other countries like the European Union, Russia, Mexico, Brazil China, and U.S.A. Now with this combination, Bayer will become the global leader in agribusiness, especially with the agriproducts like seeds, biotechnology traits, agrochemicals and herbicides.

India achieves groundbreaking success in reducing maternal mortality

The Office of the Registrar General, India, under the Ministry of Home Affairs, has released special Sample Registration System (SRS) Bulletin on *Maternal Mortality in India 2014-2016*[3]. According to the SRS Bulletin, India registered a significant decline in Maternal Mortality Ratio, with 22% reduction in maternal mortality since 2013. This significant decline means that every month nearly one thousand fewer women now die of pregnancy related complications in India. SRS is the largest demographic sample survey in the country, that among other indicators, provides direct estimates of maternal mortality through a nationally representative sample.

According to the SRS Bulletin, there were nearly 12,000 fewer maternal deaths in 2016 as compared to 2013, with the total number of maternal deaths for the first time reducing to 32,000. This effectively means that every day, as compared to 2013, 30 more pregnant women are now being saved in India.

Amongst the States, Uttar Pradesh with 30% decline has topped the chart in the reduction of Maternal Deaths. Three states have already met the SDG target for MMR of 70 per 100,000. These are Kerala, Maharashtra and Tamil Nadu, while Andhra Pradesh and Telangana are within striking distance[4].

WHO commends India for its groundbreaking progress in recent years, in reducing the maternal mortality ratio (MMR) by 77% - from 556 per 100 000 live births in 1990 to 130 per 100 000 live births in 2016. India's present MMR is below the Millennium Development Goal (MDG) target and puts the country on track to achieve the Sustainable Development Goal (SDG) target of an MMR below 70 per 100 000 live births by 2030. WHO also described the four key actions that are responsible for India's remarkable achievement:[5]

1. **Access to quality maternal health services** - Since 2005, coverage of essential maternal health services has doubled, while the proportion of institutional deliveries in public facilities has almost tripled, from 18% in 2005 to 52% in 2016 (including private facilities, institutional deliveries now stand at 79%).

2. **State-subsidized demand-side financing** - Schemes like the Janani Shishu Suraksha Karyakram entitle all pregnant women delivering in public health institutions, to free transport and no-expense delivery, including caesarian section. Overall, 75% of rural births are now supervised, as compared to 89% of urban deliveries.

3. **Social factors contributing to maternal health** - Women in India are more literate than ever, with 68% now able to read and write. They are also entering marriage at an older age, with just 27% now married before the age of 18. These factors alone have enabled Indian women to better control their reproductive lives and make decisions that reflect their own interests and wants.

4. **Government determinations** - Government has put substantial efforts in facilitating positive engagement between public and private health care providers. Campaigns such as the Pradhan Mantri Surakshit Matritva Abhiyan have been introduced with great impact, allowing women access to antenatal check-ups, obstetric gynecologists and in tracking high-risk pregnancies.

3 http://www.censusindia.gov.in/vital_statistics/SRS_Bulletins/MMR%20Bulletin-2014-16.pdf

4 http://www.who.int/pmnch/media/news/2018/pregnancy-related-complications-india/en/

5 http://www.searo.who.int/mediacentre/features/2018/india-groundbreaking-sucess-reducing-maternal-mortality-rate/en/

Conclusion:

The report shows that the strategic approach of the Indian Government, if continued, will surely help to achieve the Sustainable Development Goal (SDG) target of an MMR below 70 per 100 000 live births by 2030. It would require a focused effort in low-scoring states without any delay.

Central Tuberculosis (TB) division releases FAQs on mandatory TB notification for chemists/pharmacies

The Ministry of Health and Family Welfare (MoH&FW), on March 16, 2018, has notified that tuberculosis is a dangerous epidemic disease, a threat to life and is a major public health problem accounting for substantial morbidity and mortality in the country. Early diagnosis and complete treatment of tuberculosis is the corner-stone of tuberculosis prevention and control strategy. Further, inappropriate diagnosis and irregular or incomplete treatment with anti-tubercular drugs may contribute to complications, spread of disease and emergence of drug-resistant tuberculosis.

However, the said notice also announced mandatory TB reporting measures, where all health care providers treating TB patients, and all pharmacies/chemists/druggists dispensing anti-tubercular medicines, shall notify every TB case they find and treat, to the public health departments. The notification further suggested patients to self-notify themselves with their own details and that of treating medical practitioners[6].

On June 13, 2018, the Central Tuberculosis (TB) division has released Frequently Asked Questions (FAQs) on mandatory TB notification for easy reporting practice for Chemists/ Pharmacies[7]:

Is online submission of information mandatory for pharmacies/chemists & druggists?

Submission of information is mandatory; either electronically (online) or in hard copy (paper based). Modalities of reporting of information can be any of the following:

- Hard copy by post, courier or by hand to the nodal officer
- Electronic copy by email from persons / institutes authorized for this purpose to the nodal officer
- Uploading of information directly on to the Nikshay portal - http://nikshay.gov.in
- Using authorized mobile numbers by phone call on 1800 11 6666
- Direct online information transmission from laboratory or hospital MIS to NIKSHAY

The patient or his relative does not want to disclose their name & identity. How to notify such TB patients?

It is estimated that a TB patient, if left untreated, can spread the infection to at least 10-15 persons in a year. Hence, in case of TB, the concerned public health authorities should be informed immediately. Moreover, the information remains secured within the TB Notification system – NIKSHAY of the Government of India. Only authorized users of Nikshay, on behalf of 'Revised National TB Control Program (RNTCP), will have access to the information on patient for ensuring public health measures (to support TB patients in ensuring cure from the disease and prevent spread of the disease) as mentioned in section 5 of the Gazette. The information will not be shared outside the RNTCP and health officials. Confidentiality of the data gathered will be ensured as per EHR/ EMR standards and IT Act 2000 of Government of India & its amendment 2008.

6 http://www.egazette.nic.in/WriteReadData/2018/183924.pdf

7 https://tbcindia.gov.in/showfile.php?lid=3328

Patient and their relatives are not ready to provide detailed residential address, their ID & Mobile or Telephone Number. How to provide this information in such instances?

TB is a communicable disease and it is estimated that, if left untreated, a TB patient can spread the infection to at least 10-15 persons in a year. Hence, TB patients should be treated at the earliest and certain public health measures like contact investigation, chemoprophylaxis for the households, treatment support (if required), nutrition support, comorbidity testing and drug susceptibility testing need to be undertaken in order to ensure complete cure. To deliver this, the public health system needs at least the mobile number and residential address of the patient. Moreover, Government of India has recently initiated a scheme which provides the TB patients Rs. 500/- per month for nutrition support through Direct Benefit Transfer (DBT) for the duration of treatment. To provide this support, contact details of TB patients are essential. Mobile number is particularly useful in contacting the patient and informing him before reaching-out to him.

It is difficult to do photocopy of every anti-TB prescription, when electricity is not regular in villages. How to get records of such patients who even bring prescription?

As per the Drug and Cosmetic Rule, 1945, the supply of a drug specified in Schedule H1 shall be recorded in a separate register. Anti-TB drugs have been specified under the Schedule H1. Photograph of prescription can also be taken which later on can be printed or preserved as electronic copy.

How to report on monthly basis from remote villages where there are issues related to internet availability, courier or post services?

Reporting of anti-TB drug sale is desirable to be sent from pharmacies on monthly basis to DTO and Drug Inspector. In case of unavailability of communication measures, public health staff can support collection of such reports in consultation with DTO / Drug inspector.

If Doctor notifies TB patient at the time of prescribing medicine, why are pharmacies asked to provide information?

The Gazette mandates health facility, pharmacy and laboratories to notify each TB patient at the earliest. Accordingly, the health facility/doctor will notify TB patients. But, in case it does not happen, the Government cannot afford to lose any TB patients from being notified, as it is a public health responsibility to prevent the spread of disease in the community. Those health facilities/ doctors who are not notifying TB patients will attract the Gazette provisions and it will be ensured that health facility notifies at diagnosis. Moreover, there are now incentives for notification of TB patient, which will be provided to the provider (doctor / chemist / laboratory) whoever notifies the TB patient.

Do pharmacies have to or don't have to retain the original, or a photocopy of the prescription of the doctor?

As per the Drugs and Cosmetic Act, 1940, it is mandatory for pharmacies to keep a copy of prescription of drugs covered under Schedule H1 in a separate record and such record should be maintained for three years and be available for inspection. As per Drugs and Cosmetic Rules, 1945, the supply of a drug specified under schedule H1 shall be recorded in a separate register at the time of supply, giving name and address of prescriber, the name of patient, the name of drug and the quantity supplied and such record shall be maintained for three years and be open for inspection.

What all information need to be furnished or to be maintained with regards to TB, by the pharmacies?

Annexure III is the TB notification format for pharmacies. It includes information of medical practitioner who prescribed the anti-TB drugs in addition to TB patient's information, diagnosis and drug dispensing information. Details of the drugs prescribed are to be furnished or maintained as per annexure IV in line with Schedule H1 of Drugs and Cosmetic Rules, 1945. This includes dosages, formations (to be read as formulation) and duration of anti-TB drug dispensed for.

Note - As per the Gazette on mandatory notification of Tuberculosis (TB), it is the duty of the registered pharmacies to divulge the information to the authorized notification official as regards TB which is a notifiable disease in the country. It is estimated that a TB patient, if left untreated, can spread the infection to at least 10-15 persons in a year. Hence, in case of TB, the concerned public health authorities should be informed immediately.

Strides Shasun's Rectal Artesunate capsule gets WHO prequalification

On June 19, 2018, Strides Shasun announced the receipt of prequalification from the World Health Organization (WHO) for their 100mg Rectal Artesunate Suppositories (RAS) for the pre-referral management of severe malaria[8]. This prequalification enables countries to procure life-saving RAS with donor funding, thus ensuring increased access to this potentially life-saving intervention. This prequalification is achieved with support from Medicines for Malaria Venture (MMV) and funding from UNITAID, an international organization that invests in innovations to prevent, diagnose and treat HIV/AIDS, tuberculosis and malaria quickly, affordably and effectively.

Severe malaria is a medical emergency which can kill within 24 hours, if left untreated (particularly cerebral malaria), and travel times to hospital can be long, particularly for children, from remote rural communities. WHO TDR's 2009 study demonstrated that a single dose of RAS 100mg, given as soon as a presumptive diagnosis of severe malaria has been made, can halve the likelihood of disability and death or young patients unable to access WHO-preferred first-line treatment for severe malaria which is injectable artesunate (Inj AS), within 6 hours. After receiving RAS, patients should be referred to a facility where they can receive Injection AS to treat the severe malaria infection, followed by a course of artemisinin combination treatment when they are able to take oral medication[9].

About Rectal Artesunate Suppositories

Rectal Artesunate Suppositories 100 mg is available in the form of soft capsule. In 2005, WHO first recommended the use of RAS for pre-referral management of young children with severe malaria. Until 2018, no RAS product had met international quality standards, leaving countries with limited options to cope with children in need of pre-referral care. WHO prequalification of the Strides' product follows the approval of Cipla's RAS product earlier this year.

About Malaria

Malaria is a life-threatening disease caused by parasites transmitted to people through the bites of infected female Anopheles mosquitoes, called "malaria vectors". There are 5 parasite species that cause malaria in humans, and 2 of these species – P. falciparum and P. vivax – pose the greatest threat.

- P. falciparum is the most prevalent malarial parasite on the African continent. It is responsible for most malaria-related deaths globally.
- P. vivax is the dominant malarial parasite in most countries outside of sub-Saharan Africa.

According to WHO's 2016 report on Malaria, there were 212 million new cases of malaria worldwide in 2015 (range 148–304 million). The WHO African Region accounted for most global cases of malaria (90%), followed by the South-East Asia Region (7%) and the Eastern Mediterranean Region (2%). In 2015, there were an estimated 429,000 malaria deaths (range 235,000–639,000) worldwide. Most of these deaths occurred in the African Region (92%), followed by the South-East Asia Region (6%) and the Eastern Mediterranean Region (2%)[10].

About WHO pre-qualification

WHO prequalification aims to ensure that diagnostics, medicines, vaccines and immunization-related equipment and devices for high burden diseases meet global standards of quality, safety and efficacy, in order to optimize

8 https://extranet.who.int/prequal/medicine/3890

9 http://www.stridesarco.com/pdf/pressrelease/2018/press_release_20180621.pdf

10 http://www.who.int/malaria/media/world-malaria-report-2016/en/

use of health resources and improve health outcomes. The prequalification process consists of a transparent, scientifically sound assessment, which includes dossier review, consistency testing or performance evaluation and site visits to manufacturers[11].

11 http://www.who.int/topics/prequalification/en/

EMA modernizing the orphan designation process

On June 19, 2018, the European Medicines Agency (EMA) launched a new secure online portal for Orphan Designation (OD) applications. The portal, named *'Iris'*, provides a single window where applicants can submit and manage the information and documents related to their applications for orphan designation[12]. This initiative is expected to reduce the time required to prepare and submit the applications. During the review process, applicants can check the status of their applications from any device and receive automatic notifications when the status of the application changes.

About Iris

IRIS is the online web portal through which applicants can apply to the EMA for orphan designation for a medicine. EMA plans to expand the scope of this portal to cover other regulatory and scientific procedures.

This new process, which will become mandatory after September 19, 2018, for procuring orphan designation, requires the following steps to be completed before any activity relating to an orphan designation procedure can be carried out using the new IRIS Portal[13]:

a) Both the Applicant and Sponsor of an orphan designation, or persons acting on their behalf, must have an active EMA user account and must be registered with IRIS user access roles of either 'Orphan Industry Manager' or 'Orphan Industry Contributor.

b) The 'Organization' for which the OD application is being submitted must be registered in the EMA's Organization Management System (OMS);

c) The 'Substance(s)' for which the application is being submitted must be registered and appear on the official EMA list of all substances, the European Union Telematics Controlled Terms (EUTCT) database;

d) Each new OD application must have a Research Product Identifier (RPI) - the process for requesting an RPI will be required before OD application.

About orphan drug designation

The European Medicines Agency (EMA) plays a central role in facilitating the development and authorization of medicines for rare diseases, which are termed 'orphan medicines' in the medical world. The medicine must fulfil following criteria for designation as an orphan medicine so that it can benefit from incentives such as protection from competition once on the market-

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

12 http://www.ema.europa.eu/ema/index.jsp?curl=pages/news_and_events/news/2018/06/news_detail_002976.jsp&mid=WC0b01ac058004d5c1

13 http://www.ema.europa.eu/docs/en_GB/document_library/Regulatory_and_procedural_guideline/2018/06/WC500250762.pdf

Note- In order to help applicants with the transition, EMA has developed two guidance documents. These step-by-step guides provide detailed instructions on how to use the new system and explain what has changed with its introduction.

European Medicines Agency (EMA): Recommends approval of nine medicines in its June meeting

The European Medicines Agency's (EMA) Committee for Medicinal Products for Human Use (CHMP) has recommended nine medicines for approval, including first two CAR-T cell therapies and six orphan medicines, at its June 2018 meeting[14].

A) The nine medicines recommended for approval are:

1. Cablivi (caplacizumab) – for treatment of acquired thrombotic thrombocytopenic purpura (aTTP)

On June 28, 2018, the Committee for Medicinal Products for Human Use (CHMP) adopted a positive opinion, recommending the granting of a marketing authorisation for Cablivi, indicated for the treatment of adults experiencing an episode of acquired thrombotic thrombocytopenic purpura (aTTP), in conjunction with plasma exchange and immunosuppression[15]. Cablivi was designated as an orphan medicinal product on April 30, 2009.

Cablivi will be available as a 10 mg powder and solvent for solution for injection. The active substance in Cablivi is caplacizumab, a humanised bivalent nanobody that inhibits the interaction between von Willebrand factor and platelets (ATC code: B01AX07). As a result, caplacizumab prevents von Willebrand factor-mediated platelet adhesion, which is characteristic of aTTP. It also affects the disposition of von Willebrand factor, leading to transient reductions of total von Willebrand factor antigen levels and to concomitant reduction of factor VIII: C levels during treatment.

The applicant for Cablivi is Ablynx NV.

2. Duzallo (lesinurad / allopurinol) - for treatment of hyperuricaemia in gout patients

On June 28, 2018, the Committee for Medicinal Products for Human Use (CHMP) adopted a positive opinion, recommending the granting of a marketing authorisation for Duzallo, indicated in adults for the treatment of hyperuricaemia in gout patients who have not achieved target serum uric acid levels with an adequate dose of allopurinol alone[16].

Duzallo is a fixed dose combination of two active substances, lesinurad and allopurinol. It will be available as film-coated tablets (300 mg/200 mg and 200 mg/200 mg). Lesinurad is a selective uric acid reabsorption inhibitor that inhibits uric acid transporter 1, and allopurinol reduces uric acid production by inhibition of xanthine oxidase.

The applicant for Duzallo is Gruenenthal GmbH.

3. Kymriah (tisagenlecleucel) – for treatment of acute lymphoblastic leukaemia (ALL) and diffuse large B-cell lymphoma (DLBCL)

On June 28, 2018, the Committee for Medicinal Products for Human Use (CHMP) adopted a positive opinion, recommending the granting of a marketing authorisation for chimeric antigen receptors (CAR) T-cells medicine Kymriah. It is indicated for the paediatric treatment and for treatment of young adult patients (up to 25 years of age) with B-cell ALL that is refractory or in second or later relapse, and in adult patients with relapsed or refractory

14 http://www.ema.europa.eu/ema/index.jsp?curl=pages/news_and_events/news/2018/06/news_detail_002981.jsp&mid=WC0b01ac058004d5c1

15 http://www.ema.europa.eu/docs/en_GB/document_library/Summary_of_opinion_-Initial_authorisation/human/004426/WC500251160.pdf

16 http://www.ema.europa.eu/docs/en_GB/document_library/Summary_of_opinion_-Initial_authorisation/human/004412/WC500251152.pdf

DLBCL after two or more lines of systemic therapy[17]. Kymriah is also one of the first medicines supported through EMA's PRIority MEdicines (PRIME) scheme to receive positive opinions from the CHMP. It was granted PRIME eligibility on June 23, 2016.

Kymriah will be available as a dispersion for infusion. The active substance of Kymriah is tisagenlecleucel, an autologous, immunocellular cancer therapy which involves reprogramming a patient's own T-cells to identify and eliminate CD19-expressing cells. This is achieved by addition of a transgene encoding a chimeric antigen receptor (CAR).

The applicant for Kymriah is Novartis Europharm Limited.

4. Yescarta (axicabtagene ciloleucel) – for the treatment of diffused large cell lymphoma (DLBCL) and primary mediastinal B-cell lymphoma (PMBCL)

On June 28, 2018, the CHMP adopted a positive opinion, recommending the granting of a marketing authorisation for the medicinal product Yescarta, indicated for the treatment of adult patients with relapsed or refractory diffuse large B-cell lymphoma (DLBCL) and primary mediastinal large B-cell lymphoma (PMBCL), after two or more lines of systemic therapy[18]. Yescarta is also one of the first medicines supported through EMA's PRIority MEdicines (PRIME) scheme along with Kymriah to receive positive opinions from the CHMP.

Yescarta will be available as a dispersion for infusion. The active substance of Yescarta is axicabtagene ciloleucel, an autologous, immunocellular cancer therapy which involves reprogramming a patient's own T-cells to identify and eliminate CD19-expressing cells. This is achieved by addition of a transgene encoding a chimeric antigen receptor (CAR).

The applicant for Yescarta is Kite Pharma EU B.V.

5. Mepsevii (vestronidase alfa) – for treatment of mucopolysaccharidosis type VII

On June 28, 2018, the CHMP adopted a positive opinion, recommending the granting of a marketing authorisation for the medicinal product Mepsevii, indicated for the treatment of non-neurological manifestations of Mucopolysaccharidosis VII (MPS VII; Sly syndrome)[19]. Mepsevii was designated as an orphan medicinal product on March 21, 2012.

Mepsevii will be available as 2 mg/ml concentrate for solution for infusion. The active substance of Mepsevii is vestronidase alfa, a recombinant form of human beta-glucuronidase (ATC code: A16AB18). Mepsevii is an enzyme replacement therapy intended to provide or supplement betaglucuronidase, an enzyme that helps with the degradation of glycosaminoglycans and thus prevents their accumulation in various tissues in the body. The benefits with Mepsevii are its ability to reduce glycosaminoglycan levels in the body.

The applicant for Mepsevii is Ultragenyx Germany GmbH.

6. Veyvondi (vonicog alfa) – for treatment of von Willebrand disease

On June 28, 2018, the Committee for Medicinal Products for Human Use (CHMP) adopted a positive opinion, recommending the granting of a marketing authorisation for the medicinal product Veyvondi, indicated in adults (age 18 and older) with von Willebrand disease (VWD), when desmopressin (DDAVP) treatment alone is ineffective

17 http://www.ema.europa.eu/docs/en_GB/document_library/Summary_of_opinion_-Initial_authorisation/human/004090/WC500251211.pdf

18 http://www.ema.europa.eu/docs/en_GB/document_library/Summary_of_opinion_-Initial_authorisation/human/004480/WC500251207.pdf

19 http://www.ema.europa.eu/docs/en_GB/document_library/Summary_of_opinion_-Initial_authorisation/human/004438/WC500251165.pdf

or not indicated for the treatment of haemorrhage and surgical bleeding and prevention of surgical bleeding[20]. Veyvondi was designated as an orphan medicinal product on November 26, 2010.

Veyvondi will be available as a powder and solvent for solution for injection (650 IU and 1300 IU). The active substance of Veyvondi is vonicog alfa, a recombinant human von Willebrand factor which behaves in the same way as endogenous von Willebrand factor (ATC code: B02BD10). The benefits with Veyvondi are its ability to re-establish platelet adhesion to the endothelium at the site of blood vessel damage and to correct associated factor VIII deficiency.

The applicant for Veyvondi is Baxalta Innovations GmbH.

7. Vyxeos (daunorubicin / cytarabine) – for treatment of acute myeloid leukaemia

On June 28, 2018, the CHMP adopted a positive opinion, recommending the granting of a marketing authorisation for the medicinal product Vyxeos, indicated for the treatment of adults with newly diagnosed, therapy-related acute myeloid leukaemia (t-AML) or AML with myelodysplasia-related changes (AML-MRC)[21]. Vyxeos was designated as an orphan medicinal product on January 11, 2012.

Vyxeos is a liposomal formulation of a fixed combination of daunorubicin and cytarabine, antineoplastic agents that inhibit topoisomerase II activity and also cause DNA damage (ATC code: L01XY01). The product will be available as a powder for concentrate for solution for infusion. After reconstitution the solution will contain 2.2 mg/ml of daunorubicin and 5 mg/ml of cytarabine. The benefits of Vyxeos are its ability to increase survival compared to a standard combination of cytarabine and daunorubicin in patients with high-risk AML.

The applicant for Vyxeos is Jazz Pharmaceuticals Ireland Limited.

8. Ulipristal Acetate – for pre-operative treatment of uterine fibroids

On June 28, 2018, the CHMP adopted a positive opinion, recommending the granting of a marketing authorisation for the medicinal product Ulipristal Acetate, indicated for one treatment course as pre-operative treatment of moderate to severe symptoms of uterine fibroids in adult women of reproductive age. In adult women of reproductive age, having moderate to severe symptoms of uterine fibroids but who are not eligible for surgery[22], intermittent treatments with Ulipristal Acetate are indicated.

Ulipristal Acetate Gedeon Richter will be available as 5-mg tablets. The active substance of Ulipristal Acetate Gedeon Richter is ulipristal acetate, a selective progesterone receptor modulator (ATC code: G03XB02) that acts by depriving uterine fibroids of growth stimulation due to progesterone. The benefits with Ulipristal Acetate Gedeon Richter are its ability to reduce fibroid-related bleeding, anaemia and fibroid size.
The applicant for Ulipristal acetate is Gedeon Richter Plc

9. Nerlynx (neratinib) – for adjuvant treatment of adult patients with breast cancer

On June 28, 2018, the Committee for Medicinal Products for Human Use (CHMP), following a re-examination procedure, adopted a positive opinion, recommending the granting of a marketing authorisation for the medicinal product Nerlynx, indicated for the extended adjuvant treatment of adult patients with early-stage hormone receptor - positive HER2-overexpressed/amplified breast cancer and who are less than one year from the completion of prior adjuvant trastuzumab based therapy[23].

20 http://www.ema.europa.eu/docs/en_GB/document_library/Summary_of_opinion_-Initial_authorisation/human/004454/WC500251151.pdf

21 http://www.ema.europa.eu/docs/en_GB/document_library/Summary_of_opinion_-Initial_authorisation/human/004282/WC500251175.pdf

22 http://www.ema.europa.eu/docs/en_GB/document_library/Summary_of_opinion_-Initial_authorisation/human/005017/WC500251150.pdf

23 http://www.ema.europa.eu/docs/en_GB/document_library/Summary_of_opinion_-Initial_authorisation/human/004030/WC500251163.pdf

Nerlynx will be available as 40-mg film-coated tablets. The active substance of Nerlynx is neratinib, an irreversible pan-erythroblastic leukaemia viral oncogene homolog (ERBB) tyrosine kinase inhibitor (ATC code: L01XE45). It blocks mitogenic growth factor signal transduction through covalent, high-affinity binding to the ATP binding site of 3 epidermal growth factor receptors (EGFRs) resulting in sustained inhibition of these growth promoting pathways in breast cancers with HER2-amplified or over- expressed, or which are HER2-mutant. The benefits with Nerlynx are its ability to reduce the risk of invasive disease recurrence after two years compared with placebo.
The applicant for Nerlynx is Puma Biotechnology Limited.

B) Positive recommendations on extensions of indications:

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

Sl.no.	Name of medicine	Full Indication	Marketing-authorisation holder
1	Dexdor (dexmedetomidine)	For sedation of adult ICU (Intensive Care Unit) patients requiring a sedation level not deeper than arousal in response to verbal stimulation (corresponding to Richmond Agitation-Sedation Scale (RASS) 0 to -3). **For sedation of non-intubated adult patients prior to and/or during diagnostic or surgical procedures requiring sedation, i.e. procedural/awake sedation**.	Orion Corporation[1]
2	Inovelon (rufinamide)	Inovelon is indicated as adjunctive therapy in the treatment of seizures associated with Lennox-Gastaut syndrome in patients ~~4~~**1** year of age and older.	Eisai Ltd[2]
3	Jinarc (tolvaptan)	Jinarc is indicated to slow the progression of cyst development and renal insufficiency of autosomal dominant polycystic kidney disease (ADPKD) in adults with CKD stage ~~1 to 3~~ **1 to 4** at initiation of treatment with evidence of rapidly progressing disease.	Otsuka Pharmaceutical Europe Ltd[3]
4	Lenvima (lenvatinib)	LENVIMA is indicated **as monotherapy** for the treatment of adult patients with progressive, locally advanced or metastatic, differentiated (papillary/follicular/Hürthle cell) thyroid carcinoma (DTC), refractory to radioactive iodine (RAI). **LENVIMA is indicated as monotherapy for the treatment of adult patients with advanced or unresectable hepatocellular carcinoma (HCC) who have received no prior systemic therapy.**	Eisai Europe Ltd[4]
5	Opdivo (nivolumab)	- Melanoma: Opdivo as monotherapy or in combination with ipilimumab is indicated for the treatment of advanced (unresectable or metastatic) melanoma in adults. Relative to nivolumab monotherapy, an increase in progression-free survival (PFS) and overall survival (OS) for the combination of nivolumab with ipilimumab is established only in patients with low tumour PD-L1 expression. - **Adjuvant treatment of melanoma - Opdivo as monotherapy is indicated for the adjuvant treatment of adults with melanoma with involvement of lymph nodes or metastatic disease who have undergone complete resection.** - Non-Small Cell Lung Cancer (NSCLC): Opdivo as monotherapy is indicated for the treatment of locally advanced or metastatic non-small cell lung cancer after prior chemotherapy in adults. - Renal Cell Carcinoma (RCC): Opdivo as monotherapy is indicated for the treatment of advanced renal cell carcinoma after prior therapy in adults. - Classical Hodgkin Lymphoma (cHL): Opdivo as monotherapy is indicated for the treatment of adult patients with relapsed or refractory classical Hodgkin lymphoma after autologous stem cell transplant (ASCT) and treatment with brentuximab vedotin. - Squamous Cell Cancer of the Head and Neck (SCCHN) - Opdivo as monotherapy is indicated for the treatment of recurrent or metastatic squamous cell cancer of the head and neck in adults progressing on or after platinum-based therapy. - Urothelial Carcinoma - Opdivo as monotherapy is indicated for the treatment of locally advanced unresectable or metastatic urothelial carcinoma in adults after failure of prior platinum-containing therapy.	Bristol-Myers Squibb Pharma EEIG[5]

Sl.no.	Name of medicine	Full Indication	Marketing-authorisation holder
6	Rapamune (sirolimus)	Rapamune is indicated for the prophylaxis of organ rejection in adult patients at low to moderate immunological risk receiving a renal transplant. It is recommended that Rapamune be used initially in combination with ciclosporin microemulsion and corticosteroids for 2 to 3 months. Rapamune may be continued as maintenance therapy with corticosteroids only if ciclosporin microemulsion can be progressively discontinued. **Rapamune is indicated for the treatment of patients with sporadic lymphangioleiomyomatosis with moderate lung disease or declining lung function.**	Pfizer Limited[6]
7	RoActemra (tocilizumab)	- RoActemra, in combination with methotrexate (MTX), is indicated for: the treatment of severe, active and progressive rheumatoid arthritis (RA) in adults not previously treated with MTX. And the treatment of moderate to severe active RA in adult patients who have either responded inadequately to, or who were intolerant to, previous therapy with one or more disease-modifying anti-rheumatic drugs (DMARDs) or tumour necrosis factor (TNF) antagonists. - RoActemra is indicated for the treatment of active systemic juvenile idiopathic arthritis (sJIA) in patients 2 years of age and older, who have responded inadequately to previous therapy with NSAIDs and systemic corticosteroids. RoActemra can be given as monotherapy (in case of intolerance to MTX or where treatment with MTX is inappropriate) or in combination with MTX. - RoActemra in combination with methotrexate (MTX) is indicated for the treatment of juvenile idiopathic polyarthritis (pJIA; rheumatoid factor positive or negative and extended oligoarthritis) in patients 2 years of age and older, who have responded inadequately to previous therapy with MTX. RoActemra can be given as monotherapy in case of intolerance to MTX or where continued treatment with MTX is inappropriate. - **RoActemra is indicated for the treatment of chimeric antigen receptor (CAR) T-cell-induced severe or life-threatening cytokine release syndrome (CRS) in adults and paediatric patients 2 years of age and older.**	Roche Registration GmbH[7]

C) Withdrawal of initial application

Graspa (L-asparaginase) - On June 22, 2018, Erytech Pharma S.A. officially notified the Committee for Medicinal Products for Human Use (CHMP) that it wishes to withdraw its application for a marketing authorisation for Graspa, for the treatment of acute lymphoblastic leukaemia (ALL)[24].

Graspa is a cancer medicine that contains the active substance L-asparaginase that has been enclosed in red blood cells. Asparaginase has been used to treat cancer for many years and is authorised in EU countries under several trade names. Graspa was intended to be given by infusion (drip) into a vein. In its letter notifying the Agency of the withdrawal of the application, the company stated that the data provided were not sufficient to conclude on Graspa's benefits and risks.

24 http://www.ema.europa.eu/docs/en_GB/document_library/Medicine_QA/2018/06/WC500251169.pdf

WHO releases new International Classification of Diseases (ICD 11)

On June 18, 2018, 18 years after the launch of ICD-10, World Health Organization (WHO) released its new International Classification of Diseases (ICD-11)[25]. ICD-11 will be presented at the World Health Assembly in May 2019 for adoption by Member States and will come into effect on January 01, 2022. This release is an advance preview that will allow countries to plan how to use the new version, prepare translations, and train health professionals all over the country.

About ICD

The International Statistical Classification of Diseases and Related Health Problems (ICD) is the bedrock for health statistics. It maps human condition from birth to death - any injury or disease we encounter in life, and anything we might die of – is coded. Not only that, the ICD also captures factors influencing health, or external causes of mortality and morbidity, providing a holistic look at every aspect of life that can affect health.

Crucially, in a world of 7.4 billion people speaking nearly 7000 languages, the ICD provides a common vocabulary for recording, reporting and monitoring health problems. Fifty years ago, it would have been unlikely for a disease such as schizophrenia to be diagnosed similarly in Japan, Kenya and Brazil. Now, however, if a doctor in another country cannot read a person's medical records, they will still know the medical condition by virtue of knowing what the ICD code means. The ICD is also used by health insurers whose reimbursements depend on ICD coding; national health programme managers; data collection specialists; and others who track progress in global health and determine the allocation of health resources.

ICD 11[26]

Over a decade in the making, this version is a vast improvement on ICD-10; contains around 55 000 unique codes for injuries, diseases and causes of death.

- First, it has been updated for the 21st century and reflects critical advances in science and medicine.
- Second, it can now be well integrated with electronic health applications and information systems. This new version is fully electronic, significantly easier to implement which will lead to fewer mistakes, allows more details to be recorded, all of which will make the tool much more accessible, particularly for low-resource settings.
- A third important feature is that ICD-11 has been produced through a transparent, collaborative manner, the scope of which is unprecedented in its revision history. An overriding motive in this revision was to make the ICD easier to use.

The new ICD also includes new chapters on:

- Traditional medicine - although millions of people use traditional medicine worldwide, it has never been classified in this system. This will help in recording epidemiological data about disorders described in ancient Chinese medicine, commonly used in China, Japan, Korea, and other parts of the world.
- New chapter on sexual health conditions that were previously categorized in other ways or described differently. For example, in the ICD 11 Gender incongruence has been moved out from mental disorders to be included in sexual health conditions. The rationale being that while evidence is now clear that it is

25 http://www.who.int/health-topics/international-classification-of-diseases

26 http://www.who.int/classifications/icd/en/

not a mental disorder, and indeed classifying it as such causes enormous stigma to people who are transgenders, significant health care needs remain that can best be met if the condition is coded under the ICD.

- Disorders - For the first time, WHO is classifying Gaming Disorder as an addictive behavior disorder, which evidence shows is enough of a health problem that it requires tracking through the ICD. Other addictive behaviors such as hoarding disorder are now included in ICD-11, and conditions such as 'excessive sexual drive' have been reclassified as 'compulsive sexual behaviour' disorder.

Disease trends and the biggest killers

The data captured through ICD codes is of huge importance for countries. It allows for the mapping of disease trends and causes of death around the world, which are key indicators for the health of a population and also the social determinants that link closely to health, such as education, nutrition, and public infrastructure - in short, a snapshot of where a country's vulnerabilities lie. For example, a country in which people live in crowded, inadequate housing with no clean water are inevitably likely to have a higher incidence of diarrheal disease.

Mortality data in the Global Health Observatory shows that while ischemic heart disease and stroke are the top two killers worldwide, together accounting for 15 million deaths in 2015, zooming into the statistics by continent can show radically different pictures. In Africa, lower respiratory infections and HIV/AIDS cause the most deaths, whereas violence is one of the top 10 causes of death in the region of the Americas and the Eastern Mediterranean region.

Note - ICD-11 is linked to the WHO non-proprietary names of pharmaceutical products, and it can be used for cancer registration. ICD-11 has been designed to be used in multiple languages, a central translation platform ensures that its features and outputs are available in all translated languages. Transition tables from and to ICD-10 support migration to ICD-11. WHO will support countries as they move towards implementation of the new ICD-11[27].

27 http://www.who.int/news-room/detail/18-06-2018-who-releases-new-international-classification-of-diseases-(icd-11)

USFDA approves first marijuana derived drug - Epidiolex - to treat rare and severe forms of epilepsy

On June 25, 2018, the U.S. Food and Drug Administration approved Epidiolex (cannabidiol) oral solution for the treatment of seizures associated with two rare and severe forms of epilepsy (namely Lennox-Gastaut syndrome and Dravet syndrome) in patients two years of age and older[28]. This is the first FDA-approved drug that contains a purified drug substance derived from marijuana. It is also the first FDA approval of a drug for the treatment of patients with Dravet syndrome.

The EPIDIOLEX clinical development program included three randomized, controlled Phase 3 clinical trials and an open-label extension study. Epidiolex's effectiveness was studied in three randomized, double-blind, placebo-controlled clinical trials involving 516 patients with either Lennox-Gastaut syndrome or Dravet syndrome. Epidiolex, taken along with other medications, has shown to be effective in reducing the frequency of seizures when compared with placebo.

The FDA granted Priority Review designation for this application. Fast-Track designation was granted for Dravet syndrome. Orphan Drug designation was granted for both the Dravet syndrome and Lennox-Gastaut syndrome indications. Outside the U.S., this medicine is currently under review by the European Medicines Agency (EMA) for the treatment of seizures associated with LGS and Dravet Syndrome. An EMA decision on whether to recommend approval is expected in the first quarter of 2019.

The FDA granted approval of Epidiolex to GW Research Ltd. EPIDIOLEX will be marketed in the U.S. by Greenwich Biosciences, the U.S. subsidiary of GW Pharmaceuticals plc[29].

About EPIDIOLEX

EPIDIOLEX, the first prescription, plant-derived cannabinoid medicine in the United States and the first in a new class of anti-epileptic medications, is a pharmaceutical formulation of pure cannabidiol (CBD), is now FDA-approved for the treatment of seizures associated with Lennox-Gastaut syndrome (LGS) or Dravet syndrome in patients two years of age or older. Cannabidiol is a chemical component of the Cannabis sativa plant, more commonly known as marijuana. However, CBD does not cause intoxication or euphoria (the "high") that comes from tetrahydrocannabinol (THC). It is THC (and not CBD) that is the primary psychoactive component of marijuana. Under the Controlled Substances Act (CSA), CBD is currently a Schedule I substance because it is a chemical component of the cannabis plant. In support of this application, the company conducted nonclinical and clinical studies to assess the abuse potential of CBD, and has provided recommendations to the Drug Enforcement Administration (DEA) regarding controls under the CSA. DEA is required to make a scheduling determination.

About Dravet Syndrome

Dravet syndrome is a rare genetic condition that appears during the first year of life with frequent fever-related seizures (febrile seizures). Later, other types of seizures typically arise, including myoclonic seizures (involuntary muscle spasms). Additionally, status epilepticus, a potentially life-threatening state of continuous seizure activity requiring emergency medical care, may occur. Children with Dravet syndrome typically experience poor development of language and motor skills, hyperactivity and difficulty relating to others.

28 https://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ ucm611046.htm

29 http://ir.gwpharm.com/news-releases/news-release-details/gw-phar maceuticals-plc-and-its-us-subsidiary-greenwich

About Lennox-Gastaut syndrome

Lennox-Gastaut syndrome begins in childhood. It is characterized by multiple types of seizures. People with Lennox-Gastaut syndrome begin having frequent seizures in early childhood, usually between ages 3 and 5. More than three-quarters of affected individuals have tonic seizures, which cause the muscles to contract uncontrollably. Almost all children with Lennox-Gastaut syndrome develop learning problems and intellectual disability. Many also have delayed development of motor skills such as sitting and crawling. Most people with Lennox-Gastaut syndrome require help with usual activities of daily living.

USFDA advances on Patient-Focused Drug Development and regulatory decision-making

USFDA is requesting feedback/comments on draft Guidance from Industry, Food and Drug Administration Staff, and Other Stakeholders

On June 12, 2018, USFDA released the draft guidance on 'Patient-Focused Drug Development: Collecting Comprehensive and Representative Input[30]' for Industry, Food and Drug Administration Staff, and Other Stakeholders. This guidance is the first of four methodological Patient-Focused Drug Development (PFDD) guidance documents that FDA is developing to address in a stepwise manner, how stakeholders (patients, researchers, medical product developers and others) can collect and submit patient experience data and other relevant information from patients and caregivers for medical product development and regulatory decision making. Focusing on practical approaches and methods, this series will inform stakeholders of FDA's current thinking about methods that could be used as a bridge from important early-stage efforts to gain patients' narrative perspectives on the clinical context (e.g., meetings with patients), to development and use of methodologically-sound data collection tools in clinical trials.

These guidance documents will also address agency expectations regarding what sort of analyses might be conducted as part of this work and what sort of documents might be produced, and when appropriate, submitted to FDA.

The topics and questions that each guidance document will address are described below.

Guidance 1: Whom do you get input from, and why? How do you collect the information?

Guidance 1 will discuss sampling methods that could be used when planning to collect patient input. It will also provide a general overview of the relationship between potential research question(s) and method(s) when deciding from whom to get input (including defining the target population and development of the sampling strategy).

Guidance 2: What do you ask, and why? How do you ask non-leading questions that are well understood by a wide range of patients and others?

Guidance 2 will discuss methods for eliciting information from individuals identified in Guidance 1, gathering information about which aspects of symptoms, impacts of their disease, and other issues important to patients. It will discuss best practices in how to do qualitative research including conducting interviews, development of interview guides, selection of types of survey questions, and considerations for collecting demographics and survey information. It will also discuss survey methods and qualitative research topics to help avoid misleading results such as inadvertently priming patients in ways that can lead to results that poorly represent what is important to patients.

Guidance 3: How do you decide what to measure in a clinical trial and select or develop fit-for purpose clinical outcome assessments (COAs)?

Guidance 3 will address refining the list of important impacts and concepts from patients to develop potential study instruments. Given that not everything identified as important by patients, caregivers, and clinicians can demonstrate change in a specific treatment trial or is measurable, how to select what to measure in a medical

30 https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegula toryInformation/Guidances/UCM610442.pdf

product development program to show clinical benefit? How to identify or develop fit-for-purpose COAs to assess outcomes of importance to patients?

Guidance 4: Once you have a COA measurement tool and a way to collect data using it, what is an appropriate clinical trial endpoint?

Guidance 4 will address topics related to COA-related endpoint development and interpretation, including topics related to instrument administration and meaningful within 81 patient score changes.

Note - The draft guidance 1 contains nonbinding recommendations[31]. The four guidances are part of the FDA's PFDD efforts in accordance with the 21st Century Cures Act and the Food and Drug Administration Reauthorization Act of 2017 Title I. Through the PFDD initiative, started in the Prescription Drug User Fee Act V, the FDA has been addressing the need to better enable patients to provide meaningful inputs to drug and biologic development.

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31 https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegu lato ryInformation/Guidances/UCM610442.pdf

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