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Vol. II, Issue IV
April 2018

S&A PHARMA NEWSLETTER

EDITORIAL

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Founding Partner

It gives us immense pleasure to present Vol. II Issue IV of *S&A – Pharma Newsletter*. The aim of the Newsletter is to disseminate regulatory information on the pharmaceutical products within India as well as from foreign jurisdictions, based on information collated through research and appraisal of applicable statutory provisions.

India enjoys an important position in the global pharmaceuticals sector. Just to drop a reference, India is the largest provider of generic drugs globally with the Indian generics accounting for 20 per cent of global exports in terms of volume. Therefore, it becomes imperative for the government to keep up the vigil for safeguarding the sector; resulting in strict regulatory regime. Present issue comprises of various such regulatory issues that confirm that it is not enough for pharma companies to focus just on marketing and selling of drugs and medications. The industry also needs to have a more holistic approach which is not only compliant with the legal regime but also equipped with integrated services to best respond to healthcare problems.

To begin with, we discuss extent and implications of Health Ministry of India's recently released gazette draft proposal for public/stockholder comment regarding regulation on import, manufacture, sale and distribution of *Oxytocin* (a neurotransmitter and peptide hormone) to curb its misuse. Going forward, this edition addresses recent regulatory developments in healthcare research, new therapy approvals and notable regulatory reforms. First, the Central Government's declaration of *Tramadol* as a psychotropic substance, which now will be strictly monitored under Narcotics Control Bureau is discussed. Second, an article on reasoning behind Ministry of Health and Family Welfare's prohibition of *Antibody Detecting Rapid Diagnostic Tests* used for routine diagnosis of malaria finds a place in this issue. And third, we critically appraise Health Ministry's proposal to amend Drug and Cosmetics Rule, 1945 to define Stem Cell and Stem Cell Based Products (SCBP) and to streamline the regulatory framework for its advanced research.

From the international arena, we talk about recent developments qua regulatory authorities of foreign jurisdictions. First, we discuss USFDA's grant of Orphan Drug Designation and Priority Review to *Duvelisib* (a first-in-class oral dual inhibitor of phosphoinositide 3-kinase (PI3K)-delta and PI3K-gamma) for the treatment of relapsed or refractory chronic lymphocytic leukemia/ small lymphocytic lymphoma. Next, we have a write-up on European Medicines Agency's updated guidance for clinical development of vaccines which addresses the clinical evaluation of vaccines intended for the prevention of infectious diseases and also includes considerations for trials intended to document the safety, immunogenicity and efficacy of new candidate vaccines. Further, we deliberate upon UK's Medicines and Healthcare products Regulatory Agency (MHRA) ban of *Valproate Medicines* unless the female patient is on the pregnancy prevention programme. Later, there is an article on how the first Marijuana based drug product nearing United State Food Drug Administration (USFDA) approval, an experimental drug derived from cannabis, is well poised to become the first of its kind drug to win approval from the USFDA.

This Newsletter also has write-ups on topics such as (i) USFDA granting marketing permission to first AI based device concernign diabetic retinopathy, (ii) finalization of USFDA's Guidance for Industry on Liposome Drug Products (iii) USFDA's order restricting sale & distribution of *Essure device* (iv) USFDA's approval of *Crysvita* (burosumab) being the first drug to treat adults & children with x-linked hypophosphatemia, a rare inherited form of rickets; and lastly a note on the concerns raised by USTR (publicly for the first time in its 2018 National Trade Estimate Report on 'Foreign Trade Barriers') on India's Price Controls on Medical Devices.

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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 IV
April 2018

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Contents

Government regulates manufacture, sale and distribution of Oxytocin to curb its misuse

On April 26, 2018, Department of Health and Family Welfare, Ministry of Health and Family Welfare, Government of India, vide its notification G.S.R. 411(E)[1], issued directions regarding import, manufacture, sale and distribution of Oxytocin, to curb its misuse[2]. The government, in exercise of the powers conferred by section 26A of the Drugs and Cosmetics Act, 1940 and in suppression of the notification number G.S.R. 29(E) dated January 17, 2014, declared that the drug Oxytocin shall be manufactured for sale, or for distribution, or sold in the manner specified below:

1. The manufacture of Oxytocin formulations, for domestic use, shall be by public sector undertakings or companies only and the label of the product shall bear barcodes.

2. The manufacture of Oxytocin formulations, for export purposes, shall be open to both public and private sector companies and the packs of such manufacture for exports shall bear barcodes.

3. The manufacturers of active pharmaceutical ingredient of Oxytocin shall supply the active pharmaceutical ingredient only to the manufacturers in public sector, holding license under the Drugs and Cosmetics Rules, 1945, for manufacture of formulations of the said drug, for domestic use.

4. The manufacturers of active pharmaceutical ingredient of Oxytocin shall supply the said active pharmaceutical ingredient to the manufacturers in public and private sector, holding license under the Drugs and Cosmetics Rules, 1945, for manufacture of formulations of the said drug, for export purpose.

5. The Oxytocin formulations manufactured by the public sector companies or undertakings licensed under the Drugs and Cosmetics Rules, 1945, for domestic use shall supply the formulations meant for human and veterinary use only:

   (i). to the registered hospitals and clinics in public and private sector directly; or

   (ii). to the Pradhan Mantri Bhartiya Janaushadhi Pariyojana (PMBJP) and Affordable Medicines and Reliable Implants for Treatment (AMRIT) outlets or any other Government entity which may be specified by the Central Government for this purpose in the country, which shall further supply the drug to the registered hospitals and clinics in public and private sector.

6. The Oxytocin in any form or name shall not be allowed to be sold through retail chemists.

Oxytocin is a neurotransmitter and peptide hormone which causes uterine contractions thereby, inducing labour naturally and controls post-delivery bleeding. But it is misused in the agriculture and dairy industry where cattle are injected with it, to make them release milk., After various measures to curb oxytocin misuse oOn April 20, 2018, the Health Ministry of India has released a gazette draft proposal for public/stockholder comment regarding labeling specification of Oxytocin formulation to facilitate product traceability which has been proposed to amend rule 96, in sub-rule (1) after clause (xii) of Drug and Cosmetic Rules, 1945, which reads[3]:

> *"(Xiii) (A). The manufacturers of drug formulations of oxytocin shall print the details specified below to facilitate tracking and tracing of their products, namely:*

1 This notification shall come into force on the first day of July 2018.

2 http://www.egazette.nic.in/WriteReadData/2018/185017.pdf

3 http://www.egazette.nic.in/WriteReadData/2018/184866.pdf

a. ***Primary level packaging*** *of two-dimensional barcode encoding unique and universal global product identification code in the 14 digits Global Trade Item Number format along with batch number, expiry date and a unique serial number of the primary pack;*

b. ***Secondary level packaging*** *of one or two-dimensional barcode encoding unique and universal global product identification code in the 14 digits Global Trade Item Number format along with batch number, expiry date and a unique serial number of the secondary pack;*

c. ***Tertiary level packaging*** *of one dimensional barcode encoding unique and universal global product identification code in the 14 digits Global Trade Item Number format along with batch number, expiry date and a unique serial number of the Tertiary pack.*

(B) The manufacturer of drug formulation shall maintain the data in the parent — child relationship for all three level of packaging and their movement in its supply chain.

(C) The data referred to in sub-rule (2) shall be uploaded on the central portal of the Central Government by the manufacturer or its designated agency before release of the drugs for sale or distribution.

(D) The responsibility of the correctness, completeness and ensuring timely upload of data on the Central portal shall be that of the manufacturer."

Note – The said draft rules will be taken into consideration on or after the expiry of a period of forty-five days from the date of publication via Gazette notification. Further, these rules shall come into effect after six months of the publication of the final rules in the Gazette of India.

Conclusion

The regulation over oxytocin manufacturing by public sector undertakings or companies only, barcodes labelling specification, sale and distribution to the registered hospitals and clinics are the major step taken by government to keep strict vigilance of oxytocin misuse at various level of its demand- supply chain. Moreover, the proposed concept of oxytocin supply chain data management on a central portal with manufacturers' support will ensure a trace on its movement and delivery for the intended purpose only.

Government declares Tramadol a Psychotropic substance to curb its abuse and trafficking

On April 26, 2018, Department of Revenue, Ministry of Finance, vide its notification S. O. 1761(E), declared *Tramadol* as a Psychotropic substance to control its abuse/misuse[4] in exercise of the powers conferred by section 3 of the Narcotic Drugs and Psychotropic Substances Act, 1985. As a result, the sale & distribution of Tramadol will now be under the supervision and control of Narcotics Control Bureau (NCB).

On April 09, 2018, days before the above notification, during the 53rd meeting of the Drugs Consultative Committee (DCC) [5] at Central Drugs Standard Control Organization (CDSCO), the issue of abuse and trafficking of pharmaceutical preparations in the country especially Codeine based cough syrups and Tramadol was considered. The Deputy Director (Operations), NCB had addressed the members of DCC and raised serious concerns about the issue of abuse and trafficking of pharmaceutical preparations in the country as the official records show that huge quantities of Tramadol were seized in the country last year. The Deputy Director had requested all the State Licensing Authorities to re-consider the proposal of reduction in batch size for manufacturing such drugs to control their abuse and misuse.

The Deputy Director also insisted to verify the existence of sale premises before a license is granted by the states and to conduct surprise raids in this regard. He had also informed that the proposal for considering inclusion of Tramadol under Narcotics Drugs and Psychotropic Substances (NDPS) was under active consideration and, notification in the regard to be issued shortly. DCC deliberated and agreed for considering Tramadol under NDPS, so that the drug could be placed under restrictions of production as API and under controls on import into and export out of India. This will ensure the availability of the drug to persons who need it for pain management yet also restrict its illicit movement.

Earlier on March 19, 2014, the Drugs and Cosmetics (Fourth amendment), 2013[6], had introduced Schedule H1 for regulating sale of certain antibiotics, anti-TB Drugs and habit-forming drugs, where Tramadol was one of those habit-forming drug listed under Schedule H1. According to Schedule H1, the drugs should carry a Boxed Label Warning saying - Not to be sold without a prescription issued by Registered Medical Practitioner and self-medication of the drug preparation can be dangerous[7].

Note – The government's decision to declare Tramadol as a psychotropic substance under Narcotics Drugs and Psychotropic Substances (NDPS) will make strict monitoring of its movement possible and also empower NCB to curb the ongoing drug-abuse trend in the country. It will also enable rigorous punishment to the offenders if the drug is found illegally stocked or distributed.

4 http://www.egazette.nic.in/WriteReadData/2018/185016.pdf

5 http://www.cdsco.nic.in/writereaddata/Minutes%20of%2053rd%20DCC%20Meet.pdf

6 http://cdsco.nic.in/writereaddata/Inclusion%20of%20Schedule%20H1%20under%20the%20DC%20rules.pdf

7 http://cdsco.nic.in/writereaddata/MinutesDTAB%2062nd.pdf

Ministry of Health prohibits Antibody Detecting Rapid Diagnostic Tests for routine diagnosis of malaria

On March 23, 2018, the Ministry of Health and Family Welfare, Government of India, has, in public interest, prohibited the use of the Antibody Detecting Rapid Diagnostic Tests (ADRDT) for routine diagnosis of malaria with immediate effect. Through a gazette notification S.O. 1352(E), the ministry has informed, in exercise of the powers conferred by section 26A of the Drugs and Cosmetic Act, 1940 (23 of 1940), the Central Government prohibits the manufacture for sale, sale and distribution of the test kits used in 'Antibody Detecting Rapid Diagnostic Tests for routine diagnosis of malaria' with immediate effect.

Earlier, the matter was examined by an Expert Committee appointed by the Central Government, which recommended that the said drug was found to have no therapeutic justification. Now the Central Government is satisfied that it is necessary and expedient in public interest, to prohibit the use of the ADRDTs for routine diagnosis of malaria; therefore, it prohibits the manufacture for sale, sale and distribution of the test kits used in 'Antibody Detecting Rapid Diagnostic Tests for routine diagnosis of malaria'. It has been found that there is a rampant use of Antibody Detecting Rapid Diagnostic Tests due to low cost and free availability of these tests. But this test raises the rate of, false positive tests very high in the endemic areas, as patients with fever due to other reasons, who test negative by antigen detection, test positive by ADRDTs.

The ministry has also indicated that the use of ADRDTs is not the solution to diagnose malaria. This is because serological testing is not practical for routine diagnosis of an acute parasite infectious disease going by the time required for development of antibody. The reason to issue the guidance banning the use of ADRDTs is the persistence of antibodies even after clearance of an active infection. The government's expert committee sees that serology does not detect current infection but measures past exposure. Malaria antibody detection is performed using the indirect fluorescent antibody test for a patient who is infected with plasmodium. Because of the time required for development of antibody and, also the persistence of antibodies, serological testing is not practical for routine diagnosis of acute malaria, stated the government vide notification issued on March 23, 2018[8].

The notification also states that the only tests used in diagnosis are Antigen Detecting Rapid Diagnostic Tests and blood smear examination, and, therefore, there would not be any problems faced for malaria diagnosis by banning the Antibody Detecting Rapid Diagnostic Test.

About Malaria Rapid Diagnostic Tests

According to the World Health Organization (WHO), Malaria rapid diagnostic tests (RDTs) assist in the diagnosis of malaria by providing evidence of the presence of malaria parasites in human blood. RDTs are an alternative to make diagnosis based on clinical grounds or microscopy, particularly where good quality microscopy services cannot be readily provided. Variations occur between products such as targets and formats, though the principles of the tests are similar. Malaria RDTs detect specific antigens (proteins) produced by malaria parasites in the blood of infected individuals. Some RDTs can detect only one species (*Plasmodium falciparum*) while others detect multiple species (*P. vivax*, *P. malariae* and *P. ovale*). Blood for the test is commonly obtained from a finger-prick.

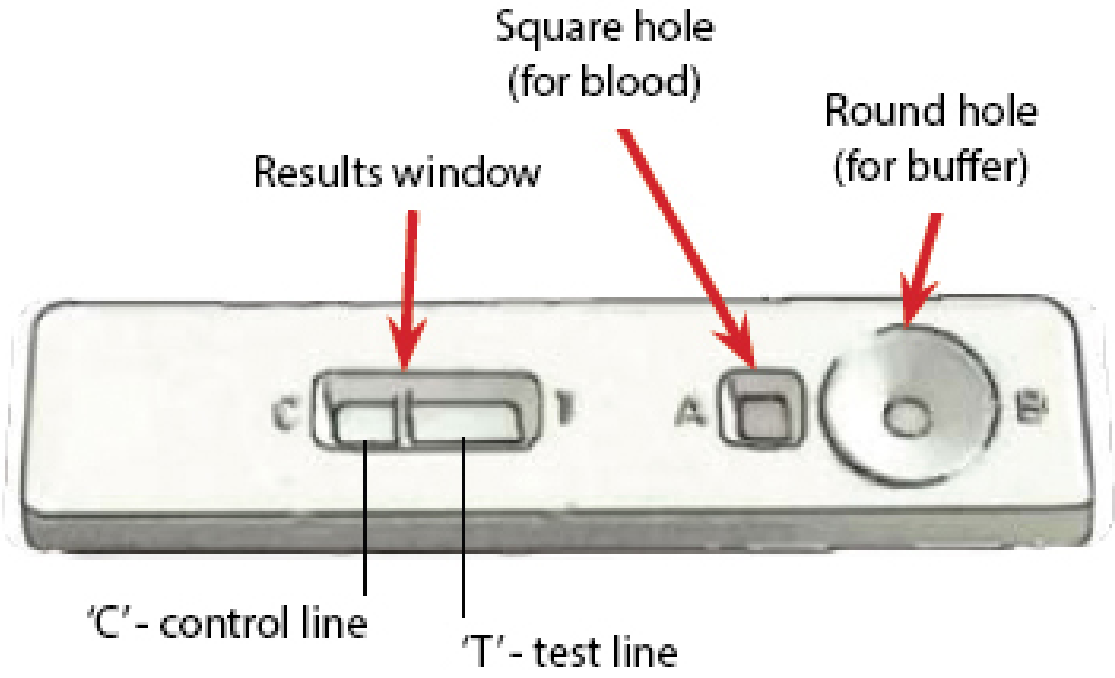
RDTs are lateral flow immuno-chromatographic antigen-detection tests, which rely on the capture of dye-labeled antibodies to produce a visible band on a strip of nitro-cellulose, often encased in plastic housing, referred to as cassettes. With malaria RDTs, the dye-labeled antibody first binds to a parasite antigen, and the resultant complex is captured on the strip by a band of bound antibody, forming a visible line (T - test line) in the results window. A

8 http://www.cdsco.nic.in/writereaddata/S_O_1352(E)%20dated%2023_03_2018.pdf

control line (C- control line) gives information on the integrity of the antibody-dye conjugate but does not confirm the ability to detect parasite antigen[9].

Typical Rapid Diagnostic Tests Cassette

Inside the cassette is a strip made of filter paper and nitrocellulose. Typically, a drop of blood is added to the RDT through one hole (A; sample well), and then a number of drops of buffer usually through another hole (B; buffer well). Buffer carries the blood along the length of the RDT.



Conclusion:

The government's decision to prohibit the use of Antibody Detecting Rapid Diagnostic Tests for routine diagnosis of malaria is in wider public interest owing to various reasons like rampant usage of these kits due to factors like their low cost and easy availability leading to a lot of false positive results for many patients.

9 http://www.who.int/malaria/areas/diagnosis/rapid-diagnostic-tests/about-rdt/en/

Central Government's proposal to define Stem Cell and Stem Cell based Product under D&C Rule

On April 04, 2018, the Ministry of Health and Family Welfare (MoHFW) proposed a draft to amend the Drug and Cosmetics Rules, 1945[10], that defines stem cell and stem cell-based products (SCBP), to streamline the regulatory framework for advanced research.

Central Government in exercise of the power conferred by section 12 and section 33 of the Drug and Cosmetics Act, 1940 and after consultation with the Drugs Technical Advisory Board, published the draft proposal via a gazette notification for information of all persons likely to be affected thereby. Further, the said draft rules will be taken into consideration on or after the expiry of a period of forty-five days from the date on which the Official Gazette containing these draft rules are made available to the public.

The proposed draft rules amend Rule 122E of the Drugs and Cosmetics Rules, 1945, where after the clause (c) and before the explanation the following new clause (d) and explanation shall be inserted -

> *"(d) Stem Cell and Cell based product means a drug which has been derived from processed cells including cell or tissue which has been processed by means of substantial or more than minimal manipulation with the objective of propagation and / or differentiation of a cell or tissue, cell activation, and production of a cell-line, which includes pharmaceutical or chemical or enzymatic treatment, altering a biological characteristic, combining with a non-cellular component, manipulation by genetic engineering including gene editing & gene modification.*
>
> *Explanation - For the purpose of this clause–*
>
> *(i) Substantial or more than minimal manipulation means ex-vivo alteration in the cell population (T-Cell depletion, cancer cell depletion), expansion, which is expected to result in alteration of function.*
>
> *(ii) The isolation of tissue, washing, centrifugation, suspension in acceptable medium, cutting, grinding, shaping, overnight culturing without biological and chemical treatment, disintegration of tissue, separation of cells, isolation of a specific cell, treatment with antibiotics, sterilization by washing or gamma irradiation, freezing, thawing and such similar procedures, regarded as minimal manipulations and are not considered as processing by means of substantial or more than minimal manipulation.*
>
> *(iii) Human cells or tissues removed from an individual for implantation of such cells or tissues only into the same individual for use during the same surgical procedure should not undergo processing steps beyond rinsing, cleaning or sizing and these steps shall not be considered as processing. "*

Earlier in October 2017, the Indian Council of Medical Research (ICMR) released the National Guidelines for Stem Cell Research 2017[11]. The guideline reiterates that any stem cell usage in patients, other than that for hematopoietic stem cell reconstitution for approved indications, is investigational at present. Accordingly, any stem cell use in patients must only be done within the purview of an approved and monitored clinical trial with the intent to advance science and medicine, and not offering it as therapy. In accordance with this stringent definition, every use of stem cell in patients outside an approved clinical trial is unethical and shall be considered as malpractice.

10 http://www.cdsco.nic.in/writereaddata/April%204th%20%202018%20GSR%20334(E).pdf

11 http://icmr.nic.in/guidelines/Guidelines_for_stem_cell_research_2017.pdf

This guideline also has some major amendments including: mandatory registration of Institutional Committee for Stem Cell Research (ICSCR) and Institutional Ethics Committee (IEC), with National Apex Committee for Stem Cell Research and Therapy (NAC-SCRT) and CDSCO respectively[12].

NOTE – The proposed draft defines Stem Cell and Cell based product as a drug, which has been derived from processed cells by means of substantial and more than minimal manipulation with the objective of differentiation of the cell or tissue. Moreover, the draft further explained substantial or more than minimal manipulation processing methods involved during stem cell preparation.

However, objections and suggestions if any, received from any person within a specified period of 45 days will be considered by the Central Government.

12 http://icmr.nic.in/guidelines/Guidelines_for_stem_cell_research_2017.pdf

Duvelisib granted Orphan Drug designation and Priority Review by the US FDA

On April 09, 2018, Verastem, a biopharmaceutical company focused on developing and commercializing medicines to improve the survival and quality of life of cancer patients, announced that the United States Food and Drug Administration (USFDA) has accepted for filing, with Priority Review, its New Drug Application (NDA) for its lead product candidate Duvelisib[13]. Duvelisib is a first-in-class oral dual inhibitor of phosphoinositide 3-kinase (PI3K)-delta and PI3K-gamma, for which Verastem is seeking full approval for the treatment of relapsed or refractory chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL) and accelerated approval for the treatment of relapsed or refractory follicular lymphoma (FL). Priority Review is granted by the FDA to drugs which, if approved, would provide significant improvements in the safety or effectiveness of the treatment, diagnosis, or prevention of a serious condition. Duvelisib has received Fast Track Designation from the FDA for patients with CLL who have received at least one prior therapy and for patients with FL who have received at least two prior therapies. In addition, Duvelisib received orphan drug designation in the United States and the European Union for patients with CLL, SLL and FL[14].

About Duvelisib

Duvelisib is a first-in-class investigational, dual inhibitor of phosphoinositide 3-kinase (PI3K)-delta and PI3K-gamma, two enzymes known to help support the growth and survival of malignant B-cells and T-cells. PI3K signaling may lead to the proliferation of malignant B- and T-cells and is thought to play a role in the formation and maintenance of the supportive tumor microenvironment.

Clinical Development

Duvelisib was evaluated in late- and mid-stage extension trials, including the DUO™ trial, and the DYNAMO™ trial. DUO™ was a randomized, Phase 3 monotherapy study in patients with relapsed or refractory chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL). DUO™, evaluated safety and efficacy of Duvelisib vs. Ofatumumab in 319 patients with relapsed or refractory chronic lymphocytic leukemia (R/R CLL). The DUO™ trial has been completed and has successfully met its primary endpoint (with some patients still in long term follow-up).

DYNAMO™ - The DYNAMO study was a Phase 2, open-label, single–arm monotherapy study evaluating the safety and efficacy of Duvelisib dosed at 25 mg BID in 129 patients with Indolent Non-Hodgkin Lymphoma (iNHL). Patients in DYNAMO who continue to derive benefit remain on treatment. DYNAMO enrollment criteria included patients with FL, the most common subtype of iNHL, Marginal zone lymphoma (MZL) and SLL, whose disease is refractory to rituximab, a monoclonal antibody treatment, and to either chemotherapy or radio-immunotherapy and who have progressed within six months of receiving their final dose of a previous therapy. The primary endpoint of the study was an Overall Response Rate (ORR) according to the International Working Group Criteria, which includes change in target nodal lesion in combination with other measurements to determine response to treatment.

The results from the DYNAMO study showed that the trial achieved the primary endpoint in a heavily pre-treated, double refractory to chemotherapy and rituximab, patient population with an ORR of 46% (p=0.0001) in the ITT population, as assessed by an IRC with a median duration of response of 10 months. The breakdown of ORR in the three subtypes of iNHL for the overall study population was 41% in FL (n=83), 68% in SLL (n=28) and 33% in MZL (n=18). 83% of patients had a reduction in target lymph nodes.

13 http://investor.verastem.com/phoenix.zhtml?c=250749&p=irol-newsArticle&ID=2341489

14 http://investor.verastem.com/phoenix.zhtml?c=250749&p=irol-newsArticle&ID=2330853

Now the FDA is reviewing New Drug Application (NDA) requesting the full approval of Duvelisib for the treatment of patients with relapsed or refractory CLL/SLL, and accelerated approval for the treatment of patients with relapsed or refractory follicular lymphoma (FL). Duvelisib is also being developed for the treatment of peripheral T-cell lymphoma (PTCL), which has Fast Track status, and is being investigated in combination with other agents through investigator-sponsored studies.

US FDA Priority Review

A Priority Review designation from USFDA means that the agency's goal is to act on an application within 6 months (compared to 10 months under standard review) of filing. A Priority Review designation directs overall attention and resources to the evaluation of applications for drugs which, if approved, would be significant improvements in the safety or effectiveness of the treatment, diagnosis, or prevention of serious conditions when compared to standard applications[15].

Significant improvement may be demonstrated by the following examples:

- Evidence of increased effectiveness in treatment, prevention, or diagnosis of condition;
- Elimination or substantial reduction of a treatment-limiting drug reaction;
- Documented enhancement of patient compliance that is expected to lead to an improvement in serious outcomes; or
- Evidence of safety and effectiveness in a new subpopulation.

Orphan Drug Designation

The Orphan Drug Act (ODA) of the United States provides for granting special status to a drug or biological product (drug) to treat a rare disease or condition upon request from a sponsor. This status is referred to as orphan designation[16]. For a drug to qualify for orphan designation, both the drug and the disease or condition must meet certain criteria specified in the ODA and FDA's implementing regulations at 21 CFR Part 316[17]. Orphan designation qualifies the sponsor of the drug for various development incentives of the ODA, including tax credits for qualified clinical testing. A marketing application for a prescription drug product that has received orphan designation is not subject to a prescription drug user fee unless the application includes an indication for other than the rare disease or condition for which the drug was designated.

Chronic Lymphocytic Leukemia/ Small Lymphocytic Lymphoma

Chronic lymphocytic leukemia (CLL) and small lymphocytic lymphoma (SLL) are cancers that affect lymphocytes. Lymphocytes, a type of white blood cell, carried along by the lymph fluid, are a part of the immune system and fight infections. CLL and SLL are essentially the same disease, with the only difference being the location where the cancer primarily occurs. When most of the cancer cells are located in the bloodstream and the bone marrow, the disease is referred to as CLL, although the lymph nodes and spleen are often involved. When the cancer cells are located mostly in the lymph nodes, the disease is called SLL[18].

15 https://www.fda.gov/ForPatients/Approvals/Fast/ucm405405.htm

16 https://www.fda.gov/ForIndustry/DevelopingProductsforRareDiseasesConditions/HowtoapplyforOrphanProductDesignation/default.htm

17 https://www.ecfr.gov/cgi-bin/retrieveECFR?gp=&SID=718f6fcbc20f2755bd1f5a980eb5eecd&mc=true&n=sp21.5.316.c&r=SUBPART&ty=HTML#se21.5.316_120

18 https://www.lymphoma.org/wp-content/uploads/2017/06/LRF_FACTSHEET_CLL_SLL.pdf

Follicular Lymphoma

Follicular lymphoma is a cancer of the lymphatic system. It occurs when a lymphocyte (a type of white blood cell that fights infection) grows out of control. There are two main groups of lymphomas: Hodgkin lymphomas and non-Hodgkin lymphomas. Non-Hodgkin lymphomas are further grouped into:

- Low-grade (slow-growing) or high-grade (fast-growing)
- T-cell lymphoma (develops from abnormal T-lymphocytes or T-cells) or B-cell lymphoma (develops from abnormal B-lymphocytes or B-cells).

Follicular lymphoma is the most common type of low-grade NHL and develops from B-cells. The abnormal B-cells often collect in lymph nodes (glands) as follicles (clumps)[19].

Conclusion:

Duvelisib presents itself as an important therapeutic option for patients with unmet need in relapsed/ refractory chronic lymphocytic leukemia (CLL), small lymphocytic lymphoma (SLL), and follicular lymphoma (FL).

19 https://www.lymphomas.org.uk/printpdf/5423

BREXIT Update: European Medicines Agency (EMA) redistributes UK's portfolio of centrally authorized products

On April 11, 2018, the European Union's 27 Member States and the European Medicines Agency (EMA) announced that they have completed the reallocation of the medicines for which the United Kingdom's (UK) Medicines and Healthcare products Regulatory Agency (MHRA) and Veterinary Medicines Directorate (VMD) are currently rapporteur or co-rapporteur appointed by the scientific committees to coordinate the evaluation of a medicine[20]. Over 370 centrally authorized products have been transferred to new rapporteurs and co-rapporteurs from the 27 EU Member States, plus Iceland and Norway, following a methodology developed by EMA's working groups on committees' operational preparedness for human and veterinary medicines. EMA will inform the relevant marketing authorisztion holders of the new (co)-rapporteurships by the end of April 2018. EMA will also facilitate knowledge transfer from the UK to the new rapporteurs and co-rapporteurs, who will only take full responsibility for these products as of March 30, 2019.

Brexit Background

The United Kingdom submitted on March 29, 2017, the notification of its intention to withdraw from the European Union pursuant to Article 50 of the Treaty on European Union. This means that unless a ratified withdrawal agreement establishes another date, all primary and secondary Union laws cease to apply to the United Kingdom from March 30, 2019, 00:00h (CET). The United Kingdom will then become a 'third country'. EMA will move its headquarters from London to Amsterdam post BREXIT. Consequent to UK's exit, the MHRA and VMD will no longer be able to engage in centralized regulatory procedures, as (Co)-Rapporteurs, which are expected to finalize after March 30, 2019.

Redistribution plan of the UK centrally authorized product portfolio

The redistribution plan covers the post-authorization stage in a medicine's lifecycle, i.e. once a medicine has a marketing authorization. It follows a multifaceted approach and takes into account both the diverse expertise in the European medicines regulatory network and the workload associated with each medicine. It allows Member States to participate in EMA activities according to their individual capacity[21].

The methodology used for the reallocation of medicines is based on Member States' current expertise with a specific class of medicines. It also builds on existing knowledge, for example, by transferring medicines to the current co-rapporteur for a particular product, or to the peer reviewer involved in the marketing authorization application. In addition, the reallocation methodology takes into account the type of product. Generic medicines, for example, were allocated to national competent authorities who traditionally have participated less in EMA evaluations but have indicated that they would like to increase their involvement with such medicines. Clusters of products with the same international non-proprietary name (INN) and/or belonging to the same marketing authorization holder have been allocated to a single rapporteur in order to facilitate review of post-authorization procedures and ultimately improve efficiency within the network.

General principles

The general principles, adopted by the EMA Management Board, to guide the redistribution of the UK product portfolio were to:

- ensure business continuity;
- ensure knowledge retention, either building on existing knowledge, or through knowledge transfer;

20 http://www.ema.europa.eu/ema/index.jsp?curl=pages/news_and_events/news/2018/04/news_detail_002937.jsp&mid=WC0b01ac058004d5c1

21 http://www.ema.europa.eu/docs/en_GB/document_library/Other/2018/04/WC500247359.pdf

- allow compliance with the legally required timelines and to maintain the quality of the output;
- be as easy as possible to implement and, in addition, to be sustainable;
- strive to allow all NCAs to participate in EMA activities, as per the capacity and capability of each NCA, so as to ensure an optimized and robust allocation of the workload across the Network

What is Centralized Authorization Procedure?

In the European Union under the centralized authorization procedure, pharmaceutical companies submit a single marketing-authorization application to EMA. This allows the marketing-authorization holder to market the medicine and make it available to patients and healthcare professionals throughout the EU on the basis of a single marketing authorization. EMA's Committee for Medicinal products for Human Use (CHMP) or Committee for Medicinal products for Veterinary Use (CVMP) carry out a scientific assessment of the application and give a recommendation on whether the medicine should be marketed or not. Once granted by the European Commission, the centralized marketing authorization is valid in all EU Member States as well as in the European Economic Area (EEA) countries Iceland, Liechtenstein and Norway[22].

Conclusion:

With the United Kingdom's (UK) scheduled exit from the European Union in about 12 months, the European Medicines Agency has reassigned overseeing of UK agencies viz. MHRA and VMD's products to the other 27 member states, plus Iceland and Norway.

22 http://www.ema.europa.eu/ema/index.jsp?curl=pages/about_us/general/general_content_000109.jsp&mid=WC0b01ac0580028a47

European Medicines Agency (EMA) issues updated rules for clinical development of vaccines

EMA launches public consultation on revised guideline on clinical evaluation of vaccines

On April 26, 2018, the European Medicines Agency (EMA) released a revised guideline on the clinical evaluation of vaccines[23] for a six-month public consultation. This guideline addresses the clinical evaluation of vaccines intended for the prevention of infectious diseases. It includes considerations for trials intended to document the safety, immunogenicity and efficacy of new candidate vaccines and to support changes in the prescribing information of licensed vaccines. It also considers the need for and use of vaccine effectiveness studies.

Since the adoption of EMEA/CHMP/VWP/164653/2005, many new vaccines have been approved in the EU or have received a positive opinion under Article 58 of Regulation (EC) No 726/2004, including several vaccines intended to prevent infectious diseases for which there was previously no vaccine available. Some of these vaccines include antigenic substances from multiple pathogens or from multiple subtypes of a single pathogen. These applications have raised several issues for vaccine clinical development programmes that were not addressed in the previous guideline. Furthermore, there have been requests for scientific advice on vaccine clinical development programmes which point to the need to provide updated or additional guidance on some issues like considerations for conducting vaccine efficacy trials, identification of immune correlates of protection, vaccines intended to be used in heterologous prime-boost regimens and vaccines to be administered to pregnant women to protect their infants during the first months of life.

Vaccines undergo a rigorous scientific review to ensure that they are safe and effective. The updated guideline introduces additional safeguards for European Union citizens and ensures that the evaluation is in line with the most up-to-date scientific knowledge and technological developments.

In response to recurring issues arising in scientific advice and in application dossiers, this revised guidance includes a discussion of factors to consider when planning and interpreting the results of comparative immunogenicity trials. For example, the importance of considering the severity, mortality and/or risk of permanent sequelae of the infectious disease to be prevented as well as the robustness of the assays to determine the immune response when selecting non-inferiority margins and assessing the clinical impact of failing to meet pre-defined criteria. In trials that compare candidate and licensed vaccines containing antigens from different numbers of subtypes of the same organism consideration is given to interpretation of immune responses to non-shared subtypes.

The revised version of the guideline also adds considerations to priming and boosting strategies, including the option of heterologous prime-boost, which entails administration of one type of vaccine first followed by a different type of vaccine for the same pathogen later. The need to develop vaccine for pathogens that may cause future epidemics and for which conducting clinical trials outside of outbreaks might be problematic, is also addressed.

EMA's draft guideline includes specific considerations for clinical trials with vaccines in special populations such as:

1. **Pregnant women:** Vaccination during pregnancy may have one or more of the following aims: i) to protect the pregnant subject; ii) to protect the fetus from intra-uterine infection; iii) to protect the infant for as long as protective levels of maternal antibody persist in the post-natal period.

23 http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2018/04/WC500248095.pdf

- If the candidate vaccine is not approved for use in non-pregnant adults, safety and immunogenicity data should be obtained from non-pregnant female subjects of childbearing age before proceeding to trials in pregnant subjects. Safety and immunogenicity trials to support selection of dose regimens should enroll subjects at a stage of pregnancy appropriate to the primary objective, i.e. as early as possible in pregnancy to protect the mother and/or fetus and later in pregnancy to maximize maternal antibody levels in the neonate.

- If the primary aim of vaccination during pregnancy is to protect the infant in the first months of life, the dose-finding trials should include measurement of antibody levels in cord blood samples taken at delivery. The data should be sufficient to provide an estimate of inter-individual variability and to assess the effect of time interval between vaccination and delivery on maternal antibody levels in infants. The persistence of detectable maternal antibody in infants against the target organism should be evaluated as part of the dose-finding process. If the overall strategy involves vaccinating pregnant subjects followed by active vaccination of their infants against the same antigen(s), the antibody decay curve in infants may provide a preliminary indication of the timing of the first infant dose.

- If an ICP is established for the infectious disease to be prevented and depending on the primary objective and the safety profile, the maternal vaccination regimen should maximise the proportions of pregnant women or cord blood samples with antibody that exceeds the ICP. If there is no ICP and there is no licensed vaccine of known efficacy to which the candidate vaccine could be compared (i.e. using immunobridging to infer efficacy), a vaccine efficacy trial would usually be necessary. In all trials conducted in pregnant subjects, adequate mechanisms should be in place to document the outcome of the pregnancy. For example, information should be collected on the duration of gestation, the condition of the infant at birth and any congenital conditions.

2. Elderly subjects: For most vaccines, elderly subjects have lower responses to vaccination compared to younger subjects, which may reflect immunosenescence and/or the prevalence of specific underlying diseases or medications that have a negative impact on the immune system. On occasion, immune responses may be higher in the elderly if they are more likely, than younger adults, to have been primed by natural exposure or prior vaccination. Therefore, it is important that adequate dose-finding studies are conducted for vaccines proposed for use in the elderly and that all age subgroups are investigated (e.g. 65-74 years, 75-84 years and 85 years or more) to determine whether different doses and/or regimens are needed as age increases.

If efficacy trials are to be conducted in elderly subjects, it is recommended that there be stratification by age sub-groups. Furthermore, the impact of any underlying conditions or medications known or likely to affect immune responses should be investigated during the clinical trials. The safety of vaccines in the elderly should be documented in subsets with certain underlying conditions and levels of frailty to determine whether the safety profile is broadly acceptable.

3. Immunodeficient subjects: Due to the wide range of types of immunodeficiency that may result from congenital or acquired conditions or from iatrogenic intervention, only some of which may impact on the immune response to a specific type of vaccine, trials that assess safety, immunogenicity or efficacy in a broad immunodeficient population are not recommended.

Trials intended to support dose recommendations for immunodeficient subjects should plan to enroll well-defined sub-populations of subjects with immune deficiencies that have been selected based on those most likely to affect the immune response to a specific vaccine. Unless there is a well-established ICP that can be applied to the data, the usual aim of such trials will be to identify a posology that achieves comparable immune responses to those observed in immunocompetent subjects.

It is not expected to be feasible to study all immunodeficient sub-populations. The extent to which any one posology may be recommended beyond the exact population in which it was studied must be decided based on what is known about the relative importance of different immunological parameters for protection.

United Kingdom's MHRA bans valproate medicines without the Pregnancy Prevention Programme

On April 24, 2018, the United Kingdom's Medicines and Healthcare products Regulatory Agency (MHRA) announced that 'to protect public health, the Medicines and Healthcare products Regulatory Agency (MHRA) has changed the license for valproate medicines (Epilim, Depakote and generic brands). Valproate must no longer be prescribed to women or girls of childbearing potential unless they are on the pregnancy prevention programme (PPP)'[24].

The MHRA regulates medicines, medical devices and blood components for transfusion in the UK. MHRA is an executive agency, sponsored by the Department of Health and Social Care, United Kingdom[25].

Background

Valproate (Epilim, Depakote and other generic brands) is associated with a significant risk of birth defects and developmental disorders in children born to women who take valproate during pregnancy.

Valproate is a treatment for epilepsy and bipolar disorder and is prescribed to thousands of women. Since its introduction in 1974, the product information for doctors has included a warning about the possible risk of birth defects. As the risks to unborn children have been increasingly understood, the warnings have been strengthened. In March 2018, the European Union's Coordination Group for Mutual Recognition and Decentralized Procedures - Human (CMDh) endorsed a strengthened regulatory position on valproate medicines[26]. Valproate must no longer be used in any woman or girl able to have children unless she has a pregnancy prevention programme in place. This is designed to make sure patients are fully aware of the risks and the need to avoid becoming pregnant.

MHRA Updates – April 2018

The agency has recommended that healthcare professionals who seek to prescribe valproate to their female patients must make sure they are enrolled in the PPP. This includes the completion of a signed risk acknowledgement form when their treatment is reviewed by a specialist, at least annually. The agency has also advised that all women and girls who are prescribed valproate should contact their General Practitioner (GP) and arrange to have their treatment reviewed. No woman or girl should stop taking valproate without medical advice.

These regulatory changes will be further supported in the upcoming months by:

- smaller pack sizes to encourage monthly prescribing
- a pictogram/warning image on valproate labelling

These new regulatory measures are being supported across the National Health Service (NHS) with other authorities also making changes – such as new General Practitioner (GP) system computer alerts – to make sure changes in prescribing behaviour take place promptly. NHS Digital has worked with GP systems suppliers to provide a search and audit function to identify women and girls on valproate as well as updating valproate prescribing alerts. A letter will be sent to all relevant healthcare professionals in the coming weeks outlining the new requirements and providing updated educational materials.

24 https://www.gov.uk/government/news/valproate-banned-without-the-pregnancy-prevention-programme

25 https://www.gov.uk/government/organisations/medicines-and-healthcare-products-regulatory-agency

26 http://www.ema.europa.eu/ema/index.jsp?curl=pages/news_and_events/news/2018/03/news_detail_002929.jsp&mid=WC0b01ac058004d5c1

Parallelly, the National Institute for Health and Care Excellence (NICE) is amending its guidelines where valproate is mentioned, to reflect the new regulatory position. NICE has also begun work on a full update of its guideline on epilepsy. This will specifically focus on areas where valproate is currently regarded as the drug of choice and where this conflicts with the new position.

Working together, across the health sector, these measures will help reduce the number of pregnancies exposed to valproate medicines to an absolute minimum and will make sure all women and girls of childbearing potential are aware of the risks.

Since it was introduced in 1974, the information provided with valproate included a warning about the possible risk of birth defects. As with all medicines, the safety of valproate has been kept under constant review and as new data have become available, and the magnitude and the nature of the risks were better understood, warnings were updated – resulting in this most recent regulatory change.

As part of the pregnancy prevention programme (PPP) the prescriber must:

- ensure the patient understands the risks to the unborn child from using valproate during pregnancy and provide patient guide;
- ensure the patient understands the need to comply with contraception throughout the treatment and undergo pregnancy testing when required e.g. if there is any reason to suggest lack of compliance or effectiveness of contraception;
- complete and sign the acknowledgement of risk form (at every annual visit), give a copy to the patient and send one to the GP;
- refer for contraception services as needed.

Advice for healthcare professionals

New contraindication unless Pregnancy Prevention Programme in place

- Valproate medicines must not be used in women and girls of childbearing potential unless the conditions of the Pregnancy Prevention Programme are met and only if other treatments are ineffective or not tolerated, as judged by an experienced specialist.
- HCPs will receive materials by post in the coming weeks to use in the implementation of the Pregnancy Prevention Programme (Patient Guide, Healthcare Professional Guide, Risk Acknowledgement Form and, for pharmacists, Patient Cards and stickers to attach a warning label to the pack)
- GPs must identify and recall all women and girls who may be of childbearing potential, provide them Patient Guide and check they have been reviewed by a specialist in the last year and are on highly effective contraception (see later for information on contraception)
- Specialists must book review appointments at least annually with women and girls under the Pregnancy Prevention Programme and re-evaluate treatment as necessary; explain clearly the conditions as outlined in the supporting materials; and complete and sign the Risk Acknowledgement Form—copies of the form must be given to the patient or patient/caregiver/responsible person and sent to their GP.

Conditions and guidance for the Pregnancy Prevention Programme

The agency has put forward strong conditions for all women and girls of childbearing potential being treated with valproate medicines, to be supported by a Pregnancy Prevention Programme. These conditions are also applicable to female patients who are not sexually active unless the prescriber considers that there are compelling reasons to indicate that there is no risk of pregnancy[27].

The Pregnancy Prevention Programme is a system of ensuring all female patients taking valproate medicines:

- have been told and understand the risks of use in pregnancy and have signed a Risk Acknowledgement Form;
- are on highly effective contraception if necessary;
- see their specialist at least every year.

The conditions of the Pregnancy Prevention Programme for valproate are consistent with other similar programmes available for other highly teratogenic drugs such as thalidomide and isotretinoin.

The Pregnancy Prevention Programme is supported by the following requirements, which have been revised to be consistent with the new requirements:

- A Patient Guide – to be provided to girls (of any age) and women of childbearing potential (or their parent/caregiver/responsible person) who are started on or are continuing to use valproate medicines;
- A Guide for Healthcare Professionals – for guidance to all prescribers, pharmacists, and other healthcare providers involved in the care of women and girls of childbearing potential using valproate medicines;
- A Risk Acknowledgement Form – for the specialist and patient (or their parent/caregiver/responsible person) to sign at initiation and at treatment reviews at least every year. The patient should receive a copy of the form; one copy should be filed in the specialist notes, and one copy sent to the patient's GP;
- A Patient Card – to be given by pharmacists to all female patients who are dispensed valproate medicines to inform them of the risks;
- Stickers with warning symbols – for pharmacists to add to the packaging of valproate medicines.

Warnings added to the packaging of valproate medicines

The agency has further recommended a visual warning symbol will be added to the carton of valproate medicines by September 2018. This symbol will show a pregnant woman in a red circle with a line through it, with warning text about the risks and information about the new measures.

Pharmacists should therefore, dispense in whole packs whenever possible. This will ensure that patients always see the warning symbol and receive the statutory information. If a pharmacist must split a pack, or if the carton does not have a symbol on it, warning labels should be added to the box – stickers will be available with the educational materials to be sent to pharmacists by post.

Pharmacists should give the patient card to female patients when dispensing valproate. Packs of valproate medicines will start to be available with a detachable patient card from December 2018.

27 https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/701831/DSU-April-2018-PDF.pdf

If a woman or girl of childbearing potential reports that she is not taking effective contraception, pharmacists should advise her to contact her GP for an urgent follow-up.

Audit functions and prescribing alerts in GP software

United Kingdom's National Health Service (NHS) Digital has asked GP systems suppliers to provide a search and audit function to allow GPs to identify women on valproate medicines. Prescribing alerts for valproate medicines will also be updated with reminders of the responsibilities of prescribing GPs in line with the regulatory position. NHS Digital has also worked with community pharmacy dispensing system suppliers so that alerts are shown when prescriptions are dispensed.

New contraindication in pregnancy

The strengthened regulatory position includes a new absolute contraindication for use of valproate medicines in pregnancy for the bipolar disorder indication. In the epilepsy indication, the contraindication for use in pregnancy applies unless there are no suitable alternatives, recognising that in some patients who are already pregnant switching antiepileptic medicines may not be feasible. In this case, access to counselling about the risks should be provided and the Risk Acknowledgement Form signed by both specialist and patient.

Conclusion:

The MHRA's ban on usage of Valproate medicines without the pregnancy prevention programme is a step towards enhancing patient safety. The agency is ensuring that women and girls are aware of the real risks of taking valproate during pregnancy. Usage of information technology, communication and alert system is a good example of how IT systems can effectively support important issues affecting public health.

Ground Breaking: First marijuana based drug product nearing US FDA approval

An experimental drug derived from cannabis is well poised to become the first of its kind drug to win approval from the United States Food and Drug Administration (USFDA). The drug in question is being developed by GW Pharmaceuticals and is currently known as Epidiolex. Epidiolex is GW's lead cannabinoid product candidate and is a proprietary oral solution of pure plant-derived cannabidiol, or CBD. GW's Epidiolex development is initially concentrating on severe, orphan, early-onset, treatment-resistant epilepsy syndromes including Dravet syndrome, Lennox-Gastaut syndrome (LGS), Tuberous Sclerosis Complex (TSC) and Infantile Spasms (IS)[28].

Cannabidiol (CBD) is a cannabinoid prepared from the *Cannabis sativa* L. plant and is a new molecular entity. It is structurally unrelated to other drugs approved for the treatment of seizures. CBD is currently a Schedule I drug. The exact mechanism of the anticonvulsant effect of CBD is unknown but does not appear to involve an interaction with cannabinoid receptors.

During the initial review with the US FDA's internal review team, the experimental drug scored a favorable review[29]. The review concluded that the company has provided "substantial evidence" of the drug's effectiveness in treating two rare forms of epilepsy, which are Lennox-Gastaut syndrome (LGS), and Dravet syndrome (DS) in patients 2 years of age and older.

Subsequently, on April 19, 2018, the Peripheral and Central Nervous System Drugs Advisory Committee of the USFDA unanimously recommended supporting the approval of the New Drug Application (NDA) for the investigational cannabidiol oral solution (CBD), also known as Epidiolex®, for the adjunctive treatment of seizures associated with Lennox-Gastaut syndrome (LGS) and Dravet syndrome in patients two years of age and older[30]. The FDA Advisory Committee is an independent expert panel and even though their votes are not binding on the agency but are considered by the agency when deciding whether to approve or not to approve a new medicine. The PDUFA (Prescription Drug User Fee Act) goal date for completion of the NDA review of the cannabidiol oral solution is currently set at June 27, 2018.

Both LGS and DS are rare, severe, refractory epilepsy syndromes with onset in early childhood. The syndromes are categorized as developmental and epileptic encephalopathies, in which the epileptic activity is thought to contribute to developmental delay and behavioral abnormalities beyond the pathology of the underlying disease. The syndromes are characterized by multiple seizure types that are generally refractory to many of the drugs typically used for the treatment of seizures. Both syndromes are associated with higher rates of mortality than in the general epilepsy population, primarily due to status epilepticus and sudden unexpected death in epilepsy patients (SUDEP).

Efficacy and Safety Data

The efficacy and safety data was assessed from the following three randomized, double-blind, placebo-controlled trials:

- Study 1414 and Study 1423 – two 14-week, multicenter, randomized, double-blind, placebo-controlled trials in patients with LGS;

28 http://www.gwpharm.com/epilepsy-patients-caregivers/patients

29 https://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/PeripheralandCentralNervousSystemDrugsAdvisoryCommittee/UCM604736.pdf

30 http://ir.gwpharm.com/news-releases/news-release-details/gw-pharmaceuticals-and-us-subsidiary-greenwich-biosciences-1

- Study 1332B – a 14-week, multicenter, randomized, double-blind, placebo-controlled trial in patients with DS

For Efficacy

The agency's preliminary review concluded that the applicant has provided positive results from three randomized, double-blind, placebo-controlled trials conducted in patients with LGS and DS. The design of the studies and primary endpoints are consistent with other studies that have been used to support drug approvals for epilepsy indications, including LGS. The studies are adequate and well-controlled. The statistically significant and clinically meaningful results from these three studies provide substantial evidence of the effectiveness of CBD for the treatment of seizures associated with LGS and DS.

For Safety

The agency's preliminary review concluded that in general, the risks associated with cannabidiol appeared to be acceptable. Although the risk of liver injury has the potential to be serious, the observed risk can be appropriately managed with inclusion of relevant language in labeling, education of prescribers regarding the risk of transaminase elevation and need for monitoring of liver enzyme levels, and further characterization of the risk in the post-market setting.

Abuse Potential

Cannabidiol (CBD) is considered to be a new molecular entity for regulatory purposes because there are currently no FDA-approved drug products containing CBD. Under the Controlled Substances Act (CSA), CBD is a Schedule I substance based on its derivation from the plant, Cannabis sativa, also known as marijuana (hereafter, cannabis). Given that CBD is proposed for the treatment of a central nervous system (CNS) condition (epilepsy), it was necessary to evaluate the abuse potential of CBD through both preclinical studies (chemistry, receptor binding, animal behavioral studies) and clinical studies (including a human abuse potential study, as well as analyses of abuse-related adverse events in all clinical studies).

The agency's preliminary review concluded that in general the 750 mg dose of CBD (the low 10 mg/kg therapeutic dose) did not produce abuse potential signals. Although the two higher doses of CBD tested in studies (1500 and 4500 mg, representing the 20 mg/kg therapeutic dose and a supratherapeutic dose) produced some signals of abuse potential, they were small and often inside or just outside the acceptable placebo range. Thus, these data show that although CBD is present in the marijuana plant, it does not produce dronabinol-like responses or depressant-like responses that are indicative of abuse potential.

Overall Conclusion – Safety & Efficacy

The agency's preliminary review overall concluded that clinically meaningful and statistically significant reductions in seizure frequency were demonstrated in three adequate and well-controlled trials in LGS and DS. The results from these three studies provide substantial evidence of the effectiveness of CBD for the treatment of seizures associated with LGS and DS. Though the review is still ongoing, the risk-benefit profile established by the data in the application appears to support approval of cannabidiol for the treatment of seizures associated with LGS and DS.

Marijuana – Medical Usage

In the United States, the use of marijuana for medical purposes is legal in 29 states, In 2017 West Virgina was the latest state to legalize usage of Marijuana for medical purpose[31].

31 https://medicalmarijuana.procon.org

Proponents of medical marijuana argue that it can be a safe and effective treatment for the symptoms of cancer, AIDS, multiple sclerosis, pain, glaucoma, epilepsy, and other conditions. Opponents of medical marijuana argue that it is too dangerous to use, lacks FDA-approval, and that various legal drugs make marijuana use unnecessary. They say marijuana is addictive, leads to harder drug use, interferes with fertility, impairs driving ability, and injures the lungs, immune system, and brain.

FDA and Marijuana – Research and Development

The FDA so far has not approved marijuana as a safe and effective drug for any indication. The agency has, however, approved two drugs containing synthetic version of a substance that is present in the marijuana plant and one other drug containing a synthetic substance that acts similarly to compounds from marijuana but is not present in marijuana[32]. The FDA has approved Marinol and Syndros for therapeutic uses in the United States, including for the treatment of anorexia associated with weight loss in AIDS patients. Marinol and Syndros include the active ingredient dronabinol, a synthetic delta-9- tetrahydrocannabinol (THC) which is considered the psychoactive component of marijuana. Another FDA-approved drug, Cesamet, contains the active ingredient nabilone, which has a chemical structure similar to THC and is synthetically derived.

Although the agency has not yet approved any drug product containing or derived from botanical marijuana, the agency is aware that there is considerable interest in its use to attempt to treat a number of medical conditions, including, for example, glaucoma, AIDS wasting syndrome, neuropathic pain, cancer, multiple sclerosis, chemotherapy-induced nausea, and certain seizure disorders. Therefore, manufacturers may be able to make investigational drugs available to individual patients in certain circumstances through expanded access, as described in the FD&C Act and implementing regulations[33]. Conducting clinical research using marijuana involves interactions with several federal agencies in the United States. This includes - obtaining the marijuana for research from the National Institute on Drug Abuse (NIDA) within the National Institutes of Health or another Drug Enforcement Administration (DEA)-registered source; review of an investigational new drug (IND) application and the research protocol by the Food and Drug Administration (FDA) and an investigator registration and site licensure by the DEA[34].

Conclusion

The United States Food and Drug Administration is expected to decide whether to approve GW Pharma's investigational cannabidiol oral solution (CBD), also known as Epidiolex® by June 27, 2018. If approved, this could help pave the way for other cannabis-based drugs and will mark a sea change in the acceptability of cannabinoids as therapy.

32 https://www.fda.gov/NewsEvents/PublicHealthFocus/ucm421163.htm

33 https://www.fda.gov/NewsEvents/PublicHealthFocus/ucm421168.htm

34 https://www.fda.gov/NewsEvents/PublicHealthFocus/ucm421173.htm

Conference Briefs from American Association for Cancer Research (AACR) Annual Meeting 2018

The American Association for Cancer Research (AACR) Annual Meeting 2018, was held from 14th -18th April 2018, at Chicago, Illinois, USA. This year's theme, "Driving Innovative Cancer Science to Patient Care", was evident throughout the meeting as the latest and most exciting discoveries were showcased from every region of cancer research. A number of presentations included exciting new data from cutting-edge clinical trials as well as companion presentations that spotlighted the science behind the trials and implications for delivering improved care to patients. New exciting presentations from AACR 2018 are discussed below:

1. Successful CAR T-Cell Treatment Needs Good T Cells to Begin With - CAR T-Cell therapy, a type of immunotherapy based on the principle of adoptive T-Cell transfer, has revolutionized treatments for blood cancers, particularly in children. This therapy has yielded striking responses in some patients with cancers deemed incurable and in those who had stopped responding to chemotherapies and even resulted in complete remission rates of up to 90 percent in clinical trials.

Last year, the U.S. Food and Drug Administration approved two CAR T-Cell therapies - tisagenlecleucel (Kymriah, Novartis) was approved for treating certain pediatric and young adult patients with acute lymphoblastic leukemia (ALL) and; axicabtagene ciloleucel (Yescarta, Gilead) was approved for treating adults with certain types of non-Hodgkin lymphoma.

According to a research presented in the AACR Annual Meeting 2018 by David M. Barrett, MD, PhD, Assistant Professor of Pediatrics at Children's Hospital of Philadelphia, one of the approaches to improve CAR T-Cell therapy and potentially making it effective against solid tumors involves going back to the drawing board and looking at the starting material. . In this study, co-sponsored by a Stand up To Cancer (SU2C) Innovative Research Grant (the AACR is the Scientific Partner of SU2C), Barrett and colleagues found that a lot can be learned by closely examining the patient T cells which are an essential starting material for the process of CAR T-Cell manufacture.

An important criterion for modifying T-Cells into CAR-T cells is that the T-Cells from the patient must be healthy enough to survive during the complex endeavor of making them express a CAR, and then have enough energy left, once reintroduced in to the patient, to efficiently attack the cancer cells.

The metabolism of normal T-Cells changes when they are stimulated to convert into a CAR-T Cell, Barrett explained. Normal T Cells rely heavily on the fuel sources in the environment. They use one of the two fuel sources, the glycolysis or the glutamine and fatty acid pathway, to build their energy. The researchers learned that while T Cells that use glutamine and fatty acid pathways as fuel sources had great CAR T-Cell potential, those that depended on glycolysis were poorly suited to the process of CAR T-cell manufacture[35].

2. Pembrolizumab Plus Chemotherapy: According to data from the phase III clinical trial KEYNOTE-189, presented at the AACR Annual Meeting 2018, Practice-Changing for mNSCLC - Patients with nonsquamous metastatic non-small cell lung carcinoma (NSCLC) lived significantly longer and had a 48% reduced risk for disease progression if they received pembrolizumab (Keytruda, Merck) in addition to chemotherapy compared with those who received standard chemotherapy alone.

"The long-term survival of patients with advanced NSCLC remains poor and the standard of care for most patients is chemotherapy, which affords a survival benefit measured in months," said Leena Gandhi, MD, PhD, Associate

35 http://blog.aacr.org/improving-the-effectiveness-of-car-t-cell-immunotherapy/

Professor in the Department of Medicine and Director of Thoracic Medical Oncology Program, Perlmutter Cancer Center at NYU Langone Health.

In May 2017, the U.S. Food and Drug Administration approved pembrolizumab plus pemetrexed and carboplatin-based chemotherapy as first-line treatment for patients with advanced nonsquamous NSCLC based on data from the phase II cohort G of the KEYNOTE-021 study, but it was not widely adopted in the absence of positive results from a phase III study, Gandhi explained[36].

3. Adjuvant Pembrolizumab for Melanoma – According to the data presented at the AACR 2018 Annual Meeting and simultaneously published online in the New England Journal of Medicine, patients with stage III melanoma may soon have access to yet another immunotherapeutic agent after they undergo surgery. New data from a pivotal phase 3 trial show that 1,019 patients with stage 3 melanoma who were at high risk of recurrence after complete resection of their tumors in the KEYNOTE-054/EORTC 1325-MG. Patients were randomized 1:1 to a flat dose of 200 milligrams of pembrolizumab or placebo every three weeks for a total of 18 doses or until disease recurrence or unacceptable toxicity. Patients receiving Pembrolizumab (Keytruda, Merck) were at a 43% reduced risk for recurrence compared to patients who received placebo. These data are expected to lead to approval for this new indication. The FDA approved ipilumumab (Yervoy) and nivolumab (Opdivo), for use as an adjuvant treatment for patients with high-risk stage 3 melanoma that has been completely resected respectively in October 2015 and December 2017. The benefits of pembrolizumab were similar when patients with PD-L1-positive and PD-L1-negative tumors were analyzed separately. This study was conducted by the European Organisation for Research and Treatment of Cancer (EORTC) and sponsored by Merck[37].

4. Children with Non-chromosomal Birth Defects Face Higher Risk of Several Childhood Cancers - According to a study presented at the AACR Annual Meeting 2018, a retrospective analysis of registry data on more than 10 million live births, the risk for childhood cancers was 2.6-fold higher in children born with non-chromosomal abnormalities than in children born without any defects. In addition, some cancers were linked with specific birth defects.

"Approximately one in 33 children is born with a birth defect," said the study's lead author, Jeremy M. Schraw, PhD, a postdoctoral fellow at Texas Children's Cancer Center, Texas Children's Hospital. Some birth defects, including the fairly common cleft palate and cleft lip, had no association with childhood cancer. Childhood cancer is rare and, therefore, the risk that a child with a non-chromosomal birth defect will develop cancer during childhood is low, Schraw said.

In this study, the researchers pooled statewide registry data from Texas, Michigan, North Carolina, and Arkansas for the period 1992-2013, and linked information from birth certificates, birth defects registries, and cancer registries. They used Cox proportional hazard models to evaluate associations between 60 birth defects and 31 childhood cancers[38].

4. Tumor Mutational Burden (TMB) as New Biomarker in NSCLC - According to data from the phase III clinical trial CheckMate -227, presented at the AACR Annual Meeting 2018, a new biomarker has emerged in lung cancer. Patients with newly diagnosed advanced non–small cell lung cancer (NSCLC) who were found to have a high TMB >10 mutations/Mb, fared better with immunotherapy than with standard-of-care chemotherapy (CT). These patients were at a significantly 42% reduced risk for disease progression if they received the immunotherapy combination of nivolumab (Opdivo, Bristol-Myers Squibb) and ipilimumab (Yervoy, Bristol-Myers Squibb) compared with patients who received standard-of-care chemotherapy (CT).

36 http://www.aacr.org/Newsroom/Pages/News-Release-Detail.aspx?ItemID=1175#.Wtm_y4huaM8

37 http://www.aacr.org/Newsroom/Pages/News-Release-Detail.aspx?ItemID=1172#.Wtm1JIhuaM8

38 http://www.aacr.org/Newsroom/Pages/News-Release-Detail.aspx?ItemID=1171#.Wtm8CohuaM8

"The results show that in TMB-high NSCLC patients, nivolumab plus ipilimumab provides improved benefit compared to chemotherapy, increases benefit compared to anti-PD-1 monotherapy, yields durable responses, spares the use of chemotherapy in the first-line setting, and could preserve an effective option in the second line of therapy, if needed," said Matthew Hellmann, MD, attending at Memorial Sloan Kettering Cancer Center.

"These practice-changing data establish the combination of nivolumab plus ipilimumab as a first-line treatment option for patients with high-TMB NSCLC," Hellmann said. This work also identifies TMB as an important and reliable biomarker that should be tested in patients with newly diagnosed NSCLC, Hellmann added.

Nivolumab plus ipilimumab was well tolerated and the safety profile was similar to the previous experience with this regimen. The rate of treatment-related grade 3-4 toxicities was 31%, versus 36% with chemotherapy. This study was supported by Bristol Myers Squibb (BMS) and Ono Pharmaceutical[39].

5. Olaparib in Breast Cancer - PFS is significant but OS is not - According to the final analysis of OlympiAD trial A few months ago, olaparib (Lynparza, AstraZeneca) became the first drug approved to treat women with advanced breast cancer with germline mutations in BRCA. The approval was based on a significant improvement in progression-free survival (PFS) compared with standard chemotherapy. Now, however, a final analysis of OlympiAD trial results presented at the AACR Annual Meeting 2018 show that overall survival (OS) did not significantly improve.

At the final analysis, of the 302 patients randomly assigned, 205 received olaparib and 91 received chemotherapy (investigator's choice of capecitabine [Xeloda, Hoffmann-La Roche]), eribulin [Halaven, Eisai], or vinorelbine [Navelbine, Pierre Fabre]). With a hazard ratio (HR) of 0.90, patients receiving olaparib had a 10% reduced risk for death compared with those receiving chemotherapy, but these data did not reach statistical significance.

Benefit with olaparib was greatest for patients who received olaparib as first-line therapy - 22.6 months with olaparib vs 14.7 months with chemotherapy (HR, 0.51; 95% confidence intervals, 0.29 - 0.90; P = .02). OS was not significant for patients who received olaparib as a later line of therapy (median OS, 18.8 months vs 17.2 months for chemotherapy).[40]

39 http://www.aacr.org/Newsroom/Pages/News-Release-Detail.aspx?ItemID=1176#.WtnITohuaM8

40 https://www.medscape.com/viewarticle/895337

United States Food and Drug Administration permits marketing of first Artificial Intelligence based device

On April 11, 2018, the United States Food and Drug Administration (USFDA) permitted marketing of the first medical device to use artificial intelligence to detect greater than a mild level of the eye disease - diabetic retinopathy in adults who have diabetes[41].

The device - IDx-DR, is a software program that uses an artificial intelligence algorithm to analyze images of the eye taken with a retinal camera called the Topcon NW400. IDx-DR is intended for use by health care providers, to automatically detect more than mild diabetic retinopathy (mtmDR) in adults (22 years of age or older) diagnosed with diabetes who have not been previously diagnosed with diabetic retinopathy. IDx-DR is indicated for use with the Topcon NW400.

IDx-DR is the first device authorized for marketing which provides a screening decision without the need for a clinician to interpret the image or results, thereby, making it usable by health care providers who may not normally be involved in eye care. The FDA is permitting marketing of IDx-DR to IDx LLC.

Diabetic retinopathy occurs when high levels of blood sugar lead to damage in the blood vessels of the retina, the light-sensitive tissues at the back of the eye. Diabetic retinopathy is the most common cause of vision loss among the more than 30 million Americans living with diabetes and the leading cause of vision impairment and blindness among working-age adults. Early detection of retinopathy is an important part of managing care for the millions of people with diabetes, yet many patients are not adequately screened for diabetic retinopathy since about 50 percent of them do not see their eye doctor on a yearly basis. This decision permits the marketing of a novel artificial intelligence technology that can be used in a primary-care doctor's office.

The FDA evaluated data from a clinical study of retinal images obtained from 900 patients with diabetes at 10 primary care sites. The study was designed to evaluate how often IDx-DR could accurately detect patients with more than mild diabetic retinopathy. In the study, IDx-DR was able to correctly identify the presence of more than mild diabetic retinopathy 87.4 percent of the time and was able to correctly identify those patients who did not have more than mild diabetic retinopathy 89.5 percent of the time.

Patients who have a history of laser treatment, surgery or injections in the eye or who have any of the following conditions should not be screened for diabetic retinopathy with IDx-DR: persistent vision loss, blurred vision, floaters, previously diagnosed macular edema, severe non-proliferative retinopathy, proliferative retinopathy, radiation retinopathy or retinal vein occlusion. IDx-DR should not be used in patients with diabetes who are pregnant as diabetic retinopathy can progress very rapidly during pregnancy and the device is not intended to evaluate rapidly progressive diabetic retinopathy. IDx-DR is only designed to detect diabetic retinopathy, including macular edema; it should not be used to detect any other disease or condition. Patients will still need to get a complete eye examination at the age of 40 and at 60, and also if they have any vision related symptoms like persistent vision loss, blurred vision or floaters.

IDx-DR was reviewed under the FDA's De Novo premarket review pathway, a regulatory pathway for some low- to moderate-risk novel devices for which there is no prior legally marketed device. IDx-DR was granted Breakthrough Device designation - which means that the FDA provided intensive interaction and guidance to the company on efficient device development, to expedite evidence generation and the agency's review of the device. To qualify for such designation, a device must provide for more effective treatment or diagnosis of a life-threatening or irreversibly debilitating disease or condition and meet one of the following criteria - the device must represent a

41 https://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm604357.htm

breakthrough technology; there must be no approved or cleared alternatives; the device must offer significant advantages over existing approved or cleared alternatives; the availability of the device is in the best interest of patients.

How IDx-DR works

A doctor uploads the digital images of the patient's retinas to a cloud server on which IDx-DR software is installed. If the images are of sufficient quality, the software provides the doctor with one of two results: (1) "more than mild diabetic retinopathy detected: refer to an eye care professional" or (2) "negative for more than mild diabetic retinopathy; rescreen in 12 months." If a positive result is detected, patients should see an eye care provider for further diagnostic evaluation and possible treatment as soon as possible.

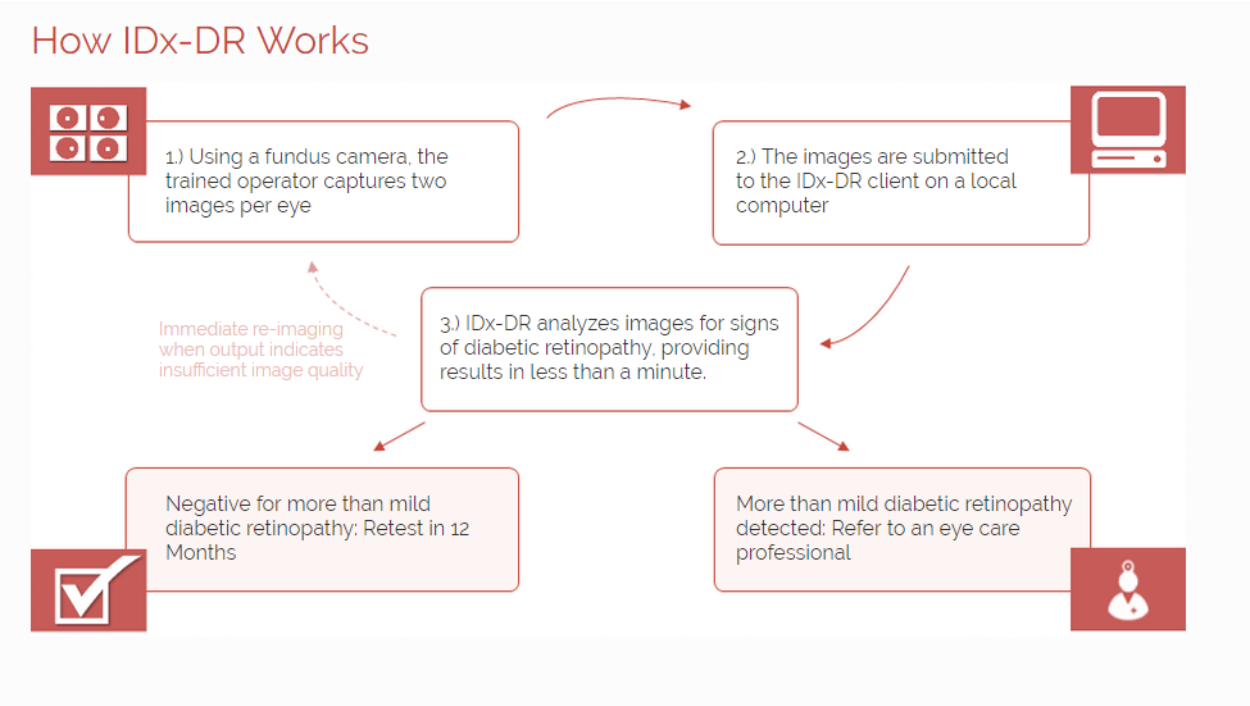


Figure 1: Illustration on how IDx-DR works (Adapted from: Product Catalogue[42])

Recent updates on Artificial Intelligence, Deep Learning & Technology companies

This approval from the US FDA is a welcome news for large technology companies like Google, Microsoft, and IBM, all of whom have made big investments in the medical AI space. Google had recently announced its AI breakthrough which can successfully predict cardiovascular problems such as heart attacks and strokes simply from images of the retina, with no blood draws or other tests necessary. The results of the Google AI research have been published in an article entitled "Prediction of Cardiovascular Risk Factors from Retinal Fundus Photographs via Deep Learning" in Nature Biomedical Engineering[43]. The study concluded that - the results have provided evidence that deep learning may uncover additional signals in retinal images that will allow for better cardiovascular risk stratification. In particular, they could enable cardiovascular assessment at the population level by leveraging the existing infrastructure used to screen for diabetic eye disease.

42 https://www.eyediagnosis.net/idx-dr

43 http://www.nature.com/articles/s41551-018-0195-0

United States Trade Representative raise public concerns on India's price control on medical devices

The United States Trade Representative (USTR), in its 2018 National Trade Estimate Report on 'Foreign Trade Barriers', has for the first time publicly raised concerns on India's price controls on medical devices. In a subsection on India titled 'Other barriers', the USTR speaks specifically about the National Pharmaceutical Pricing Authority's (NPPA) Price Control Order on Medical Devices[44].

Background

The 2018 National Trade Estimate Report on Foreign Trade Barriers (NTE) is an annual series that highlights significant foreign barriers to U.S. exports. This document is a companion piece to the President's 2018 Trade Policy Agenda and 2017 Annual Report published by Office of the United States Trade Representative in March.

The NTE Report is based upon information compiled within USTR, the Departments of Commerce and Agriculture, and other U.S. Government agencies, as well as U.S. Embassies and supplemented with information provided in response to a notice published in the Federal Register, and by members of the private sector trade advisory committees.

The report discusses the largest export markets for the United States, covering 60 countries including the European Union, Taiwan, Hong Kong, and one regional body. The NTE covers significant barriers, whether they are consistent or inconsistent with international trading rules. The report classifies foreign trade barriers into ten different categories. These categories cover government-imposed measures and policies that restrict, prevent, or impede the international exchange of goods and services. The categories covered include:

1. Import policies (e.g., tariffs and other import charges, quantitative restrictions, import licensing, customs barriers, and other market access barriers);
2. Sanitary and phytosanitary measures and technical barriers to trade;
3. Government procurement (e.g., "buy national" policies and closed bidding);
4. Export subsidies (e.g., export financing on preferential terms and agricultural export subsidies that displace U.S. exports in third country markets);
5. Lack of intellectual property protection (e.g., inadequate patent, copyright, and trademark regimes and enforcement of intellectual property rights);
6. Services barriers (e.g., limits on the range of financial services offered by foreign financial institutions, restrictions on the use of foreign data processing, and barriers to the provision of services by foreign professionals);
7. Investment barriers (e.g., limitations on foreign equity participation and on access to foreign government-funded research and development programs, local content requirements, technology transfer requirements and export performance requirements, and restrictions on repatriation of earnings, capital, fees and royalties);
8. Government-tolerated anticompetitive conduct of state-owned or private firms that restricts the sale or

44 https://ustr.gov/sites/default/files/files/Press/Reports/2018%20National%20Trade%20Estimate%20Report.pdf

purchase of U.S. goods or services in the foreign country's markets;

9. Digital trade barriers (e.g., restrictions and other discriminatory practices affecting cross border data flows, digital products, Internet-enabled services, and other restrictive technology requirements); and,

10. Other barriers (barriers that encompass more than one category, e.g., bribery and corruption, or that affect a single sector).

2018 National Trade Estimate Report – Specific Sections on India

The NTE report raises concerns on various issues impacting trade between the two countries; concerns raised w.r.t areas of pharmaceuticals, life-sciences, medical, biotechnology, and medical devices are discussed below:

IMPORT LICENSES

The report highlights that India maintains various forms of nontariff regulation on three categories of products - banned or prohibited items (e.g., tallow, fat, and oils of animal origin); restricted items that require an import license (e.g., livestock products and certain chemicals); and "canalized" items (e.g., some pharmaceuticals) which can be imported only by government trading monopolies and are subject to cabinet approval regarding import timing and quantity. These requirements are often not fully transparent as the timing and quantity restrictions are infrequently published in its Official Gazette or notified to WTO committees.

OTHER BARRIERS

Price Controls on Medical Devices

The report highlights that on February 13, 2017, India's National Pharmaceutical Pricing Authority (NPPA) announced a price control order on all coronary stents for sale in India. The order set price categories that do not "fully differentiate for advanced technologies within a product class", requiring newer technology stents be sold at the same prices as older technology products, resulting in some technologically advanced stents selling at a loss.

The report further states that several U.S. companies have applied to "withdraw their most technologically advanced products from the Indian market due to the policy", but those requests have been repeatedly rejected by Indian regulators. U.S. stakeholders claim they must "continue to sell their products at a loss in the Indian market for up to 18 months".

The United States has asked that India further differentiate the price controls for advanced products, allow the withdrawal of products, and not extend the policy to additional products. Despite these concerns, on August 16, 2017, NPPA issued an additional price control order on 15 different orthopedic knee implant systems.

USTR Announces New GSP Eligibility Reviews of India

Soon after the release of the NTE report, the USTR announced that it will be reviewing India's status as a recipient of the US's Generalized System of Preferences (GSP)[45].

The Generalized System of Preferences (GSP) is a U.S. trade preference programs that provides opportunities for many of the world's poorest countries to use trade to grow their economies and climb out of poverty. GSP is the largest and oldest U.S. trade preference program, "designed to promote economic development" for developing countries. It allows duty-free entry for some imports from certain developing countries into the US[46].

45 https://ustr.gov/about-us/policy-offices/press-office/press-releases/2018/april/ustr-announces-new-gsp-eligibility

46 https://ustr.gov/issue-areas/trade-development/preference-programs/generalized-system-preference-gsp

Now the USTR has announced that it is launching a self-initiated GSP eligibility review of India based on concerns related to its compliance with the GSP market access criterion and is also accepting two petitions related to the same criterion. The petitions filed by the U.S. dairy industry and the U.S. medical device industry requested a review of India's GSP benefits, given Indian trade barriers affecting U.S. exports in those sectors. India has implemented a wide array of trade barriers that create serious negative effects on U.S. commerce. The acceptance of these petitions and the GSP self-initiated review will result in one overall review of India's compliance with the GSP market access criterion.

One of such petition concerning India's GSP review was filed by the AdvaMed (Advanced Medical Technology Association) which is a trade association that claims lead the effort to advance medical technology. AdvaMed in October 2017, filed a petition with the U.S. Trade Representative (USTR) requesting that India's benefits under the Generalized System of Preferences (GSP) be suspended or withdrawn[47].

Conclusion:

There has been fierce lobbying in India and the United States through various Industry bodies, Trade Unions and Lobby groups for the dilution or revocation of India's pricing control mechanism specifically for cardiac stents, and medical devices. Now for the first time the US government has published a report which contains its public comments against India's decision to impose price control on the medical devices.

47 https://www.advamed.org/newsroom/press-releases/advamed-seeks-relief-india-price-controls-under-us-trade-laws

US FDA finalizes guidance on Liposome Drug Products

On April 04, 2018, the United States Food and Drug Administration (USFDA) finalized its Guidance for Industry on Liposome Drug Products - Chemistry, Manufacturing, and Controls; Human Pharmacokinetics and Bioavailability; and Labeling Documentation. The guidance provides unique aspects and the types of information sponsors should submit for new drug applications (NDAs) and abbreviated new drug applications (ANDAs) for liposome drug products[48].

The 18-page guidance describes the following topics for liposome drug products: (A) chemistry, manufacturing, and controls (CMC); (B) human pharmacokinetics and bioavailability or, in the case of an ANDA, bioequivalence and (C) labeling. Sections of the guidance also touch on descriptions and composition, physicochemical properties, critical quality attributes, description of manufacturing process and process controls, control of lipid components, drug product specification, stability and post-approval changes in manufacturing. The guidance does not provide recommendations on clinical efficacy and safety studies, nonclinical pharmacology and/or toxicology studies, liposome formulations of vaccine adjuvants or biologics or drug-lipid complexes.

Background

Liposomes are vesicles composed of a bilayer (uni-lamellar) and/or a concentric series of multiple bilayers (multi-lamellar) separated by aqueous compartments formed by amphipathic molecules such as phospholipids that enclose a central aqueous compartment. In a liposome drug product, the drug substance is generally contained in liposomes.

Typically, water soluble drugs are contained in the aqueous compartment(s) and hydrophobic drugs are contained in the lipid bilayer(s) of the liposomes. Release of drugs from liposome formulations, among other characteristics such as liposomal clearance and circulation half-life, can be modified by the presence of polyethylene glycol and/or cholesterol or other potential additives in the liposome. A liposome drug formulation is different from (1) an emulsion, which is a dispersed system of oil in water, or water in oil phases containing one or more surfactants, (2) a microemulsion, which is a thermodynamically stable two-phase system containing oil or lipid, water and surfactants, and (3) a drug-lipid complex.

A. Chemistry, Manufacturing, and Controls

The guidance recommends the following information should be included in the application:

1) Description and Composition; 2) Physicochemical Properties; 3) Critical Quality Attributes; 4) Description of Manufacturing Process and Process Controls; 5) Control of Lipid Components; 6) Drug Product Specification; 7) Stability; and 8) Post-approval Changes in Manufacturing

B. Human Pharmacokinetics: Bioavailability and Bioequivalence

The guidance says that for ANDA (Abbreviated New Drug Application) submissions for liposome drug products, the applicant should refer to applicable product-specific FDA guidance documents that outline recommendations regarding human pharmacokinetic and other bioequivalence studies for generic liposome drug products. These guidance documents also discuss additional characterization studies and information (e.g., drug product composition and active ingredient loading) necessary to demonstrate pharmaceutical equivalence to the RLD. When no product-specific guidance exists for a generic product, this guidance applies. If an applicant is contemplating submitting an ANDA, it should consider contacting Office of Generic Drugs to request a pre-ANDA meeting.
The guidance further states that because of the complex interaction between drug release from the liposome drug product and the tissue and/or cellular uptake of the drug substance and/or the liposome, a simple

48 https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM070570.pdf

measurement of total drug substance concentration in plasma may not be reflective of bioavailability of the drug at the intended target organ (i.e., site of action). Therefore, for NDA submissions, the applicant should consult the appropriate Center for Drug Evaluation and Research (CDER) review division for advice concerning the determination of bioavailability of liposome drug products.

C. Labeling

The guidance provides specific recommendations regarding labeling content for liposome drug products.

1. Nonproprietary Names of Drug Products Approved under the Federal Food, Drug, and Cosmetic Act

The nonproprietary name of a drug product approved under the Federal Food, Drug, and Cosmetic Act is its established name, which, in most instances, will be the United States Pharmacopeia (USP) drug product monograph title for that product. The liposome drug product nonproprietary name should include terminology to express that the product is a liposome or a pegylated liposome.

2. Description Section

The applicant should include a cautionary note emphasizing that liposome drug products may behave differently from non-liposome drug products or other liposome products even though the active ingredient is the same. The applicant should specifically describe such differences. Note: It is not necessary for liposome drug products determined by FDA to be therapeutically equivalent.

3. Dosage & Administration

The applicant should include a statement recommending against substituting the liposome drug product for the non-liposome product or another liposome drug product that contains the same active ingredient unless FDA has determined that the products are therapeutically equivalent.

The guidance also recommends where appropriate, reconstitution instructions and a statement regarding the appropriate in-use period should be provided. This information should be provided for both unloaded liposomes that are reconstituted with a drug substance-containing solution at the time of use and for products in which the drug substance is loaded into the liposomes during manufacturing. For liposome drug products that are labeled for use after mixing with other approved drug products (e.g., large volume injectable solutions), admixing instructions and a statement regarding the appropriate in-use period of the admixed product should be included. As warranted, include storage conditions for the reconstituted drug, robustness of the liposome drug product under varied reconstitution conditions (e.g., degree of shaking), and use of in-line filters.

United State FDA restricts sale and distribution of Bayer's Essure device

On April 9, 2018, the United States Food and Drug Administration (US-FDA) issued an order to restrict the sale and distribution of the Essure device to ensure that all women considering use of the permanent contraception device are provided with adequate risk information so that they can make informed decisions[49]. The FDA is taking this step after becoming aware that some women were not being adequately informed of Essure's risks before getting the device implanted, despite previous significant efforts to educate patients and doctors about the risks associated with this device.

The FDA is requiring a unique type of restriction, using its authority to restrict the sale and distribution of a device, which imposes additional requirements needed to provide a reasonable assurance of its safety and effectiveness. The FDA is committed to continuing to use its full authority to ensure the post-market safety of medical products.

What is Essure®?

Essure is a permanent birth control procedure that works with your body to create a natural barrier against pregnancy. The Essure procedure involves placing soft, flexible inserts into your fallopian tubes. Over a period of about three months, tissue forms around the inserts. The build-up of tissue creates a barrier that keeps sperm from reaching the eggs and prevents conception. Essure was approved in 2002 by the FDA. Over 750,000 women and their doctors have chosen Essure for permanent birth control (based on units sold worldwide).

Essure is the only permanently implanted birth control device for women in the market that does not require a surgical incision. Some patients implanted with Essure have experienced adverse events, including perforation of the uterus and/or fallopian tubes, migration of inserts to the abdominal or pelvic cavity, persistent pain and suspected allergic or hypersensitivity reactions. In addition, women have also reported experiencing headache, fatigue, weight changes, hair loss and mood changes, such as depression. It is unknown whether these symptoms are related to Essure.

Background

Since Essure's approval in 2002, the agency has continued to monitor the product's safety and effectiveness by reviewing the medical literature, clinical trial information, post-approval study data and medical device reports submitted to the agency. Based on this review, in February 2016, the agency ordered Bayer to conduct a post-marketing (522) study to better evaluate the safety profile of the device when used in the real world. The agency is currently monitoring the company's progress.

In November 2016, the FDA also required Bayer to add a boxed warning to the product labeling, stating information about adverse events associated with the device "including perforation of the uterus and/or fallopian tubes, identification of inserts in the abdominal or pelvic cavity, persistent pain, and suspected allergic or hypersensitivity reactions." In addition to the warning, the FDA also required a more comprehensive patient decision checklist be added to the device labeling to provide women considering Essure information about the benefits and risks of this device before deciding to use it.

Since the FDA ordered Bayer to conduct a post-market study, and then to add a boxed warning and a patient decision checklist to the labeling, there has been an approximately 70 percent decline in sales of Essure in the U.S.

49 https://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm604098.htm

The FDA has determined, however, that some women still are not receiving information about the known risks of Essure before implantation.

The new Essure labeling, which will now be legally required when this product is offered to a patient, restricts the sale and distribution of the device to only health care providers and facilities that provide information to patients about the risks and benefits of this device. Specifically, the patient brochure[50], titled "Patient-Doctor Discussion Checklist – Acceptance of Risk and Informed Decision Acknowledgement," must be reviewed with the prospective patient by the health care provider to ensure the patient understands the risks, benefits and other information about Essure implantation. The patient must be given an opportunity to sign the acknowledgment, and it must be signed by the physician implanting the device.

Bayer, the device manufacturer, is required to implement the restrictions immediately and ensure that the process going forward results in health care provider compliance with the sales restriction. The FDA will review and monitor Bayer's plan to ensure the company complies with the restriction. The FDA plans to enforce these requirements and will take appropriate action for a failure to comply, including applicable criminal and civil penalties.

50 http://labeling.bayerhealthcare.com/html/products/pi/essure_pib_en.pdf

USFDA approves first therapy for rare, inherited form of rickets - x-linked hypophosphatemia

On April 17, 2018, the United States Food and Drug Administration (US-FDA) approved Crysvita (burosumab), the first drug approved to treat adults and children aged 1 year and older with x-linked hypophosphatemia (XLH), a rare, inherited form of rickets[51]. XLH causes low levels of phosphorus in the blood. It leads to impaired bone growth and development in children and adolescents and problems with bone mineralization throughout a patient's life.

The FDA granted approval of Crysvita to Ultragenyx Pharmaceutical Inc., a biopharmaceutical company focused on the development of novel products for rare and ultra-rare diseases.

The safety and efficacy of Crysvita were studied in four clinical trials. In the placebo-controlled trial, 94 percent of adults receiving Crysvita once a month achieved normal phosphorus levels compared to 8 percent of those receiving placebo. In children, 94 - 100% of patients treated with Crysvita every two weeks, achieved normal phosphorus levels. In both children and adults, X-ray findings associated with XLH improved with Crysvita therapy. Comparison of the results to a natural history cohort also provided support for the effectiveness of Crysvita.

About X-Linked Hypophosphatemia (XLH)

According to the National Institute of Health (NIH) of the United States, X-linked hypophosphatemia (XLH) is an inherited disorder characterized by low levels of phosphate in the blood. Phosphate levels are low because phosphate is abnormally processed in the kidneys, which causes a loss of phosphate in the urine (phosphate wasting) and leads to soft, weak bones (rickets). XLH is usually diagnosed in childhood. Features include bowed or bent legs, short stature, bone pain, and severe dental pain[52].

XLH is caused by mutations in the PHEX gene on the X chromosome, and inheritance is X-linked dominant. Treatment generally involves supplements of phosphate and high-dose calcitriol (the active form of Vitamin D), and may also include growth hormones, corrective surgery, and dental treatment. The long-term outlook varies depending on severity and whether complications arise. While some adults with XLH may have minimal medical problems, others may experience persistent discomfort or complications.

XLH is a serious disease affecting approximately 3,000 children and 12,000 adults in the United States. Most children with XLH experience bowed or bent legs, short stature, bone pain and severe dental pain. Some adults with XLH experience persistent discomfort or complications, such as joint pain, impaired mobility, tooth abscesses and hearing loss.

Crysvita is designed to bind the excess FGF23 in these patients, normalizing phosphorus levels, improving bone mineralization, improving rickets in children and healing fractures in adults.

About Crysvita

Crysvita is a recombinant fully human monoclonal IgG1 antibody, discovered by Kyowa Hakko Kirin, against the phosphaturic hormone fibroblast growth factor 23 (FGF23). FGF23 is a hormone that reduces serum levels of phosphorus and active vitamin D by regulating phosphate excretion and active vitamin D production by the

51 https://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm604810.htm

52 https://rarediseases.info.nih.gov/diseases/12943/x-linked-hypophosphatemia

kidney. Phosphate wasting in XLH is caused by excessive levels and activity of FGF23. Crysvita is designed to bind to and thereby inhibit the biological activity of FGF23. By blocking excess FGF23 in patients, Crysvita is intended to increase phosphate reabsorption from the kidney and increase the production of active vitamin D, which enhances intestinal absorption of phosphate and calcium[53].

Earlier, Crysvita was granted *Breakthrough Therapy designation*, under which the FDA provides intensive guidance to the company on efficient drug development, and expedites its review of drugs that are intended to treat serious conditions where clinical evidence shows the drug may represent a substantial improvement over other available therapies. Crysvita also received *Orphan Drug designation*, which provides incentives to assist and encourage the development of drugs for rare diseases.

The sponsor also received a *Rare Pediatric Disease Priority Review Voucher.* According to the Federal Food, Drug, and Cosmetic Act (FD&C Act), FDA awards priority review vouchers to sponsors of rare pediatric disease product applications that meet certain criteria. Under this program, a sponsor who receives an approval for a drug or biologic for a "rare pediatric disease" may qualify for a voucher that can be redeemed to receive a priority review of a subsequent marketing application for a different product[54].. This is only the 14th Rare Pediatric Disease Priority Review Voucher issued by the FDA since the program began.

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53 http://ir.ultragenyx.com/news-releases/news-release-details/ultragenyx-and-kyowa-kirin-announce-fda-approval-crysvitar

54 https://www.fda.gov/ForIndustry/DevelopingProductsforRareDiseasesConditions/RarePediatricDiseasePriorityVoucherProgram/default.htm

notes

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