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Vol. II, Issue V
May 2018

S&A PHARMA NEWSLETTER

EDITORIAL

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Founding Partner

It gives us immense pleasure to present Vol. II Issue V of *S&A – Pharma Newsletter*. The aim of the Newsletter is to disseminate regulatory information on 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. 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 regimen but also equipped with integrated services to best respond to healthcare problems.

To begin with, we discuss extent and implications of union cabinet's recently approved Protocol under World Health Organization (WHO) Framework Convention on Tobacco Control (FCTC), to eliminate illicit trade in tobacco products in the country. Going forward, this edition addresses the recent regulatory developments in healthcare research, new therapy approvals and notable regulatory reforms. This issue therefore, covers the release of Final guideline for implementation of Public Procurement (Preference to Make in India) Order (PPO), 2017 with respect to public procurement of goods and services in medical devices, released by Department of Pharmaceuticals (DoP); followed by an article on 79th meeting of Drug Technical Advisory Board (DTAB) recommendation to amend the provisions of Medical Device Rules (MDR), 2018.

From the international arena, we talk about recent developments qua regulatory authorities of foreign jurisdictions. First, we discuss the World Health Organization's (WHO) call upon member states and partners to accelerate efforts to end rabies, which causes a number of painful deaths globally every year, mostly affecting children and the poor population. Next, we have a write-up on European Medicines Agency's updated ICH S9 guideline, which aims to assist in the design of non-clinical studies for the development of anti-cancer pharmaceuticals. Further, we provide highlights from the the EMA's Pharmacovigilance Risk Assessment Committee's (PRAC) Meeting held in May 2018, which confirmed its recommendation to suspend of Zinbryta (daclizumab beta) and Esmya (ulipristal acetate) from European Market, and issued precautionary advice on HIV medicine Dolutegravir.

This Newsletter also has write-ups on topics such as (i) United States Food and Drug Administration (USFDA) approval to Aimovig (erenumab-aooe) for the preventive treatment of migraine in adults (ii) USFDA announcement of a list of drug makers who are delaying the generic completion by prohibiting access of Reference Listed Drug (RLD); and lastly (iii) the USFDA approval to Tafinlar (dabrafenib) and Mekinist (trametinib) combination for the treatment of anaplastic thyroid cancer (ATC) which cannot be removed by surgery or has spread to other parts of the body (metastatic), and has a type of abnormal gene, BRAF V600E (BRAF V600E mutation-positive), this is the first FDA-approved treatment for patients with this aggressive form of thyroid cancer.

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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Volume II, Issue V
May 2018

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Singh & Associates
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Cabinet approves the Protocol under WHO-FCTC to eliminate illicit trade in tobacco products

The Union Cabinet, chaired by the Prime Minister of India, has given approval to accede to the Protocol under World Health Organization (WHO) Framework Convention on Tobacco Control (FCTC) to eliminate illicit trade in tobacco products[1]. It will be applicable to all smoking and chewing products and smokeless tobacco (SLT) forms as negotiated and adopted under Article 15 of the World Health Organization Framework Convention on Tobacco Control (WHO FCTC). At present India is a party to WHO FCTC.

The WHO FCTC Protocol

The protocol lays down obligations of the parties. It spells out the supply chain control measures which must be adopted by the parties viz. licensing of manufacture of tobacco products and machinery for manufacturing of tobacco products, due diligence to be kept by those engaged in production, tracking and tracing regime, record keeping, security; and measures to be taken by those engaged in e-commerce, manufacturing in free-trade zones and duty-free sales.

The protocol lists out offences, enforcement measures such as seizures and disposal of seized products. It calls for international cooperation in information sharing, maintaining confidentiality, training, technical assistance and cooperation in scientific and technical and technological matters.

Impact of protocol approval

It is envisaged that elimination of illicit trade in tobacco products through strengthened regulation will help in strengthening comprehensive tobacco control, leading to reduction in tobacco use which in turn, will result in reduction in disease burden and mortality associated with tobacco use.

Accession to such treaty will provide actionable alternatives against such prevailing practices that are affecting public health at large. India, being at the forefront of tobacco control, will be able to influence the international organizations including World Custom Organization in controlling such illicit trade.

The protocol to eliminate illicit trade in tobacco products is a path breaking initiative in strengthening global action against tobacco and is also a new legal instrument for improving public health. It is a comprehensive tool to counter and eventually eliminate illicit trade in tobacco products and to strengthen legal dimensions for international health cooperation.

About WHO FCTC

The WHO Framework Convention on Tobacco Control (WHO FCTC) is the first international public health treaty negotiated under the auspices of the WHO. The WHO FCTC was developed in response to the globalization of the tobacco epidemic and is an evidence-based treaty that reaffirms the right of all people to the highest standard of health. The Convention represents a milestone for the promotion of public health and provides new legal dimensions for international health cooperation.

The objective of FCTC is to provide a framework for supply and demand reduction measures for tobacco control at the regional, national and global levels. One of the key tobacco supply reduction strategies contained in Article 15 of WHO FCTC envisages elimination of all forms of illicit trade and tobacco products, including smuggling, illicit manufacturing and counterfeiting. Accordingly, the said Protocol was developed and adopted by the Conference of Parties (COP) which is the governing body of FCTC. The protocol is divided into 10 parts and contains 47 Articles.

1 http://pib.nic.in/PressReleseDetail.aspx?PRID=1530953

Department of Pharmaceuticals (DoP) releases final guidance on procurement of Medical Devices under Public Procurement Order (PPO), 2017

On May 18, 2018, the Department of Pharmaceuticals (DoP), Ministry of Chemicals and Fertilizers, released final guideline for implementation of provisions of the Public Procurement (Preference to Make in India) Order (PPO), 2017, with respect to public procurement of goods and services in medical devices[2].

The Department of Industrial Policy and Promotion (DIPP) issued PPO, 2017, and to facilitate the implementation of the order it had identified DoP as the Nodal Ministry for implementing certain provisions of the PPO 2017 related to medical devices product category. i.e.

- Para 3 of PPO, 2017, makes it mandatory for procuring entities to give purchase preference to local suppliers,
- Para 5 of PPO, 2017, empowers Nodal Ministry to prescribe percentage and the manner of calculation of minimum local content in respect of any particular item relating to Pharmaceutical sector, and
- Para 9 of PPO, 2017, deals with verification of local content.

Now DoP has issued the following guidelines with respect to public procurement of good and services in Medical Devices under PPO, 2017-

Percentage of Minimum Local Content

Medical Device Industry (MDI) is a multiproduct industry responsible for provisioning of wide variety of crucial medical products ranging from simple tongue depressors & glucometer strips to large radiology & electronic medical equipments. Individually there are around 5000 different kinds of medical devices and it is not practical to prescribe the local content and percentage of preference in domestic procurement for each medical device. Moreover, DoP needs accurate & reliable data regarding:

- total capacity and production of various categories of medical devices in India,
- the level of competition in the market in different segment of medical devices
- the processes involved in the manufacture of medical devices for prescribing the percentage of minimum local content for each category of medical devices,

The percentage of local content, the manner of calculation of local content and the provision of supplies to be procured from local supplier may be revised after relevant data in this regard becomes available.

However for the time being, based on the present level of the understanding of the medical device market in India and discussion with various industry representatives, DoP, in accordance with Para 5 of PPO, 2017, prescribes the following percentages of minimum local content for various categories of medical devices for preference in public procurement:

2 http://pharmaceuticals.gov.in/sites/default/files/Final%20Guidelines.pdf

S l . No.	Category of Medical Devices	% of Minimum Local Content	% of Local Content proposed to be increased in phased manner over next three years
1	Medical disposables and consumables	50%	50% to 75%
2	Medical electronics, hospital equipment, surgical instruments	25%	25% to 45%
3	Implants	40%	40% to 60%
4	Diagnostic Reagents/IVDs	25%	25% to 45%

Manner of calculation of local content:

i. Local content of Medical Device shall be computed on the basis of the cost of domestic components in the device/service compared to the total cost of the device/ service. The total cost of product shall be the cost incurred for the production of the medical device including direct component i.e. material cost, manpower cost and overhead costs including profit but excluding taxes and duties.

ii. The determination of local content cost shall be based on the following:

a) in the case of direct component (material), based on the country of origin;

b) in the case of manpower, based on domestic manpower

iii. The calculation of local content of the combination of several kinds of goods shall be based on the ratio of the sum of multiplication of local content of each goods with the acquisition price of each goods to the acquisition price of combination of goods.

iv. Format of calculation of local content:

Name of Manufacturer	Calculation by Manufacturer (Cost per unit of product)		
Cost component	Cost (Domestic Component) a	Total Cost b	Percentage of local content C=(a/b)*100
1. ------- 2. ------- 3. Total Cost (Excluding Tax and Duties)			

Requirement of Purchase Preference

Purchase preference shall be given to local suppliers by all procuring entities as per provisions laid down in para 3 of PPO, 2017. Further, as per the provision of para 3(a) of PPO 2017, in procurement of goods where sufficient local capacity and local competition exist, and estimated value of procurement is upto Rs. 50 Lakhs or less, a list of goods will be issued by this department in due course. Till the time such a list is issued, provision of Para 3(b) and Para 3(c) of PPO, 2017, as applicable, shall apply for all procurements without regards to value of procurement.

Verification of Local Content

I. The local supplier, at the time of tender, bidding or solicitation, shall be required to furnish self-certification of local content in the format as contained in the Guidance.

II. In case of procurement for a value in excess of Rs. 10 crores, the local supplier shall be required to provide a

certificate from a statutory auditor or cost auditor of the company (in case of companies); from a practicing cost accountant and practicing chartered accountant (in respect of suppliers other than companies) giving the percentage of local content.

III. In each tender, procuring entity shall clearly mention the details of its competent authority empowered to look into procurement related complaints and the fees for such complaints, relating to implementation of PPO, 2017.

IV. In case a complaint is received by the procuring entity against the claim of a bidder regarding domestic value addition in medical device, the procuring entity shall have full rights to inspect and examine all the related documents and take a decision. In case any clarification is needed, matter may be referred to DoP to the grievance redressal committee.

V. Any complaint referred to the procuring entity shall be submitted along with all necessary documentation in support of the complaint regarding domestic value addition claimed in medical device and shall be disposed of within 4 weeks of the reference by the procuring entity.

VI. In case, the complaint is referred to DoP by a bidder or procuring entity, the grievance redressal committee to be set up under DoP for the purpose shall dispose-off the complaint.

VII. In case, the matter is referred to DoP, the grievance redressal committee shall dispose-off the complaint within 4 weeks of its reference and receipt of all documents from the bidder after taking in consideration, the view of the procuring entity. The bidder shall be required to furnish the necessary documentation in support of the local content claimed in medical devices to the grievance redressal committee of DoP within 2 weeks of the reference of the matter. If no information is furnished by the bidder, the grievance redressal committee may take further necessary action, in consultation with procuring entity to establish the bonafides of the claim.

VIII. In case of reference of any complaint to DoP by the concerned bidder, there would be a fee of Rs. 2 Lakh or 1% of the value of the medical devices being procured (subject to a maximum of Rs. 5 Lakh), whichever is higher, to be paid by way of a Demand Draft to be deposited with the procuring entity, along with the complaints by the complainant. In case, the complaint is found to be incorrect, the complaint fee shall be forfeited. In case, the complaint is upheld and found to be substantially correct, deposited fee of the complainant would be refunded without any interest.

Note - All other provisions of PPO, 2017 shall be applicable as such, and shall be adhered to by all procuring agencies for procurement of any medical device. This guideline shall remain applicable for one year from the date of issuance or until further orders are released in this regard.

Drug Technical Advisory Board (DTAB) recommends amendments to the Medical Devices Rules, 2017

The Medical Devices Rules (MDR), 2017, was published vide G.S.R. 78(E) dated January 31, 2017 under the provisions of Drugs and Cosmetics Rules by the Ministry of Health and Family Welfare (MoH&FW). The MDR, 2017, rules were made effective from January 01, 2018 to regulate the clinical investigation, manufacture, import, and sale & distribution of Medical Devices in the country.

On May 16, 2018, the 79th meeting of Drug Technical Advisory Board (DTAB) considered the representations from the industry/ stakeholders/ associations for amending the MDR, 2017.The DTAB deliberated the matter and recommended to amend the following provisions of DMR, 2018[3]:

The DTAB deliberated the matter and recommended the environmental requirements for the final packing of sterile surgical dressings and also for final packing of condoms. Annexure A of 5th Schedule of DMR, 2017, may be amended as follows:

"a) Annexure A of the Fifth Schedule of said rules may be amended as follows:

i. Environmental conditions for weaving and assembly and gauzing should be deleted and only final primary packing for sterile surgical dressings should be included, accordingly, for sterile surgical dressings, Annexure A should be amended and the provision should be substituted with following:

Name of the device	Type of operation	ISO Class (At rest)
Sterile Surgical Dressings	Final primary packing	9

ii. Similarly, for condoms neat & clean environment free from dust etc. shall be replaced instead of 5 µ filter."

1. The Board (DTAB) deliberated the matter and agreed for the proposal to amend the provisions in Rule 64, making it identical for waiver of clinical performance evaluation of In-vitro Diagnostic medical devices in-line with waiver given for medical devices under Rule 63 of the Medical Device Rules, 2017.

2. The Board recommended that in case a medical device which already exists in the Indian market for use is brought in future under regulation, then such device shall not be a new medical device with condition that the applicant need to provide evidences of safety, performance & effectiveness.

3. The Board deliberated the matter and agreed for the proposal for enabling NABL accredited laboratories or any hospital accredited by national accreditation board for hospitals and health care providers (NABH) for issuing performance evaluation report under Medical Devices Rules, 2017, to harmonize the requirements at par with the international rules and accordingly, the requirements specified in sub-clause (h) of clause (ii) of Part II of the Fourth Schedule may be amended.

4. The Board deliberated the matter and agreed for the proposal to include the following medical devices and other high end equipments under the purview of Section 3(b) (iv) of the Drugs and Cosmetics Act, 1940:

   a. All implantable medical devices

   b. CT scan equipment

3 http://www.cdsco.nic.in/writereaddata/Final%20Minutes%20for%2079th%20DTAB%20meeting%20held%20on%2016_05_2018(1).pdf

c. MRI equipment

d. Defibrillators

e. Dialysis Machine

f. PET equipment

g. X-Ray Machine

5. The Board deliberated the matter and agreed for the proposal to incorporate pharmacy degree/ post-graduation as a qualification in Medical Devices Rules, 2017.

6. The Board deliberated the matter and agreed for the proposal to accept the eIFU (electronic Instructions for Use) as an option in place of traditional paper IFU (Instructions for Use).

7. The Board recommended the sale of Invitro Diagnostic products shall be undertaken by a valid, whole license holder to Hospitals, Pathology Laboratories, Blood Banks & other such institutions, based on requisition for such products, & the records of which shall be maintained. In case an In-vitro Diagnostic product is to be sold directly to the consumer, it shall be supplied through a valid license holder, for retail sale for such products.

8. The Board deliberated the matter and agreed for the proposal for notification of bone marrow cell separator as a medical device under Section 3(b) (iv) of the Drugs and Cosmetics Act, 1940.

9. The Board deliberated the matter and agreed for the proposal for inclusion of medical devices approved by Licensing Authority under Drugs & Cosmetics Rules, 1945, to bear CDSCO logo on its labels.

10. The Board deliberated the matter and agreed for the proposal for adding to the definition of medical device in clause (ii) of rule 2 and clause (ii) of rule 3(zb) listed currently as, "substances including mechanical contraceptives (condoms, intrauterine devices, tubal rings), disinfectants and insecticides notified under sub-clause (ii)" the following words and to read –

"disinfectants that are used to pre-clean or decontaminate medical devices prior/after to patient use and substances including mechanical contraceptives (condoms, intrauterine devices, tubal rings), notified under sub-clause (ii)".
Further, the Board also recommended for allied amendments in preamble/scope in the rules.

About DTAB

The Drugs Technical Advisory Board is constituted by Central Government under the Drug and Cosmetic Act, 1940, to advise the Central Government and the State Governments on technical matters arising out of the administration of this Act and to carry out the other functions assigned to it by this Act.

World Health Organization asks member states to fast-track efforts to eliminate rabies

On May 03, 2018, the World Health Organization (WHO) called upon Member States and partners to accelerate efforts to end rabies which causes 59 000 agonizing and painful deaths globally every year, one person every nine minute, mostly children and the poor[4].

Eight out of the 11 Member countries of WHO South-East Asia Region, account for nearly 26000 rabies deaths, 45% of the global rabies toll, as over 1.5 million people in the region remain at risk of rabies.
"Human rabies is caused mostly by dogs and can be eliminated by increasing awareness about the disease, vaccinating dogs and most importantly by making the already available life-saving rabies vaccines, medicines, tools and technologies affordable and available to all. We can, and must break the disease cycle and save lives," said Dr Poonam Khetrapal Singh, Regional Director, WHO South-East Asia, at the global meeting 'Driving progress towards rabies elimination'.

The global rabies partners comprising of WHO, the World Organization for Animal Health (OIE), the Food and Agriculture Organization (FAO) and the United Nations International Children's Emergency Fund (UNICEF) and rabies endemic countries from Asia-Pacific and Africa, shared and deliberated on measures to fast-track elimination of dog transmitted rabies by 2030.

Countries from Africa and Asia, including Bangladesh, Bhutan, Cambodia, India, Kenya, Nepal, Sri Lanka and Vietnam, who have assessed access, delivery and distribution of rabies post-exposure prophylaxis, shared outcomes of their studies. These studies were conducted with WHO support to enable GAVI (a global Vaccine Alliance) take an informed decision to support rabies vaccines. The rabies endemic countries are seeking GAVI support to improve affordability and access to rabies vaccines for vulnerable populations, especially children. WHO has been advocating for a shift from intramuscular to intradermal rabies vaccination, which is not only 60 to 80% cheaper, but is of shorter treatment regimen of just one week. Most countries in WHO South-East Asia Region are now using intradermal route for anti-rabies vaccines.

Zero by 30: The Strategic Plan

At the meeting, member countries shared initiatives being rolled out as part of the new 'Zero by 30: The Strategic Plan', to be launched by WHO and its partners to end dog transmitted rabies. The plan centres-on One Health approach and addresses the disease in a holistic and cross-sectoral manner. It aims at:

- Preventing and responding to dog-transmitted rabies by improving awareness and education, reducing human rabies risk through expanded dog vaccinations, and
- Improving access to healthcare, medicines and vaccines for populations at risk.
- It also aims at continued stakeholder engagement at all levels to sustain financing for achieving "Zero by 30". Investing in rabies control and elimination improves equity and access to healthcare and contributes to sustainable development.

The plan calls for generating and measuring impact by implementing proven effective guidelines for rabies control and encouraging the use of innovative surveillance technologies to monitor progress towards 'Zero by 30'.

4 http://www.searo.who.int/mediacentre/releases/2018/1688/en/

About Rabies

Rabies is a viral disease that occurs in more than 150 countries and territories – is usually fatal once symptoms appear. Dog-transmitted rabies accounts for about 99% of human rabies cases. It is estimated that 59,000 people die from rabies every year. 40% of people bitten by suspect rabid animals are children under 15 years of age. The world's poorest are the most affected as they cannot afford treatment or transport for care. People's livelihoods are also affected when livestock get rabies, a loss estimated at over US$ 500 million per year globally. However, rabies is 100% preventable by ensuring access vaccines and to life-saving treatment following dog bites; and by vaccinating dogs to reduce risks and ultimately to eliminate the disease.

EMA adopts ICH S9 guideline on non-clinical evaluation of anti-cancer pharmaceuticals

On 16 May 2018, the European Medicines Agency's (EMA) Committee for Medicinal Products for Human Use (CHMP) adopted the ICH S9 guideline on non-clinical evaluation of anti-cancer pharmaceuticals (Step 5)[5]. This guideline aims to assist in the design of non-clinical studies for the development of anti-cancer pharmaceuticals. It provides recommendations for non-clinical evaluations to support the development of anti-cancer pharmaceuticals in clinical trials for the treatment of patients with advanced disease and limited therapeutic options, while avoiding unnecessary use of animals, in accordance with the 3R principles (reduce/refine/replace), and other resources.

The ICH S9 Guideline: Non-clinical Evaluation for Anti-cancer Pharmaceuticals reached Step 4 in November 2009 and the guideline was a significant advance in promoting anti-cancer drug development. Since reaching Step 4, all the parties using the guideline have experienced some challenges around implementation.

For this reason, an Implementation Working Group (IWG) was formed in October 2014, by the International Council for Harmonization (ICH), to develop Questions[6] and Answers to provide additional clarity around anti-cancer pharmaceutical development, as described below –

Why is non-clinical evaluation of anti-cancer pharmaceuticals needed?

Because malignant tumors are life-threatening, the death rate from these diseases is high. Since existing therapies have limited effectiveness, it is desirable to provide new, effective anti-cancer drugs to patients more expeditiously. There have been no internationally accepted objectives or recommendations on the design and conduct of non-clinical studies to support the development of anti-cancer pharmaceuticals in clinical trials for the treatment of patients with advanced disease and limited therapeutic options. Non-clinical evaluations are conducted to:

1) identify the pharmacologic properties of a pharmaceutical,

2) establish a safe initial dose level for the first human exposure, and

3) understand the toxicological profile of a pharmaceutical (e.g., identification of target organs, exposure-response relationships, and reversibility).

In which type of studies and population will the principles of ICH S9 be applied?

- This guideline applies on both small molecule and biotechnology-derived pharmaceuticals (biopharmaceuticals), regardless of the route of administration.
- This guideline describes the type and timing of non-clinical studies in relation to the development of anti-cancer pharmaceuticals in patients with advanced cancer, whose disease is refractory or resistant to available therapy, or where current therapy is not considered to be proving beneficial.
- If the First in Human (FIH) study is conducted in a patient population with resistant and refractory disease, will subsequent Phase I studies in a different cancer, but still a resistant and refractory population, still be covered under S9? In some situations where the development pathway is not clear, regulatory agencies should be consulted.

5 http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general_content_000957.jsp&mid=WC0b01ac0580029570

6 http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2018/05/WC500248965.pdf

- The guideline also prescribes further non-clinical data to be collected during continued clinical development in patients with advanced cancer. When an anti-cancer pharmaceutical is further investigated in cancer patient populations with long expected survival, the recommendations for and timing of additional non-clinical studies depend upon the available non-clinical and clinical data and the nature of the toxicities observed.

Is the use of the Highest Non-severely Toxic Dose (HNSTD) selected as an appropriate starting dose applicable to biopharmaceuticals?

The HNSTD may be appropriate in determining a starting dose of a biopharmaceutical (e.g., when drug is not an immune agonist) taking into consideration differences in binding affinity between animals and humans and pharmacological properties of the biopharmaceutical (including Antibody Drug Conjugates (ADCs)).

Does the ICH S9 Guideline apply to the drug itself having no anti-tumor activity, such as an enhancer, that is intended to be developed as the pharmaceutical combined only with the certain anti-tumor pharmaceutical for the treatment of patients with advanced disease in late stage development?

Yes, these pharmaceuticals are within the Scope of S9 if they are intended to treat cancer. Data to show that the enhancer is non-active should be provided. General toxicology, safety pharmacology, and reproductive toxicology assessments should be done for the combination. The enhancer alone may have a more limited safety assessment either as an arm in the general toxicology combination study or as a standalone general toxicology study of up to one-month duration.

If a drug with an impurity is first developed for patients with late-stage disease, and later moves to a different population with longer expected survival, how should the impurities in the drug be managed?

When an anti-cancer pharmaceutical is further investigated in cancer patient populations with longer expected survival, ICH Q3A/B and ICH M7 should both be considered for the control of impurities.

Are there any nonclinical studies to support trials in paediatric populations?

The general paradigm for investigating most anti-cancer pharmaceuticals in paediatric patients is first to define a relatively safe dose in adult populations and then to assess some fraction of that dose in initial paediatric clinical studies. The recommendations for non-clinical testing outlined elsewhere in this document also apply for this population. Studies in juvenile animals are not usually conducted in order to support inclusion of paediatric populations for the treatment of cancer. Conduct of studies in juvenile animals should be considered only when human safety data and previous animal studies are considered insufficient for a safety evaluation in the intended paediatric age group.

The guideline states that data to support a rationale for the combination should be provided prior to starting the clinical study. What comprise "data to support a rationale for the combination study"?

A scientific rationale should be provided to justify a combination clinical study. Data demonstrating increased anti-tumor activity by combined pharmaceuticals in pharmacology studies (e.g., animal tumor models, in-vitro or in-vivo studies based on mechanistic understanding of target biology) should be provided to support rationale for the combination, if feasible. This data could be from in-house studies or the scientific literature.

Note-This ICH S9 Guideline does not apply to pharmaceuticals intended for cancer prevention, treatment of symptoms or side effects of chemotherapeutics, studies in healthy volunteers, vaccines, or cellular or gene therapy. If healthy volunteers are included in clinical trials, the ICH M3 guideline should be followed. Radiopharmaceuticals are not covered in this guideline, but some of the principles could be adapted.

Highlights from Pharmacovigilance Risk Assessment Committee (PRAC) Meeting held in May 2018

On May 18, 2018, the European Medicines Agency's (EMA) Pharmacovigilance Risk Assessment Committee (PRAC) concluded two referrals for Zinbryta (daclizumab beta) and Esmya (ulipristal acetate), maintained recommendation on hydroxyethyl-starch (HES) solutions for infusion and issued precautionary advice on HIV medicine Dolutegravir[7]. The resulting recommendations subsequent to PRAC meeting are:

1. PRAC confirms its recommendation to suspend hydroxyethyl-starch (HES) solutions for infusion in the European Union (EU)

PRAC has confirmed its recommendation to suspend marketing authorizations for hydroxyethyl starch (HES) solutions for infusion across the EU following a request from the European Commission to look into certain aspects related to it.

In January 2018, the PRAC recommended suspending the marketing authorizations for HES solutions for infusion because they continued to be used in critically ill patients and patients with sepsis despite restrictions introduced in 2013 to reduce the risk of kidney injury and death in such patients.

In April 2018, the European Commission requested the PRAC to consider whether suspending the marketing authorizations could result in an unmet medical need. It also requested the PRAC to consider the feasibility and likely effectiveness of additional risk minimization measures. After having assessed the relevant data on these specific aspects, the PRAC confirmed its previous recommendation that HES solutions for infusion should be suspended.

About Hydroxyethyl-Starch (HES)

HES solutions for infusion are used for the management of hypovolemia (low blood volume) caused by acute blood loss, where treatment with alternative infusion solutions known as 'crystalloids' alone is not considered to be sufficient. They are given by infusion (drip) into a vein and are used as blood volume expanders to prevent shock following acute bleeding. They belong to the class of medicines known as colloids. Besides blood products, there are two types of medicines used for plasma volume replacement: crystalloids and colloids. Colloids contain large molecules such as starch, whereas crystalloids, such as saline or Ringer's solutions, are pure electrolyte solutions.

2. PRAC recommends new measures to minimize risk of rare but serious liver injury with Esmya for fibroids

PRAC has completed its review of Esmya (ulipristal acetate), following reports of serious liver injury and has concluded that it may have contributed to the development of some cases of serious liver injury. The Committee has therefore, made the following recommendations to minimize this risk:

- Esmya must not be used in women with known liver problems.
- A liver function test should be performed before starting each treatment course and treatment must not be started if liver enzyme levels are more than 2 times the upper limit of normal.
- Liver function tests should be performed once a month during the first two treatment courses and two to four weeks after stopping treatment. If the test is abnormal (liver enzyme levels more than 3 times the upper limit of normal), the doctor should stop treatment and closely monitor the patient.

7 http://www.ema.europa.eu/ema/index.jsp?curl=pages/news_and_events/news/2018/05/news_detail_002954.jsp&mid=WC0b01ac058004d5c1

- Esmya should be used for more than one treatment course only in women who are not eligible for surgery. Women who are about to have surgery should continue to use only one course.
- A card will be included in the box of the medicine to inform patients about the need for liver monitoring, and to contact their doctor should they develop symptoms of liver injury (such as tiredness, yellowing of the skin, darkening of the urine, nausea and vomiting).
- Studies should be performed to determine the effects of Esmya on the liver and whether these measures are effectively minimizing the risks.

In February 2018, while the review was ongoing, the PRAC had issued temporary recommendations that no new patients should be started on Esmya. Having finalized its review, the Committee has now concluded that new patients can start treatment in line with the above recommendations to minimize the risk of liver injury.

About Esmya (ulipristal acetate)

Esmya works by attaching to the targets cells (receptors) that the hormone progesterone normally attaches to, preventing progesterone from having its effect. Since progesterone may promote the growth of fibroids, by preventing the effects of progesterone ulipristal acetate reduces the size of the fibroids. Esmya is used to treat moderate to severe symptoms of uterine fibroids (benign tumors of the womb). The medicine has been shown to be effective at reducing bleeding and anaemia, as well as the size of the fibroids.

3. PRAC review of Zinbryta confirms medicine's risks outweigh benefits

PRAC has confirmed that the multiple sclerosis medicine Zinbryta (daclizumab beta) poses a risk of serious and potentially fatal immune reactions affecting the brain, liver and other organs[8]. There are no immediate consequences of the PRAC's review as Zinbryta is no longer authorized in the EU.

On March 6, 2018, while the review was ongoing, the PRAC had recommended suspension of the marketing authorization of Zinbryta in the EU and a recall of the product from pharmacies and hospitals, following 12 reports of serious inflammatory brain disorders worldwide, including encephalitis and meningoencephalitis. On March 27 2018, the European Commission withdrew the marketing authorization of the medicine at the request of the marketing authorization holder Biogen Idec Ltd.

About Daclizumab (Zinbryta)

Zinbryta (Daclizumab) was authorised in 2016 for treating relapsing forms of multiple sclerosis. Following a 2017 review of the medicine's effects on the liver, the use of the medicine was restricted to patients who had tried at least two other disease-modifying treatments and could not be treated with any other multiple sclerosis treatments. To date over 8,000 patients have been treated with Daclizumab worldwide. The majority of EU patients have been treated in Germany.

4. New study suggests risk of birth defects in babies born to women on HIV medicine Dolutegravir

EMA's Pharmacovigilance Risk Assessment Committee (PRAC) has issued precautionary advice regarding risk of birth defects in babies born to women on HIV medicine Dolutegravir[9]. As a precaution, healthcare professionals in the EU are advised of the following:

- Do not prescribe Dolutegravir for women of child bearing potential who are trying to become pregnant.
- Exclude pregnancy in women of child bearing potential before starting Dolutegravir.

8 http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/human/referrals/Zinbryta/human_referral_prac_000074.jsp&mid=WC0b01ac05805c516f

9 http://www.ema.europa.eu/ema/index.jsp?curl=pages/news_and_events/news/2018/05/news_detail_002956.jsp&mid=WC0b01ac058004d5c1

- Advise women of child bearing potential who are taking Dolutegravir to use effective contraception throughout treatment.
- If pregnancy is confirmed in the first trimester while a woman is taking Dolutegravir, switch to an alternative treatment unless there is no suitable alternative.

The PRAC is evaluating preliminary results from a study which found four cases of birth defects such as spina bifida (malformed spinal cord) in babies born to mothers who became pregnant while taking the HIV medicine Dolutegravir. Women who have been prescribed Dolutegravir should not stop taking their medicine without first consulting their doctor.

About Dolutegravir

Dolutegravir is an integrase inhibitor. This means that it blocks an enzyme called integrase that is needed by the HIV virus to make new copies of itself in the body. When it is given with other medicines, it helps to prevent the spread of HIV and keep the amount of the virus in the blood at a low level. Dolutegravir does not cure HIV infection or AIDS, but it may hold off damage to the immune system and the development of infections and diseases associated with AIDS.

Conclusion:

The PRAC recommendation for HES will be sent to the CMDh (Coordination Group for Mutual Recognition and Decentralised Procedures - Human) for further consideration. The PRAC's referrals for Esmya and Zinbryta will now be sent to the Committee for Medicinal Products for Human Use (CHMP) for the adoption of EMA's final opinion, and further to the European Commission for a final legal decision. Moreover, the EMA's review of Dolutegravir is ongoing, and the agency will update the recommendations as necessary when it concludes its assessment.

USFDA approves novel preventive treatment for migraine

On May 17, 2018, the United States Food and Drug Administration (USFDA) has approved Aimovig (erenumab-aooe) for preventive treatment of migraine in adults[10]. The treatment is given by once-a-month self-injections. Aimovig is the first FDA-approved preventive migraine treatment in a new class of drugs that work by blocking the activity of calcitonin gene-related peptide, a molecule that is involved in migraine attacks.

The effectiveness of Aimovig for the preventive treatment of migraine was evaluated in three clinical trials:

1) The first study included 955 participants with a history of episodic migraine and compared Aimovig to placebo. Over the course of six months, Aimovig-treated patients experienced, on an average, one to two fewer monthly migraine days than those on placebo.

2) The second study included 577 patients with a history of episodic migraine and compared Aimovig to placebo. Over the course of three months, Aimovig-treated patients experienced, on an average, one fewer migraine day per month than those on placebo.

3) The third study evaluated 667 patients with a history of chronic migraine and compared Aimovig to placebo. In that study, over the course of three months, patients treated with Aimovig experienced, on an average, 2 ½ fewer monthly migraine days than those receiving placebo.

The FDA granted the approval of Aimovig to Amgen Inc.

About Migraine

Migraine headache is an intense pulsing or throbbing pain in one side of the head. Additional symptoms include nausea and/or vomiting and sensitivity to light and sound. Approximately one-third of affected individuals can predict the onset of a migraine because it is preceded by an aura – transient sensory or visual disturbances that appear as flashing lights, zig-zag lines or a temporary loss of vision. People with migraine tend to have recurring attacks triggered by a number of different factors, including stress, hormonal changes, bright or flashing lights, lack of food or sleep and diet. Migraine is three times more common in women than in men and affects more than 10 percent of people worldwide.

About Aimovig™ (erenumab-aooe)

Aimovig is a calcitonin gene-related peptide receptor antagonist indicated to prevent migraine by blocking the CGRP-R, which is associated with migraine. Aimovig has been studied in several large global, randomized, double-blind, placebo-controlled studies to assess its efficacy and safety in migraine prevention. More than 3,000 patients have participated in the Aimovig clinical program across four placebo-controlled Phase 2 and Phase 3 clinical studies and their open-label extensions[11].

10 https://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm608120.htm

11 https://www.amgen.com/media/news-releases/2018/05/fda-approves-aimovig-erenumabaooe-a-novel-treatment-developed-specifically-for-migraine-prevention/

USFDA publishes a list of drug makers who are delaying generic competition

On May 17, 2018, USFDA Commissioner Scott Gottlieb issued a statement saying, "no patients should be priced out of medicines they need to support their health. As stressed by the President and Secretary Azar last week, one of the Administration's highest priorities is advancing policies that increase competition as a way to help make drugs more affordable and improve access".

He also said that "there isn't one single action that's going to solve this issue. We will achieve these public health goals through the coordinated effort of different federal agencies working in partnership with industry and other stakeholders. Among these efforts, we are especially focused on addressing tactics we sometimes hear of branded companies pursuing as a way to forestall expected generic entry".

One of the stalling tactics is when potential generic applicants are prevented from obtaining samples of certain brand products necessary to support approval of a generic drug. The inability of generic companies to purchase the samples they need slows down, or entirely impedes, the generic drug development process – leading to delays in bringing affordable generic alternatives to patients in need.

USFDA has received numerous inquiries from prospective generic applicants indicating interest to develop a generic version of a marketed drug but are unable to obtain the necessary samples of the reference listed drug (RLD) – typically referred to as the brand drug – because the RLD is subject to limited distribution. The USFDA received inquiries on drugs that are under Risk Evaluation and Mitigation Strategy (REMS) and those that are not-

- Risk Evaluation and Mitigation Strategy (REMS) - A REMS is a drug safety program that the U.S. Food and Drug Administration (FDA) can require for certain medications with serious safety concerns to help ensure the benefits of the medication outweigh its risks. REMS are designed to reinforce medication use behaviors and actions that support the safe use of that medication. While all medications have labelling that informs health care stakeholders about medication risks, only a few medications require a REMS with elements to assure safe use (ETASU).
- In other cases, the brand companies have placed restrictions in their commercial contracts or agreements with prescription drug distributors, wholesalers or specialty pharmacies that limit the ability of these intermediaries in the drug supply chain to sell samples to generic drug developers for testing.

USFDA, to address this issue of RLD access and to provide transparency regarding these inquiries, has released a list of companies that have potentially been blocking access to the samples of their branded products. The list identifying all drug products for which FDA has received an RLD access inquiry related to limited distribution of the marketed RLD, with details regarding the RLD sponsor, the drug product, and the number of inquiries is as follows:

RLD Access Inquiries

RLD Sponsor3	RLD product	Inquiries Received	REMS with ETASU	Date(s) of Safety Determination Letter(s) Issued
RANBAXY INC/SUN PHARMACEUTICAL INDUSTRIES INC	Absorica (isotretinoin)	5	Yes	12/9/2015
GALENA BIOPHARMA	Abstral (fentanyl citrate)	1	Yes	
ROCHE PALO ALTO LLC	Accutane (isotretinoin)	2	Yes	6/23/2009
BAYER HEALTHCARE PHARMACEUTICALS INC	Adempas (riociguat)	2	Yes	9/27/2016; 5/2/2017
NOVARTIS PHARMACEUTICALS CORP	Afinitor (everolimus)	1	No	N/A
MYLAN PHARMACEUTICALS INC	Amnesteem (isotretinoin)	3	Yes	
ACORDA THERAPEUTICS INC	Ampyra (dalfampridine)	4	No	N/A
ASTRAZENECA LP	Brilinta (ticagrelor)	1	No	N/A
TEVA PHARMACEUTICALS USA	Claravis (isotretinoin)	4	Yes	
HERITAGE LIFE SCIENCES BARBADOS INC	Clozaril (clozapine)	1	Yes	
ORPHAN EUROPE SARL	Cystadane (betaine hydrochloride)	1	No	N/A
ALPHARMA PHARMACEUTICALS LLC KING PHARMACEUTICALS	Embeda (morphine sulfate; naltrexone hydrochloride)	1	No	N/A
CUBIST PHARMACEUTICALS INC	Entereg (alvimopan)	5	Yes	
NOVARTIS PHARMACEUTICALS CORP	Exjade (deferasirox)	6	No	N/A
JAZZ PHARMACEUTICALS III INTERNATIONAL LTD	Fazaclo ODT (clozapine)	1	Yes	
CEPHALON INC	Fentora (fentanyl citrate)	1	Yes	
APOPHARMA INC	Ferriprox (deferiprone)	1	No	N/A
SHIRE ORPHAN THERAPIES INC	Firazyr (icatibant acetate)	2	No	N/A
NPS PHARMACEUTICALS INC	Gattex Kit (teduglutide recombinant)	1	No	N/A
BOEHRINGER INGELHEIM	Gilotrif (afatinib dimaleate)	1	No	N/A
QUESTCOR PHARMACEUTICALS INC	H.P. Acthar Gel (corticotropin)	2	No	N/A
PHARMACIA AND UPJOHN CO	Hemabate (carboprost tromethamine)	1	No	N/A
AEGERION PHARMACEUTICALS INC	Juxtapid (lomitapide mesylate)	3	Yes	
CORCEPT THERAPEUTICS INC	Korlym (mifepristone)	1	No	N/A
BIOMARIN PHARMACEUTICAL INC	Kuvan (sapropterin dihydrochloride)	3	No	N/A
GILEAD SCIENCES INC	Letairis (ambrisentan)	10	Yes	9/1/2015; 7/5/2016
ROXANE LABORATORIES INC	Methadone Hydrochloride	1	No	N/A

RLD Sponsor3	RLD product	Inquiries Received	REMS with ETASU	Date(s) of Safety Determination Letter(s) Issued
DANCO LABORATORIES LLC	Mifeprex (mifepristone)	1	Yes	
BAYER HEALTHCARE PHARMACEUTICALS INC	Nexavar (sorafenib tosylate)	2	No	N/A
MEDA PHARMACEUTICALS INC	Onsolis (fentanyl citrate)	1	Yes	
ACTELION PHARMACEUTICALS LTD	Opsumit (macitentan)	8	Yes	7/5/2016; 12/8/2016; 4/23/2018
SWEDISH ORPHAN BIOVITRUM AB PUBL	Orfadin (nitisinone)	2	No	N/A
CELGENE CORP	Pomalyst (pomalidomide)	8	Yes	
GLAXOSMITHKLINE	Promacta (eltrombopag olamine)	2	Yes	
GLAXOSMITHKLINE	Promacta (eltrombopag olamine)	1	No	N/A
VIVUS INC	Qsymia (phentermine hydrochloride; topiramate)	8	Yes	8/13/2015
HYPERION THERAPEUTICS INC	Ravicti (glycerol phenylbutyrate)	1	No	N/A
CELGENE CORP	Revlimid (lenalidomide)	13	Yes	7/31/2012; 5/19/2014; 2/22/2017; 8/15/2017
LUNDBECK LLC / LUNDBECK PHARMACEUTICALS LLC	Sabril (vigabatrin) for solution	3	Yes	
LUNDBECK LLC / LUNDBECK PHARMACEUTICALS LLC	Sabril (vigabatrin) tablet	4	Yes	
INSYS THERAPEUTICS INC	Subsys (fentanyl)	2	Yes	
NOVARTIS PHARMACEUTICALS CORP	Tasigna (nilotinib hydrochloride monohydrate)	3	No	N/A
BIOGEN IDEC INC	Tecfidera (dimethyl fumarate)	1	No	N/A
CELGENE CORP	Thalomid (thalidomide)	10	Yes	12/11/2007; 1/17/2008
PFIZER PHARMACEUTICALS PRODUCTION CORP LTD	Tikosyn (dofetilide)	4	Yes	
ACTELION PHARMACEUTICALS LTD	Tracleer (bosentan)	14	Yes	7/31/2013; 9/1/2015; 9/1/2015; 10/16/2015; 1/29/2016
GILEAD SCIENCES INC	Truvada (emtricitabine; tenofovir disoproxil fumarate)	1	No	N/A
SMITHKLINE BEECHAM CORP DBA GLAXOSMITHKLINE	Tykerb (lapatinib ditosylate)	1	No	N/A
ACTELION PHARMACEUTICALS LTD	Veletri (epoprostenol sodium)	1	No	N/A
VALEANT INTERNATIONAL BERMUDA/VALEANT PHARMACEUTICALS NORTH AMERICA LLC	Xenazine (tetrabenazine)	4	No	N/A
ACTELION PHARMACEUTICALS LTD	Zavesca (miglustat)	3	No	N/A
NOVARTIS PHARMACEUTICALS CORP	Zortress (everolimus)	1	No	N/A

In the above list a total of 52 reference listed drugs (RLDs) have been described, whereas, roughly half of RLD comes under REMS with Elements to Assure Safe Use (ETASU), but it doesn't mean that generic companies would

not get these RLD samples for testing. In this regard, USFDA developed a process for informing the RLD sponsor in writing that FDA will not consider providing the RLD for these purposes to be a violation of the REMS.

According to it, upon request from a prospective generic applicant, FDA reviews their bioequivalence study protocols to assess whether they contain safety protections comparable to those in the applicable REMS for the RLD. If FDA determines that they do, they (FDA) notify the prospective generic applicant of this determination by letter. The prospective generic applicant can then request that FDA send a second, separate letter (the Safety Determination Letter) directly to the RLD sponsor stating that FDA will not consider providing product to the particular generic applicant to be a violation of the REMS for the RLD.

In the list, in cases where there is no such REMS program in place, the FDA informs the generic drug developer that there are no FDA-required restrictions on the distribution of the drug that would impede obtaining samples. They also notify the same to the Federal Trade Commission (FTC), the agency responsible for addressing anticompetitive business practices about these inquiries.

Conclusion:

The USFDA's actions to make RDL accessible to generic companies is a way to bring more competition to the prescription drug market, to make drugs more affordable and more accessible.

USFDA approves Novartis combo for treatment of aggressive form of thyroid cancer

The U.S. Food and Drug Administration approved Tafinlar (dabrafenib) and Mekinist (trametinib) combination for the treatment of anaplastic thyroid cancer (ATC) that cannot be removed by surgery or has spread to other parts of the body (metastatic), and has a type of abnormal gene, BRAF V600E (BRAF V600E mutation-positive)[12].

"This is the first FDA-approved treatment for patients with this aggressive form of thyroid cancer, and the third cancer with this specific gene mutation that this drug combination has been approved to treat," said Richard Pazdur, M.D., director of the FDA's Oncology Center of Excellence and Acting Director of the Office of Hematology and Oncology Products in the FDA's Center for Drug Evaluation and Research. "This approval demonstrates that targeting the same molecular pathway in diverse diseases is an effective way to expedite the development of treatments that may help more patients."

The FDA granted this approval to Novartis Pharmaceuticals Corporation. The FDA granted Priority Review, Breakthrough Therapy designation and Orphan Drug designation for this indication.

Both Tafinlar and Mekinist are also approved for use, alone or in combination, to treat BRAF V600 mutation-positive metastatic melanoma. Additionally, Tafinlar and Mekinist are approved for use, in combination, to treat BRAF V600E mutation-positive, metastatic non-small cell lung cancer.

The efficacy of Tafinlar and Mekinist in treating ATC was shown in an open-label clinical trial of patients with rare cancers with the BRAF V600E mutation. Data from trials in BRAF V600E mutation-positive, metastatic melanoma or lung cancer and results in other BRAF V600E mutation-positive rare cancers provided confidence in the results seen in patients with ATC. The trial measured the percent of patients with a complete or partial reduction in tumor size (overall response rate). Of 23 evaluable patients, 57 percent experienced a partial response and 4 percent experienced a complete response; in nine (64 percent) of the 14 patients with responses, there were no significant tumor growths for six months or longer.

About Thyroid Cancer

Thyroid cancer is a disease in which cancer cells form in the tissues of the thyroid gland. Anaplastic thyroid cancer is a rare, aggressive type of thyroid cancer. The National Institutes of Health estimates there will be 53,990 new cases of thyroid cancer and an estimated 2,060 deaths from the disease in the United States in 2018. Anaplastic thyroid cancer accounts for about 1 to 2 percent of all thyroid cancers.

About Tafinlar + Mekinist Combination

Mekinist (Trametinib) is a reversible inhibitor of mitogen-activated extracellular signal-regulated kinase 1 (MEK1) and MEK2 activation and of MEK1 and MEK2 kinase activity. MEK proteins are upstream regulators of the extracellular signal-related kinase (ERK) pathway, which promotes cellular proliferation. BRAF V600E mutations result in constitutive activation of the BRAF pathway which includes MEK1 and MEK2. Trametinib inhibits cell growth of various BRAF V600 mutation-positive tumors in vitro and in vivo[13].

Tafinlar **(**Dabrafenib) is an inhibitor of some mutated forms of BRAF kinases with in vitro IC50 values of 0.65, 0.5, and 1.84 nM for BRAF V600E, BRAF V600K, and BRAF V600D enzymes, respectively. Dabrafenib also inhibits wild-

12 https://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm606686.htm

13 https://www.pharma.us.novartis.com/sites/www.pharma.us.novartis.com/files/mekinist.pdf

type BRAF and CRAF kinases with IC50 values of 3.2 and 5.0 nM, respectively, and other kinases such as SIK1, NEK11, and LIMK1 at higher concentrations.

Tafinlar + Mekinist target two different kinases in the RAS/RAF/MEK/ERK pathway. Use of dabrafenib and trametinib in combination result in greater growth inhibition of BRAF V600 mutation-positive tumor cell lines in vitro and prolonged inhibition of tumor growth in BRAF V600 mutation positive tumor xenografts compared with either drug alone[14].

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14 https://www.pharma.us.novartis.com/sites/www.pharma.us.novartis.com/files/tafinlar.pdf

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