SINGH & ASSOCIATES

FOUNDER MANOJ K SINGH

ADVOCATES & SOLICITORS

Vol. II, Issue II
February 2018

S&A PHARMA NEWSLETTER

EDITORIAL

Manoj K. Singh
Founding Partner

In this era of rapid evolutions in the healthcare setting, where Patients, healthcare providers and consumer are continuously seeking cost effective, high quality care with superior outcomes. Therefore, it is not just enough for Pharma companies to focus merely on marketing and selling of drugs and medications, the industry also needs to target more holistic approach with integrated services, customization and personalized services as best response to healthcare problems.

In our present newsletter we start with an article on Pharmaceutical Research and Manufacturers of America's (PhRMA) Special 301 submission Report 2018 to the United States Trade Representative (USTR), , the article focuses on India and the report highlights unpredictable patent environment, regulatory data protection failures, high tariffs and taxes on medicines, discriminatory and non-transparent market access policies, and unpredictable environment for clinical research as the key challenges before US companies that operate or wish to tap the Indian market. The report goes on to recommend that for these reasons India should remain on the Priority Watch List in 2018 as well.

The current edition of our Pharma newsletter also addresses; the recent regulatory developments from Health Research, new therapy Approvals worldwide, and regulatory reforms. The current issue covers the Ministry of Health and Family Welfare's (MoHFW) draft Clinical Trial (CT) rules 2018, which will be applicable to all new drugs, investigational new drugs for human use, clinical trial, bioequivalence study, bioavailability study, and ethics Committee. The next article is on Annual price revision of coronary stents by National Pharmaceutical Pricing Authority (NPPA) of India.

Then we adress the Indian drug regulator's proposals on strict regulation of Oxytocin to curb its misuse, as the whole issue of Oxytocin is of paramount importance for protection of human and animal health. Next we highlight the National Institution for Transforming India (NITI) Aayog's comprehensive Health Index report on "Healthy States, Progressive India". The report ranks Indian states and union territories innovatively on their year-on-year incremental change in health outcomes, as well as, their overall performance with respect to each other.

Our current issue then covers the WHO's recommendation on composition of influenza virus vaccines for use in 2018-2019 northern hemisphere season. We also address the United States Food and Drug Administration (USFDA) intensified warning against Kratom classifying it as an 'opioid' underscoring potential for abuse, the agency said that it will also oversee destruction and recall of kratom products from the United States. We then have an article on menace of cancer in emerging countries, and how the disease results in loss of billions of US dollars in productivity due to premature mortality owing to cancer in BRICS region.

We wrap up this issue of the newsletter with the USFDA's finalized rule that require medical device clinical investigations conducted outside the US to flexibly conform to good clinical practice (GCP) standards.

Contributors to the current issue:
Mr Manoj K. Singh
Mr Shahnawaz Ibrahim
Ms Vijaylaxmi Rathore

Thank you.

All ©Copyrights owned by Singh & Associates

S&A Pharma Newsletter
Volume II, Issue II
February 2018

SINGH & ASSOCIATES
ADVOCATES & SOLICITORS

NEW DELHI
E-337, East of Kailash
New Delhi - 110065 INDIA

GURUGRAM
7th Floor, ABW Tower, MG Service Road
Sector 25, IFFCO Chowk, Gurugram
Haryana-122001 INDIA

MUMBAI
Unit No. 48 & 49, 4th Floor, Bajaj Bhavan,
Barrister Rajni Patel Marg, Nariman Point,
Mumbai, Maharashtra - 400021, INDIA

BENGALURU
N-304, North Block, Manipal Centre,
47, Dickenson Road
Bengaluru - 560042, INDIA

Ph : +91-11-46667000
Fax : +91-11-46667001

Email: india@singhassociates.in
Website: www.singhassociates.in

www.singhassociates.in

Managing Editor
Manoj K. Singh

Published by
Singh & Associates
Advocates and Solicitors

Contents

1. PhRMA Special 301 Submission Report to United States Trade Representative: Focus on India 04

2 Health Ministry Releases Draft New Drug & Clinical Trial Rule 2018 08

3. NPPA revises coronary stent price after a year of price cap 11

4. CDSCO advises strict regulation of Oxytocin to curb its misuse 14

5. INITI Aayog releases "Healthy States, Progressive India" Report 16

6. Productivity losses due to premature mortality from cancer in Brazil, Russia, India, China, and South Africa (BRICS) 19

7. NPPA UPDATES FOR THE MONTH OF FEBRUARY 2018 21

8. European Medicines Agency (EMA): Recommends Approval of Five medicines in its February 2018 Meeting 26

9. European Medicines Agency's Pharmacovigilance Risk Assessment Committee recommends new measures to avoid valproate exposure in pregnancy 31

10. WHO recommends quadrivalent Influenza vaccines for use in the Northern Hemisphere Influenza Season, 2018-19 34

11. WHO announces Independent Global High-level Commission to beat Non-Communicable Diseases (NCDs) 36

12. World Health Organization (WHO) recommendations: Intrapartum care for a positive childbirth experience 38

13. FDA intensifies its warning against Kratom, classifying it as an 'opioid' underscoring potential for abuse 44

14. United States FDA Issues Final Rule that Requires Medical Device Trials Outside US to Conform to Good Clinical Practices (GCP) 47

15. US FDA expands approval of Imfinzi to reduce the risk of non-small cell lung cancer progression 49

PhRMA Special 301 Submission Report to United States Trade Representative: Focus on India

On February 08, 2018, the Pharmaceutical Research and Manufacturers of America (PhRMA) submitted its annual submission to the United States Trade Representative (USTR) in the form of Special 301 Report, 2018[1]. The Special 301 review gives the Administration a critical tool to address damaging market access and intellectual property barriers abroad that harm America's leading innovative and creative industries. The report identifies trade barriers to U.S. companies and products due to the intellectual property laws, such as copyright, patents and trademarks, in other countries[2].

The Office of the United States Trade Representative (USTR) is the United States' government agency responsible for developing and recommending the United States Trade Policy to the President of the United States, conducting trade negotiations at bilateral and multilateral levels and coordinating trade policy within the government[3].

PhRMA, in its report, has highlighted unpredictable patent environment, regulatory data protection failures, high tariffs and taxes on medicines, discriminatory and non-transparent market access policies, and unpredictable environment for clinical research as the key challenges before the US companies which operate or wish to tap the Indian market. For these reasons the lobby group wants India to remain on the Priority Watch List in the 2018 Special 301 Report of USTR until India addresses these concerns.

Special 301 Submission 2018

The PhRMA 2018 report says that it supports the Indian Government's efforts to create a stronger business, innovation and healthcare environment through the "Make in India" initiative, the National Intellectual Property Rights (IPR) Policy and the new National Health Policy. These efforts can improve access to healthcare for Indian patients, while driving economic growth by enhancing India's global competitiveness and improving ease of doing business. However, despite some positive signs, PhRMA's members remain concerned about the challenging policy environment in India.

The report goes on to highlight that:

- Market access challenges persist; and
- Despite important announcements to expand healthcare programs, Indian Government has not increased investment in this critical area, leaving public healthcare spending at a meagre 1.5 % (approx.) of GDP during the year 2016-17.
- Delays and cumbersome procedures prevent India from becoming a part of global clinical trial programs, thereby, limiting patient access to innovative medicines in India.
- The report also highlights data from the Indian drug regulator which shows that since 2011, a total of only 41 new medicines were approved; the number continues to remain significantly low, with only 22 new approvals in 2016.

1 http://phrma-docs.phrma.org/download.cfm?objectid=50939AE0-0D22-11E8-B0560050569A4B6C

2 https://en.wikipedia.org/wiki/Special_301_Report

3 https://en.wikipedia.org/wiki/Office_of_the_United_States_Trade_Representative

Key Concerns:

- **Unpredictable Patent environment:** The report highlights that India's legal and regulatory systems pose procedural and substantive barriers at every step of the patent process, ranging from impermissible hurdles to patentability posed by Section 3(d) of India's Patents Act, narrow patentability standards applied in pre-grant and post-grant opposition proceedings, to onerous patent application disclosure requirements that disproportionately affect foreign patent applicants. This a concern not only in the Indian market, but also in other emerging markets which may see India as a model to be emulated. Between May and December 2017, at least 149 patent applications faced rejections under Section 3(d), infringement due to state-level marketing authorization for generic versions of on-patented drugs and the threat of compulsory licenses (CLs), all of which demonstrate that much work needs to be done to improve the patent environment in India.

- **Regulatory data protection failures:** The Indian Regulatory Authority relies on test data submitted by originators to seek approval in India and/or another country when granting marketing approval to follow-on pharmaceutical products. This reliance results in unfair commercial use prohibited by the World Trade Organization (WTO) Agreement on Trade-Related Aspects of Intellectual Property Rights (TRIPS) and discourages the development and introduction into India of new medicines for unmet medical needs.

- **High tariffs and taxes on medicines:** Medicines in India face high effective import duties for active ingredients and finished products. The basic import duties for pharmaceutical products average about ten percent, and when combined with the Integrated Goods and Service Tax the effective import duty can exceed 20%. This is in addition to the recently initiated 5-12% General Sales Tax (GST) on medicines.

- **Discriminatory and non-transparent market access policies:** The recent price control orders on coronary stents and knee implants and the threat of an existing recommendation to implement price controls on patented medicines, represent an effort to significantly reduce the benefits of patent protection and create an unviable government pricing framework and business environment for medicines in India. In addition, the National Pharmaceutical Pricing Authority (NPPA) recently revised price controls on medicines for which prices were already fixed under the Drug Price Control Order (DPCO) 2013. The DPCO 2013 discriminates against foreign pharmaceutical companies by exempting new medicines developed through indigenous research from price controls. These pricing decisions, as well as the broad authority granted to NPPA, do not adhere to the need for transparency, predictability and trust in the decision-making process, which hinders industry's ability to further invest in India.

- **Unpredictable environment for clinical research:** While the Government is keen to reinvigorate clinical research in India, ambiguities in the Indian regulatory space prevail. In particular, the definition of "trial related injury" is not well defined and the determination of local clinical trials requirements is highly subjective and perpetuates a burdensome environment for clinical research that undermines the availability of new treatments and vaccines for Indian patients.

Citing these above reasons, PhRMA has requested that India remain on the Priority Watch List in the 2018 Special 301 Report, and that the U.S. Government continue to seek assurances that the problems described herein are quickly and effectively resolved.

The report also has a detailed section on Intellectual Property Protection in India which highlights various challenges with the IP regime like:

Restrictive Patentability Criteria

The report highlights that TRIPS, an agreement on Trade-Related Aspects of Intellectual Property Rights, requires that an invention that is new or involves an inventive step and is capable of industrial application, be entitled to patent protection. However Section 3(d) of the Indian Patents Act as amended by the Patents (Amendment) Act 2005 adds an impermissible hurdle to patentability by adding a fourth substantive criterion of "enhanced efficacy" to the TRIPS requirements. Moreover, this additional hurdle appears to be applied only to pharmaceuticals. Under this provision, salts, esters, ethers, polymorphs and other derivatives of known substances are presumed to be the same substance as the original chemical entity and thus not patentable, unless it can be shown that they differ significantly in properties with regard to efficacy. Further, indiscriminate and routine use of Section 3(d) in patent applications by the Indian Patent Office even for a novel compound or a derivative with onus of proof on the applicant to prove otherwise, poses unnecessary burden on the innovators.

The report opines that additional substantive requirements for patentability, beyond those enumerated in the TRIPS Agreement, are inconsistent with India's international obligations. From a policy perspective, Section 3(d) undermines incentives for biopharmaceutical innovation by preventing patentability for improvements that do not relate to efficacy, for example an invention relating to the improved safety of a product. Further, Section 3(i) of the Indian Patents Act excludes method-of-treatment claims preventing U.S. biotechnology companies with needed treatment methods from entering the Indian market and providing life-saving products.

India's pre- and post-grant patent opposition system

The report also highlights the lack of clear rules regarding pleading and evidentiary standards during pre-grant opposition proceedings which further create uncertainty relating to the patentability of inventions. Further, pre-grant opposition procedures under Section 25 of India's Patents Act have created significant uncertainty and delayed the introduction of new inventions by undermining patent office efficiency and delaying patent prosecution – exacerbating India's already significant patent examination backlog of approximately 6 years.

Weak Patent Enforcement

The report also highlights that Indian law permits state drug regulatory authorities to grant manufacturing approval for a generic version of a medicine four years after the original product was first approved. State regulatory authorities are not required to verify or consider the remaining term of the patent protection on the original product. Therefore, an infringer can obtain marketing authorization from the state government for a generic version of an on-patent drug, forcing the patent holder to seek redress in India's court system, which often results in irreparable harm to the patent holder.

Compulsory Licensing (CL)

The report also focuses on the area of Compulsory Licensing (CL). The report says that the grounds for issuing a CL in India are broad, vague and appear to include criteria that are not clearly related to legitimate health emergencies. While the Indian Government continues to take a more measured and cautious approach in responding to recent CL cases, the Ministry of Health (MOH) continues to entertain potential recommendations to impose CLs on certain anti-cancer medicines under the special provisions of Section 92 of India's Patents Act, which would make it even more difficult for patent owners to defend their patents.

The report concluded that CL is not a sustainable or effective way to address healthcare needs. Voluntary arrangements independently undertaken by member companies can better ensure that current and future patients have access to innovative medicines. India should at least ensure that CLs are exercised with extreme caution and only as a measure of last resort. India should also clarify that importation satisfies the "working" requirement, pursuant to TRIPS Article 27.1.

Administrative Burdens

Another challenge highlighted in the report is the administrative burden and inordinately long time taken by the Indian authorities in Patent examination. Backlogs undermine incentives to innovate and hinder timely patient access to valuable new treatments and cures. Because the term of a patent begins on the date an application is filed, unreasonable delays can directly reduce the value of granted patents and undermine investment in future research activity. PhRMA however said that it welcomes the Indian Government's ongoing work to address India's patent examination backlog including the commitment to reduce examination periods from up to six years to 18 months.

High Tariffs and Taxes on Medicines

The report highlights that PhRMA member companies operating in India face high effective import duties for active ingredients and finished products. Though the basic import duties for pharmaceutical products average about ten percent, due to the Integrated Goods and Service Tax imposed on imports, the effective import duty can exceed 20%. Compared to other Asian countries in similar stages of development, import duties in India are very high. And while certain essential and life-saving medicines may be granted exemptions from some of the taxes, the eligibility criteria are vague and subject to constant revision and debate. The report recommends that proposals to exempt certain life-saving drugs from Goods & Service Tax (GST) and customs duties should be expanded to all medicines.

Conclusion:

PhRMA in its annual submission to the United States Trade Representative has raised various concerns with India's regulatory framework and pharmaceutical policies, requesting USTR to keep India in the India Priority Watch List until India addresses their concerns. PhRMA report also highlights that greater clarity and predictability are needed for administrative procedures of drug registration applications and drug review standards and procedures in order to make the latest research products available in India.

Health Ministry Releases Draft New Drug & Clinical Trial Rule 2018

The Ministry of Health and Family Welfare of Government of India has released draft Clinical Trial (CT) Rules 2018, which will come in force after its final publication in the Official Gazette. The new rules have been drafted after consultation with the Drugs Technical Advisory Board (DTAB) and under Part XA and Schedule Y of the Drugs and Cosmetics Rules, 1945, and section 12 and 33 of the Drugs and Cosmetics Act, 1940.

The new rule contains 12 chapters and 8 schedules and will be applicable to all new drugs, investigational new drugs for human use, clinical trial, bioequivalence study, bioavailability study and ethics Committee. The new regulations clearly define features of an academic study, the role of central licensing authority, trial protocol, biomedical and health research. According to the new rules, **the CT in relation to a new drug or investigational new drug in humans has to generate data for discovering or verifying its pharmacological interactions including pharmacodynamics, pharmacokinetic and adverse effects in order to determine the safety, efficacy or tolerance of new drugs.**

As per the new rules the Drugs Controller General of India (DCGI), with the prior approval of the central government, can delegate all or any of the powers of the Central Licensing Authority (CLA) to any other Officer of the Central Drugs Standard Control Organization (CDSCO) not below the rank of Assistant Drugs Controller (ADI). The officers to whom the powers have been delegated under sub-rule (1) would implement all or any of the rules of the CLA.

The DCGI may designate any officer not below the rank of Assistant Drugs Controller as Controlling Officer and will assign the areas and powers of the Controlling Officer through an order. The Controlling Officer will then supervise the work of subordinate officers and will exercise powers and perform functions which may be assigned to that Officer.

In case of an application for permission to undertake a clinical trial of a new drug formulation, which is already approved in the country, no pharmaceutical & clinical data is required to be submitted provided the trial is proposed to be conducted with a new drug manufactured/imported by a firm.

The Key highlights of the Draft CT Rules:

Ethics Committee (EC) and Central Licensing Authority (CLA):

- Any institution or organization, which intends to conduct CT or bioavailability study or bioequivalence study, is required to have an Ethics Committee (EC). Every such EC has to get registration from the CLA and must have a minimum of seven members from Medical Science, Scientific, Non-medical, Non-scientific, and layperson and a woman member. A member of the EC will be the Chairperson, who should not be related in any manner with the institute or the organization. The registration of EC will be valid for a period of three years.
- No person or institution or organization shall conduct a CT of a new drug or investigational new drug without getting permission from the CLA. If granted, permission will remain valid for a period of two years from the date of its issue unless suspended or canceled by the Authority.
- However, there shall be no permission required from CLA for conducting an academic CT for any drug in the following circumstances:

a The CT drug formulation is intended solely for academic research purposes,

b The CT has been approved by the EC,

c The observations of such CT are not required to be submitted to the CLA; and

d The observations of such CT are not used for promotional purposes.

- If a CT site does not have its own EC, the CT at that site may be initiated after getting the protocol approved from the Institutional Ethics Committee of another trial site or an independent EC constituted under the Draft Rules.
- In case of termination of any CT, the detailed reasons for such termination should be communicated to the CLA within thirty days of such termination.
- Any report of a serious adverse event occurring during the CT to a subject of the CT, after due analysis, should be forwarded to the CLA, the chairperson of the EC and the Institute where the CT has been conducted within fourteen days of its occurrence.
- In case of an injury during a CT to the subject of such trial, complete medical management and compensation should be provided by the firm and details of compensation provided in such cases shall be intimated to the CLA within thirty days of the receipt of recommendations made by EC.
- In case of a CT related death or permanent disability of any subject during the trial, compensation shall be provided within thirty days of receipt of the order issued by the CLA. Whereas, the details of compensation provided in such cases should be intimated to the CLA

New Drugs or Investigational New Drugs:

- A license has to be obtained by the institutions or organizations for manufacturing or importing new drugs or investigational new drugs or for the manufacture of unapproved active pharmaceutical ingredient for the development of any formulation, for a CT, bioavailability, bioequivalence study etc.
- The institutions or organizations have to also obtain a license to manufacture or import new drugs for sale or for distribution under the Rules.

Bioavailability and Bioequivalence study:

- No bioavailability or bioequivalence study of any new drug or investigational new drug shall be conducted in human subjects by any person or institution or organization except in accordance with the permission granted by the CLA and EC.
- The work of every bioavailability or bioequivalence study center shall be overseen by an EC. Whereas, any officer authorized by the CLA, who may, if considered necessary, be accompanied by an officer authorized by the State licensing authority, may enter with or without prior notice to premises and bioavailability or bioequivalence study center to inspect, search or seize, any record, statistical result, document, investigational drug and other related material and reply to queries raised by the inspecting authority in relation to the conduct of such bioavailability or bioequivalence study.

Investigator:

- The investigator shall be responsible for the conduct of the trial according to the Standard operating procedures (SOP) and the Good Clinical Practices (GCP) Guidelines. SOP are required to be documented and maintained by the investigators for the tasks performed by them.

- The investigator should ensure that adequate medical care is provided to the participant in case of any adverse events. In case of serious adverse events, the investigator shall report to all authorities like CLA, EC and sponsor within twenty-four hours of their occurrence.
- The investigator shall provide all essential information of CT to the trial subject through informed consent process including information of sponsors and compensation in case of trial related injury or death.

Sponsor:

- The CT sponsor is responsible for implementing and maintaining quality assurance systems to ensure that the CT is conducted and data generated, documented and reported in compliance with the protocol and GCP.
- Sponsors are required to submit a status report on the CT to the CLA at prescribed periodicity.
- In case a serious adverse event occurs at trial site, the sponsor, after due analysis, shall forward SAE report to the CLA, shall make payment for medical management of the subject and also provide financial compensation for the CT related injury or death.
- The sponsor shall provide post-trial access of the investigational drug by giving the drug free of cost to the trial subject as per the directions of the CLA; in special circumstances on the recommendations of the investigator and the ethics committee and written consent of the patient.

Informed Consent:

- In all trials, a freely given, informed, written consent is required to be obtained from each study subject. The Investigator must provide information about the study verbally as well as using a patient information sheet, in a language that is non-technical and understandable by the study subject.
- Where a subject is not able to give informed consent (e.g. an unconscious person or a minor or those suffering from severe mental illness or disability), the same may be obtained from a legally acceptable representative or in the presence of impartial witness.
- In case of CT on pediatrics, the subjects are legally unable to provide written informed consent, the consent should be obtained from the parent or legal guardian. Where appropriate, pediatric participants should additionally assent to enroll in the study.
- An audio-video recording of the informed consent process in case of vulnerable subjects, CT of New Chemical Entity or New Molecular Entity including procedure of providing information to the subject and his understanding on such consent, shall be maintained by the investigator for record. It is provided that in case of clinical trial of anti-HIV and anti-leprosy drugs, only audio recording of the informed consent process of individual subject including the procedure of providing information to the subject and his understanding on such consent shall be maintained by the investigator for record.

Conclusion:

The proposed draft clinical trial rules cover the full spectrum of clinical trial activities, from ethics committees and manufacturing permissions to inspections and injury compensation. Publication of the draft rules marks an important step in India's attempts to codify its approach towards clinical trials. These draft rules are also an attempt to recover from the regulatory problems that had throttled the clinical trial industry. With these proposed new regulations the clinical trial industry should revive in the country. The draft is currently open to receive comments from industry/ stakeholders for 45 days.

NPPA revises coronary stent price after a year of price cap

The National Pharmaceutical Pricing Authority (NPPA) is under constitutional obligation to provide fair, reasonable and affordable price for Coronary Stents and to check unethical profiteering and exploitive pricing. In order to protect public interest in extraordinary circumstances under paragraph 19 of the Drug Pricing Control Organization (DPCO), 2013, NPPA fixed the ceiling price of cardiac stent for the first time and notified the same vide S.O. 412 (E) dated February 13, 2017 for a year[4].

NPPA, further in various meetings and discussions with expert committee and all concerned stakeholders/ organizations against the concerns of sub-classification of drug eluting stents (DES), rewarding incremental innovation, an upward revision or no change in the ceiling price in ceiling prices, increase in trade margins and freedom to withdraw unviable brands from Indian market, has observed some key points that:

- There was an increased indigenous manufacturing activity and enhanced imports and availability of cardiac stents made in India in year 2017. There was a clear overall 5% growth in the indigenously manufactured stents.
- The year 2017 witnessed an overall marginal increase of 1% in imports of stents from US based manufacturers while as much as 35% increase in imports of stents from non-US manufacturers was seen.
- The year 2017 also saw entry of some new companies, both Indian and foreign like USA, Singapore, Spain, China and UK having its manufacturing primarily in UAE, in the market.
- The decision of putting only 8% trade margins cap eliminated almost all unethical payment and profiteering in the system and also disrupted status quo in trade of stents which was based on profiteering at each level.

NPPA finally concluded that cardiac stents are an essential drug under Schedule I of DPCO, 2013 and part of NLEM, 2015 and have paramount importance on public health. Therefore, the category needs to continue to be kept under price regulation in larger public interest[5].

Further, on February 12, 2018[6], NPPA revised the ceiling prices of drug eluting stents (DES) to Rs 27,890 from Rs. 29,600, while marginally raising the cap on bare metal stents to Rs 7,660 from Rs 7,260 as listed below:

S.No.	Coronary Stents (Sl. 31 in Schedule I of DPCO 2013)	Unit (in Number)	Ceiling Price (In Rs.)
1	Bare metal stents	1	7,660
2	Drug Eluting Stents (DES) including metallic DES and Bioresorbable Vascular Scaffold (BVS)/ Biodegradable Stents	1	27,890

Trade margin & GST on revised stent price:

GST: The manufacturers may add goods and services tax and no other charges in the calculation of MRP, if they have actually paid such taxes or if it is payable to the Government on the ceiling price specified in the above table.

4 http://www.nppaindia.nic.in/ceiling/press13Feb2017/so412e-13-02-17.pdf

5 http://www.nppaindia.nic.in/minutes/minutes-2017-18/Authority_minutes.pdf

6 http://www.nppaindia.nic.in/order/revised_prices(coronary-stents).pdf

Trade margin:

The revised ceiling prices are inclusive of 8% maximum permissible trade margin which is sacrosanct and no additional charge whatsoever, over and above the ceiling price specified hereinabove, in the price notification shall be charged from the consumer/patient except applicable goods and services tax, if any, paid or payable. Trade margin in excess of 8% specified above, in whatsoever form, shall be construed as 'violation' and whoever is involved in such transactions, jointly and severally, shall be liable to appropriate action including prosecution, for violation of the provisions of the DPCO, 2013 under the Essential Commodities Act, 1955.

Monitoring Price of Essential Accessories used during angioplasty

Various accessories like cardiac catheters, balloon catheters and guide wires are integral part of the angioplasty package and are necessarily used during angioplasties. NPPA took serious note of trade margins of these essential accessories and decided further monitoring of their respective MRPs not only on the basis of manufacturer's data but also the retail usage data.

NPPA directed all healthcare institutions, which are performing angioplasty and billing the patients, to mention cost of cardiac catheters, balloon catheter and guide wire separately along with their respective brand name, company name, batch number and specifications in order to bring in greater transparency in the billing and monitoring of compliance with the MRPs set by the NPPA under Para 20 of DPCO, 2013.

Industry compliance with revised ceiling price

The revised ceiling price as specified above shall be applicable from February 13, 2018, and shall also be applicable to all the stocks of coronary stents including "Covered coronary stents "available for sale in the trade channel. In this regard –

- All manufacturers/marketers of above coronary stents are advised to revise the price of all such stents, plus goods and services tax as applicable and paid, if any.
- The manufacturers under Paragraph 24 of DPCO, 2013 shall issue price list in Form–V to the NPPA through online Integrated Pharmaceutical Database Management System (IPDMS) along with a certified hard copy, and submit a copy of the same to all the State Drug Controllers and all its distributors/dealers/ cardiac healthcare institutions performing angioplasties.
- All the manufacturers will continue to ensure the availability of all the brands of coronary stents and ensure that no disruption is caused in the supply chain.
- Every distributor, dealer and institution shall display price list and the supplementary price list, if any, as furnished by the manufacturer/importer, on a conspicuous part of the premises where he carries on business including its publication on its website.
- Since cardiac catheters are necessarily used during angioplasties and are integrated part of the angioplasty package; healthcare institutions which are performing angioplasty and billing the patients, shall also mention cost of cardiac catheters, balloon catheter and guide wire separately.
- No healthcare institution, such as hospitals/nursing-homes/clinics performing angioplasty procedures using coronary stents, shall solicit any patient to purchase coronary stents from it, in case, the patient is interested in procuring such stents from any other third-party sources.

Note:

- Any manufacturer intending to discontinue production or import of any Coronary Stent shall furnish information to the NPPA, in respect of discontinuation of production and / or import in Form-IV of Schedule-II of the DPCO, 2013 at least six months prior to the intended date of discontinuation as prescribed under paragraph 21(2) of the DPCO, 2013 and follow the ceiling price in such manner and till such a time prescribed by the Government.
- The revised ceiling price hereinabove shall be applicable till March 31, 2019, unless revised by another notification.

CDSCO advises strict regulation of Oxytocin to curb its misuse

Oxytocin is a neuro-hormone and neurotransmitter normally produced by the paraventricular nucleus of the hypothalamus and released in large amounts by the posterior pituitary gland in mammals. Oxytocin is known to induce contractions of the uterus during labour, and stimulate the ejection of milk during breastfeeding. Oxytocin also known as love-hormone as it plays a role in the female reproductive functions including sexual activity, child birth and maternal nurturing behavior along with general psychological stability.

In this view, synthetic Oxytocin is being widely administered in obstetric practice for induction of labour, control of bleeding following delivery and for stimulation of milk letdown reflex in human and cattle as well. However, people have started using Oxytocin injections unsystematically on milch animals not only during delivery of a calf, but more frequently to accrue greater benefit/profit - for example a milch cattle is injected 5 ml of Oxytocin twice a day just five minutes prior to milking so that milk flows out faster from the udder[7].

The Central Drug Standard Control Organization (CDSCO) observed many complaints regarding misuse of Oxytocin injection by dairy owners in milch cattles and by farmers to increase the size of vegetables and fruits. However, no scientific data on the support of such practices is available. According to the "National Dairy Research Institute (NDRI)" and "Indian Council of Agricultural Research (ICAR)" there is no scientific evidence that artificial use of Oxytocin has adversely affected progeny of cattle and buffaloes resulting in dwindling of livestock. However, continuous Oxytocin use could lead to a progressive addiction and lack of response to normal let down of milk[8].

Central government restricts manufacture, sale and distribution of Oxytocin

On January 17, 2014, Ministry of Health and Family Welfare (MoHFW) issued a notification under Section 26A of the Drugs and Cosmetics Act, 1940 restricting the manufacture and sale of Oxytocin thereunder:

- The manufacturers of bulk Oxytocin drug shall supply the active pharmaceutical drug only to the manufacturers licensed under the Drugs and Cosmetics Rules, 1945 for manufacture of formulations of the said drug.
- The formulations meant for veterinary use shall be sold to the veterinary hospitals only[9].

Further, the Department of Animal Husbandry, Dairying and Fisheries have also issued an advisory to all the State Governments to comply with the provisions of the above-mentioned notification. Despite this, continued misuse of Oxytocin injection in the country has been considered by the Drug Consultative Meeting (DCC) as well as Drug Technical Advisory Board (DTAB) in its various meetings. The problem of misuse of Oxytocin is related more to the degree of control over the manufacture and sale of the drug especially through clandestine channels.[10]

CDSCO's strict regulatory control over manufacture, sale and distribution of Oxytocin

On September 22, 2017, CDSCO, with the intimation of Ministry of Health and Family Welfare (MoHFW), has directed all state drug controllers regarding strict regulatory control over manufacture, sale and distribution of Oxytocin and to curb its misuse as described below-

I. Constitution of special task force in each District of each State to ensure that no prohibited/regulated drug including Oxytocin is freely available in any district in open market, save and except in the pre-

7 http://www.bwcindia.org/Web/Awareness/LearnAbout/Oxytocin.html

8 http://dahd.nic.in/sites/default/files/LS%20328.pdf

9 http://cdsco.nic.in/writereaddata/G.S.R.%2029%20(E).pdf

10 http://www.cdsco.nic.in/writereaddata/70th%20DTAB%20minutes.pdf

scribed manner.

II. Concerned State Drug Controllers of the States where licenses of manufacturing of Oxytocin have been issued shall examine the license of all existing manufacturers of Oxytocin to ensure that the same have been issued strictly in accordance to the Drug and Cosmetic Act, 1940 and Rules 1945 and that the manufacturers mandatorily comply with all the conditions of the Act and rules framed there under. Immediate appropriate actions as per the statutory provisions may be taken wherever violations of the rules are found.

III. The State Drug controllers shall place on their respective websites, by 10th of each month, details of licenses issued to various manufacturers along with the monthly statement of production and sales of Oxytocin with complete particulars and details submitted by manufacturers. The manufacturers of Oxytocin, shall in turn, submit these details beforehand so as to reach the office of drug Controller by 7th of every month.

IV. The wholesaler and retailers of all prohibited scheduled drugs including Oxytocin shall maintain records, as required under law and the same shall be produced for inspection after every quarter before the officer specifically deployed for this purpose by drug controller.

V. The State Drug Controllers may take appropriate steps for undertaking IEC activities for sensitizing public about ill effects of Oxytocin both on humans and on animals' especially milch cattle, and about penal provisions for abuse/misuse of Oxytocin[11].

On February 22, 2018, CDSCO met with all manufacturers of oxytocin to discuss illegal manufacture, import and sale of oxytocin and its misuse. Further, CDSCO on February 28, 2018, has released proposals via public notice requesting comments/suggestions from stakeholders in this regard. The CDSCO's notice says that "As the whole issue of Oxytocin is of paramount importance for protection of human and animal health, following proposals are under consideration to curb its misuse:

I. To prohibit the import of the Oxytocin and its formulations for human use as well as animal use under section 10A of the Drugs and Cosmetics Act, 1940.

II. To regulate and restrict the Oxytocin formulations for human use under Section 26A of the Drugs and Cosmetics Act, 1940, so that the drug is supplied only to registered hospitals and clinics in public and private sector.

III. To adopt bar-coding system for manufacture of Oxytocin formulations so as to ensure trackability and traceability of the product to avoid its misuse.

IV. Manufacturing of Oxytocin (formulation) shall be restricted in public sector units only".

However, above proposals shall not be applicable for Oxytocin meant for export purpose[12].

Conclusion:

The manufacture, sale and distribution of Oxytocin are well described under the Drugs and Cosmetics Act, 1940 and the Drugs and Cosmetics Rules, 1945. However, a strict vigilance and regular monitoring/inspection of Oxytocin misuse by Central and state drug authorities are recommended. As per CDSCO's Data bank updated earlier in February this year, there are 3 registered bulk manufacturers and 113 formulation manufacturers of Oxytocin in India.

11 http://www.cdsco.nic.in/writereaddata/notice22_9_2017.pdf

12 http://www.cdsco.nic.in/writereaddata/Public%20Notice28.pdf

NITI Aayog releases "Healthy States, Progressive India" Report

- Kerala, Punjab & Tamil Nadu ranked on top in terms of overall performance
- Jharkhand, Jammu & Kashmir, and Uttar Pradesh ranked top three States in terms of annual incremental performance

On February 09, 2018 The National Institution for Transforming India (NITI) Aayog released a comprehensive Health Index report titled, "Healthy States, Progressive India"[13]. The report ranks states and Union territories innovatively on their year-on-year incremental change in health outcomes, as well as, their overall performance with respect to each other. The report was released jointly by the CEO, NITI Aayog; Secretary, Ministry of Health & Family Welfare; and World Bank India Country Director. It is the first attempt to establish an annual systematic tool to measure and understand the heterogeneity and complexity of the nation's performance in Health. The report has been developed by NITI Aayog, with technical assistance from the World Bank, and in consultation with the Ministry of Health and Family Welfare (MoHFW),

States and UTs have been ranked in three categories namely Larger States, Smaller States and Union Territories (UTs) to ensure comparison among similar entities. The Health Index is a weighted composite Index which for the Larger States is based on indicators in three domains: (a) Health Outcomes (70%); (b) Governance and Information (12%); and (c) Key Inputs and Processes (18%), with each domain assigned a weight based on its importance.

Among the Larger States, Kerala, Punjab, and Tamil Nadu are ranked on top in terms of overall performance, while Jharkhand, Jammu & Kashmir, and Uttar Pradesh are the top three ranking States in terms of annual incremental performance. Jharkhand, Jammu & Kashmir, and Uttar Pradesh showed the maximum gains in improvement of health outcomes from base to reference year in indicators such as Neonatal Mortality Rate (NMR), Under-five Mortality Rate (U5MR), full immunization coverage, institutional deliveries, and People Living with HIV (PLHIV) on Anti-Retroviral Therapy (ART).

Among Smaller States, Mizoram ranked first followed by Manipur on overall performance, while Manipur followed by Goa were the top ranked States in terms of annual incremental performance. Manipur registered maximum incremental progress on indicators such as PLHIV on ART, first trimester antenatal care (ANC) registration, grading quality parameters of Community Health Centres (CHCs), average occupancy of key State-level officers and good reporting on the Integrated Disease Surveillance Programme (IDSP).

Among UTs, Lakshadweep ranked best in overall performance as well as the highest annual incremental performance. Lakshadweep showed the highest improvement on indicators such as institutional deliveries, tuberculosis (TB) treatment success rate and transfer of National Health Mission (NHM) funds from State Treasury to implementation agency.

The Health Index report notes that while States and UTs that start at lower levels of development are generally at an advantage in notching up incremental progress over States with high Health Index scores, it is a challenge for States with high Index scores to maintain their performance levels. For example, Kerala ranks on top in terms of overall performance but sees the least incremental change as it has already achieved a low level of Neonatal Mortality Rate (NMR) and Under-five Mortality Rate (U5MR) and replacement level fertility, leaving limited scope for any further improvements.

However, the incremental measurement reveals that **about one-third of the States have registered a decline in their performance in 2016 as compared to 2015**, stressing the need to pursue domain-specific, targeted

13 http://pib.nic.in/PressReleseDetail.aspx?PRID=1520074

interventions. **Common challenges for most States and UTs include** the need to focus on addressing vacancies in key positions, establishment of functional district Cardiac Care Units (CCUs), quality accreditation of public health facilities and institutionalization of Human Resource Management Information System (HRMIS). Additionally, almost all Larger States need to focus on improving the Sex Ratio at Birth (SRB).

Linking this Index to incentives under the National Health Mission by the Ministry of Health and Family Welfare underlines the importance of such an exercise. The report also notes that rich learnings have emerged in the first year and these will guide in refining the Index for the coming year and also address some of the limitations. It notes that there is an urgent need to improve data systems in the health sector, in terms of terms of representativeness of the priority areas, periodic availability for all States and UTs, and completeness for private sector service delivery. This Index is expected to **nudge States towards further achieving a rapid transformation of their health systems and population health outcomes.**

Health Index has been developed as a tool to leverage co-operative and competitive federalism to accelerate the pace of achieving health outcomes. It would also serve as an instrument for "nudging" States & Union Territories (UTs) and the Central Ministries to a much greater focus on output and outcome based measurement of annual performance than the current practice. With the annual publication of the Index and its availability on public domain on a dynamic basis, it is expected to keep every stakeholder alert to the achievement of Sustainable Development Goals (SDGs) Goal number 3, which is to "Ensure healthy lives and promote well-being for all at all ages[14]."

The process of index refinement involved inputs from the States and UTs, national and international sector experts and development partners. Data submitted by the States & UTs was validated by an Independent Validation Agency, following which index values and ranks were generated on the web portal, and certified by the Independent Agency.

Conclusion:

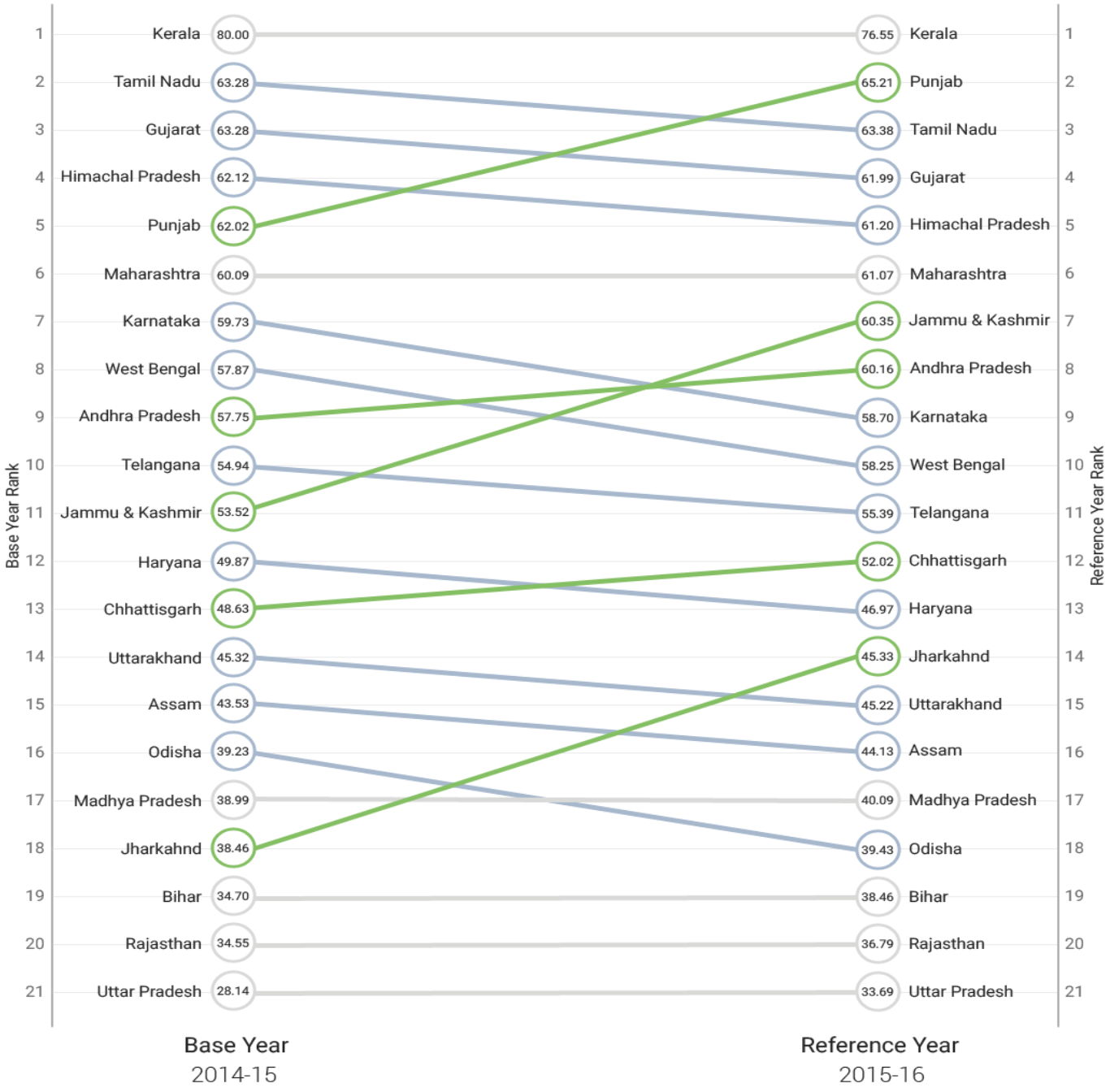
The Health Index is a useful tool for systematic measurement of annual performance across the country. The Health Index is an important aid in understanding the heterogeneity and complexity of the nation's performance in health. It is a first attempt at establishing an annual systematic tool for measurement of performance across States and UTs on a variety of health parameters within a composite measure.

14 https://sustainabledevelopment.un.org/sdg3

Annexure1: Larger States: Overall performance - Composite Index score and rank, base and reference years

- Top overall performers: Kerala, Punjab and Tamil Nadu
- 5 States improved their position: Punjab, Andhra Pradesh, Jammu & Kashmir, Chhattisgarh and Jharkhand
- 10 States have slipped from their original positions

Larger States: Overall Performance - Composite Index Score And Rank, Base And Reference Years



Note: Lines depict changes in composite Index score rank from base to reference year. The composite Index score is presented in the circle.

Productivity losses due to premature mortality from cancer in Brazil, Russia, India, China, and South Africa (BRICS)

According to a new study released by World Health Organization's (WHO) International Agency for Research on Cancer (IARC), billions of US dollars are lost in productivity in major emerging economies[15], due to premature mortality owing to cancer.

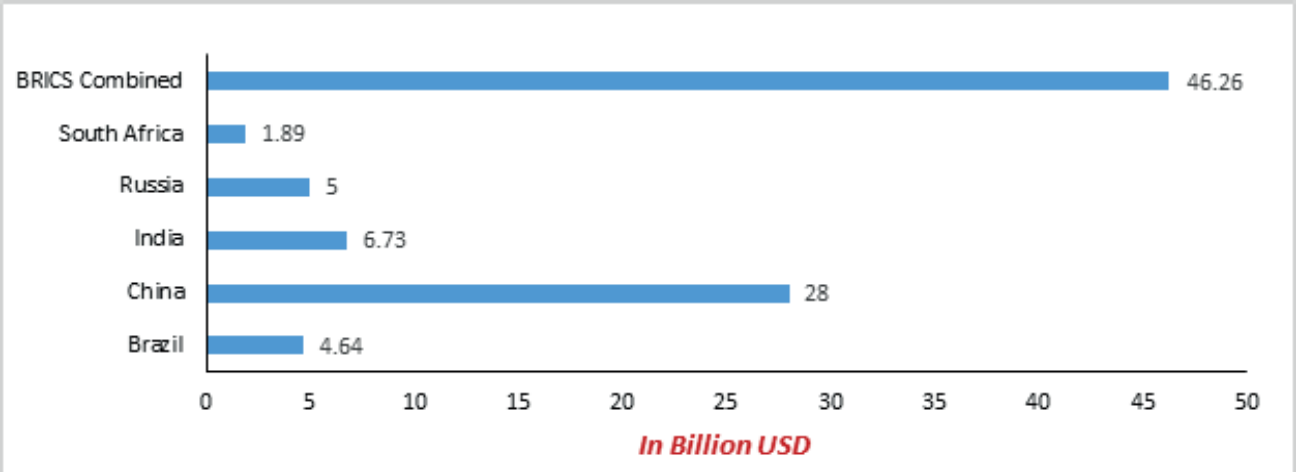
Led by the International Agency for Research on Cancer (IARC) in partnership with leading cancer research institutions in these countries, the study shows that the productivity loss in Brazil, the Russian Federation, India, China, and South Africa, collectively known as the BRICS countries, reached $46.3 billion in 2012. This represents 0·33% of their combined GDP, with country-specific proportions of GDP ranging from 0·21% in Brazil to 0·49% in South Africa[16].

The BRICS countries account for more than 40% of the world's population, 25% of the global gross domestic product (GDP), and 42% of the world's cancer deaths. Although they have diverse levels of wealth, and health indicators, the BRICS countries have all undergone particularly rapid demographic and economic growth. They are affected by infection-related cancers as well as cancers associated with changing lifestyles (changes in diet, lack of physical activity, obesity, reproductive patterns etc.). Yet each of these countries has a distinct cancer profile, and therefore, a tailored approach to national cancer control policy is required.

Economic impact of major cancers in BRICS countries

The aim of this study was to estimate – for the first time – the value of productivity lost due to cancer-related premature mortality in Brazil, the Russian Federation, India, China, and South Africa (collectively known as the BRICS countries) in 2012.

Figure 1 (below) shows country wise Economic Loss productivity wise due to premature Cancer Mortality in the BRICS region



15 http://www.iarc.fr/en/media-centre/pr/2018/pdfs/pr255_E.pdf

16 https://doi.org/10.1016/j.canep.2017.12.013

Figure 1

Across all the BRICS countries, liver cancer and lung cancer have the largest impact on total productivity lost. In the BRICS countries, combined together, liver ($8·8 billion), lung ($8·0 billion), stomach ($4·7 billion), oesophagus ($2·7 billion), and colorectal cancer ($2·5 billion) contributed the greatest lost productivity.

Among males, total productivity loss was highest for liver ($8·2 billion), lung ($7·1 billion), stomach ($4·1 billion), oesophagus ($2·5 billion), and colorectal ($1·9 billion) cancers. Among females, total productivity loss was highest for breast ($2·1 billion), cervix ($1·5 billion), lung ($0·9 billion), stomach ($0·7 billion), and liver ($0·7 billion) cancers.

The largest total productivity loss ($28 billion) was in China, which is particularly affected by liver cancer. Infection with hepatitis B virus and dietary exposure to aflatoxins are major contributors to this productivity loss.

In the Russian Federation, the considerable contribution of liver cancer and head and neck cancers to overall premature cancer mortality was probably associated with high consumption of alcohol.
The impact of tobacco smoking on lung cancer mortality was also observed in South Africa and Brazil. Despite successful tobacco control policies, such as those implemented in Brazil, tobacco remains a significant risk factor in these countries and rising tobacco-related productivity losses are expected in future. In India, the use of chewing tobacco was a leading cause of economic loss due to premature mortality from cancers of the lip and oral cavity.

Other lifestyle-related risk factors were also shown to have an effect on the cancer burden, such as rapidly increasing rates of obesity in Brazil.

The study further highlighted the potential economic benefits that could be accrued from introducing, or increasing coverage of, vaccinations for hepatitis B (HBV, for the prevention of liver cancer), human papilloma virus (HPV, for the prevention of cervical and ano-genital cancers), and Helicobacter pylori (for the prevention of stomach cancer). Vaccination for HBV and HPV is clearly cost-effective (based on developed country thresholds), but remains beyond the reach of many low income countries without additional funding or implementation support.

Conclusion:

This research, for the first time, provides the estimates of lost productivity related to premature cancer-related mortality in the BRICS economies. The results show that these costs are significant – $46·3 billion, representing 0·33% of the combined GDP of BRICS countries. The markedly different patterns of cancer burden measured as lost productivity across the BRICS countries highlight the need for local cancer control priorities and strategies.

NPPA UPDATES FOR THE MONTH OF FEBRUARY 2018

The National Pharmaceutical Pricing Authority (NPPA), is an executive body under the Drugs (Prices Control) Order (DPCO), 2013 under Department of Pharmaceuticals, Ministry of Chemicals and Fertilizers, Government of India. NPPA regulates drug prices and availability of the medicines in the country by fixing/revising the prices of controlled bulk drugs and formulations. The NPPA's key announcements/notices of February 2018 are apprised and described below:

1. **NPPA fixed/revised ceiling/retail prices of 30 formulations under DPCO 2013,**
2. **NPPA releases clarification regarding partially revised format of Form – I for applications of new drug under Para 2(u) of DPCO 2013**
3. **Analysis of Trade margin in Cardiac guide wire/Balloon catheter/ Guiding catheter,**
4. **Revision of coronary stents price**
5. **NPPA fixed/revised ceiling/retail prices of 09 formulations under DPCO 2013**
6. **Price analysis based on the complaints received in NPPA regarding overcharging in bills by four hospitals,**
7. **NPPA fixed/revised ceiling/retail prices of 14 formulations under DPCO 2013.**

1. NPPA has fixed/revised ceiling prices/retail prices of 30 formulations: On February 06, 2018, NPPA has fixed ceiling prices/retail prices of 30 formulations under DPCO, 2013. Amongst the 30 formulation included in this price fixation notice, included drugs are used for treatment of conditions like Pain, Infections, Hypertension, Epilepsy, Diabetes, Cancer etc. as described below -

Sl. No.	Name of the Formulation / Brand Name	Strength	Unit
(1)	(2)	(3)	(4)
1.	Paracetamol + Dicyclomine Tablet (Pacimol Spas)	Each Uncoated tablet contains: Paracetamol IP 500mg, Dicyclomine Hydrochloride IP 20 mg	1 Tablet
2.	Amoxicillin Potassium Clavulanate Tablet (Clavam Forte DT)	Each uncoated dispersible tablet containing: Amoxicillin Trihydrate IP eq. to Amoxicillin 400mg, Potassium Clavulanate diluted IP eq. To Clavulanic acid 57 mg	1 Tablet
3.	Telmisartan + Chlorthalidone Tablet (Tigatel CH40)	Each film coated Tablet contains: Telmisartan IP 40mg, Chlorthalidone IP 12.5mg	1 Tablet
4.	Cilnidipine + Telmisartan tablet (Telvacil 80mg)	Each Tablet contains: Cilnidipine 10mg , Telmisartan IP 80mg	1 Tablet
5.	Metoprolol ER Tablet	Each film coated extended release Tablet contains: Metoprolol Succinate IP 71.25mg eq. to Metoprolol Tartrate 75mg.	1 Tablet
6.	Paracetamol + Caffeine Tablate (Pacimol Active)	Each film coated Tablet contains: Paracetamol IP 650mg, Caffeine Anhydrous IP 50mg	1 Tablet
7.	Doxycyclilne + Lactic Acid Bacillus capsules	Each hard Gelatin capsule contains: Doxycycline Hyclate eq. to Doxycycline 100mg, Lactic Acid Bacillus 5 Billion Spores	1 Capsule

Sl. No.	Name of the Formulation / Brand Name	Strength	Unit
8.	Doxycyclilne + Lactic Acid Bacillus capsules	Each hard Gelatin capsule contains: Doxycycline Hyclate eq. to Doxycycline (Pellets) 100mg, Lactic Acid Bacillus (enteric coated Pellets) 5 Billion Spores	1 Capsule
9.	Cilnidipine + Telmisartan Tablet	Each film coated tablet contains: Cilnidipine 10mg, Telmisartan IP 40mg	1 Tablet
10.	Cilnidipine + Telmisartan Tablet	Each film coated tablet contains: Cilnidipine 10mg, Telmisartan IP 40mg	1 Tablet
11.	Levetiracetam Tablet	Each film coated tablet contains: Levetiracetam IP 1000mg	1 Tablet
12.	Levetiracetam Tablet	Each film coated prolonged release tablet contains: Levetiracetam IP 1000mg	1 Tablet
13.	Phenylephrine + Chlorpheniramine Syrup	Each 5 ml Contains: Phenylephrine Hydrochloride IP 5mg, Chlorpheniramine Maleate IP 2mg	1 ML
14.	Sumatriptan + Naproxen Tablet (NAXCOM)	Each uncoated bilayer tablet contains: Sumatriptan Succinate IP eq. to Sumatriptan 85mg, Naproxen Sodium USP 500mg	1 Tablet
15.	Cilnidipine + Telmisartan + Chlorthalidone Tablet	Each film coated tablet contains: Cilnidipine 10mg, Telmisartan IP 40mg, Chlorthalidone IP 6.25mg	1 Tablet
16.	Telmisartan + Amlodipine + Chlorthalidone Tablet	Each film coated tablet contains: Telmisartan IP 40mg, Amlodipine Besylate IP eq. to Amlodipine 5mg, Chlorthalidone IP 12.5mg	1 Tablet
17.	Telmisartan + Amlodipine + Chlorthalidone Tablet (Tigatel ACH 40)	Each film coated tablet contains: Telmisartan IP 40mg, Amlodipine Besylate IP eq. to Amlodipine 5mg, Chlorthalidone IP 12.5mg	1 Tablet
18.	Telmisartan + Amlodipine + Chlorthalidone Tablet (Tigatel ACH 80)	Each uncoated tablet contains: Telmisartan IP 80mg, Amlodipine Besylate IP Eq. to Amlodipine 5mg & Chlorthalidone IP 12.5mg	1 Tablet
19.	Human Insulin Injection	Insulin Biophasic Isophane Ph. Eur./ USP (30% as soluble Insulin Injection and 70% as Isophane Insulin Injection) Each ml contains: r-human Insulin (Regular) 100 IU/vial, m-Cresol USP – 0.16% w/v, Phenol IP 0.065% w/v	1 ML
20.	Human Insulin Injection	Insulin Biophasic Isophane Ph. Eur./ USP (50% as soluble Insulin Injection and 50% as Isophane Insulin Injection) Each ml contains: r-human Insulin (Regular) 100 IU/vial, m-Cresol USP – 0.16% w/v, Phenol IP 0.065% w/v	1 ML
21.	Human Insulin Injection	Soluble Insulin Ph. Eur./USP Each ml contains: r-human Insulin (Regular) 100IU/vial	1 ML
22.	Docetaxel Injection (Docetaxel IP 120mg/3ml)	Each ml of concentrate contains: Docetaxel (as anhydrous) 40mg, Polysorbate 80 – 566mg, Ethanol Anhydrous 326mg, Citric Acid Monohydrate 2mg (for PH adjustment), water for injection	Each Pack (120mg/3 ml)
23.	Escitalopram + Clonazepam Tablet (Szetalo Plus 5)	Each film coated tablet contains: Escitalopram Oxalate IP eq. to Escitalopram 5mg, Clonazepam IP 0.5mg	1 Tablet
24.	Telmisartan + Amlodipine Tablet (Telmiduce AM)	Each uncoated tablet contains: Telmisartan IP 40mg, Amlodipine Besylate IP eq. to Amlodipine 5mg	1 Tablet

Sl. No.	Name of the Formulation / Brand Name	Strength	Unit
25.	Telmisartan + Hydrocholrothiazide Tablet (Telmiduce H 40)	Each uncoated tablet contains: Telmisartan USP 40mg, Hydrocholrothiazide USP 12.50mg	1 Tablet
26.	Rosuvastatin + Aspirin + Clopidogrel Capsule (Rozucor Gold 10)	Each Hard Gelatine Capsule contains: Rosuvastatin Calcium IP eq. to Rosuvastation 10mg (As pellets), Aspirin IP 75mg (As Gastro - resistant pellets), Clopidogrel Bisulphate IP eq. to Clopidogrel 75mg (As pellets)	1 Capsule
27.	Rosuvastatin + Aspirin + Clopidogrel Capsule (Rozucor Gold 20)	Each Hard Gelatine Capsule contains: Rosuvastatin Calcium IP eq. to Rosuvastation 20mg (As pellets), Aspirin IP 75mg (As Gastro - resistant pellets), Clopidogrel Bisulphate IP eq. to Clopidogrel 75mg (As pellets)	1 Capsule
28.	Amoxycillin + Clavulante Suspension	Each combipack contains: (a) One bottle of Amoxycillin & Potassium Clavunate Oral Suspension I.P. Each 5ml of reconstituted suspension contains: Amoxycillin Trihydrate IP eq. to Amoxycillin 400mg, Potassium Clavulante Diluted IP eq. to Clavulnic Acid 57mg	1 ML
29.	Paracetamol + Mafenamic Suspension (Pacimol MF 125)	Each 5ml contains: Paracetamol IP 125mg, Mafenamic acid IP 50mg Flavoured Syrup base	1 ML
30.	Etoricoxib + Paracetamol Tablet (Etomax P)	Each film coated tablet contains: Etoricoxib IP 60mg, Paracetamol IP 325mg	1 Tablet

2. NPPA releases clarification regarding partially revised format of Form – I: On February 05, 2018, NPPA released clarification regarding partially revised format of Form – I for applications of new drug under Para 2(u) of DPCO, 2013. NPPA clarified that in order to expedite the retail price of new drug applications, the applicant company has been asked to indicate drug category as per the report of Kokate committee and Drug Technical Advisory Board (DTAB) to save time spent by NPPA on seeking this information from Drug Controller General of India (DCGI)[17].

3 Analysis of Trade margin in Cardiac guide wire/Balloon catheter/ guiding catheter: On February 12, 2018, NPPA analyzed the trade margins in the Cardiac Guidewire/Balloon Catheter and Guiding wire based on available data from the official sources and manufacturer/importer as described below –

SI No	Particulars	Average Margin % (MRP — import price)	Average Margin % (MRP - PTD)
1	Cardiac Balloon Catheter	405%	234%
2	Cardiac Guidewire	158%	112%
3	Cardiac Guiding Catheter	295%	93%
4	Cardiac Drug Eluting Balloon or Cutting Balloon	292%	140%
5	Cardiac Guiding Catheter — Special feature	172%	62%

*MRP: Maximum Retail Price, PTD: Price to Distributor/Stockist.[18]

17 http://www.nppaindia.nic.in/order/om_revisedformat(09022018).pdf

18 http://www.nppaindia.nic.in/order/trade_margin(Catheters).pdf

4. Revision of coronary stents price: On February 12, 2018,[19] NPPA fixed and notified the revised ceiling prices of drug eluting stents (DES) from Rs. 29,600 to Rs 27,890, while marginally raising the cap on bare metal stents from Rs 7,260 to Rs 7,660, exclusive of goods and services tax applicable, if any. Whereas, any manufacturer intending to discontinue production or import of any Coronary Stent shall furnish information to the NPPA, in respect of discontinuation of production and / or import in Form-IV of Schedule-II of the DPCO, 2013 at least six months prior to the intended date of discontinuation as prescribed under paragraph 21(2) of the DPCO, 2013 and follow the ceiling price in such manner and till such a time prescribed by the Government. The revised ceiling price hereinabove shall be applicable till March 31, 2019 unless revised by another notification[20].

5. NPPA has fixed/revised ceiling/retail prices of 09 formulations: On February 13, 2018, NPPA revised the ceiling prices of nine scheduled formulations under DPCO, 2013. The said formulations are used to treat a range of ailments from infertility in women to arthritis to seizures. The formulations included in this price revision are Clomiphene tablets, Adenosine injection 3mg/ml, Povidone Iodine Solution 10 per cent (1 ml), Methylprednisolone injection 40mg/ml (1 ML), Sodium Valproate CR tablets 300 mg,& 500mg, Isosorbide 5 Mononitrate tablet 20 mg, and Lignocaine Topical Forms 2-5 per cent (1 gm or 1 ml)[21].

6. Price analysis based on the complaints received by NPPA regarding overcharging in bills by four hospitals: On February 20, 2018, NPPA released Price analysis report after receiving complaints of overpricing and inflated bills from the relatives of deceased patients. NPPA, within its jurisdiction under Drug Prices Control Order, 2013 had asked for details of billing from these hospitals and analyzed the same in great detail.

The report suggests that the total expenditure on drugs and devices and diagnostics is substantially high (46%) and does not make part of the publicized 'estimate' or 'package'. This is a clear case of market distortion where manufacturers after accounting for their profits print inflated MRPs to meet the demands of a distorted trade channel without getting any benefits from this 'artificial inflation' and patients have to incur huge out-of-pocket expenditure in hospitalization cases. The major beneficiaries of profits in all these cases because of inflated MRPs have been hospitals rather than drugs and devices manufacturers. The violation of ceiling price and corresponding MRPs is detected only in very few cases which shall be pursued further by NPPA for recovering the overcharging amounts from defaulters[22].

7. NPPA fixed/revised ceiling/retail prices of 14 formulations under DPCO 2013: On February 27, 2018, NPPA fixed/revised the retail/ceiling prices of 14 scheduled formulations under DPCO, 2013. The revised formulations are used for the treatment of diabetes, hypertension, cancer and Hyperlipidemia etc. as described below-

Sl. No.	Name of the Formulation / Brand Name	Strength	Unit
1.	Amlodipine +, Valsartan Tablet (Valembic 80 AM)	Each film coated tablet contains: Amlodipine Besylate eq. to Amlodipine USP 5mg, Valsartan USP 80mg Tablet	1 Tablet
2.	Amlodipine +, Valsartan Tablet (Valembic 160 AM)	Each film coated tablet contains: Amlodipine Besylate eq. to Amlodipine USP 5mg, Valsartan USP 160mg Tablet	1 Tablet
3.	Paclitaxel (Protein Bound Particles) for Injectable Suspension (Nabtoxol)	Each vial contains: Paclitaxel 100mg Human albumin	1 Vial
4.	Telmisartan + Chlorthalidone Tablet	Each uncoated bilayered tablet contains: Telmisartan IP 40mg, Chlorthalidone IP 6.25mg	1 Tablet

19 http://www.nppaindia.nic.in/order/revised_prices(coronary-stents).pdf

20 http://www.nppaindia.nic.in/minutes/minutes-2017-18/Authority_minutes.pdf

21 http://www.nppaindia.nic.in/ceiling/press13feb18/Formulation_Prices(09).pdf

22 http://www.nppaindia.nic.in/order/overcharging_details(20022018).pdf

Sl. No.	Name of the Formulation / Brand Name	Strength	Unit
5.	Glimepiride + Metformin + Voglibose Tablet (TRIVOGO 2/0.3 Mg)	Each uncoated bilayered tablet contains: Glimepiride IP 2mg, Metformin Hydrochloride IP 500mg (As SR form) Voglibose IP 0.3mg	1 Tablet
6.	Etoricoxib + Paracetamol Tablet	Each film coated tablet contains: Etoricoxib IP 60mg , Paracetamol IP 325mg	1 Tablet
7.	Sofosbuvir + Velpatasvir Tablets	Each film coated tablet contains: Sofosbuvir IH 400mg, Velpatasvir IH 100mg	1 Tablets
8.	Atorvastatin + Clopidogrel Capsule	Each hard gelatin capsule contains: Atorvastatin Calcium IP eq. to Atorvastatin 10mg (As Pellets) Clopidogrel Bisulphate IP eq. to Clopidogrel 75mg (As Pellets)	1 Capsule
9.	Atorvastatin + Clopidogrel Capsule	Each hard gelatin capsule contains: Atorvastatin Calcium IP eq. to Atorvastatin 20mg (As Pellets) Clopidogrel Bisulphate IP eq. to Clopidogrel 75mg (As Pellets)	1 Capsule
10.	Rosuvastatin + Aspirin + Clopidogrel Capsule	Each hard gelatin capsule contains: Rosuvastatin Calcium IP eq. to Rosuvastation 20mg (As pellets) Aspirin IP 75mg (As enteric coated pellets) Clopidogrel Bisulphate IP eq. to Clopidogrel 75mg (As pellets)	1 Capsule
11.	Ferrous Ascorbate + Folic Acid Suspension	Each 5ml of suspension contains: Ferrous Ascorbate eq. to elemental Iron 30mg, Folic Acid IP 550mcg In a flavoured Syrupy base.	1 ML
12.	Bortezomib Injection	Each vial contains: Bortezomib IP 3.5mg Injection	1 Vial
13.	Teneligliptin + Metformin HCl Tablet	Each uncoated bilayered tablet contains: Teneligliptin Hydrobromide Hydrate eq. to Teneligliptin 20mg Metformin HCl 500mg (SR)	1 Tablet
14.	Teneligliptin + Metformin HCl Tablet	Each uncoated bilayered tablet contains: Teneligliptin Hydrobromide Hydrate eq. to Teneligliptin 20mg Metformin HCl 1000mg (SR)	1 Tablet[2]

European Medicines Agency (EMA): Recommends Approval of Five medicines in its February 2018 Meeting

The European Medicines Agency's (EMA) Committee for Medicinal Products for Human Use (CHMP) recommended five medicines for approval, including two orphan medicines, at its February 2018 meeting[23].

A. The five drugs recommended for approval are:

1. Alpivab (peramivir) - Treatment of uncomplicated influenza

The European Medicines Agency's (EMA) Committee for Medicinal Products for Human Use (CHMP) adopted a positive opinion and has recommended the granting of a marketing authorization for Alpivab (peramivir)[24]. Alpivab is indicated for the treatment of uncomplicated influenza in adults and children 2 years and older.

Uncomplicated influenza illness is characterized by the abrupt onset of constitutional and respiratory signs and symptoms (e.g., fever, myalgia, headache, malaise, nonproductive cough, sore throat, and rhinitis). Among children, otitis media, nausea, and vomiting also are commonly reported with influenza illness. However, influenza virus infections can cause primary influenza viral pneumonia; exacerbate underlying medical conditions (e.g., pulmonary or cardiac disease); lead to secondary bacterial pneumonia, sinusitis, or otitis media; or contribute to coinfections with other viral or bacterial pathogens[25].

Alpivab is an inhibitor of influenza virus neuraminidase, an enzyme important for viral entry into uninfected cells and release and spread of new virus once cells have been infected. The benefits with Alpivab are its ability to speed alleviation of symptoms and recovery of normal temperature in patients with uncomplicated influenza. The most common side effects are gastro-intestinal disorders, such as diarrhea and vomiting.

The applicant for Alpivab is Biocryst UK Limited.

2. Mylotarg (gemtuzumab ozogamicin) - Treatment of acute myeloid leukaemia

The European Medicines Agency's (EMA) Committee for Medicinal Products for Human Use (CHMP) has recommended the granting of a marketing authorization for Mylotarg[26], indicated for combination therapy with daunorubicin (DNR) and cytarabine (AraC) for the treatment of patients age 15 years and above with previously untreated, de novo CD33-positive acute myeloid leukaemia (AML), except acute promyelocytic leukaemia (APL)

Mylotarg is a humanized immunoglobulin G subtype 4 (IgG4) antibody directed at CD33 which is conjugated to calicheamicin, a toxin which induces breaks in double-stranded DNA, subsequently inducing cell cycle arrest and apoptotic cell death. The benefit with Mylotarg is improvement in event-free survival.

The applicant for Mylotarg is Pfizer Limited.

23 http://www.ema.europa.eu/ema/index.jsp?curl=pages/news_and_events/news/2018/02/news_detail_002907.jsp&mid=WC0b01ac058004d5c1

24 http://www.ema.europa.eu/docs/en_GB/document_library/Summary_of_opinion_-_Initial_authorisation/human/004299/WC500244135.pdf

25 https://www.cdc.gov/flu/professionals/acip/clinical.htm

26 http://www.ema.europa.eu/docs/en_GB/document_library/Summary_of_opinion_-_Initial_authorisation/human/004204/WC500244277.pdf

3. Amglidia (glibenclamide) – First medicine to treat neonatal Diabetes

The CHMP has recommended granting a marketing authorization in the European Union (EU) for Amglidia (glibenclamide)[27], a medicine indicated for the treatment of neonatal diabetes mellitus (NDM), for use in newborns, infants and children.

Neonatal diabetes is an extremely rare form of diabetes that is diagnosed in the first six months of life. It is life-threatening and debilitating because of the symptoms caused by high blood sugar levels and the risk of ketoacidosis, a serious problem that can occur in people with diabetes if their body starts to run out of insulin and ketones build up in the body. Different gene mutations have been identified which cause this type of diabetes.

Amglidia is a new oral formulation of glibenclamide, a medicine which is already authorized for treating type 2 diabetes, specifically developed for use in newborns, toddlers and children with neonatal diabetes. It works on insulin-producing cells in the pancreas by attaching to an ATP-sensitive potassium (KATP) channel, which controls the release of insulin. In many newborn babies with neonatal diabetes, the cells in the pancreas produce insulin but they are not able to release it into the blood because their gene mutations lead to dysfunctional KATP channels.

The applicant for Amglidia is AMMTeK.

4. Riarify - Maintenance treatment of adult patients with moderate to severe chronic obstructive pulmonary disease (COPD)

The EMA's CHMP has recommended the granting of a marketing authorization for Riarify[28], intended for the maintenance treatment of adult patients with moderate to severe chronic obstructive pulmonary disease (COPD).

Riarify is a triple combination of an inhaled glucocorticoid (beclometasone dipropionate), a long-acting beta-2 receptor agonist (formoterol fumarate dihydrate) and a long-acting muscarinic antagonist (glycopyrronium bromide). It will be available as a pressurized metered dose inhaler delivering a solution with a nominal dose per actuation of 87 micrograms / 5 micrograms / 9 micrograms of the active substances respectively. Beclometasone reduces inflammation in the lungs, whereas formoterol and glycopyrronium relax bronchial smooth muscle helping to dilate the airways and make breathing easier. The benefits with Riarify are its ability to relieve and prevent symptoms such as shortness of breath, wheezing and cough and to reduce exacerbations of COPD symptoms.

The applicant for Riarify is Chiesi Farmaceutici S.p.A.

5. Trydonis - Maintenance treatment of adult patients with moderate to severe chronic obstructive pulmonary disease (COPD)

The European Medicines Agency's (EMA) Committee for Medicinal Products for Human Use (CHMP) has recommended the granting of a marketing authorization for the medicinal product Trydonis[29], intended for the maintenance treatment of adult patients with moderate to severe chronic obstructive pulmonary disease (COPD).

Trydonis is a triple combination of an inhaled glucocorticoid (beclometasone dipropionate), a long-acting beta-2 receptor agonist (formoterol fumarate dihydrate) and a long-acting muscarinic antagonist (glycopyrronium bromide). It will be available as a pressurized metered dose inhaler delivering a solution with a nominal dose per actuation of 87 micrograms / 5 micrograms / 9 micrograms of the active substances respectively. Beclometasone

27 http://www.ema.europa.eu/ema/index.jsp?curl=pages/news_and_events/news/2018/02/news_detail_002908.jsp&mid=WC0b01ac058004d5c1

28 http://www.ema.europa.eu/docs/en_GB/document_library/Summary_of_opinion_Initial_authorisation/human/004836/WC500244279.pdf

29 http://www.ema.europa.eu/docs/en_GB/document_library/Summary_of_opinion__Initial_authorisation/human/004702/WC500244283.pdf

reduces inflammation in the lungs, whereas formoterol and glycopyrronium relax bronchial smooth muscle helping to dilate the airways and make breathing easier. The benefits with Trydonis are its ability to relieve and prevent symptoms such as shortness of breath, wheezing and cough and to reduce exacerbations of COPD symptoms.

The applicant for this medicinal product is Chiesi Farmaceutici S.p.A.

B. Negative opinion on two medicines:

1. Nerlynx (neratinib) – Intended to treat breast cancer

The EMA's Committee for Medicinal Products for Human Use (CHMP) has recommended the refusal of marketing authorization for Nerlynx[30], intended for the treatment of breast cancer.

Nerlynx is a tyrosine kinase inhibitor, a cancer medicine. It attaches to the HER2 protein on the cancer cells, and so blocks its action. Because HER2 helps cancer cells to grow and divide, blocking it helps to stop them growing and prevent the cancer from coming back.

The CHMP considered that though a greater proportion of women given Nerlynx in the study lived for 2 years without their disease coming back than women given placebo (around 94% versus 92% respectively); it is uncertain that this difference in benefit would be seen in clinical practice. Furthermore, Nerlynx causes side effects in the digestive system, particularly diarrhoea, which affected most patients and might be difficult to manage. The Committee therefore, concluded that the benefits were not enough to outweigh the risk of side effects and recommended that Nerlynx be refused marketing authorization.

Application for authorization for Nerlynx was made by Puma Biotechnology Ltd.

2. Sutent (sunitinib) - Expected to be used to delay or prevent the return of kidney cancer

The EMA's CHMP has recommended the refusal of a change to the marketing authorization for Sutent[31]. The CHMP considered that the evidence that Sutent delays the return of cancer was not convincing. Given the known side effects of the medicine, the Committee concluded that the benefits did not outweigh the risks and recommended that the change to the marketing authorization of Sutent be refused.

Sutent is a protein kinase inhibitor. This means that it blocks some specific enzymes known as protein kinases involved in the growth and spread of cancer cells and the development of new blood vessels supplying them. By blocking these enzymes, Sutent can reduce the growth and spread of cancer and cut off the blood supply that keeps cancer cells growing.

The company that applied for the change to the authorization is Pfizer Limited.

C. Six recommendations on extensions of therapeutic indication:

The CHMP has recommended a change to the terms of the marketing authorization for six drugs on extensions of therapeutic indication as described in table-

30 http://www.ema.europa.eu/docs/en_GB/document_library/Summary_of_opinion_-_Initial_authorisation/human/004030/WC500244282.pdf

31 http://www.ema.europa.eu/docs/en_GB/document_library/Summary_of_opinion/human/000687/WC500244293.pdf

Sl.no.	Name of medicine	Existing Indication	Marketing-authorisation holder
1	Bosulif (bosutinib)	-**Newly-diagnosed chronic phase (CP) Philadelphia chromosome-positive chronic myelogenous leukaemia (Ph+ CML)*** -CP, accelerated phase (AP), and blast phase (BP) Ph+ CML previously treated with one or more tyrosine kinase inhibitor(s) [TKI(s)] and for whom imatinib, nilotinib and dasatinib are not considered appropriate treatment options.	Pfizer Limited[3]
2	Feraccru (ferric maltol)	-In adults for the treatment of iron deficiency ~~anaemia (IDA). In adults for the treatment of iron deficiency anaemia (IDA) in patients with inflammatory bowel disease (IBD)~~****	Shield TX (UK) Ltd. [4]
3	Isentress (raltegravir)	-In combination with other anti-retroviral medicinal products for the treatment of human immunodeficiency virus (HIV-1) ~~infection in adults, adolescents, children, toddlers and infants from the age of 4 weeks~~****	Merck Sharp & Dohme Limited[5]
4	Kineret (anakinra)	-Kineret is indicated in adults for the treatment of the signs and symptoms of Rheumatoid Arthritis (RA) in combination with methotrexate, with an inadequate response to methotrexate alone. -Kineret is indicated in adults, adolescents, children and infants aged 8 months and older with a body weight of 10 kg or above for the treatment of Cryopyrin-Associated Periodic Syndromes (CAPS), including: • -Neonatal-Onset Multisystem Inflammatory Disease (NOMID) / Chronic Infantile Neurological, Cutaneous, Articular Syndrome (CINCA) • -Muckle-Wells Syndrome (MWS) • -Familial Cold Autoinflammatory Syndrome (FCAS) **-Kineret is indicated in adults, adolescents, children and infants aged 8 months and older with a body weight of 10 kg or above for the treatment of Still's disease, including Systemic Juvenile Idiopathic Arthritis (SJIA) and Adult-Onset Still's Disease (AOSD), with active systemic features of moderate to high disease activity, or in patients with continued disease activity after treatment with non-steroidal anti-inflammatory drugs (NSAIDs) or glucocorticoids.** **-Kineret can be given as monotherapy or in combination with other anti-inflammatory drugs and disease-modifying antirheumatic drugs (DMARDs)***.	Swedish Orphan Biovitrum AB (publ) [6]
5	Lynparza (olaparib)	-The CHMP recommended the approval of new strengths **Lynparza 100 mg and 150 mg tablets***, where indication remains same as previous for these Dose stregths: -Lynparza is indicated as monotherapy for the maintenance treatment of adult patients with platinum-sensitive relapsed BRCA-mutated (germline and/or somatic) high grade serous epithelial ovarian, fallopian tube, or primary peritoneal cancer who are in response (complete response or partial response) to platinum-based chemotherapy.	AstraZeneca AB[7]

Sl.no.	Name of medicine	Existing Indication	Marketing-authorisation holder
6	Xgeva (denosumab)	-Prevention of skeletal related events (pathological fracture, radiation to bone, spinal cord compression or surgery to bone) in adults adults with ~~bone metastases from solid tumours~~**advanced malignancies involving bone**.	Amgen Europe B.V[8].

**New text in bold, ** Removed text as strikethrough*

D. Withdrawal of application for extension of indication

1. Zydelig (idelalisib) – Treatment of chronic lymphocytic leukaemia (CLL) and follicular lymphoma

Gilead Sciences International Ltd. officially notified the Committee for Medicinal Products for Human Use (CHMP) that it wishes to withdraw its application to use the cancer medicine Zydelig in combination with the cancer medicines rituximab and bendamustine for the treatment of chronic lymphocytic leukaemia (CLL).

Zydelig blocks the effects of an enzyme called PI3K-delta. This enzyme plays a role in the growth, migration and survival of white blood cells but is overactive in blood cancers, where it enables the survival of the cancer cells. By targeting this enzyme and blocking its effects, idelalisib causes death of the cancer cells, thereby delaying or stopping the progression of the cancer.

The CHMP noted that patients treated with Zydelig in addition to rituximab and bendamustine lived longer without their disease getting worse than those receiving placebo in addition to rituximab and bendamustine. However, because of the design of the study and the side effect profile of Zydelig, the CHMP considered that longer term data was needed to show that the benefits of Zydelig outweighed its risks in this combination[32].

32 http://www.ema.europa.eu/docs/en_GB/document_library/Medicine_QA/2018/02/WC500244301.pdf

European Medicines Agency's Pharmacovigilance Risk Assessment Committee recommends new measures to avoid valproate exposure in pregnancy

New restrictions on use; pregnancy prevention programme to be put in place

On February 09, 2018, the European Medicines Agency's experts in medicines safety - the Pharmacovigilance Risk Assessment Committee (PRAC), has recommended new measures to avoid exposure of babies to valproate medicines in the womb. Babies exposed are at risk of malformations and developmental problems[33].

Main measures recommended by the PRAC

- Where licensed for migraine or bipolar disorder:
    - In pregnancy - valproate must not be used.
    - In female patients from the time they become able to have children – valproate must not be used unless the conditions of a new pregnancy prevention programme (as below) are met.
- For epilepsy:
    - In pregnancy - valproate must not be used. However, it is recognised that for some women with epilepsy it may not be possible to stop valproate and they may have to continue treatment (with appropriate specialist care) in pregnancy.
    - In female patients from the time they become able to have children – valproate must not be used unless the conditions of the new pregnancy prevention programme are met.
- The PRAC has also recommended that the outer packaging of all valproate medicines must include a visual warning about the risks in pregnancy. In addition to boxed text, this may include a symbol/ pictogram, with the details to be adapted at national level.
- A patient reminder card will also be attached to the outer package for pharmacists to discuss with the patient each time the medicine is dispensed.
- Companies that market valproate should also provide updated educational materials in the form of guides for healthcare professionals and patients.

Main points of the new valproate pregnancy prevention programme

- Assessing patients for the potential of pregnancy, and involving the patient in evaluating her individual circumstances and supporting informed decision making,
- Pregnancy tests before starting and during treatment as needed,
- Counselling patients about the risks of valproate treatment,
- Explaining the need for effective contraception throughout treatment,
- Carrying out reviews of treatment by a specialist at least annually,

33 http://www.ema.europa.eu/ema/index.jsp?curl=pages/news_and_events/news/2018/02/news_detail_002903.jsp&mid=WC0b01ac058004d5c1

- Introduction of a new risk acknowledgement form that patients and prescribers will go through at each such review to confirm that appropriate advice has been given and understood.

Medicines containing valproate have been approved nationally in the EU to treat epilepsy, bipolar disorder and in some countries for prevention of migraine. They are known to pose a considerable risk of malformations and developmental problems in babies who are exposed to valproate in the womb. An earlier review[34] had recommended measures aimed at better informing women about these risks in order to reduce the use of the medicine during pregnancy, and not starting treatment unless other options were ineffective or could not be used because of side effects. The current review was launched because of concerns that these measures had not been sufficiently effective.

The PRAC examined the available evidence and consulted widely with healthcare professionals and with patients, including women and their children who have been affected by valproate use during pregnancy, through written submissions, expert meetings, meetings with stakeholders including healthcare professionals, patients' organizations, patients and their families, and via a public hearing. The PRAC noted that women were still not receiving the right information always and in a timely manner and that further measures were needed to help avoid use during pregnancy. However, it was also clear that for some women, such as those with particular forms of epilepsy, valproate is the only appropriate treatment and might be life-saving.

The PRAC therefore considered that the way the products are used should be changed. It recommended strengthening restrictions on their use and introducing new measures to require appropriate counselling and information for affected women.

The PRAC also recommended that the companies marketing these medicines carry out additional studies to further characterize the nature and extent of the risks posed by valproate and to monitor ongoing valproate use and the long-term effects from affected pregnancies.

Because valproate medicines are all licensed at national level, the PRAC recommendations will now be sent to Co-ordination Group for Mutual Recognition and Decentralized Procedures – Human (CMDh), which will adopt a position.

In the meantime, women who have any concerns should consult their doctor. Women and girls who have been prescribed valproate should not stop taking their medicines without consulting their doctor as doing so could result in harm to them or to an unborn child.

More about Valproate

Valproate medicines are used to treat epilepsy and bipolar disorder. In some EU Member States, they are also authorized to prevent migraine headaches. The active ingredient in these medicines may be valproic acid, magnesium valproate, sodium valproate, valproate semisodium or valpromide.

Valproate medicines have been authorized via national procedures in all EU Member States and in Norway and Iceland. They are marketed under several brand names including: Absenor, Convival Chrono, Convulex, Delepsine, Depakin, Depakine, Depakote, Depamag, Depamide, Deprakine, Diplexil, Dipromal, Epilim, Episenta, Epival, Ergenyl, Espa-Valept, Hexaquin, Kentlim, Leptilan, Micropakine L.P., Orfiril, Petilin, Valepil, Valhel PR, Valpal, Valpro and Valprolek.

34 http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/human/referrals/Valproate_and_related_substances/human_referral_prac_000032.jsp&mid=WC0b01ac05805c516f

About the procedure

The review of valproate medicines was initiated on March 9, 2017, at the request of the French medicines regulator - ANSM, under Article 31 of Directive 2001/83/EC. This type of referral is triggered when the interest of the Union is involved, following concerns relating to the quality, safety or efficacy of a medicine or a class of medicines[35]. The review has been carried out by the Pharmacovigilance Risk Assessment Committee (PRAC), the Committee responsible for the evaluation of safety issues for human medicines, and it has made a set of recommendations. The PRAC recommendations will now be sent to Co-ordination Group for Mutual Recognition and Decentralised Procedures – Human (CMDh), which will adopt a position. The CMDh is responsible for ensuring harmonised safety standards for medicines authorized via national procedures across the EU.

35 http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general_content_000150.jsp&mid=WC0b01ac05800240d0

WHO recommends quadrivalent Influenza vaccines for use in the Northern Hemisphere Influenza Season, 2018-19

WHO Consultation and Information Meeting held from February 19-21, 2018, at Geneva, Switzerland has recommended the composition of influenza virus vaccines for use in the Northern Hemisphere Influenza Season, 2018-2019. As the periodic replacement of viruses contained in influenza vaccines is necessary in order for the vaccines to be effective due to the constant evolving nature of influenza viruses, including those circulating and infecting humans.

WHO Consultation and Information Meeting which meets twice annually, in the February 2018 meeting designed to -

- Review of the global influenza activity;
- Analysis of results of vaccine serological studies;
- Recommendations for the composition of influenza virus vaccines for use in the Northern Hemisphere Influenza season, 2018-2019;
- Review of the need and subsequent selection of new A (H7N9), A (H5) and other subtype or variant viruses for the development of new candidate vaccine viruses for pandemic preparedness purposes.

WHO recommended Quadrivalent Influenza vaccines:

WHO Consultation and Information Meeting has recommended quadrivalent vaccines for use in the 2018-2019 northern hemisphere influenza season[36] which contains the following viruses:

- An A/Michigan/45/2015 (H1N1)pdm09-like virus;
- An A/Singapore/INFIMH-16-0019/2016 **(H3N2)-**like virus;
- A B/Colorado/06/2017-like virus **(B/Victoria/2/87 lineage)**; and
- A B/Phuket/3073/2013-like virus (B/Yamagata/16/88 lineage).

It is recommended that trivalent vaccines contain the B/Colorado/06/2017-like virus, of the B/Victoria/2/87-lineage.

The influenza B/Victoria lineage virus component and the A (H3N2) virus component have been updated compared to the viruses recommended for the 2017-2018 northern hemisphere influenza seasons. The update is as follows:

- Replacement of the A/Hong Kong/4801/2014 (H3N2)-like virus with an A/Singapore/INFIMH-16-0019/2016 (H3N2)-like virus.
- Replacement of the B/Brisbane/60/2008-like virus with a B/Colorado/06/2017-like virus.

36 http://www.who.int/influenza/vaccines/virus/recommendations/2018_19_north/en/

Recommendation for northern or southern hemisphere influenza season:

Influenza viruses circulate at varying times through the year in tropical and sub-tropical countries. In selecting which vaccine formulation to use, these countries should consider their surveillance information, in particular epidemiological and virological data to decide when to start vaccination and whether to use the formulation recommended for the northern or southern hemisphere influenza season. WHO has formulated guidance for countries in tropical and sub-tropical regions to assist them in choosing which vaccine composition (February/ March or September) is most appropriate[37].

Development of Candidate Vaccine Viruses (CVVs):

WHO Consultation and Information Meeting provides a review on the zoonotic influenza virus activity and virus characterization, and describes the current status of the development of CVVs for pandemic preparedness purposes[38]. It is meant to provide guidance for national authorities and vaccine companies on the selection of candidate viruses for use in vaccine development.

Influenza A (H5)

Since their emergence in 1997, highly pathogenic avian influenza (HPAI) A (H5) viruses of the A/goose/ Guangdong/1/96 haemagglutinin (HA) lineage have become enzootic in some countries, have infected wild birds and continue to cause outbreaks in poultry and sporadic human infections. These viruses have diversified genetically and antigenically, including the emergence of viruses with replacement of the N1 gene segment by N2, N3, N5, N6, N8 or N9 gene segments, leading to the need for multiple CVVs. For example- recent A (H5) activity in India is hosted by Poultry with Genetic clade (subtype): 2.3.4.4 (H5N8), and the recent A (H5) activity in United Kingdom is hosted by wild birds with genetic clade (Subtype): 2.3.4.4 (H5N6). Therefore -

- The development of influenza candidate vaccine viruses (CVVs), coordinated by WHO, remains an essential component of the overall global strategy for pandemic preparedness.
- Selection and development of CVVs are the first steps towards timely vaccine production and do not imply a recommendation for initiating manufacture. National authorities may consider the use of one or more of these CVVs for pilot lot vaccine production, clinical trials and other pandemic preparedness purposes based on their assessment of public health risk and need.
- Zoonotic influenza viruses continue to be identified and evolve both genetically and antigenically, leading to the need for additional CVVs for pandemic preparedness purposes. Changes in the genetic and antigenic characteristics of these viruses relative to existing CVVs, and their potential risks to public health, justify the need to select and develop new CVVs[39].

Conclusion:

WHO recommendations and updates on list of CVVs are used by the national vaccine regulatory agencies and the pharmaceutical companies to develop, produce and license influenza vaccines. Further, approval of the composition and formulation of vaccines that will be used in each country is the responsibility of national or regional regulatory authorities. However, it is the responsibility of the vaccine manufacturer to obtain the appropriate CVVs and to obtain approval from the local regulatory agency.

37 http://www.who.int/influenza/vaccines/virus/recommendations/201802_qanda_recommendation.pdf

38 http://www.who.int/influenza/vaccines/virus/201802_zoonotic_vaccinevirusupdate.pdf

39 http://www.who.int/influenza/vaccines/virus/201802_zoonotic_vaccinevirusupdate.pdf

WHO announces Independent Global High-level Commission to beat Non-Communicable Diseases (NCDs)

On February 16, 2018, World Health Organization (WHO) announced a new **Independent Global High-level Commission** on Non-Communicable Diseases (NCDs), comprising of Heads of states and Ministers, leaders in health and development, and entrepreneurs. The commission's aim is to identify innovative ways to curb the world's biggest causes of death and extend life expectancy for millions of people. The commission will support ongoing political efforts to accelerate action on cardiovascular disease, cancers, diabetes and respiratory diseases, as well as reducing suffering from mental health issues and the impacts of violence and injuries.

NCDs kills 15 million people, between the ages of 30 and 69, each year. Low- and lower-middle income countries are particularly affected by NCDs, with almost 50% of such premature deaths occurring in these countries. WHO's **Non-Communicable Diseases (NCDs) Progress Monitor 2017,** which was published last year, has listed countries' plan of actions - to set targets, implement policies, to address four main, shared and modifiable, NCDs risk factors (tobacco, unhealthy diet, physical inactivity and harmful use of alcohol) and build capacities to reduce and treat NCDs. It also shows that progress around the world has been uneven and insufficient to control NCDs[40].

The need to accelerate action to beat NCDs is high on the global political agenda in 2018, with world leaders expected to participate in the third United Nations General Assembly High-level Meeting on NCDs.

The WHO Independent Global High-level Commission is co-chaired by:

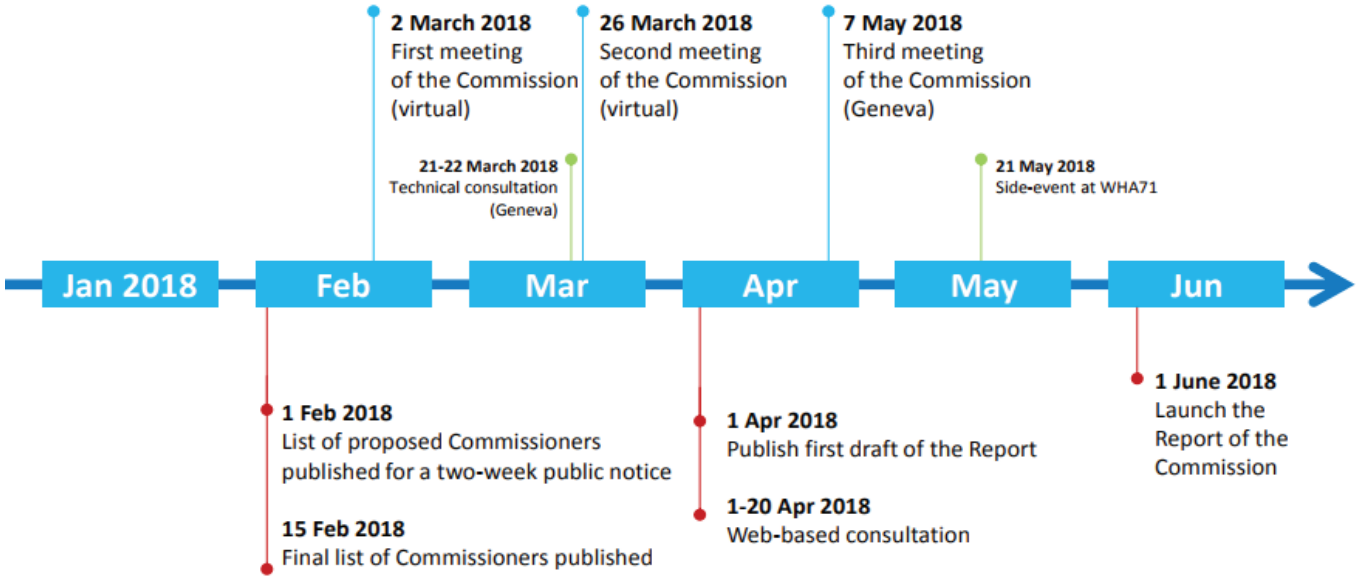
- Sauli Niinistö, President of Finland
- Maithripala Sirisena, President of Sri Lanka
- Tabaré Vázquez, President of Uruguay
- Veronika Skvortsova, Minister of Healthcare, Russian Federation
- Sania Nishtar, former Federal Minister of Pakistan and Civil Society leader.

Initial outputs (Phase I) of the Commission will include:

- Establishing an independent platform to mobilize stakeholders to identify innovative recommendations for accelerating the response on NCDs.
- Providing actionable recommendations that will contribute to preparations for the Third United Nations General Assembly High-level Meeting on NCDs in 2018. This will include the submission of its first report to the WHO Director-General in May 2018.

40 http://www.who.int/nmh/publications/ncd-progress-monitor-2017/en/

WHO Independent High-level Commission on NCDs
Tentative timeline for the first phase
(Version dated 30 January 2018)



The Commission will define its additional outputs (phase II) after the submission of the first report to the Director-General in May 2018 (end of phase I).

The Commission will convene periodically and will be supported by working groups, knowledge networks, and invited experts. It will hold public hearings and calls for open submissions. The Commission will be supported by a dedicated secretariat at WHO, which will be responsible for the day-to-day work, including the preparation of background materials, organization of consultations and meetings, translation, organizational arrangements, logistics, and communications associated with the work of the Commission[41].

Conclusion:

Globally, every 7 out of 10 deaths, are due to NCDs such as diabetes, heart diseases, cancers, arthritis, lung disease etc., the highest contributors to which are tobacco use, harmful use of alcohol, unhealthy diets, and physical inactivity. A commission comprising world leaders is a way to support bold and innovative solutions/ideas to help accelerate prevention and control measures of such leading killers worldwide.

World Health Organization (WHO) recommendations: Intrapartum care for a positive childbirth experience

On February 15, 2018, the WHO issued new recommendations to establish global care standards for healthy pregnant women and reduce unnecessary medical interventions. The agency said that worldwide, an estimated 140 million births take place every year. Most of these occur without complications for women and their babies. Yet, over the past 20 years, practitioners have increased the use of interventions that were previously used only to avoid risks or treat complications, such as oxytocin infusion to speed up labour or caesarean sections[42].

The agency further said that childbirth is a normal physiological process that can be accomplished without complications for the majority of women and babies. However, studies show a substantial proportion of healthy pregnant women undergo at least one clinical intervention during labour and birth. They are also often subjected to needless and potentially harmful routine interventions. The new WHO guideline includes 56 evidence-based recommendations where care is needed throughout labour and immediately after for the woman and her baby. These include having a companion of choice during labour and childbirth, ensuring respectful care and good communication between women and health providers, maintaining privacy and confidentiality, and allowing women to make decisions about their pain management, labour and birth positions and natural urge to push, among others.

Every labour is unique and progresses at a different rate

The new WHO guideline recognizes that every labour and childbirth is unique and that the duration of the active first stage of labour varies from one woman to another. In a first labour, it usually does not extend beyond 12 hours. In subsequent labours, it usually does not extend beyond 10 hours. To reduce unnecessary medical interventions, the WHO guideline states that the previous benchmark for cervical dilation rate at 1 cm/hr during the active first stage of labour (as assessed by a partograph or chart used to document the course of a normal labour) may be unrealistic for some women and is inaccurate in identifying women at risk of adverse birth outcomes. The guideline emphasizes that a slower cervical dilation rate alone should not be a routine indication for intervention to accelerate labour or expedite birth.

Recommendations

The WHO technical consultations have led to 56 recommendations on intrapartum care - 26 of these are newly developed recommendations and 30 are recommendations integrated from existing WHO guidelines. Recommendations are presented according to the intrapartum care context to which they are relevant, namely, care throughout labour and birth, care during the first stage of labour, care during the second stage of labour, care during the third stage of labour, immediate care of the newborn, and immediate care of the woman after birth. Each of these 56 recommendation have also been classified into one of the following categories defined below:

- Recommended: This category indicates that the intervention or option should be implemented.
- Not recommended: This category indicates that the intervention or option should not be implemented.
- Recommended only in specific contexts: This category indicates that the intervention or option is applicable only to the condition, setting or population specified in the recommendation, and should only be implemented in these contexts.
- Recommended only in the context of rigorous research: This category indicates that there are important uncertainties about the intervention or option. In such instances, implementation can still be undertaken

42 http://www.who.int/mediacentre/news/releases/2018/positive-childbirth-experience/en/

on a large scale, provided that it takes the form of research that is able to address unanswered questions and uncertainties related both to effectiveness of the intervention or option, and its acceptability and feasibility.

Summary list of recommendations on intrapartum care for a positive childbirth experience

Care option	Recommendation	Category of recommendation
Care throughout labour and birth		
Respectful maternity care	1. Respectful maternity care – which refers to care organized for and provided to all women in a manner that maintains their dignity, privacy and confidentiality, ensures freedom from harm and mistreatment, and enables informed choice and continuous support during labour and childbirth.	Recommended
Effective communication	2. Effective communication between maternity care providers and women in labour, using simple and culturally acceptable methods.	Recommended
Companionship during labour and childbirth	3. A companion of choice for all women throughout their labour and childbirth.	Recommended
Continuity of care	4. Midwife-led continuity-of-care models, in which a known midwife or small group of known midwives supports a woman throughout the antenatal, intrapartum and postnatal continuum, are recommended for pregnant women in settings with well-functioning midwifery programmes.	Context-specific recommendation
First stage of labour		
Definitions of the latent and active first stages of labour	5. The latent first stage is a period of time characterized by painful uterine contractions and variable changes of the cervix, including some degree of effacement and slower progression of dilatation up to 5 cm for first and subsequent labours. — The active first stage is a period of time characterized by regular painful uterine contractions, a substantial degree of cervical effacement and more rapid cervical dilatation from 5 cm until full dilatation for first and subsequent labours.	Recommended
Duration of the first stage of labour	6. Women should be informed that a standard duration of the latent first stage has not been established and can vary widely from one woman to another. However, the duration of active first stage (from 5 cm until full cervical dilatation) usually does not extend beyond 12 hours in first labours, and usually does not extend beyond 10 hours in subsequent labours.	Recommended

Care option	Recommendation	Category of recommendation
Progress of the first stage of labour	7. For pregnant women with spontaneous labour onset, the cervical dilatation rate threshold of 1 cm/hour during active first stage (as depicted by the partograph alert line) is inaccurate to identify women at risk of adverse birth outcomes and is therefore not recommended for this purpose. 8. A minimum cervical dilatation rate of 1 cm/hour throughout active first stage is unrealistically fast for some women and is therefore not recommended for identification of normal labour progression. A slower than 1-cm/hour cervical dilatation rate alone should not be a routine indication for obstetric intervention. 9. Labour may not naturally accelerate until a cervical dilatation threshold of 5 cm is reached. Therefore, the use of medical interventions to accelerate labour and birth (such as oxytocin augmentation or caesarean section) before this threshold is not recommended, provided fetal and maternal conditions are reassuring.	Not recommended Not recommended Not recommended
Labour ward admission policy	10. For healthy pregnant women presenting spontaneous labour, a policy of delaying labour ward admission until active first stage is recommended only in the context of rigorous research.	Research-context recommendation
Clinical pelvimetry on admission	11. Routine clinical pelvimetry on admission in labour for healthy pregnant women.	Not recommended
Routine assessment of fetal well-being on labour admission	12. Routine cardiotocography is not recommended for the assessment of fetal well-being on labour admission in healthy pregnant women presenting in spontaneous labour. 13. Auscultation using a Doppler ultrasound device or Pinard fetal stethoscope is recommended for the assessment of fetal wellbeing on labour admission.	Not recommended Recommended
Perineal/pubic shaving	14. Routine perineal/pubic shaving prior to giving vaginal birth.	Not recommended
Enema on admission	15. Administration of enema for reducing the use of labour augmentation.	Not recommended
Digital vaginal examination	16. Digital vaginal examination at intervals of four hours is recommended for routine assessment of active first stage of labour in low-risk women.	Recommended
Continuous cardiotocography during labour	17. Continuous cardiotocography is not recommended for assessment of fetal well-being in healthy pregnant women undergoing spontaneous labour.	Not recommended
Intermittent fetal heart rate auscultation during labour	18. Intermittent auscultation of the fetal heart rate with either a Doppler ultrasound device or Pinard fetal stethoscope is recommended for healthy pregnant women in labour.	Recommended
Epidural analgesia for pain relief	19. Epidural analgesia is recommended for healthy pregnant women requesting pain relief during labour, depending on a woman's preferences.	Recommended

Care option	Recommendation	Category of recommendation
Opioid analgesia for pain relief	20. Parenteral opioids, such as fentanyl, diamorphine and pethidine, are recommended options for healthy pregnant women requesting pain relief during labour, depending on a woman's preferences.	Recommended
Relaxation techniques for pain management	21. Relaxation techniques, including progressive muscle relaxation, breathing, music, mindfulness and other techniques, are recommended for healthy pregnant women requesting pain relief during labour, depending on a woman's preferences.	Recommended
Manual techniques for pain management	22. Manual techniques, such as massage or application of warm packs, are recommended for healthy pregnant women requesting pain relief during labour, depending on a woman's preferences.	Recommended
Pain relief for preventing labour delay	23. Pain relief for preventing delay and reducing the use of augmentation in labour is not recommended.	Not recommended
Oral fluid and food	24. For women at low risk, oral fluid and food intake during labour.	Recommended
Maternal mobility and position	25. Encouraging the adoption of mobility and an upright position during labour in women at low risk.	Recommended
Vaginal cleansing	26. Routine vaginal cleansing with chlorhexidine during labour for the purpose of preventing infectious morbidities is not recommended.	Not recommended
Active management of labour	27. A package of care for active management of labour for prevention of delay in labour.	Not recommended
Routine amniotomy	28. The use of amniotomy alone for prevention of delay in labour .	Not recommended
Early amniotomy and oxytocin	29. The use of early amniotomy with early oxytocin augmentation for prevention of delay in labour	Not recommended
Oxytocin for women with epidural analgesia	30. The use of oxytocin for prevention of delay in labour in women receiving epidural analgesia.	Not recommended
Antispasmodic agents	31. The use of antispasmodic agents for prevention of delay in labour is not recommended.	Not recommended
Intravenous fluids for preventing labour delay	32. The use of intravenous fluids with the aim of shortening the duration of labour.	Not recommended
Second stage of labour		
Definition and duration of the second stage of labour	33. — The second stage is the period of time between full cervical dilatation and birth of the baby, during which the woman has an involuntary urge to bear down, as a result of expulsive uterine contractions. — Women should be informed that the duration of the second stage varies from one woman to another. In first labours, birth is usually completed within 3 hours whereas in subsequent labours, birth is usually completed within 2 hours.	Recommended
Birth position (for women without epidural analgesia)	34. For women without epidural analgesia, encouraging the adoption of a birth position of the individual woman's choice, including upright positions, is recommended.	Recommended

Care option	Recommendation	Category of recommendation
Birth position (for women with epidural analgesia)	35. For women with epidural analgesia, encouraging the adoption of a birth position of the individual woman's choice, including upright positions, is recommended.	Recommended
Method of pushing	36. Women in the expulsive phase of the second stage of labour should be encouraged and supported to follow their own urge to push.	Recommended
Method of pushing (for women with epidural analgesia)	37. For women with epidural analgesia in the second stage of labour, delaying pushing for one to two hours after full dilatation or until the woman regains the sensory urge to bear down is recommended in the context where resources are available for longer stay in second stage and perinatal hypoxia can be adequately assessed and managed.	Context-specific recommendation
Techniques for preventing perineal trauma	38. For women in the second stage of labour, techniques to reduce perineal trauma and facilitate spontaneous birth (including perineal massage, warm compresses and a "hands on" guarding of the perineum) are recommended, based on a woman's preferences and available options.	Recommended
Episiotomy policy	39. Routine or liberal use of episiotomy for women undergoing spontaneous vaginal birth.	Not recommended
Fundal pressure	40. Application of manual fundal pressure to facilitate childbirth during the second stage of labour	Not recommended
Third stage of labour		
Prophylactic uterotonics	41. The use of uterotonics for the prevention of postpartum haemorrhage (PPH) during the third stage of labour is recommended for all births. 42. Oxytocin (10 IU, IM/IV) is the recommended uterotonic drug for the prevention of postpartum haemorrhage (PPH). 43. In settings where oxytocin is unavailable, the use of other injectable uterotonics (if appropriate, ergometrine/ methylergometrine, or the fixed drug combination of oxytocin and ergometrine) or oral misoprostol (600 µg)	Recommended Recommended Recommended
Delayed umbilical cord clamping	44. Delayed umbilical cord clamping (not earlier than 1 minute after birth) is recommended for improved maternal and infant health and nutrition outcomes.	Recommended
Controlled cord traction (CCT)	45. In settings where skilled birth attendants are available, controlled cord traction (CCT) is recommended for vaginal births if the care provider and the parturient woman regard a small reduction in blood loss and a small reduction in the duration of the third stage of labour as important.	Recommended
Uterine massage	46. Sustained uterine massage is not recommended as an intervention to prevent postpartum haemorrhage (PPH) in women who have received prophylactic oxytocin.	Not recommended
Care of the newborn		
Routine nasal or oral suction	47. In neonates born through clear amniotic fluid who start breathing on their own after birth, suctioning of the mouth and nose should not be performed.	Not recommended

Care option	Recommendation	Category of recommendation
Skin-to-skin contact	48. Newborns without complications should be kept in skin-to-skin contact (SSC) with their mothers during the first hour after birth to prevent hypothermia and promote breastfeeding.	Recommended
Breastfeeding	49. All newborns, including low-birth-weight (LBW) babies who are able to breastfeed, should be put to the breast as soon as possible after birth when they are clinically stable, and the mother and baby are ready.	Recommended
Haemorrhagic disease prophylaxis using vitamin K	50. All newborns should be given 1 mg of vitamin K intramuscularly after birth (i.e. after the first hour by which the infant should be in skin-to-skin contact with the mother and breastfeeding should be initiated).	Recommended
Bathing and other immediate postnatal care of the newborn	51. Bathing should be delayed until 24 hours after birth. If this is not possible due to cultural reasons, bathing should be delayed for at least six hours. Appropriate clothing of the baby for ambient temperature is recommended. This means one to two layers of clothes more than adults, and use of hats/caps. The mother and baby should not be separated and should stay in the same room 24 hours a day.	Recommended
Care of the woman after birth		
Uterine tonus assessment	52. Postpartum abdominal uterine tonus assessment for early identification of uterine atony is recommended for all women.	Recommended
Antibiotics for uncomplicated vaginal birth	53. Routine antibiotic prophylaxis is not recommended for women with uncomplicated vaginal birth.	Not recommended
Routine antibiotic prophylaxis for episiotomy	54. Routine antibiotic prophylaxis is not recommended for women with episiotomy.	Not recommended
Routine postpartum maternal assessment	55. All postpartum women should have regular assessment of vaginal bleeding, uterine contraction, fundal height, temperature and heart rate (pulse) routinely during the first 24 hours starting from the first hour after birth. Blood pressure should be measured shortly after birth. If normal, the second blood pressure measurement should be taken within six hours. Urine void should be documented within six hours.	Recommended
Postnatal discharge following uncomplicated vaginal birth	56. After an uncomplicated vaginal birth in a health care facility, healthy mothers and newborns should receive care in the facility for at least 24 hours after birth.	Recommended

Conclusion:

These recommendations from the WHO aim to increase the care for women during pregnancy and childbirth; they also aim to reduce the surge in interventions like caesarean sections that the agency considers could be unnecessary in cases where the cervical dilation happens at a slower pace. A slower cervical dilation rate than the benchmark of 1 cm/hr during the active first stage of labour should not be seen as a routine indication for interventions to accelerate labour or expedite birth. These guidelines are a step towards reducing high rates of unnecessary or ineffective medical interventions.

FDA intensifies its warning against Kratom, classifying it as an 'opioid' underscoring potential for abuse

On February 06, 2018, the United States Food and Drug Administration (US-FDA) intensified its warnings about Kratom, stating that new research provides strong evidence that the unregulated botanical substance has 'opioid properties'[43].

A new analysis by scientists at the US -FDA shows that compounds in Kratom act like prescription-strength opioids. The agency also said that Kratom has now been linked to 44 deaths. The agency said that over the past several months, many questions have been raised about the botanical substance known as Kratom. FDA has taken some significant steps to advance the scientific understanding of this product and how it works in the body. The agency provided details of some of the important scientific tools, data and research that have contributed to the FDA's concerns about Kratom's potential for abuse, addiction, and serious health consequences including death.

The agency recently conducted a novel scientific analysis using a computational model developed by agency scientists, which provided even stronger evidence of Kratom compounds' opioid properties. These kinds of models have become an advanced, common and reliable tool for understanding the behavior of drugs in the body. The agency also learnt more about deaths that involved Kratom use and have identified additional adverse events related to this product. This new data adds to the substantial scientific evidence supporting agency's concern about the safety and abuse potential of Kratom.

The agency has been especially concerned about its use to treat opioid withdrawal symptoms, as there is no reliable evidence to support the use of Kratom as a treatment for opioid use disorder and significant safety issues also exist. The agency further said that it recognizes the need and desire for alternative treatments for both the treatment of opioid addiction, as well as the treatment of chronic pain, and stands ready to evaluate evidence that could demonstrate a medicinal purpose for Kratom. However, to date, the agency has not received any such submissions and is not aware of any evidence that would meet the agency's standards for approval.

About Kratom

Mitragyna speciosa (commonly known as Kratom also ketum) is a tropical evergreen tree in the coffee family (Rubiaceae) native to Southeast Asia in the Indochina and Malaysia phytochoria (botanical regions). M. speciosa is indigenous to Thailand, Indonesia, Malaysia, Myanmar, and Papua New Guinea[44].

The FDA's PHASE model used to assess Kratom

The FDA developed the Public Health Assessment via Structural Evaluation (PHASE) methodology – a tool to help simulate, using 3-D computer technology, how the chemical constituents of a substance (such as the compounds/ alkaloids found in Kratom) are structured at a molecular level, how they may behave inside the body, and how they can potentially affect the brain. In effect, PHASE uses the molecular structure of a substance to predict its biological function in the body.

Using this computational model, scientists at the FDA first analyzed the chemical structures of the 25 most prevalent compounds in Kratom. From this analysis, the agency concluded that all compounds share the most structural similarities with controlled opioid analgesics, such as morphine derivatives. Next, the scientists analyzed the chemical structure of these Kratom compounds against the software to determine its likely biologic targets.

43 https://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm595622.htm

44 https://en.wikipedia.org/wiki/Mitragyna_speciosa

The model predicted that 22 (including mitragynine) of the 25 compounds in Kratom bind to mu-opioid receptors. This model, together with previously available experimental data, confirmed that two of the top five most prevalent compounds (including mitragynine) are known to activate opioid receptors ("opioid agonists").

The new data provides even stronger evidence of Kratom compounds' opioid properties.

The computational model also predicted that some of the Kratom compounds may bind to the receptors in the brain that may contribute to stress responses that impact neurologic and cardiovascular function. The agency has previously warned of the serious side effects associated with Kratom including seizures and respiratory depression.

The third aspect of the model is the 3-D image, the agency generated to look at, not just where these compounds bind, but how strongly they bind to their biological targets. The agency found out that Kratom has a strong bind to mu-opioid receptors, comparable to scheduled opioid drugs.

Learnings from reports of death associated with Kratom

US-FDA has been carefully monitoring the use of Kratom for several years and have placed Kratom products on import alert to prevent them from entering the country illegally. The agency has also conducted several product seizures. These actions were based, in part, on a body of academic research, as well as reports the agency has received, suggesting harm associated with its use. Numerous countries, states and cities have banned Kratom from entering their jurisdictions.

The agency also shared more information about the tragic reports it has received of additional deaths involving the use of Kratom. Looking at the information the agency has received from sources like academic research, poison control data, medical examiner reports, social science research and adverse event reports – it is reported that 44 deaths are associated with the use of Kratom.

The agency also released the reports of the 36 deaths it had referenced to in November last year. These reports underscore the serious and sometimes deadly risks of using Kratom and the potential interactions associated with this drug. Overall, many of the cases received could not be fully assessed because of limited information provided; however, one new report of death was of particular concern. This individual had no known historical or toxicologic evidence of opioid use, except for Kratom. The FDA is continuing to investigate this report, but the information it has received so far reinforces its concerns about the use of Kratom. In addition, a few assessable cases with fatal outcomes raise concern that Kratom is being used in combination with other drugs that affect the brain, including illicit drugs, prescription opioids, benzodiazepines and over-the-counter medications, like the anti-diarrheal medicine, loperamide. Cases of mixing Kratom, other opioids, and other types of medication is extremely troubling because the activity of Kratom at opioid receptors indicates there may be similar risks of combining Kratom with certain drugs, just as there are with FDA-approved opioids.

However, unlike Kratom, FDA-approved drugs have undergone extensive review for safety and efficacy, and the agency continuously tracks safety data for emerging safety risks that were previously unknown. So the agency now has better information about the risks associated with these products; and can better inform the public of new safety concerns. For example, in August 2016, the FDA required a class-wide change to drug labeling to help inform health care providers and patients of the serious risks (including respiratory depression, coma and death) associated with the combined use of certain opioid medications and benzodiazepines. In June 2016, the agency also issued a warning that taking significantly high doses of loperamide, including through abuse or misuse of the product to achieve euphoria or self-treat opioid withdrawal, can cause serious heart problems that can lead to death. The FDA also recently took steps to help reduce abuse of loperamide by requesting packaging restrictions for these products sold "over-the-counter[45]."

45 https://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm594443.htm

Overall, the scientific evidence of the agency provides a clear picture of the biological effect of this substance. Kratom should not be used to treat medical conditions, nor should it be used as an alternative to prescription opioids. There is no evidence to indicate that Kratom is safe or effective for any medical use. The agency further said that claiming that Kratom is benign because its "just a plant" is shortsighted and dangerous. After all, even heroin, which is derived from the seed pod of various opium poppy plants, is an illegal, dangerous, and highly-addictive substance containing the opioid morphine. Further, as the scientific data and adverse event reports have clearly revealed, compounds in Kratom make it, even though a plant, an opioid. And this opioid is associated with novel risks because of the variability in how it is being formulated, sold and used recreationally and by those who are seeking to self-medicate for pain or who use Kratom to treat opioid withdrawal symptoms.

USFDA added that individuals seeking treatment for opioid addiction, who are being advised that Kratom can be an effective treatment, should seek help from a health care provider. There are safe and effective, FDA-approved medical therapies available for the treatment of opioid addiction. Combined with psychosocial support, these treatments are effective. Importantly, there are three drugs (buprenorphine, methadone, and naltrexone) approved by the FDA for the treatment of opioid addiction. Also, there are safer, non-opioid options to treat pain.

FDA to oversee destruction and recall of Kratom products

Further, the agency on February 21, 2018, announced the voluntary destruction and recall of a large volume of Kratom-containing dietary supplements manufactured and distributed nationwide under various brand names. The FDA said all companies currently involved in the sale of products containing Kratom intended for human consumption should take similar steps to take their products off the market and submit any necessary evidence, as appropriate, to the FDA to evaluate them based on the applicable regulatory pathway. Additionally, the FDA and the U.S. Centers for Disease Control and Prevention were also monitoring an active nationwide outbreak across 20 states of a rare type of salmonella associated with Kratom products[46]. This outbreak associated with Kratom-containing capsules, teas and powders, underscores the risk that harmful bacteria may contaminate these products when not subjected to manufacturing controls to eliminate that risk, in addition to the overall safety concerns regarding Kratom itself.

Conclusion:

The U.S. Food and Drug Administration is warning consumers not to use *Mitragyna speciosa*, commonly known as Kratom. FDA is concerned that Kratom, which affects the same opioid brain receptors as morphine, appears to have properties that expose users to the risks of addiction, abuse, and dependency. Further, the agency has reiterated that currently there are no FDA-approved uses for Kratom.

46 https://www.fda.gov/Food/RecallsOutbreaksEmergencies/Outbreaks/ucm597265.htm

United States FDA Issues Final Rule that Requires Medical Device Trials Outside US to Conform to Good Clinical Practices (GCP)

On February 20, 2018, the United States Food and Drug Administration (US FDA) finalized a rule that requires medical device clinical investigations conducted outside the US to flexibly conform with good clinical practice (GCP) standards[47].

Good clinical practice (GCP) is an international ethical and scientific quality standard for designing, conducting, recording, and reporting trials that involve the participation of human subjects. Compliance with this standard provides public assurance that the rights, safety, and wellbeing of trial subjects are protected, consistent with the principles that have their origin in the Declaration of Helsinki, and that the clinical trial data are credible[48].
The new rule requires that sponsors and applicants provide statements and information about how their clinical investigations conform with GCP.

The new rules apply to clinical data submitted to support investigational device exemptions (IDE), premarket notifications (510(k)), requests for De Novo classification, premarket approvals (PMA), product development protocols (PDP), and humanitarian device exemptions (HDE). The final rule also amends the IDE, 510(k) and HDE regulations for FDA acceptance of data from clinical investigations conducted within the US to require a statement regarding compliance with FDA regulations for human subject protection, institutional review boards, and IDEs.

In addition to the rule, FDA has also published a guidance on "Acceptance of Clinical Data to Support Medical Device Applications and Submissions Frequently Asked Questions[49]."The question and answer guidance provides clarifications and recommendations to help ensure that studies conducted in the US or foreign countries comply with the new rule and revised regulations.

Summary of the Major Provisions of the Final Rule

This rule requires that sponsors and applicants of submissions and applications, that include clinical investigations conducted outside the United States and submitted to support an IDE or device marketing application or submission, provide statements and information regarding how the investigations conform with GCP. FDA defines GCP as a standard for the design, conduct, performance, monitoring, auditing, recording, analysis, and reporting of clinical investigations in a way that provides assurance that the data and results are credible and accurate and that the rights, safety, and well-being of subjects are protected. GCP includes review and approval by an IEC (Independent Ethics Committee) before initiating an investigation, continuing IEC review of ongoing investigations and obtaining and documenting the freely given informed consent of subjects.

FDA is also including requirements for the acceptance of data from clinical investigations conducted in the United States submitted to support an IDE application, an HDE application, or a premarket notification submission. The changes require a statement regarding compliance with FDA regulations for human subject protection, institutional review boards, and IDEs when the investigations are conducted in the United States. With the above described changes, the rule is intended to update the standards for FDA acceptance of data from clinical

47 https://s3.amazonaws.com/public-inspection.federalregister.gov/2018-03244.pdf

48 https://www.fda.gov/downloads/drugs/guidances/ucm073122.pdf

49 https://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/UCM597273.pdf?utm_campaign=FDA%20 releases%20final%20rule%20on%20Acceptance%20of%20Data%20from%20Clinical%20Investigations%20for%20Medical%20Devices&utm_medium=email&utm_source=Eloqua&elqTrackId=F4F5E63809CD6EC32B7CD25DAE698BDF&elq=6ea7d47ac83346968d955da3404e3a6c&elqaid=2484&elqat=1&elqCampaignId=1788

investigations and to help ensure the quality and integrity of data obtained from these investigations and the protection of human subjects.

Effective Date

The effective date will be 1 year after the publication of this final rule in the Federal Register. This final rule will apply to all clinical investigations that enroll the first subject on or after the effective date of this rule.

Conclusion:

Conformance of investigations with GCP in support of device applications and submissions ensures that the FDA's decisions are based on scientifically valid and ethically derived data. Conformance with GCP is one way to help ensure credible, accurate, and ethically procured clinical data.

US FDA expands approval of Imfinzi to reduce the risk of non-small cell lung cancer progression

On February 16, 2018, the United States Food and Drug Administration (US-FDA) approved Imfinzi (Durvalumab) for the treatment of patients with stage III non-small cell lung cancer (NSCLC) whose tumors cannot be surgically removed (unresectable) and whose cancer has not progressed after treatment with chemotherapy and radiation (chemoradiation)[50]. The FDA granted the approval of Imfinzi to AstraZeneca. The FDA has granted this application with Priority Review and Breakthrough Therapy designations.

This is the first treatment approved for stage III unresectable non-small cell lung cancer to reduce the risk of the cancer progression, when the cancer has not worsened after chemoradiation. For patients with stage III lung cancer that cannot be removed surgically, the current approach to prevent progression is chemoradiation. Although a small number of patients may be cured with the chemoradiation, the cancer may eventually progress. Patients now have an approved therapy that has been shown to keep the cancer from progressing for a longer time after chemoradiation.

Lung cancer is the leading cause of cancer deaths in the United States, with an estimated 222,500 new diagnoses and 155,870 deaths in 2017, according to the National Cancer Institute at the National Institutes of Health. The most common type of lung cancer, NSCLC occurs when cancer cells form in the tissues of the lung. Stage III NSCLC means tumors have spread to nearby lymph nodes or into other parts of the body near the lungs.

Imfinzi targets the PD-1/PD-L1 pathway (proteins found on the body's immune cells and some cancer cells). By blocking these interactions, Imfinzi may help the body's immune system attack cancer cells. Imfinzi was previously granted accelerated approval in 2017 for the treatment of certain patients with locally advanced or metastatic bladder cancer.

Imfinzi's current approval

The approval of Imfinzi for the treatment of stage III, unresectable NSCLC was based on a Phase III randomized trial (PACIFIC Trial) of 713 patients whose cancer had not progressed after completing chemotherapy and radiation[51].713 patients were randomized in a 2:1 ratio, to receive durvalumab (at a dose of 10 mg per kilogram of body weight intravenously) or placebo every 2 weeks for up to 12 months. The study drug was administered 1 to 42 days after the patients had received chemoradiotherapy.

The trial measured the length of time the tumors did not have significant growth after starting treatment with Imfinzi or a placebo (progression-free survival). The median progression-free survival (PFS) for patients taking Imfinzi was 16.8 months compared to 5.6 months for patients receiving a placebo. Therefore, Imfinzi demonstrated an improvement in median PFS of 11.2 months compared to placebo, representing a 48% reduction in relative risk of progression or death vs. placebo in all patients, regardless of PD-L1 status.

Overall, the incidence and severity of adverse events were comparable for patients receiving Imfinzi and the patients receiving placebo. In patients receiving Imfinzi, the most common adverse reactions (greater than or equal to 20% of patients) were cough (40%), fatigue (34%), pneumonitis or radiation pneumonitis (34%), upper respiratory tract infections (26%), dyspnoea (25%), and rash (23%). Discontinuation after concurrent CRT due to adverse reactions, regardless of causality, occurred in 15% of patients receiving Imfinzi vs. 10% of patients receiving placebo.

50 https://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm597217.htm

51 http://www.nejm.org/doi/full/10.1056/NEJMoa1709937

About Stage III Non-Small Cell Lung Cancer

In this stage, tumors are more than 3 cm wide and are already spread to the lymph nodes in the center of the chest or other structures outside the lung. In stage III lung cancer, the affected lymph nodes are restricted to the same side of the body as the tumor. Stage III lung cancers are classified as either stage IIIA or IIIB, depending on the size and location of the tumor or how far it has spread. This differentiates it from Stage IV disease, when the cancer has spread (metastasised) to distant organs[52].

About 30 percent of patients diagnosed with lung cancer are at stage III at the time of diagnosis. The five-year survival rate for stage IIIA lung cancer varies widely, and is about 23 percent on average. For stage IIIB lung cancer, the survival rate is about 10 percent.

For many stage IIIA cancers and nearly all stage IIIB cancers, the tumor may be difficult and sometimes impossible to remove as most likely the the tumor may have spread outside the lung to lymph nodes located in the center of the chest. Or the cancer may have spread into structures near the lung. In either case, the thoracic surgeon may not able to remove all the cancerous cells and may recommend chemotherapy combined with radiation treatments prior to considering surgery.

About Imfinzi

Imfinzi (durvalumab), is a human monoclonal antibody that binds to PD-L1 and blocks the interaction of PD-L1 with PD-1 and CD80, countering the tumour's immune-evading tactics and releasing the inhibition of immune responses. Durvalumab is a selective, high-affinity, human IgG1 monoclonal antibody that blocks programmed death ligand 1 (PD-L1) binding to programmed death 1 (PD-1) and CD80, allowing T cells to recognize and kill tumor cells[53]. Imfinzi has already received accelerated approval in the US for the treatment of patients with locally-advanced or metastatic urothelial carcinoma, who have disease progression during or following platinum-containing chemotherapy, or whose disease has progressed within 12 months of receiving platinum-containing chemotherapy before (neoadjuvant) or after (adjuvant) surgery.

Conclusion:

Imfinzi (durvalumab) is the first treatment to be approved for stage III unresectable non-small cell lung cancer to reduce the risk of the cancer progressing, when the cancer has not worsened after chemoradiation.

***

52 https://www.cancercenter.com/lung-cancer/stages/tab/non-small-cell-lung-cancer-stage-III/

53 http://www.nejm.org/doi/10.1056/NEJMoa1709937

notes

notes

SINGH & ASSOCIATES

FOUNDER MANOJ K SINGH

ADVOCATES & SOLICITORS

NEW DELHI
E-337, East of Kailash
New Delhi-110065, INDIA

GURUGRAM
7th Floor, ABW Tower, MG Service Road
Sector 25, IFFCO Chowk, Gurugram
Haryana-122001, INDIA

MUMBAI
Unit No. 48 & 49, 4th Floor
Bajaj Bhavan, Nariman Point
Mumbai - 400021, INDIA

BENGALURU
N-304, North Block, Manipal Centre
47, Dickenson Road
Bengaluru - 560042, INDIA

india@singhassociates.in
www.singhassociates.in