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05

UNDERSTANDING USFDA GUIDANCE ON DATA INTEGRITY – ALCOA PLUS - AN OVERVIEW

B. S. Rao and B. S. Reddy

Abstract

Data is a collection of numerical or non-numerical information that includes pre-clinical, clinical, raw material, manufacturing, analytical, regulatory, marketing, distribution, sale, environmental activities etc. Data is either static or dynamic in nature. Every drug regulatory authority ensures quality, safety, efficacy and reliability of a drug product and approves it's release into the market. The most authentic way of ensuring this is by documentation because it includes logical link documentation that ensures an activity has been done. 21 CFR parts 211, 212 speaks about documentation, it's controls, providing complete information, retaining, storing, saving as backup and retrieving. The current review article is to enlighten the integrity of data collected and documentation.

Keywords: Data, integrity, ALCOA, ALCOA plus, USFDA, guidance

Introduction

As per the Drugs and Cosmetics Act, 1940 one comes across the definitions- drug, manufacture, cosmetic, quality, misbranded drug, adulterated drug and spurious drug. The latter three definitions clearly indicate Good Manufacturing Practices (Schedule M) violations and their consequences illustrating how the unintentional becomes intentional errors and vice versa. Similarly, other countries have their terminology accordingly. The new generation terminology are the counterfeits, falsified medicines, suspect products, illegitimate product, diverted, stolen, fraudulent transactions, unfit for distribution at the Indian, United States and international perspectives. The guidance is as per 21 CFR part 210, 211, 212 for current Good Manufacturing Practices (cGMP) with respect to manufacturing, processing, packing or holding; finished; positron emission tomography drugs respectively. As per the United States FD & C Act, current Good Manufacturing Practices (cGMP) are the minimum guidelines of drug standard with respect to safety, identity, strength, quality and purity. Industry's responsibility is to ensure safety, efficacy and quality through data integrity. The present review is at the educational, academic and industrial levels.

Understanding Data Integrity-ALCOA Plus

As per USFDA, data integrity refers to completeness, consistency and accuracy. In order to achieve these, it is necessary to follow ALCOA, which means Attributable, Legible, Contemporaneous, Original and Accurate.

Attributable indicates who has, when was, where was data generated or collected and whether the person clearly indicated his/her signature, date and time with countersign by the higher authority.

Legible indicates that any written and computer generated data should be easily read. Several times, errors occur and especially human hand written should be single line stricken off so that any person understands what the error was. The person who made the error has to have an asterisk at the error place and as noted with the same asterisk at free space in the page has to indicate the reason for striking, for which an error is made. Where free space in the table where no information is written has to be stricken with 'NA-Not Applicable' and to be signed by the person who has collected or generated data. Printed documents that are not legible or not properly printed have to be carefully monitored and if necessary documented after having proper print documents.

Contemporaneous indicates that a person has to immediately document the conducted event after completion and not the vice versa. This means the individual must complete the activity and immediately document it and definitely not document and later conduct the activity.

Original indicates that the data is true information that has been collected or generated through experimentation or during an activity.

Accurate indicates that correct and exact information that was collected or generated.

The appended version of ALCOA is called the ALCOA plus, which additionally includes Complete, Consistent, Enduring and Available.

Complete indicates the whole information that also includes the metadata from which presentable data has been made. **Consistency** indicates that data generated by several researchers/individuals should be uniform in presentation. This means that if the organization has decided, for instance, a 'dd-mm-yyyy' format of date, every researcher/individual has to follow the same. **Enduring** indicates that the data collected or generated has to be maintained for the stipulated period of time decided i.e., the life cycle. If an authority asks for the data, entire metadata has to be produced as well to the authority, if asked. **Available** indicates that at any point of time the data and the metadata should be available and easily accessible.

Other Aspects

In a pharmaceutical company, an audit indicates who, when, what and why a data is generated, modified, deleted with the exact time when the data is accessed either it is manual or computer generated. When a chromatogram is generated, the original dynamic data has to be modified to static to the required presentable form. In either case, proper procedures are established in generating, converting and saving as both dynamic and static forms. It is necessary that every data generated has to be saved as backup immediately directly in the main server and not in any temporary computer drives and later transferred into the server. The data should be saved carefully indicating backup in original format and not the regular saving done by an individual saving in temporary saving folders and retrieving when data is lost. USFDA suggests planned audit trails to be conducted so that systems are well set so as to overcome cGMP violations.

As part of cGMP, every data generated and computer saved should be saved by the person generated and counter scrutinized, protected by the immediate higher authority so that the data is restricted for access through appropriate logins thus minimizing shared logins. At the manufacturing level, machinery with common logins and separate logins for machine recipe and operations are usually maintained. Where two persons are not available, the same person has to double check and make the signatures where necessary. Digital signatures are the unique sequence of numbering allotted for an individual. List of authorized personnel having access has to be established and maintained. Documentation, traceability and appropriate electronic signature linking has to be established.

Blank documents may be issued in a controlled manner with appropriate numbering system and an authority has to ensure all the pages issued whether received back. The blank leftover should be stricken off with appropriate person's signature, time, date as 'Not Applicable' and should be placed with the original document in complete format.

USFDA indicates, usage of notebooks with page numbers officially leads to a scrutiny of unofficial, blank space left notebooks. Hence, it is a best practice not to use any notepads, rough notes or loose papers for temporary storage and retrieval of information.

For regular day to day administration, execution of activities, education and training, USFDA permits physical, electronic copies of original physical or electronic documents provided the intended use, content and meaning are preserved. Proper controls have to be developed, documented to be executed.

Conclusion

As per American National Standard Institute (ANSI), a system is defined as people, machines and methods organized to accomplish a set of specific functions. In day to day work, several errors are documented as data integrity issues or cGMP issues. Such errors documented within the company can be retrieved from data bases established in the company throughout the company's life span whether the employee exists in the company or not. Such issues impact delays in the approvals of new products. To avoid these, USFDA suggests appropriate systems, scrutiny procedures to be established, documented and executed. Quality personnel, experienced personnel have to ensure that the activities are as per established documentation and, scrutiny and rectifying errors as per established and validated procedures. In analytical perspective, USFDA indicates violations to cGMP for disguising tests for achieving compliance, sampling and testing to overcome unacceptable results. Proper education, training and experience is expected for effective implementation of cGMP. Suspected, falsified, altered records should be investigated with the problem's scope, root cause, risk assessment and necessary corrective actions should be initiated and documented. FDA authority has all the rights to scrutinize any document in the industry since the industry plans drug products approved to be released in the US market. Pharmaceutical industries establish pre-planned schedules of internal (inter/intra departmental), external (third party) audits so as to fulfill customer and regulatory authority audits.

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Conflict of Interest

The author/s declare that there is no conflict of interest regarding the publication of this review article. The legal status of the document has to be ensured with the corresponding drug regulatory authority.

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CLINICAL TRIALS STATUS AND APPROACHES OF COVID-19 VACCINES DEVELOPED GLOBALLY: THE RECENT UPDATES

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Abstract

All around the world COVID-19 pandemic has influenced human life massively since 2019. Although many precautionary measures are followed worldwide, it is strongly believed that this vicious pandemic can be controlled only by an effective and safer vaccine. After the outbreak of COVID-19, China first initiated the vaccine development strategies and then it was declared as pandemic by WHO globally. By different technologies like viral vector, DNA, RNA, protein subunit, live attenuated and inactivated and approach efficacious and safe vaccines are designed for development. The researchers around the universe are associating with various medical agencies, pharmaceutical companies and educational institutions for designing and developing SARS-CoV2 advanced vaccines. This review illustrates details on vaccine development technologies for COVID-19, protocols, clinical Phase status and vaccines that failed to progress further.

Keywords: COVID-19, viral vector, DNA, RNA, protein subunit, live attenuated.

Vaccine Strategies

Around the globe many researchers and scientists had made greater efforts towards the evolution of vaccines against COVID-19. Currently, until 2nd week of May 2021, 25 vaccines are in Phase III, 35 vaccines in Phase II, 32 vaccines in Phase I and 184 vaccines are in pre-clinical Phase globally[1]. Regulatory authorities approved 14 vaccines and 4 vaccines are in Phase IV clinical trials in different countries. The enormous vaccine development approaches like protein subunit, viral vector, RNA, DNA, inactivated, live attenuated have been prospected. However, prior to comprehensive evolution of a vaccine with safety, efficacy and no side effects, considerable facts have to be taken into account[2].

Vaccine Development Approach

Protein Subunit Vaccine:

As protein subunit has less immunogenicity to potentiate immune responses that are induced by vaccine; it requires support of adjuvant[3]. It is of different types such as bacterial or viral pathogen, chains of sugar moieties are there in polysaccharide vaccines as found in the cell wall of many strains of bacteria (Figure 1). By using recombinant DNA technology, there is development of viral surface protein and by whole pathogen preparation purification there is development of bacterial protein vaccine[4]. Polysaccharide vaccine is prepared by bacteria grown in industrial bioreactors; they are opened and harvested for polysaccharides from cell walls before splitting them (Table 1).

Novax-CoV2373

Novavax in the United States of America developed this vaccine. By implanting nanoparticle technology this vaccine was designed for the spike protein of SARS-CoV-2 to develop antigen[5]. In August, 2020 Phase III clinical trials were started in South Africa and in September, 2020 Phase III clinical trials were initiated in the United Kingdom and in December, 2020 in the United States of America. Phase III trials demonstrated an 89.3% efficacy rate in the United Kingdom.

ZF2001

The Chinese Academy of Sciences and Anhui Zhifei Longcom Biopharmaceutical Company in China jointly developed the ZF2001 vaccine. In October, 2020 Phase I/II clinical trials were completed and now it is in the final Phase of clinical trials in Indonesia, Pakistan and Uzbekistan[6]. This vaccine was permitted for emergency use from 01st March, 2021 in Uzbekistan.

VAT00002

Sanofi Pasteur in France followed the same principle used in Flublok (vaccine for influenza virus) and developed the VAT00002 vaccine. In December 2020, Phase I/II clinical trials demonstrated that the old population were not responding firmly to VAT00002[7]. In February 2021 Phase II clinical trials are initiated with different formulations of VAT00002 and if there are promising results Phase IV trials will be initiated in 2021.

Finlay-FR-1

It is a protein subunit vaccine popularly known as Soberaba 01. In January 2021, Instituto Finlay De Vacunas in Cuba made an agreement with Pasteur Institute of Iran to initiate Phase III clinical trials for this vaccine[8].

EpiVacCorona

It is designed in Russia by the Russian Biological Research Center. Currently this vaccine is in Phase III trials but in October 2020, regulatory approval was given by the president of Russia. This is the 2nd vaccine for SARS-CoV-2 that got approval from the Russian government[9].

Abdala

Abdala was designed in Cuba by the Center for Genetic Engineering and Biotechnology of Cuba. In February 2021, Phase II clinical trials were initiated and expected that Phase III clinical studies will be done on 40,000 volunteers this year[10].

SCB- 2019

It is an s-trimer vaccine designed by Clover Biopharmaceuticals in Australia. In December 2020, Phase II/III clinical studies will be initiated.

UB-612

UB-612 (United Biomedical-612), Vaxxinity (also known as COVAXX) is a protein subunit vaccine. In February 2021, they started Phase II/III clinical trials in Brazil[11].

Plant based VLP

It is a unique plant based VLP (virus like particle). This vaccine was funded by Philip Morris. Tobacco plant species are used to design this vaccine. By transporting viral genome into the tobacco leaves, plant cells design proteins that imitate exactly those found on COVID-19 virus. Phase II/III trials are started by Medicago in Canada[12].

RBDBV

In China, West China Hospital of Sichuan University designed this protein subunit vaccine. It encodes receptor binding domain in a gene[13].

MCV-CoV1901

It is a protein subunit vaccine. The company Medigen in Taiwan in January 2021 started Phase II clinical trials and are expected to involve 3700 volunteers of age between 20 years and older.

KBP-201

KBP-201 (Kentucky Bioprocessing) in the United States of America designed this vaccine which is similar to plant based vaccine (Medicago). For designing ZMapp drug for Ebola virus this company has utilized a similar process earlier. In July, 2020 Phase I/II clinical trials are registered for this vaccine[14].

BECOV2A

It is also a protein subunit vaccine designed by Biological E Limited, India. In India, in November 2020, Phase I/II clinical trials were launched.

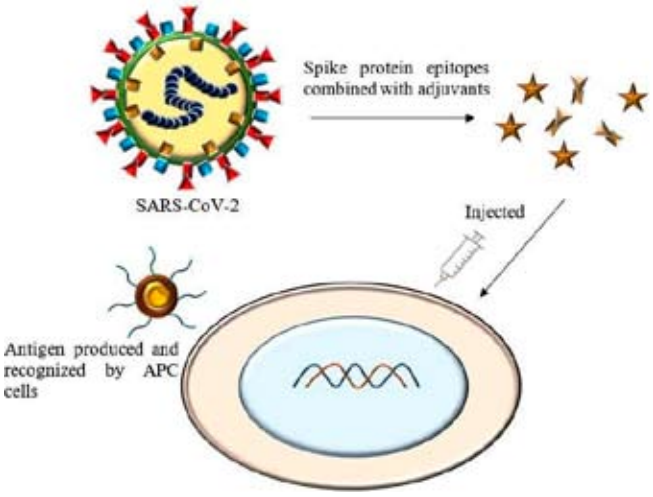

Figure 1. Strategies for protein subunit vaccine

GBP510

The SK Bioscience company in South Korea designed this vaccine[15]. In February 2021 company started Phase I/II the company has started Phase-I/II clinical trials in 200 healthy volunteers.

COVAX-19

Biotechnology based company in South Australia developed COVAX-19 which contains SARS-Cov-2 proteins with adjuvants that cause stimulation of immunogenic response in the human body. In 2021, Phase II clinical trials are expected[16].

Razi Cov-Pars

It is also a protein subunit vaccine designed by Razi Vaccine and Serum Research Institute, Iran which contains spike proteins similar to corona virus. It is administered in 3 doses: 2 injections and 1 nasal spray. This is the 1st injectable inhaled SARS-Cov-2 vaccine.

SpFN

It is also a protein subunit vaccine designed by Walter Reed Army Institute of Research, United States of America[17]. Phase I clinical trials are started. It is a nanoparticle vaccine that destroys spike proteins with ALFQ (liposomal formulation adjuvant).

Table 1. Details, Merits and Demerits of COVID-19 protein subunit vaccines

S.No.	Vaccine Name	Country	Clinical Phase	Merits	Demerits
1	NVX-CoV2373	USA	III	Safer because viral protein s not able to induce infection	Cellular immunity is adequate. Less immunogenicity. Requires booster dose.
2	ZF2001	China	III		
3	VAT00002	France	III		
4	Finlay-FR-1	Cuba	III		
5	EpiVacCorona	Russia	III		
6	Abdala	Cuba	III		
7	SCB-2019	Australia	II/III		
8	UB-612	USA	II/III		
9	Plant based VLP	Canada	II/III		
10	RBDBV	China	II		
11	MVC-CoV1901	Taiwan	II		
12	KBP-201	USA	I/II		
13	BECOV2A	India	I/II		
14	GBP510	South Korea	I/II		
15	COVAX-19	Australia	I		
16	Razi Cotv-Pars	Iran	I		
17	SpFN	USA	I		

COVID-19 Viral Vector vaccine:

This vaccine is different from conventional vaccines. This viral vector based vaccine do not contain vaccine does not contain antigen, but to produce them it uses its own body cells. In virus vector based vaccine 1 virus genome is utilized to deliver antigen to other viruses, this will infect cells and instruct them to produce antigens which trigger immune response (Figure 2). This approach employs non-replicating or live vectors like measles, adenovirus and many more[18]. The replicating viral vector vaccines are capable of producing new viral particles in the infected cells, later they infect new cells that can produce the vaccine antigen. On the other hand, new viral particles are not produced by non-replicating vectors but can only make vaccine antigen. So currently non-replicating viral vectors are used for the development of COVID-19 viral vector based vaccines (Table 2).

AZD1222

AstraZeneca COVID-19 vaccine (AZD1222) was developed by the University of Oxford, United Kingdom. Efficacy was estimated to be 90%. This vaccine was certified and acknowledged by the governments of India, United Kingdom, Mexico, Brazil, Argentina and European Medicines Agency (EMA). Phase III clinical trials were done on more than 10,000 citizens in the United Kingdom. Phase IV trials were initiated from February 2021 in collaboration with the Ministry of Interior and Health, Denmark[19].

Ad5-nCoV

CanSino Biologics, China in association with Academy of Military Medical Sciences China developed the vaccine Convidecia (Ad5-nCoV). The approach used to design the Ebola virus vaccine was utilized to develop this vaccine. The health ministry of Kingdom of Saudi Arabia (KSA) gave permission on 9th August, 2020 to initiate Phase III clinical trial.

Sputnik

Also known as Gam-Covid-Vac. It is also a viral vector vaccine designed by Gamaleya Research Institute, Russia. In more than 40,000 volunteers Phase III clinical trials were done in Latin America, United Arab Emirates (UAE) and Russia. Efficacy of this vaccine was 91.6%. For emergency use, the government of India has certified this vaccine[20].

Ad26.CoV2.S

Johnson & Johnson Company in the United States of America developed Johnson & Johnson COVID-19 vaccine or Janssen. This company also designed a vaccine for Ebola virus by using recombinant adenovirus serotype 26 (Ad26). Over 60,000 volunteers from Latin America participated in Phase III clinical trials done in September, 2020. Efficacy rate was 66%.

GRAd-CoV2

An Italian company, ReiThera designed a viral vector vaccine GRAd-CoV2. In July 2020, Phase I clinical trials were initiated. Recently Phase II/III clinical studies were launched[21].

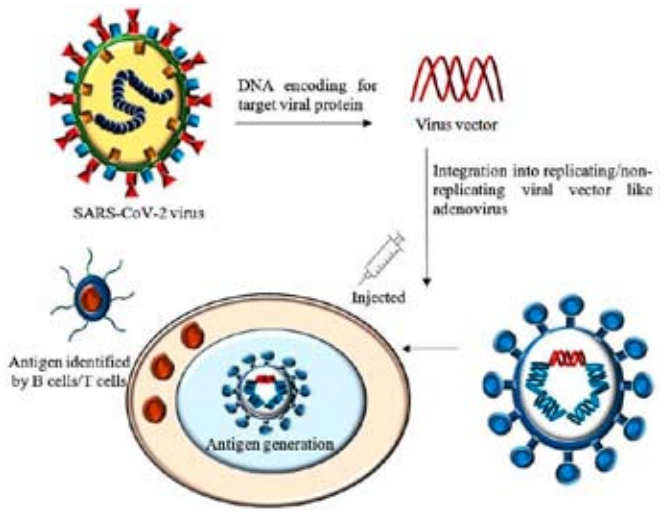

Figure 2. Developmental strategies for viral vector vaccine

Viral vector nasal

It is a nasal spray vaccine designed by Beijing Wantai Biological Pharmacy, China which is effective against SARS-CoV-2 spike proteins. In November 2020 Phase II clinical trials were initiated in 720 volunteers in China[22].

IIBR-100

In Israel, Israel Institute for Biological Research has developed this vaccine. Phase I studies were done on 1000 volunteers and in 2021 they are expected to reach Phase IV trials.

Covishield

Serum Institute of India developed this viral vector vaccine. It is a combination of recombinant technology and replication deficient adenovirus vectors in chimpanzees which encodes SARS- CoV-2 spike proteins[23]. This is produced by human embryonic kidney cells (KEK, 293 cells) which are genetically modified. The government of India has authorized the use of this vaccine in India.

hAd5-COVID-19

ImmunityBio and Nantkwest, United States of America is a company that initiated Phase I trials in population up to the age of 55 years. It is an adenovirus vaccine (Ad5) that triggers immunity (cellular and humoral immunity) by delivering both nucleocapsid DNA and spike proteins[24].

VXA-CoV2-1

Vaxart Company in the United States of America designed this vaccine for oral administration by using adenovirus (Ad5) to deliver SARS-CoV-2 viral contents into the host body to trigger immunity.

Table 2. Details, Merits and Demerits of COVID-19 viral vector vaccines

S. No.	Vaccine name	Country	Clinical Phase	Merits	Demerits
1	AZD1222	UK	IV	Development is fast. Invigorate humoral and cellular immunity.	Manufacturing process Cost is high. Illness may be caused due to recombinant virus in patients with less immunity. Need low temperature storage.
2	Ad5-nCoV	China	IV		
3	Sputnik	Russia	IV		
4	Ad26.CoV2.S	USA	III		
5	GRAd-CoV2	Italy	II/III		
6	Viral vector nasal	China	II		
7	IIBR-100	Israel	II		
8	Covishield	India	II/III		
9	hAD5-COVID-19	USA	I		
10	VXA-CoV2-1	USA	I		

COVID-19 RNA Vaccine:

From the last 20 years, synthesis, alteration and automation delivery techniques of mRNA, inspired the research towards

mRNA. The mRNA is non-contagious, arising and non-integrating scaffold and has low risk of mutagenicity[25]. So to discover and develop mRNA vaccines a great competency has been established globally (Figure 3). In a lipid polysaccharide nano shell of mRNA vaccine, spike proteins of SARS-CoV2 are present. Permitting these nanoparticles of mRNA to enter into the host body is the final target, later cell components of the host body identifies and transfers the mRNA which initiates spike protein generation (Table 3).

mRNA-1273

It is also known as the Moderna vaccine designed by Cambridge, Massachusetts and was financed by NIAID (National Institute of Allergy and Infectious Diseases). It is a mRNA vaccine and has to be preserved in a deep ultra freezer[26]. In about 30,000 healthy volunteers Phase III trials were studied and efficacy was 94%. In February 2021 Phase IV clinical trials were initiated in collaboration with the Ministry of Interior and Heath, Denmark.

BNT162b1

The government of the United Kingdom 1st approved this BNT162b1 which is a RNA based vaccine. In about 30,000 healthy volunteers of Argentina, United States of America, Germany and Brazil, Phase II/III clinical trials were started in July 2020. Additionally Pfizer and BioNTech, Germany in October 2020 initiated Phase III clinical trials in South Africa and revealed that the efficacy was 95%.

CVnCoV

The CureVac Company in Germany in association with Elon Musk (owner of Tesla) is trying to design mRNA factories that can develop and deliver billions of vaccine doses globally. Phase III clinical trials were initiated in December, 2020 by involving 36,500 volunteers[27].

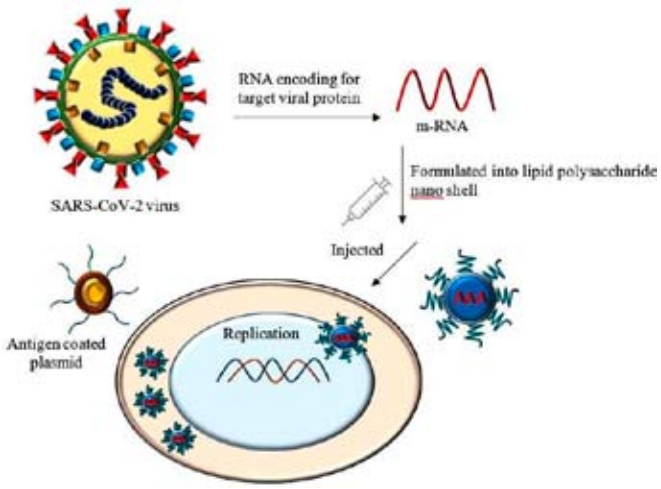

Figure 3. Developmental strategies for RNA vaccine

ARCT-021

Arcturus is designed by the USA and Duke-Nus, Singapore. Phase III clinical trials are initiated in the United States of America and Singapore.

ARCoV

Walvax Biotechnology in China designed this RNA vaccine. Phase I clinical trials are initiated on this vaccine[28].

mRNA-1273.351

This vaccine was designed in the USA by the National Institute of Allergies and Infectious Diseases to target a specific variant (SARS-CoV-2 B.1.351) first identified in South Africa.

Table 3. Details, Merits and Demerits of COVID-19 RNA vaccines

S. No.	Vaccine Name	Country	Clinical Phase	Merits	Demerits
1	mRNA-1273	USA	IV	Both cellular and humoral immunity are triggered. As vaccine delivers into host cell cytosol this prevents the risk of integration. Fast to develop and manufacture.	Limited immune response. Stability issues. Needs advanced formulations. Require cool temperature for storage.
2	BNT162b1	UK	IV		
3	CVnCoV	Germany	III		
4	ARCT-021	USA	II		
5	ARCov	China	II		
6	mRNA-1273.351	USA	I		

COVID-19 DNA Vaccine:

Design and development of DNA vaccine is the subversive execution as this involves adaptive immunity in humans. They are comparatively easy to develop and stable moderately. They contain an antigen encoding gene that inserts into bacterial plasmid (Figure 4). Mammalian expression promoters are present in bacterial plasmid that is expressed in individuals after vaccination. T causes stimulation of both cell mediated and humoral immunity in the individuals. DNA plasmids in DNA vaccine containing antigen is injected into muscle, the challenge here is how the plasmid crosses the plasma membrane and reaches the cell nucleus to get translation into proteins[29] so, bio-injection and electroporation which are considered as sophisticated delivery modules are required for DNA vaccination (Table 4).

ZyKoV-D

It's a DNA vaccine designed by Zydus Cadila Healthcare in India. Phase III clinical trials are initiated which involves 300,000 volunteers.

AG0303-COVID-19

AnGes Company in Japan in association with Takara Bio and Osaka University developed this vaccine. In June 2020 Phase I clinical trials are initiated and in December 2020 Phase II/III clinical trials are started.

INO-4800

Inovio Pharmaceuticals in the United States of America designed this DNA vaccine. Phase II/III clinical trials are initiated in China, United States and South Korea population[30].

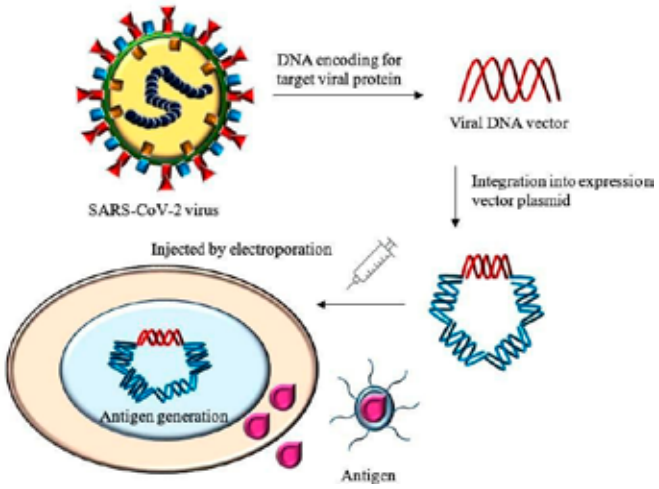

Figure 4. Developmental strategies for DNA vaccine

GX-19

The Genexine Consortium in South Korea in association with Binex, Korea, GenNBio, International Vaccine Institute, Pohang University of Science and Technology and Advanced Institute of Science and Technology developed this GX-19 vaccine. Phase I/II trials are initiated in 190 healthy volunteers of age between 18-50 years[31].

Covid-eVax

Takis and Rottapharm Biotech Italy designed this DNA vaccine. Phase I/II clinical trials are to start in February 2021. The vaccine is administered intramuscularly following EGT (electro-gene-transfer) procedure.

Table 4. Details, Merits and Demerits of COVID-19 DNA vaccines

S.No.	Vaccine Name	Country	Clinical Phase	Merits	Demerits
1	ZyKoV-D	India	III	Triggers T and B cells. Long self-life. No risk of illness. Stable even at high temperature.	Require advanced delivery devices. There may be integration of foreign DNA with recipients DNA causing mutagenesis. Induce poor immune response.
2	AG0303-COVID19	Japan	II/III		
3	INO-4800	USA	II/III		
4	GX-19	South Korea	I/II		
5	Covid-eVax	Italy	I/II		

COVID-19 Inactivated Vaccine:

Vaccines prepared from killed microorganisms are called inactivated vaccines. This is a very traditional technology from which numerous vaccines are led[32]. Virus or a part of a virus is present in an inactivated vaccine but by physical or chemical methods their genetic material is inactivated (Figure 5). As the vaccine developed by this method is having more stability than live attenuated vaccine, this could be used in people with less immune response. Even though there is inactivation of genetic material in the pathogen, many proteins are still present and to this protein immune system responds[33]. They also cause stimulation of antibody mediated response in the host body. So mainly relates to short duration of immune memory that demands inoculation of higher amounts of vaccine or booster dose or association of inactivated microorganisms with an adjuvant to stimulate the immune system (Table 5).

CoronaVac

Sinovac Company in China developed this inactivated vaccine. Phase III clinical trials were done in Turkey, Indonesia and Brazil[34]. Emergency use was limited to this vaccine by the government of China in July 2020. In February 2021, Phase IV trials were initiated.

BBIBP-CorV

Beijing Institute of Biological Products in China in association with the Chinese Centre of Disease Control and Prevention developed a vaccine BBIBP-CorV. Phase IV clinical trials for this vaccine had started recently[35].

Inactivated vero cells

Wuhan Institute of Biological Products in China in association with (China) Sinopharm started Phase III clinical trials in the United Arab Emirates (UAE). UAE is the 1st country which approved this vaccine globally for emergency use in September 2021[36]. The efficacy for this vaccine was 86%.

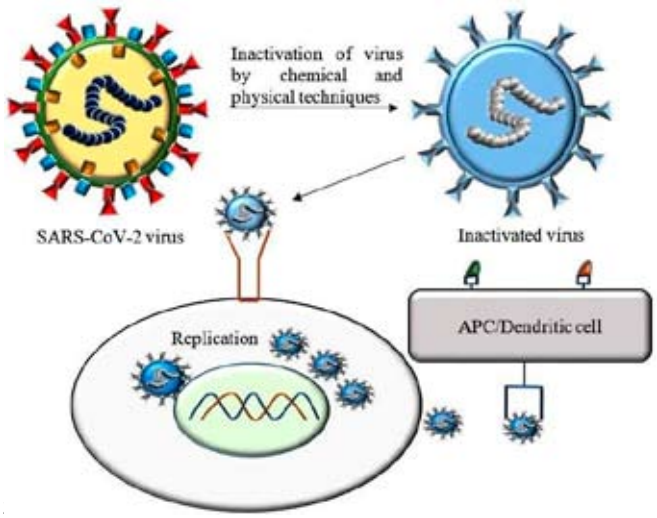

Figure 5. Developmental strategies for inactivated virus vaccine

Covaxin

National Institute of Virology (NIV) in Pune in collaboration with Bharat Biotech International Limited, Hyderabad and Indian Council of Medical Research (ICMR) in New Delhi developed this vaccine[37]. Across 25 centers Phase II clinical trials are started in India. This vaccination program was authorized by the Indian government all over the country.

QazCovid

In Kazakhstan, the Research Institute for Biological Safety Problems developed this vaccine. Phase II trials are initiated in September 2020. Reports indicated maximum immune response in the volunteers[38]. Phase III trials were started and the vaccine was approved in March 2021.

COVIran Barekat

In Iran, Shifa Pharmed Industrial Company developed this vaccine and in Tehran Phase I clinical trials are started in 56 volunteers.

Fakhravac (Mivac)

In Iran, the Organization of Defensive Innovation and Research developed this vaccine. This vaccine was injected at 2 dose schedules in 2 different dose strengths at a difference of 2 or 3 weeks. In March 2021 Phase I clinical trials were started[39].

Table 5. Details, Merits and Demerits of COVID-19 inactivated vaccines

S.No.	Vaccine Name	Country	Clinical Phase	Merits	Demerits
1	Corona-Vac	China	IV	Development is fast. Stable and safe. Pre-existing technology track record.	Booster dose needed. Use of adjuvants may cause inflammatory disorders. For large scale production, plenty of sophisticated proficiency and live virus are required.
2	BBIBP-CorV	China	IV		
3	Inactivated vero cells	China	III		
4	Covaxin	India	III		
5	QazCovid	Kazakhstan	III		
6	COVIran Barekat	Iran	I		
7	Fakhravac (Mivac)	Iran	I		

COVID-19 Live Attenuated vaccine:

It is a traditional technique in which the whole virus is used to trigger immune response in the participants[40]. Here use of exhausted configuration of virus that is able to reduplicate and flourish was used, so sickness is not caused. By rational modifications (like deleting the genes responsible for countering recognition of innate immune response or by codon deoptimization) in the virus or by conforming to unpromising status (like growth in non-human cells, growth in declined temperature) of the virus, t is possible to execute the attenuation (Figure 6).

Codagenix

In India, Serum Institute of India has developed this as the second vaccine for the treatment of SARS-CoV-2 infection[41]. It has started Phase I clinical trials in January 2021.

MV-014-212

In the United States of America, Meissa Vaccine was designed and its route of administration was intranasal. It is a single dose adjuvant free vaccine. In March 2021 Phase I trials were started[42].

Vaccines which FAILED to progress:

V590 and V591

Merck in the United States of America stopped development of replicating viral vector vaccines (V590 & V591) in January 2021. It started developing other two vaccines MK-4482 and Mk-7110. V590 and V591 vaccines were well tolerated in Phase I clinical trials but when compared to other COVID-19 vaccines, immunogenic responses are less. So the progress of this is discontinued[43].

COVAC1 (Imperial College London, United Kingdom)

In the United Kingdom, Imperial College London designed a RNA vaccine by employing synthetic strands of SARS-CoV2 RNA which is a saRNA (self-amplifying ribonucleic acid) vaccine[44]. Its basic background concept was similar to mRNA vaccine. So the development of this vaccine is discontinued. However, saRNA will produce multiple duplications quickly which results in production of more proteins.

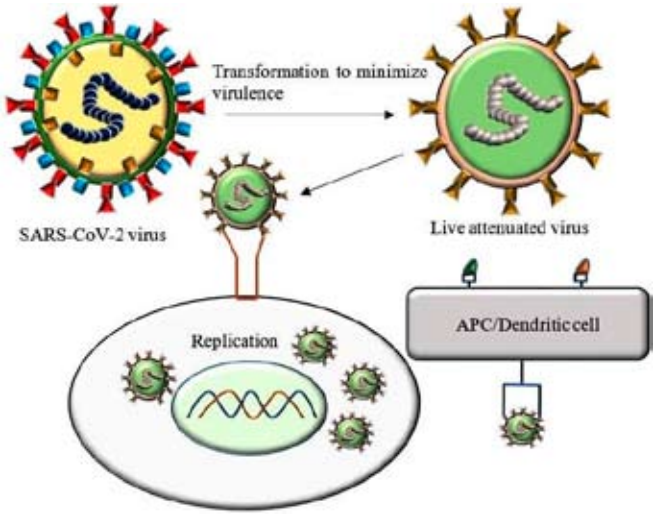

Figure 6. Developmental strategies for live attenuated virus vaccine

COVID-19-101

In France, Institut Pasteur designed a replicating viral vector based vaccine. In August 2020, Phase I clinical trials were obtained[45]. The vaccine was well tolerated but immunogenic response was minor compared to other COVID-19 vaccines in patients recovered from COVID-19 infection.

V451

It is a protein subunit vaccine developed by University of Queensland, Australia. Phase I studies revealed that it is a powerful immunogenic agent which acts by producing antibodies for a protein fragment (gp41) and has a good safety index. The vaccine exhibited HIV positive in candidates who are involved in Phase I clinical trials[46]. So Phase II/III clinical trials are stopped by the Australian government.

Conclusion

Still immense research has to be done and a lot has to be learned at COVID-19 in addition to many vaccines which induce protective immunity. For children, infants, pregnant women, lactating mothers and in particular immune deficient individuals miscellaneous vaccines are required. To induce protection against COVID-19, innate immunity also is required in addition to adaptive immunity which is expressed by some reports. The researchers have to concentrate on mechanisms of genetic changes that induce cellular and humoral immunity towards SARS-CoV2[47]. This can be done by understanding and determining precise targets at epitope level for cellular and humoral immunity, indicating T cell/B cell receptors evoked by SARS-CoV2 infection or by post vaccination for verification of protective immune response for long term in individuals. WHO declared SARS-CoV2 has vz become a blazing research field. The researchers around the universe are associating with various medical agencies, pharmaceutical companies and educational institutions for designing and developing SARS-CoV2 advanced vaccines. For developing a vaccine, the protocol is very tedious which involves pre-clinical and clinical trials. Sufficient data is now available about SARS-CoV2 vaccine so skipping few stages is recommended for designing and developing vaccines with a high speed regulatory review, getting approval, starting manufacturing and quality control. COVID-19 is dangerous to single individuals and every human being[48]. Hence strong understanding, association and partnership between government health regulatory organizations, pharmaceutical industries, national and international institutes has to be made for universal benefits of every individual in this world.

Conflicts of Interest

The authors declare that there are no conflicts of interest.

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FEATURE SCALING ON SVM CLASSIFIER FOR BREAST CANCER DETECTION WITH HIGHER ACCURACY

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Abstract

As a sub-domain of Artificial Intelligence (AI), ML is nothing but a boon for the human race. Machine Learning algorithms and techniques are being used to improve the overall throughput of the various processes and that too by a significant difference. ML algorithms are used in various sectors and find implementation in all walks of life. The field of Medical science is just another domain where ML aims to play a very important role, to be specific, the accurate and timely detection of different diseases. The work presented here is to exemplify the implementation of the Support Vector Machine (SVM) as the ML algorithm for detection of breast cancer in the early stage of the disease to save patients' life. Breast cancer being one of the most fatal diseases amongst the women community is a serious concern across the globe. With old techniques and manual procedures alone, the timely detection of the cases is very difficult and thus a large number of patients do not get the due treatment on time, leading to a very high death rate. As the data show, over 2.3 million women were diagnosed with breast cancer and around 0.7 million lost their lives in 2020. There are various Machine Learning (ML) algorithms used for detection and prediction of different diseases. This paper deals with the experiments on a dataset created from the diagnosis of patients checked up for the possibility of having breast cancer. Dataset used for such experiments needs to be normalized or scaled for a balanced execution. To ascertain higher accuracy, the work demonstrates the improved accuracy of the SVM classifier after scaling the data.

Keywords: Machine Learning; Breast cancer; Supervised learning; Support Vector classifier; Feature Scaling.

Introduction

AI has made us even more able in all walks of life. The medical science too, isn't immaculate of the valuable and significant applications of AI and ML. In this paper, conversation is done around one of the common and serious issues of worry for the women communities worldwide i.e. timely detection of breast cancer in patients. On the off chance that not identified on schedule, the infection results in the demise of the patients. "Fig. 1" Mostly, the disease begins either from the Ductal area (A) or the Lobular area (B) and can be recognized as sporadic protuberances in the breast mass of the patient. The manual diagnosis is not enough at all for detection of cancerous cells in early phases and the overall accuracy is likewise extremely low. Utilizing the SVM classifier to characterize the clinical information and with the assistance of the different traits, it is far more proficient to analyze a plausible or a current malignant growth of cells in the breast mass. The rising number of cases and resulting deaths[1] of the patients in the current situation, is a very serious concern for mankind. The model introduced here is a binary classification model that classifies the cancer analyzed in the patients in the objective classes B (for benign or harmless growths) and M (for malignant or dangerous growths) with a higher precision and in the early phases to change what is happening.

A review, based on similar experiments, research papers and published articles for the suitability of the work, is discussed first, then a suitable dataset is taken for further implementations, trailed by the strategies for execution in addition to the notion of improving the accuracy. In this work, the Wisconsin Diagnostic Breast Cancer (WDBC) dataset[7] is considered. From that point, Python's development environment and a portion of the well-known Python libraries are utilized to deal with the data processing steps and to produce the outcome. The process of classification is done with the Support Vector Machine (SVM) classifier, first with the fetched data (non-scaled set of data) and then with the scaled data (feature scaling). The accuracy attained in both cases is then compared to ascertain the conclusiveness of the model.

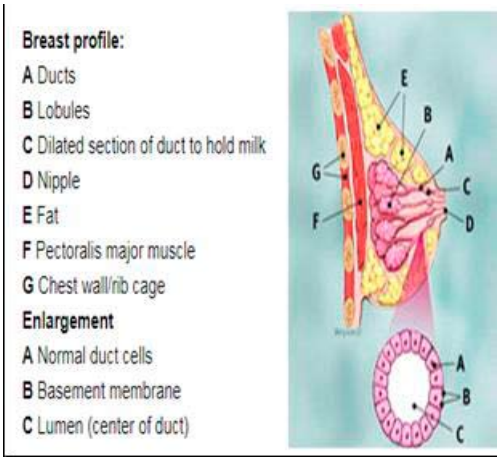

Fig. 1. Human Breast profile

Literature Review

The review is based on the plan to set the idea of utilizing Machine Learning algorithms and procedures to help or supplant the manual execution of critical processes. To be exact, the work is centered around the demonstration of diagnosis of Breast Cancer in very early phases. Breast cancer, to be understood, is a harmful tumor in the breast mass that can influence different cells and can be spread in various body parts[2,12], in the event that not being identified and treated on time could bring about loss of lives[1,6]. This disease often starts in the cells of the lobules (B) or the ductal area (A). Sometimes, it might start in the other tissues (E) as well[12]. Appropriate finding in manual mode is both troublesome and unusual in the event of the initial phases of the disease [4,8]. Therefore, the tumor can't be handily separated whether harmless or threatening. The growth might additionally spread the destructive cells and may harm the other cells in the close by locales of the body, which at last lead to the death of the patient. Utilizing the Machine learning procedure is thoughtful in decreasing the general danger implied with the disease [3, 4, 5] and with similarly much better

exactness it might lessen the figure of deaths at a large scale, in light of the fact that the cancers can be classified at initial phases with an algorithm having higher precision[9, 10].

There are a few factors, for example, hormonal changes, way of life issues and other natural factors that give rise to the possibilities of a person fostering this illness[2]. Over 5%-6% of patients having breast cancer, carry it because of hereditary gene mutations. Different issues that add to the risk of having breast cancer are stoutness, aging, postmenopausal hormonal irregularities and most of these issues can't be handily analyzed[13] on time, as large numbers of them are by all accounts exceptionally normal and regular for a human.

There are several studies done on the diagnosis of breast cancer utilizing AI strategies. Various comparative experiments are likewise done. Some with higher level of precision, while others with somewhat less on numbers. Presented work has drawn nearer to set such endeavors and to devise a model for such experiments with an undeniable degree of precision with the assistance of SVM classifier on non-scaled and scaled data. Various researchers using various methodologies have attempted from integration of data mining with ML based classifiers[13] to experiments on Weighted Naïve Bayes classifier[10], Outlier detection algorithms in combination with decision tree classifiers[11] and Convolutional Neural Networks[3] also. This work shows the implementation of the SVM classifier for discovering the maximum precision with the help of feature scaling for prediction of the disease in the early phase of the cancer.

Dataset

The WDBC dataset used in the presented work has 569 records. Each of these records can be uniquely identified by their unique id attribute, the output class is represented as the diagnosed attribute value (B / M) along with the 30 attributes as features. The data is generated with a digitized image of a Fine Needle Aspirate (FNA) used in diagnosis of the breast mass of various patients as depicted in "Fig. 2".

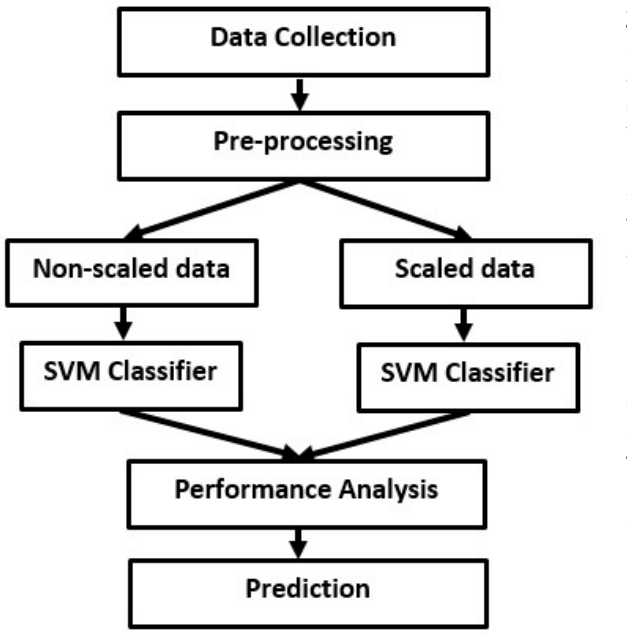

Fig. 3. Proposed Model's Workflow

```
data.info()
```

```
<class 'pandas.core.frame.DataFrame'>
RangeIndex: 569 entries, 0 to 568
Data columns (total 33 columns):
 #   Column                   Non-Null Count  Dtype
---  ------                   --------------  -----
 0   id                       569 non-null    int64
 1   diagnosis                569 non-null    object
 2   radius_mean              569 non-null    float64
 3   texture_mean             569 non-null    float64
 4   perimeter_mean           569 non-null    float64
 5   area_mean                569 non-null    float64
 6   smoothness_mean          569 non-null    float64
 7   compactness_mean         569 non-null    float64
 8   concavity_mean           569 non-null    float64
 9   concave points_mean      569 non-null    float64
 10  symmetry_mean            569 non-null    float64
 11  fractal_dimension_mean   569 non-null    float64
 12  radius_se                569 non-null    float64
 13  texture_se               569 non-null    float64
 14  perimeter_se             569 non-null    float64
 15  area_se                  569 non-null    float64
 16  smoothness_se            569 non-null    float64
 17  compactness_se           569 non-null    float64
 18  concavity_se             569 non-null    float64
 19  concave points_se        569 non-null    float64
 20  symmetry_se              569 non-null    float64
 21  fractal_dimension_se     569 non-null    float64
 22  radius_worst             569 non-null    float64
 23  texture_worst            569 non-null    float64
 24  perimeter_worst          569 non-null    float64
 25  area_worst               569 non-null    float64
 26  smoothness_worst         569 non-null    float64
 27  compactness_worst        569 non-null    float64
 28  concavity_worst          569 non-null    float64
 29  concave points_worst     569 non-null    float64
 30  symmetry_worst           569 non-null    float64
 31  fractal_dimension_worst  569 non-null    float64
 32  Unnamed: 32              0 non-null      float64
dtypes: float64(31), int64(1), object(1)
memory usage: 146.8+ KB
```

Fig. 2. Wisconsin Diagnostic Breast Cancer Dataset

The whole set of the data was further divided into the training data and testing data from the features and the target arrays. However, there was one more twist before the actual classification took place. The training dataset was duplicated, and the features were scaled using the NumPy method and used as a separate training set. Afterwards, the classification algorithm was implemented, once based on the non-scaled dataset for training and again for the feature scaled set of training data.

After that the process of classification was carried out on the test dataset, the two outputs then compared for the higher value of the obtained accuracy. Then after the heatmap and classification reports are generated for the higher value of accuracy, to ascertain the viability of the model.

Methodology

The WDBC dataset was downloaded from Kaggle's repository[7]. For the python environment, Google's Colab platform was used. After importing the required libraries, the dataset was read from the downloaded CSV file. The dataset was then checked for initial pre-processing, such as removal of unnecessary attributes viz. "id" and "unnamed: 32".

Below presented "Fig. 4" represents the Heatmap of the Correlation of the data values in the data-frame so obtained.

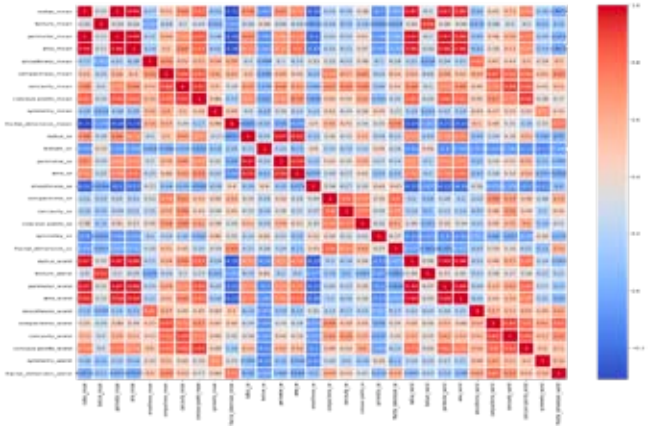

Fig. 4. Heatmap of correlation

For the presented work, the focus was on the significant differences between feature scaled and non-scaled data. Thus, a separate set for the training of the model was created for scaled data. Initially the data-frame was divided into groups of features and target class values. Using the NumPy library the groups are converted into arrays. Using the Seaborn library, visuals are generated for various outputs. Using the skLearn library the training and testing datasets were generated and then after the SVC algorithm was implemented. Afterwards, each of the outputs were compared and analyzed for higher accuracy with the non-scaled and the scaled training dataset respectively.

In both cases, training data was the same except for the feature scaling on the latter one. Each of these are used to predict the type of tumor, based on the features' data fed into. The comparison, of the achieved accuracies, is shown in Table-I below.

TABLE I.

Comparison of accuracy [a] of prediction by SVM Classifier	
with Non-scaled data	**with Scaled data**
0.938596	0.964912

a.(rounded off to 6 decimal places)

Analysis & Discussions

The output obtained in the form of the accuracy values was compared and then analyzed for the feasibility of the one with higher value. The accuracy was found better when the feature scaled dataset was provided for training the model, in this case. Thus, the confusion matrix was generated to confirm the viability of the model and the heatmap for the same is represented in "Fig. 5" .

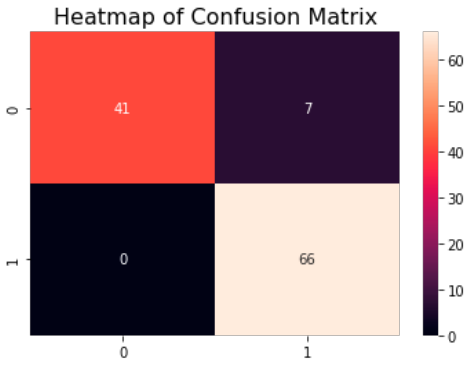

Fig. 5. Heatmap of the confusion matrix

The confusion matrix so obtained clearly depicts that the total count of False-negative cases is "0" i.e. the chances of wrongly identifying a patient as normal in spite of having a malignant tumor, are zero. On the other hand, the model predicts very few, as compared to the overall size of the dataset, patients for having cancer despite they were normal, i.e. False-positive cases. The model thus proves to be a fairly good one and especially in case of malignant tumors, which is a rather more significant case, to be an accurate one as well for detection of breast cancer in patients at early stages with the help of the clinical data of diagnosis. Further, the counts of true-positive and true-negative cases were also found to be quite large, considering the dataset. It shows that the model is able to correctly diagnose the patients whether they need treatment for cancer or not, and thus serves the purpose.

In the end, the classification report was prepared to support the conclusion. Table-II depicts the classification report so obtained. The precision and recall figures were near to the highest possible values i.e. 1 and so as the value for the f1-score.

TABLE II.

	Classification Report			
	precision	**recall**	**f1-score**	**support**
0	0.98	0.94	0.96	48
1	0.96	0.98	0.97	66
accuracy			0.96	114
macro avg	0.97	0.96	0.96	114
weighted avg	0.97	0.96	0.96	114

The classification report thus ascertained that the presented model is good to go for breast cancer detection with higher accuracy using the SVM classifier and feature scaling on the clinical dataset.

Conclusion

Support of AI and ML algorithms and techniques for medical science is no less than a boon. There are so many examples where technology has saved human lives by aiding the medical practitioners and due processes. Moving one step further to take help from advanced algorithms like the SVM classifier in diagnosis of diseases at an early stage, is definitely going to turn the table around. Manual procedures have their own limitations, the technological aid can efficiently fill that gap. To provide early warnings is truly significant in case of many severe diseases viz. cancer or even worse situations like a pandemic. Such implementations are able to save human lives to a great extent. Therefore, Machine Learning algorithms and techniques must see implementations on a wider scale, the human race will move towards a much-sophisticated health ecosystem.

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IPC's 2nd edition of Guidance Manual for Herbs and Herbal Products Monographs released

The Indian Pharmacopoeia Commission's (IPC) new 2nd edition of Guidance Manual for Monographs Development of Herbs and Herbal Products including Phytopharmaceutical Drugs will facilitate the concerned manufacturers and other stakeholders for understanding the process and development of monographs of herbs and herbal products.

The guidance document also aims to encourage and promote research and development in the quality of herbs and herbal products in India and overseas. Further, the manual also gives latest Standard Operating Procedures (SOPs) for the development of monographs as well as Botanical Reference Substances (BRS) and Phytochemical Reference Substances (PRS) and invites suggestions for further updating.

The Commission indicated that it will look forward to consider submission of data and draft monographs adopting this guidance document for inclusion in upcoming IP edition subject to such data meeting the criteria laid down.

According to Dr DBA Narayana, chairman, sub-committee on Herbal and Phytopharmaceutical Drugs, Indian Pharmacopeia Commission, it is important that the processes involved in developing quality monographs for multi component botanicals are documented . This will help botanists and pharmacognists and industrial al R&D personnel and the whole sector to follow common scientific practices.

Noting that it is heartening to see that having led this effort for many years and bringing out an updated edition of the manual is a step in the right direction, Dr Narayana said that the pace at which the monographs are published in IP needs to has to be hastened. Pharmacy college researchers and professors should also contribute to this national effort. Health ministry also needs to enhance the infrastructure within the Indian Pharmacopoeia Commission to achieve it speedily.

Commenting on the release of the Manual for Monographs Development of Herbs and Herbal Products including Phytopharmaceutical Drugs, Rajesh Bhushan, secretary, ministry of health and family welfare said that herbal and plant medicine are playing a pivotal role in the diagnosis, prophylaxis and treatment of diseases in humans and animals. Bringing out the 2nd edition is to ensure seamless compliance of standards related to herbal medicine.

"The manual addresses the emerging areas and advanced tools such as DNA for fingerprinting for identification, phytopharmaceutical ingredient (PPI) category monographs. It will control the limits of herbal contamination. This will also open new frontiers of research and development of these products enabling these drugs to gain international recognition. Since this is a dynami document, there is always scope for further amendment, stated Dr. Mandeep K Bhandari, joint secretary, ministry of health and family welfare.

Pharmacovigilance Programme of India (PvPI) in public health:

Creating a better tomorrow

The medicines play a vital role in the life of an individual. India is among the top ten formulation exporting countries in the world. Every drug formulation meant for human or animal use should be of acceptable quality, safety and efficacy. The safety data of medicines is managed through the Pharmacovigilance Programme of India.

The Pharmacovigilance Programme of India **(PvPI)** was launched in the year 2010 with a broad objective to safeguard the health of Indian population. Pharmacovigilance Programme of India (PvPI) was operationalized in July, 2010 by the Ministry of Health & Family Welfare (MoHFW), Government of India with a mission to reduce the risks associated with the use of medicines in Indian population. The AIIMS, New Delhi was established as National Coordination Centre for PvPI. Later on, MoHFW, Government India vide an Order on 15 April 2011, recasted this programme and shifted the National Coordination Centre from AIIMS, New Delhi to Indian Pharmacopoeia Commission (IPC), Ghaziabad. Since then, the programme has been gaining momentum towards inculcating the culture of ADR reporting and building trust in the safety of medicines among the public. The programme has undergone vast expansion during the last one decade. There are 505 ADR Monitoring Centres under PvPI all over India till date. The programme is fully supported by the Ministry of Health and Family Welfare, Govt. of India. The regulatory recommendations derived from the PvPI data are sent to the Central Drugs Standard Control Organization (CDSCO) on continuous basis.

The Materiovigilance Programme of India (which deals with safety monitoring of medical devices) and Haemovigilance Programme of India (which deals with the safety monitoring of blood transfusion / blood products adverse events) are also under the ambit of PvPI. These programmes are coordinated by National Coordination Centre for MvPI at IPC, Ghaziabad and National Institute of Biologicals, Noida.

India is the 9th largest adverse event reporting country to the WHO Programme for International Drug Monitoring. There are 12 regional training centers across India for providing training and technical support in area of Pharmacovigilance to AMCs under PvPI. PvPI regularly organizes skill development programmes on Pharmacovigilance of medical products on quarterly basis for the benefit of stakeholders.

Modes of reporting adverse events/adverse drug reactions

Today there are various modes of reporting adverse events available - electronic reporting (such as “ADR PvPI” mobile application freely downloadable from Google play store and emails etc), PvPI Toll free number 1800 180 3024 (9 AM - 5:30 PM on all five working days from Monday to Friday), suspected ADR reporting forms for healthcare professionals and consumers. The Medicines side effects reporting form for consumers is available in 10 different regional languages (https://www.ipc.gov.in/mandates/pvpi/pvpi-updates/8-category-en/430-adr-reporting-form-for-consumers-in-hindi-other-vernacular-languages.html). The healthcare professionals, pharmaceutical industry, patients or their caregivers or attendants are requested to report the adverse events of medical products to the nearby ADR monitoring centres under PvPI. The list of ADR Monitoring Centres is displayed on the website https://www.ipc.gov.in/mandates/pvpi/pvpi-updates.html

Role of PvPI during COVID-19 pandemic

The PvPI coordinates with different national health programmes for reporting of adverse events. PvPI also designed a new comprehensive suspected ADR reporting form for drugs being used for prophylaxis and treatment of COVID-19 and rolled it out through ADR monitoring centres in April 2020. The Pharmacovigilance staff was trained for handling the adverse event data from drugs being used in COVID-19 before the launch of the vaccination drive in the country. Since 2021, PvPI has taken an initiative for celebration of National Pharmacovigilance Week (17th September – 23rd September) throughout the country, which will be an annual event in future.

Trainings/Skill development programmes in pharmacovigilance

PvPI organizes the trainings and skill development programmes for the stakeholders on regular basis. The pharmaceutical industry stakeholders are also provided trainings for bringing the improvement in the quality and completeness score of the individual case safety reports (ICSRs).

Resource materials of PvPI

PvPI publishes the resource materials like Guidance document, PvPI Newsletter, Annual Performance Report, Poster for dissemination of information to stakeholders and general public.

PvPI is committed for monitoring the safety of medicines for better tomorrow. For more information, please visit the website on regular basis. https://www.ipc.gov.in/

UNDERSTANDING CLEANING IN THE PHARMACEUTICAL INDUSTRY

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Technical Director, Dober – Pharma Division

VARIABLES IMPACTING CLEANING PROCEDURES (PART 2)

Last month, we discussed about the cleaning variables related to cleaning capabilities. In this article, we would be talking about the variables related to residue and detergents in detail.

2. Residue related

a. Nature of the soil

The ingredients in a formulation that create the residue plays an important role during development of a cleaning procedure at a small scale. The residue tested in the lab must be a representative of the actual residue to be cleaned in the production scale.

It is possible that there is only one hard-to-clean ingredient in the formula and the rest is water or Acid / base soluble. However, in a mixture, the total residue behaves differently. The ratio of the ingredients could also alter the cleaning requirements.

For example, in a mixture of a pH dependent enteric polymer with a pH independent sustained release polymer, it is assumed that the neutral Sustained release polymer should be attacked with a suitable detergent. But after trials, it was understood that the cleaner for the enteric polymer was more efficient in cleaning this mixture as compared to the detergent for the 'tougher' to clean polymer.

The aim must be on cleaning the entire formulation at once rather than individual formulation components. This approach is time consuming in the beginning but guarantees highest cleaning efficiency in the long term. A classic example of this is the cleaning of pigmented formulations. It is seen that the base or polymer itself is not difficult to clean, and water or alkaline detergents strip off the base/polymer, leaving behind the pigment (usually iron oxides or titanium dioxides). This results in coloration or haze formation which is tough to clean and may require strong corrosive acids and manual cleaning to physically scrub it off the surface of the equipment, which is not desired. A detergent having pigment carrying capability removes the entire formulation in a single detergent step, preventing the pigment from bonding to the equipment surface and eliminating the need to re-clean.

b. Application method & processing conditions

The knowledge of the soiling process is important as the nature of the residue on the equipment surface post application and processing determines the physical and chemical characteristics of the residue.

A formulation might not be difficult to clean as a powder mixture but the same, when processed through a hot melt extruder, might be extremely tough and hard to clean off the extruder screws.

Similarly, the lab trial must replicate processes such as AIL (Air liquid Interface), pressure during processing such as blending, roller compaction, granulation or compression and heat conditions of processes such as mixing, granulating, coating, drying or any other processing based on the equipment and residue to be cleaned.

Another aspect to be considered in case of multi-step processes like multi-layer coating is whether different coating layers are sprayed alternately and then cleaned at once or whether one type of product is layered in campaign & cleaned followed by second type of layering and cleaning.

c. Cleaning frequency

It is of common knowledge and understanding that the campaign batch size determines the thickness of the residue and cleaning is easier and faster as the cleaning frequency is increased. A cleaning process validated for 3 batches might fail if cleaning is carried out after more than 3 batches.

d. Dirty hold time

As the residue 'ages', it becomes harder to clean. Experiments have shown that a coupon with a residue after 3 days hold time could be cleaned within an hour with the identified detergent under specified conditions, but the same residue under similar conditions with the same detergent couldn't be cleaned even after 4-5 hours when the dirty hold time was increased to 7 hours.

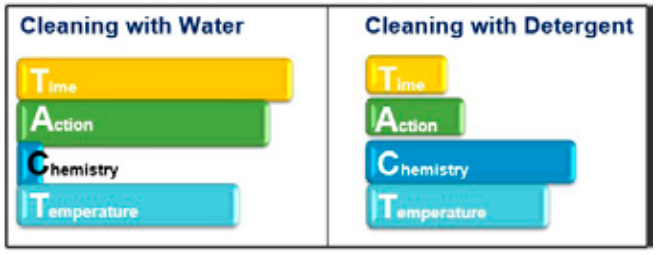
3-day dirty hold time
- 1 hour cleaning in beaker

7-day dirty hold time
- 4-hour cleaning in beaker

3. Detergent related

The 4 main detergent-related variables that need to be controlled are the T.A.C.T (Time, Action, Chemistry, Temperature) parameters, which define the final cleaning process. They are interdependent and if one parameter is to be decreased, it might have to be compensated by one or more of the other parameters.

The interdependency of these parameters can be best demonstrated by noting the difference between cleaning with and without detergent. In a cleaning process without the detergent (lack of Chemistry), the Time, Action and Temperature have to be increased, whereas while cleaning with the right detergent, in other words, using the right Chemistry, the other parameters can be decreased.



a. Time

Cleaning time is time where the equipment is not producing product, which is why it considered down time. All industries look for options to reduce this cleaning time for improving productivity of their equipment. While developing a cleaning process, the overall equipment downtime must be considered. Cleaning of individual parts in Clean-Out-of-Place (COP) system might be easy but the time required for dismantling and re-assembling the equipment for this kind of process adds to the extended downtime and is therefore, not desirable.

- Time of contact: The cleaning depends on the time of contact between the soil and the detergent solution. This time must be sufficient for the desired chemical reaction and removal of the residue + detergent mixture from the surface of the equipment and this can be determined after multiple trials.

  The time of contact necessary for a cleaning cycle depends on the type of soil, amount of residue and the type of surface to be cleaned.

- Time in between cleaning process steps: Must be kept as short as possible to avoid drying of the residue or the detergent onto the surface before the final rinse.

b. Action

It is the physical force applied to a surface being cleaned. It has been observed that higher the action, better is the cleaning.

- Manual: It includes wiping, scrubbing and cleaning with jet or pipes, where the force of the spray is directed manually onto the surface to be cleaned. This action is best avoided in a GMP cleaning process as it is operator dependent and inconsistent. Also, due to microbial contamination possibility, safety and ergonomic issues, manual cleaning action must be minimized or eliminated in cleaning of production scale equipment.

- Cleaning devices: Action from devices like COP, WIP and CIP will have a direct impact on effectively removing the soil from the surfaces being cleaned.

c. Chemistry

Chemistry refers to the cleaning agent that is targeted towards soil removal

- Detergent: Formulated detergents do not rely on solubility alone. They remove the soil from the surface and hold it in solution to make sure it can be rinsed away.

- Concentration: It depends on various residue related variables such as residue thickness and dirty hold time.

- Volume: The volume of the detergent solution must be sufficient to remove the residue and hold it in solution or suspension. If low volumes of detergent solutions are used, even at higher concentration, cleaning might not be effective as the solution might get saturated with the residue and after a limit, the residue remaining on the equipment will not react with it.

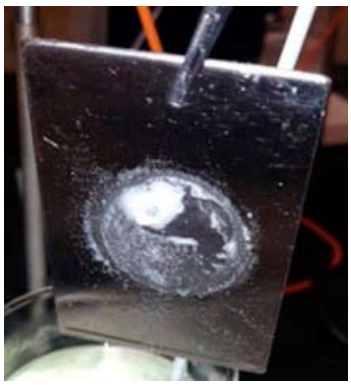
d. Temperature

- Pre-rinse, detergent cycle and post rinse temperatures: These temperatures must be optimized with trials and validation as these temperatures play an important role in the effective cleaning of the equipment.

- Manual cleaning: When the detergent is applied manually, temperatures above 55°C could cause safety issues and thus, should be avoided.

- Material of construction: Higher temperatures might cause damage to certain polymeric components of the equipment. This aspect is to be considered while developing a cleaning procedure for that equipment.

- Adverse reaction with soils: At unsuitable temperatures, the cleaning process might lead to worsening of the soil residue and cause cleaning failures. A few examples include swelling and flake formation of polymers at higher pre-rinse temperatures. Another example is the flash drying of pigments when cleaning is done at high temperatures, above 60°C. which is then very difficult to clean and require rigorous cleaning with corrosive chemicals



Other aspects influencing Cleaning in a GMP environment are the Health & safety and the regulatory requirements.

It is very important to consider all variables before defining the final cleaning recommendations to ensure efficient cleaning.

In the next article, we would be seeing some case studies where we have put in all our knowledge base on cleaning and solved cleaning issues for 'hard to clean' products.

INDIAN PHARMACEUTICAL ASSOCIATION ANNUAL CONVENTION (IPAC) 2021 ABSTRACT PROCEEDINGS

Parthenolide shows anticancer activities by generating reactive oxygen species, inhibiting Wnt Pathway, EMT and cell migration in HCT-116 Metastatic Colorectal Cancer Cells: Sananda Dey, Biplab Giri, University of Gour Banga

Colorectal cancer (CRC) has become a predominant cancer and now accounts for 3rd most fatal and 4th most frequent identified cancer worldwide. Aggressive metastasis is the major cause of death in 50% of CRC patients. In metastatic cancer, tumour cells migrate, invade by degrading their attachments with the extracellular matrix and ultimately colonize to the distant organ. Parthenolide (PTL) is a secondary metabolite of feverfew (Tanacetum parthenium) plant. It shows its cytotoxicity towards cancer cells by inhibiting different cellular signaling pathways like of NF-κB, STAT3, MAPK, JNK pathways etc. In this study, we have studied anti-cancer and anti-migratory potential of PTL against human metastatic colorectal cancer cells (HCT-116). PTL disrupts cellular oxidative status of HCT-116 cells. 48 hr of PTL treatment showed a significant decrease ($p<0.05$) in GSH level whereas significant increase ($p<0.05$) of GSSG level was observed. It also amplified the amount of intracellular reactive oxygen species (ROS). PTL down-regulates c-fos, c-jun and N-cadherin expression and up-regulates E-cadherin expression indicating the inhibition of cell migration and EMT pathway. PTL inhibited the MMP-9 expression in a dose-dependent manner and hindered cancer cell migration by regulating Wnt/β-catenin signalling through the up-regulation of DKK-1 protein expression. These altogether indicate the promising anticancer potential of PTL against HCT-116 metastatic colorectal carcinoma cells.

Neuroprotective effect of mulmina against chemotherapy-induced cognitive decline in mouse model of mammary carcinoma: Jeena John, Manas Kinra, Niraja Ranadive, Rajesh N. Jagdale, Syed, Mushtaq Ahmed, Kaggundi V Raghavendra, Jayesh Mudgal, Krishnadas Nandakumar, Manipal College of Pharmaceutical Sciences

The post-treatment status of breast cancer survivors has become a concern because of the toxicity induced by chemotherapeutic agents in the brain tissues causing cognitive deficits, which is generally referred to as “Chemobrain”.This study assessed the effect of a proprietary ayurvedic formulation Mulmina Mango against chemotherapy-induced cognitive impairment(CICI).We had previously identified that Mulmina inhibits Cyclophosphamide+Methotrexate+5-Fluorouracil (CMF) induced cognitive decline in healthy female mice.However, it was also important to establish that it does so in animals with mammary carcinoma without compromising the antitumor potential of the CMF regimen.Mammary carcinoma was induced by subcutaneously inoculating 4T1 cells into the mammary fat pad of the animals. Intraperitoneal administration of cyclophosphamide (50mg/kg) + methotrexate (5mg/kg) + 5-fluorouracil (50mg/kg) was carried out once a week for three weeks (21 days).Treatment of Mulmina began one week before chemotherapy and continued till the end of the chemotherapy cycle. After three cycles of chemotherapy, locomotor activity was assessed by the open-field test followed by assessment of cognitive decline by Morris water maze task.Tumour progression was evaluated by measurement of tumour volume. Levels of oxidative stress markers in brain homogenate were estimated via ELISA.CMF treatment significantly reduced tumour size and volume. Pre-treatment with Mulmina did not significantly alter tumor suppression potential of CMF,suggesting that Mulmina does not influence its anticancer activity. We found chemotherapy negatively affected spatial learning ability and oxidative parameters and that Mulmina ameliorated these cognitive impairments and restored antioxidant levels.The combination of phytochemicals in Mulmina proved its possible ability to alleviate CICI without affecting chemotherapeutic efficiency and could pave the way for identifying treatment strategies to combat chemobrain.

Evaluation of Clitoria ternatea L. for autism spectrum disorders, An extensive lead seeking preclinical trial for drug discovery and development: Jiji K.N, Muralidharan P, C.L. Baid Metha College of Pharmacy

Aim

To evaluate the neuroprotective effects of ethanolic root extract of Clitoria ternatea L.(EECT) against propionic acid induced autistic rat models for new drug development.

Methods

Experimental animals (adult wistar rats were segregated into 4 groups and administered the vehicle/extract for 28 days. Group I and Group II: Received vehicle alone p.o (1% Tween -80 solution) Group III and Group IV: Received Ethanolic root extract of Clitoria ternatea L.(EECT) at dose of 250 mg/kg and 500 mg/kg respectively (suspended in 1% Tween- 80 solution) p.o., Induction of autism was done by intra- cerebro- ventricular (ICV) infusion of propionic acid (PPA) between 22nd-28th day of the study. During this infusion period rats were subjected to various in vivo behaviour and memory evaluation methods by performing

elevated plus maze and novel object recognition test. On 29th day of the study animals were sacrified to get the brain tissue homogenates and carried out the estimation of various in vitro neuroinflammatory markers levels (TNF-α and IL-6).
Results
Pre-treatment of rats with EECT at two dose levels (250 mg/kg and 500 mg/kg) significantly (p<0.001) reduced the neuroinflammation, memory and cognitive impairment produced by the propionic acid.
Conclusion
Study results concluded that the ethanolic extract of Clitoria ternatea.L roots possess potent neuroprotective effects against PPA induced autistic neuroinflammation, as it lowers the central TNF-α and IL-6 levels.

Validated stability indicating HPTLC method for determination of Ulipristal Acetate: Shruti Srivastava, Suneela Dhaneshwar, Neha Kawathekar, Amity Institute of Pharmacy, Amity University

Stability indicating method is a method, used for quantifying the decrease in amount of active pharmaceutical ingredient in drug product due to degradation. For the analysis of ulipristal acetate both in bulk drug and dosage form, a sensitive, selective, HPTLC method of stability indicating was developed. The method employed pre-coated silica gel 60F254 plates as the stationary phase, with mobile phase of dichloromethane: methanol (9.5:0.5; v/v). At 312 nm absorbance mode, the densitometric scanning was performed. The aimed study was found linear, with co-relation coefficient of 0.998 in the concentration span of 30-150 ng per spot. LOD and LOQ values obtained were 9.57ng and 29.022 ng/spot, respectively. Forced degradation studies of ulipristal acetate indicated the degradation under acidic, basic, peroxide, thermal, and photolytic stress conditions. The degradants were resolved significantly at different Rf values from the pure drug. The aimed analysis verified that the method for estimating ulipristal is repeatable and specific. Since the method demonstrates the effective separation of drug from its degradation products, it can be applied as a stability-indicating method for pre-formulation studies, stability studies and regarding the development of proper storage requirements in quality control laboratories.

In vitro interaction study of resveratrol with dapagliflozin and empagliflozin by equilibrium dialysis method using uv spectroscopic method: Aswathi KS, David Paul, Maneesha Dinilkumar, Roshitha K R, Sujith Unnikrishnan, Dineshkumar, Krishnakumar, St. James College of Pharmaceutical Sciences

In the current, work we studied the possibility of displacement interaction between selected SGLT2 inhibitors (dapagliflozin, empagliflozin) and phytochemical resveratrol using the UV spectroscopic method for the first time. Free fraction and percentage binding of drugs in the mixture to BSA were calculated. The in-vitro displacement interaction study of SGLT2 inhibitors with resveratrol and the interaction of resveratrol on SGLT2 inhibitors were also carried out. The binding interaction of the drugs with the protein was confirmed by molecular docking studies. The stability of all the three drugs at different physiological pH conditions (empty stomach pH 1.2, simulated gastric pH 4.5, blood pH 7.4, and intestinal pH 9) was also carried out.

In silico screening and molecular docking studies of novel piperidines in the treatment of alzheimer's disease - A MTDL approach: K. Dhunmati, C. N. Nalini, N. Ramalakshmi, C.L. Baid Metha College of Pharmacy

Alzheimer's Disease (AD) is a progressive mental deterioration that can occur in middle or old age, due to generalized degeneration of the brain causing premature senility. Alzheimers disease is the most common cause of dementia - a continuous decline in thinking, behavioral and social skills that affects a persons ability to function independently. In order to combat the prevalence of AD, piperidines were chosen as the lead scaffolds having potent activity owing to the nitrogen atom present. Donepezil (piperidine derivative) marketed as Aricept possesses neuroprotective, neurotropic and memory enhancing properties. Flavonoids were chosen as substructures because experimental evidence supports hypothesis that they may protect against AD in part by interfering with the generation and assembly of Amyloid beta peptides into neurotoxic oligomeric aggregates and also by reducing tau aggregation. Novel in silico screening has great potential in drug discovery, drug repositioning, virtual screening of chemical libraries. The multifunctional nature of AD provides the base for opting a multi targeted approach which are used to develop a variety of hybrids to act simultaneously in multiple biological targets.Thus these drug candidates would aim multiple targets like Acetylcholine esterase, Butyryl choline esterase, Beta amyloid and Tau protein involved in AD pathogenesis. The binding interactions were studied using molecular docking (Auto Dock Vina) which showed significant scores. In silico predictions were also performed to predict toxicity and ADME properties of the piperidine leads and

were found to be within drug likeness range. Therefore, the designed piperidine leads could be promising multi-functional compounds that can be used for further development of novel drugs for Alzheimer disease.

Clerodane diterpenes from polyalthia longifolia var. pendula as novel anti-tubercular agents: Sony Priya Kurati, W. A. Uma Rani, Sariki Suneetha, Purna Nagasree Kurre, M M K Kumar, Pharmaceutical Chemistry research labs, Andhra university

Over the ages, people have relied upon nature to meet their fundamental needs, including medicines to treat a wide variety of diseases. The second leading cause of death on the planet earth is tuberculosis (TB) from bacillus mycobacterium tuberculosis. The most effective oral anti-TB drugs are isoniazid, rifampicin, ethambutol and pyrazinamide. Although the adverse reaction is small, many patients experience untoward effects when simultaneously taking more tablets / capsules together, which is the major cause of non-compliance. With these in perspective, trying to find new anti-TB drugs and the interaction of anti-TB drugs by natural plant materials is relevant to conduct the present investigation. The clerodane diterpenes 16α-hydroxycleroda-3,13 (14)-Z-dien-15,16-olide (Compound 1) , 16-Oxoecleroda-3, 13(14) E diene-15 oic acid (Compound 2), (2E)-5-((8aR)-1,2,3,4,4a,7,8,8a-octahydro-1,2,4a,5- tetramethylnaphthalen-1-yl) 3 methyl pent-2enoic acid (methyl ester) (Compound 3), (2Z) methyl 3-formyl-5-((8aR)-1,2,3,4,4a,7,8,8a-octahydro-1,2,4a,5-tetramethylnaphthalen-1-yl) pent-2-enoate (methyl ether) (Compound 4) and Kolavenic acid (Compound 5) isolated from Polyalthia longifolia var. pendula (Linn.) were previously reported for their antimicrobial activity. As a result, the current study is designed to look into the anti-tubercular activity inhibiting potential of these diterpenoids using MABA assay (Microplate Alamar Blue Assay). Compounds 1 and 2 at 3.125 µg/ml showed significant anti-tubercular activity against mycobacterium tuberculosis H37Rv +ve. At the same time, these compounds at 50 mg/ml have shown significant antibacterial activity against gram +ve (Staphylococcus aureus NCIM 2122) and gram -ve (Escherichia coli NCIM 2137). The study's main goal is to investigate anti-TB appraisals for bio-enhancing the clerodane diterpenes from seeds of Polyalthia longifolia var pendula.

Randomised controlled trial of L-Carnosine supplementation in children with autism spectrum disorder: Debi Ann Abraham, Sri Ramachandra Faculty of Pharmacy

Background
Autism spectrum disorder (ASD) is a neurodevelopmental disability characterized by difficulties with social interaction, communication, and repetitive and restricted behaviours. L-Carnosine is an aminoacid that has shown to help children with ASD. However, research on L-Carnosine supplementation in children with ASD is lacking. The goal of the study is to determine the effect of L-Carnosine in children with ASD and to estimate serum levels of L- Carnosine before and after supplementation.
Methods
A randomised controlled trial was conducted on 63 ASD children aged 3-10 years. ASD children were randomised to receive 10-15 mg/kg L-Carnosine and standard therapy (occupational/speech therapy) or standard therapy alone for a period of 2 months and serum L-Carnosine were measured before and after supplementation. Autism severity was assessed by Childhood Autism Rating Scale 2 nd Edition, Standard version (CARS2-ST) and Autism Treatment Evaluation Checklist (ATEC). The study was registered in Clinical Trial Registry-India (CTRI/2019/07/020102).
Results
L-Carnosine supplementation had no statistically significant effect on autism severity as measured by CARS2-ST or ATEC scores (p>0.05). Similarly, serum L-Carnosine levels before and after supplementation showed no statistically significant difference(p>0.05).
Conclusion
This is the first study to evaluate L-Carnosine levels in Indian ASD children before and after supplementation. L-Carnosine supplementation did not improve serum levels or alleviate ASD symptoms when used in conjunction with standard therapy. As a result, it may not be appropriate for children with ASD. More study with different doses of L-Carnosine and a large number of participants is needed to validate the efficacy and safety of L-Carnosine in ASD.

Clinical pharmacist aided augmentation of appropriate antibiotic therapy in surgery units of a tertiary care hospital - A handshake approach: Ann Vazhayil Kuruvilla, M Ramesh, C. P Madhu, JSS College of Pharmacy, JSSAHER

Background

Inappropriate use of antibiotics plays a vital role in the emergence of resistant strains of microbes. This study assesses the appropriateness of antibiotic use in the surgery units of a tertiary care hospital.
Methods
This prospective interventional study was conducted over a period of nine months in general surgery wards of a tertiary care hospital. Appropriateness of the prescribed antibiotics was assessed based on the available antibiotic susceptibility reports and evidence-based medicine. Whenever the clinical pharmacist identified an inappropriate antibiotic use, it was discussed with the concerned surgeon and suggestions were made for the remedial action in person. The predictors were assessed by using bivariate logistic regression analysis by using
SPSS version 21.0.
Results
A total of 1085 antibiotics were prescribed and beta-lactam class (70.6%) was the most frequently prescribed class of antibiotics. In 64% of the cases, antibiotics were prescribed inappropriately. The cases that involved the gastro-intestinal system (28.03%) accounted for the greatest number of inappropriate antibiotic prescriptions. Among the inappropriate cases,
excessive regimen of antibiotic use (35.29%) was the highest. Percentage increase in the appropriate use of antibiotics resulting from pharmacist intervention was 95.06%. There was a strong association between inappropriate antibiotic use, comorbid conditions, use of 2 antibiotics, 6-10 days and 16-20 days of length of stay ($P < 0.05$).
Conclusion
Although antibiotics form an inevitable part of surgical care, the cautious and rational use of antibiotics is warranted.

Drug Information Services at Community Pharmacies: What Are the Barriers?: Atiqulla Shariff, Aishwarya S, Ankitha G, Bhuvaneshwaran S, Dhanvanth Kumar C, Supriya SM, Srikanth MS., JSS College of Pharmacy, JSSAHER

Introduction
Pharmacists have special knowledge and skills related to various aspects of drug use. Therefore, irrespective of their practice settings, they are at right position to provide the drug
information services. Provision of drug information at community pharmacies is a well-recognized professional service in many developed countries. However, in India, this concept is very rare and unheard most of the times.
Objectives
To assess the perceptions and barriers related to provision of drug information services at their practice settings.
Methodology
This cross-sectional interview-based study was conducted over a period of six months in South Karnataka. Study respondents were interviewed to gather demographic data and to capture their perceptions and barriers for provision of drug information services at community
pharmacies. Collected data was collated and analyzed descriptively.
Results
A total of 538 respondents participated in the study. A majority of the respondents opined that there is a need for provision of drug information services in the community pharmacies [369, 68.5%], and there must be a dedicated pharmacist available in the community pharmacies for
provision of drug information services [392, 72.8%]. A total of seven system-related and five person-related barriers were identified for the provision of drug information services at community pharmacies. Lack of awareness about the service [321, 59.6%] was the most frequently identified barrier followed by lack of training [299, 55.5%].
Conclusion
The identified barriers indicate that there is a need for capacity building among the practicing community pharmacist for promoting drug information services at their practice sites.

Solid phase reversible immobilization (SPRI) beads based detection of mycobacterium leprae positive samples through isothermal technique: Nupur Garg, Farhan Jalees Ahmad, Sudeshna Kar, School of Pharmaceutical Education and Research, Jamia Hamdard

Mycobacterium leprae, responsible for dermato-neurological disease leprosy, has vast genomic similarity with mycobacterium tuberculosis due to which cases of misdiagnosis occur. Since, there has been a re-emerging situation of leprosy owing to the perpetuating transmission in endemic areas, a specific, sensitive, rapid and economical diagnostic method with minimum field settings is obligatory. Loop-mediated isothermal (LAMP) DNA amplification method was employed that amplified mycobacterium

leprae gene sequence using three sets of primers with reaction reagents in 60 min at constant temperature of 66 ^{0}C. Conventionally, detection of amplicons is done by gel electrophoresis which is qualitative and tedious, or fluorescent dyes that cause non-specific binding. We coupled LAMP assay with solid phase reversible immobilization detection of mycobacterial presence in samples. Solid phase reversible immobilization beads are paramagnetic nanobeads consisting polystyrene core enveloped by magnetite and carboxylate coating. Under magnetic field, the nanobeads bind with amplified DNA and form a visible pellet in contrast to a dispersion in the absence of target DNA. The sensitivity of method was evaluated using serial dilutions and found to be in picograms. The selectivity was evaluated using mycobacterium tuberculosis as negative control and found to be specific for mycobacterium leprae. Hence, LAMP-SPRI assay displays the potential to be a rapid and affordable diagnostic tool for leprosy.

Green carbon dot as fluorescence turn-on probe for selective estimation of zinc ion in blood plasma: Payel Mukherjee, Goutam Mukhopadhyay, Manas Chakraborty, M. R. College of Pharmaceutical Sciences and Research,

Zinc is an essential micronutrient and the 24th most abundant element on earth crust. The permissible dietary intake of Zn ion is 8-11 mg/day. It has significant roles in innumerable biological processes and enzymatic reactions that occur in human body. Excess zinc in human body causes different diseases like diabetes, cerebral ischemia, epilepsy, neural degeneration. Alzheimer's disease and deficiency of zinc causes acrodermatitis enteropathica. So, early monitoring of zinc ion in body fluid and tissue would be helpful in early detection of deadly diseases. In this study CDs of ~1 nm size was synthesized from onion extract using hydrothermal method. They were quasi-spherical in shape and had lattice stripes due to graphitic core. Particle surface was decorated with polyhydroxy group and amino group. When excited at 325 nm, the presence of Zn2+ ions significantly enhanced the fluorescence intensity in Tris buffer and blood plasma, whereas others common cations like Fe3+, Pb2+, Cu2+, Ca2+, and Hg2+ ions had similar effect in quenching the fluorescence intensity. The quantum yield was 6.214 % and was very much sensitive to the presence of Zn2+ ions. Thus it will be beneficial for biomedical field and can serve the mankind.

Development and optimization of pH responsive nanogels of fluocinolone acetonide for psoriasis: Apeksha Gupta, Saima Amin, Kanchan Kohli, School of Pharmaceutical Education and Research, Jamia Hamdard

Introduction
The word psoriasis is derived from greek words meaning "an itching condition". Due to differences in the pH on the surface of healthy skin and psoriatic skin, pH responsive nanogels are intelligent candidates for psoriasis. The aim of this study is to develop pH responsive nanogels (designated as FA-NG) containing fluocinolone acetonide (FA) and N,N,N-Trimethyl Chitosan (TMC) and its optimization by the box- behnken design (BBD) expert software.
Methods
FA-NGs were prepared by chemical cross-linking method. TMC solutions were prepared in deionised water and stirred well. FA dissolved in PEG 400 was added drop wise with constant stirring and sonicated. Gels were then cross-linked by glutaraldehyde solution, stirred to form nanogels. A 3-factor 3-level BBD was used for optimization of FA-NGs. 17 formulations of FA-NGs were successfully developed by varying the independent variables: % TMC conc. (X1), % Glutaraldehyde conc. (X2) and sonication time (X3).
Results
The optimized FA-NG was formulated using 3.98% X1, 9.7577 % X2 and 4.7 minutes X3.
Conclusion
FA was effectively entrapped in the FA-NG using chemical cross-linking method. FA-NG can prove to be an ideal and novel candidate for treatment of psoriasis.

Digital marketing in pharmaceutical companies: Lokesh Sharma, Jaipur National University

Most significant trend in pharmaceutical industry nowadays is digital marketing. Through online communities, mobile applications and a wealth of web content, people now have wide access to a range of pharma-based insights. From a facebook or instagram campaign to the augmented and virtual reality, all this is a part of digital movement. In today's marketing world pharmaceutical companies are also engaging their customers with social media influencer though it is limited to a small range

of OTC drugs, supplements and some medical devices (basically biosensors). Digital marketing is not only helping pharmaceutical companies, but also new emerging start-ups like e-pharmacy, telemedicine and e-diagnostics platforms. These are very significant statistics, especially when you consider that the vast majority of people spend a lot of time every day on social networks, and there they inform themselves, compare information, and form ideas and opinions. It may help pharmaceutical companies and new startups to create brand awareness through campaigns and direct promotion in market at the same time introduce new products. Digital marketing is directly related to the content marketing where companies focused on creating, sharing and distribution of valuable content to win new customers and retain existing customers. So, digital marketing is more about meeting the expectations of those customers on the channels that they choose and prefer to use. This is what marketing is all about.

Synthesis, docking, anti breast cancer, anti oxidant, and anti bacterial activities of novel chromone linked [1,2,3] triazole derivatives: Joolakanti Hima Bindhu, B. Satyanarayana, K. Ramanjaneyulu, Vishnu Institute of Pharmaceutical Education and Research

Estrogen receptor-positive (ER+) breast cancer is the most commonly occurring cancer in women. ERα is the major one involved in breast cancer and chosen as an important target for endocrine therapy. Chromone and 1,2,3-Triazole derivatives possess wide range of pharmacological activities and also inhibit the proliferation of breast cancer cells. In our study we combine both chromone and triazole moieties by using acrylic acid as a linker. A series of chromone linked [1,2,3] triazoles were designed based on docking and literature studies. The docking studies indicate that (2E) (1R-1,2,3-triazol-4-yl) methyl 3 (6-methyl-4-oxo-4H-chromen-3-yl) acrylate derivatives exhibit good docking score at ligand binding domain of ERα (1xp6). So a new series of ten Chromone linked [1,2,3] triazoles have been synthesized by employing molecular hybridization, click chemistry approach and characterized by LC-MS, 1H NMR, and 13C NMR and IR spectral studies. All compounds evaluated for cytotoxicity in MCF-7 cell line, anti bacterial and anti oxidant activities. The compounds exhibit most potent cytotoxicity, anti oxidant activity and moderate anti bacterial activity. 9f, 9a compounds show most potent cytotoxicity with IC 50 value of 18.61, 20.39 μg/mL respectively. 9c, 9d, 9e and 9j compounds show potent cytotoxicity with IC 50 value of 45 μg/mL. 9b, 9c, 9f, 9g, 9j show most potent anti oxidant activity with IC 50 value of 30 μM i.e. DPPH scavenging activity levels more than that of standard ascorbic acid. 9a, 9e, 9f, 9j were most active against staphylococcus aureus with a MIC value of 250 μM, 9a, 9c, 9e, 9f, 9h, 9j were most active against E.coli with a MIC value of 250 μM, 9c, 9e, 9f, 9h, 9j were most active against pseudomonas aeruginosa with a MIC value of 240 μM, 9c, 9h were most active against proteus vulgaris with a MIC value of 240 μM.

LC–MS/MS method for simultaneous determination of ivacaftor and tezacaftor in rat plasma: Application to a pharmacokinetic study: Lakshmana Rao Atmakuri, V. V. Institute of Pharmaceutical Sciences

Ivacaftor and tezacaftor belong to CFTR potentiator class, in combination approved to manage cystic fibrosis. The objective of proposed work is to establish a sensitive LC-MS/MS approach for the synchronized analysis of ivacaftor and tezacaftor and its appliance to rat pharmacokinetic investigation. Method is developed with protein precipitation by acetonitrile and ivacaftor-d4, tezacaftor-d4 are used as internal standards. Separation is done on an eclipse plus C 18 analysis column (100 mm × 4.6 mm 1.8 μm) with a mobile phase consisting of 0.1% trifluoroacetic acid: acetonitrile (ratio 60:40, v/v, and pH 2.5) and flow stream of 1.0 mL/min at ambient temperature. The approach developed showed fine calibration curve in the quantity range of 1.5-22.53 ng/mL for ivacaftor and 1-15.02 ng/mL for tezacaftor and the accuracy and precision meets FDA guidelines. The newly designed and validated approach was simple, fast and applied effectively for rat pharmacokinetic investigation.

A study on degradation of ifetroban by LC-MS including validation: Bharani Pandilla, K. Chitra, C.L. Baid Metha College of Pharmacy

The present study reports the characterization of degradation products of Ifetroban through Liquid Chromatography-Mass Spectrometry (LC-ESI-MS method) .The forced decomposition of Ifetroban was carried out under acidic, basic, oxidative, photolytic and thermal conditions. Successful chromatographic separation of Ifetroban and its degradation products was achieved through a Waters XEVO-TQS system with Mass Lynx 4.1 software in MRM scan mode. Separation was done using Intersil ODS 3V C18 (250 x 4.6 mm, 5 μ) with the mobile phase consisting of 10 mM ammonium acetate: Acetonitrile (60:40, v/v) at a flow rate of 1.0mL/min

in isocratic elution. Diluent was acetonitrile: methanol (1:1, v/v). UV detection was performed at 215nm and the run time was 60 minutes. The retention time for Ifetroban was 10.50 minutes. The forced degradation samples were analysed on LC-MS/MS to obtain the molecular masses of the potential degradants. In ESI positive ion mode, the mass spectrum of the drug degradant has shown molecular ion peaks at m/z values of 257 269 and 424 respectively. The developed method was able to separate Ifetroban from itsdegradation products. The drug was found to be slightly degraded under basic hydrolysis and thermal conditions. The developed LC method was validated as per ICH guidelines with respect to accuracy, selectivity, precision, linearity, and robustness. Thus, the developed method can also be used for the identification of stress degradation products along with routine quality control analysis.

Redesigning healthcare models in chronic disease management: Bogireddy Sahithi, Yiragamreddy Padmanabha Reddy, Jawaharlal Nehru Technological University Anantapur

Globally 41 million people each year (~ 71%) of all deaths are due to chronic diseases. Around 75% of the elderly in India suffer from one or the other chronic disease, 40% have a disability and 20% go through issues related to mental health. The traditional health care system is designed to provide a symptom driven response to acute illnesses, it is poorly configured to meet the needs of those with chronic illnesses. Over the last years, care delivery for people with chronic diseases has gradually shifted from a mostly disease-specific approach to a more integrated or comprehensive approach in which the multiple health and social care needs of these people are addressed. Though almost all the existing models have same core concepts it can't be applied in all the countries. The challenges in developing countries to implement care models includes lack of qualified and trained staff, multi-morbid conditions, laboratory support for basic biochemistry, no mechanism to track patients and lack of active involvement of patients. So, it is required to redesign the framework of the care model in a more feasible way considering the existing scenarios. The current crisis highlights the role of digitalization in providing health care services that benefits patients. Several studies also emphasized the positive impact of patient centred management and pharmacist mediated in improving patient conditions. The refinement of the care model framework integrating the finest components will help in improving the clinical, humanistic and economic outcomes of the patients.

Generation of 3D printed multi-functional customized drug delivery systems In vitro, and in vivo evaluations: Purushottam Bhaskarrao Suryavanshi, Subham Banerjee, NIPER, Guwahati

Selection of appropriate polymer, for the preparation of amorphous solid dispersion via hot-melt extrusion, deals with the study of various solid-state properties of drug and polymer. Hence, before going to hot-melt extrusion it is necessary to have appropriate knowledge of drug-polymer miscibility, drug-polymer interaction upon mixing, and Gibb's free energy of mixing upon mixing for the respective drug-polymer system. Besides, Additive manufacturing (3D printing) is predicted to be a transformative manufacturing process due to its ability to formulate custom-made entities of precisely any form and dimension in a layer-by-layer manner. The pharmaceutical scientist merged 3D printing technology with hot-melt extrusion for the formulation of drug delivery system. According to our knowledge, this is the first time where we prepared ASD of NOR through hot-melt extrusion for the carrier-controlled release combined with stereolithography (SLA) 3D-printing technology with hot-melt extrusion. In the present work, we evaluated the miscibility and interaction parameter between norfloxacin (NOR) and Kollidon ® SR Powder (KSR-P) using solubility parameter approach and Flory-Huggins theory. The Flory-Huggins theory-based temperature-composition phase diagram was used for the selection of appropriate hot-melt extrusion process variables. The prepared extrudate batch was evaluated and optimized by DSC, XRD, ATR analysis, and norfloxacin assay. Spheronization technique was used for the conversion of optimized extrudate into micropelltes. Besides, the SLA 3D printing technology was used to fabricate capsule body and cap. The prepared capsule body and cap was filled with micropelltes and evaluated using Mastersizer, SEM, in-vitro release study, and in-vivo absorption study.

IPA BUILDING PROGRESS REPORT




WORK STATUS AS ON MARCH 2022 & PROPOSED ACTIONS FOR THE IPA BUILDING PROJECT

1. The Total building construction including tiling, plumbing, electrical and painting work, is over
2. For the Storm water drain work, the internal work including the concrete covering is over. The work to connect this drain to the Municipal sewer including cutting & reinstating the road/footpath outside our plot has been given to an agency who operates in such works. This work is expected to get over within 6 to 8 weeks.
3. The application for the water supply will be done in the next week.
4. The meter for Fire fighting & the common meter is fixed by M/s Adani.
5. The Fire fighting pumps, the pressure is checked. NOC is expected to be obtained by this month.
6. Rain water harvesting pit & related work is going on at 3 places & shall get over within next 2 weeks.
7. After the storm water drain connection is done, the application & follow up for the OC shall begin.
8. The balance work for the IPA Building is about the various permissions / NOC s. The licensing agencies are on their job and will try to complete at the earliest.

PHARMASCENE

NEW DRUG APPROVALS

www.drugs.com

Pyrukynd (Mitapivat) Tablets

Company: Agios Pharmaceuticals, Inc.

Date of Approval: February 17, 2022

Treatment for: **Pyruvate Kinase Deficiency**

Pyrukynd (mitapivat) is a pyruvate kinase activator indicated for the treatment of hemolytic anemia in adults with pyruvate kinase (PK) deficiency.

Enjaymo (Sutimlimab-jome) Injection

Company: Sanofi

Date of Approval: February 4, 2022

Treatment for: **Cold Agglutinin Disease (CAD)**

Enjaymo (sutimlimab-jome) is a classical complement inhibitor indicated to decrease the need for red blood cell (RBC) transfusion due to hemolysis in adults with cold agglutinin disease (CAD).

Fleqsuvy (Baclofen) Oral Suspension

Company: Azurity Pharmaceuticals

Date of Approval: February 4, 2022

Treatment for: **Spasticity**

Fleqsuvy (baclofen) is an oral suspension formulation of baclofen for the treatment of spasticity resulting from multiple sclerosis, particularly for the relief of flexor spasms and concomitant pain, clonus, and muscular rigidity.

Spikevax (Moderna COVID-19 Vaccine) (COVID-19 Vaccine, mRNA) Injection - formerly mRNA-1273

Company: Moderna, Inc.

Date of Approval: January 31, 2022

Treatment for: **Prevention of COVID-19**

Spikevax (COVID-19 Vaccine, mRNA) is an mRNA vaccine indicated for active immunization to prevent COVID-19 caused by SARS-CoV-2 in individuals 18 years of age and older.

Vabysmo (Faricimab-svoa) Intravitreal Injection

Company: Genentech, Inc.

Date of Approval: January 28, 2022

Treatment for: **Macular Degeneration, Diabetic Macular Edema**

Vabysmo (faricimab-svoa) is a bispecific antibody targeting the vascular endothelial growth factor (VEGF) and angiopoietin 2 (Ang-2) pathways for the treatment of neovascular (wet) age-related macular degeneration (AMD) and diabetic macular edema (DME).

Kimmtrak (tebentafusp-tebn) Injection

Company: Immunocore

Date of Approval: January 25, 2022

Treatment for: **Uveal Melanoma**

Kimmtrak (tebentafusp-tebn) is a bispecific gp100 peptide-HLA-directed CD3 T cell engager indicated for the treatment of HLA-A*02:01-positive adult patients with unresectable or metastatic uveal melanoma.

VACCINES AND DRUG APPROVALS

Gennova Biopharmaceuticals developing Omicron specific vaccine

www.economictimes.indiatimes.com;12th February, 2022

Gennova Biopharmaceuticals, a subsidiary of Pune-based drugmaker Emcure Pharmaceuticals, is developing a Covid-19 vaccine on its mRNA platform which will target the Omicron variant, the strain that is driving the third coronavirus infection wave in the country. The company intends to use it as a booster shot for those who have received two jabs of a primary Covid-19 vaccine. The heterologous booster trial will be conducted on people who have got two shots of Covid-19 vaccines Covaxin or Covishield. Gennova's Covid-19 mRNA vaccine will not require sub-zero temperature for storage, a feature that would make its rollout in India easy. The mRNA Covid-19 vaccines developed by Pfizer and Moderna need sub-zero temperature. Gennova is hopeful of introducing the vaccine soon. Gennova is also working on an mRNA platform-based primary Covid-19 vaccine. The vaccine candidate is moving well through phase 3 trials and the company will soon approach the drug regulator for emergency use authorisation (EUA).

GSK-Vir therapy works against Omicron sub-variant, data suggests

www.economictimes.indiatimes.com; 10th February, 2022

An antibody-based COVID-19 therapy developed by GSK and Vir Biotechnology retains neutralising activity against the emerging BA.2 form of the Omicron coronavirus variant. It is expected to release preprint data in the coming week, with live virus data to follow. Based on pseudovirus and extensive pharmacokinetic data, the company said it believed the 500 mg dose of sotrovimab is sufficient to retain activity against the BA.2 variant, which is in line with all other variants of concern and interest. The monoclonal antibody therapy, sotrovimab, is authorised for emergency use in the United States. The companies are sharing the latest data with global regulatory authorities. Sotrovimab is one of the few COVID-19 treatments shown to have worked against the fast-spreading Omicron variant, spurring demand. It was amongst GSK's top selling offerings in 2021.

Zydus Pharma gets final USFDA approval to market Roflumilast tablets

www.business-standard.com; 14th February, 2022

Zydus Pharmaceuticals (USA) Inc has received final approval from the US health regulator to market its generic version of Roflumilast tablets in the strength of 500 mcg indicated to reduce the risk of chronic obstructive pulmonary disease (COPD) exacerbations. Zydus, being one of the first applicants for Roflumilast Tablets, 500 mcg, is eligible for 180 days of shared generic drug exclusivity. The US Food and Drug Administration (USFDA) has also given a tentative approval for Roflumilast tablets, 250 mcg. The drug will be manufactured at the group's formulation manufacturing facility at the SEZ, Ahmedabad. Roflumilast tablets are indicated as a treatment to reduce the risk of COPD exacerbations in patients with severe COPD associated with chronic bronchitis and a history of exacerbations. The group now has 327 approvals and has so far filed over 400 abbreviated new drug applications (ANDAs) since the commencement of the filing process in FY 2003-04.

Single-dose Sputnik Light gets DCGI nod for emergency use

www.business-standard.com; 6th February, 2022

India has got its ninth Covid vaccine as the country's drug regulator approved the use of Sputnik Light or the single dose regime of Sputnik V for use in the country. Dr. Reddy's Laboratories announced that the Drugs Controller General of India (DCGI) has granted

approval to the single-shot Sputnik Light vaccine for restricted use in emergency situation for COVID-19 in India. Dr Reddy's Laboratories (DRL) is the marketing partner for Sputnik vaccines from Russia here. There are several Indian manufacturing partners for the vaccine, including Serum Institute of India, Panacea Biotec and Hetero, among others. Sputnik V is a heterogeneous vaccine that uses two different components in its two doses — Ad26 and Ad5. Sputnik Light is the first dose of Sputnik V. So far, 1.2 million Sputnik V vaccines have been administered to Indians, according to Cowin data. The vaccine is available in the private channel only, and the Centre has not procured it for free vaccination.

Glenmark, Canadian firm SaNOtize's Nitric Oxide nasal spray against Covid launched in India

www.thehindubusinessline.com; 10th February, 2022

The Indian tool-kit to treat Covid now has a Nitric Oxide nasal spray (NONS) in it from Glenmark Pharmaceuticals and Canadian pharmaceutical company SaNOtize Research & Development Corp. Approved for the treatment of adult patients with Covid, who have a high risk of disease progression, the spray will be available at chemists. Marketed under the FabiSpray brand name in India, the spray will be available on doctor's prescription. Priced at ☐850 for a 25 ml bottle, it covers the length of one person's treatment. The spray has established safety and is given in six doses through the day. At present it is given to adults with mild Covid-19, in the first 3-5 days, a treatment timeline similar to more expensive antivirals such as molnupiravir and favipiravir.

Vaccine will soon be available for 12-18 age group: Cadila Healthcare

www.economictimes.indiatimes.com; 4th February, 2022

Cadila Healthcare (Zydus Cadila) said it plans to soon roll out its Covid-19 vaccine ZyCoV-D for the 12-18 age group. The company said it has approval from DCGI (Drug Controller General of India) for children, NTAGI (National Technical Advisory Group on Immunisation) meeting has also cleared 12-18 (age group). The vaccine has to be given in three doses. The government placed an order with the company to procure 10 million doses at ☐265 per dose, along with a needle-free applicator which is offered at ☐93 per dose, excluding GST. However, challenges in ramp-up of production have delayed the launch.

Dr Reddy's Labs launches generic Vasostrict vials in US market

www.pharmabiz.com; 10th February, 2022

Dr Reddy's Laboratories announced the launch of its authorized generic version of Par Pharmaceutical's Vasostrict (vasopressin injection, USP) vials in the US market approved by the US Food and Drug Administration (FDA). The Vasostrict brand market had US sales of approximately $878.5 million MAT for the most recent twelve months ending in December 2021 according to IQVIA Health. Dr Reddy's Vasopressin injection, USP, is supplied in a carton of 25 single-dose vials each containing vasopressin 1 mL at 20 units/mL.

Lupin's Solosec receives US FDA approval to treat bacterial vaginosis in females and trichomoniasis

www.pharmabiz.com; 18th February, 2022

Lupin Pharmaceuticals, (Lupin) announced that the US Food and Drug Administration has approved the company's supplemental New Drug Application (sNDA) to expand the use of Solosec (secnidazole) in the treatment of bacterial vaginosis (BV) for female patients 12 years of age and older and in the treatment of trichomoniasis for all patients 12 years of age and older. Bacterial vaginosis is a common vaginal infection and trichomoniasis is the most common non-viral, curable sexually transmitted infection in the US. The supplemental adolescent approval enhances Solosec's strong position as the first and only single-dose oral prescription antimicrobial agent approved for the treatment of both trichomoniasis and BV. Solosec (secnidazole) 2 g oral granules is the first and only single-dose oral prescription approved to treat both bacterial vaginosis (BV), a common vaginal infection, in female patients 12 years of age and older and trichomoniasis, a sexually transmitted infection, in patients 12 years of age and older. Solosec is designed to be easy to take and one oral dose contains a complete course of treatment.

Alembic receives USFDA tentative approval for Fesoterodine Fumarate ER Tablets

www.business-standard.com; 2nd February, 2022

Alembic Pharmaceuticals announced that it has received tentative approval from the US Food & Drug Administration (USFDA) for its Abbreviated New Drug Application (ANDA) for Fesoterodine Fumarate Extended Release Tablets, 4 mg and 8 mg. The tentatively approved ANDA is therapeutically equivalent to the reference listed drug product (RLD) Toviaz Extended-Release Tablets, 4 mg and 8 mg, of Pfizer Inc. (Pfizer). Fesoterodine Fumarate Extended Release Tablets are indicated for the treatment of overactive bladder (OAB) in adults with symptoms of urge urinary incontinence, urgency, and frequency. It may not be indicated for certain other uses due to unexpired exclusivities for the RLD for such uses.

REGULATORY AFFAIRS

Abbott voluntary recalls powder formulas, Similac, Alimentum & EleCare manufactured in Sturgis, Michigan plant

www.pharmabiz.com; 19th February, 2022

Abbott is initiating a proactive, voluntary recall of powder formulas, including Similac, Alimentum and EleCare manufactured in Sturgis, Michigan, one of the company's manufacturing facilities. The recall does not include any metabolic deficiency nutrition formulas. Abbott is voluntarily recalling these products after four consumer complaints related to Cronobacter sakazakii or Salmonella Newport in infants who had consumed powder infant formula manufactured in this facility. Additionally, as part of Abbott's quality processes, the company also conducts routine testing for Cronobacter sakazakii and other pathogens in their manufacturing facilities. During testing in the Sturgis, Mich., facility,evidence of Cronobacter sakazakii was found in the plant in non-product contact areas. This investigation is ongoing. Importantly, no distributed product has tested positive for the presence of either of these bacteria. Abbott conducts extensive quality checks on each completed batch of infant formula, including microbiological analysis prior to release. While Abbott's testing of finished product detected no pathogens, we are taking action by recalling the powder formula manufactured in this facility with an expiration of April 1, 2022, or later. No Abbott liquid formulas, powder formulas, or nutrition products from other facilities are impacted by the recall.

Brut, Sure Brand Deodorants under Recall Due to Benzene

www.drugs.com; 18th February, 2022

Six Brut and Sure aerosol antiperspirant and deodorant sprays sold in the United States and Canada have been recalled by their maker due to the presence of the chemical benzene. Benzene is classified as a human carcinogen. Exposure to benzene can occur by inhalation, orally, and through the skin and it can result in cancers including leukemia and blood cancer of the bone marrow and blood disorders which can be life-threatening. Similar recalls have been issued for other consumer products that surprisingly contained benzene in the past six months: Pantene/Herbal Essence dry spray shampoos; Old Spice spray deodorants; and Neutrogena/Aveeno

spray sunscreens. Five of the recalled TCP products are: Brut Classic Antiperspirant Aerosol; Brut Classic Antiperspirant Aerosol; Brut Classic Deodorant Aerosol; Sure Regular Antiperspirant Aerosol; and Sure Unscented Antiperspirant Aerosol. A sixth recalled product was sold only in Canada: Brut Classic Deodorant Aerosol (154 g; UPC 00827755070177). Consumers should stop using the recalled products immediately and dispose of them appropriately, said the company, which also advised consumers to contact a health care provider if they experience any problems that may be associated with use of the recalled products.

U.S. FDA advisers call for new trial of Lilly, Innovent lung cancer drug

www.reuters.com; 11th February, 2022

Innovent Biologics and Eli Lilly and Co should be required to conduct a trial of their lung cancer drug that is applicable to the U.S. population, a panel of advisers to the U.S. Food and Drug Administration recommended. The recommendation, which sent Innovent shares down more than 10%, raises concerns for some other Chinese drugmakers who have been seeking to bring their products to the U.S. market at lower costs by conducting a single-country clinical trial. There are at least 25 applications from China in drug development phases, planned to be submitted or already under review by the FDA, that are predominantly or solely based on trial data from China, the FDA said ahead of the panel vote, without naming the products. The outside expert panel voted 14-1 that the FDA require more data from Innovent and Eli Lilly which had conducted the trial only in China. Lilly said it was "disappointed" with the outcome of the advisory panel meeting, but that it would continue to work with the FDA as the agency completes its review of sintilimab. Sintilimab, in the Chinese trial of patients with the most common form of advanced or recurrent lung cancer, met the main goal of progression free survival (PFS), or the time a patient lived without the disease worsening. In addition to the lack of population diversity, experts raised concerns over the use of PFS as the study's main goal rather than overall survival, the gold standard for cancer drugs. They also noted a lack of urgency for this medicine given the availability of other effective drugs from the same class of immunotherapies, known as PD-1 inhibitors, such as Merck & Co's Keytruda and Bristol Myers Squibb's Opdivo.

AuroMedics Pharma LLC Issues Voluntary Nationwide Recall of Polymyxin B for Injection USP, 500,000 Unit per Vial, Due to the Presence of Particulate Matter

www.drugs.com; 28th January, 2022

East Windsor, New Jersey, AuroMedics Pharma LLC has initiated a voluntary recall of lot number CPB200013 of Polymyxin B for Injection USP, 500,000 Units/Vial, to the consumer level from the USA market due to a product complaint for the presence of particulate matter, identified as hair being discovered in a vial within this lot. The administration of an intravenous product containing hair, even with the use of a filter, could cause a patient to experience serious hypersensitivity reactions that may be life-threatening. To date, AuroMedics Pharma LLC has not received reports of any adverse events or identifiable safety concerns attributed to the product consumed from this lot. The affected Polymyxin B for Injection lot being recalled is CPB200013 with an expiration date of 09/2022. AuroMedics shipped the entire lot to wholesalers nationwide from March 19, 2021, through June 14, 2021. AuroMedics Pharma LLC is notifying its distributors by recall letters and is arranging for return/replacement of all recalled product. Consumers/distributors/retailers that have the product lot which is being recalled should immediately stop using and return to place of purchase/contact their doctor as appropriate.

MERGERS, ACQUISTIONS AND COLLABORATION

Agilent acquires AI technology developed by Virtual Control to enhance lab productivity

www.pharmabiz.com; 19th February, 2022

Agilent Technologies Inc. announced it has acquired advanced artificial intelligence (AI) technology developed by Virtual Control, an AI and machine learning software developer that creates innovative analysis solutions in lab testing. Agilent will integrate the software, known as ACIES, into its industry-leading gas chromatography and mass spectrometry (GS/MS) platforms to improve the productivity, efficiency and accuracy of high-throughput labs the company serves around the world.ACIES automates the labor-intensive task of gas chromatography/mass spectrometry data analysis improving efficiency in the laboratory workflow, from sampling to reporting. Agilent will integrate the technology into its MassHunter software package for LC/MS and GC/MS instruments.The acquisition is Agilent's latest investment in digital technology to improve lab productivity. It builds on the company's existing investments and innovations to advance the analytical lab and transform its capabilities with new technology, better integration of instruments and data, and more efficient lab workflow.

Remix collaborates with Janssen to advance small molecule therapeutics using REMaster drug discovery platform to modulate RNA processing

www.pharmabiz.com; 19th February,2022

Remix Therapeutics (Remix), a biotechnology company, announced a strategic collaboration with Janssen Pharmaceutica NV, one of the Janssen Pharmaceutical Companies of Johnson & Johnson, for the discovery and development of small molecule therapeutics that modulate RNA processing using Remix's REMaster drug discovery platform. The agreement was facilitated by Johnson & Johnson Innovation. Under the terms of the agreement, Remix will receive an initial payment of $45 million in cash for upfront and research funding, and may also receive preclinical, clinical, commercial, and sales milestone payments and tiered royalties for any resulting products. In exchange, Janssen will have exclusive rights to three specific targets with applications in immunology and oncology. Remix will have the ability to opt into a portion of the costs of clinical development on one program in exchange for higher royalties. Under the agreement, Remix is eligible to receive total payments potentially exceeding $1 billion, subject to regulatory approvals and other conditions.

Moderna, ROVI expand collaboration to manufacture mRNA medicines over next ten years

www.pharmabiz.com; 17th February,2022

Moderna, Inc., a biotechnology company pioneering mRNA therapeutics and vaccines, and Laboratorios Farmacéuticos Rovi, S.A. (ROVI), a pan-European pharmaceutical company, announced a long-term collaboration to increase capacities for the compounding, aseptic filling, inspection, labelling, and packaging of ROVI's facilities, located in Madrid, San Sebastián de los Reyes and Alcalá de Henares. This new agreement, which has a term of ten years, includes a series of investments expected to allow the manufacturing capacity to increase across ROVI's facilities in Madrid, Spain. In addition to producing Moderna's Covid-19 vaccine, ROVI's platform could also be utilized to service future Moderna mRNA vaccine candidates. In 10 years since its inception, Moderna has transformed from a research-stage company advancing programs in the field of messenger RNA (mRNA) to an enterprise with a diverse clinical portfolio of vaccines and therapeutics across seven modalities, a broad intellectual property portfolio in areas including mRNA and lipid nanoparticle formulation, and an integrated manufacturing plant that allows for both clinical and commercial production

at scale and at unprecedented speed.ROVI is a pan-European pharmaceutical company specializing and engaging in the research, development, contract manufacturing and marketing of small molecules and biological specialties.

Adcentrx, AvantGen ink three-year partnership to discover antibodies for novel antibody-drug conjugates

www.pharmabiz.com; 16th February,2022

Biotechnology company, Adcentrx Therapeutics and AvantGen, biotechnology company, announced a three-year, multi-target partnership for the discovery of antibodies to be developed into novel ADC therapeutic candidates. Under the terms of the collaboration, Adcentrx will specify targets against which AvantGen will screen for novel antibodies using its yeast display system. Adcentrx will be responsible for engineering the antibodies into ADC therapeutic candidates and has worldwide development and commercialization rights. AvantGen will be eligible to receive milestone payments for achievement of certain development milestones Adcentrx is a biotechnology company focused on accelerating breakthroughs in protein conjugate therapeutic development for cancer and other life-threatening diseases.AvantGen, Inc is a leader in the use of yeast display technology for antibody discovery and optimization. Founded by experts in the creation of antibody discovery and optimization platforms, AvantGen excels in the rapid generation of antibodies for therapeutic, diagnostic and research tool applications.

RESEARCH

Study suggests increased risk of mental health disorders after COVID-19 infection

www.worldpharmanews.com;17th February, 2022

A study published by The BMJ finds that COVID-19 is associated with an increased risk of mental health disorders, including anxiety, depression, substance use, and sleep disorders, up to one year after initial infection. A comprehensive assessment of the mental health manifestations in people with COVID-19 at one year has not yet been undertaken. To address this, researchers used data from the US Department of Veterans Affairs national healthcare databases to estimate the risks of mental health outcomes in people who survived at least 30 days after a positive polymerase chain reaction (PCR) test result between March 2020 and January 2021. They identified data for 153,848 individuals and matched them to two control groups without covid-19: 5,637,840 contemporary controls and 5,859,251 historical controls who predated the pandemic. Participants were mostly white men with an average age of 63 years. The COVID-19 group was further divided into those who were or were not admitted to hospital during the acute phase of infection, and information was collected on potentially influential factors including age, race, sex, lifestyle, and medical history. The researchers then followed all three groups for one year to estimate the risks of a set of prespecified mental health outcomes, including anxiety, depression and stress disorders, substance use disorders, neurocognitive decline, and sleep disorders. Compared with the non-infected control group, people with COVID-19 showed a 60% higher risk of any mental health diagnosis or prescription at one year (equivalent to an additional 64 per 1,000 people). When the researchers examined mental health disorders separately, they found that COVID-19 was associated with an additional 24 per 1,000 people with sleep disorders at one year, 15 per 1,000 with depressive disorders, 11 per 1,000 with neurocognitive decline, and 4 per 1,000 with any (non-opioid) substance use disorders.

BriOri BioTech's topical formulation of rofecoxib receives US patent

www.pharmabiz.com; 17th February, 2022

BriOri BioTech, an emerging pre-clinical stage biotech company, announces it has received a March 1, 2022, patent issue notification for "Topical Compositions Containing Rofecoxib and Methods of Making and Using the Same." This patent covers a reformulation of rofecoxib, a COX-2 specific NSAID, from an oral to topical formulation with the intention of alleviating osteoarthritis related pain of the knee and joint pain, and reducing the need for opioids in certain patient populations. With the global market for topical pain relief treatments estimated to be $8.8 billion in 2019 and projected to grow to $12.2 billion by 2027, BriOri BioTech aims to bring a safer and more effective solution to the market to meet a large unmet need. Their novel topical reformulation called Relva, of rofecoxib, will likely be significantly safer than the oral NSAIDs due to a lower systemic exposure than OTC NSAIDs like Aleve or Advil or prescription COX-2 NSAIDs like Celebrex, while providing strong, non-addictive pain relief. With more years of experience with NSAIDs and topical NSAIDs than any other private company and proven success in several development and commercialization arcs, the team at BriOri BioTech is working to repurpose oral NSAIDS to topical formulations. Oral therapeutic doses have been shown to cause gastrointestinal bleeds and cardiovascular events. These adverse side effects are dose dependent. The higher the dose the more GI and CV events. Topical NSAIDs applied to the point of pain will reduce the systemic exposure to help reduce serious adverse side effects while alleviating pain. BriOri BioTech's pre-clinical research to date has indicated the company's product formulation will most certainly outperform the competition. These findings include: 3x better human skin penetration than competitors; Lower systemic exposure than oral dosing; Accumulates in the synovium more than oral dosing; Superior pain efficacy to oral dosing at 8 hours and 24 hours; Mini-pig Draize scores (skin irritation) all zero.

Study shows new drug combination more effective against SARS-CoV-2

www.worldpharmanews.com;14th February, 2022

Researchers at the University of Maryland School of Medicine (UMSOM) and University of Pennsylvania Perelman School of Medicine have identified a powerful combination of antivirals to treat COVID-19. The researchers showed that combining the experimental drug brequinar with either of the two drugs already approved by the U.S. Food and Drug Administration for emergency use, remdesivir or molnupiravir, inhibited growth of the SARS-CoV-2 virus in human lung cells and in mice. Their findings suggest that these drugs are more potent when used in combination than individually. The researchers identified 122 drugs that showed antiviral activity against the coronavirus. One drug identified was remdesivir, which has been FDA-approved to treat COVID-19 infection via injection through an IV, and another was molnupiravir, which comes in a pill that was authorized for use in December. These drugs look similar to one of the four RNA-building blocks that comprise the genetic sequence of the virus. Remdesivir gets incorporated into the RNA when the virus replicates and essentially stops it from making copies of itself. Molnupiravir gets incorporated into the replicating virus and causes its genetic sequence to change - essentially mutating the virus so it cannot grow.Another category of drug candidates they identified prevents the virus from making the RNA building blocks the virus needs to replicate. One of these included the experimental drug brequinar, which is currently being tested in clinical trials as a COVID-19 treatment and as part of a potential combination therapy for cancer. The team hypothesized that combining brequinar with one of fake RNA building block drugs, such as remdesivir or molnupiravir, could work synergistically to create a more potent effect against the virus.

CAMPUS NEWS

Bharati Vidyapeeth's Poona College of Pharmacy, Pune, Maharashtra

AICTE sponsored STC on National Education Policy 2020

One-week AICTE sponsored short term course (STC) on National Education Policy 2020 was organized by Bharati Vidyapeeth's Poona College of Pharmacy, Pune from 17th to 22nd January, 2022. The Chief Guest and Keynote speaker of the inauguration of STC was Hon. Col. B. Venkat (Director, Faculty Development cell, AICTE). The Chief Guest for the valedictory function was Dr. V.K. Mourya (Principal, Govt. College of Pharmacy, Aurangabad). Total 69 participants from all across the country participated in the STC. The program was coordinated by Dr. Hemant K. Jain.

Graduate School of Pharmacy, Gujarat Technological University

International Conference on New Horizons of Natural Products and AYUSH Remedies

The International Conference on 'New Horizons of Natural Products and AYUSH Remedies' and 25th National Convention of Society of Pharmacognosy was organized from 27th to 28th November, 2021 by Graduate School of Pharmacy, Gujarat Technological University in association with the Society of Pharmacognosy at GTU campus, Ahmedabad in hybrid mode. Prof. (Dr.) Pramod Yeole, Vice-Chancellor of Dr. Babasaheb Ambedkar Marathwada University, Aurangabad and Acting President, Pharmacy Council of India graced and inaugurated the event as chief guest. Dr. U.K. Patil, General Secretary of Society of Pharmacognosy gave an overview of the activity of the Society along with the Lifetime Achievement Award 2021 being conferred upon Prof. N.M. Patel. Prof. Bhushan Patwardhan, National Research Professor, AYUSH, in his address on pharmacognosy research in pandemic conveyed that COVID-19 therapeutics needs safer drugs to treat infections, immunological and mental health problems and also stated that Pharmacognosy-based drug discovery, development and repurposing can play an important role in offering promising candidates, especially Ayurveda-based immunomodulators have shown beneficial effects in moderate cases of COVID-19. He also mentioned that the Ayush Clinical Case Repository (ACCR) Portal is conceptualized and developed by the Ministry of Ayush as a platform to support both Ayush practitioners and the public. Prof. Sanjay M. Jachak, Head of Department of Natural Products, NIPER, Mohali, in his address on 'Translational Research in Drug Discovery and Development from Natural Products' conveyed that the last four decades have shown the importance of natural products in drug discovery with about 50 percent of natural compounds competent of being formulated into drugs. Dr. Kamalesh Prasad, Senior Principal Scientist, Central Salt & Marine Chemicals Research Institute, Bhavnagar, Gujarat, discussed the pharmaceutical potential of seaweeds and products derived from them. Total 45 posters and 48 oral presentations were presented by the participants on six different themes with about 200 delegates mainly from 30 pharmacy colleges of 12 states participating and benefitting from the proceedings. Mr. Uday Vegad and Ms. Jigna Vadalia served as coordinators of the event.

Annamacharya College of Pharmacy, Rajampet, Kadapa district, Andhra Pradesh

World Cancer Day 2022– An Awareness Program

An awareness program to celebrate World Cancer Day 2022 was conducted by Annamacharya College of Pharmacy, Rajampet, Kadapa dist, Andhra Pradesh. Principal, Dr. D. Swarnalatha, pledged with students and enlisted various healthy food ingredients that can help prevent many cancer diseases. The Secretary, Sri. C. Gangi Reddy; Vice Chairman, C. Yella Reddy; Treasurer & Executive Director, Sri. C. Abhishek Reddy, and Chairman, Dr. C. Ramachandra Reddy were among the dignitaries present in the program.

Amar Shaheed Baba Ajit Singh Jujhar Singh Memorial College of Pharmacy, Bela (Ropar)

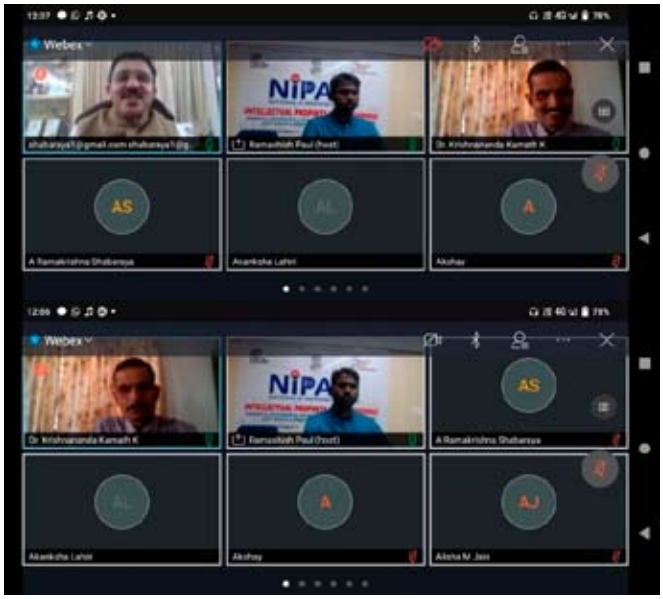
World Cancer Day

Amar Shaheed Baba Ajit Singh Jujhar Singh Memorial College of Pharmacy, Bela (Ropar) celebrated World Cancer Day on 4th

February, 2022 through online mode. Dr. Shailesh Sharma, Director, emphasized the need for awareness about the disease. He discussed about the various types of cancers and also pointed out that along with pollution and stress due to excessive use of technology, an unhealthy lifestyle of people was also one of the reasons for the disease. He also stated that the college's work on various projects on cancer research with government grants and has also published many papers and obtained patents. Dr. Ajay Singh Kushwa, Head of Department, Pharmacology delivered the Vote of Thanks.

Srinivas College of Pharmacy, Mangalore, Karnataka

Webinar on Intellectual Property Rights (IPR)



On the occasion of the 75th anniversary of Independence, the Government of India has begun a mission to spread awareness on IPR under the scheme National Intellectual Property Awareness Mission (NIPAM). As a part of this mission, Office of the Controller General of Patents and Designs Trademarks (CGPDTM), in association with Srinivas College of Pharmacy, Mangalore, conducted a live online webinar on awareness programs on IPR on 11th February 2022 at 11:00 am by Mr. Ramashish Paul, Examiner of Patents and Design in Intellectual Property Office, Chennai under DPIIT, Ministry of Commerce & Industry, Chennai. This awareness program exposed the students of the institution to various types of IPR. Convener of the programme Dr. A. R. Shabaraya, Principal, Srinivas College of Pharmacy and President, Indian Pharmaceutical Association, D.K District Local Branch, Mangalore introduced the Chief Guest and welcomed the delegates. Dr. Krishnananda Kamath initiated and proposed a vote of thanks. Coordinators Dr. EVS Subramanyam, Head, Department of Quality Assurance, Mr. Viresh K Chandur and Mr. Shripathy D were present during the programme. Nearly 200 delegates from various Pharmaceutical fields registered and attended the webinar and made it a successful one.

Kasthooribha Gandhi Pharmacy College, Namakkal, Tamil Nadu

One day National Webinar

Kasthooribha Gandhi Pharmacy College, Rasipuram, Namakkal District, Tamil Nadu organized a one day national webinar on 'Recent Trends in Analytical Instruments Calibration and Validation' on 10th February 2022. The session was inaugurated by Chairman Mr. K. Chidambaram and Dr. M. Senthilraja, Principal welcomed the gathering of the webinar. The speaker of the session was Mr. Poornachnadra M. N. Shetty, Associate Professor, Akshya Institute of Pharmacy, Tumkuru, Karnataka. More than 250 people participated in the webinar. The session was quite interesting and useful to all the budding pharmacists and other delegates about how to calibrate glassware and equipment in the present scenario pre and post covid-19 in the laboratory conditions and Pharma Industry. Finally, the vote of thanks was given by Mr. C. Manikandhan, Associate Professor and the session was ended by National Anthem.

Ph.D. Award

Name: Dr. Kiran Chandrakant Mahajan

Title: Formulation and Optimization of Self Emulsifying Drug Delivery System for Effective Anthelmintic Therapy

University: Savitribai Phule Pune University, Pune.

Guide: Dr. Smita S. Pimple, Professor, Modern College of Pharmacy, Nigdi, Pune.

Name: Dr. Rajni Bhanot

Title: Formulation and Optimization of Fast Dissolving Dosage Form of Anti-Emetic Drugs

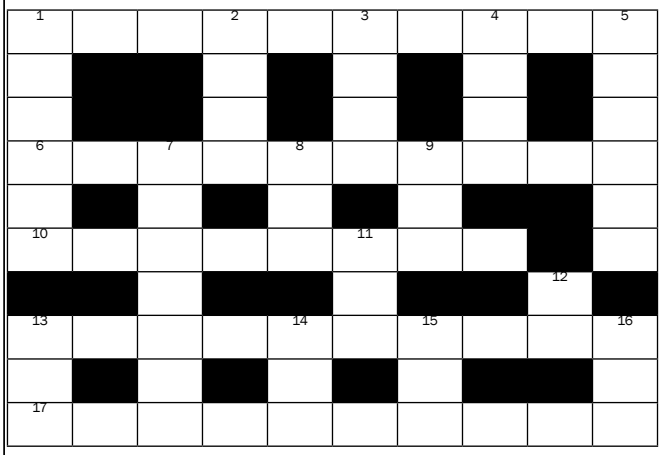
University: IKG- Punjab Technical University, Kapurthala, Punjab

Guide: Dr. Shailesh Sharma, Professor, Amar Shaheed Baba Ajit Singh Jujhar Singh Memorial College of Pharmacy (An Autonomous College) BELA, Ropar Punjab

PHARMA WITS AND LEISURE

- Raj Vaidya

PHARMA CROSSWORD 67



CLUES

ACROSS

1. The alkynes have this strong 'tie' (6,4)
6. Reaction in which 2 aldehydes get converted into an alcohol and acid (10)
10. The brain 'prefix' [1st 8 of 9 letters] (8)
13. Breaking down intermolecular bonds of starch with heat and water (10)
17. Tablet made by pressure in machine and not a pill made by hand (10)

DOWN

1. Lozenge, Pastille (6)
2. The new name for our TB programme [in reverse direction] (1,1,1,1)
3. All PPIs end in these letters [in reverse direction] (4)
4. The renal hormone made by the gland which caps the kidney [in reverse direction, 1st 4 of 11 letters] (4)
5. When 2 iodines sit on a molecule, they call it (6)
7. This is put into culture medium to grow more microbes (last 7 of 8 letters) (7)
8. Pressure in the organ of sight (1,1,1)
9. The suffix for 'organisms' (3)
11. India's Homeo version of I.P. (1,1,1)
12. The syndrome when tumours produce lots of gastrin [in reverse direction] (1,1)
13. The grand seizure fit (1,1,1)
14. The coal shampoo for psoriasis (3)
15. The health Dept. in UK (1,1,1)
16. The point at which colour changes in a conical flask (3)

PHARMA MUMBO-JUMBO - 67-

Unscramble each of the following 6 sets of letters to form pharma related words. Then select the letters in the circles, and use each letter once, to make another pharma related 13 – letter word taking clue from the hint provided.

OLTC	X	X	(X)	(X)		
AAPMLS	(X)	X	X	(X)	X	(X)
ZMEEYN	(X)	X	X	X	X	(X)
RAETH	X	X	X	(X)	(X)	
KTOERS	(X)	X	X	X	(X)	X
IIBRRN	X	X	X	X	(X)	(X)

Clue: The first drug attack in case of 'attack'

Master Word ◯◯◯◯◯◯◯◯◯◯◯◯◯

This Quiz is open to IPA members only.

You need to send your completed entries, along with your name, designation/affiliation, address, contact details, and IPA membership number to **pharmatimesquiz@ipapharma.org.** You can complete the quiz on this page itself & scan the page & mail it to us. Alternatively, you can download the quiz from the IPA website at **www.ipapharma.org** & send it across.

The first 3 correct entries (a correct entry is one in which both the quizzes – crossword and unscramble – are all correct) would be declared winners of the quiz.

Last date for receiving entries : April 20th, 2022

Read the May 2022 issue for the quiz results & the names of the winners !!

PHARMA CROSSWORD - 66

1P	A	2R	O	3X	Y	S	4M	A	5L
O	■	E	■	A	■	■	A	■	E
6L	A	T	E	N	T	■	S	■	V
Y	■	I	■	T	■	7I	T	R	O
8M	E	N	T	H	O	L	■	■	D
E	■	A	■	O	■	9E	C	H	O
10R	O	L	■	11M	H	U	■	■	P
A	■	■	12R	A	■	13M	14R	N	A
S	■	■	A	■	15K	■	O	■	■
16E	X	C	I	P	I	E	N	T	S

PHARMA MUMBO JUMBO 66

Unscramble each of the following 6 sets of letters to form pharma related words. Then select the letters in the circles, and use each letter once, to make another pharma related 13 –letter word taking clue from the hint provided.

DOLBO	X	X	(X)	(X)	X		BLOOD
RBIEF	X	(X)	X	(X)	X		FIBRE
ELESVS	(X)	X	X	(X)	X	X	VESSEL
RANWOR	(X)	X	X	(X)	(X)	X	NARROW
RTTCA	(X)	X	(X)	(X)	(X)		TRACT
LCUEMS	X	X	(X)	(X)	X	X	MUSCLE

Clue: Agent reducing inner diameter of walls

- **Master word :** VASOCONSTRICTOR

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