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IDMA BULLETIN

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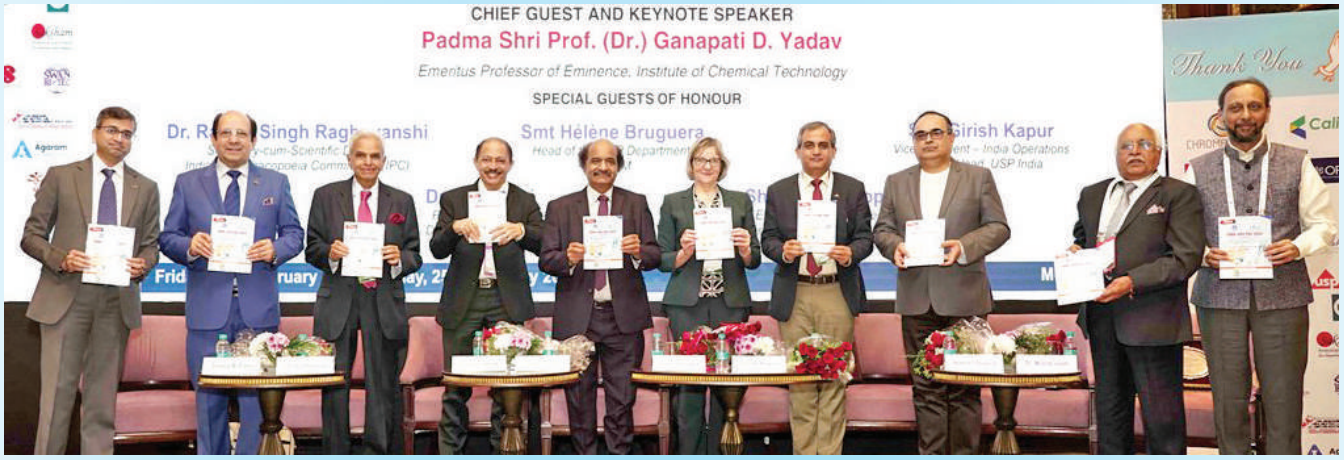
SPECIAL EDITION
22nd IDMA – APA Pharmaceutical Analysts' Convention (PAC) 2023

INDIAN PHARMA - GLOBAL HEALTH CARE

INDIAN DRUG MANUFACTURERS' ASSOCIATION



22nd IDMA-APA PAC 2023 Souvenir released

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22nd IDMA – APA Pharmaceutical Analysts' Convention (PAC) 2023 – A Report

IDMA along with Association of Pharmaceutical Analysts (APA) organised the Two-Day 22nd Pharmaceutical Analysts' Convention (PAC) on Friday, 24th and Saturday, 25th February 2023 at Hotel Four Seasons, Mumbai on the theme **"Towards Creative Global Quality & Compliance".**

The Convention was well-attended with participation of over 250+ persons comprising of delegates, speakers, invitees, supporters, etc. from more than 90+ companies. The delegates included professionals and experts from various disciplines such as Pharma Analysis, Quality Control, Quality Assurance, Regulatory, Production, R & D and many others from Academia, Marketing, Media etc. **This year PAC was well graced and supported by The European Directorate for the Quality of Medicines & Healthcare (EDQM), Indian Pharmacopoeia Commission (IPC) and USP India.**

The event was supported by over 23 companies. The major supporters were as follows:

Caliber Technologies Pvt. Ltd.	Saga Lifesciences Ltd.
Chromachemie Laboratory Pvt. Ltd.	Thermofisher Scientific India Pvt. Ltd.
Image Pro Vision Technology Pvt. Ltd.	United States Pharmacopoeia (USP) India Pvt. Ltd.
Micro Labs Ltd.	Waaree Energies Ltd.
Optel Vision India Pvt. Ltd.	

The other supporters were as follows:

ACG Group	Saksham Analytical Instruments Pvt. Ltd.
Agaram Technologies	Sotax India Pvt. Ltd.
Cleanchem Laboratories LLP	Spinco Tech Systems LLP
Electrolab India Pvt. Ltd.	Spookfish Innovations Pvt. Ltd.
LGC	Swan Biotech Pvt. Ltd.
Manisha Analytical Labs P. Ltd.	Toshvin Analytical Pvt. Ltd.
Mercury Laboratories Ltd.	Valgenesis

Mr Daara B Patel, Secretary General, IDMA commenced the inaugural session of PAC 2023 with his welcome address and mentioned that it gives him great pleasure to welcome all at this prestigious convention, which is the most sought after event and is also known as the flagship event of IDMA. He further added that this is the 22nd Pharmaceutical Analysts' Convention which is popularly known as PAC. He informed the august gathering that our National President, Dr Viranchi Shah would be joining us shortly.

Mr. Patel said that we would be having some wonderful deliberations with the excellent speakers lined up for both the days and on very relevant topics. He assured the august gathering that this PAC would really be worth the wait as the event was happening after a period of three years.

Mr. Daara B Patel welcomed the dignitaries on the dais

- Padma Shri Prof G. D. Yadav, Emeritus Professor of Eminence, Institute of Chemical Technology
- Ms. Hélène Bruguera, Head of the CEP Department, EDQM
- Mr. Girish Kapur, Vice President – India Operations & Site Head, USP India
- Dr. Ajit Dangi, President & CEO, Danssen Consulting
- Mr. Nikhil Chopra, CEO & Whole Time Director, J B Chemicals & Pharmaceuticals Ltd.
- Dr. Vinay Nayak, Chairman, Quality Management & Technical Committee – IDMA.
- Dr. Milind Joshi, Member, Quality Management & Technical Committee – IDMA

He also welcomed our Past National President Dr. Gopakumar G Nair, Our Senior Vice President Mr. Bharat Shah and our Vice President, Western Region Dr. George Patani. He welcomed Mr. Shirish Belapure from IPA and all the other senior members from IDMA as well as from the various pharmacopoeias.

Mr. Patel informed the august gathering that the PAC's journey began almost 22 years ago when a couple of diehard supporters of the Pharmaceutical Industry, especially the analysts came together and they thought that the analysts have to be given the right status, the right importance. Thus forming the Association of Pharmaceutical Analyst (APA). He said that Bulk drug or a formulation is only the creation. But what is important is the complete analysis and the entire process which goes into creating this creation and this is done by the analysts and over the years the position of the analyst has improved and has been evolved. He said that PAC has had some excellent speakers in the past USP Chief, the IPC Chief and also USFDA were with us. EDQM, Anvisa have been with us. We believe in harmonization; we don't want the Indian pharmacopeia to be in isolation. We want such sort of a harmonization that it becomes easy for our manufacturers to fall in line while meeting the Global challenges, Global standards so that is why the PAC is considered very important and he once again welcomed everyone. Mr. Daara B Patel facilitated the inaugural session in his own usual dynamic style.

Dr. Vinay Nayak, Chairman, Quality Management & Technical Committee, IDMA, set the Context for the day's proceedings. He said that this program has been very carefully crafted to meet the expectations of the industry at large, be the Chemical Engineer who is in the API manufacturing, be the R&D personnel who is developing the products, be somebody from the laboratories, the program will cover all these aspects in the coming two days. He gave an example of Dr. Dangi who started as a chemist and went on to become the Managing Director of Johnson and Johnson and today he is consultant to so many companies including the Government of India. **He said that Dr Dangi is an inspiration to all of us.**

Dr Nayak mentioned that many of the companies are now continuously face inspections and the challenges have increased incredibly. He said that the pharmacopeia is also upgrading at a very fast pace, in 1980 we were relying on UV spectra and IR for identifying the impurities, but today even small impurities are tested by GCMS and LCMS. The level of people's understanding has to be very good and thus comes the area of training and sharpening your minds to deliver. He said that this PAC we would be having very interesting topics and he hopes that everyone would have a very fruitful session. He hopes that what the delegates anticipates and what is delivered in this conference will be matching the expectations of the delegates. Dr Nayak personally thanked everyone - the participants as well as the speakers from the bottom of his heart.

Ms Hélène Bruguera, Head of the CEP Department, EDQM is an graduated in Biochemistry from the University of Nancy, France and has obtained a Master in Industrial Pharmacy from the University of Strasbourg, France. She joined EDQM in year 2000 and she is currently the Head of the Certification Department. She deals with the management of CEP applications as well as the EDQM inspection programme for active substances manufacturers. She is also involved in international platforms related to the quality of medicines and active pharmaceutical ingredients (ICH, IPRP).

Ms Hélène thanked the organizers and extended greetings from Dr Petra Dorr. She said that Dr Petra Dorr is the new Director of EDQM and has wished all the very best to everyone for the success of this convention. She further mentioned that Dr Petra Dörr was pleased & impressed with the theme of the convention **"Towards Creative Global Quality & Compliance"**.

Ms. Helene said that Dr. Petra Dörr strongly believes that such events are necessary to ensure continuous dialogue to share experiences and to cooperate and to address the challenges globally. It is a unique mission to contribute to good quality medicines and to protect human and animal health by engaging with experts and stakeholders.

Ms. Helene said that the European pharmacopeia began its journey almost 60 years ago in 1964 when eight countries committed to signing a convention in order to equip Europe with one unique reference tool for the quality of medicines. She further added that today

39 countries are pulling resources to build together the European pharmacopeia which is in its 11th edition and which contains almost 3000 quality standards. She further added that given the globalization of pharmaceutical activities, regulators and pharmacopoeias worldwide are actively seeking to exchange information and to move towards International Harmonization, regulatory convergence and reliance. She said that keeping this in mind EDQM is very happy that the Indian Pharmacopoeia Commission had granted observer status to the EP in 2016 wherein Indian experts have formed technical groups like the PDG (a Pharmacopoeial discussion group) to work together and bring together the European Pharmacopeia, the Japanese pharmacopeia and the US Pharmacopoeia. She said that WHO has welcomed the Indian Pharmacopoeia Commission last year in October as the first participant in their plans for global expansion this is indeed a critical step towards expanding the recognition of harmonized pharmacopoeia standards and to facilitate global convergence.

Ms. Helene mentioned that the European Pharmacopeia conducts the Certification of Suitability Procedures which was established 30 years ago and has been remarkably expanding. She said that this CEP has significant benefits to the industry and regulatory authorities. The procedure enables the European pharmacopeia to revise its monographs and to keep state-of-the-art by providing information on the quality of substance available in the market. She further said that the COVID-19 pandemic hit the planet in an unexpected manner and it created significant challenges for human beings and for health systems including regulatory authorities and the victims as well. But this also generated creative ideas to overcome the challenges and it allowed stronger cooperation between industry and regulatory authorities and these priorities were the key to achieving global convergence. She concluding by saying that EDQM were collaborating with Indian organizations for many years and we are very much looking forward to continuing dialogue and cooperation.

Mr. Girish Kapur, Vice President, India Site Operations & Site Head, USP India. He is a member of USP's Global Leadership Team, Global Science & Standards and Operations Division Leadership teams. Currently he also heads the Global Scientific Affairs team at USP. He champions initiatives related to advancing multiple activities out of India units and has played a key role in footprint expansion and capability building during his tenure at USP.

Mr. Girish Kapur thanked IDMA and on behalf of USP welcomed all the dignitaries on the Dais along with IDMA members, Industry leaders and Government representatives, IP members and representatives from different pharmacopoeias and Subject Matter Experts (SME) who were present to attend the 22nd PAC Pharmaceutical Analysts' Convention. He said that it was his privilege and honour to represent US Pharmacopeia at such a milestone event and share his thoughts with such a highly distinguished and August gathering.

Mr. Girish Kapur said that US Pharmacopeia is an independent scientific not-for-profit organization and for over 200 years (this is the 203rd year) of existence of USP which was established in 1820. He said that since then USP has worked to build trust where it matters most in the world's medicines, dietary supplements and foods. Through our rigorous scientific efforts and quality standards USP helps to protect patient safety and improve the health of people around the world. He said that USP envisions a world where all have access to high quality safe and beneficial medicines. USP standards are trusted around the world, recognized and accepted in more than 140 countries across the world and in several countries they are governed by specific laws and regulations. He further said that this gathering will provide a good insight wherein most of the problems can be resolved. He said that this forum also provides robust platform for all key stakeholders to interact, to think and to share with US Pharmacopeia and learn from each other and also network and see what are the strengths of different participating companies.

Mr. Girish Kapur mentioned that the contribution of IDMA to the Pharma Industry is great, since it was established in 1961. He further said that IDMA has been of immense help to USP standard setting process and as well as USP gets a lot of collection of monographs from manufacturers (IDMA Members) and this helps in developing the standards which eventually protects the patient safety. He said that key partners USP and IDMA have come together on several platforms and have done various conferences seminars for the larger awareness of industry.

Mr. Girish Kapur mentioned that USP would like to acknowledge and put it on record the contributions and

take this partnership forward to strengthen our professional relationship in order to create the maximum of public health impact. He thanked IDMA for inviting USP to this marquee event and giving him an opportunity to address the audience.

Dr. Ajit Dangi, founder President of Danssen Consulting, a strategy firm specialising in Pharmaceuticals & Healthcare Sector. He currently serves as director on the Board of Atul Bioscience Ltd. He has served as the chairman of the Board of Fulford India Ltd, a subsidiary of Merck & Co. Inc, USA for ten years & also as Director General of OPPI, a premier association of research based international pharmaceutical companies for over seven years. Dr. Dangi is former President and CEO of Johnson & Johnson India Ltd. where he served for 20 years in various capacities. Dr. Dangi is a life member of Indian Pharmaceutical Association & serves as member of its Executive Council. He was conferred 'Life Time Achievement Award' by the IPA in the year 2020.

Dr. Ajit Dangi mentioned to the august gathering that if we scratched him there would be a small analytical analyst as he started his career in this exciting industry as an analyst. He said that Mr. Phillip Crosby who was the Director Global Quality Assurance of a multibillion-dollar American corporation AT&T said that **Quality is free** and defined cost of quality as well as the cost of compliance plus cost of non-compliance. He said that the cost of compliance is the cost of department such as the manpower, the various analytical instruments, reagents used etc. whereas cost of non-compliance is the recalls, above all the reputation of the company which can get attainted. He further said that he championed the concept of Quality is free meaning that an investment in improving the quality is based on four points:

1. The definition of quality is conformance to requirements
2. The system of quality
3. Prevention, the performance standard is Zero defect
4. The measurement of qualities is the price of non-conformance. This point one should continuously strive to reduce because this saving directly goes into the company's bottom line and improving the profitability.

Dr. Ajit Dangi then shared his personnel experiences and the challenges he faced during the start of his career wherein he joined an MNC (American) company after completion of his studies in England as an assistant quality assurance manager. He spoke about their number one product which was a weird combination of Aspirin, Caffeine and Quinine and which he felt should have been called irrational. He said that he went through so many procedures and finally got a new product approved by FDA Maharashtra. Thus saving about 5-6 Crores to the company which was appreciated & applauded by the CEO of the company.

Dr. Ajit Dangi mentioned that the key lessons in this reference is that one should go beyond your responsibility and help your company in improving the profitability by reducing non-compliance. He said that they should remember that they work for a commercial organization wherein improving the sales revenue and profitability are key result areas. He said that they should remember that their job is indispensable and they should notice what's happening around them as it is the evolution wherein survival of the fittest is now being changed to survival of the fastest. He said that the analyst has to be agile, be resilient and continuously keep learning as more importantly you cannot solve tomorrow's problems with yesterday's knowledge and skills.

Mr. Nikhil Chopra, CEO & Whole Time Director, J B Chemicals & Pharmaceuticals Ltd. mentioned that Dr. Dangi was saying that survival of the fittest has changed to survival of the fastest but according to him it is survival of those who are adapt to change. He further said that Indian pharmaceutical industry is worth **approximately US$ 50 billion** with over US$ 25 billion of the value coming from exports and the market is increasing day by day. He said that in this two-day event, we would be talking in a different level, not only about formulation development but analytical part of work which is a very critical part. He said that we would be discussing about the instrument's resources and also, about impurities identification and our focus should be on 99% pure products and eliminating that 1% impurity. He concluded by saying that it is our responsibility that we develop, we analyse, because consumer who purchases our medicine is our responsibility.

Release of the PAC 2023 Souvenir: The Chief Guest accompanied by the other dignitaries on the dais released the 22nd IDMA-APA-PAC 2023 Souvenir. The Souvenir was sponsored by our National President, Dr Viranchi Shah of Saga Lifesciences Ltd.

Inauguration of the Table Spaces Area

The Chief Guest Padma Shri Prof G. D. Yadav, Mr Nikhil Chopra & Dr Ajit Dangi, Ms Helene Bruguera, Mr. Girish Kapoor inaugurated the table spaces area wherein there were 18 Tables Spaces. They visited each tables and inquired about their products.

Padma Shri Professor Ganapati D Yadav is one of the topmost, highly prolific and accomplished engineering-scientists in India. He is the Chairman, National Science, Government of India, which is a very prestigious national honour. He is also the Emeritus Professor of Eminence and the former Vice Chancellor of the Institute of Chemical Technology, Mumbai. He is internationally recognized with over 125 prestigious and rare awards as an academician, researcher and innovator, including his seminal contributions to education, research and innovation in Green Chemistry and Engineering, Catalysis, Chemical Engineering, Energy Engineering, Biotechnology, Nanotechnology, and Development of Clean and Green Technologies. His patented work on the net zero goal, green hydrogen production technology, carbon dioxide refineries and valorisation of (waste) biomass and waste plastics is internationally acclaimed. Currently, he is the President of the Indian Chemical Society and the Maharashtra Academy of Sciences.

Prof. Dr G D Yadav made a presentation on **Applications of Green Chemistry and Engineering for Sustainable & Profitable Pharmaceutical Industry.** He mentioned that many of the green chemistry principles represent a new area of focus to further reduce manufacturing costs, build in greater process robustness, and to reduce the environmental footprint of the industry. The pharmaceutical industry is known for using highly polluting technologies with E-factor ranging from 25-100 (waste/kg useful product) due to complex reactions, different solvents and a series of reactors and separators which are not designed from the first principles but as a multi-product facility. The manufacture of any chemicals, pharma or otherwise has the potential to generate significant amounts of waste by-products and pollutants, such as contaminated solvents, depleted reagents, and air pollutants. This must be taken in perspective, since the medicinal and regulatory requirements of stringent pharmaceutical purity will naturally lead to more waste per kilogram product as compared to making less sophisticated compounds of less stringent purity.

Prof. G D Yadav further mentioned that several named reactions using hazardous reagents and solvents which lead to run-away situations, VOCs, effluents problems etc. It is not the purity, but the type and amount of impurity matters greatly. The development of new pharmaceutical products by organic synthesis over the past few decades has contributed to a revolution in medical care, enabling dramatic reductions in hospitalization, suffering, death and has contributed to luxury, comfort and longevity. However, this achievement is faulty if the environment is adversely affected. With the increasing emphasis on applications of green chemistry and engineering, pharmaceutical process chemists have concentrated their focus and creative energies toward minimizing the environmental impact of their art.

Prof Dr G D Yadav mentioned that Pharma industry is known to use 'crazy' solvents or combination of solvents in successive steps leading-to-difficult-to-purify impurities. Solvents are rampantly and incorrectly used in the pharma industry and not changed due to the DMF restrictions and having profit margins despite using dirty and unsafe processes. Active Pharmaceutical Ingredient (API) manufacturing facilities and drug process development are beset with about 80% of their waste due to Solvent-Focusing on the selection, use, recovery, and disposal of solvents will contribute dramatically to alleviating this problem and the processes can be made greener and cheaper. Use of water, supercritical CO2, ionic liquids coupled with heterogeneous catalysis, and the so-called flow chemistry will be discussed. Making processes safer and greener, using principles of retro-synthesis and safer plants (whether the process in green or not) will provide tremendous challenges and opportunities to chemical engineers, process chemists, and toxicologists. A few examples were discussed. How to use greener and sustainable processes to overcome the aforesaid problems were covered.

Prof. G D Yadav thanked IDMA and wished all the participants fruitful deliberations.

Dr. Viranchi Shah, Ph D, National President, IDMA and Director, Saga Lifesciences Ltd. informed the august gathering that last week Forbes published an interesting article which says that between 2020 and 2050 the economic impact of cancer globally is likely to be the tune of $25 trillion, and this article has considered 99% of the incidences of cancer and the fact that it shows is $25 trillion in terms of the economic impact it would have on lives that would be lost. He said that we have to build a Pharma industry not only for cancer but with cardiovascular diseases, diabetes, communicable diseases, non-communicable diseases with infections and further added that there's a huge responsibility that is set upon us. He proudly mentioned about Cipla's significant contribution wherein in the fight against HIV, Cipla's intervention in bringing down the cost and increasing the availability of the HIV drugs resulted in almost 1/3 of the population of Africa being saved. He said that this is the kind of impact this industry can make.

Dr Viranchi Shah mentioned that India is supplying essential medicines to almost 200 countries across the globe, though this is still the tip of an iceberg. If we do certain things right the Amrit Kal that we all speak about, we can certainly reach there. The first thing would be how do we bring our position from number 3 to number 1 in terms of the generic products that we are manufacturing and how do we continue to focus and strengthen our abilities in leading the world as a number one generic supplier? And the second thing is innovation and we all have realized that without adding innovative products, innovative solutions it is not possible to simply multiply ourselves from $50 to $500 million value. He said that Innovation is a very important area that we are trying to address and mentioned that as Dr. Yadav spoke about the industry and academic interaction or involvement and he is happy to state that a policy soon is likely to come out and in the budget 2023 it was the first budget in the Indian history where innovation in pharma would recognized as a very important area to invest and the government has allocated close to 1250 crores for this year for helping the pharma innovation grow.

Dr. Viranchi Shah further mentioned that as our industry would be taking the innovation solution from academia, so ultimately this money is going to the academic institutes and creating this industry academia interaction or rather partnership for bringing innovative products. He said that the academic institutes will have to rise to the occasion and so will the industry too and if we work hand in hand with each other, he thinks that the entire growth is possible for all of us. He said that today we have with us people who are involved in analysis and quality systems and he said that your role is going to be very important because about 0.04% of the samples that have been picked from the market are spurious in terms of statistics - it is very good, but we still have to improve. Therefore, the analysts working in the industry has a greater role to play because that is where the identity of the industry is created today. We are proud of our nation that it has the highest number of USP approved plants outside the US and a large number of EU approved centres. Half of our country's export goes to US and Europe we also have the largest number of WHO certified sites.

Dr Shah mentioned that this being the 22nd conference that IDMA is organizing and is doing it for 22 long years and there was a break in between due to COVID it only endorses the commitment of IDMA towards focusing on good quality products not only in India but to the world. He once again thanked everyone for coming here, joining us and providing that important interaction within the industry which will help us to achieve our ultimate target of getting to number one in the next 25 years and he wished everyone very good deliberations at the convention.

Awards Ceremony

1. **Prof Dr R T Sane Outstanding Pharmaceutical Analyst of the Year Award: Mr. Sunil Kashiram Rane**

   The Indian Drug Manufacturers' Association and Association of Pharmaceutical Analysts presented **Mr. Sunil Kashiram Rane** the **Prof Dr R T Sane-Outstanding Pharmaceutical Analyst Award 2023** at the 22nd Pharmaceutical Analysts' Convention for the great contribution he has made in the field of Pharmaceutical Analysis & Method Development.

2. **Outstanding Young Analyst of the Year: Mr. Ganesh Suresh Darode**

The Indian Drug Manufacturers' Association and Association of Pharmaceutical Analysts presented **Mr. Ganesh Suresh Darode** the **Outstanding Young Pharmaceutical Analyst Award 2023** at the 22nd Pharmaceutical Analysts' Convention for the contribution he has made in the field of Pharmaceutical Analysis.

3. **Eminent Scientist of the Year Award: Dr Rajeev Singh Raghuvanshi**

   The Indian Drug Manufacturers' Association and Association of Pharmaceutical Analysts presented **Dr Rajeev Singh Raghuvanshi** the **Eminent Scientist of the Year Award 2023** at the 22nd Pharmaceutical Analysts' Convention for the great contribution he has made in the Pharmaceutical Industry.

4. **Lifetime Achievement Award: Padma Shri Prof (Dr.) Ganapati D. Yadav**

   The Indian Drug Manufacturers' Association and Association of Pharmaceutical Analysts presented **Padma Shri Prof (Dr.) Ganapati D. Yadav** the **Lifetime Achievement Award 2023** at the 22nd Pharmaceutical Analysts' Convention for his excellence and great contribution to Science and Engineering.

Vote of Thanks during the Inaugural Session

Dr Milind Joshi, Member, Quality Management & Technical Committee - IDMA proposed the Vote of Thanks during the Inaugural Session. He thanked the participants and dignitaries on the dais and off the dais. He thanked Madam Helene Bruguera, Padma Shri Professor Dr G. D Yadav, Mr. Girish Kapoor, Dr. Ajit Dangi, Mr. Nikhil Chopra, Dr. Viranchi Shah, Dr Vinay Nayak, Mr. Bharat Shah, Dr. George Patani and Mr. Daara Patel along with EDQM, IPC and USP India. He thanked the supporting companies specially Kit Bags Sponsored by Micro Labs Ltd., Souvenir Sponsored by Saga Laboratories and Tea / Coffee Sponsored by Mercury Laboratories. He also thanked all the members of the Regulatory Affairs Committee, Quality Management & Technical Committee, members of the press, the participants/delegates and finally the IDMA Secretariat team for putting together a grand successful event.

22nd IDMA-APA PAC 2023

Prof Dr R T Sane Outstanding Pharmaceutical Analyst Award 2023

The Indian Drug Manufacturers' Association and Association of Pharmaceutical Analysts take immense pleasure in awarding **Mr. Sunil Kashiram Rane** the Prof Dr R T Sane-Outstanding Pharmaceutical Analyst Award 2023 at the **Twenty Second Pharmaceutical Analysts' Convention** for the great contribution he has made in the field of **Pharmaceutical Analysis & Method Development.**

Mr. Sunil Kashiram Rane has obtained his Post Graduate Diploma in Analytical Chemistry from Ruia College, Mumbai. He did his Degree in Chemistry from Mumbai University. He has over 31 years of wide experience in Pharmaceutical industry.

Mr. Sunil Kashiram Rane started his career as QC Analyst, Cipla Limited, Patalganga unit and further promoted as:

- Section Head and Head Quality Control at Cipla Limited Patalganga unit (May 1992 – July 2001)
- Site Quality Control Head at Cipla Limited Goa Unit (Aug 2001 – July 2007).
- Corporate QA (Head Quality IT System, Documentation, Resource Management) at Cipla Limited Vikhroli Mumbai Unit (January 2014 – March 2016).

He is currently serving as a Director, Quality Control in Marksans Pharma Ltd., Goa since 2016.

He has vast expertise in Laboratory operations, Process, Method and Product Development, Quality & Regulatory documentation. He also has Expertise in the planning and preparations of regulatory documents and requirements. He has strong belief in importance of Quality System as backbone to the success of the organization. Building dynamic multidisciplinary teams at manufacturing site. He successfully handled regulatory audits like FDA, WHO, MHRA, USFA, ANVISA etc. He has attended 27 workshops / Training programme.

In recognition of his excellent achievements, we take great pleasure in conferring on him this citation and the prestigious "**Prof Dr R T Sane Outstanding Pharmaceutical Analyst Award 2023"**.

Mumbai
24th February 2023

Dr Viranchi Shah
National President, IDMA

22nd IDMA-APA PAC 2023
Outstanding Young Pharmaceutical Analyst Award 2023

The Indian Drug Manufacturers' Association and Association of Pharmaceutical Analysts take immense pleasure in awarding **Mr. Ganesh Suresh Darode** the **Outstanding Young Pharmaceutical Analyst Award 2023** at the **Twenty Second Pharmaceutical Analysts' Convention** for the contribution he has made in the field of **Pharmaceutical Analysis.**

Mr. Ganesh Suresh Darode passed the B Pharm Examination from Sharadchandra Pawar College of Pharmacy, Pune and M. Pharm in Pharmaceutical Chemistry from Amrutvahini College of Pharmacy, Sangamner, Pune. He has a good academic track record of securing first division in both courses.

Mr. Darode started his career as a Trainee in the AR & D Department at Glenmark Pharmaceuticals Ltd., Sinnar and is currently working as a Research Officer. **Mr. Darode** with his ability to gather, analyze, understand complex data and with a strong academic background, has an excellent hand on pharmaceutical analysis and validation.

In recognition of his achievements and the promising future of his ever-growing career we take great pleasure in conferring on him this citation and the prestigious **"Outstanding Young Pharmaceutical Analyst Award 2023".**

Mumbai
24th February 2023

Dr Viranchi Shah
National President, IDMA

22nd IDMA-APA PAC 2023
Eminent Scientist of the Year Award 2023

The Indian Drug Manufacturers' Association and Association of Pharmaceutical Analysts take immense pleasure in awarding **Dr Rajeev Singh Raghuvanshi** the **Eminent Scientist of the Year Award 2023** at the **Twenty Second Pharmaceutical Analysts' Convention** for the great contribution he has made in the Pharmaceutical Industry.

Dr Rajeev Singh Raghuvanshi has completed his Bachelors and Masters from IIT-BHU (Formerly IT-BHU), Varanasi and PhD from National Institute of Immunology, New Delhi. His PhD work is in the area of Extended Release Formulation of Vaccines, a project conceptualized to help reduce the number of injections required to be given for complete immunization. He has also done ISB-Kellogg Global Advanced Management Program.

After working for 7 yrs at National Institute of Immunology, New Delhi, **Dr Raghuvanshi** moved to join the leading Indian multinational, Ranbaxy Laboratories Ltd., where he worked for development, registration and launch of NDDS, Generics and Branded Generics in various global markets. After having spent 12 years with Ranbaxy, he then moved to another Indian Multinational organisation, Dr Reddy's Laboratories Ltd, Hyderabad.

Dr Raghuvanshi's expertise lies in dosage for design and development, mainly in the domain of pharmaceutical innovation. He has been involved in development of different kind of products like Oral Solids, Oral liquids, Topicals, Injections, Nasal Sprays, Auto-injectors, Sublingual, Mouth Dissolve, Extended Release and Delayed Release for global markets. More than 200 products developed by him and his teams are currently being sold in India, US Europe and Emerging Markets.

Dr Raghuvanshi has 14 granted US patents along with more than 250 published PCTs and Indian Patents. He has more than 25 publications in peer reviewed journals and has co-authored 6 chapters in books. He has been a visiting faculty at NIPER – Hyderabad and IIT-BHU and has taught students of NIPER-Mohali. He is a regular speaker at different International and National conferences on Pharmaceutical Innovation. For his contribution, Dr Reddy's Labs has twice awarded him with "Dr Reddy's Excellence Award". Leadership development has been his passion and many of his team members mentored by him are holding leadership roles in Indian and global pharmaceutical companies. After a very successful career with corporate pharma, he decided to do something completely different and has joined Ministry of Health and Family Welfare, Govt. of India as Secretary-cum-Scientific Director of Indian Pharmacopoeia Commission on 16 Feb '21.

In recognition of his excellent achievements, we take great pleasure in conferring on him this citation and the prestigious **"Eminent Scientist of the Year Award 2023"**.

Mumbai
24th February 2023

Dr Viranchi Shah
National President, IDMA

22nd IDMA-APA PAC 2023
Lifetime Achievement Award 2023

The Indian Drug Manufacturers' Association and Association of Pharmaceutical Analysts take immense pleasure in awarding **Padma Shri Prof (Dr.) Ganapati D. Yadav** the **Lifetime Achievement Award 2023** at the **Twenty Second Pharmaceutical Analysts' Convention** for his excellence and great contribution to **Science and Engineering.**

Professor G. D. Yadav is one of the topmost, highly prolific, and accomplished engineering-scientists in India. He is the National Science Chair of Govt. of India, which is a very prestigious national honour and is Emeritus Professor of Eminence and is the former Vice Chancellor of the Institute of Chemical Technology, Mumbai. As the VC he created several records, brought ICT to an international ranking, with establishment of 2 new campuses in Bhubaneswar and Jalna, creation of 23 new programmes, several centers of excellence and 5 departments.

Professor G. D. Yadav is internationally recognized over 125 prestigious and rare awards as an academician, researcher and innovator, including his seminal contributions to education, research and innovation in Green Chemistry and Engineering, Catalysis, Chemical Engineering, Energy Engineering, Biotechnology, Nanotechnology, and Development of Clean and Green Technologies. His patented work on the net zero goal, green hydrogen production technology, carbon dioxide refineries and valorization of (waste) biomass and waste plastics is internationally acclaimed.

Professor G. D. Yadav serves as the Adjunct Professor at University of Saskatchewan, Canada; Conjoint Professor, University of New Castle, Australia; Distinguished Adjunct Professor, IIT Guwahati and SOA University Bhubaneswar.

Professor G. D. Yadav was conferred Padma Shri by the President of India in 2016 for his outstanding contributions to Science and Engineering. He has been recipient of two honorary doctorates and has addressed 6 convocations of renowned universities. He is elected to the fellowship of all Science and Engineering academies in India, TWAS, RSC (UK), IChemE (UK) among others. He was elected to two prestigious foreign academies: US National Academy of Engineering; only 23 living Indians are elected to this Academy, and as a Fellow of US National Academy of Inventors in 2022 to be the second Indian to be so honoured.

Professor G. D. Yadav has been involved with many prestigious policy making committees of the Central government and as a consultant to industries and industry associations. His research productivity is phenomenal with supervision of 107 Doctoral and 140 Masters Theses, which is the first record for any Engineering Professor in India. Besides, he has supervised 48 post-doctoral fellows, several summer fellows and research staff. He has published 515 original research papers, acquired120 granted national and PCT patents, 8 new patent applications; written 3 books; 16,500+ citations. He is on the board of 6 listed companies as an independent director. He is on the editorial boards of international journals of ACS, RSC and Elsevier. Currently he is the President of the Indian Chemical Society and the Maharashtra Academy of Sciences.

In recognition of his stupendous contribution, we take great pleasure in conferring on him this citation and the prestigious **"Lifetime Achievement Award 2023"**.

Mumbai
24th February 2023

Dr Viranchi Shah
National President, IDMA

Report of 22nd IDMA - APA PAC Technical Sessions Day 1 - 24th Feb 2023

Technical Sessions

The Technical Sessions on Day 1 & Day 2 were facilitated by Dr. Milind Joshi, Member, Quality Management & Technical Committee – IDMA. The following presentations were made by eminent speakers / faculty members during PAC 2023.

Technical Session 1 – Compliance

This Technical Session 1 (One) was Moderated by **Dr Louis Coutinho,** CEO, Nuleap Technologies Pvt. Ltd.

Ms Hélène Bruguera, EDQM commenced the Technical Session with a presentation on

Recent Updates on the EDQM Inspections.

Ms. Helene briefed the august gathering on the EDQM Inspection programme and highlighted the following points:

- Integral part of the Certification of Suitability to the monographs of the European Pharmacopoeia (CEP) Procedure
- Involving manufacturing sites of active substances (APIs) involved in CEP(s), which are required to work under EU GMP Part II
- Aim: to verify the compliance with
  - ✓ submitted CEP dossier
  - ✓ EU GMP Part II & any applicable annex such as 1 for sterile substances, 11 for computerised systems etc.

EDQM on-site inspections

Risk-based selection of sites to be inspected

- Inspections organised by EDQM are performed by team composed of one EDQM inspector and one inspector from an EU/EEA/MRA authority
- Joint inspections may also be performed, e.g. With WHO, USFDA etc.
- Local authorities informed and invited to participate as observers
- A list of deficiencies is issued within 6 weeks, the final report is issued after CAPA evaluation

Ms. Helene informed the gathering about the Outcomes of the EDQM Inspections

- ❖ Positive conclusion:
  - After satisfactory evaluation of CAPA
  - Delivery of an Attestation by EDQM, stating the compliance with the CEP dossier that was subject of the inspection and with EU GMP
  - Granting of a (EU) GMP Certificate by the EEA participating Inspectorate via the EUDRAGMDP database (public information on the EMA website)
- ❖ Negative outcome:
  - In case of critical/major deficiencies to the GMP and/or the CEP dossier
  - Actions taken on the CEP(s) / CEP application(s): suspension or withdrawal
  - Information is published on the EDQM website
  - Statement of GMP non-compliance issued by the EEA Inspectorate (public in EudraGMDP database)

Dr Mrunal Jaywant, Vice President – R&D, USP India delivered a presentation on **Nitrosamine Impurities: Current USP Approaches and Future Strategy.**

Dr Mrunal Jaywant mentioned the following in her presentation

- ✓ Simple to Complex Nitrosamines
  - – The journey so far...
  - – USP's Nitrosamine Program
  - – USP's Tools and Solutions
- ✓ USP's Current Strategy
  - – Non-compendial solution
  - – Pharmaceutical Analytical Impurities
  - – Strategy for excipents

Key findings:

- **Nitrosamines is the topmost impurity of concern for Drug products and Drug substances,** whereas Elemental impurities and Residual solvents top the list in Excipients category.
- **Uncertainty in observing and controlling nitrates and nitrites** levels is noted for each product category.
- This uncertainty level **goes even higher for Excipients**.

Mr. Santosh Savarkar, Head Regulatory Affairs, Umedica Laboratories Pvt Limited delivered a presentation on **Smart Filing - Anticipating Regulators Mind set while Reviewing Submitted Documents for Approval**

Mr. Santosh Savarkar began his presentation with an interesting topic - **Mind Reading**

- Humans cannot literally read the minds of others, but can create mental models so as to effectively intuit people's thoughts and feelings.
- This is known as empathic accuracy, and it involves "reading" cues telegraphed by the words, emotions, and body language of another person.

ICH Harmonisation for better health

- With ICH Q/S/E/M Guidance and Common Technical Documentation Template adopted by all major agencies.
- Many ICH countries already moved to eCTD tree.
- With harmonisation of dossier template across the ICH countries.
- Introduction of electronic CTD format by many ICH countries.
- This aspect also introduced a requirement of regulatory intelligence...
- Improving quality of regulatory filings, study of historical set of queries, documentation and data compliance in line with ICH and Health agency specific guidance is essential...

Regulatory Intelligence – Approaches!!

- Regulatory intelligence can help company to go global. As well as reduce the regulatory risks, achieve faster approvals, and help manage the cost and time impact of global regulatory changes.
- Regulatory intelligence thus allows companies to identify issues and trends and focus on proactive compliance.
- It identifies and eliminates high-risk areas preventing fines and delays in approval.
- It also empowers businesses to make faster and better business decisions.
- Having a correct regulatory inputs of knowledge, helps an organization to respond to the market, legislative, and competitive demands in a timely manner.

Mr. Santosh Savarkar concluded his presentation by mentioning "*You have to apply yourself each day to becoming a little better. By becoming a little better each and every day, over a period of time, you will become a lot better*"

Technical Session 2 – Digitalization / Automation

The Moderator of Technical Session 2 (Two) was **Mr. Kaushik Desai, Member, Quality Management & Technical Committee – IDMA.**

Mr. S G Belapure, Senior Technical Advisor, IPA delivered a presentation on **Excellence in automation & continuous manufacturing**

Mr S G Belapure began his presentation on **Indian Pharma Industry Contributes Significantly**

I. India - 36% lower per person disease burden (DALY,1990-2016)
II. US approx. 40% of all drugs consumed in the USA
III. Global 3rd largest share of drugs by volume

Why Automation & Digitalization?

1) Consistent Quality
2) Sustained Compliance

3) High Productivity

4) Human error avoidance

Mr. John DiBella, Simulations Plus Inc. (through **Electrolab India Pvt. Ltd.)** delivered a presentation on **The Future Is Now: Applying Physiologically-Based Biopharmaceutics Modelling to Accelerate Generic Product Development and Inform Regulatory Decisions**

Mr. John DiBella mentioned in his presentation the Project Summary & Outcomes.

- Mechanistic model was constructed and validated across dose levels using clinical data from products manufactured with NPE API.
- Parameter sensitivity analysis helped define and justify specifications for CMAs (particle size distributions) for the new PE product lots
- Virtual bioequivalence trial simulations showed the population-derived C_{max} and AUC values would be bioequivalent between products manufactured with NPE vs. PE API, within the validated CMA specifications, regardless of the dose

Outcomes

- Regulatory agencies approved the sponsor's bio waiver application
- Sponsor got to market ~12 months before it would have running the full trials.

Mechanistic Modelling Saves Resources Today in R&D and Regulatory Interactions

- Prioritize and make better investments
- Integrate data to tell a compelling story
- Eliminate unnecessary animal/human studies
- Improve productivity to be the first to market
- Reduce regulatory burden
- Improve patient lives

Mr. Samir Haddouchi, Managing Director, SPS Pharma Services, France (through **Sotax India Pvt. Ltd.)** delivered a presentation on **Implementing Automation in the Laboratories**

Mr. Samir Haddouchi mentioned that Automation is already widely used in a pharmaceutical laboratory. He said that in addition, several other automated systems are available and widely used:

- Automated physical testing
- Automated dissolution systems
- Automated sample preparation systems

He mentioned the advantages of using automated systems?

- Productivity
- Time to market
- Safety
- Data quality

He mentioned the two most obvious reason to invest on automated systems:

- ✓ Automated systems can operate a defined process without any interaction of the analyst. This releases time for other added-value activities (i.e. paperwork, method development...).
- ✓ Few full time equivalents may be gained in this manner. The return of investment is usually quite easy to evaluate based on the salary, cost of analysis, etc..

Mr. Samir Haddouchi gave the following take-home Message

- ✓ Using automated systems can help enhancing the quality of data by minimizing analytical variables, ensuring better compliance to methods and complete Data Integrity ➔ Quality and Compliance
- ✓ Implementing automated systems can help improving the productivity. Hence decreasing the testing costs ➔ Productivity
- ✓ Automated dissolution testing can facilitate and speed up the formulation development process ➔ Time to market
- ✓ It is of importance to consider all the laboratory processes to identify the bottlenecks and select appropriate technical solutions.

Mr. Samir Haddouchi concluded by saying **Science should drive Guidance, that will induce Practice. Only then, we will ensure Compliance and then Quality!!**

Mr. Florent Bouguin, VP, Chief Technology Officer, Optel Vision India Pvt. Ltd. delivered a presentation on **The Future of the Pharmaceutical Supply Chains.**

Mr. Florent Bouguin mentioned about the Persisting problem of fake and counterfeit medicines

- Around 11% of all medicines are counterfeited worldwide
- Fake drugs kill more than 2,50,000 children a year
- Counterfeiting is a USD 600 billion market

Mr. Florent said that Supply chain becomes a national security asset

- Localize supply chain and reduce dependencies
- Secure stocks of critical product
- Excise and Taxation
- Inflation Reduction Act
- Green deal

Mr. Florent mentioned about accelerating supply chain digitization, and making your businesses more resilient and sustainable.

Technical Session 3 – Innovations and Compliance

The Moderator of Technical Session 3 (Three) was **Ms. Prathibha Pilgaonkar, CEO, Rubicon**

Ms. Vishakha Metkar, Senior Manager - Regulatory Affairs, Colorcon Asia delivered a presentation on **Excipients – Specifications & Analysis – Need for Global Compliance.**

The following points were the highlights of her excellent presentation:

- **Harmonization of individual monographs is Critical, but cannot occur without harmonization of general test chapters**
  - ✓ Addition of Functional Equivalence of Pharmacopoeias into the strategic framework
  - ✓ Involvement with ICH, PDG Expansion programs
- **Nitrosamine**
  - ✓ continues to be a global issue
  - ✓ excipients are one of the several factors to consider in the potential formation of nitrosamine formation in the drug product.
  - ✓ Communication with suppliers is key where mitigation is needed
- **Residual solvents and Elemental Impurities**
  - ✓ Limited information available with suppliers and very little test data for Elemental impurities, however information for Residual Solvents should be shared by Excipient supplier.
  - ✓ Risk assessment / Specification / testing – communication with supplier is necessary

Mr. Sunil Kumar, Sr. Product Marketing Manager - Mass Spectrometry, Thermofisher Scientific delivered a presentation on **Comprehensive workflow analysis of Extractable & Leachable Analysis**

- **EXTRACTABLE**
  - ✓ Chemical released from process equipment, packaging or delivery system; under laboratory extraction conditions.
- **LEACHABLE**
  - ✓ Chemical that migrates from process equipment, packaging or delivery system; into drug formulation under normal usage conditions.
- **Analysis of Extractables & Leachables: GC-MS, GC-HRMS, Headspace, EI & CI, Library etc**
  - ✓ All QC parameters automatically reported.
  - ✓ -High concentration samples automatically diluted.
  - ✓ -Full compliance and automatic reporting.

Dr. Prabha Maheswaran, Assistant General Manager – SSD, Chromachemie Laboratory Private Limited delivered

a presentation on **Computational Chemistry - helping hand for pharmaceutical compliance including prediction of ADMET behaviour of Nitrosamine**

❖ **Computational Chemistry -pharmaceutical industry**

✓Challenges in pharmaceutical industry- delivering quality products.

- ✓ The issues pertaining to the quality of the product are variable starting material, lack of manufacturing process automation and control, poor understanding of the chemical reaction and product parameters etc.,
- ✓ Quantitative structure activity/property relationships (QSAR/QSPR) of substances – helping hand to reduce the cost and time needed from discovery to market, while at the same time raising standards of quality.
- ✓ Quality risk assessment-In silco calculations act a risk assessment tool to identify the stability, spectral property and toxicity of the molecule.
- ✓ ECHA, EMA article- In vitro, in chemico and in silico studies (e.g. computational tools such as OECD QSAR Toolbox, EPI Suite, ECOSAR, VEGA, T.E.S.T, Catalogic) may increase the robustness of a case.

Computational toxicology -We provide methodology to investigate the toxic potentials of impurities and secure the development according to the ICH M7 guideline.

Computational Spectroscopy- helping hand for characterizing unknown molecule.

Overview – Computational calculations acts as a helping hand to address the issues pertaining to the quality of the product such as toxicity, structure, stability and understanding of the chemical reaction.

Mr. Daara Patel thanked everyone and requested them to join for the dinner.

Report of 22nd IDMA - APA PAC Technical Sessions Day 2 - 25th Feb 2023

Mr. Daara Patel welcomed everyone on the second day and mentioned that today also we have lined up excellent speakers along with two exciting panel discussions. He informed the participants that IDMA is going to present awards for the two best questions and an award for the highest number of Registrations.

Mr. Daara B Patel facilitated the first session on Day 2. He informed the august gathering that Dr. Rajeev Raghuvanshi is appointed as the new DCG(I) of India and due to some work exigencies he is unable to attend this convention. Mr. Patel congratulated Dr Rajeev Raghuvanshi for his elevation to DCG(I) and assured him of IDMA's full support for his future initiatives and activities.

Mr. Patel informed everyone that Dr. Pawan Saini, Senior Scientific Officer at IPC would be delivering a presentation on Dr Raghuvanshi's behalf on the **Updates on Pharmacopoeial Monographs and the future initiatives of IPC**.

Dr. Pawan Saini, Senior Scientific Officer, IPC delivered a presentation on **Updates on Pharmacopoeial Monographs - Future Roadmap**

Brief on Indian Pharmacopoeia Commission (IPC)

✓An autonomous Institute under Ministry of Health & Family Welfare, Government of India

- ✓ Established on 1st January, 2009 to set official standards of drugs in India
- ✓ Three tier structure comprising of the General Body, Governing Body, and Scientific Body
- ✓ Expert Working Groups (EWGs) with subject experts to guide on standards setting

Indian Pharmacopoeia (IP)

1) Book of drug standards as per Drugs & Cosmetics Act 1940. Published by the Indian Pharmacopoeia Commission (IPC)
2) Monograph development by public comments and expert consultations.
3) IP standards are authoritative and legally enforceable
4) Helps ensuring quality of marketed medicinal products in India
5) Contains monographs on APIs, formulations, excipients, veterinary medicines etc.

New Initiatives at IPC with High Impact On Public Health

- Digital IP – Should Be Available by End of FY 2023
- Increasing Inventory and Stakeholder Awareness On Impurity Standards Use and Importance.
- Bringing Dissolution Testing in Prolonged Release Formulation Monographs
- Impurity Limits Harmonized with ICH Recommendation
- Joining PDG Pilot – Global Initiative Towards Harmonization of Pharmacopoeia
- New MoU Being Signed with Ministry of AYUSH and NIPER, Guwahati

<u>Panel Discussion</u>:

CEO's vision for Integrating Business with Quality & Compliance

Session Chairperson : Mr. Mehul Shah, CMD, Encube Ethicals Ltd.

Panellists :

1. **Mr. Manish Doshi,** Managing Director, Umedica Labs & Amoli Organics
2. **Ms. Aditi Kare Panandikar,** Managing Director, Indoco Remedies Ltd.
3. **Mr. Rashesh Gogri**, Managing Director, Aarti Inds. Ltd.
4. **Dr. (Ms.) Satya Ramani Vadlamani**, Chairperson and Managing Director, Murli Krishna Pharma Pvt. Ltd

Technical Sessions

The Technical Sessions on Day 2 were facilitated by Dr. Milind Joshi, Member, Quality Management & Technical Committee – IDMA.

Technical Session 4: Updates on Pharmacopoeial Monographs - Future Roadmap

The Moderator of Technical Session 4 (Four) was **Dr Vinay G Nayak,** Chairman, Quality Management & Technical Committee – IDMA.

Ms. Hélène Bruguera, EDQM commenced the technical session with a presentation on **Updates on the EDQM CEP Procedure.** She mentioned the following:

EDQM Certificate of Suitability (CEP) and CEPs as a model of Reliance

- More than 5900 valid Certificates of Suitability (CEPs) issued to more than1250 manufacturers of pharmaceutical ingredients, mostly located in India (27%) and in China (28%)

- Recognised/relied upon in 70 countries worldwide and WHO

Transparency for CEP documents & guidelines Updated process adopted for CEP public documents & guidelines

- Clear and transparent process which includes public consultation for governance documents, technical guidelines, etc.
- Draft guidelines and forms for comments will be available via the EDQM website (dedicated webpage) and will be announced via news.

The CEP of the Future = the CEP 2.0

- Ongoing project to reshape the CEP and its content
- Goals
  - ✓ Meet the current needs of stakeholders: CEP holders/manufacturers, drug product manufacturers, regulatory agencies (worldwide) including quality assessors
  - ✓ Ease the registration activities linked to the use of CEPs;
  - ✓ Increase the acceptance of CEPs worldwide.

Another on-going project

- Business Process Review for CEP:
  - ✓ **Goal:** assess performance of the procedure with the view of improving it
  - ✓ **Focus:** evaluation and inspection processes performed by EDQM
  - ✓ **External company** supporting the project: QdB group
  - ✓ **Survey** sent to targeted Industry stakeholders (including IDMA)

Deadline extended to 1st March 2023 - Your voice matters!

Mr. Girish Kapur, USP delivered a presentation on **Current trends in Pharmacopoeial Monographs & General Chapters**

Mr. Girish Kapur informed the august gathering that USP is a private Not-For-Profit organization, engaged in the development and revision of compendial standards related to identity, strength, purity, quality, packaging, labeling for drugs (and other products). By sharing scientific expertise and providing technical support and leadership, USP helps regulators across the globe improve and sustain public health and enable manufacturers to supply quality medicines thereby strengthening global supply chain. USP's new Stakeholder engagement model provides opportunities to share their comments at early stage of development. As the world is adopting new technologies and moving towards automation and digitalization, USP is embracing the change and implementing innovative ideas to remain current and relevant. He said that his talk highlights USP's new initiatives that addresses the current needs and future expectations of its stakeholders and provides insights into USP's collaboration efforts with local regulators to achieve our mission.

Dr Antony Raj Gomas, Head of Global OSD & API Quality, Viatris delivered a presentation on **Quality Culture & Compliance**

Dr Antony Gomas informed about **Compliance in traditional sense**

- Men/Machine excepted to operate within SOP/ Control parameters and deviations are flagged.
- Compliance by traditional approach (supervision)is neither efficient nor always effective!

Some of the key elements of quality culture

- From "adherence to compliance" to "achieving Excellence"
- From "Supervision" based assurance to "vision" based assurance.
- Ownership, commitment & compliance at all levels at all times.
- Integrated high performance.
- Learning from mistakes.
- Migrating from "Reactive" assurance of quality to "Pro-active" assurance of quality.

He mentioned few guides and tools for Quality Culture

- USFDA's white paper on QMM
- ISPE's APQ guide

- PDA's culture assessment tool.

He concluded his address with the following points:

- Culture of quality is a journey.
- Several well established approaches are published on facilitating this journey.
- Each organisation, based on its own DNA, needs to adapt and leverage such approaches.
- While it is surely an endeavour that should cover all aspects, there are several low hanging fruits that can be savoured for quicker benefit.
- There is a potential in converting some of the GMP system tools are already existing into culture changing tools by appropriate tweaking.

Technical Session 5 – Quality Management Systems

The Moderator of Technical Session 5 (Five) was **Dr Nandkumar Chodankar,** Founding Promoter, A-Solutions Pharmaceuticals and Member of Quality Management & Technical Committee - IDMA

Ms. Deepsikha Jakate, Abbott commenced the Technical Session 5 with a presentation on **Quality Risk Management and Risk-Based Quality.**

What is Quality Risk Management?

- A particular event that MAY happen
- It's a PROACTIVE measure to reduce the effects or eliminate the risk itself
- It is done through a Scientific Assessment and is ultimately linked to patient safety
- While the level of risk may determine the effort required, what's most important is that all potential risks need to be taken seriously, with patient well-being at the center of everything we do.

How to write a "Good" Risk Statement?

- There is a Risk that .....(What will happen) .....Due to (A condition not being fulfilled or an existing situation) ..... Leading to (What is the ultimate impact)

Example:

There is a risk that the Qualification of FBD may fail due to the unavailability of a trained technician, leading to disruption in the manufacturing schedule which may lead to deviation from the manufacturing plan.

- It is important to know what the risk affects and who owns the risk

Risk-based thinking is defined as "a systematic application of information, knowledge, and actions to address uncertainty and potential opportunity.

- There can be ambiguity in things
- Rely on science and facts for best outcomes in terms of quality
- The objective is to put the patients' well-being at the center of the decision-making.

Examples of Risk Based Quality

- Supplier Management
- Shelf-Life Estimation
- AQL (Acceptable Quality Level)
- Statistical Tools – ppk, cpk (Process Capability) – Predictive Models
- Sampling Plans
- Quality Risk Assessment
- Continuous Process Verifications

Ms. Deepsikha Jakate summarized her presentation by mentioning that an effective quality risk management approach can further ensure the high quality of the product to the patient by providing a proactive means to identify and control potential quality issues during development and manufacturing and post manufacturing Quality surveillance. It is critical to protect patients in terms of quality, safety and efficacy of products and medicines.

Mr. Sekhar Surabhi, Founder, Caliber Technologies delivered a presentation on **INTEGRATED QUALITY MANAGEMENT**

The highlights of Mr Sekhar Surabhi presentation is as follows:

MAKE QUALITY A HABIT -

Process Capability Index, Quality Risk Prediction and other Quality Metrics to ensure you make the right decisions, every time.

INTER-DEPARTMENT CORRELATION - Data is further analysed to arrive at Inter-department correlation & APQR with Artificial Intelligence, Predictive Trend Analysis, etc.

DEPARTMENT ANALYTICS - Data Mart is created by bringing together and analysing data from different sources to arrive at departmental analytics of weak spots, trends, and efficiency analysis

CLEAN DATA - Accurate, Available, Actionable data collection is the foundation of good decision-making.

Dr Sanjay Shetgar, Vice President, NSF - Health Sciences delivered a presentation on **Proactive Quality Management System**

Dr Sanjay Shetgar gave a brief about NSF. He said that NSF is an independent, not-for-profit, non-governmental public health and safety organization. Our mission and focus have always been protecting and improving human health

What Is Quality Management System (QMS)?

A structured collation of business processes that is designed to meet the objectives of the Quality Policy to meet customer and regulatory requirements on a continual basis. An effective quality management system is defined in ICH Q 10 and is commonly referred as the `Pharmaceutical Quality System' (PQS).

Based on ISO 9000:2005 concepts of quality, it includes GMP requirements and complements the ICH-Q8 `Pharmaceutical Development' and ICH-Q9 `Quality Risk Management' Applicable across the product life cycle.

ICH Q10 augments regular GMP by describing specific quality elements and management responsibility

Learning from Regulatory citations

- One mayn't see citations specifically referring to ICH Q10. Legally, 483's must still be referred under the CFR/FD&C Acts
- However, the language used in the warning letters is predominantly related to .... senior management.

Management Review

- Continual improvement of process performance and product quality – performance of manufacturing processes Ex: Yield/Rejection, process capability, defect rate, in-process failure rate, reworks
- Continual improvement of Pharmaceutical Quality System (PQS) – effectiveness of processes.

Ex: CAPA effectiveness, Closure rate of Deviations, Investigations without root cause, Human errors as root cause.

Dr Sanjay Shetgar briefed the august gathering about **Advanced Program in Pharmaceutical Quality Management (APPQM). He appreciated the program and requested everyone interested to** connect with him at NSF or through IDMA.

Featured Innovation

Mr. Sandeep Kulkarni, CEO, Image Pro Vision Inc. delivered a presentation on **Artificial Intelligence based Particle Characterization complying to regulatory requirements**

The highlights of his presentation is as follows:-

Why particle properties are important?

- Better control of product quality
- Improve product performance
- Troubleshoot manufacturing and supply issues
- Better understanding of products, ingredients and processes
- Optimization of efficiency of manufacturing process
- Yield improvement
- Stay ahead of the competition

Role of Particle Characterization

In the pharmaceutical industry, Particle Size, Particle Size Distribution and Particle Shape of active pharmaceutical ingredients (API) is known to strongly affect the stability and aesthetics of drug formulation.

The size and shape of particles used in a pharmaceutical product can impact the dissolution rate

and influence the solubility, adhesion, and dispersion of particles.

Automated microscopic analysis Convert any microscope to an Imaging Workstation

Disruptive Capabilities

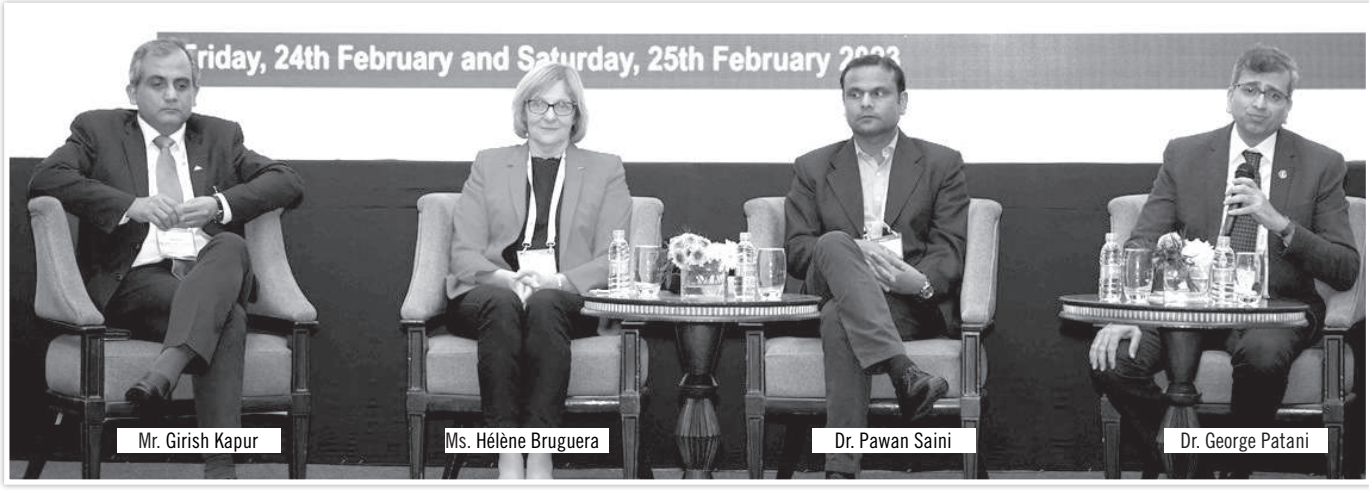
- Reduce particle analysis time by 50%
- Reduce development time by 30%
- From development, through formulation to release
- Improve product knowledge and process understanding
- Eliminate inefficient, error-prone and tedious data processing tasks.

Panel Discussion - Highlights of Future Roadmap on Pharmacopoeia

Session Chairperson: Dr. George Patani, Vice President (Western Region), IDMA

Panellist:

1) **Ms. Hélène Bruguera, EDQM**
2) **Mr. Girish Kapur, USP**
3) **Dr. Pawan Saini, IPC**



SUMMING UP, CONCLUDING REMARKS & VOTE OF THANKS

Dr. George Patani, Vice President (Western Region), IDMA diligently summed up the Two-day Convention and delivered his concluding remarks and vote of thanks.

Firstly, he thanked all the participants for being present in large numbers at the convention. He thanked all the speakers for a fantastic session this morning. He said that from the CEO's Panel Discussion, there is one message that he wants all of us to take home and that is in India we need to look at innovations. We are good at innovations but most important it's now time for us to start owning our innovation, another very good point that came out is that now we are going to collaborate more with innovators.

Dr George thanked the speakers for today Dr. Pawan Saini Senior Scientific Officer IPC, our panellists that were there for the CEO session Mr. Mehul Shah along Mr. Manish Doshi, Ms Aditi Kare Panandikar, Mr. Rashesh Gogri and Dr. (Ms.) Satya Ramani Vadlamani.

Dr George said that we had very good technical sessions with Ms. Hélène Bruguera, EDQM and Mr. Girish Kapur, USP. He thanked Ms Deepsikha Jakate, Mr. Sekhar Surabhi and Dr Sanjay Shetgar. He thanked Mr. Sandeep Kulkarni for his presentation on Particle Size Artificial intelligence and also thanked all our sponsors once again and to our excellent organizing team led by Dr. Vijay Nayak and last but not the least he thanked IDMA secretariat all of them led by Mr. Daara Patel. Thank you so much.

22nd IDMA – APA PAC 2023

GLIMPSES

Inaugural Session by lighting the lamp

Shri Daara B Patel, Secretary- General delivering the Welcome address

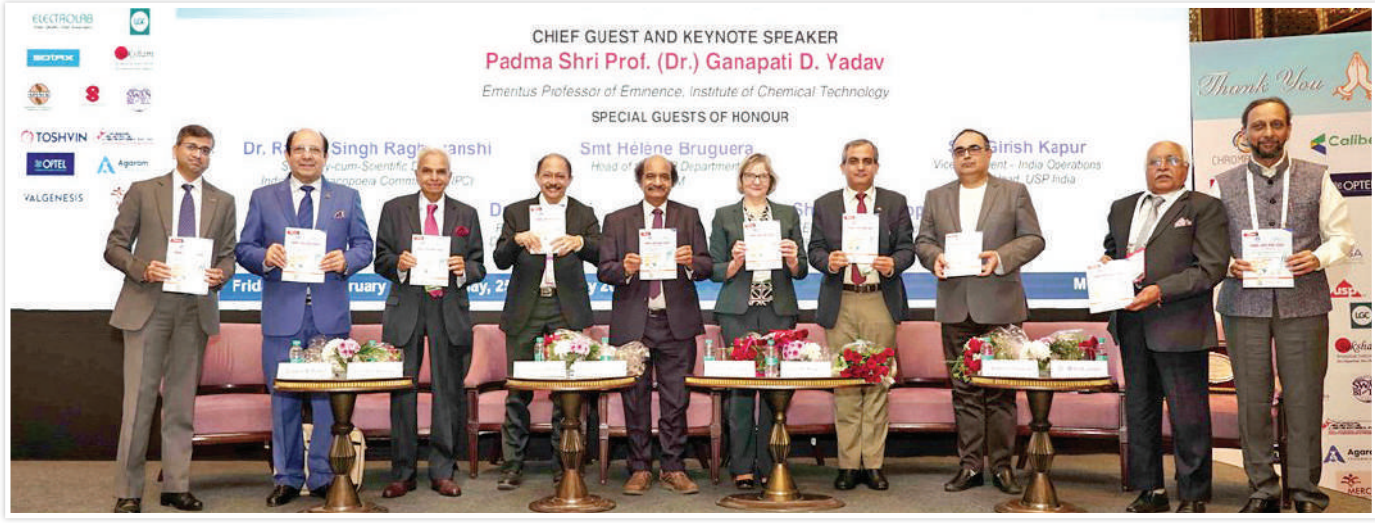
Dr. Vinay G Nayak, Chairman, Quality Management & Technical Committee, IDMA, Setting the Tone

Address by Ms. Hélène Bruguera, Head of the CEP Department, EDQM

Address by Shri Girish Kapur, Vice President – India Operations & Site Head, USP India

Address by Special Guest of Honour Dr Ajit Dangi, President & CEO, Danssen Consulting on Role & Responsibilities of an Analytical Chemist in Today's Environment

Address by Special Guest of Honour Shri Nikhil Chopra, CEO & Whole Time Director, J B Chemicals & Pharmaceuticals Ltd.



22nd IDMA-APA PAC 2023 Souvenir released

Inauguration of Table Spaces Area

Address by Chief Guest & Keynote Speaker, Padma Shri Prof G. D. Yadav, Emeritus Professor of Eminence, Institute of Chemical Technology on ***Applications of Green Chemistry and Engineering for Sustainable & Profitable Pharmaceutical Industry***

Address by National President IDMA, Dr Viranchi Shah

Padma Shri Prof G. D. Yadav, Emeritus Professor of Eminence,
Institute of Chemical Technology receiving ***Lifetime Achievement Award 2023***

Shri Sunil Kashiram Rane, Director, QC, Marksans Pharma Ltd., receiving ***Prof Dr R T Sane Outstanding Pharmaceutical Analyst of the Year Award 2023***

Shri. Ganesh Suresh Darode, Research Officer, Glenmark Pharmaceuticals Ltd., receiving ***Outstanding Young Analyst of the Year 2023***

Dr. Milind Joshi, Member, Quality Management & Technical Committee, IDMA delivering an Inaugural Vote of thanks

Dr. Milind Joshi, Member, Quality Management & Technical Committee, IDMA Facilitating the Technical sessions

Speakers at the Technical Session I on Compliance : *(From Left to Right) Dr Louis Coutinho, CEO, Nuleap Technologies P Ltd., as a Moderator, Ms. Hélène Bruguera, EDQM, Dr Mrunal Jaywant, Vice President – R&D, USP India and Shri. Santosh Savarkar, Head Regulatory Affairs, Umedica Laboratories Pvt. Ltd.*

Speakers at the Technical Session II on Digitalization / Automation: *(From Left to Right) Shri Kaushik Desai, Member, Quality Management & Technical Committee – IDMA as a Moderator; Shri S G Belapure, Senior Technical Advisor, IPA; Shri John DiBella, President, Simulations Plus Inc.; Shri Samir Haddouchi, Managing Director, SPS Pharma Services, France and Shri Florent Bouguin, VP, Chief Technology Officer, OPTEL*

Speakers at the Technical Session III on Innovations and Compliance: *(From Left to Right) Smt. Prathibha Pilgaonkar, CEO, Rubicon as a Moderator; Smt. Vishakha Metkar, Senior Manager - Regulatory Affairs, Colorcon Asia; Shri Sunil Kumar, Sr. Product Marketing Manager- Mass Spectrometry, Thermofisher Scientific and Dr. Prabha Maheswaran, Assistant General Manager – SSD, Chromachemie Laboratory Private Limited*

Shri Daara B Patel Facilitating the session at Day 2

Dr Pawan Saini, Senior Scientific Officer, IPC addressing on Updates on Pharmacopoeial Monographs – Future Roadmap

Panellist at the CEO's vision for Integrating Business with Quality & Compliance: *(From Left to Right) Shri Rashesh Gogri, Managing Director, Aarti Inds. Ltd.; Dr. (Ms.) Satya Ramani Vadlamani, Chairperson and Managing Director, Murli Krishna Pharma Pvt. Ltd.; Shri. Mehul Shah, CMD, Encube Ethicals Ltd chairing the session; Ms Aditi Kare Panandikar, Managing Director, Indoco Remedies Ltd. and Shri Manish Doshi, Managing Director, Umedica Labs / Amoli Organics*

Speakers at the Technical Session IV : Updates on Pharmacopoeial Monographs - Future Roadmap: *(From Left to Right) Ms. Hélène Bruguera, EDQM and Shri Girish Kapur, USP*

Speakers at the Technical Session 5 – Quality Management Systems:
(From Left to Right) Dr Nandkumar Chodankar, Founding Promoter, A-Solutions Pharmaceuticals as a moderator; Smt. Deepsikha Jakate, Abbott; Shri Sekhar Surabhi, Founder, Caliber Technologies; Dr Sanjay Shetgar, Vice President, NSF - Health Sciences, India

Shri Sandeep Kulkarni, CEO, ImageProVision Inc. made a presentation on Artificial Intelligence based Particle Characterization complying to regulatory requirements

Panel Discussion - Highlights of Future Roadmap on Pharmacopoeia (*From Left to Right): Shri Girish Kapur, USP; Ms Hélène Bruguera, EDQM; Dr Pawan Saini, IPC and Dr George Patani, Director, Inga laboratories P. Ltd., and Sr Vice President (Western Region), IDMA chairing the session*

Dr Antony Raj Gomas, Head of Global OSD & API Quality, Viatris made a presentation on Quality Culture & Compliance

22nd IDMA APA PAC 2023 Organising Committee *(Left to Right): Ms. Sapna Patil; Dr. Milind Joshi, Dr. Nandkumar Chodankar; Shri. Daara B Patel, Dr. Vinay Nayak, Dr. Pramod Manjrekar; Dr. George Patani, Mr. Melvin Rodrigues and Dr. Gaurav Pathak*

ACG worldwide and IPCA receiving Best Question award

Mylan Labs receiving highest registration award. Dr Antony Raj Gomas, Head of Global OSD & API Quality, Viatris receiving the award

Audience View

Felicitation of Speakers and Dignitaries

IDMA team thank Hotel Four Seasons staff for their Support and Cooperation. Shri Daara B Patel presenting memento to Ms Hema Narayane

Vote of Thanks by Dr George Patani, Director, Inga laboratories P. Ltd., and Sr Vice President (Western Region), IDMA

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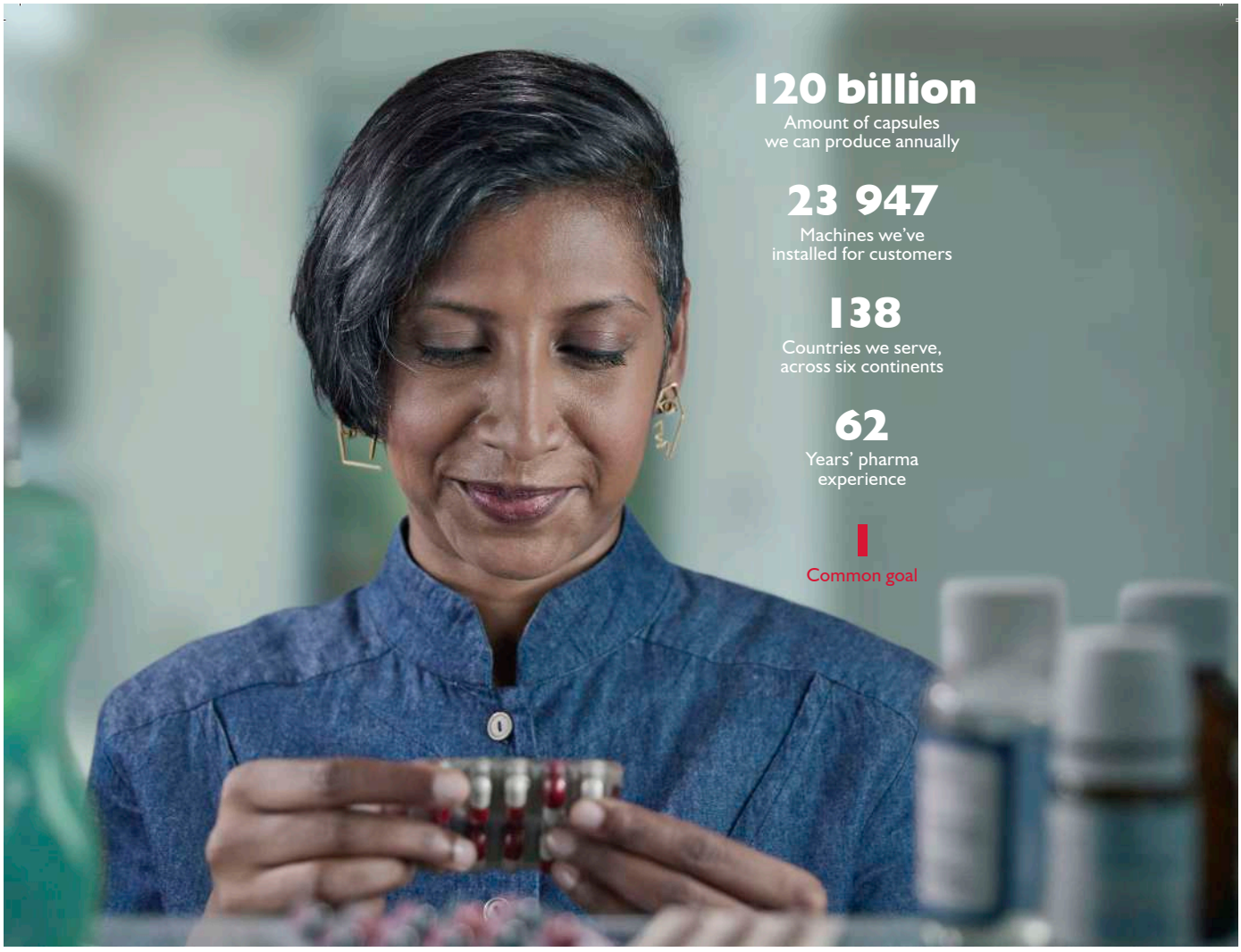

It may have something to do with home schooling three children, but Lakshmi is suffering more frequently from headaches at the moment, and relies on paracetamol to help her through.

Now, as an integrated pharma supply company, ACG may not actually make the analgesics Lakshmi uses. But we do provide the machines needed to form them, blister packs to protect them, and track and trace systems to ensure they always arrive safely in her hands.

And the benefits of using an integrated supplier go beyond things simply working better together. It also means having a single source of supply. So, while you help Lakshmi cope with her headaches, you should experience far fewer too.

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ACG

Make it better.

Update on the EDQM Inspection programme

Ms Hélène Bruguera, Head of the CEP Department, EDQM

THE EUROPEAN DIRECTORATE FOR THE QUALITY OF MEDICINES & HEALTHCARE (EDQM)

Update on the EDQM Inspection programme

IDMA PAC conference,
Mumbai, February 2023

Hélène Bruguera, Head of the Certification of Substances Department, EDQM, Council of Europe

The EDQM Inspection programme

- Integral part of the Certification of Suitability to the monographs of the European Pharmacopoeia (CEP) Procedure
- Involving manufacturing sites of active substances (APIs) involved in CEP(s), which are required to work under EU GMP Part II
- Aim: to verify the compliance with
  - ✓submitted CEP dossier
  - ✓EU GMP Part II & any applicable annex such as 1 for sterile substances, 11 for computerised systems etc.

EDQM GMP Assessment: the tools

On-Site Inspections	Documentation based GMP Assessment	Real Time Remote Inspections (RTEMIS)
• Traditional inspection approach • EDQM inspects about 40 sites per year	• Complementary to on-site inspections • Recognition of inspections • Documentation review • Up and running since 2010	• Third pillar for the supervision of the GMP compliance of API manufacturers • Adopted as permanent tool in 2022

EDQM **on-site inspections**

- Risk-based selection of sites to be inspected
- Inspections organised by EDQM are performed by team composed of one EDQM inspector and one inspector from an EU/EEA/MRA authority
- Joint inspections may also be performed, eg. with WHO, USFDA etc
- Local authorities informed and invited to participate as observers
- A list of deficiencies is issued within 6 weeks, the final report is issued after CAPA evaluation

Outcomes

- Positive conclusion :
  - ➢After satisfactory evaluation of CAPA
  - ➢Delivery of an Attestation by EDQM, stating the compliance with the CEP dossier that was subject of the inspection and with EU GMP
  - ➢Granting of a (EU) GMP Certificate by the EEA participating Inspectorate via the EUDRAGMDP database (public information on the EMA website)
- Negative outcome :
  - ➢In case of critical/major deficiencies to the GMP and/or the CEP dossier
  - ➢Actions taken on the CEP(s) / CEP application(s): suspension or withdrawal
  - ➢Information is published on the EDQM website
  - ➢Statement of GMP non-compliance issued by the EEA Inspectorate (public in EudraGMDP database)

Recognition/Reliance of Inspections

Source EEA inspections

- No API inspections on EEA territory
- Use of GMP Certificates for API sites involved in CEP scheme
- Direct recognition possible in most of the cases
- Use of Statement of GMP Non-Compliance for API sites involved in CEP scheme

Source Inspection Reports

- Documentation based assessment
- Evaluation of inspection reports from Trusted Authorities* (e.g. PIC/S)
- Comparison of scope, duration, extend
- Result: accept outcome and include in re-inspection framework

* high degree of similarity between EU and the authority's inspection procedures and GMP standards (currently equivalent inspections can be considered in connection with an MRA, AACA and PIC/S).

Optimising use of inspection resources worldwide

International API Inspection Programme

✓The objective of the programme is **to foster greater international collaboration and information sharing** to help better distribute inspection capacity, allowing more sites to be monitored, **increasing inspectional oversight and reducing duplication**. Building on equivalent GMP standards and mutual confidence, the collaboration is a voluntary agreement between the participants:

- to coordinate inspection planning taking into account risk based approaches and conduct inspections;
- to share information on inspection outcomes.

Programme to rationalise international GMP inspections of active pharmaceutical ingredients/active substances manufacturers

more info here

Planned inspections are shared with the group on monthly basis

EDQM **RTEMIS** - in brief

- Preparation of inspection is key
  - ➢Connectivity test, verification of connection in areas to be inspected
  - ➢Test of web conference tools
- Documents access prior to inspection
  - ➢Upload of core QA SOPs
  - ➢Upload of API specific information (# of batches, validation documentation etc.)
- Fully interactive remote inspection
  - ➢2 inspectors (like on-site inspections)
  - ➢Connected with company during the entire time of the inspection
  - ➢Live video streaming of production, storage, QC facilities, utilities, screens and computer sharing
  - ➢Documents sharing on demand
- Follow-up and outcomes identical to on-site inspection (CAPA review etc)

Visual feedback

Real Time Remote Inspections: Scope

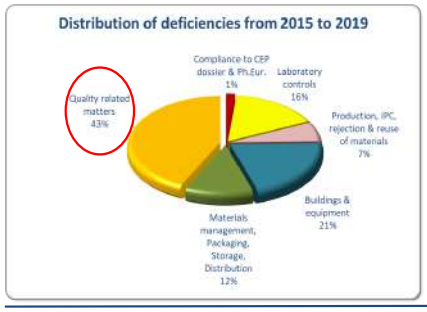
- Travel restrictions, e.g. pandemic situations, safety concerns in destination country etc.
- For re-inspections of sites which showed a good level of GMP compliance during previous inspections
- A potential process to verify the implementation of specific parts of a CAPA if deemed necessary
- If urgent GMP evaluation is needed, e.g. specific topic evaluation. In this case, the RTEMIS would not replace an on-site inspection, but allows an immediate assessment of a specific situation/aspect that might pose a risk to public health

The EDQM Inspection programme - Figures

2019	2020	2021	2022
• 33 on-site inspections • 18 GMP recognitions • 2 Statements of GMP non-compliance • 1 DA (trusted authorities)	• 7 on-site inspections • 2 RTEMIS • 31 GMP recognitions • 4 Statements of GMP non-compliance • 17 DA (trusted authorities)	• 11 RTEMIS • 17 GMP recognitions • 22 DA (trusted authorities)	• 14 on-site inspections • 9 RTEMIS • 0 GMP recognitions • 0 statements of GMP non-compliance • 10 DA (trusted authorities)

Impact of Covid-19 pandemic

API inspections deficiencies & trends



Decrease: Observations in Facilities & Equipment

Increase: Quality related matters

The 43%

Quality Management System

- **Quality Risk Management**
- **Lack of QA Oversight**
- **Change Control**
- **Investigations (OOS, Complaints, Deviations)**
- **Inadequate overview of production and laboratory activities**
- **Control of Documentation (paper and electronic)**

Quality Risk Management

- ICH Q9: Introduction section

It is neither always appropriate nor always necessary to use a formal risk management process (using recognized tools and/ or internal procedures e.g., standard operating procedures).

The use of informal risk management processes (using empirical tools and/ or internal procedures) can also be considered acceptable.

Quality Risk Management (cont.)

- ICH Q9 #4.6: Risk Review

… Once a quality risk management process has been initiated, that process should continue to be utilized for events that might impact the original quality risk management decision, whether these events are planned (e.g., results of product review, inspections, audits, change control) or unplanned (e.g., root cause from failure investigations, recall). …

Indicators of ineffective deviation and CAPA management

- Examples that raise attention of inspectors and should raise attention of QA
  - Investigations not holistic and/or comprehensive
  - Root causes not supported by scientific rationale; not robust
  - High rate of recurrent deviations
  - Recurring CAPAs for the same issue
  - Significant number of critical deviations
  - "planned deviations"
  - Deviations open for a long time
  - Few deviations (underreporting)
  - Incorrect categorisation

Similar indicators for OOS and complaint investigations

Evolution of API inspections over time

- Increased inspectional oversight of API manufacturers worldwide during the last decade led to:
  - Increased understanding and implementation of GMP regulations
  - Less regulatory actions
- Lower level of discrepancies to the CEP dossiers inspected - increased efforts of companies to comply with their commitments and the conditions under which their CEPs were granted
- Finished products manufacturers should still improve their ability to select GMP compliant API suppliers and audit/monitor them accordingly

To know more

- www.edqm.eu/the-inspection-programme (here)
- Training resources on the EDQM website (e.g. how to prepare for an EDQM inspection): here

Thank you for your attention

www.edqm.eu

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Update on the EDQM CEP procedure

Ms Hélène Bruguera, Head of the CEP Department, EDQM

THE EUROPEAN DIRECTORATE FOR THE QUALITY OF MEDICINES & HEALTHCARE (EDQM)

Update on the EDQM CEP procedure

IDMA PAC Convention,
Mumbai, February 2023

Hélène Bruguera, Head of the Certification of Substances Department, EDQM, Council of Europe

EDQM Certificate of Suitability (CEP)

Granted by the EDQM, Strasbourg, France

One of the 3 routes to provide data on the quality of an active substance in Europe

- **Certificate of Suitability**
- **Active substance Master File (ASMF)**
- **Full details of manufacture in marketing authorisation application (as part of CTD)**

Certification of Suitability to the monographs of the Ph. Eur.

Coordination and conduct of GMP inspections of API manufacturers involved in CEPs

Benefits→ Centralised assessment, global acceptance & sharing practices between peers (assessors & inspectors)

CEPs as a model of Reliance*

- >5900 valid Certificates of Suitability (CEPs) issued to >1250 manufacturers of pharmaceutical ingredients, mostly located **in India (27%)** and in China (28%)
- Recognised/relied upon in 70 countries worldwide and WHO

* WHO Good Reliance Practice (2021)

Operational updates to the CEP procedure

- Implementation of IDMP principles (ISO identification of medicinal products):
  - **2022: Optional use** of **ORG_ID** and **LOC_ID** in line with EMA **SPOR OMS** data management services

NB. **Use of SPOR OMS will be mandatory for CEPs in 2023 !**

EMA is organising trainings/webinars on how to register in SPOR OMS (EMA website here)

- 2022: Revised policy for GPS coordinates for manufacturing sites
  - Alignment with PIC/S principles
  - GPS coordinates expressed in Degrees to at least 5 decimal places
  - Removed requirement to provide DUNS number

Operational updates to the CEP procedure (2)

- **Change of policy regarding polymorphs**

  Possibility to get a CEP for a specific polymorph even if the Ph. Eur. monograph does not contain any information on this – → claim as « grade » and data on polymorph characterisation to be included in the CEP dossier

- **Procedural updates**
  - Change of Contact details (updated form + procedure)
  - User Guide for the « DCEP Sharing Tool »

- **CEP holders responsibilities towards their customers (available here)**

CEP holders responsibilities towards their costumers

To address gaps and lack of awareness of CEP holders regarding their responsibilities towards their **costumers :** Marketing authorisation applicants / holders and sponsors that use CEPs

- Identifies regulatory frameworks supporting responsibilities
- Holder is responsible for **sharing necessary information** with their costumers so they can fulfil their respective legal responsibilities
- Provides examples (e.g. sharing most recent CEP version in a timely manner, info on impurities, transparency in case of GMP non-compliance, etc)

Transparency for CEP documents & guidelines

Updated process adopted for **CEP public documents & guidelines**

- Clear and transparent process which includes public consultation for governance documents, technical guidelines, etc
- Document available : here

WATCH THE SPACE

- Draft guidelines and forms for comments will be available via the EDQM website (dedicated webpage) and will be announced via news

Nitrosamines in CEP dossiers

- Applicants to include risk assessments:
  - ✓ **In new CEP dossiers, renewals, sister files**
  - ✓ **In revisions** where a risk of nitrosamine formation may be introduced (i.e. changes to the manufacturing process, change of suppliers of starting materials or intermediates, etc.)
  - ✓ **If step 1 deadline was "missed", in case of new finding,** a revision application to introduce a risk assessment is required
- **How to submit a risk assessment**: here
- If a risk is identified, test results and implementation of controls/measures are needed
- The EMA document EMA/409815/2020 (Q&As - here) is **fully implemented** in the context of the Certification Procedure
- The EDQM shares toxicological data for NDSRIs (Nitrosamine Drug Substance Related Impurities) given by CEP holders with **EU/EMA network** and relies on their assessment

Nitrosamines – call for review for substances covered by CEPs

- Work still on-going
- International focus is on drug products (outside EDQM scope) and on NDSRIs
- Status:

Step 2 Confirmatory testing (26th September 2022)
- provide test results to EDQM, and if needed a corrective actions plan with timelines

Step 3 Update of CEP application
- implement additional controls or process changes
- send revision application to EDQM as needed
- **Deadline extended to 1st October 2023**

Nitrosamines - information sharing & communication

The EDQM has been **co-operating continually with regulatory authorities at national, EU and international level**

Cooperation with authorities worldwide:

✓ via the Nitrosamines International Strategic Group (NISG – chair Health Canada) and its technical Group (NITWG)

Sharing information with international partners under confidentiality agreements:

- Sharing signals on presence of nitrosamines in sources of APIs & in medicinal products - trigger review of CEP dossiers if necessary
- Sharing root causes etc.
- Alignment of decisions

CEPs and the Ph. Eur.

- Ph. Eur. monographs are necessary to get a CEP
- Revision of monographs have an impact on CEPs
  - ✓CEP holders are contacted by EDQM and are requested to update their application
  - ✓Systematic process, which gives assurance that a CEP always refer to the current version of a monograph

Revisions of Ph. Eur. monographs

- Draft revisions published in Pharmeuropa
  - 4 issues/year
  - Invitations to comment posted on the EDQM website (+ target to CEP holders)
  - **Important to look at draft monographs and to comment!**
- Review of comments, additional work if needed
- Adoption of the revised monograph
- Publication in Ph. Eur. supplement/edition
  - CEP holders requested to update specification accordingly and if needed to demonstrate suitability of the revised monograph to control their impurities (eg. Suppl 11.1 here
- Implementation – 6 months after publication

Too late to provide comments...

The CEP of the Future = the CEP 2.0

The CEP 2.0

- **Ongoing project to reshape the CEP and its content**
- **Goals**
  - Meet the current needs of stakeholders: CEP holders/manufacturers, drug product manufacturers, regulatory agencies (worldwide) including quality assessors;
  - Ease the registration activities linked to the use of CEPs;
  - Increase the acceptance of CEPs worldwide.

The journey

31 Aug. - 31 Dec. 2020
- **Wide Public consultation**

2021
- **Analysis of the results ► Outcomes published here**
- **Action plan shaped around 5 areas**

Q1-Q3 2022
- **Design of new CEP**
- **Discussions with relevant stakeholders & decision making bodies**

Nov 2022
- **Decisions taken by the CEP Steering Committee**

What will change and benefits

Review information to be stated on the CEP
- Enhanced transparency on approved specification & quality attributes for the substance (will be appended to the CEP)
- Strong encouragement to have retest period assessed by EDQM

Reduce revisions of CEPs and facilitate handling of changes
- Stop granting "renewed" CEPs (after renewal procedure)
- The numbering system will change
- No revised CEP after a change if there is no impact on quality

Enhance digital tools and public databases
- CEP as a digital document (pdf)
- Addition of SPOR OMS id for companies on the CEP
- More information on CEP lifecycle in databases (public and for authorities)

What will change and benefits (2)

Foster information sharing between CEP holders and medicines manufacturers
- Enforcement of EDQM guideline « CEP holders responsibilities »
- Commitment by CEP applicant at time of submission
- Implementation of Letter of access instead of a box on the CEP
- Via enhancement of public database

Train users on content and use of CEP

Guidelines, communication on EDQM website & training materials for users and CEP applicants

Status of the project and next steps

Q1- Q2 2023
- **Communication** about new expectations regarding CEP dossiers
- **Communication** about future changes to the CEP document
- **Webinars** for stakeholders
- Implementation process at EDQM (in May)
- Start developing IT tools (databases)

Q3 2023
- **Implementation** of the new CEP

WATCH THE SPACE

Stepwise & smooth implementation

Smooth transition for CEP holders, EDQM and users
- Issuance of « **New look CEPs** » for any new CEP and at renewal
- Issuance of « **Hybrid look** » after revision of existing dossiers
- Valid « **Old look** » CEPs (= current layout) will remain for a while
- Possibility for CEP holders to submit a special type of revision to move to « New look » CEP for existing ones – optional

- EDQM will provide guidance and support to identify and understand the different layouts.
- Dedicated webpage for the project here

WATCH THE SPACE

Another on-going project

- **Business Process Review for CEP:**
  - **Goal:** assess performance of the procedure with the view of improving it
  - **Focus:** evaluation and inspection processes performed by EDQM
  - **External company** supporting the project: QdB group
  - **Survey** sent to targeted Industry stakeholders (including IDMA)

Deadline extended to 1st March 2023

Your voice matters!

Thank you for your attention

www.edqm.eu

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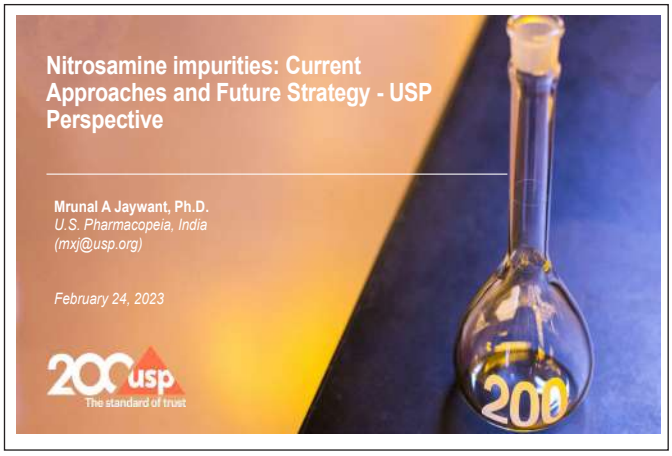
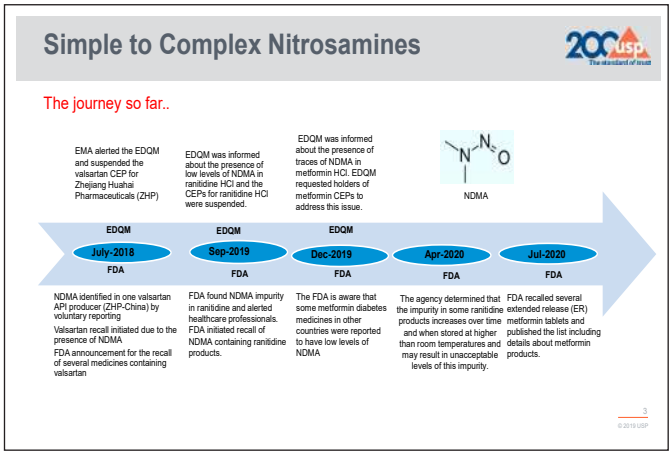
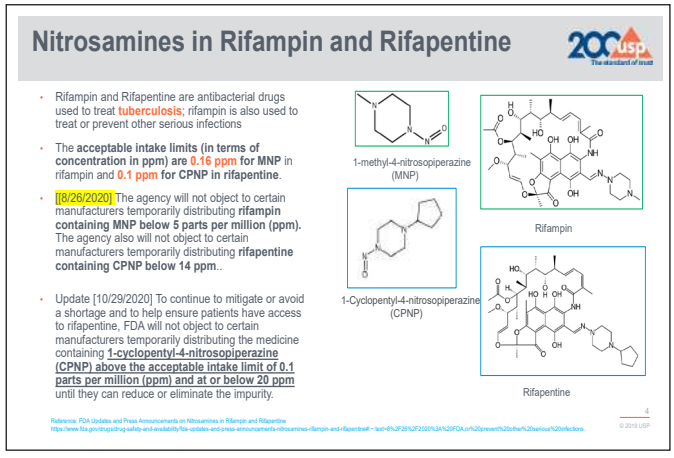
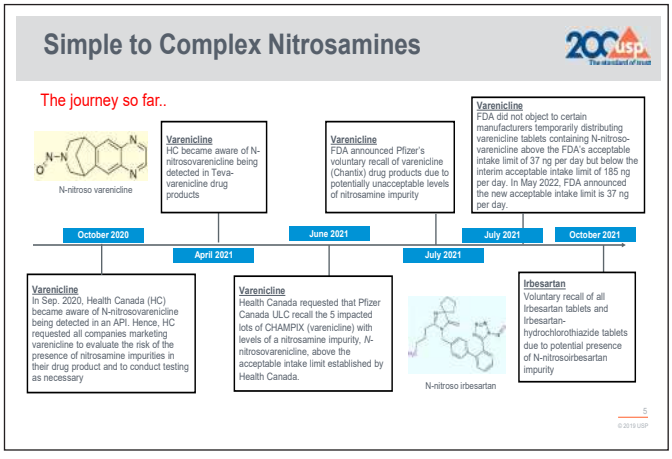
Nitrosamine Impurities: Current Approaches and Future Strategy- USP Perspective

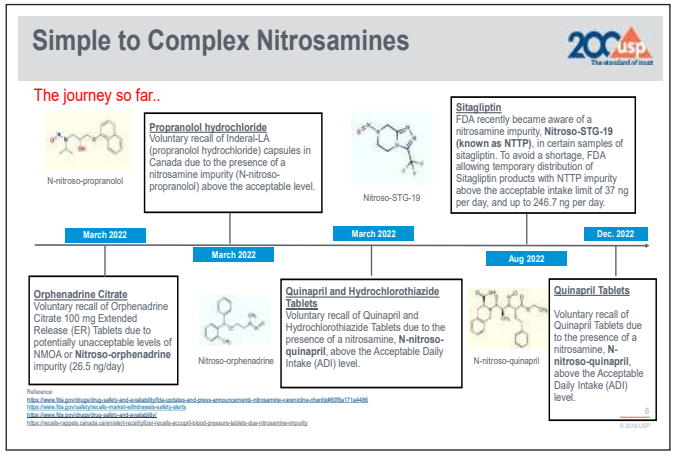
Dr Mrunal Jaywant, Vice President – R&D, USP India











Regulatory Guidances: Recommended AIs

N-Nitrosamine (CAS Number)	FDA AI Limit (ng/day)	EMA AI Limit (ng/day)/ Source
N-Nitrosodimethylamine, NDMA[3,4] (62-75-9)	96	96
N-Nitrosodiethylamine, NDEA[3,4] (55-18-5)	26.5	26.5
N-Nitrosoethylisopropylamine, EIPNA[3,5] (16339-04-1)	26.5	26.5
N-Nitrosodiisopropylamine, DIPNA[3,5] (601-77-4)	26.5	26.5
N-Nitroso-N-methyl-4-aminobutyric acid, NMBA[3,6] (61445-55-4)	96	96
1-Methyl-4-nitrosopiperazine, MeNP[5] (16339-07-4)		26.5 (Rifampicin)
N-Nitroso-di-n-butylamine, NDBA[3,5] (924-16-3)		26.5
N-Nitroso-N-methylaniline, NMPA[3,4] (614-00-6)	26.5	34.3
N-Nitrosomorpholine, NMOR[3,7] (59-89-2)		127
N-Nitrosovarenicline, NNV[8]		37 (Varenicline)
N-Nitrosodipropylamine, NDPA (621-64-7)[3,5]		26.5

(Ref Questions and answers for marketing authorisation holders/applicants on the CHMP Opinion for the Article 5(3) of Regulation (EC) No 726/2004 referral on nitrosamine impurities in human medicinal products EMA/409815/2020 Rev.14 and https://www.fda.gov/regulatory-information/search-fda-guidance-documents/control-nitrosamine-impurities-human-drugs Rev. 1, Feb. 2021)

7

Regulatory Guidances: Recommended AIs

N-Nitrosamine (CAS Number)	EMA AI Limit (ng/day)/ Source
N-Nitrosomethylphenidate[9], NMPH, (55557-03-4)	1300 (Methylphenidate)
N-Nitrosopiperidine[3] (100-75-4)	1300
N-Nitrosorasagiline[10]	18 (Rasagiline)
7-Nitroso-3-(trifluoromethyl)-5,6,7,8-tetrahydro[1,2,4]triazolo- [4,3-a]pyrazine[11]	37 (Sitagliptin)
N-Nitroso-1,2,3,6-tetrahydropyridine, NTHP[3] (55556-92-8)	37
N-Nitrosonortriptyline[12]	8 (Amitryptylin, Nortryptylin)
N-Methyl-N-nitrosophenethylamine, NMPEA[3] (13256-11-6)	8
N-Nitrosodabigatran[10]	18 (Dabigatran)
4-(Methylnitrosoamino)-1-(3-pyridinyl)-1-butanone (NNK)[7]	100

(Ref Questions and answers for marketing authorisation holders/applicants on the CHMP Opinion for the Article 5(3) of Regulation (EC) No 726/2004 referral on nitrosamine impurities in human medicinal products EMA/409815/2020 Rev.14)

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Regulatory Guidances: Recommended AIs

N-Nitrosamine (CAS Number)	EMA AI Limit (ng/day)/ Source
N-nitrosoduloxetine[13]	100 Duloxetine
N-nitroso-fluoxetine[13]	100 Fluoxetine
N-nitrosoparoxetine[9]	1300 Paroxetine
N-nitroso-diphenylamine NDPh[14] (86-30-6)	78000
N-nitroso-mefenamic acid[15]	78000 Mefenamic acid
N-nitroso-pyrrolidine NPYR[3,7] (930-55-2)	1700
N-nitroso-diethanolamine NDELA[3,7](1116-54-7)	1900

(Ref Questions and answers for marketing authorisation holders/applicants on the CHMP Opinion for the Article 5(3) of Regulation (EC) No 726/2004 referral on nitrosamine impurities in human medicinal products EMA/409815/2020 Rev.14)

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FDA's Post on 'Possible Mitigation Strategies'

Posted on 11/18/2021

Updates on possible mitigation strategies to reduce the risk of nitrosamine drug substance-related impurities in drug products

FDA issued a guidance for industry, *Control of Nitrosamine Impurities in Human Drugs*, in September 2020 to help ensure the safety of the U.S. drug supply by recommending steps manufacturers of active pharmaceutical ingredients (API) and drug products should take to detect and prevent objectionable levels of nitrosamine impurities in pharmaceutical products. The guidance also described conditions that may introduce nitrosamine impurities and described a three-step mitigation strategy.

Recently, FDA has received additional reports of certain types of nitrosamine impurities that formed in several drug products. These nitrosamine drug substance-related impurities (NDSRIs) are a class of nitrosamines sharing structural similarity to the API. NDSRIs can be generated during manufacturing or during the shelf-life storage period of the drug product. In some cases, the root cause of NDSRI formation has been attributed to nitrite impurities present in excipients at parts-per-million amounts. Nitrite impurities have been observed in a range of commonly used excipients (as well as water) and may lead to the formation of NDSRIs in certain drug products.

https://www.fda.gov/drugs/drug-safety-and-availability/updates-possible-mitigation-strategies-reduce-risk-nitrosamine-drug-substance-related-impurities

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Possible Mitigation Strategies:

- Nitrite impurities present in excipients at parts-per-million amounts: A supplier qualification program that takes into account potential nitrite impurities across excipient suppliers and excipient lots to reduce the risk of nitrosamine formation in the drug product.
- Mitigation strategies related to formulation design:
- Example: The addition of antioxidants to formulations may significantly inhibit the formation of NDSRIs in drug products.
- The formation of nitrosamines typically occurs under acidic conditions, whereas, in a neutral or basic environment, the kinetics of these reactions are significantly reduced. Thus, formulation designs that incorporate excipients such as sodium carbonate that modify the micro-environment to neutral or basic pH, should in principle inhibit the formation of NDSRIs.

Reference: https://www.fda.gov/drugs/drug-safety-and-availability/updates-possible-mitigation-strategies-reduce-risk-nitrosamine-drug-substance-related-impurities

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Possible Mitigation Strategies:

FDA encourages manufacturers to consider these as well as other innovative strategies to reduce the formation of NDSRIs to acceptable levels in drug products.

FDA will consider meeting requests, as appropriate, to discuss innovative mitigation strategies with prospective applicants or manufacturers.

The data in the NDA/BLA and ANDA meeting package should include, at a minimum, the following:

•Description of the formulation design strategy employed to reduce the formation of NDSRIs in the drug product.

•Supporting manufacturing information and, at a minimum, three months of accelerated stability data demonstrating control of NDSRI.

•For approved NDAs and ANDAs that require reformulation as part of a mitigation strategy, in vitro or in vivo bioequivalence bridging studies.

Reference: https://www.fda.gov/drugs/drug-safety-and-availability/updates-possible-mitigation-strategies-reduce-risk-nitrosamine-drug-substance-related-impurities

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Recent Recalls Due to NDSRIs

- The October announcement of a recall of two lots of the hypertension medication Quinapril and Hydrochlorothiazide from the U.S. market is putting nitrosamine drug substance related impurities (NDSRI) in the spotlight once again.
- In December 2022 the FDA announced a voluntary recall of four lots of Quinapril Tablets due to the presence of a nitrosamine impurity observed in testing above FDA's proposed interim limit, adding to the growing number of recalls due to nitrosamine impurities in recent years.
- Amidst the latest recall related to NDSRIs, USP continues to lead the charge by providing quality standards-based solutions, organizing workshops and training courses and hosting a forum for the exchange of crucial knowledge to help keep our medicine supply chain strong and protect patient health.

Reference:
https://www.fda.gov/safety/recalls-market-withdrawals-safety-alerts/aurobindo-pharma-usa-inc-initiates-voluntary-nationwide-recall-two-2-lots-quinapril-and
https://www.fda.gov/safety/recalls-market-withdrawals-safety-alerts/lupin-pharmaceuticals-inc-issues-voluntary-nationwide-recall-four-lots-quinapril-tablets-due

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USP's Nitrosamine Program: Accomplishments so far…

1 **Documentary Standard**
To address the nitrosamine impurities safety concern from a pharmacopeial perspective, a USP Joint Expert Subcommittee (JSC) was convened in February 2020 to develop *General Chapter <1469> Nitrosamine Impurities*.

2 **Reference Standard**
Eight USP Reference Standards have been established to support *General Chapter <1469> Nitrosamine Impurities*

3 **Advocacy and capability building**
USP Education course
Webinar, Round Table Discussion, Workshop, User Forums
Trainings to Regulators

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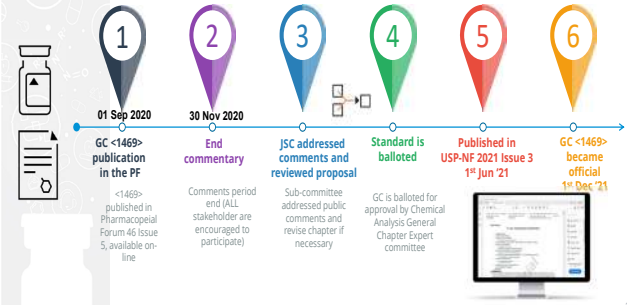
GC <1469> Nitrosamines Impurities

Timeline



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GC <1469> Nitrosamines Impurities

CONTENT

1. INTRODUCTION
2. NITROSAMINE IMPURITIES
3. SOURCES OF NITROSAMINES
4. NITROSAMINE RISK ASSESSMENTS – DEVELOPMENT OF A CONTROL STRATEGY
5. LIMITS OF NITROSAMINE
6. TESTING FOR THE PRESENCE OF NITROSAMINES
7. TEST METHOD PERFORMANCE CHARACTERISTICS OF NITROSAMINE METHODS
8. ANALYTICAL PROCEDURES (Quantitative Analytical Procedures)
9. ADDITIONAL SOURCES OF INFORMATION
10. USP REFERENCE STANDARDS

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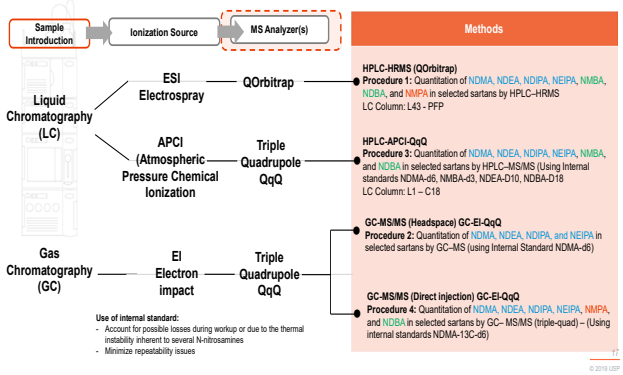
GC <1469> Test Procedures



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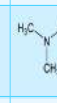
USP Nitrosamine Reference Standards

- USP developed eight USP Nitrosamine Reference Standards for use with General Chapter <1469> Nitrosamine Impurities

Catalog # Name Label value	Structure	Catalog # Name Label value	Structure	Catalog # Name Label value	Structure
1466674 N-Nitroso dimethylamine (NMDA) 1.00 mg/mL in Methanol		1466663 N-Nitroso disopropylamine (NDIPA) 1.00 mg/mL in Methanol		1466607 N-Nitrosomethyl phenylamine (NMPA) 1.00 mg/mL in Methanol	
1466652 N-Nitroso diethylamine (NDEA) 1.00 mg/mL in Methanol		1466641 N-Nitroso dibutylamine (NDBA) 1.00 mg/mL in Methanol		1175800 Deutero N-Nitrosodimethylamine (NDMA-d6) 1.00 mg/mL in Methanol	
1466685 N-Nitroso ethylisopropylamine (NEIPA) 1.00 mg/mL in Methanol		1466696 N-Nitroso methtylamino butyric acid (NMBA) 1.00 mg/mL in Acetonitrile			

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Nitrosamine Training Materials

Modules

USP <1469> Nitrosamines Impurities: Launched in June 2021

Module 1—Nitrosamines Overview
Module 2—Risk Assessment
Module 3— Testing Methods - Mass Spectrometry Fundamentals, Analytical Challenges and Validation of Procedures
Module 4 — Analytical Procedures

Introduction to Proposed USP General Chapter <1469> and Handling of Nitrosamine Impurities Reference Standards: Posted on YouTube in Nov. 2020

Nitrosamine Exchange – Online Community

Nitrosamine Exchange Knowledge Community

Join http://nitrosamines.usp.org

Overview of USP Nitrosamine activities

Documentary Standards	Nitrosamine USP Reference Standards	Nitrosamine Training material/ Education course	USP Workshops / Webinars / Conferences	Global Public Health
<1469>- Nitrosamine Impurities	NDIPA NDMA NDBA NDEA NMBA NEIPA	Developed a tutorial and education course on Nitrosamine impurities to train industry stakeholders	Scientific Webinars/ Workshops Round table discussions/ stakeholder forums Industry connect forums	Training and guidance for global regulators Nitrosamine test methods for essential tuberculosis drugs

Nitrosamine Impurities Survey 1.0

Research Goal

Understanding current challenges and practices for controlling & testing Nitrosamines' impurities and what else is required in this space.

What?

Online survey distributed via Qualtrics and emails from regional USP teams.

When?

Fieldwork date: August 9 – August 31, 2021

Who?

Survey targeted USP stakeholders and customers.
Total sample for analysis and reporting =**242** (incl. 18 partials)

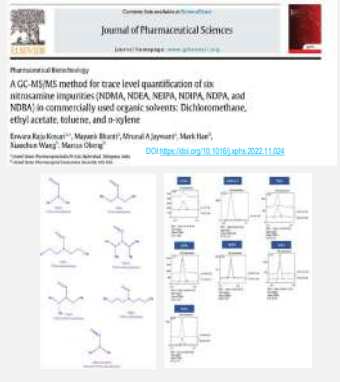
Key findings:

- ***Nitrosamines is the topmost impurity of concern*** for ***Drug products and Drug substances***, whereas Elemental impurities and Residual solvents top the list in Excipients category.
- ***Uncertainty in observing and controlling nitrates and nitrites levels*** is noted for each product category.
- This uncertainty level ***goes even higher for Excipients***.

USP's Current Approaches

- Non-compendial solutions:
  - Publications
  - Analytical Hub
    - Analytical Procedures:
      - Solvent Method
      - Ranitidine
      - Rifampin and Rifapentine
      - Universal Method
  - Pharmaceutical Analytical Impurities (PAI)
- Strategy for Excipients:
  - Nitrite and Nitrate in Excipients
- Advocacy and Capability Building:
  - Pharmacopeial Education
  - Nitrosamine Workshop/ User Forums
  - Nitrosamine Tutorial

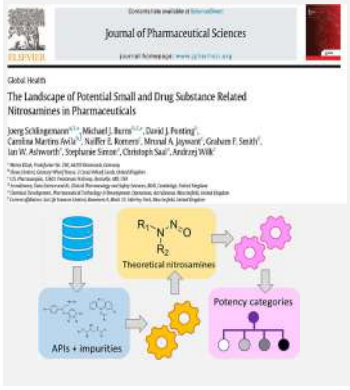
Non-compendial solutions: Publication



- **Solvents** are widely used as a **reaction media** and other steps in the **production** of drug substances and products in pharmaceutical **industries**.
- Nitrosamine **contamination** can occur when fresh solvents (ortho-xylene, toluene, and methylene chloride) get contaminated during **shipment** from vendors (e.g., during **transfer between storage vessels**).
- The determination of **nitrosamines** in **solvents** plays an important control in the **manufacturing** of quality drug substances and drug products.
- The current study provides a **highly sensitive** procedure for the determination of **six nitrosamines** in widely used solvents: **dichloromethane**, **ethyl acetate**, **toluene**, and **o-xylene**.

https://www.fda.gov/media/141720/download

Non-compendial solutions: Publication



- An **in-silico analysis** of more than **12,000** small molecule drugs and drug impurities.
- In total, **41.4 %** of the **APIs** and **30.2 %** of the **API impurities** listed in the GSRS database are **potential nitrosamine precursors.**
- Most structures identified through this workflow could form **complex API-related nitrosamines (NDSRIs)**.
- **Analytical standards** that would allow for quantification in the pharmaceuticals concerned are currently only available for **less than 5 %** of all potential NDSRIs.

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Non-compendial solutions: USP Analytical Hub

- Launched in December 2022

USP App Note - Nitrosamines analysis in Solvents by GC-MS-MS V2.pdf

- Public **online repository** containing **non-compendial** analytical procedures (analytical notes) for the testing of nitrosamine impurities and related substances.
- USP's scientists curate these analytical procedures through **internal development/validation** or through scientific review of non-compendial donations. They are **NOT** compendial standards.
- The **procedures** contained in the analytical notes should be **validated** by the user. USP is **not** and will not be responsible for the use or implementation of the procedures.
- Hosted in **The Nitrosamine Exchange**. The Analytical Hub allows keyword searches and the view of key analytical procedure parameters and chromatograms.

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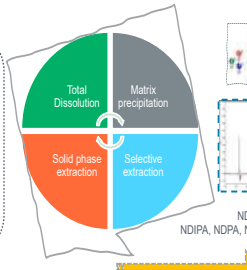
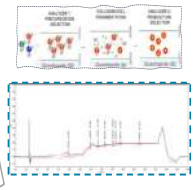
Non-compendial solutions: Common Method

Approach

Different class of drugs → Sample preparation optimization → Mass spectrometric detection

- Angiotensin II Receptor Blockers (Sartans)
- Histamine-2 Receptor Antagonists (Ranitidine and Nizatidine)
- Antidiabetic Agents (Metformin Hydrochloride)
- Antimicrobial Agents (Rifampin and Rifapentine)





NDMA, NMBA, NDEA, NEIPA, NDIPA, NDPA, NMPA, NDBA, and additional nitrosamines

Optimization in-process

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Pharmaceutical Analytical Impurities (PAI)

Available in April 2023 and later

RFI CAS	Impurity name or Chemical formula	API	Molecular Formula
621-64-7	N-Nitrosodipropylamine (NDPA)	–	C6H14N2O
61379-66-6	1-Cyclopentyl-4-nitrosopiperazine	Rifapentine	C9H17N3O
16339-07-4	1-Methyl-4-nitrosopiperazine	Rifampin	C5H11N3O
930-55-2	N-Nitrosopyrrolidine	–	C4H8N2O
138768-62-4	N-Nitroso Metoprolol	Metoprolol	C15H24N2O4
2248746-67-8	N-Nitroso Carvedilol	Carvedilol	C24H25N3O5
84418-35-9	N-Nitroso Propranolol	Propranolol	C16H20N2O3
2820170-74-7	N-Nitroso Labetalol	Labetalol	C19H23N3O4
134720-04-0	N-Nitroso Atenolol	Atenolol	C14H21N3O4
2820170-76-9	N-Nitroso Bisoprolol	Bisoprolol	C18H30N2O5

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Additional PAIs being prepared and coming soon!

- Includes a mix of both simple nitrosamine impurities and **N**itrosamine **D**rug **S**ubstance **R**elated **I**mpurities (NDSRI)
- Therapeutic categories of medicines with the potential to be affected by these impurities include:
  - Antidotes, Deterrents, and Toxicologic Agents
  - Central Nervous System Agents
  - Cardiovascular Agents
  - Genitourinary Agents
  - Blood Products/Modifiers/Volume Expanders
  - Antidepressants
  - Antiparkinson Agents

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Strategy for Nitrosamines in Excipients

Scope:

To develop a strategy for the control of Nitrosamines in Excipients in collaboration with the Excipients Test Method Expert Committee

Work plan:

Determination of Nitrates and Nitrites in at risk excipients

Preliminary Findings:

- Challenging sample preparation
- Interferences from other ions
- Inconsistent recoveries

Status:

- Work in-progress to establish a sensitive and robust method

Formation of NDMA from Nitrite

Nitrite in Excipients

- As part of risk assessment, the level of Nitrites and Nitrates in excipients needs to be evaluated and a control strategy needs to be established by the drug product manufacturers.

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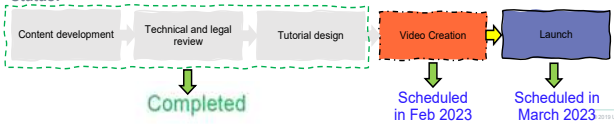
Advocacy and Capability Building: Nitrosamine Tutorial

Scope:

To design and create video tutorials on Nitrosamine methods highlighting critical troubleshooting involved in nitrosamine methods (LC-MS/MS & GC-MS/MS) covered under the nitrosamine education course.

Work Plan:

Status:



Future Roadmap

- Method for NDSRIs
- Risk Assessment Tool
- Additional Nitrosamine RS (PAI)
- Training to Regulators: Lab Demonstration
- Strengthening collaboration with FDA

Method For NDSRIs

Scope:

To develop analytical procedure for determination of NDSRIs.

Work Plan:

Identify a specific class of drug products.
Synthesis and characterization of reference materials.
Develop sensitive and robust analytical procedures (LC-MS/MS).

Status:

- Synthesis and characterization completed
- Method development is in progress

- N-Nitrosoatenolol
- N-Nitrosobisoprolol
- N-Nitrosocarvedilol
- N-Nitrosolabetalol
- N-Nitrosometoprolol
- N-Nitrosopropranolol

Risk Assessment Tool

Scope:

To develop a 'practical' guidance document for Risk Assessment [What ← → How]

Work Plan:

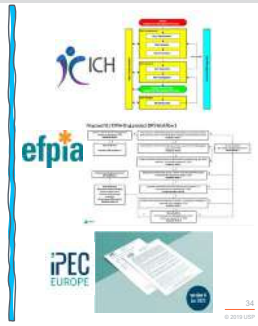
Development through a collaborative process with Nitrosamine Exchange community members

Inputs from Expert Committee and FDA liaisons

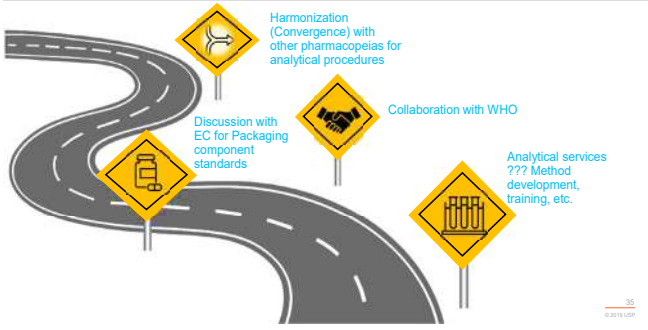
Publication of final guidance document (White Paper, Stimuli Article, Peer-review article)

Status:

- Kicked off Jan '23



Future projects under consideration…



Questions?

Anticipating Regulators Mindset

Mr. Santosh Savarkar, Head Regulatory Affairs, Umedica Laboratories Pvt. Ltd.

Anticipating Regulators Mindset…

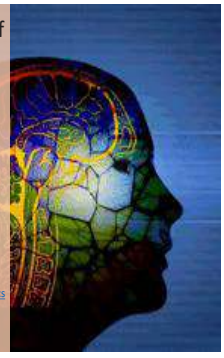
… While Reviewing
Submitted Documents for Approval

By
Santosh Savarkar

Mind Reading

- Humans cannot literally read the minds of others, but can create mental models so as to effectively intuit people's thoughts and feelings.
- This is known as ***empathic accuracy***, and it involves "reading" cues telegraphed by the words, emotions, and body language of another person.

Reference - https://www.psychologytoday.com/us/basics



Mind games and anticipation of Opponents strategy in sports

Regulators Mindset…

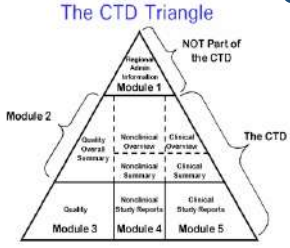
- What does it mean?
- Is it possible?
- How…?

Answer to these Questions – YES!!

ICH harmonisation for better health

Q S E M

The CTD Triangle



- With ICH Q/S/E/M Guidances and Common Technical Documentation Template adopted by all major agencies.
- Many ICH countries already moved to eCTD tree.
- With harmonisation of dossier template across the ICH countries.
- Introduction of electronic CTD format by many ICH countries.
- This aspect also introduced a requirement of regulatory intelligence…
- Improving quality of regulatory filings, study of historical set of queries, documentation and data compliance in line with ICH and Health agency specific guidance is essential…

Adaptive pathways

Scientific guidelines

- The European Medicines Agency's prepares scientific guidelines in the European Union (EU).
- This is to help applicants prepare marketing authorization applications.

- Guidelines reflect a harmonized approach of the EU Member States and the Agency on how to interpret and apply the requirements for the demonstration of quality, safety and efficacy set out in the Community directives.

- ...cy strongly encourages ... holders to interpret and follow the... guidelines.
- Applicants must justify any **deviation from guideline/s** in their MA applications at the time of submission.
- Before that, they are encouraged to seek scientific advice, and discuss any proposed deviations during development.

- FDA has listed all official FDA Guidance Documents and other regulatory guidance.
- One can search for documents using key words, and narrow or filter the results by...
  - product,
  - date issued,
  - FDA organizational unit,
  - type of document,
  - subject,
  - draft or final status, and
  - comment period.
- This feature is provided to enable convenient way to search for all FDA guidance documents at single location.

Reading Regulator's Mindset...

Compliance cannot be an afterthought.

If the correct information is precisely cascaded throughout the organization. Everyone within the organization is made well aware of the basic issues and how they should be handled!!

More importantly, they must know, exactly what the rules are!!!

Almost all pharma companies are under pressure to monitor the changes happening in the regulations and agency approaches and respond with technically justified answers to the queries...

Hence, deep insight, quick and accurate data analysis, and timely publication are critical to lead for multitude of business benefits....

This brings to new role within Regulatory Affairs profession...

Pharmaceutical regulatory intelligence

It is about understanding the trends, players, the regulations themselves, bureaucracies that regulate the industry, an entire market map, and the regulatory forces that impact the business.

Expectations with Regulatory Intelligence...

- Study the trends, patterns, and opportunities in the global markets...
- Be vigilant, Identify, analyze, and interpret regulatory updates from global pharma Regulatory Landscape...
- Prepare reports, and keep the stakeholders posted with changing regulatory environment...
- Communicating information top management effectively...
- Developing strategic recommendations on regulatory filings...
- Supporting business development and R&D teams...

Regulatory Intelligence...

Regulatory Submissions and compliance to the regulatory guidelines is dependent on fact. How and whether, organization and its technical teams are well informed about changing regulatory requirements?
Here the need of keeping the database, keep track of amendments and new guidances issued by various agencies, ICH etc...
In order to manage this and keep technical and regulatory teams well informed about changing regulatory expectations... Is something dealt thru Regulatory Intelligence...

Regulatory intelligence has gained significant importance with increasingly global considerations for product development, clinical trials, and submissions to ensure market access in key regions.
The regulatory intelligence team, tasked with providing strategic input to ensure regulatory compliance.
It has determination to fulfill the changing needs of various departments within the company and by senior leadership.
By strategically analyzing relevant regulations and product competitive landscapes.

Regulatory Intelligence...

The regulatory intelligence function can have many applications within regulatory affairs and within the company CFTs.
But, plays a key role in designing appropriate regulatory strategy for targeted market filings and registration.

Regulatory intelligence becoming more strategic & operational

Re.: Evolution of the regulatory intelligence profession
by
Daanish Ashraf, PharmD, and Kirsten Messmer, PhD, RAC

An organization's ability to learn and translate that learning into action rapidly is the ultimate competitive advantage.
- Jack Welsh
CEO of General Electric between 1981-2001

- In the current dynamic regulatory environment. Regulatory intelligence is specifically
  - **monitoring,**
  - **gathering, and**
  - **analyzing of publicly available and**
  - **experience-based regulatory information.**
- This is used to design and execute the development and filing strategies to save time & cost on development and focused to reduce No. of assessment cycles to fast-track the approvals of submitted MA applications.

Regulatory intelligence is not just...
Information
& Knowledge
& Data management.

- It must have the skills or **"intelligence"** to conduct...
  - *an impact analysis and*
  - *disseminating acquired knowledge*

  to build regulatory strategies for development, execution and filing till approval of the product.
- *Regulatory intelligence adds value to the acquired information and help to shape the environment to create a competitive advantage.*

Need of Regulatory Intelligence

Business development and licensing side, companies are using predictive models of regulatory intelligence, to streamline their product development and business and R&D spending.
Within regulatory affairs, there is a substantial increase in the volume of available datasets.
The challenges in this changing regulatory landscape…

- Rapid increase in the number of drugs under observation and
- continuously evolving standards & scientific guidelines by regulatory agencies.

Consequently, the amount of data that needs to be searched and analyzed has increased exponentially.
Life science regulations are bit complex and the amount of data that needs to be analyzed is huge.

Information sources for regulatory intelligence
Source: *TCS ADD*

Regulatory Intelligence – Approaches !!

- Regulatory intelligence can help company to go global. As well as reduce the regulatory risks, achieve faster approvals, and help manage the cost and time impact of global regulatory changes.
- Regulatory intelligence thus allows companies to identify issues and trends and focus on proactive compliance.
- It identifies and eliminates high-risk areas preventing fines and delays in approval.
- It also empowers businesses to make faster and better business decisions.
- Having a correct regulatory inputs of knowledge, helps an organization to respond to the market, legislative, and competitive demands in a timely manner.

Examples of Anticipating Regulators Mindset…

1. DMF Type II –

Change notification sent by API Manufacturer.

It was categorized as a minor change in API manufacturing process.

Against supplied supporting data, ANDA Holder evaluated it as a Major change. As there were multiple minor changes in API Mfg. Process at all stages of manufacture.

DMF Holder still filed the DMF amendment and ANDA Holder's management insisted to file the change under moderate change – CBE 30 suppl. !!

FDA on preliminary review converted CBE30 to PAS (Major change)

Examples…

5. DMF Process Amendment –

DMF Holder proposed change in API process. Filed DMF amendment. With available change notification, CBE 30 filed.

CBE 30 was granted as per FDA standard procedure.

But during FDA ongoing review, DMF Holder received CR Letter.

On scrutiny of CR Letter, it was understood that DMF amendment submitted by DMFH was with change of API process. But, uninformed proposal to use of second crop DS crude was added by DMFH.

FDA objected on use of 2nd crop and asked to provide impurity purging data including the results from impurity spike/purge studies for the drug substance batches manufactured using **second crop of DS crude.**

Subsequently, DMF Holder was not having any impurity spike/purge studies for 2nd crop.

DMF H agreed to withdraw the DMF amendment for use of second crop of DS crude.

Examples … (CRO issue)

- Lack of communication from CRO, hinders the anticipation of any issue/s related to Biopharmaceutics…
- ANDAs were submitted. Many ANDAs were approved with one of the FDA Inspected BA/BE Center (CRO) in India.
- Due to GCP/GxP non compliance, FDA sent various communications to CRO.
- Communication from FDA for not adhering to the applicable statutory requirements and regulations governing the conduct of bioequivalence studies (Data Integrity Issues).
- But, CRO did not inform to the Drug product manufacture and ANDA Holder.
- Due to this lack of communications from CRO, ANDA Holders, received CR Letter for its approved ANDA as well as under assessment ANDAs.

Example … Drug Product(Cont..)

2. ANDA Para IV Filing…

- It was Para IV filing. Formulation was developed non infringing, different than RLD formula.
- Product was recommended for Bio Waiver as per product specific FDA guidance.
- During development and before filing, RA suggested to file **Controlled Correspondence** Related to Generic Drug Development to get the difference in formulation, notified and clarified from FDA.
- R&D and Project management Team, did not agree to file the CC.
- After filing, 2 IR and 1 DR Letters received. On responding all these DR/IRs. FDA did not agree with provided justification.
- Finally before Goal Date, CR Letter received from FDA. Questions related to formulation with noticeable difference with approved RLD were raised. Biowaiver, due to differences in the formulation of test vs RLD was also queried.
- Based upon CR, Drug product manufacturer / R&D finally agreed to reformulate the drug product to satisfactorily respond to CR Letter.

Examples …

- *API is practically insoluble across the physiological pH range.*
- *Necessity of the surfactant is justified based on solubility and dissolution data with and without surfactant.*
- *Tween 20 in 0.5% concentration is chosen; selection of the respective type and concentration is adequately discussed.*
- *The method is finalized with pH 6.8 Phosphate buffer + 0.5% Tween20/ 900 ml/ Paddle 75 rpm.*
- *Discriminatory power of the selected method is demonstrated against change in API particle size and level of disintegrant.*

With all above detailing… Agency still raised following query…

- *Applied changes in concentration of surfactant and use of dissolution method are not considered realistic (very high particle size in comparison to proposed specification and omission of the whole quantity of disintegrant) and are not suitable for demonstrating discriminatory power.*

Agency suggested…

- *Discriminatory power of the method should be demonstrated by justified and realistic changes.*

RA Ignorance and gaps in reviews… Fetching the queries…

- We note that you have provided the hold time study protocol but have not proposed any actual hold times.
- State the polymorphic form of the API(s) used in the unitary batch formula in 32P1.
- Submit a bulk formula for each batch size for each strength as three master manufacturing batch records were submitted with different batch sizes…
- The reason for the overage should be stated/justiied, e.g., with reference to batch results, in 3.2.P.2.2.2
- The description of the manufacturing procedure must include duration of treatment, manufacturing conditions (temperature and humidity) and specifications for machine settings and capacity.
- Quantitative and qualitative composition of the colorant must be included. (3.2.P.4.1)
- The dissolution specification must be brought in line with the profiles of the biostudy and reference products. All the strengths of both test and reference products demonstrated very rapid dissolution whereas the specification is not in line with the definition of rapid dissolution!!
- Bring the FPP specifications in line with those indicated in a recognized pharmacopoeia monograph.
- Provide a justification for the out of trend assay results. The shelf-life specifications are incomplete or have missing criteria or parameters.
- Typical… for injectable… Justify sterilization by filtration. Heat instability during autoclaving has been determined at 121 °C/20 min. Need to confirm that terminal sterilization is not feasible!!
- Extractability and leaching studies of the selected filter should be submitted
- Bacterial endotoxin test (BET) should be included as a specification either as initial product release specification or as an in-process control.

Not only queries…
But, agencies give you suggestions in assessment…

- Biopharmaceutics
- The Agency reviewed the additional dissolution data provided for the xxmg drug product and xxmg bio-batch at additional sampling time-points.
- Based on the overall dissolution data, the proposed in-house dissolution method [USP Apparatus 2 (paddle) with cage sinker at 50 rpm in 900 mL 0.1N HCl at 37°C] appears to be adequate.
- However, the dissolution data for each strength of the proposed drug product supports
  - **15-35% in 1 hour;**
  - **45-65% in 6 hours;**
  - **56-76% in 10 hours and**
  - **NLT 80% in 24 hours'**

  as the dissolution acceptance criteria at batch release.
- Implement the recommended acceptance criteria and update your drug product release and stability specifications accordingly.
- In addition, please be advised, that all proposed exhibit batches are expected to meet these revised dissolution specifications in your stability program through your proposed expiry period.

Current Topic – Nitrosamine Impurities Risk management

Typical Example on Nitrosamine impurities risk assessment from EU Agencies…

- N-nitrosamine formation in the FP.
- API intermediate has a secondary amine.
- This secondary amine impurity is controlled at Limit NMT 0.05 % (500 ppm), in the API specification.
- Nitrosamine impurity risk assessment in API is accepted.
- But, excipients in the formulation, may contain significant Nitrate / Nitrite traces.
- Possibility to form the corresponding N-nitrosamines with intermediate impurity in formulation must be evaluated. Possibility of formation of N-Nitrosamine impurities on storage also need to be evaluated.
- Applicant must conduct confirmatory testing and present a risk assessment for any new Nitrosamine Impurity detected or identified in the product.

Risk evaluation of possible nitrosamine impurities has to be conducted during development phase.

Technology – A Game Changer

Mr S G Belapure, Senior Technical Advisor, IPA

TECHNOLOGY
A GAME CHANGER

S G Belapure
24/02/23

CONTENT

- Contribution of Indian Pharma
- Why Automation & Digitalization ?
- Evolution in Pharma Manufacturing
- Emerging Technologies in Pharmaceuticals.
  - Continuous Manufacturing
  - 3D Printing
  - Automation
  - Digitalization
- Case Studies on Automation & Digitalization.

02

INDIAN PHARMA INDUSTRY CONTRIBUTES SIGNIFICANTLY

India	US	Global
36% lower per person disease burden (DALY, 1990-2016)	**~40%** Of all drugs consumed in the USA	**3rd largest** share of drugs by volume
95% lower treatment costs of life threatening diseases (Hep-C, Leukemia)	**395 (42%)** Indian ANDA's approved in 2019 (% of global share)	**60%** of global vaccine production
100% eradication of Polio through active collaboration between manufacturers, providers, government, etc.	**1st (665)** in number of USFDA approved plants outside of US (# of US FDA approved plants in India)	**37%** AIDS Patients receiving treatment (in 2009) in Africa, due to greater availability & affordability of Indian drugs

02

WHY AUTOMATION & DIGITALIZATION ?


Consistent Quality


High Productivity

Sustained Compliance


Human error avoidance

SOLID ORALS PROCESSING...EVOLUTION

From.....


- Traditional Granulation using PLM


- Manual compression Machine


- Conventional Coating Pans

.....To


- Highly automated single Pot / automated RMG


- Fully automated CFC compression machine


- Automated PLC controlled Coating Machines

SOLID ORALS PROCESSING...EVOLUTION


- Manual Visual Inspection


- 100 % online automated Inspection Machines


- Manual Packaging


- Robotic Packaging System


- Hand filling of hard capsule


- Automatic 100% online check weighed capsule filling

ASEPTIC PROCESSING...EVOLUTION


Sterilization of articles, 1917 *Conventional clean room* *LAF with barriers* *Complete Isolator , RABs*

From.....

- Use of DHS for Vials sterilization
- Manual Cleaning & Sterilization of assembly and tanks
- Manual collection and loading of Vials in Lyophilizer
- Offline filtration
- Offline check weighing
- Manual EM monitoring

.....To

- Online dehydrogenation Tunnel & RTU
- In line CIP SIP
- Automatic Lyo -loading / unloading
- Online Filtration
- 100% Online check weighing
- Online continuous EM monitoring

PHARMA EVOLUTION...DOSAGE FORMS

Shift from conventional IR products to...Complex Products like

- Delayed Release (DR) & ER / SR Products
- Multilayered Fixed Dose Combinations
- Liquid / Tablet / Pellet in Capsules
- Wruster Coated Products
- Biosimilars
- Complex Injectable
- Transdermal Patches

EMERGING NEW TECHNOLOGIES IN PHARMA MANUFACTURING


- Continuous Manufacturing - Formulations / API


- 3D Printing


- Automation & Digitalization

TRANSFORMING CORE MANUFACTURING TECH: COMPANIES ARE SELECTIVELY PILOTING CONTINUOUS MANUFACTURING IN API AND FORMULATIONS

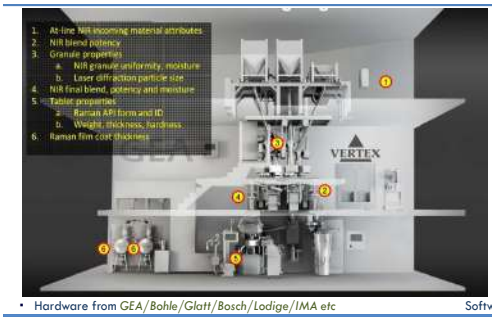
ILLUSTRATIVE

Manufacturing area	Vision	Illustrative examples
A **API manufacturing**	Pilot continuous manufacturing for large volume APIs	Use of plug flow reactor (continuous reactor) for sensitive and difficult to control reaction steps instead of traditional reactor
B **Formulations manufacturing**	Pilot continuous manufacturing for large volume products, and integrate key unit operations	Continuous manufacturing line for high volume formulations (e.g. roll compactor, continuous coating) Single pot granulation and drying to integrate unit-operations

These initiatives are only being taken up as initial exploratory pilots by select companies, each with a different end-state vision for continuous manufacturing (e.g. end-to-end vs. modular deployment of continuous manufacturing)

05

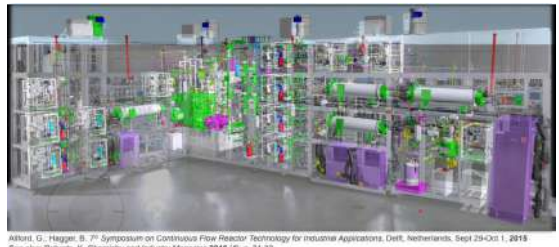
CONTINUOUS MANUFACTURING - FORMULATIONS



- Hardware from *GEA/Bohle/Glatt/Bosch/Lodige/IMA etc* Software from *Siemens/Emerson*

CONTINUOUS MANUFACTURING - API

GSK Continuous API Manufacturing (Singapore)



Allford, G.; Hegger, B. *7th Symposium on Continuous Flow Reactor Technology for Industrial Applications*, Delft, Netherlands, Sept 29-Oct 1, **2015**
See also: Roberts, K. *Chemistry and Industry Magazine* **2016** (6), p. 31-33

05

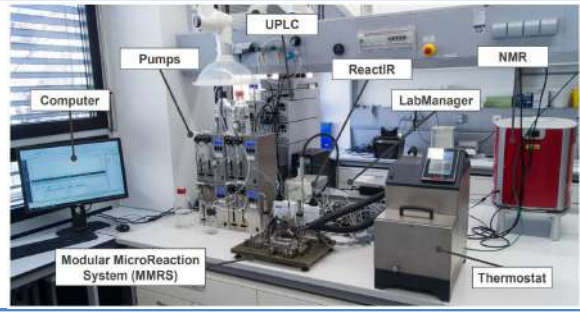
CONTINUOUS PROCESSING AND FLOW TECHNOLOGY

- Safer, more robust (in-line PAT) and scalable processes
- New chemistries ("designer reagents") and processing windows in fit-for-purpose reactors
- Allows redesigning of APIs syntheses utilizing "forbidden" chemistries
- Cheaper and more sustainable access to APIs and essential medicines (on-site, on-demand

Novartis Continuous Manufacturing Lab (2018)

05

INTEGRATION OF MULTIPLE TYPES OF PAT TOOLS TO A SINGLE FLOW PLATFORM



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CONTINUOUS MANUFACTURING

Benefits:

Highly efficient operation,

- Low conversion cost
- Less manpower required due to automation
- Considerably higher OEEs & Yield
- Lower end-to-end batch lead time
- Smaller physical footprint of the equipment
- Higher Safety

Higher Quality,

- Low product deviations
- Online process controls reducing offline testing
- Scale up not required if CM is already applied in clinical trial stage
- Faster tech transfers since processes are fully automated

Concerns:

- High CAPITAL intensive
- Understanding of PAT tools and product characteristics
- Defining the batch size
- Regulatory consideration

3D PRINTING

- Requires software, hardware and chemical inks.
- Idea to have a universal set of inks that we put out with the printer and you download the blueprint, the organic chemistry for that molecule, and you make it in the device. And so you can make your molecule in the printer using this software.
- First drug "SPIRTAM" by Apprecia pharma- Levitracetam approved by USFDA.

AUTOMATION…

AUTOMATION

Automatic Storage & Retrieval System (ASRS)

Automated Guided Vehicle (AGV)

Robotics in Mfg, QC, Potent / Harazdeous Substances , End of packing line Automation

AUTOMATION

- Few Automation in Mfg & Pkg equipment


Integrated Granulation Line


Continuous Coater


Case Packer


Track & Trace System


Vial / Ampule - Inspection


Tablet / Cap - Inspection

AUTOMATION

- Video

https://staubli.showpad.com/share/sB3uWSe5MNYYk6f9jLVzj

DIGITALIZATION...

OVER THE LAST DECADE, INDIA PHARMA COMPANIES HAVE UNDERTAKEN SEVERAL INITIATIVES TO DRIVE DIGITIZATION IN OPERATIONS

Focus area	Illustrative examples undertaken by different companies
1 **Manufacturing:** digitization and standardization of data entry for key GMP operations	• Electronic equipment logs • BMS systems for environmental monitoring • Electronic batch records • Central data acquisition of key process parameters from machines
2 **Quality control:** deployment of laboratory and testing management systems	• Laboratory information management systems (LIMS) • Electronic lab notebooks • Lanza Moda (Microbiology)
3 **Quality management:** deployment of multiple systems to simplify document-ation, events and training management	• eData management systems for BMR, BPR, tech transfer documents etc. • OOS, OOT, market complaints and incident management systems • Training management systems • Regulatory submission management systems
4 **Enterprise wide systems:** integration and management of key business processes	• SAP

These elements have been initiated in different degrees across companies / facilities / areas in Indian Pharma

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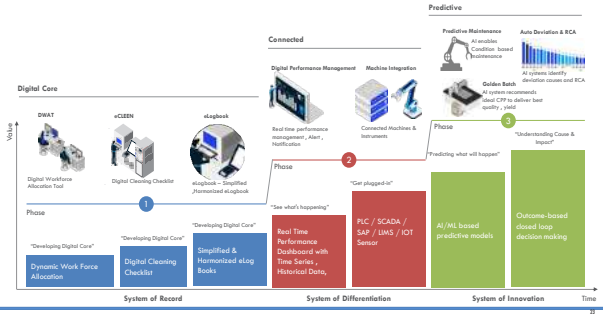
DIGITALIZATION – MANUFACTURING



FOUNDATIONAL ELEMENTS TO DRIVE DIGITIZATION AND AUTOMATION

Foundational layers for digital & analytics	Description	Illustrative applications
IV Data layer	Enterprise-wide integration of data	Data lake; Data Warehouse
III IT layer	IT applications to capture data across functions / areas	ERP (e.g. SAP); eTRACK; LIMS; TRACKWISE; MES (eBMR); Local apps (BMS, EHS, EMS, etc.)
II Operating technology layer	Recording & storage of operations data (e.g. from sensors)	SCADA Remote Viewer, Historians, SQL DB; PLC, HMI; SCADA/DCS
I IIOT and sensors	Sensors on equipment to capture process, and environment data	Sensor; Equipment

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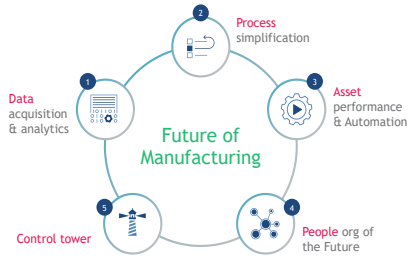
DIGITAL AND ANALYTICS (DNA) IN PHARMA OPERATING SYSTEMS

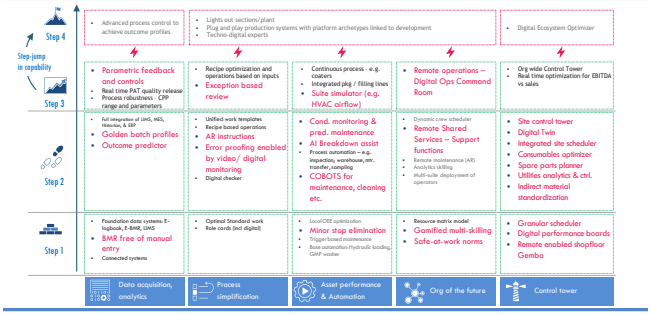
- *Augmented Reality (AR) led remote supervision of shop floor*
- *Advance Analytics (AA)-led increase in asset capacity*
- *Digital Twin scheduler – along with Digital performance management*

FUTURE OF WORK THINKING AROUND 5 CORE OPERATING THEMES

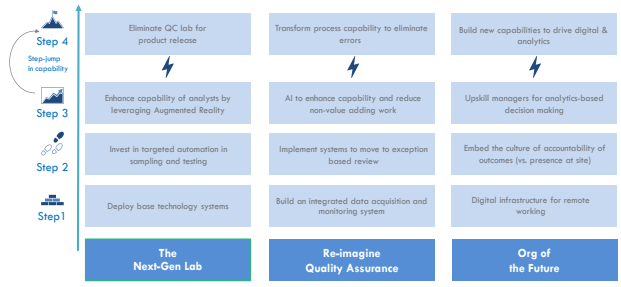


Source: Interviews with industry experts, BCG analysis

NEXT GENERATION MANUFACTURING



NEXT GENERATION QUALITY



LEVEL 3 EXAMPLE – ANALYSTS USING AR

	Analyst 1 Instructions	Analyst 2 Instructions
	"Golden / ideal analyst"	Needs guidance to error proof
1	Weigh and powder 20 aspirin tablets	Weigh and powder 20 aspirin tablets.
2	Transfer 100 mg of aspirin to the suitable container	Transfer 100 mg of aspirin to the suitable container ⚠ Hope you have made sure that you have no left over of aspirin
3	Add 20ml of diluting soln. of acetonitrile and formic acid	Add 20ml of diluting soln. of acetonitrile and formic acid ⚠ Do avoid the parallax error/ look at the lower meniscus
4	Shake vigorously for 10 mins and centrifuge to prepare stock soln.	Shake vigorously for 10 mins and centrifuge to prepare stock soln. ⚠ Make sure apparatus setting is default
1:9	Mix stock soln. & diluting soln. (1:9)	Mix stock soln. & diluting soln. (1:9)

COMPANIES - EMPLOYING DIGITAL SOLUTION (1/3)

	Lilly	Pfizer	Janssen
Location	Indianapolis, USA Carolina, Puerto Rico	Groton, Connecticut, USA	Beerse, Belgium
Description of what the site produces	• Continuous Oral Solid Dosage (OSD) production facility	• Continuous Oral Solid Dosage (OSD) production facility	• Continuous Oral Solid Dosage (OSD) production facility
Levers deployed	• Application of near-infrared (NIR) integrated with residence time distribution model • Soft sensors to estimate CQAs • Linkages with laboratory, raw material and product development database • Progressive control scheme anchored by advanced automation and PAT technology	• PCMM (portable, continuous, miniature, modular), a platform technology, allows unit operations to be 'plugged in' when needed • Process analytical technology and advanced process control for real time monitoring and control system	• Continuous manufacturing (CM) platform, integrating 3 different processes • 7 PAT applications, automation control system, SynTQ data mgmt. system • Vertical integration of the equipment minimizing product transfers • Predictive modelling tools, product traceability system, RTD models
Impact	• Reduced complexity, faster startup times, easier maintenance, improved ergonomics • Reduced technical transfer time, lower development costs	• 35% energy and resource savings • 10x less material usage; 10x faster	• Shorter development cycle times, reduced energy consumption, footprint, process scale up efforts and risks

COMPANIES - EMPLOYING DIGITAL SOLUTION (2/3)

	nephron	COOK
Location	West Columbia, USA	Bloomington, Indiana, USA
Description of what the site produces	• Blow fill seal (BFS) manufacturing facility	• Ready to use vials through a flexible filling line (FFL)
Levers deployed	• Laser guided vehicles, automated warehousing, robotics and track and trace technology • Fully integrated control tower with inventory mgmt. systems, laboratory info. mgmt., environmental monitoring system	• Robotics technology and automation to serve clinical and commercial mfg. needs • Use of 'No Touch' transfers to ready to use components; de-nesting and de-traying of ready to use vials • Multiple format flexibility, component sizes and dosing options
Impact	• Improved OEE & manpower cost	• Zero rejects, increased product yield, filling speeds upto 140 vials/minute

COMPANIES - EMPLOYING DIGITAL SOLUTION (3/3)

	SANOFI	Lilly	Pfizer
Location	Massachusetts, USA	County Cork, Ireland	Hangzhou, China
Description of what the site produces	• Continuous Biomanufacturing facility	• Continuous drug substance manufacturing facility	• Global biotechnology Centre (GBC)
Levers deployed	• Full integration of LIMS, MES, Historian, ERP systems with automated data transfer • Plant performance managed through electronic boards available throughout the facility • Fully electronic batch records enabling review and release by exception	• 'Plug and play' modular processing skids that can be configured in multiple sequences • Continuous manufacturing through continuous crystallization and continuous automated filtration • Data mgmt. system (SynTQ) to deliver real time process control	• Disposable bioreactors and modular constructed facility • Central spine corridor to connect drug substance, drug product, warehouse, utilities building • Identical platforms from a hardware and software perspective enabling smooth tech transfers across
Impact	• 80x more capacity than traditionally achieved	• 20x reduction in impurities • Reduction in operator exposure	• Early commissioning through rapid assembly and significant planning

FUTURE MANUFACTURING

Lights Out Plants !!!!

THANK YOU

The Future Is Now: Applying Physiologically-Based Biopharmaceutics Modelling to Accelerate Generic Product Development and Inform Regulatory Decisions

Mr. John DiBella, President, Simulations Plus Inc.

The Future Is Now:
Applying Physiologically-Based Biopharmaceutics Modeling to Accelerate Generic Product Development and Inform Regulatory Decisions

22nd IDMA-APA PHARMACEUTICAL ANALYSTS CONVENTION (PAC) 2023

John DiBella
President, Simulations Plus
john.dibella@simulations-plus.com

What Are We Having a Conversation About Today?

- The Regulatory Push and Basic Definitions
- Where Did PBBM Come From?
- Case Studies
  - Virtual BE to Establish CMA Specs to Support Biowaiver
  - Study Leverage + PBBM to Support Biowaiver in New Market
- The Next Frontier(s) and Conclusions

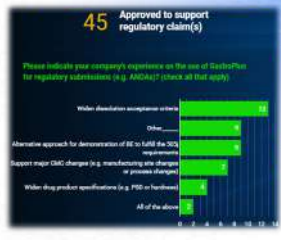
Evolving Relationship Between Mechanistic Modeling and R&D

- **Model "supported" (first questions 20 years ago)**:
  Will modeling and simulation help?
- **Model "based" (questions 5 years ago)**:
  How can I maximize the value of modeling and simulation in my development program?
- **Model "informed" (questions today)**:
  How do I change the R&D process to reflect the availability of *in silico* tools and techniques?

Mechanistic Modeling to Support Regulatory Interaction: The Push!

2020 Generic Drug Company Survey

- 30+ generic drug companies surveyed applying mechanistic M&S
- Invited responses to:
  - Guide GastroPlus® R&D activities
  - Describe use cases and regulatory interactions with GastroPlus®



What About India Regulators?

Wednesday, February 22, 2023

Working Definitions of Key Phrases

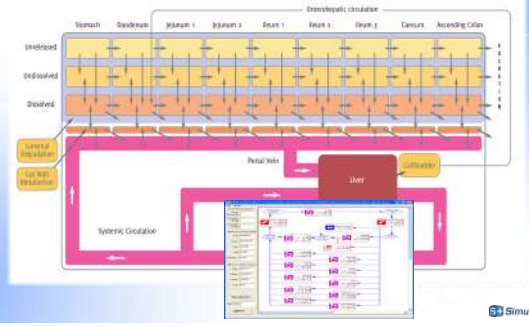
PBPK Model: Physiologically-Based Pharmacokinetic Model

The baseline model that combines physiology, population, and drug characteristics to mechanistically describe the PK and/or pharmacodynamic behaviors

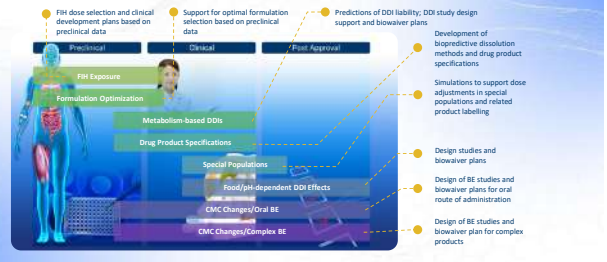
PBBM: Physiologically-Based Biopharmaceutics Model

The application of the baseline (PBPK) model to support drug product development – e.g., IVIVCs, virtual bioequivalence

Advanced Compartmental Absorption and Transit Model (ACAT™)

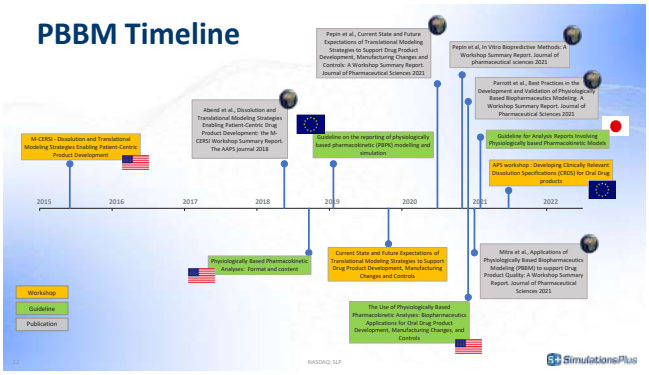


Common Mechanistic M&S Industry Applications

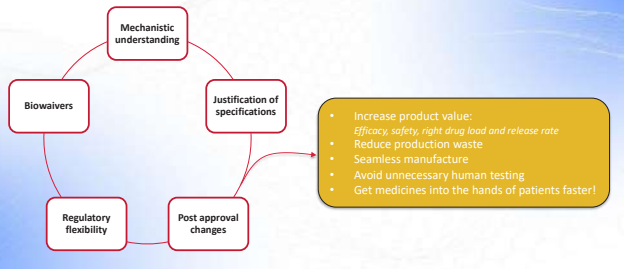


Where Did PBBM Come From?

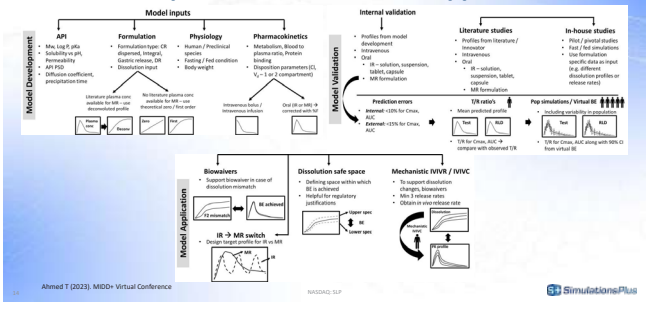
PBBM Timeline



PBBM in the Pharma/Generic Industry



The 3 Stages of PBBM: Development, Validation, and Application



Typical Savings of PBBM Along the Value Chain

Mechanistic understanding → increase product value	Quality by Design to reduce the time to market; Avoid bridging between phase 1-3 formulations; Increase confidence in pilot/pivotal studies	6-12 months per project
Clinically relevant design spaces Justify drug product specifications Support PACs	Ensure manufacturing ability: Increase yield and reduce wastage	20% annual yield increase
Regulatory flexibility	Answer regulatory questions at time of submission (e.g., validation campaign to redo)	6 months per project
Biowaivers	Typical BE study costs: variable if healthy volunteers or patients	$100K USD per study + 2 months

Typical total savings per project:
- 12-18 months acceleration to market = sales
- 20% increase in yield and $100K+ savings

Virtual BE to Establish CMA Specifications Following Process Changes

Problem Statement

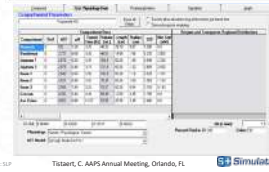
- Post approval, sponsor's manufacturing process change resulted in different particle size distributions for new lots
  - Inline milling step added to crystallization process
- With mechanistic modeling, could they apply for a biowaiver:
  - assessing the effects of changes in particle size distribution of the active pharmaceutical ingredient (API) on its oral bioavailability?
  - predicting the virtual bioequivalence between the "new" and "old" API lots?

Model Development – Key inputs

- BCS Class IV drug
- Neutral compound
- Aqueous solubility = 10 µg/mL
- Significant solubilization by bile salts
- Intermediate lipophilicity
- No food effect

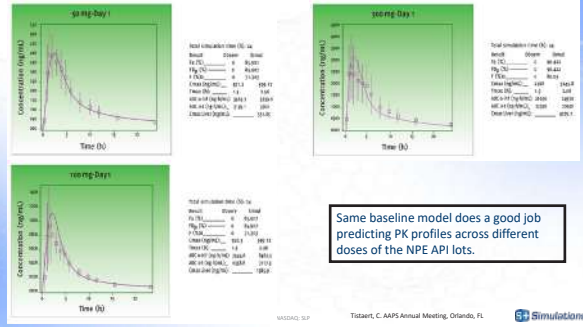
Parameter	Value
CL	0.115 L/h/kg
First pass extraction	17%
Vc	0.324 L/kg
K12	0.26 h^{-1}
K21	0.1 h^{-1}

Various Particle Size Used in Clinical Studies



Tistaert, C. AAPS Annual Meeting, Orlando, FL

Model Validation Results of NPE Lots



Same baseline model does a good job predicting PK profiles across different doses of the NPE API lots.

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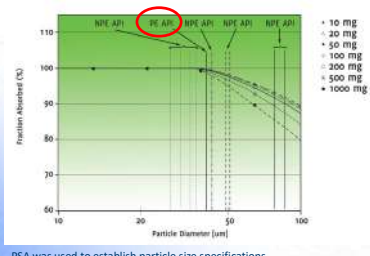
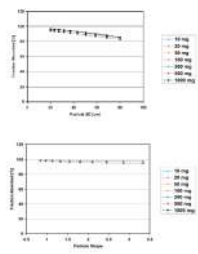
Establishing Drug Product CMA Specs





PSA was used to establish particle size specifications.
Results indicated significant changes in Fa% would not be seen until D(50) of NPE lots (30 - 40 µm) were reached *and* dose exceeded 100 mg.

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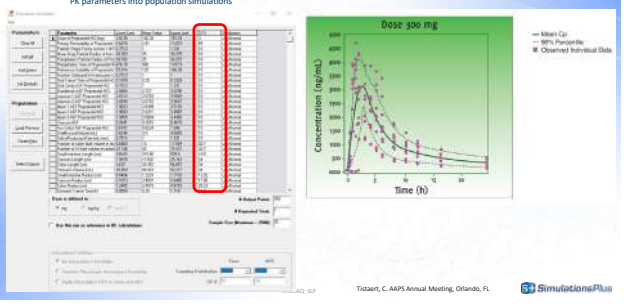
Virtual Bioequivalence Trial Simulations

Incorporate variability for physicochemical, formulation, physiology and PK parameters into population simulations

Validate simulated variability from existing clinical PK studies



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Virtual Bioequivalence Study Simulations

API Lot	PE/NPE	Dose (mg)	AUC_∞ (ng·h/mL) (N=250)		C_{max} (ng/mL) (N=250)	
			GM	GMR (90% CI)	GM	GMR (90% CI)
Lot 5	PE	50	4180	113.3 (110.7, 116.1)	551	139.3 (136.0, 142.7)
Lot 1	NPE	50	3688		395	
Lot 5	PE	100	8242	103.0 (100.9, 105.1)	551	106.4 (104.3, 108.6)
Lot 3	NPE	100	8001		395	
Lot 5	PE	300	24998	102.2 (99.8, 104.6)	3118	100.0 (97.7, 102.4)
Lot 2	NPE	300	24460		3117	
Lot 5	PE	100	8242	98.2 (96.2, 100.2)	1068	95.1 (93.2, 97.0)
Lot 4	NPE	100	8395		1123	
Lot 5	PE	300	24998	101.9 (99.8, 104.1)	3118	98.3 (96.3, 100.4)
Lot 4	NPE	300	24525		3171	

API: active pharmaceutical ingredient, AUC_∞: area under the plasma concentration-time curve from time 0 to infinite time, CI: confidence interval, C_{max}: maximum observed plasma concentration, GM: geometric mean, GMR: geometric mean ratio, NPE: non-particle-engineered, PE: particle-engineered

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Project Summary & Outcomes

- Mechanistic model was constructed and validated across dose levels using clinical data from products manufactured with NPE API.
- Parameter sensitivity analysis helped define and justify specifications for CMAs (particle size distributions) for the new PE product lots
- Virtual bioequivalence trial simulations showed the population-derived C_{max} and AUC values would be bioequivalent between products manufactured with NPE vs. PE API, within the validated CMA specifications, regardless of the dose.

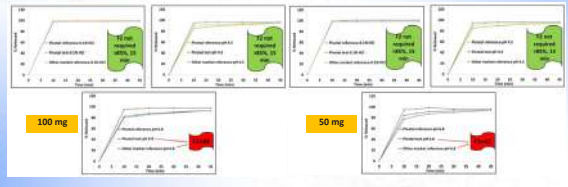
Outcomes

- **Regulatory agencies approved the sponsor's biowaiver application**
- **Sponsor got to market ~12 months before it would have running the full trials**

Study Leverage + PBBM to Support Biowaiver in New Market

Study Leverage + PBBM to Support Biowaiver in New Market

- BCS Class III API: formulation available in 50 mg and 100 mg dose strengths
- BE fasting study was successfully conducted at 100 mg in Market A
- Leveraging the generic product to new Market B, the Market B reference product demonstrated f2<50 in pH 6.8 against pivotal test for both dose strengths
- Market B agency denied BCS biowaiver of both strengths and requested that the BE study was warranted

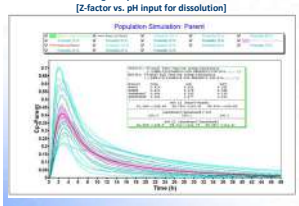


PBBM modeling strategy was proposed to support the biowaiver of the BE study for both dose strengths

Bhattiprolu et al. (2022) J. Pharm. Sci. Sep 9:S0022-3549(22)00399-9
Ahmed T. (2023) MIDD+ Virtual Conference

Study Leverage + PBBM to Support Biowaiver in New Market

Pivotal 100 mg study validation – PBBM simulations [Z-factor vs. pH input for dissolution]



PK parameter	Predicted values	
	Geometric mean ratio	90% confidence intervals
	100mg	
Pivotal Ref vs Pivotal Test		
C_{max} (ng/mL)	100.4 [104.36] *	91.64-109.90 [97.63-111.56] *
AUC_{0-inf} (ng/mL)	100.1 [100.66] *	89.711-111.79 [98.39-102.98] *
Pivotal Ref vs Market-B Ref		
C_{max} (ng/mL)	99.0	90.30-108.54
AUC_{0-inf} (ng.h/mL)	99.0	88.78-110.40
Market-B Ref vs Pivotal Test		
C_{max} (ng/mL)	101.4	92.46-111.14
AUC_{0-inf} (ng.h/mL)	101.2	90.71-112.4

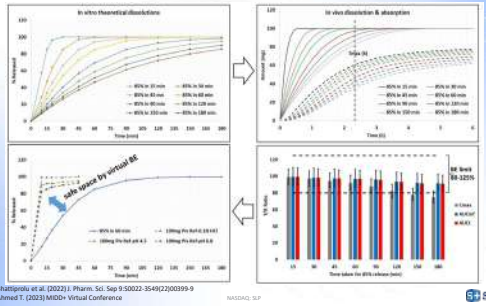
* observed T/R ratio's and CI's

Study outcome: biowaiver granted for both 50 mg and 100 mg doses – regulatory agency provided favorable feedback

Bhattiprolu et al. (2022) J. Pharm. Sci. Sep 9:S0022-3549(22)00399-9
Ahmed T. (2023) MIDD+ Virtual Conference

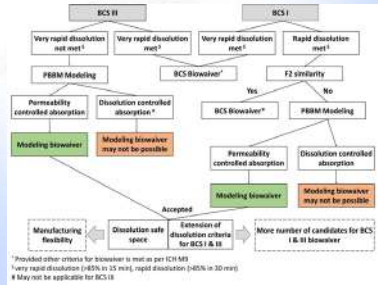
Study Leverage + PBBM to Support Biowaiver in New Market

BE safe space of 85% in 60 minutes was determined without impacting bioequivalence



Bhattiprolu et al. (2022) J. Pharm. Sci. Sep 9:S0022-3549(22)00399-9
Ahmed T. (2023) MIDD+ Virtual Conference

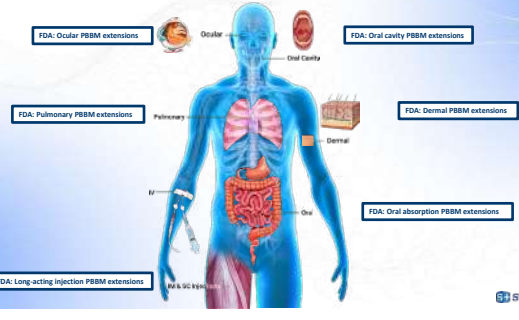
Proposed Biopharmaceutics Risk Assessment Strategy for BCS I & III Biowaivers

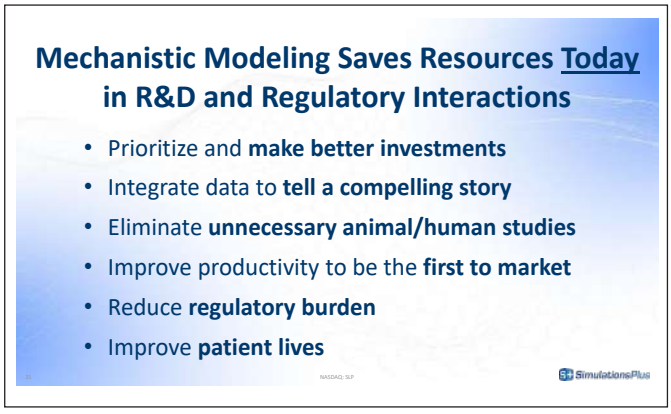


Bhattiprolu et al. (2022) J. Pharm. Sci. Sep 9:S0022-3549(22)00399-9
Ahmed T. (2023) MIDD+ Virtual Conference

The Next Frontier(s) and Conclusions

Partners Driving M&S: Scientific Collaborations to Advance on PBBM





Implementing Automation in the Pharmaceutical Labs

Mr. Samir Haddouchi, Managing Director, SPS Pharma Services, France

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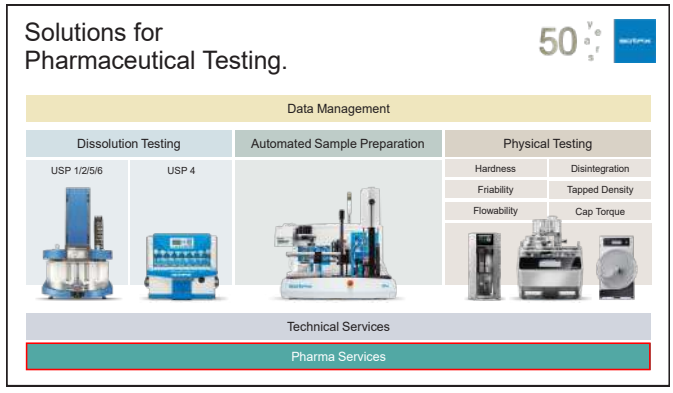

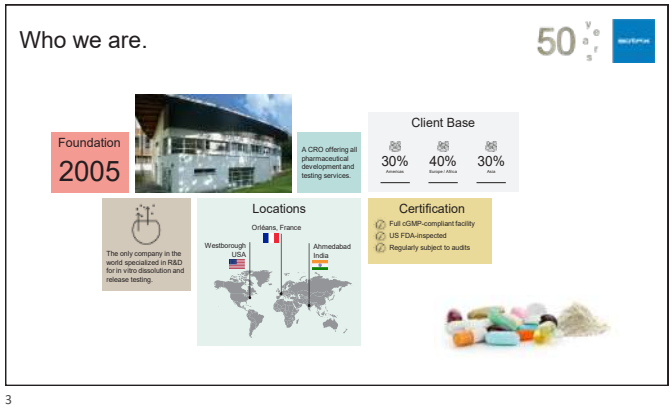

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R&D Services – All Analytical Techniques.

API screening & characterization	Solubility Studies	Method Development for all analytical techniques (LC, GC, IC, UV-Vis)	IVRT In-Vitro Release Testing (USP 1-7)	Novel Microdialysis based IVRT studies
IVPT In-Vitro Permeation Testing of Oral Dosage Forms	IVPT In-Vitro Permeation Testing of Topical Dosage Forms	Reverse Engineering / Deformulation	Q3 Characterization (physico-chemical)	
IVIVC (in silico simulation, modeling)	Analytical Method Automation	Cleaning Validation		

Back to SEGMENTS

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Routine Testing Services (GMP) – Compliant Reliability.

Analytical Method Validation / Method Transfer	In-Vitro Bioequivalence (BE)	Stability Studies	Clinical & Commercial Batch Release	
QC Analysis Dissolution / IVRT	QC Analysis Analytical Methods (LC, GC, IC, UV-Vis)	QC Analysis		
QC Analysis Assay / CU and Degradation Products	QC Analysis Physical Testing	QC Analysis LC-MS Testing for Impurities / Nitrosamines		

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Support Services – Whenever you need help.

Consulting	Troubleshooting & Investigations	Training	
Audits	Support for Q1/Q2 Regulatory Clearance		

Back to SEGMENTS

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Implementing Automation in the Pharmaceutical Labs.

- Why automation ?
- Automation for dissolution testing
- Method transfer
- Case studies
- Conclusion

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Automation is already widely used in a pharmaceutical laboratory !

Who is injecting manually samples onto the HPLC ?

9

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Automation is already widely used in a pharmaceutical laboratory !

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Automation is already widely used in a pharmaceutical laboratory !

Who is injecting manually samples onto the HPLC ?

In addition, several other automated systems are available and widely used:
- Automated physical testing
- Automated dissolution systems
- Automated sample preparation systems

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Why using automated systems ?

- Productivity
- Time to market
- Safety
- Data quality

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Productivity

Most obvious reason to invest on automated systems !

Automated systems can operate a defined process without any interaction of the analyst. This releases time for other added-value activities (ie paperwork, method development…).

Few full time equivalents may be gained in this manner.
The return of investment is usually quite easy to evaluate based on the salary, cost of analysis, etc...

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Time to market

Instead of the previous situation where the aim was to carry out more analyses throughout the year, automation can also help to decrease the impact of time-consuming steps.

In development, automated systems (especially dissolution) can support the formulation development by analyzing different variants overnight and giving the opportunity to improve the formula the day after…

In production, the time needed to release a batch is reduced and therefore the following steps can be done with no risk (ie packaging, shipment, etc…).

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Safety

Some active ingredients used in the pharmaceutical domain are extremely dangerous:
- cytotoxics
- cytostatics
- highly potent drug
- nanoparticles, etc…

We are no more accepting the idea of risk, trying whenever to minimize it.
➔ **Automated systems can help avoiding employees exposure to such products.**

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Data quality and Compliance (1)

Be careful to the difference between:
- Quality Assurance
- Quality

What is the goal when developing a characterization method for a product ?

To ensure that the data generated reflect the **quality of the product** and are not related to the **quality of the method** !

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Data quality and Compliance (2)

USP published several papers on the influence of different factors and parameters on the results of Performance Verification Tablets (Prednisone).

One of the main reason identified to be a root cause for non compliant results was the operator.

By using automated systems, one can eliminates this variable and therefore ensure having an overall better method.

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Quality Assurance

Rough estimation of the cost for an OOS report : $3000….
and that was for an investigation with an obvious assignable cause which could be concluded very quickly (lost time, paperwork…).
Some companies handle tens of such reports per month !!
Using automated systems can help **minimizing the risk** of analytical errors or mix-ups.

Another area of concern for the FDA is the documentation.
From a FDA official: *« If you didn't document it, it didn't happen. In God we trust, for everyone else we require documentation ».*

It is way easier to verify a secured/ protected database/audit trail than a lab book.
…. and what about auditing a human brain !

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Implementing Automation in the Pharmaceutical Labs.

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Automated sampling

This is the first step in automation.

Allows to perform sampling automatically i.e. over night, for Extended Release products.

Samples can be stored in tubes or vials for a further quantification (called HPLC or UV off-line)

Or measurements can be done online (UV-Visible photometry) and then the results are available "on the fly" (more cost effective)

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Automated sampling

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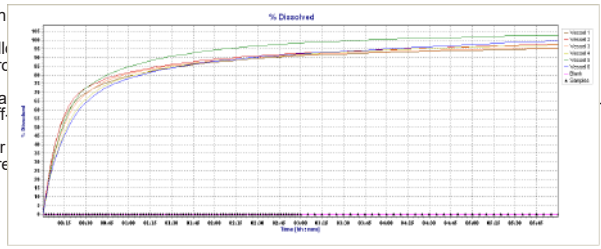

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USP2 instrument online/ offline

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Fully automated systems

Allow to automate:
- the preparation of the test (heating, degassing and filling the dissolution media in the vessels)
- the dissolution test itself (with offline collection or online readings)
- The cleaning of the system to be able to start another test

All these steps are repeated successively without user interaction.

These systems are more expensive than a semi automated system but they allow to have one single operator producing 10 to 15 dissolution tests per day. Moreover, tests could be done during week ends.
Decision should be made based on the type of products (IR, ER), the number of batches/ day, etc…

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Fully automated systems

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Implementing Automation in the Pharmaceutical Labs.

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Regulation

The only reference appears in USP <1092> which is a recommendation, not enforceable.
For automation considerations:
Medium preparation, Sample introduction and timing, Sampling and filtration
Cleaning, Software and data handling (the software used must be validated as per 21 CFR part 11)

Tentative proposal for acceptance criteria:
A typical acceptance criterion is that the difference in the mean value does not exceed:
- an absolute 10% at time points with <85% dissolved
- an absolute 5% for time points >85%.

Acceptance criteria may be product specific, and other statistical tests and limits may be used.

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Filtration

Often, the filters used on automated systems are different than those validated for the manual method.

Aim: Confirms that the drug tested does not adsorb onto the filter.

Procedure: Manually filtered samples and automated filtered samples are compared.

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Cross validation

The Pharmacopeias are expressely mentioning:
"If automated equipment is used for sampling ... verification that this automated apparatus will produce results equivalent to those obtained with the standard apparatus is necessary."

Aim: Confirms that automated results are not significantly different than manual results.
This is done by performing at least two automated runs (12 replicates), at each dosage concentration, using all sampling points, compared to manually sampled runs of the same samples.

Remark:
It may also be possible, depending on the instrument design, to withdraw manual samples while the system is running automated sampling/ measurements (on the same dissolution runs)

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Cleaning

As fully automated systems are cleaning vessels, it is expected that the cleaning verification is done for every product.

Aim: Confirms that automated cleaning cycle is sufficient to prevent carryover.

Procedure: Run a normal dissolution test, followed by a “blank” run.

If applicable, use the highest dosage strength for the carry-over verification.

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Implementing Automation in the Pharmaceutical Labs.

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Existing manual method

Parameter	Description
Apparatus	USP 2 (Paddle)
Medium	XXX, pH 4.5 with 0.5% SDS
Volume	900ml
Speed	100rpm
Temperature	37°C
Sample	1.0mL for HPLC
Filtration	GF 0.7 µm
Sampling Profile	0 ; 150 ; 390 ; 720 min.

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Results obtained on fully automated.

	Dissolution profiles – AT70 method Batch ZZZYYY (n=6)							
Time (min)	Vessel 1	Vessel 2	Vessel 3	Vessel 4	Vessel 5	Vessel 6	Mean	SD
0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
150	14.3	13.3	14.1	10.8	16.4	13.3	13.7	1.8
390	47.6	50.3	48.9	44.9	54.1	50.4	49.4	3.1
720	95.1	98.6	93.8	91.1	104.2	98.4	96.9	4.6

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Cleaning verification

	Dissolution profiles – AT70 method Batch NO TABLET (n=6)							
Time (min)	Vessel 1	Vessel 2	Vessel 3	Vessel 4	Vessel 5	Vessel 6	Mean	SD
0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	-
150	0.0	0.0	0.0	0.0	0.0	0.0	0.0	-
390	0.0	0.0	0.0	0.0	0.0	0.0	0.0	-
720	0.0	0.0	0.0	0.0	0.0	0.0	0.0	-

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Results comparison

	Dissolution profiles – AT70 method Batch ZZZYYY (n=6)							Manual
Time (min)	Vessel 1	Vessel 2	Vessel 3	Vessel 4	Vessel 5	Vessel 6	Mean Auto	Mean Manual
0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
150	14.3	13.3	14.1	10.8	16.4	13.3	13.7	18.0
390	47.6	50.3	48.9	44.9	54.1	50.4	49.4	53.0
720	95.1	98.6	93.8	91.1	104.2	98.4	96.9	98.0

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Case study conclusion

- The dissolution method, when tested on the AT 70smart system, shows similar results. The comparison of the results obtained with the two types of system seems consistent (mean profiles are similar).
- The automated cleaning cycle of the system was successfully verified, no cross contamination between the initial dissolution test and the following blank test.

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Pfizer Case Study

Acknowledgements to Sean Space, Pfizer US

Apparatus	USP <711> Dissolution Apparatus I (baskets) and Apparatus II (paddles)
Media	500 mL of water 500 mL of 0.01N HCl 500 mL of 0.1N HCl 500 mL of pH 4.5 buffer 500 mL of pH 6.8 buffer
Basket Speed	50 and 100 rpm
Paddles speed	50, 75 and 100 rpm
Total number of dissolution runs	340 in 3 months

- Varenicline Film-Coated Tablets
  - Approved nicotinic receptor partial agonist smoking cessation.
  - Approved in over 60 countries
  - BCS Class 1

Two dosage strengths subject to SUPAC screen

Aberrant and variant dosage forms evaluated with selected conditions

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Varenicline: Why automation?

- Automated system used to:
  - Evaluate effects of agitation, media, and apparatus type on the release of both 0.5 and 1.0 mg tablets with 5 media, 2 paddle speeds, 2 basket speeds
  - Evaluate release characteristics of aberrant/variant tablets
  - Used to analyze ICH and Site Validation stability studies (4 lots of each strength in 3 packaging configurations each)
- Over 600 dissolution tests in one quarter ➔ 50 dissolution tests per week !!
- Approved in 71 countries
- Launched in 48 countries

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Teva Canada: Cost Saving Evaluation

Acknowledgements to Krystyna Pobloka, Teva Canada

	Cost Saving in $CND/Batch	Cost Saving in $CND/Year
Product I	$282.00	$140,625
Product II	$175.00	$87,500
Product III	$175.00	$25,200

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Teva's conclusion

- Validation has been focused on **high volume products**.
- As a result of transfer to automated methods, time of release of the finish product decreased due to the overnight and weekend runs.
- Significant cost saving per batch (runs unattended - available resources for other tasks).
- Reduced number of the investigations due to lab errors (locked methods).

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Implementing Automation in the Pharmaceutical Labs.

- Why automation ?
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- Method transfer
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Take-home Message.

- Using automated systems can help enhancing the quality of data by minimizing analytical variables, ensuring better compliance to methods and complete Data Integrity ➔ Quality and Compliance
- Implementing automated systems can help improving the productivity hence decreasing the testing costs ➔ Productivity
- Automated dissolution testing can facilitate and speed up the formulation development process ➔ Time to market
- It is of importance to consider all the laboratory processes to identify the bottlenecks and select appropriate technical solutions.

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We are our patients...

Science should drive Guidance, that will induce Practice.
Only then, we will ensure Compliance and then Quality !!

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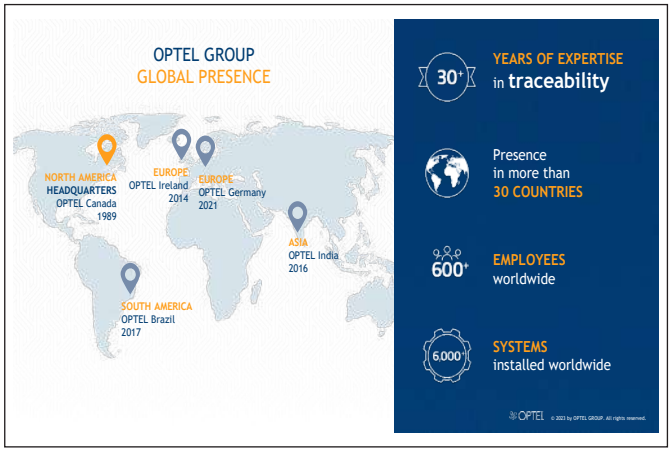
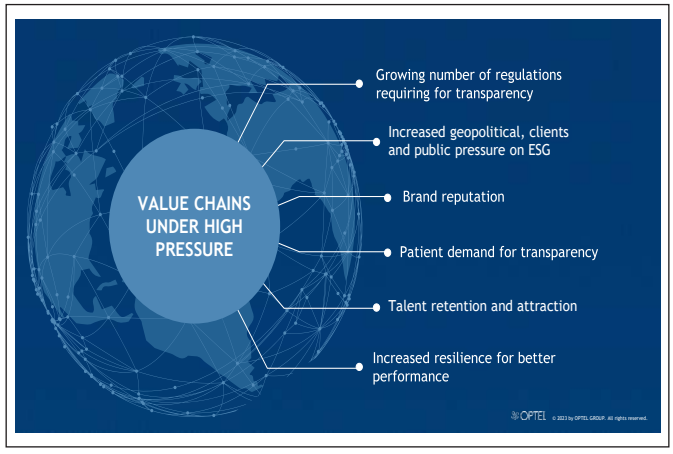
The Future of the Pharmaceutical Supply Chains

Mr. Florent Bouguin, Vice President, Chief Technology Officer, OPTEL Vision India P. Ltd.






Supply chain becomes a national security asset
Localize supply chain and reduce dependencies
Secure stocks of critical product
Excise and Taxation
Inflation Reduction Act
Green deal


ESG regulations in scaling across the globe
ESG's three central factors are:
Environmental
criteria, which examines how a business performs as a steward of our natural environment, focusing on:
Waste and pollution
Resource depletion
Greenhouse gas emission
Deforestation
Climate change
Social
criteria, which looks at how the company treats people, and concentrates on:
Employee relations & diversity
Working conditions, including child labor and slavery
Local communities; seeks explicitly to fund projects or institutions that will serve poor and underserved communities globally
Health and safety
Conflict
Governance
criteria, which examines how a corporation polices itself - how the company is governed, and focuses on:
Tax strategy
Executive remuneration
Donations and political lobbying
Corruption and bribery
Board diversity and structure
https://marketbusinessnews.com/financial-glossary/esg-definition-meaning/
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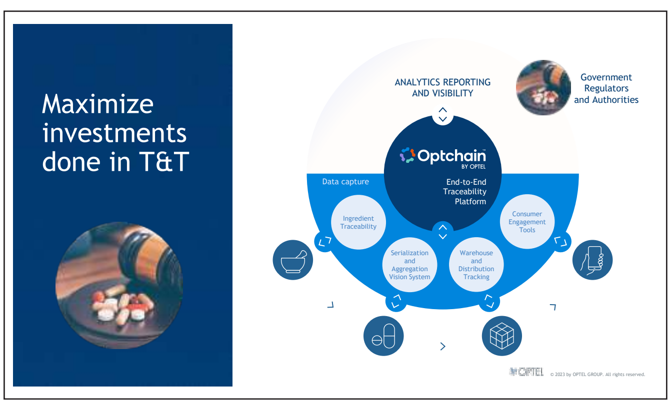
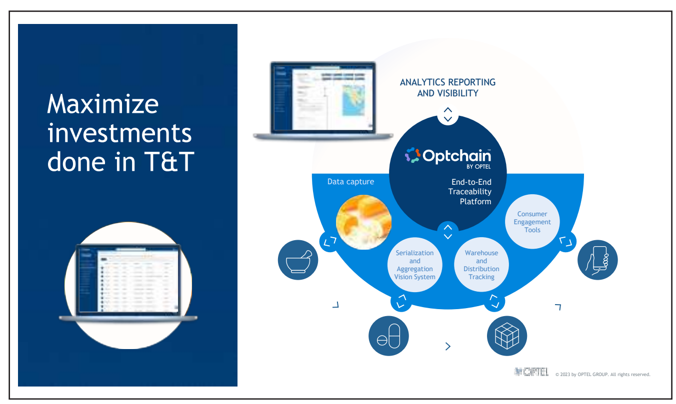
Businesses have no visibility on their supply chain!
"One of the solution: traceability"
Let's now see how it could work!


End-to-end supply chain digitization
Sustainability
Traceability
Performance
Compliance
Supplier (API)
Manufacturer
Wholesaler/ Distributor
Consumer / Patient
Waste and Recycling
VALUE DATA
EMPOWER DATA
CAPTURE DATA


Maximize investments done in T&T
ANALYTICS REPORTING AND VISIBILITY
Government Regulators and Authorities
Optchain BY OPTEL
End-to-End Traceability Platform
Data capture
Ingredient Traceability
Serialization and Aggregation Vision System
Warehouse and Distribution Tracking
Consumer Engagement Tools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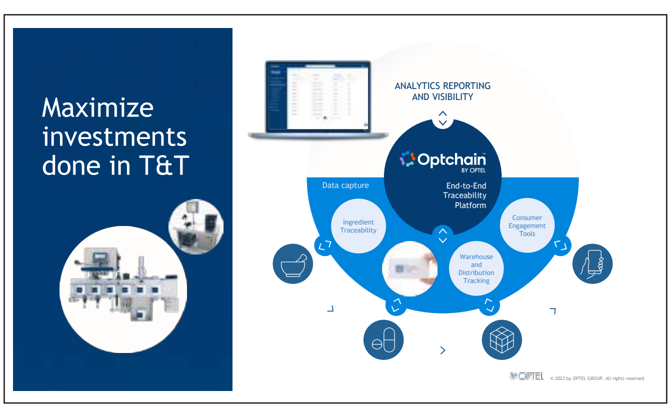
End-to-End Traceability Platform
Data capture
Serialization and Aggregation Vision System
Warehouse and Distribution Tracking
Consumer Engagement Tools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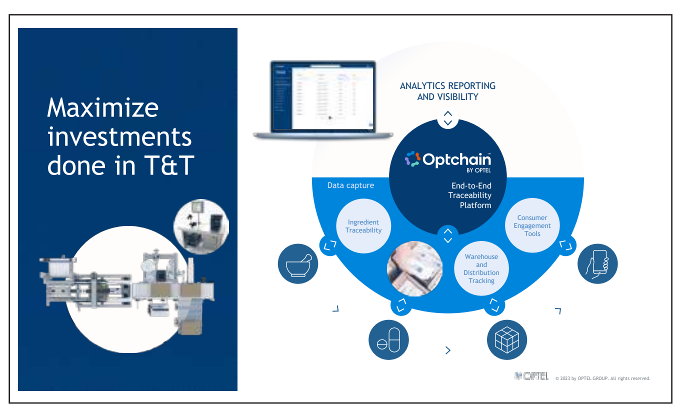
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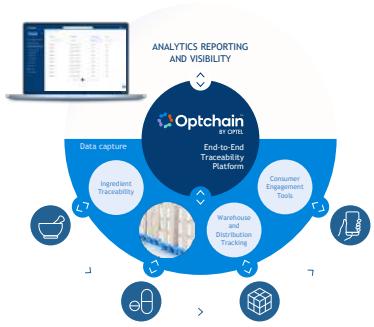

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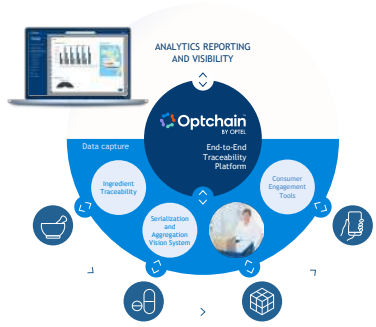

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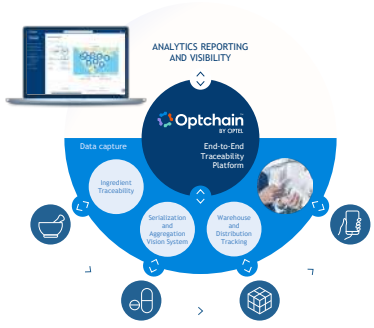

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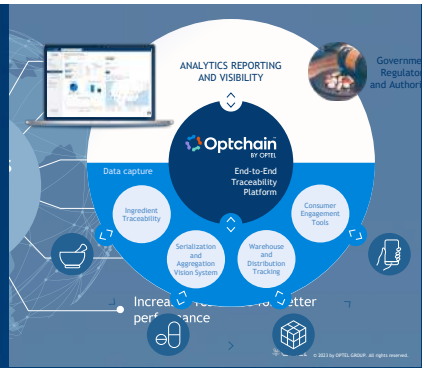

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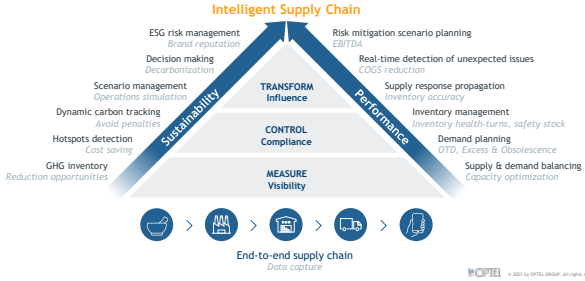
Trustable outputs

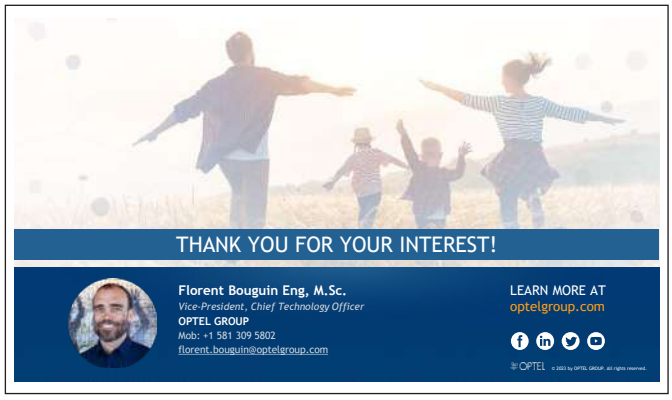
- Scientific credibility
- Proven
- Assured, verified and audited
- Security, immunity and privacy
- Accuracy, timeliness and precision

FAST AND TANGIBLE RETURN ON INVESTMENT



BOLD MOVES

Accelerate supply chain **digitization,** and make your businesses more **resilient** and **sustainable**



Excipients - Specifications and analysis need for Global Compliance

Ms. Vishakha Metkar, Senior Manager - Regulatory Affairs, Colorcon Asia

EXCIPIENTS – SPECIFICATIONS AND ANALYSIS – NEED FOR GLOBAL COMPLIANCE

22nd IDMA-APA PAC 2023
Pharmaceutical Analysts Convention
MUMBAI
Friday 24 – Saturday 25 February 2023

BY

Vishakha Metkar
Chairman –Regulatory Affairs and GMP Committee
International Pharmaceutical Excipients Council of India (IPEC INDIA)
Senior Regulatory Affairs Manager – Colorcon Asia Pvt Ltd – India

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Disclaimer

"The views and opinions expressed in this presentation are only of the author, and should not be construed to represent IPEC India, IPEC Federation or other IPEC Member view or policies"

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Outline of Presentation

Excipient – definition, magnitude and impact on industry

Harmonization of Standards
- – current status
- – Evolution of Regulatory systems
- – What's in future

Specifications and Analysis of Impurities in Excipients – (Nitrosamines/ Elemental Impurities/ Residual solvents)
- – Support from Suppliers
- – Concerns
- – Communication with Suppliers
- – Considerations while setting Specifications

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Pharmaceutical Excipients - Definition

What are Excipients
The word *excipient* is derived from the Latin *excipere*, meaning 'to except', which is simply explained as 'other than'. Pharmaceutical excipients are basically everything other than the active pharmaceutical ingredient in a dosage form

"**All other components of a drug formulation other than the active drug.**"
Lou Blecher (founder of IPEC-Americas), 1991

"**Excipients are substances other than the API that are intentionally included in a drug delivery system.**"
USP-NF General Information Chapter <1078>

"**Substances other than the API which have been appropriately evaluated for safety and are intentionally included in a drug delivery system.**"
IPEC General Glossary of Terms and Acronyms, 2014

The Common Theme in each definition is that the excipient is differentiated from the API –

Reason is because they are VERY different than APIs

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What is Excipient Industry AND Why different than Drugs

Diverse Materials Base

- **Chemical synthesis** (Polymer mixtures, Cellulose derivatives – substances often less defined than low mol wt entities)
- **Mining of minerals**
- **Harvesting of vegetation**
- **Formulated Products**
- **Biotechnology & Fermentation**
- **Genetic Modification**
- **Animal by-products**

Majority of Pharmaceutical Excipient Suppliers are Chemical Industry subsidiaries

- Products targeted at Food, Beverage, Industrial, and Cosmetics
- Small fraction of Main Production Volumes for excipient sometimes less than 0.1% of business
- Varying degrees of dedicated R&D related to excipient uses
- Specifications-driven by main market (usually not Pharma)
- Global Market and Manufacturing Base

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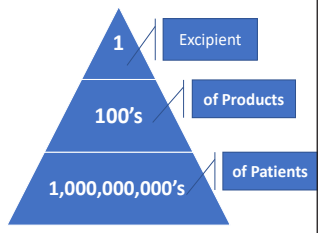
Magnitude and Impact of Excipients

- Over 8,000 excipients in use
- Can represent up to 95% of the formulation
- Patients consume more excipients than active ingredients
- Serve important functions in formulations



Growing Importance of Excipients in Drug Formulations

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Harmonization of Standards And Current Status

- **With increase in companies targeting multiple markets, harmonization of standards becomes a very important requirement.**

Harmonization of individual monographs is Critical, but cannot occur without harmonization of general test chapters

Harmonization has been proven to be slow and challenging

Harmonization is politically difficult

Pharmacopoeial Harmonization has been limited to PDG & original ICH countries

ICH *does not* want to reopen ICH Q4B

PDG *does* not want to expand

Now have agreed to start a pilot phase for expansion of membership & IPC has been chosen to be a part of this. It's the only pharmacopoeia that met all requirements of the entry criteria.

PDG welcomes Indian Pharmacopoeia Commission to pilot for global expansion - European Directorate for the Quality of Medicines & HealthCare (edqm.eu)

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CONCERN

- **Regulatory Authorities and Pharmacopoeias continue to develop guidelines and standards**
- **Increasing the complexity of the situation**
  - Does not necessarily increase patient safety
- **Lack of a harmonized approach globally to guidelines and pharmacopoeial standards impacts the ability of companies to ensure products can be available to multiple markets**

SO FAR ....

- **The ICH journey has mainly focused on finished product and API**
  - Despite excipients playing a central role in the drug development process
  - Despite the fact that few formulations can exist WITHOUT excipients
- **The previous view of excipients as "inert"**
  - Leads to failure to recognize the impact
  - Focus was primarily on conformance to pharmacopoeial monographs
- **ICH has lacked excipient experts**
  - So there was little pressure to consider excipient related topics

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Functional Equivalence

What is it?	• Performs the same function and provides the same utility
How is it used?	• Allows recognition of standards where they are focused on public health, safety, quality
Opportunities	• All compendia are focused on public health and safety

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Evolution of Regulatory Systems

- **Quality Risk Management (ICHQ Q9)**
- **Mutual Recognition Agreements**
- **ICH Expansion**
- **PIC/s expansion**
- **ICMRA (International Coalition of Medicines Regulatory Authorities)**
- **IPRP (International Pharmaceutical Regulators Programme)**

- **PIC/s (Pharmaceutical Inspectorate Cooperation Scheme)**
- Harmonization of GMP/GDP is fundamental to PIC/s
- Pharmacopoeial compliance/ testing is fundamental to GMP
- Common standards are necessary to accept inspection results

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What's Next?

- Industry supports / encourages establishing a process for engagement with the global pharmacopoeias to continue collaboration and discussions
- Addition of Functional Equivalence of Pharmacopoeias into the strategic framework
- Concept Enhancement
  - Expand upon the initial concept submitted by US FDA to ICH
  - Break the pieces up into distinct topics with rationale
- Education
  - Identify areas and regions where additional education on excipients (or specific excipient topics is needed)
- Advocacy
  - Work with key ICH members and observers to increase understanding of the impact
  - Collaborate with regulators that have expressed interest in excipient related matters

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Specifications and Analysis of Impurities in Excipients

Nitrosamines/ Elemental Impurities/ Residual Solvents

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Nitrosamines – a global issue

US FDA Guidance

- Control of Nitrosamine Impurities in Human Drugs, February 2021 (original September, 2020)
- Updates on possible mitigation strategies to reduce the risk of nitrosamine drug substance-related impurities in drug products, November, 2021
- FDA's recommended timeline for completion of confirmatory testing and reporting changes (steps 2 and 3) is **October 1, 2023.**

EMA Guidance

- EMA finalised a review under Article 5(3) of Regulation (EC) No 726/2004 in June 2020 to provide guidance to marketing authorisation holders on how to avoid the presence of nitrosamine impurities in human medicines
- A question-and-answer document is available for marketing authorisation holders on implementing the Article 5(3) CHMP opinion.

Guidance

- Recommends steps manufacturers of APIs and drug products should take to detect and prevent unacceptable levels of nitrosamines
- Describes conditions that may introduce nitrosamine impurities
- Additional points to consider in developing nitrosamine mitigation strategies, including consideration of the role of formulation design for controlling nitrosamine levels in drug products.

Role of Excipients in the Risk Assessment

Questions to consider for excipients during the drug product risk assessment

- Does the excipient introduce nitrosamines directly?
- Are nitrites or vulnerable amines present in the excipient? If so, is there a risk for nitrosamine formation in the drug product?

There are no regulatory requirements for excipient manufacturers to complete risk assessments on their excipients.

Is the Presence of Nitrites in Excipients a Concern?

It depends…
The impact of nitrites in an excipient should be evaluated individually for each product.

Wu et al, Reactive Impurities in Excipients, PharmSciTech, 2011

- Literature sources and Lhasa database available to provide some insights into the amount of nitrites present in excipients
  - Variability of nitrites exists between lots and excipient manufacturers
- **Best strategy is to engage with your excipient supplier to better understand if nitrites are present in an excipient and at what levels**

Conditions That Lead to Nitrosamine Formation

Confluence of factors

1. Nitrosating agent
2. Secondary or tertiary amine (vulnerable)
3. Appropriate conditions (elevated temperatures, acidic conditions, liquid phase)

Under acidic conditions, nitrite salts may form nitrous acid, which can react with an amine to form a nitrosamine

Sources of Nitrites in Excipients & vulnerable Amines in Drug Products

Process water used to manufacture the excipient can have trace levels of nitrites

Potable water has nitrite levels below 0.1 ppm and nitrate levels of 10 ppm and would not likely be a concern as a source of nitrosating agents. Purified water is even less likely to be a concern

Raw materials used to manufacture excipients may contain trace levels of nitrites

Nitrite can result from a process impurity or reaction by-product

API Contamination /API Manufacture (interactions during manufacture of drug substance)

- **The active drug substance**
- **Impurities or degradants in the active drug substance**
- **Counterion in pharmaceutical salts**
- **Excipients**

Similar to nitrites, the potential risk that may come from a vulnerable amine present in trace amounts in an excipient will depend on the formulation composition and should be evaluated accordingly

Removing nitrites not as simple as turning off a valve

Why is it difficult to control nitrites in Excipients

- Natural source: impacted by growing conditions
- Small demand from pharma industry versus other industries
- Could require different manufacturing equipment or processes to eliminate these.
- General scarcity of supply due to world events of commodity products
- What level is ok? Differs from drug to drug!
- Accurate test data is not currently available – most excipient manufacturers have statements based theoretical information or process knowledge
- Test methods not developed
- Testing of mixed excipients even more difficult

Mitigation strategies

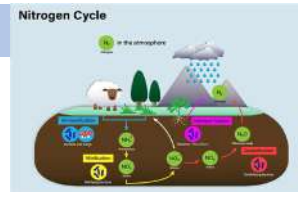
First FDA suggestion: Control nitrites in excipient suppliers

- Not easy or even possible in some cases

"FDA recognizes that **this is only one strategy**, and other approaches may be equally or more effective in controlling nitrosamine levels. Therefore, **FDA encourages manufacturers to explore other approaches** to mitigate or prevent formation of NDSRIs."

Reality

- Starch comes from corn/maize which is grown in the earth and is watered by rain.
- To make it into a pharmaceutical excipient no chemicals added, but rather the physical action of heat and shear.
- This is as close to a natural material as you can get, yet users say nitrite levels are too high!
- These cannot be reduced, as there is little to control, we live on a planet with a nitrogen based atmosphere!
- Risk needs to be assessed properly and pragmatically by users, and any limits applied by regulators need to be realistic or drug products will be lost from the market.



- WHO Guideline values for chemicals in water:
  - Nitrites 3mg/L (ppm)
  - Nitrates 50mg/l (ppm)

Bottle of Evian Spring Water contains 3.8mg/L nitrates

Is It Necessary to Introduce Limits for Nitrites in Excipients?

- Expectations from Drug formulators & Regulators
  - unreasonable or unrealistic expectations coming from formulators and regulators:
    - Some formulators are looking for zero nitrosamines, and nitrites.
    - Others claim they cannot use certain natural ingredients as the nitrite content is too high. For example starches used at 70% in a capsule formulation
- Implementing limits for nitrites will not alleviate the risk of nitrosamine formation
- The amount of nitrite present in a drug product as a result of an excipient is dependent upon the amount of excipient used in the formulation
- A thorough risk assessment on the drug product is required to determine if the presence of nitrites in an excipient (at any level) is a risk for nitrosamine formation

Communicate with Excipient Suppliers

- Work with excipient suppliers to understand the possible contributions / risk factors for nitrosamines formation from excipients
- Excipient manufacturers may not…
  - Test for amine-compounds or nitrosating agents on old batches or current batches
  - Have the capabilities to control these compounds in order to set specifications
  - Understand what information is available & what is not
- Excipient manufacturers generally have a detailed understanding of their manufacturing processes and the basic chemistry of the raw materials used. Understand these.
- Drug Product Manufacturer should work with the excipient supplier to determine IF they can do anything to assist with mitigation.
- Don't make unreasonable demands – e.g. .nitrite/ nitrate free or zero nitrite / nitrate
- Assess what other mitigation strategies may be available

It is in the interests of excipient manufacturers to provide information that would facilitate the use of their products.

Generating and Sharing of data

- **Where data is generated the below considerations should be followed**
  - Generate Meaningful Data
    - Avoid / Prevent Common Sources of Lab Testing Issues & False-Positives:
      - Avoid Non-optimized test methods
      - Avoid poor standard and sample storage & handling (volatile contamination risk)
  - Ensure Calculations and dilutions are correct to prevent inadvertent Limit of Detection/Limit of Quantitation issues
  - Looking at the raw data (injection by injection) ensures system suitability & potential trends are detected

IPEC Questionnaire & Expectations

Questionnaires Were Developed to Assist Excipient Manufacturers in Addressing Nitrosamine Questions.
There are no regulatory requirements for excipient manufacturers to complete risk assessments on their excipients

- IPEC federation published the **Questionnaire for Excipient Nitrosamines Risk Evaluation** Version 1 - February 2023
- This was developed to aid gathering data in order to assess the risks posed by nitrosamine formation.
- IPEC Europe also held a free Webinar on the use of their template
  - Link to YouTube Recording
- The Questionnaire is available for download immediately via the website www.ipec-federation.org and the websites of regional IPEC (IPEC-Americas, IPEC China, IPEC Europe, IPEC Japan and IPEC India).

Summary – nitrosamines

- Nitrosamines in drug products continue to be a concern
- Excipients are one of the several factors to consider in the potential formation of nitrosamine formation in the drug product.
- Communication with suppliers is key where mitigation is needed
- Be realistic about what can be achieved and consider other potential strategies

Residual Solvents Q3C & Elemental Impurities Q3D

What Applies to Excipients, What does Not??

What is it? –ICH Q3C and Q3D

ICH Q3C – Guideline on Control of Residual Solvents in Drug Products

ICH Q3D – Guideline for control of Elemental Impurities in Drug Products

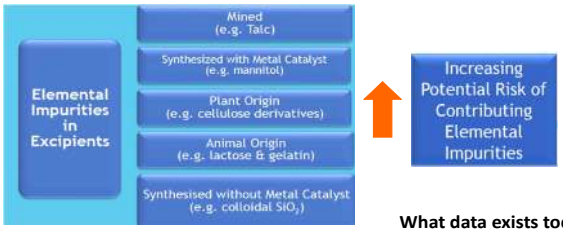
- **Applies to:**
  - **All** human drug products.
- **Does not specifically apply to:**
  - Components, i.e.Drug Substance/ **Excipients**
- **However, the Pharma Company needs to understand the levels potentially present to do THEIR Risk Assessment!!**

Emphasizes the use of Risk Assessment as opposed to testing wherever possible

What is it ?– ICH Q3C and Q3D

- **Key point** –the PDE requirements apply ONLY to the drug product itself! Responsibility for compliance is placed **completely with the drug manufacturer.**
- There is **NO** compliance requirement for excipient suppliers other than to share what they may know and what they do not know about Elemental Impurities in their excipients –may be very little!
- The Excipient supplier should have data on RS and share it with the Drug product manufacturer
- This is appropriate since many of these materials are primarily produced for other markets and the risk to the patient is from the drug product, not the ingredient!

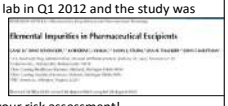
Risk Potential for Elemental Impurities in Excipients



What data exists today

What Data is available for Risk Assessment of EI

- **IPEC Americas –FDA – study**
  - IPEC Americas request for "blinded samples" to be tested by FDA lab in Q1 2012 and the study was completed in 2014
  - The test data was published by FDA & IPEC in a journal in 2015.
  - **Appropriate Use of Published Data** –
    Data is blinded so it will be important to establish a scientifically sound bridging from this data to the grades and suppliers actually used in the drug product –cannot simply use the data in your risk assessment!



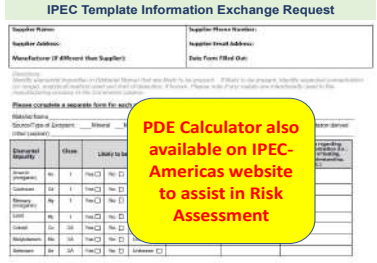
- **Use of LHASA DATABASE** (created by EI Pharma Consortium to gather a critical mass of data for excipients)
  - Aid in risk assessment and overall understanding of excipient risks.
  - Intent to publish key findings to de-risk common excipients.
  - Current membership mainly from big pharma in partnership with Lhasa.
  - Contact: CrinaHeghes(crina.heghes@lhasalimited.org)

Lhasa Limited

ICH Q3D – EI – Information from supplier

- Some excipient suppliers are fully engaged with this initiative, while others will not engage at all and their **business potential will drive decisions, not regulatory requirements**
- Most suppliers will only have EI information for elements which may have previously been listed in a compendial monograph
- Most suppliers **do not** plan to do any additional routine testing for elemental impurities due to ICH Q3D and have no intention of agreeing to any new specifications –**there may be some exceptions**
- Some suppliers have done some designed studies on a limited number of batches to improve their knowledge of potential EI in their products so they can provide some risk assessment assistance to their customers. The level of information provided will typically vary quite a bit from supplier to supplier.
- **Users should not try to pressure suppliers** for EI data that may not exist, otherwise supplier may leave the market and availability will then be a problem.
- Requests should be for whatever information the supplier is willing to share about their products and processes but not focus on the development of specifications since many suppliers will not agree to specifications on EI.

Sharing Information between Makers & Users



PDE Calculator also available on IPEC-Americas website to assist in Risk Assessment

IDEAL WORLD....
Pro-actively completed by suppliers and sent to users

REAL WORLD...
A limited number of suppliers have data or will complete and return the form to users

download THE LETTER

download THE TEMPLATE

PQRI Collaborative Study – Analytical Challenges – Interlab Study

- 28 Laboratories Involved
- Results have been finalized and will be published later this year:
  - ❑ Several elements were comparable between participants, reference laboratory. Exceptions: Cd, Hg, V.
  - ❑ Reproducibility was good for high conc elements. Reproducibility was better for total digestion than for exhaustive extraction.
  - ❑ Many more results and conclusions will be in publication
- **An Interlaboratory Study of Elemental Impurities in a Simulated Pharmaceutical Product: Results and Implications for the Industry**
- Will be published in **The Journal of Trace Elements and Minerals** – **Stay Tuned**

EI – Implications for Pharmacopeia

- As the Drug Product Manufacturer's are conducting an assessment of the EI content of finished products the heavy metals test has been removed from many pharmacopeial monographs.
- But not all in the Ph Eur the titanium dioxide monograph still contains limits for mineral content. The reason for this is that based on risk and typical metal content it was deemed to be necessary to monitor these levels.
  - However this does flag up pharmacopeial divergence as the USP does not have this testing any longer.
  - Additionally in Europe the use of colours in pharmaceuticals is governed by the food legislation:
    - EC 1333/2008 colour list, and EC 231/2012 purity criteria……which still contains limits for testing.
- So this topic has lead to divergence of standards in different regions.

ICH Q3C – Residual solvents – supplier information

- **The FDA's Q&A published in October 2008 clarified many doubts about RS.**
  - Q#9 of this Q&A clarified that Information of residual solvents **in coating materials, colorants, flavors, capsules, and imprinting inks is generally not needed** unless Class 1 solvents are used in the manufacture of these components.
  - It also clarified that an excipient manufacturer's statement that solvents are not used does not require the ANDA sponsor's verification.
- Most Excipient Suppliers will not test for RS but will provide statement based on process knowledge.
- Few Excipient suppliers will analyze their excipients and provide RS levels
- RS levels in Excipients may exceed Option 1 limits and should not be a concern if the final Drug Product has lower values than the PDE levels for the formulation.

ICH Benefit

- The main benefit of the ICH Q3C and Q3D Guidelines is that they both establish a reliable Permitted Daily Exposure for the relevant solvent or element.
- This is essential in conducting a risk assessment and allows there to be a defined outcome when this is done properly.
  - However the inexperienced (formulators and regulators) can get hung up on the Option 1 levels or simply the presence of the solvent or mineral and they determine it must be removed, reduced or controlled.
  - Whereas if the actual risk assessment is conducted properly this allows a reasonable and pragmatic approach to determine if any mitigation measures are necessary.

Summary

- Harmonization of individual monographs is Critical, but cannot occur without harmonization of general test chapters
  - Addition of Functional Equivalence of Pharmacopoeias into the strategic framework
  - Involvement with ICH, PDG Expansion programs
- Nitrosamine –
  - continues to be a global issue
  - excipients are one of the several factors to consider in the potential formation of nitrosamine formation in the drug product.
  - Communication with suppliers is key where mitigation is needed
- Residual solvents and Elemental Impurities
  - Limited information available with suppliers and very little test data for Elemental impurities, however information for Residual Solvents should be shared by Excipient supplier.
  - Risk assessment / Specification/ testing – communication with supplier is necessary

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- Alexa Smith – Colorcon Inc
- Kevin Hughes – IPEC Europe
- Andrew Teasdale – IPEC Europe

THANK YOU

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Comprehensive Workflow Solutions for E&L Analysis

Mr. Sunil Kumar, Sr. Product Marketing Manager- Mass Spectrometry, Thermofisher Scientific

ThermoFisher SCIENTIFIC

Comprehensive Workflow Solutions for E&L Analysis

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Sr. Product Marketing Manager- Mass Spectrometry

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Agenda

ThermoFisher SCIENTIFIC

- E&L Introduction
- Regulatory Landscape
- Sample preparation
- Workflow for volatile/semi volatile/nonvolatile compounds
- Databases

sunil.kumar@thermofisher.com

Extractables & Leachables

- **EXTRACTABLE**
  - Chemical released from process equipment, packaging or delivery system; **under laboratory extraction conditions**.

1 month

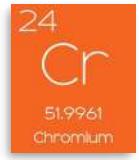
- **LEACHABLE**
  - Chemical that **migrates** from process equipment, packaging or delivery system; into drug formulation **under normal usage conditions**.

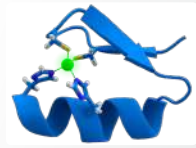
2-4 years

Areas of concern

CONTAMINANT TOXICITY

DRUG EFFICACY





Is there risk of harm to the patient?

Is there impact on drug potency?

Extractables versus Leachables

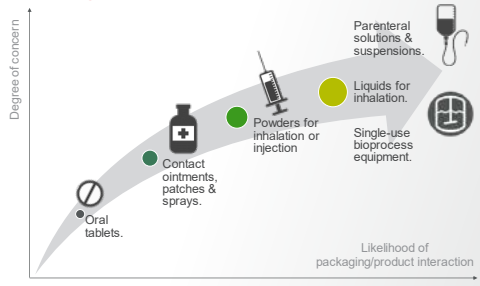
EXTRACTABLE

Test the materials

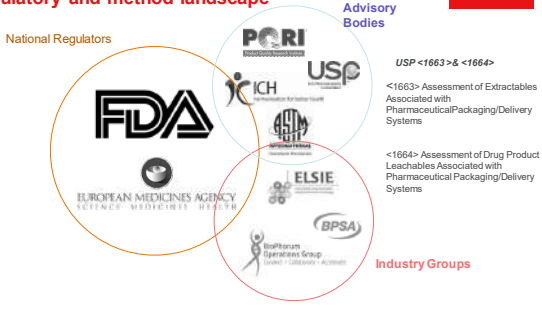
LEACHABLE

Test the product

Where are is the greatest concern for leachables?



E&L Regulatory and method landscape



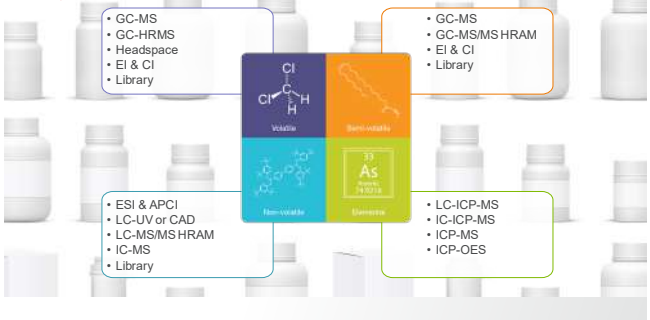
USP <1663> & <1664>

<1663> Assessment of Extractables Associated with PharmaceuticalPackaging/Delivery Systems

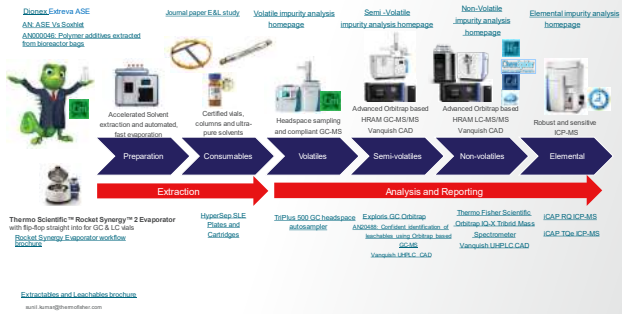
<1664> Assessment of Drug Product Leachables Associated with Pharmaceutical Packaging/Delivery Systems

How to test for extractables and leachables

Analysis of Extractables & Leachables



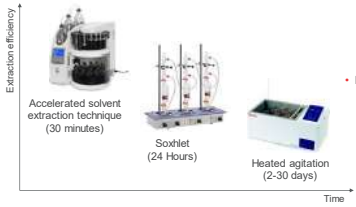
Comprehensive Extractables and Leachables Workflow



Principle and Best Practices Recommended

Guidelines:

- USP Chapter <1663> & <1664>
- Product Quality Research Institute (PQRI)
- BioPhorum Operations Group (BPOG)



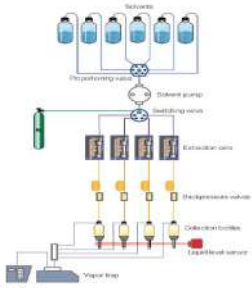
PQRI - A Controlled Extraction Study should:

- OINDP Recommendation (2006):
  - ***Employ vigorous extraction** with **multiple solvents of varying polarity***
  - *Incorporate **multiple extraction techniques**.*
- PODP Recommendation (2013):
  - *Controlled extraction studies should use a combination of **multiple extraction solvents** and extraction techniques as appropriate for, and consistent with, the **intent and purpose** of the controlled extraction study*

ASE- Accelerated Solvent Extraction

Drug manufacturers are required to prove product containers and contact materials are not reactive or additive

- The question is "What is in this sample?"



Automation from sample to vial eliminates the pressures of sample preparation

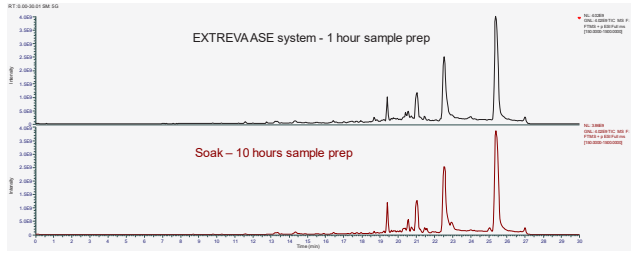
Extractables and leachables

- Traditional methods involve soaking a device or material in solvent for many hours
- Accelerated solvent extraction **saves many hours and** is recommended by PQRI

EXTREVA ASE system = About one hour per 4 samples
Soaking method = 10 hours for extraction alone

Extraction		
Extraction solvent	IPA	Hexane
Extraction cell size (mL)	10	
Temperature (°C)	125	100
Pressure (psi)	200	
Extraction time (min)	20	25
Rinsing volume (mL) - post rinse	10	
Purge time	120	
Gas-assisted mode	N_2 at 10 mL/min each channel	
Cell fill volume (%)	50	
Solvent flow rate (mL/min)	0.35	
Dead volume (mL) Initial fill volume (50%) mL Dynamic extraction volume (mL) Total solvent volume (mL)	5 5=10 x 50% 7= 0.35 mL/min x 20 min 17	5 5=10 x 50% 8.75 = 0.35 mL/min x 25 min 18.75
Evaporation		
Vacuum	2 psi (100 torr)	
Mode	Dryness	
Collection bottle	60 mL bottle	
Evaporation temperature (°C)	60	
N_2 flow rate	50 mL/min per channel	
Evaporation time (min)	45	30

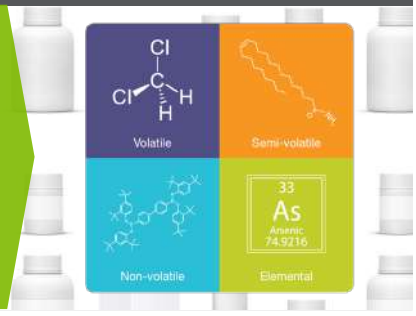
EXTREVA ASE system gives comparable results, faster



Chromatogram comparison of hexane extraction by the EXTREVA ASE system and 10 h soaking method

14 Proprietary & Confidential | chris.shevlin@thermofisher.com | 4-October-2022

Elemental impurities



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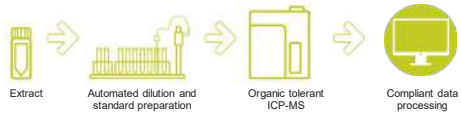
Elemental impurity workflow



- Workflow analogous to ICH Q3D and USP 232 & 233
- Demands organic tolerance and robust trace analysis
  - Polymer, extraction solvent and cell media
  - Thermo Scientific™ iCAP™ RQ ICP-MS with prepFAST
  - Thermo Scientific™ Qtegra™ ISDS software

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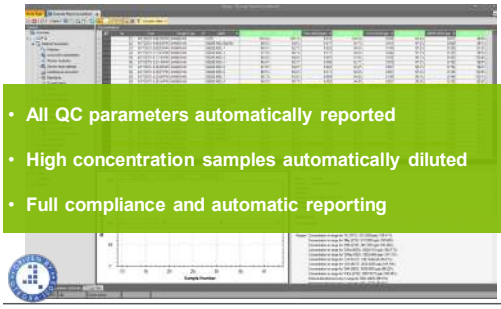
Analysis of pharmaceutical valve o-rings to USP 232/233



- **All QC parameters automatically reported**
- **High concentration samples automatically diluted**
- **Full compliance and automatic reporting**

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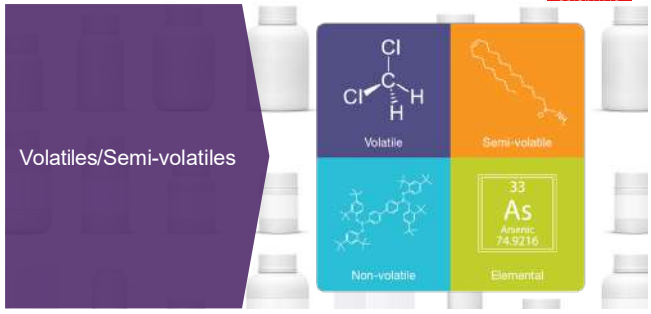
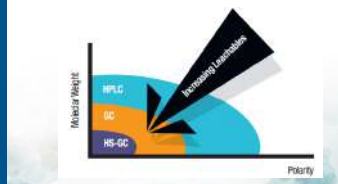
Volatiles/Semi-volatiles



Detect the Volatiles/Semivolatiles

- Low molecular weight, non-polar organic compounds are typically volatile, with the highest probability to migrate from or through polymeric contact materials
- Testing of contact materials is typically conducted by headspace sampling followed by GC-MS

Volatiles Impurities



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Extractable Analysis- Elastomeric Plunger – Dental Injectable cartridge

- Aqueous extraction of the plunger material followed by DCM extraction , no derivatization
- DCM extract derivatized with BSTFA
- Isopropanol Extraction

ISQ Mass Spectrometer	
Ion source type:	Thermo Scientific "ExtractaBrite"
Ion source temp.:	220 °C
Ionization mode:	EI, 70 eV
Emission current:	50 µA
Full-scan:	25–700 Da, 4 scans/s (250 ms/scan)

TRACE GC 1310 Headspace	
Injector:	Split/splitless, 320 °C Split 20 mL/min
Injection volume:	1 mL headspace
Inlet liner:	Splitless liner with glass wool, 4 mm ID (P/N 453A1925)
Oven program:	30 °C, 3 min, 8 °C/min to 280 °C 280 °C, 10 min

TRACE GC 1310 Liquid injection	
Injector:	Split/splitless, 320 °C 1 min splitless time for liquid extracts
Injection volume:	1 µL of liquid extract
Inlet liner:	Splitless liner with glass wool, 4 mm ID (P/N 453A1925)
Oven program:	40 °C, 1 min, 8 °C/min to 325 °C 325 °C, 10 min

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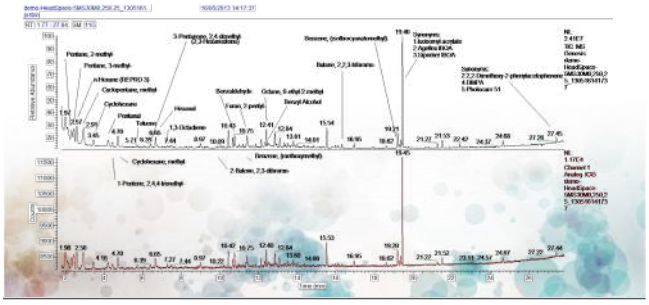
Chromatogram of Elastomeric Plunger- Headspace Analysis



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Limitations of Single quad

- Co-eluting compounds have interfering spectra. Difficult to identify and quantify.
- Compound m/z is in unit mass. Difficult to identify.
- Matrix interference not completely isolated by SIM. Difficult to identify and quantify.

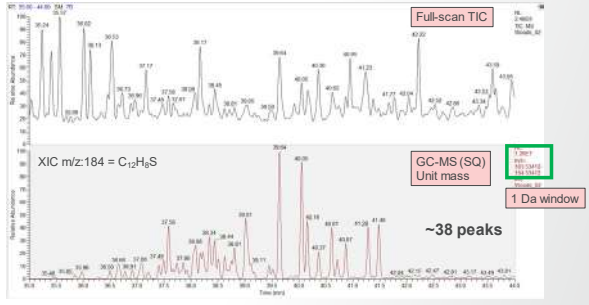
Nominal or Accurate Mass: An Example

$C_{12}H_8S$

Element	MW GC-MS	MW Orbitrap GC-MS
C	12	11.99945
H	1	1.00727
S	32	31.97152
$C_{12}H_8S$	**184**	**184.03412**

Nb: MW minus electron weight 0.005

Extracted Ion for Known Compound (Nominal Mass)



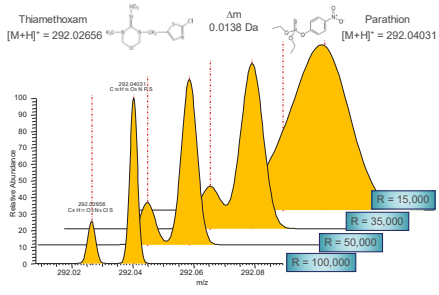
Component Identification- USP <1663>

Recommended process

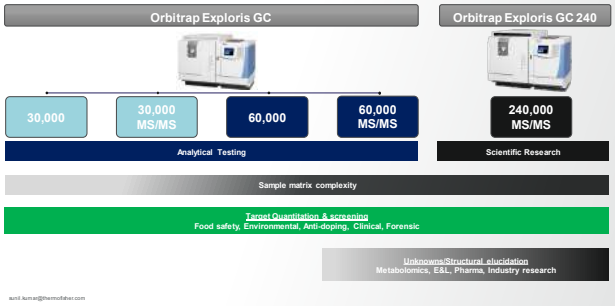
- **Scouting**-Provide information about bulk properties of the packaging materials
- **Discovery**-multiple analytical techniques to analyze the sample extracts
- **Identification**-A complex process, requiring expertise and advanced instrumentation
- **Quantitation**-"How much of the compound is in the sample?"

Identification- high end analytical instrumentation and analytical skills
Tentative- Library Search
Confident- HRAM
Confirmed – HRAM + Reference standard

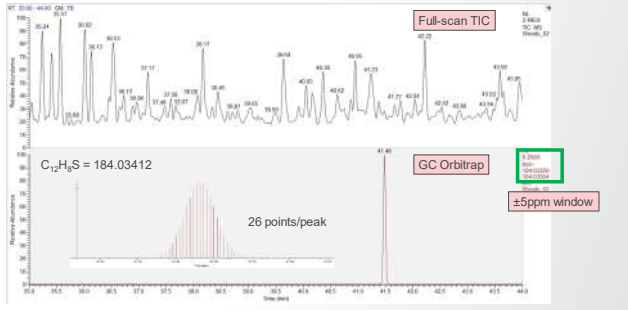
Isobaric Compounds



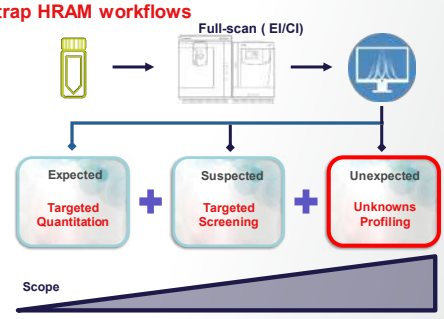
Orbitrap Exploris GC – HRAM



Extracted Ion for Known Compound (Accurate Mass)



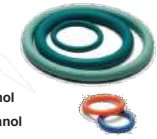
GC Orbitrap HRAM workflows



Pharmaceutical O-Rings extractables study

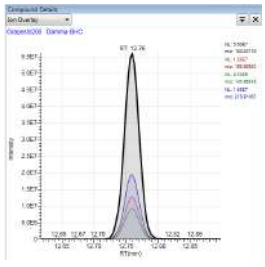
- 4 O-ring samples
  - **A** Red
  - **B** Brown
  - **C** White
  - **D** Black
  - **Blank** (control)

- Solvents
  - **Water**
  - **5M NaCl**
  - **50% Ethanol**
  - **100% Ethanol**
  - 1% PS-80
  - 0.5N NaOH
  - 0.1M Phosphoric Acid
- **40 °C for 30 days**



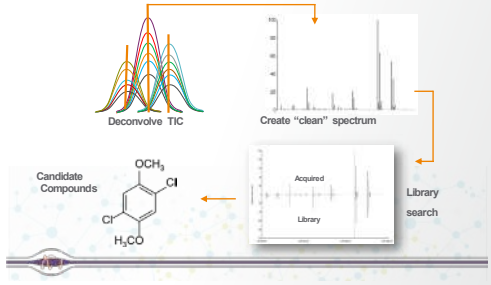
SMITHERS RAPRA

Points of identification with GC-Orbitrap

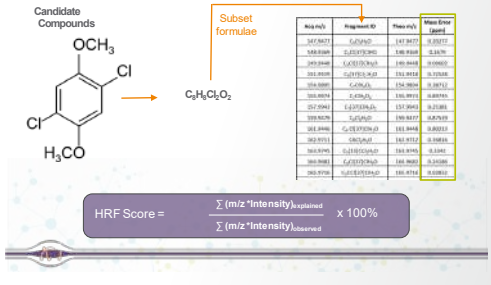


- Extracted accurate mass ±5ppm
- Retention time match standard
- Fragment ion confirm
- Ion ratio match standard
- Isotope pattern match
- Spectrum library match

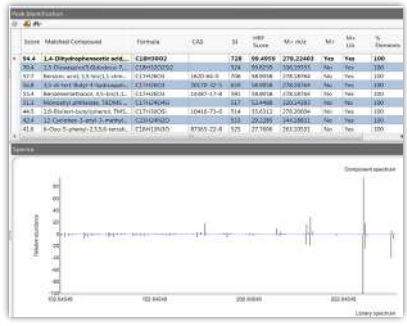
Peak Detection and Candidate Matching



High Resolution Filtering



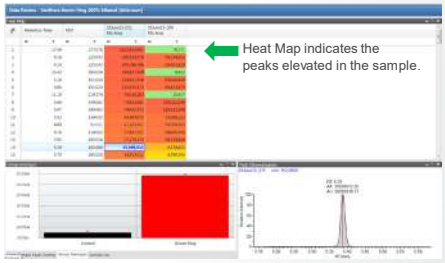
Identify the compound – searching NIST Library



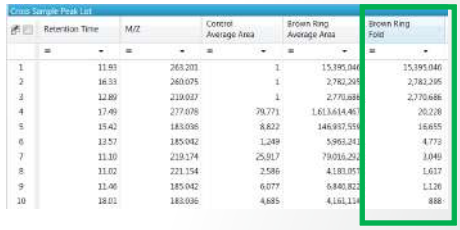
- 26 Hits from NIST are sorted based on:
  - Spectral matching
  - High Resolution Filtering (HRF) score.

Quickly isolate the peaks of interest

- 2051 peaks were extracted from the brown O-ring sample



Top 10 differential peaks in Brown O-ring

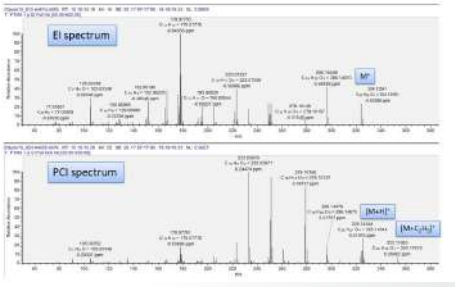


Peaks list can also be sorted by fold difference compared with control to isolate the differential peaks that could be low or high intensity.

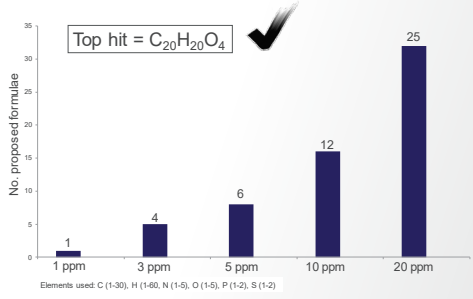
Identifying without a library hit?

Exploris GC: Compound Discovery and Identification

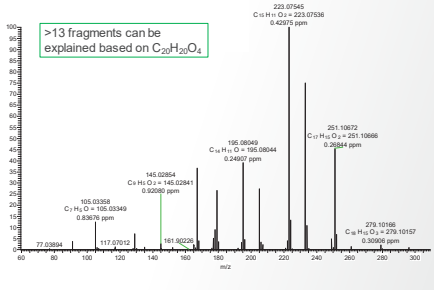
EI & PCI spectra for peak at 15.17 mins.



No. of proposed formulae for *m/z* 324.13541



MS/MS *m/z* 325.14 to support proposed formula



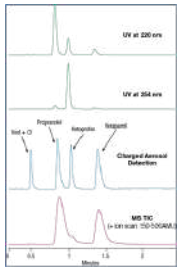
See what you're missing with Charged Aerosol Detection

- Detection without chromophore
- Quantify without exact standards
  - Relative quantification due to consistent response
  - Use virtually any standard for simplified AET calculations
- Consistent analyte response
- Four orders dynamic range

Thermo Scientific™ Vanquish™ Charged Aerosol Detector — Full integration with Thermo Scientific™ Vanquish™ UHPLC platform, slide-in module design, reduced flow path for optimum operation

#BuiltForBiopharma

Comparison of Charged Aerosol Detection to UV and MS



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ThermoFisher SCIENTIFIC

CAD for extractables and leachables

IPA blank

- *"Virtually universal detection"*
- *"able to detect and measure a large number of compounds that were completely transparent to UV detection."*
- *"CAD can provide a level of information that has until now been lacking with methods such as UV and even Mass Spec."*

Data from ESA Biosciences, Inc., Chelmsford, MA

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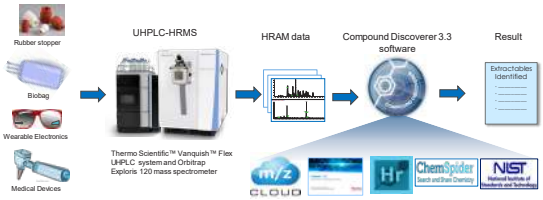
ThermoFisher SCIENTIFIC

LC-HRMS workflow for E&L analysis

ThermoFisher SCIENTIFIC



Multiple online/offline databases search in parallel

mzLogic and mzCloud are trademarks of Highchem LLC
ChemSpider is a trademark of the Royal Society of Chemistry

sunil.kumar@thermofisher.com

Screening and Quantitation Applications Benefit from the HRAM Orbitrap Exploris MS

Superior selectivity from outstanding resolution	**Mass stability and mass accuracy**	**Fast polarity switching**
Separate target compounds from interference	Maintain calibration for days to weeks with unrivaled scan:scan mass accuracy & precision	Quick positive-negative switch maintaining accurate mass/charge determination
No trade-off between resolution and sensitivity	**Minimum scan to scan variance**	**Experiment flexibility**
Both resolution and sensitivity are retained	Excellent signal/noise, no need for averaging	Easy to use plug and play device

All your screening and quantitation applications benefit!

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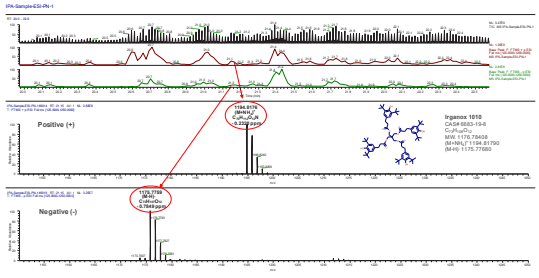
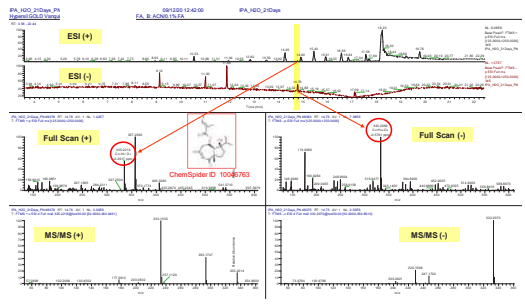
For research use only. Not for use in diagnostic procedures.

ThermoFisher SCIENTIFIC

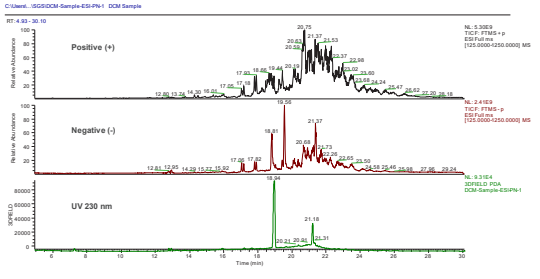
HRMS Polarity Switching with Sub-ppm Mass Accuracy



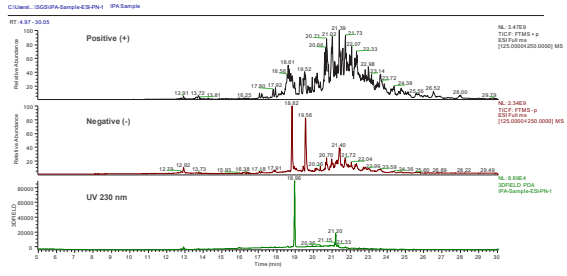
Full Scan MS/MS with Polarity Switching with Sub-ppm Mass Accuracy



Total Ion Chromatogram of Rubber Stopper DCM Extract



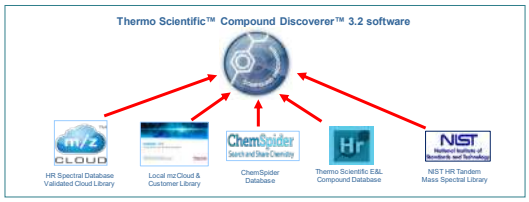
Total Ion Chromatogram of Rubber Stopper IPA Extract



Data Processing

Data processing software, database, and spectral library

Common practice "searching of internal and commercial databases with in-house expertise"



mzCloud™ High-resolution Tandem Mass Spectral Database

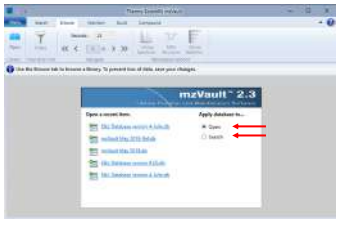
- A searchable, extensively-curated high-resolution tandem mass spectra database
- It allows searches of spectra, structures, monoisotopic masses, peaks (m/z), precursors, and names, etc.
- Identify compounds even when they are not present in the library using mzlogic through fragment ion information

https://www.mzcloud.org/

Free, cloud-based publicly available mass spectral fragmentation library
Please use "Internet Explorer" web browser

Thermo Scientific™ mzVault™ 2.3 Mass Spectral Database

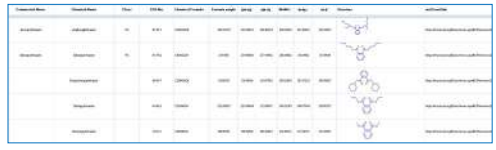
- Tool to create custom library
- Searching custom library
- Local mzCloud in Compound Discoverer software



Thermo Scientific E&L Compound Database with Structures

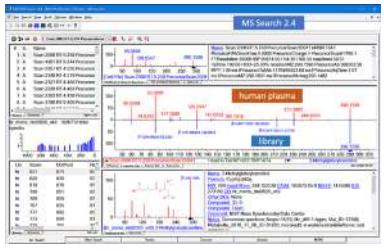
This Excel sheet database contains ~2000 common E&L related compounds and is incorporated into Compound Discoverer 3.2 software as "E&L Mass List".

This is a "living document" and new E&L related compounds are added periodically.



NIST High-resolution Tandem Mass Spectral Library - ESI

- Contains more then 40,000 reference standards with MS^n (n=2-4) using HCD, CID
- Fully integrated into Thermo Scientific™ software Xcalibur™, TraceFinder, and Compound Discoverer (in mzVault format)



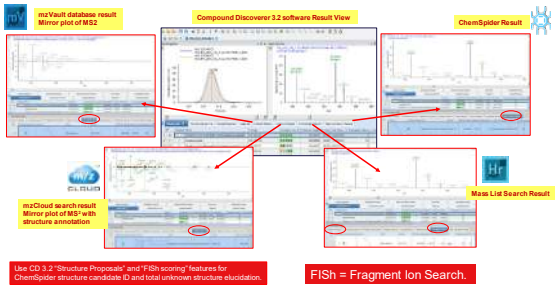
mzLogic Analysis in Compound Discoverer 3.2 for Structure Identification

- When an mzCloud search yields no matches for candidate structures from ChemSpider or E&L Mass List, mzLogic analysis use extensive, fully curated MS^n fragment ions in mzCloud for spectral similarity search, to rank putative structures and aid compound identification.
- When there is no match in database or spectral library, mzLogic compares mzCloud similarity matches against database hits, looking for common substructure, ranking the putative structures based upon spectral similarity and sub-structural information, for unknown compounds.

Use mzLogic Analysis in Compound Discoverer 3.2 software

Smart Note: Accelerating small-molecule unknown identification with mzLogic
https://assets.thermofisher.com/TFS-Assets/CMD/brochure/sn-65387-ms-mzlogic-data-analysis-algorithm-sn65387-en.pdf

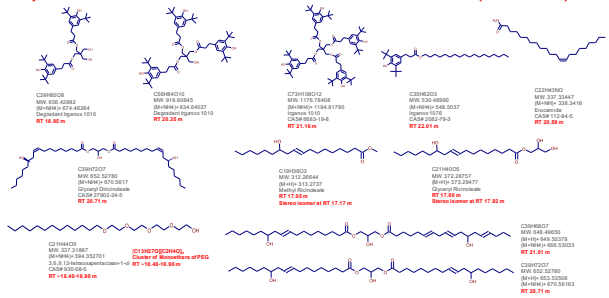
Multiple Database Search Results



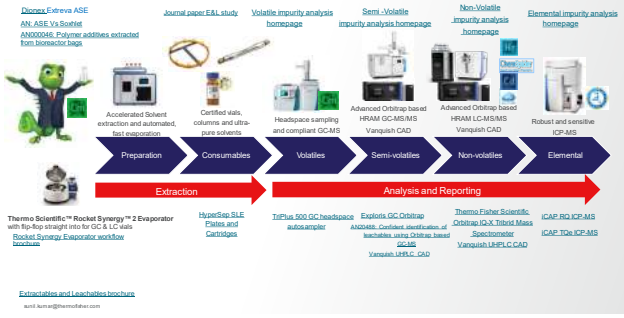
Use CD 3.2 "Structure Proposals" and "FISh scoring" features for ChemSpider structure candidate ID and total unknown structure elucidation.

FISh = Fragment Ion Search.

Proposed Structures of Extractables in IPA and DCM Extracts (Partial List)



Comprehensive Extractables and Leachables Workflow



E&L Resources

- Webinars
- Applications
- Blogs
- Regulatory updates
- White papers
- And more…

www.thermoscientific.com/Leachables

60

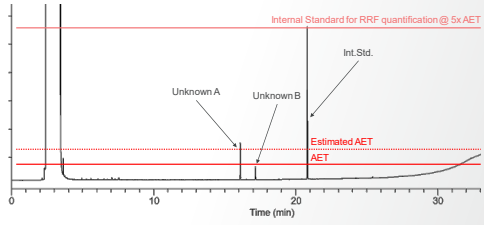
Thank you

Definitions

- **Safety Concern Threshold (SCT)**
  - Level proposed by toxicologists at which leachables need to be identified
  - *<0.15 µg/day* for individual organic leachable
- **Estimated Analytical Evaluation Threshold (Estimated AET)**
  - This value takes into account the SCT & number of expected doses per day to calculate a level at which unknowns should be identified.
  - $Estimated\ AET = \left(\frac{SCT}{Doses/day} \times Doses\ in\ container\right) = \mu g\ per\ container$
- **Analytical Evaluation Threshold (AET)**
  - This is the Estimated AET minus the analytical uncertainty of quantifying an unknown versus internal standard;
    - Uncertainty can be calculated using RRF tables,
    - However, typically **50% method uncertainty** is used.
  - $AET = Estimated\ AET \times Method\ Uncertainty$

200 doses
Max 8/day
Est.AET = 3.8 µg/container
AET = 1.9 µg/container

What does this mean in practice?



Identify and risk asses everything above AET

Computational Chemistry-helping hand for pharmaceutical compliance including prediction of Toxic behaviour of Nitrosamine

Dr. Prabha Maheswaran, Assistant General Manager – SSD, Chromachemie Laboratory Private Limited

22nd IDMA-APA PHARMACEUTICAL ANALYSTS CONVENTION (PAC) 2023

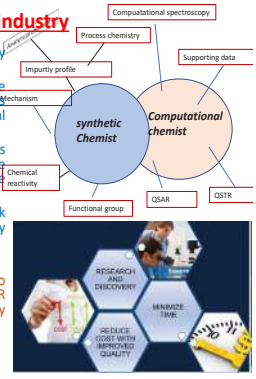
CHROMACHEMIE

Computational Chemistry-helping hand for pharmaceutical compliance including prediction of Toxic behaviour of Nitrosamine.

Dr. Prabha Jayapal
Assistant General Manager-SSD Division
Chromachemie Laboratory Private Limited

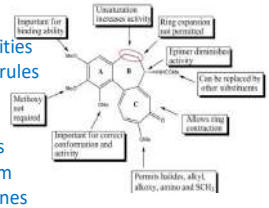
Computational Chemistry -pharmaceutical industry

- Challenges in pharmaceutical industry- delivering quality products.
- The issues pertaining to the quality of the product are variable starting material, lack of manufacturing process automation and control, poor understanding of the chemical reaction and product parameters etc.,
- Quantitative structure activity/property relationships (QSAR/QSPR) of substances – helping hand to reduce the cost and time needed from discovery to market, while at the same time raising standards of quality.
- Quality risk assessment-In silco calculations act a risk assessment tool to identify the stability, spectral property and toxicity of the molecule.
- ECHA, EMA article- In vitro, in chemico and in silico studies (e.g. computational tools such as OECD QSAR Toolbox, EPI Suite, ECOSAR, VEGA, T.E.S.T, Catalogic) may increase the robustness of a case.



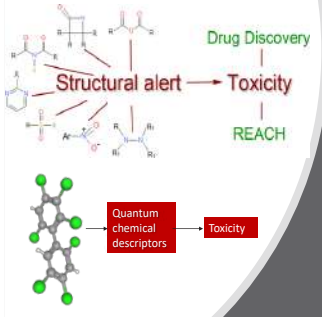
Computational structure-activity relationship (SAR):

- Presented by Crum-Brown and Faser in1865.
- SAR- consistent relationship between molecular property and biological activities for a series of compound so that these rules can be used to evaluate new chemical entity.
- Reveals the impact of structural features upon reactivity eg: Activation mechanism
- The structure of the compound determines it biological effects
- A. to metabolically active enzyme
- B. Non-covalent toxicity
- Properties of the structure affects its ADME



Moving On

- Computational toxicology
- Computational spectroscopy – predicting the structural features of unknown molecule.
- Predicting the structure and binding interaction of molecule with protein.



In silico prediction of chemical toxicity

- The evaluation of toxicological testing can place large R&D investments at risk.
- Time and cost of toxicology testing is generally too high to complete the testing early in the development process.
- Alternative to animal testing -to prioritize laboratory tests, preclinical and clinical studies.
- Computational toxicology-reliable, cost-effective means for predicting toxicity of molecule.
- Efficient computational software and servers are available in market.
- *Two methods- (a) QSAR prediction method-* Identifying structural alerts (SA) (substructures responsible for certain toxic behavior).
- *(b) Electronic structure method-Quantum chemical descriptor.*

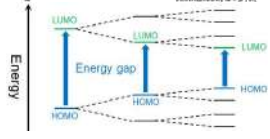
Pizzo et al. Chemistry Central Journal (2015) 9:62; Reenu, Vikas. J. Molecular.Graphics and modelling61(2015)89.

Our *in-silico* methodology:

1. Quantum chemical molecular descriptor-electronic structure method → DFT calculation
2. SAR prediction methodology : statistical-based and expert rule-based.

Examples of Commonly Used Descriptors in In Silico Toxicology to Construct Predictive Models

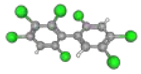
Descriptor Type/Group	Definition
Electronic descriptors	These represent diverse properties which are associated with many effects
E_{LUMO}	Energy of the lowest unoccupied molecular orbital
E_{HOMO}	Energy of the highest occupied molecular orbital
μ	Chemical potential (negative of electronegativity) $\mu = (E_{LUMO} + E_{HOMO})/2$
η	Chemical hardness $\eta = (E_{LUMO} - E_{HOMO})/2$
σ	Chemical softness $\sigma = 1/\eta$
ω	Electrophilicity $\omega = \mu^2/2\eta$



Genotoxic database:

- The model is based primarily on data from the Ames test conducted following standard test protocol (OECD).
- Using a standardized Ames genotoxicity dataset containing 12,500 compounds compiled from popular public databases such as DrugBank , ChEMBL and CPDB peer reviewed scientific papers, and high-throughput screening projects such as Tox21 and CYP450 .
- The dataset used have per validated and explored models studied which are run in rodents.
- The dataset contains 213 nitrosamine molecules.
- 187 known to be mutagenic
- 26 known to be non mutagenic

Method Validation:



2,2',3,4,4',5',6-Heptachlorobiphenyl Exp. LD_{50} 2.0 (g/kg)

Toxicity predicted profile — Classification	Value	Probability
Carcinogenicity (binary)	-	0.5032
Carcinogenicity (trinary)	Non-required	0.6630
Acute Oral Toxicity (c)	III	0.8273

Acute oral toxicity :

- 12,204 diverse compounds with LD50 were classified into four categories based on the criterion of US EPA
- Category II contains compounds with LD50 values greater than 50mg/kg but less than 500mg/kg.
- Category III includes compounds with LD50 values greater than 500mg/kg but less than 5000mg/kg.
- Category IV consisted of compounds with LD50 values greater than 5000mg/kg).

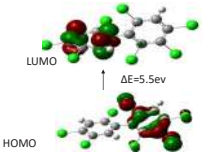
Carcinogenicity:

1. Binary: The Computer-Aided Prediction of Rodent Carcinogenicity by PASS and CISOC-PSCT was used as the reference data set.

2. Trinary: 981 structurally diverse chemicals for rat carcinogenicity - extracted from Carcinogenic Potency Database (CPDB) were divided into three classes, labeled "Danger", "Warning" and "Nonrequired", according to the TD50 values

Quantum chemical molecular descriptor:

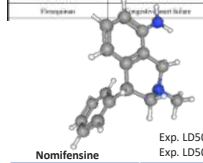
- The HOMO-LUMO gap is one of the main parameters relating to the electron-mediated bonding
- Indication of stability in similar molecules.
- Larger gap implies a more stable molecule with respect to reactions with biomolecules.
- HOMO-LUMO energy gap acts as the overarching indicator of PCBs toxicity

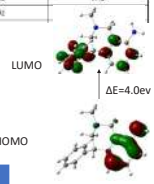


Scientific African 10 (2020) e00587 frontiers in marine sciencet (2014)).

Our method validation on Some of the Drugs Withdrawn from the Market due to Toxicity

Drug	Disease	Reason for withdrawal	Year of approval	Year of withdrawal
Azurbine	Psoriasis	Stroke	1975	1976
Nomifensine	Antidepressant	Hemolytic anemia	1984	1986
Encainide	Irregular heart beat	Fatal arrhythmia	1986	1991
Temafloxacin	Antibiotic	Kidney failure	1992	1992
Flosequinan	Congestive heart failure	Increased deaths	1992	





Nomifensine

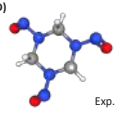
Exp. LD50 rat intravenous 72 mg/kg
Exp. LD50 mouse oral 260 mg/kg

Toxicity predicted profile — Classifications	Value	Probability
Carcinogenicity (binary)	-	0.9200
Carcinogenicity (trinary)	Non-required	0.6509
Acute Oral Toxicity (c)	II	0.7289

- Category II contains compounds with LD50 values greater than 50mg/kg but less than 500mg/kg.
- More toxic

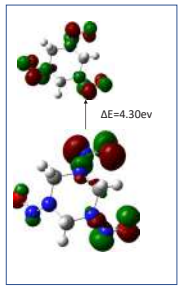
The presence of Nitrosamine in drug product is found to be a global issue.

Hexahydro-1,3,5-trinitroso-1,3,5-triazine (NITROSAMINE COMPOUND)



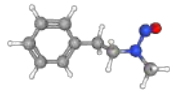
Exp. LD50 mouse oral 160 mg/kg

Toxicity predicted profile — Classifications	Value	Probability
Carcinogenicity (binary)	-	0.7212
Carcinogenicity (trinary)	Non-required	0.6371
Acute Oral Toxicity (c)	II	0.7370

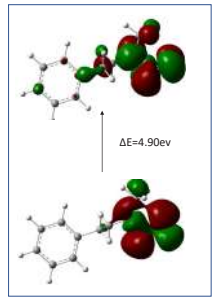


- Category II contains compounds with LD50 values greater than 50mg/kg but less than 500mg/kg.
- More toxic

Phenethylamine, N-methyl-N-nitroso-(compound)



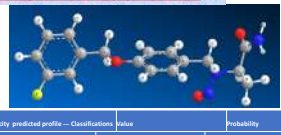
Toxicity predicted profile — Classifications	Value	Probability
Carcinogenicity (binary)	+	0.5653
Carcinogenicity (trinary)	Danger	0.7853
Acute Oral Toxicity (c)	I	0.7780



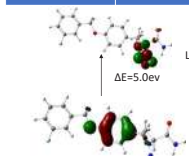
- Category - compounds with LD50 values greater than 50mg/kg but less than 500mg/kg.
- Highly toxic.

List of the Nitrosamine molecule:

Predicting unknown toxicity of the molecule:



Toxicity predicted profile — Classifications	Value	Probability
Carcinogenicity (binary)	+	0.6000
Carcinogenicity (trinary)	Non-required	0.4092
Acute Oral Toxicity (c)	III	0.6442



Acute oral toxicity :

Our result: Prediction on Nitroso safinamide:

Nitroso safinamide in the category III which indicates LD50 values greater than 500mg/kg but less than 5000mg/kg which shows that the compound is less toxic

Prediction for Nitroso safinamide:

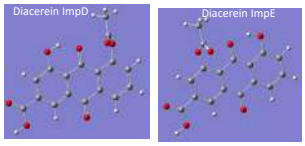
- Positive binary value, but the probability is low.
- The trinary model predicts the compound to be noncarcinogen according to TD50 value

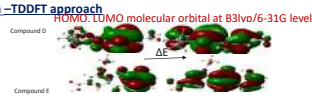
Structural Characterization of unknown impurities

Computational spectra - addressing the structural features of unknown molecule

The UV Absorption spectrum –TDDFT approach

HOMO, LUMO molecular orbital at B3lvp/6-31G level.



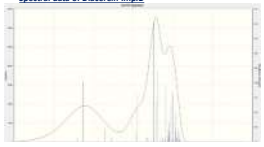


Diacerein IMPC	Band (λmax) nm (excitation energy)	Oscillator strength f (nm)	Epsilon ϵ_{max}
IMP D	248	0.43	33000
IMP E	250	0.356	25600

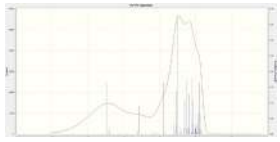
Our prediction is in comparable with the experiment, that Diacerein Imp D has higher value of both oscillator strength (~0.08) and the epsilon when compared to Diacerein Imp E

TD-DFT computed absorption spectrum along with the oscillator strength and epsilon

Spectral data of Diacerein Imp.D

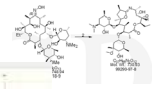


Spectral data of Diacerein Imp.E



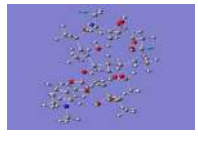
Characterization of unknown impurities:

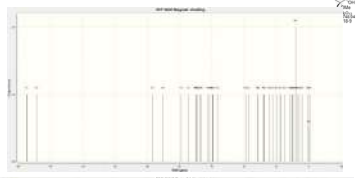
➢ **Simulation of NMR chemical shift-2GIAO-DFT**



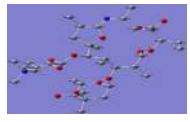
Computed C^{13} NMR chemical shift

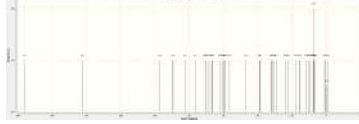
Imp A





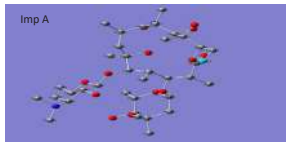
Imp B

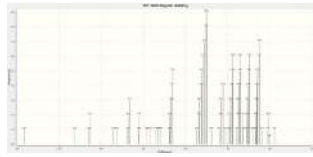




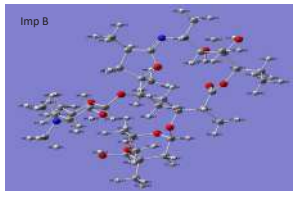
TD-DFT computed H^1 NMR chemical shift

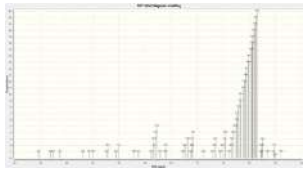
Imp A





Imp B

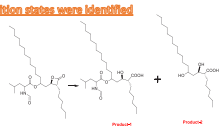


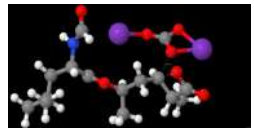


Determining the product reaction mechanism and stability

Reaction Modelling (ring opening reaction)

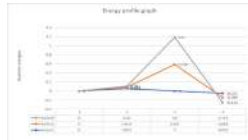
-possible transition states were identified





Activation and reaction energies along with the energy profile graph (Hartree and at 298 K) (including zero-point correction).

ENERGY	Activation energy 1 (ΔG1)	Activation energy 2 (ΔG2)	Reaction energy
Reactant+ NaOH	0.055	----------	-0.051
Reactant+KOH	0.033	0.587	-0.089
Reactant+K_2CO_3	0.020	0.600	-0.115

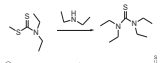


In the graph chart the series 1 belong to the reaction energies with NaOH , Series 2 energies belong to KOH reaction, series 3 belong to K_2CO_3 reaction.

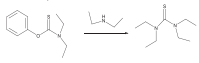
Feasibility and stability of unknown molecule at different temperature, NBO analysis

Molecule 1:

Scheme 1

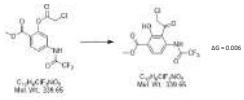


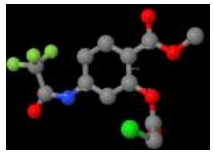
Scheme 2



ΔE=3.9ev

Molecule 2:



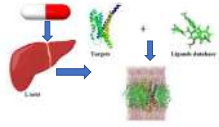


QSAR – Structural determination of the unknown molecule

- The WNT/β-catenin/Adenomatous polyposis coli (CTNNB1/APC) pathway has been identified as a regulator of drug-metabolizing enzymes in rodent liver.
- Little is known about the role of this pathway in drug metabolism regulation in human liver.

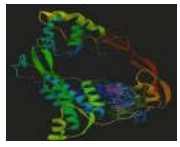
- To identify and optimize novel small molecules
- Able to inhibit the enzymatic function of interest.
- Multiscale computational approach

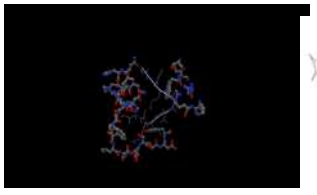
Understanding xenobiotic metabolism

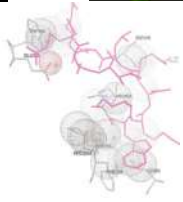


Structural determination of the unknown molecule

- The structure and binding interaction of the unknown molecule was revealed by the multiscale modelling



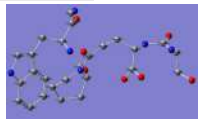


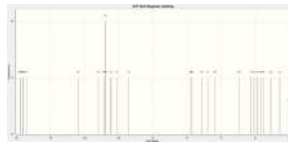


Characterization of unknown molecule

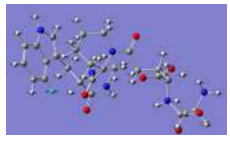
The UV Absorption spectrum –TDDFT approach

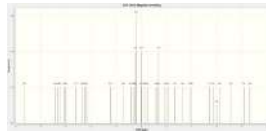
C^{13} NMR chemical shift of the SMMS:



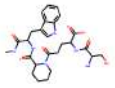


TD-DFT computed H^1 NMR chemical shift





Predicting unknown toxicity of the molecule:



Acute oral toxicity :

Our result:

- Category III-indicates LD50 values greater than 500mg/kg but less than 5000mg/kg
- Not toxic

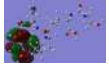
Toxicity predicted profile -- Classifications	Value	Probability
Carcinogenicity (binary)		0.9000
Carcinogenicity (trinary)	Non-required	0.6393
Acute Oral Toxicity (c)	III	0.6125

Carcinogenicity

- Carcinogenity - negative
- The trinary model predicts the compound to be noncarcinogen according to TD50 value

LUMO

ΔE=8.4ev



HOMO

***Computational toxicology*-**We provide methodology to investigate the toxic potentials of impurities and secure the development according to the ICH M7 guideline.

***Computational Spectroscopy*-** helping hand for characterizing unknown molecule.

Overview – *Computational calculations acts as a helping hand to address the* issues pertaining to the quality of the product such as toxicity, structure, stability and understanding of the chemical reaction.

Our Research & Development Laboratories

SYNTHETIC CHEMISTRY SERVICES

- Synthesis of impurity standards and reference standards
- Synthesis of metabolites and degradation impurities
- Synthesis of Genotoxic impurities
- Synthesis of API's and advanced intermediates (milligram to kilogram scale)
- Synthesis of stable isotope labelled compounds
- Process development
- Peptide synthesis

Synthesis Laboratory

Quality Control and Analytical Laboratory

List of Major Equipment in Our Analytical and Quality Control Laboratories

Nuclear Magnetic Resonance Spectrometer (NMR)
LC/MS/MS-Triple quadrupole Spectrometer
LC-MS-Single quadrupole Spectrometer
LC-MS-Ion trap Spectrometer
GC-MS-single quadrupole Spectrometer
CHNS-O Analyzer
IR Spectrophotometer
HPLC with PDA and UV detector
HPLC with PDA and RI detector
UHPLC with PDA detector
HPLC with Mass detector
Gas Chromatography with Flame ionization detector
Preparative HPLC with PDA /UV detector
MPLC with UV detector
Flash chromatography
Polarimeter
Karl Fischer Coulometer

Quality Control and Analytical Laboratory

ANALYTICAL SERVICES

Analytica Chemie Inc. has GMP & GLP compliant, state-of-the art analytical chemistry services laboratory, which is accredited by NABL (ISO/IEC 17025:2005), We offer analytical services to various pharmaceutical companies in India.

- Isolation and characterization of unknown Impurities
- Analytical testing services
- Analytical method development and method validation
- Extractable and leachable studies
- Stability studies
- Residual solvent method validation

Quality Control and Analytical Laboratory

Quality Control and Analytical Laboratory

Scale-up Lab

Scale-up Lab

Updates on Pharmacopoeial Monographs-Future Roadmap

Dr. Pawan Saini, Senior Scientific Officer, IPC

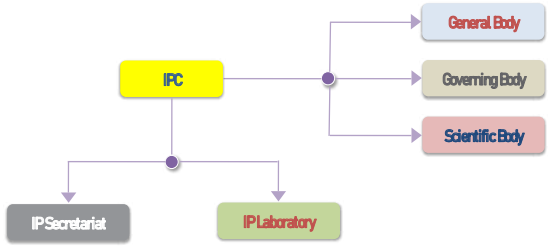
Updates on Pharmacopoeial Monographs - Future Roadmap

Dr. Pawan Saini
Senior Scientific Officer

Indian Pharmacopoeia Commission
Ministry of Health & Family Welfare, Govt. of India
Sector 23, Raj Nagar, Ghaziabad 201002
Website: www.ipc.gov.in; Email: lab.ipc@gov.in

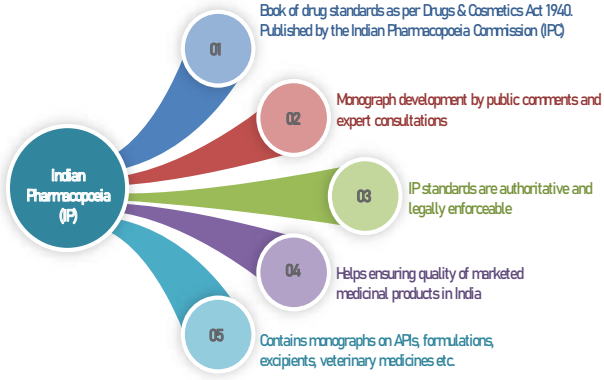
Indian Pharmacopoeia Commission (IPC)

- An autonomous Institute under Ministry of Health & Family Welfare, Govt. of India
- Established on 1st January, 2009 to set official standards of drugs in India
- Three tier structure comprising of the General Body, Governing Body, and Scientific Body
- Expert Working Groups (EWGs) with subject experts to guide on standards setting



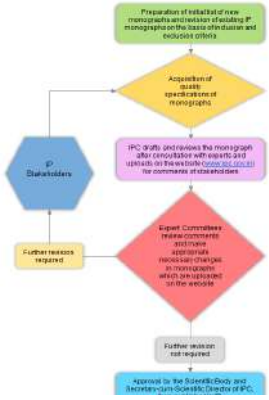
IPC Mandates & Functions

Indian Pharmacopoeia (IP)

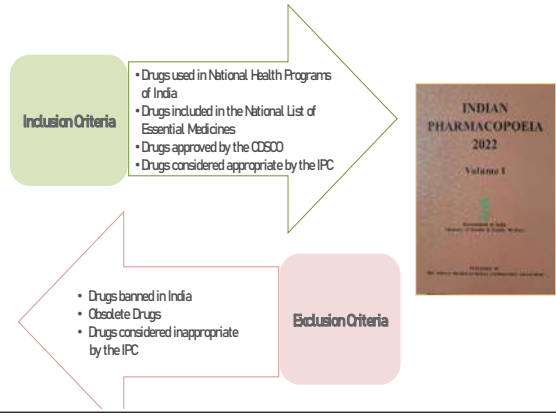


Monograph Development Process

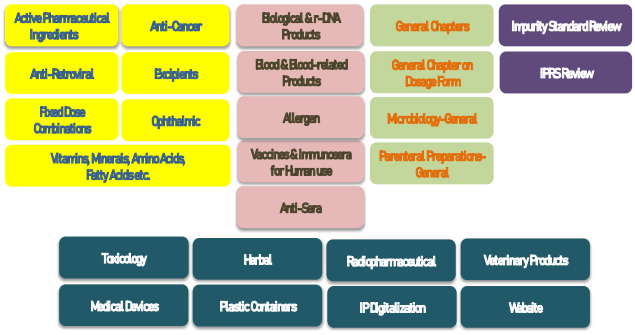
- Selection of monographs based on specific inclusion criteria
- Quality specifications sourced from manufacturers
- Monograph development in consultation with experts of EWGs and stakeholders
- Pharmacopoeia text published on IPC website for inviting public comments
- Approval of the Scientific Body before publication in the IP



Monograph Inclusion & Exclusion Criteria



EWGs of IP



History of IP Editions

Structure of IP Standards

General Notices
- Provides rules to understand pharmacopoeia text for its interpretation and application
- Applicable to all pharmacopoeia texts

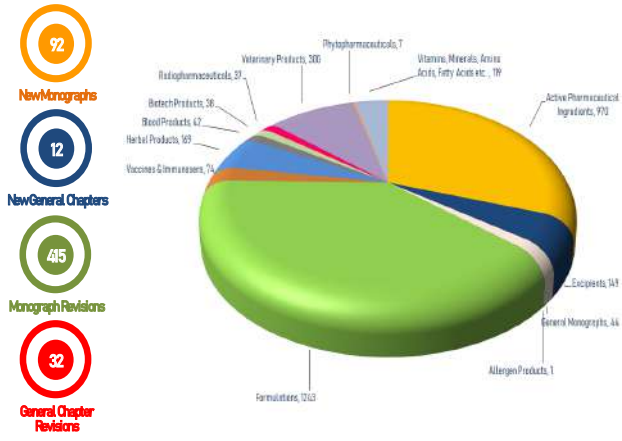
General Chapters
- Not mandatory '*per se*'
- Mandatory when referred to in a specific monograph
- Some General Chapters are not referred in monographs and are published as useful guidance
- Can be used for substances not covered by monographs
- May contain validity or equipment-verification requirements

General Monographs
- Containing centralized methods and specifications common to all dosage forms (e.g. tablets, capsules, injections)
- Include aspects that cannot be treated in each specific monograph
- Mandatory for all the products within the scope of definition section
- Usually referred for substances where there is no monograph

Specific Monographs
- Developed based on approved specifications for drug substances or finished products
- Analytical procedures and acceptance criteria to demonstrate that the substance meets required quality standards
- Specifications for pharmaceutical products in commerce (from release through product shelf life)

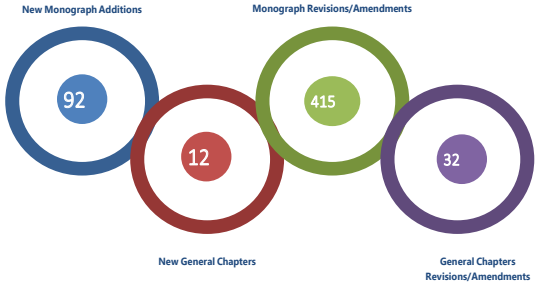
Reference Standards
- Physical materials to be used in conjunction with the test methods in the monograph
- Assesses specific quality attributes of the drug product or ingredient, including assay and impurities
- Established specifically for use in monographs or general chapters

IP 2022: Monograph Status



IP 2022: SALIENT FEATURES

Effective Date: 1st December 2022



IP-2022: MONOGRAPH DETAILS

Total New Monographs- 92

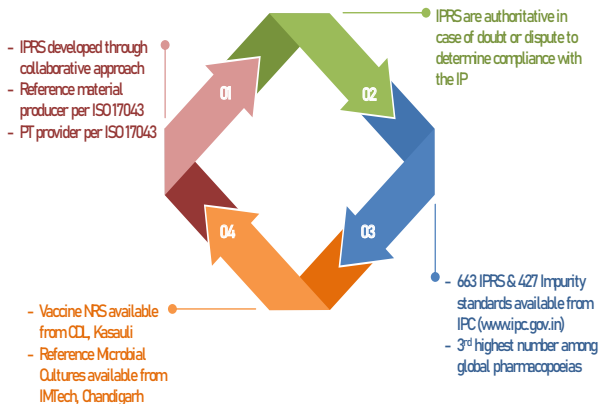
60 Chemical monographs
- 27 API
- 33 Formulations

09 Biological Monographs
- 04 Vaccines and Immunosera
- 03 Biotechnology derived therapeutic products
- 02 Blood and blood related products

02 Herbal Monographs
- 21 Vitamins, Minerals, Amino Acids, Fatty acids etc.

9th Edition - IP 2022

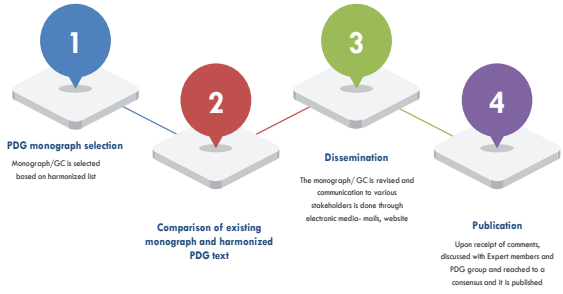
IP Reference Standards & Impurity Standards



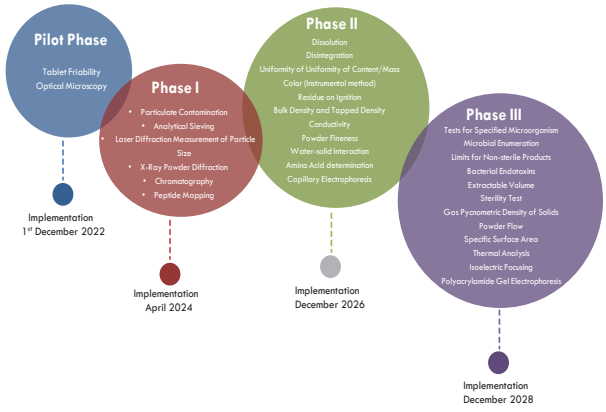
IPC participation in PDG

- **India** participated in **PDG pilot phase for global expansion** (Dec 13, 2021)
- IPC gave intent to participate in **pilot phase** (Dec 31, 2021)
- IPC staff participated in **informational follow-up videoconferencing** (Feb 28, 2022)
- Submitted the application for **PDG pilot for global expansion of membership** (April 6, 2022)
- Responded to **additional clarifications on application** (June 7, 2022)
- PDG welcomes Indian Pharmacopoeia Commission to pilot for global expansion (September 9, 2022)

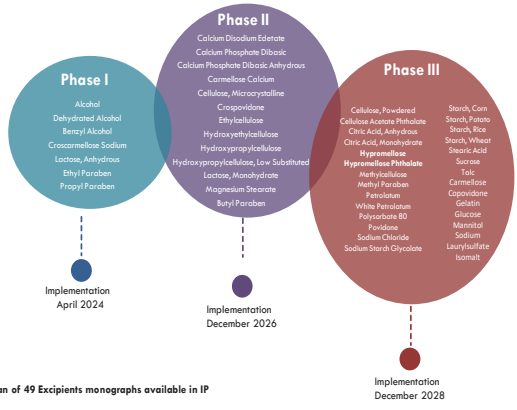
Excipient Monograph/ General Chapter (GC) Harmonisation process



PDG General chapters

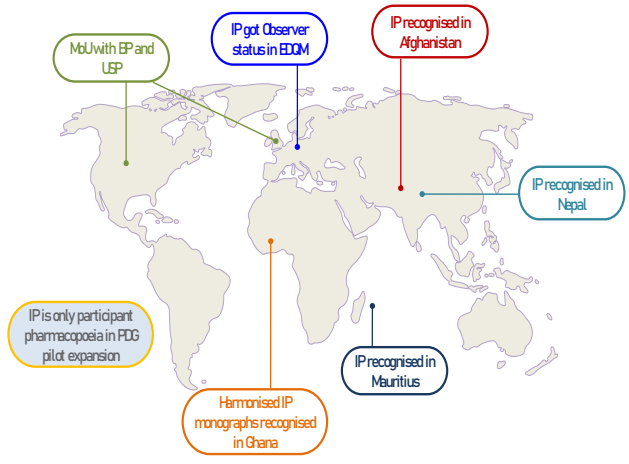


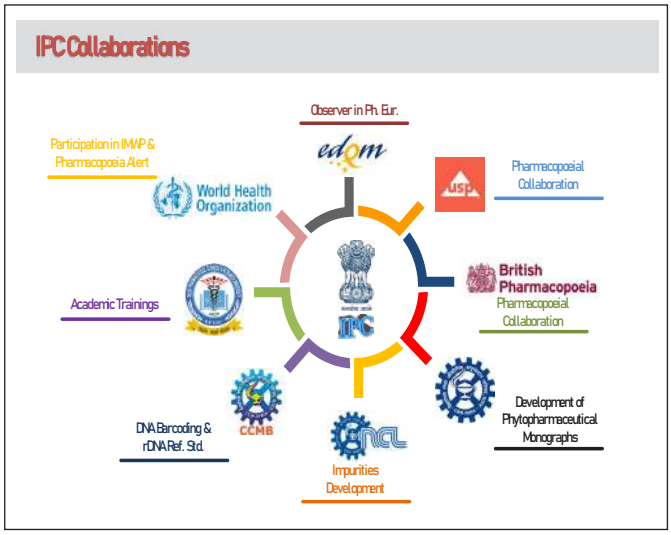
PDG Excipient Monographs

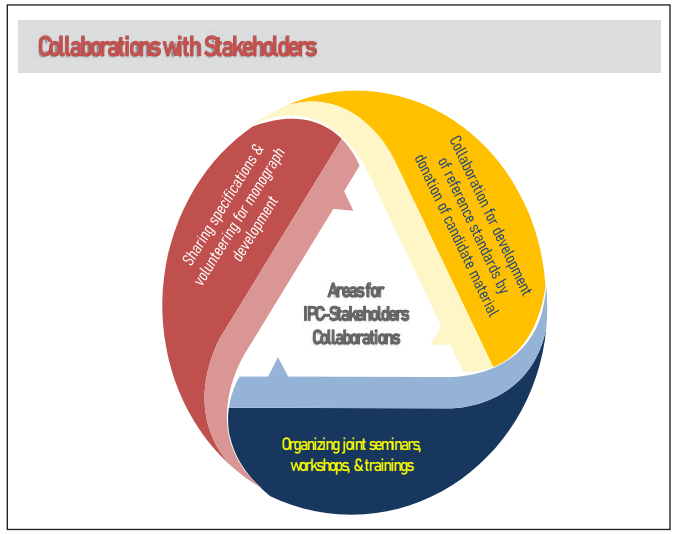


Harmonisation Plan of 49 Excipients monographs available in IP

Global Recognition of IP







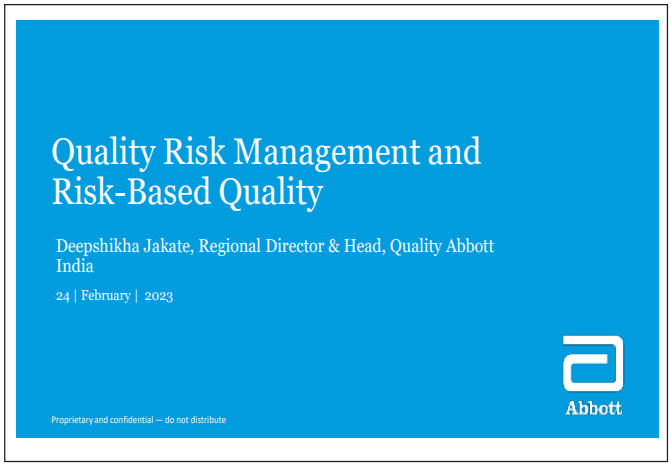
NEW INITIATIVES AT IPC WITH HIGH IMPACT ON PUBLIC HEALTH

1	DIGITAL IP – SHOULD BE AVAILABLE BY END OF FY'23
2	INCREASING INVENTORY AND STAKEHOLDER AWARENESS ON IMPURITY STANDARDS USE AND IMPORTANCE
3	BRINGING DISSOLUTION TESTING IN PROLONGED RELEASE FORMULATION MONOGRAPHS
4	IMPURITY LIMITS HARMONIZED WITH ICH RECOMMENDATION
5	JOINING PDG PILOT – GLOBAL INITIATIVE TOWARDS HARMONIZATION OF PHARMACOPOEIA
6	NEW MoU BEING SIGNED WITH Ministry of AYUSH and NIPER GUAHATI

Acknowledgements

Quality Risk Management and Risk Based Quality

Ms. Deepshika Jakate, Regional Director & Head Quality, Abbott India

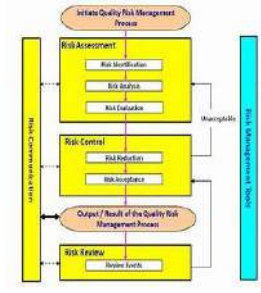


Introduction

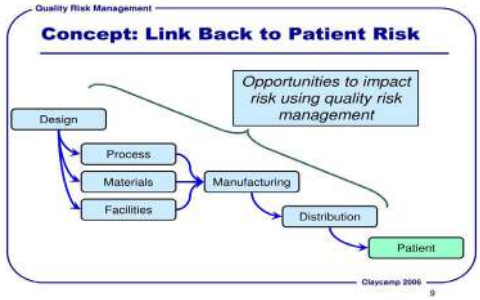
What is Quality Risk Management

- A particular event that MAY happen
- It's a PROACTIVE measure to reduce the effects or eliminate the *risk* itself
- It is done through a Scientific Assessment and is ultimately linked to patient safety
- While the level of risk may determine the effort required, what's most important is that all potential risks need to be taken seriously, with patient well-being at the center of everything we do

ICH Quality Risk Management Process



ICH Quality Risk Management Process Application



Writing a risk statement

How to write a "Good" Risk Statement

- There is a Risk that .....(What will happen).....Due to (A condition not being fulfilled or an existing situation)..... Leading to (What is the ultimate impact)

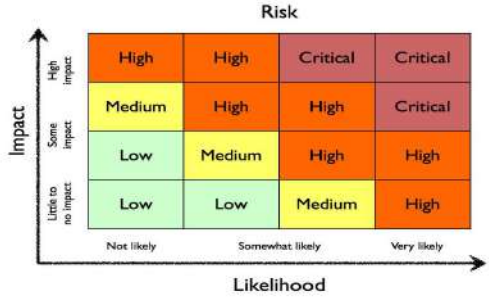
Example:

There is a risk that the Qualification of FBD may fail due to the unavailability of a trained technician, leading to disruption in the manufacturing schedule which may lead to deviation from the manufacturing plan.

- It is important to know *what* the risk affects and who *owns* the risk

Risk Analysis (Rating)

Factor of Impact (Severity) and Likelihood (Probability)



Risk Control (Mitigation)

EXISTING CONTROL AND MITIGATION ACTION

- Must be through Root Cause Analysis
- Ensure that existing controls provide interim controls on identified root cause
- Thorough CAPA (Mitigation actions) – Ensure that Risk is either reduced OR eliminated
- Calculate MIV (Mitigated Index Value)
- Severity doesn't reduce – only likelihood is reduced – Unless the risk is eliminated
- Idea is to reduce the risk: Red-Yellow – Green in a stepwise manner

THOUGHT BEHIND MITIGATION ACTIONS

- Elimination
- Substitution
- Engineering controls
- Administrative CAPA
- Strength reduces with descending order

Risk Treatments

- Risk Mitigation (Elimination or Control)
- Risk Acceptance
- Risk Avoidance
- Risk Transfer

Communication

Risk Assessment Tools

- FMEA (Failure Mode and Effect analysis)
- 5 Why's
- FTA (Fault Tree Analysis)
- Risk Scoring

What is Risk Based Quality

Risk-based thinking is defined as "a systematic application of information, knowledge, and actions to address uncertainty and potential opportunity."

- There can be ambiguity in things
- Rely on science and facts for best outcomes in terms of quality
- The objective is to put the patients' well-being at the center of the decision-making

Examples of Risk Based Quality

- Supplier Management
- Shelf-Life Estimation
- AQL (Acceptable Quality Level)
- Statistical Tools – ppk , cpk (Process Capability) – Predictive Models
- Sampling Plans
- Quality Risk Assessment
- Continuous Process Verifications

To summarize

An effective quality risk management approach can further ensure the high quality of the product to the patient by providing a proactive means to identify and control potential quality issues during development and manufacturing and post manufacturing Quality surveillance.

It is critical to protect patients in terms of quality, safety and efficacy of products and medicines.

Quality Matters - Integrated Quality Management

Mr. Sekhar Surabhi, Founder, Caliber group of Companies - India

Cost of Quality is … cost you pay for NOT having Quality!

ISPE Quality Metrics Initiative June 2015

Figure 3: Summary of Final Metrics Collected During ISPE Industry Wave 1 Pilot

The 3 Key Themes of Future Readiness

Regulatory Requirements
- FDA demands regarding Quality Metrics
- FDA is asking for more quality data, not just during audits, but across the year
- Annual Product Quality Review
- Stronger Data Integrity

Compliance

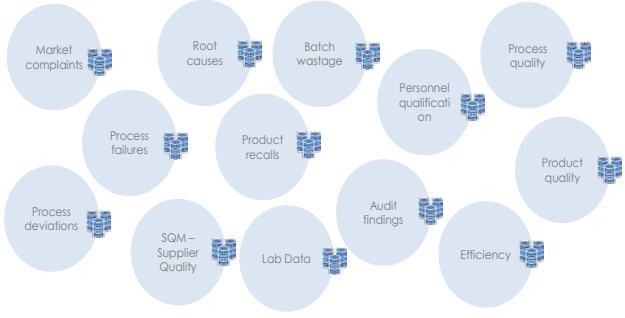
Operational Efficiency
- Better decision-making for profitability, growth, and value creation
- Need for lower cost of mfg, making medicine available quickly
- Quicker to market
- Getting it right the first time (RFT)

Quality

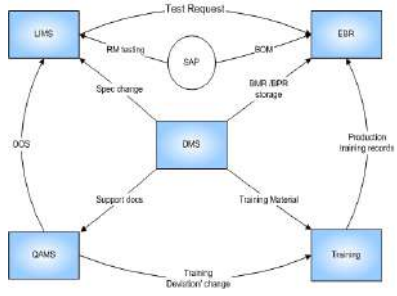
Industry 4.0
- Lab of the Future, Operations of the Future
- Automated data analysis and representation ensuring simplicity in interpretation
- Machine learning and Artificial Intelligence for outcome predictions and preparedness

Automation

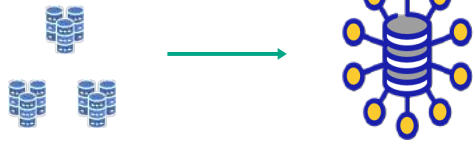
Quality Data Across Departments



Understand Data Interactions



Making the Move



Quality Management in siloes leading to inefficient management of quality assurance processes within the organization

Integrated Quality Management which eliminates dependency on inter-departmental information exchange and builds better quality metrics

Example – QMS Data Interaction

Quality Processes + Document Management
- Change control raised in QAMS needing a document modification or creation. The request is pushed to DMS, the document life cycle is completed, the change request can be closed in QAMS.
- Option will also be available to integrate QAMS with a third party (share point) DMS.

Quality Processes + Competency & Training
- Change control raised in QAMS needing a training. Change control closed after receiving the information of training closure from Nichelon
- Change control raised in QAMS for SOPs that needs trainings (incase DMS is not provided or involved)
- Training information to be available at the source point for reference to the status of training

Document Management + Competency & Training
- Training identified as a result of a new Document creation or existing document modification.
- Training identified as a result of re-issuance of a document after the review period is reached.
- In case of SOPs and other training content mapped for courses, the documents or content should reside in DMS and not in Nichelon.

Strategic Planning for Resilience

At an organization level, you should first start with asking and answering important questions that will help you strategize your future

- ***What process efficiencies do you want to build?***
- ***What are the key parameters for success? And what data do you need to collect to track success?***
- ***How do you ensure Quality by Design?***
- ***What data gaps do you have now? Where is time & effort getting wasted in data retrieval and data analysis?***
- ***How efficiently do you use your data now?***
- ***How does our data interact? How should it interact in order to achieve your long term goals?***

Integrated Quality Management

MAKE QUALITY A HABIT
Process Capability Index, Quality Risk Prediction and other Quality Metrics to ensure you make the right decisions, every time.

INTER-DEPARTMENT CORRELATION
Data is further analysed to arrive at inter-department correlation & APQR with Artificial Intelligence, Predictive Trend Analysis, etc.

DEPARTMENT ANALYTICS
Data Mart is created by bringing together and analysing data from different sources to arrive at departmental analytics of weak spots, trends, and efficiency analysis

CLEAN DATA
Accurate, Available, Actionable data collection is the foundation of good decision-making

What is Clean Data?

Accurate
Data is correct, clean, and authentic that allows for accurate interpretation

Available
Data is available on demand and does not need be prepared when requested

Actionable
Data should give the right insights for decision-making

Building Clean Digital Data & Integrations

Identify your data sources and start the clean up by digitalizing processes (lab, manufacturing, quality assurance, etc.)

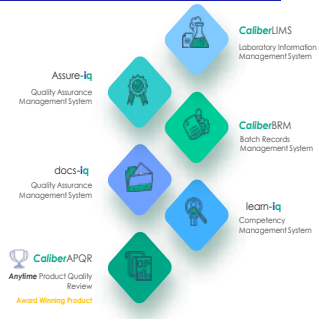
Prioritize the areas which will get digitalized

Decide how the departments, data, and people should interact

Assign integration scenarios and get ready for your integrated quality journey

Integrated quality management across the value chain.

Caliber Products are robust, secure, and are created on **Low Code Platform**



epiq by Caliber

Enterprise Platform for Integrated Quality

By Caliber

Strategy 2021 & Beyond

With our customers at the center of our focus, we have created a vision with **4 Pillars of Excellence**

- Deliver World-class Products
- Reach Users Across the Globe
- Streamline Processes
- Build Dynamic Teams

Proactive Quality Management System

Dr. Sanjay Shetgar Ph.D, Vice President, NSF Health Sciences - India

What Is Quality Management System (QMS) ?

A **structured collation** of business processes that is designed to meet the **objectives of the Quality Policy** to meet customer and regulatory requirements on a **continual basis**

Regulatory Requirements

An effective quality management system is defined in ICH Q 10 and is commonly referred as the **`Pharmaceutical Quality System' (PQS)**.
Based on ISO 9000:2005 concepts of quality, it **includes GMP requirements** and complements the ICH-Q8 **`Pharmaceutical Development'** and ICH-Q9 **`Quality Risk Management'**

Applicable across the **product life cycle**

ICH Q10 Pharmaceutical Quality System

ICH Q10 **augments** regular GMP by describing **specific quality elements** and **management responsibility**

Key Quality Elements of Pharmaceutical Quality System

- ❑ Process Performance & Product Quality Monitoring System
- ❑ Corrective Action / Preventive Action (CAPA) System
- ❑ Change Management System
- ❑ Management Review

Applicable across the product life cycle of Development to product discontinuation

3 Key Objectives of ICH Q10 Pharmaceutical Quality System

- ❖ Achieve **product realization***
- ❖ Establish and maintain a **state of control**
- ❖ Facilitate **Continual improvement**

* Collection of processes involved in product life cycle from conception to its completion

Enablers to support the PQS objectives

- ❖ Knowledge Management
- ❖ Quality Risk Management

Product Life Cycle & Continual Improvement

Learning from Regulatory citations

- One mayn't see citations specifically referring to ICH Q10. Legally, 483's must still be referred under the CFR/FD&C Acts
- However, the language used in the warning letters is predominantly related to …. senior management

India Inspection Citations Period 2020-2023

FDA Citation Categories (Total Citations)
(Source: USFDA Inspection Observations)

Quality System (Standard Operating Procedures), Deviations Management and Laboratory Controls emerge as the areas with the most citations/deficiencies

Citations and summary in Warning Letters

February 2023	a) A remediation plan that better **assures ongoing management oversight throughout the manufacturing lifecycle** of all drug products. b) Your use of a consultant does not relieve your firm's obligation to comply with CGMP. Your firm's **executive management remains responsible** for resolving all deficiencies and systemic flaws to ensure ongoing CGMP compliance
December 2022	The **role of senior management leadership is critical** to ensure successful functioning of a robust and effective quality system. See FDA's guidance document Quality Systems Approach to Pharmaceutical CGMP Regulations for help implementing quality systems and risk-management approaches to meet the requirements of CGMP regulations 21 CFR, parts 210 and 211
December 2022	A **management strategy for your firm** that includes the details of your global CAPA plan.
October 2022	a) Provide a report that evaluates if it includes staff with proper investigation competencies, effectively conducts root cause analysis, assures CAPA effectiveness, regularly reviews investigations trends, implements improvements to the CAPA program when needed, ensures appropriate quality unit decision rights, and is **fully supported by executive management** b)Also describe **how top management supports quality assurance and reliable operations**; including but not limited to timely provision of resources to proactively address emerging manufacturing/quality issues and to assure a continuing state of control c) Long-term measures describing any remediation efforts and enhancements to procedures, processes, methods, control s, systems, **management oversight,** and human resources (e.g., training, staffing improvements) designed to ensure the integrity of your company's data.

Management Responsibility

Important to understand what do we mean by
"*management*"

Senior Management: Person(s) who direct and control a company or site at the highest levels with the authority and responsibility to mobilize resources within the company or site.
(ICH Q10 based on ISO 9000:2005)

Management Responsibility

Management Commitment
Quality Policy and Planning
Resource and Internal communication
Management Review

Management Review

- **Continual improvement of process performance and product quality - performance of manufacturing processes**
  Ex: Yield/Rejection, process capability, defect rate, in-process failure rate, reworks
- **Continual improvement of Pharmaceutical Quality System (PQS) - effectiveness of processes**
  Ex: CAPA effectiveness, Closure rate of Deviations, Investigations without root cause, Human errors as root cause

Management Review

- Defined management review team - can add additional as experts, where necessary
- Keep **quality objectives** in mind to **drive decisions**
- Evaluate metrics - look for **trends, patterns** considering **continual improvement**
- Also check for **external factors** that could impact quality
- **Link actions** with quality systems through **Change control, Risk Assessment and CAPA**

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Management Review

- Two steps to ensure appropriate management review
  - Quality Oversight
  - Quality Metrics

- **Quality Oversight**

Basic expectation a `watchful eye' with `ownership' on identified elements. Just stating Quality oversight is a large term and needs tons of experience

- **Quality Metrics**

These are elements of the quality system are set up to monitor process (Ex. Implementation of a new process) and drive continual improvement

Supplemented with well educated and trained people

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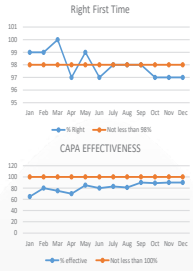
Quality Metrics



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Quality Metrics

- There could be several metrics -
- Measure what is **most relevant**, in order to improve
- **Prioritize** the measure - use simple **tools like 80:20**
- Develop **`Lead'** indicators - to generate proactive actions
- Don't wait to get cited and then measure
- Look out for elements that are **borderline** and at same time important
- Review **what you want to improve** - even if it means taking baby steps
- Provide resources where necessary - aptly utilized based on criticality

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Quality Metrics

Risks : **Watch Out**

- Don't make it over complicated
- Comparing data that is not defined
- Making conclusions out of one data point
- Review actions - evidence based
- Limited thinking - think beyond to either eliminate, make it efficient

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CASE STUDY

Background: *Quality Pharma has been witnessing that their staff are making **several small improvements**. However, the staff **work in isolation** and there is **no overall benefit** to the organisation. At the same time, staff **attrition is on the rise** and now touching 17%.*

What was done	- Brain storming - Understanding areas where improvements were made - Levels at which the improvements were being made - Options for staff engagement
Actions Taken (Over 3 month period)	- Each stream with oversight of senior management member - Management introduced skill upgradation scheme - 6 sigma training with certification from well know bodies - yellow, green and black levels with emphasis on structured process and meaningful outcome. -Staff engagement - townhall meet, communication and recognition of initiatives
Current Status (After 6 months)	- The use of 80: 20 rule is routinely applied - Several improvements made which created value to organisation. ✓ 50% improvement in time taken for cleaning (Process flow mapping) ✓ Eliminating false rejects of blisters (type of sensor used) ✓ Validated simpler in-process check (UV instead of HPLC) ✓ Eliminate redundant steps (Reduction in deviation reporting time) - Periodic internal training and certification through external body - Attrition down to 10%

What is QMM

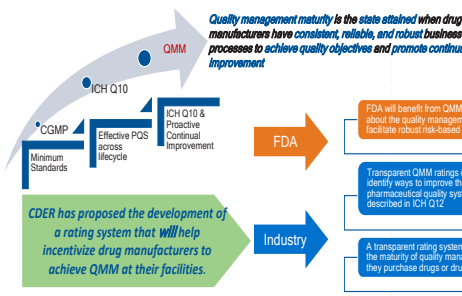
Quality Management Maturity an initiative by FDA to basically address **drug shortage and risk-based inspection** and in turn assist manufacturers

Remember : Metrics remain an important tool to monitor the overall health of a facility and the FDA's Quality Metrics Program remains an active and vital aspect of QMM program development.

QMM - A Holistic Assessment of Quality

Note - *QMM is more than just Quality Metrics. It is a holistic assessment of the Quality System*

Background on QMM



Quality management maturity is the state attained when drug manufacturers have consistent, reliable, and robust business processes to achieve quality objectives and promote continual improvement

Note - *QMM is a quantitative score obtained through a assessment checklist across predefined focus areas*

CDER has proposed the development of a rating system that will help incentivize drug manufacturers to achieve QMM at their facilities.

FDA
- FDA will benefit from QMM ratings by being more informed about the quality management practices at sites which will facilitate robust risk-based decision-making

Industry
- Transparent QMM ratings could empower manufacturers to identify ways to improve the effectiveness of their pharmaceutical quality systems, realize regulatory flexibilities described in ICH Q12
- A transparent rating system could also inform purchasers about the maturity of quality management practices at sites where they purchase drugs or drug products

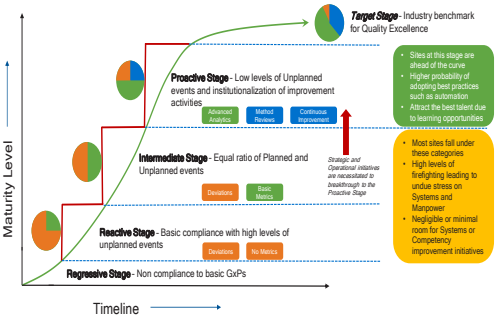
Patients
- Patients and consumers will have more reliable access to drugs when industry has a stronger commitment to continual improvement.

Source: CDER Quality Management Maturity

Quality Assurance - Maturity Evolution

- The 2019 **US Federal Drug Shortages Task Force** report* concluded that, **82% of shortages** between 2013 and 2017 were attributed to **manufacturing or product quality problems**
- The report found that, one of the root causes was that the **market does not recognize and reward** manufacturers for having **mature quality management systems**
- The USFDA is piloting a **Quality Management Maturity (QMM) rating system**.

** Source - OPQ White paper for Quality Management Maturity*



- Sites at this stage are ahead of the curve
- Higher probability of adopting best practices such as automation
- Attract the best talent due to learning opportunities

- Most sites fall under these categories
- High levels of firefighting leading to undue stress on Systems and Manpower
- Negligible or minimal room for Systems or Competency improvement initiatives

Unplanned Events | Planned Events | Quality Excellence/Sustainability Initiatives

QMM - The Journey so far..

QMM Advisory Committee	**Multi Stakeholder Advisory Committee** The advisory committee was formed to drive the QMM program design and implementing a proactive rating system
QMM Pilot Programs • Domestic FDF Sites • Foreign API Sites	**QMM Pilot Assessments** Assessments across multiple areas such as Leadership/Governance, Operations etc. Assessment outcomes helped fine tune QMM
QMM White Paper	**CDER (Office of Pharmaceutical Quality) White Paper on QMM** White Paper outlined the intent of the program and its importance for a stable supply chain
QMM Stakeholder Workshop	**FDA Experts and Guest Speakers led Workshop (May 2022)** The two day workshop outlined CDER's vision of QMM, learnings from Pilot, outlined opportunities and perspectives pertaining to stakeholders

Pilot Assessment and Outcome

The Assessment

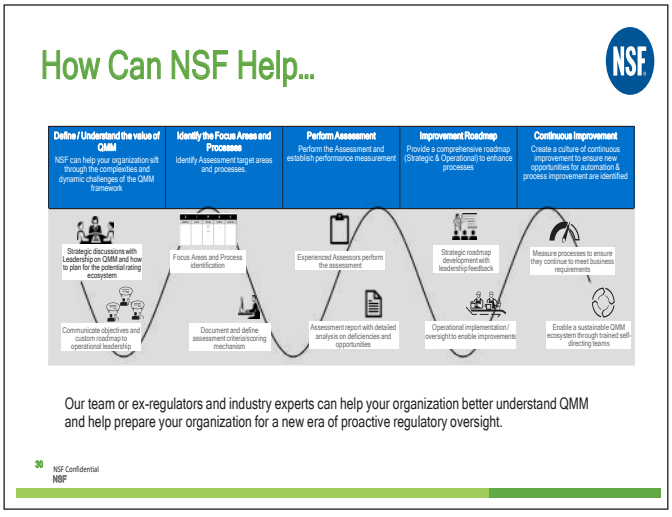
Domestic Pilot
- Two Stage Process - Self Assessment and Follow up questions
- Six Assessment Areas
  - Leadership & Governance
  - Operations
  - Continual Improvement
  - Stakeholder Engagement & Satisfaction
  - Knowledge Management
  - Workforce Engagement

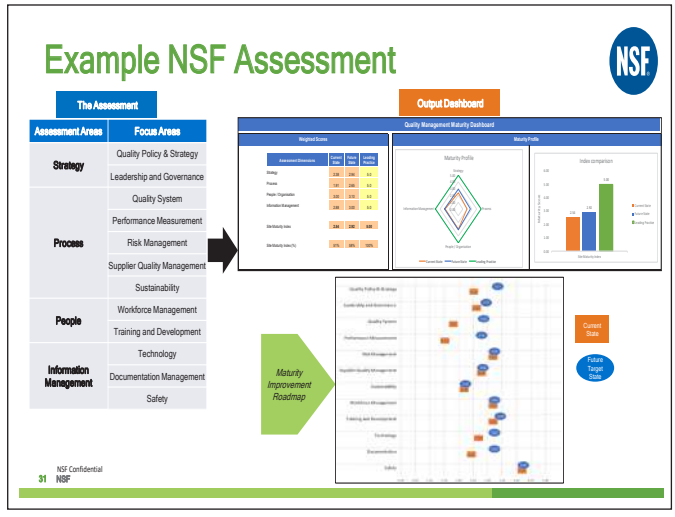
Foreign Pilot
- Facilitated Virtual Assessment
- 15 Areas (66 Questions)
- Four QMM Pillars/Themes
  - Sustainability
  - Risk Management
  - Compliance
  - Quality Culture

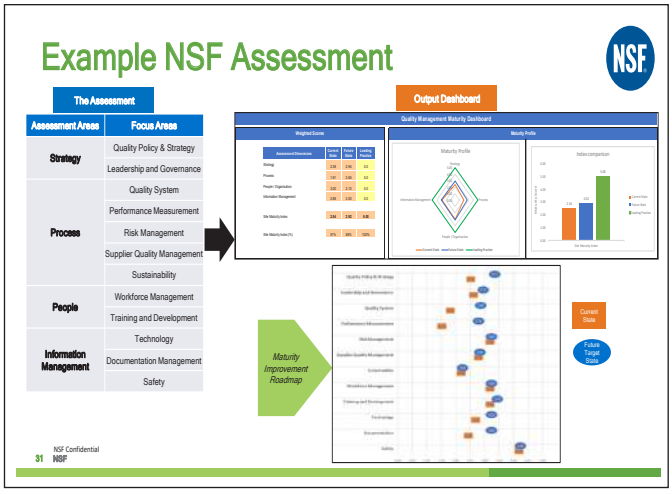
Key Learnings

Scoring
1. Standardized Scoring Mechanism - Domestic and Foreign Pilots had different scoring mechanisms
2. Objective evaluation criteria - Multiple evaluators & objective approach to manage conflicting scores
3. Assessment responses to be substantiated through objective evidence

Participant Feedback
1. Questionnaire must be direct (Avoid complex/compound questions)
2. The assessment helped identify strengths and opportunities
3. Some areas/topics were not considered previously by the site
4. Holistic evaluation mechanism helped the sites to look at the larger picture







Artificial Intelligence based Particle Characterization complying to regulatory requirements

Mr. Sandeep Kulkarni, CEO, ImageProVision Inc.

Why particle properties are important

- Better control of product quality
- Improve product performance
- Troubleshoot manufacturing and supply issues
- Better understanding of products, ingredients and processes
- Optimization of efficiency of manufacturing process
- Yield improvement
- Stay ahead of the competition

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Role of Particle Characterization

In the pharmaceutical industry, Particle Size, Particle Size Distribution and Particle Shape of active pharmaceutical ingredients (API) is known to strongly affect the stability and aesthetics of drug formulation.

The size and shape of particles used in a pharmaceutical product can impact the dissolution rate and influence the solubility, adhesion, and dispersion of particles.

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Comparing the Biopharmaceutical properties (Apparent Dissolution) of different batches of API and SR Granules having different Particle Sizes

Table 1: Mean particle size of theophylline batches

Product	Mean diameter (µm)
Theophylline monohydrated	128
Theophylline crystallized	135
Theophylline fine powder	120
Theophylline granular SR	675
Theophylline granular SR8	625

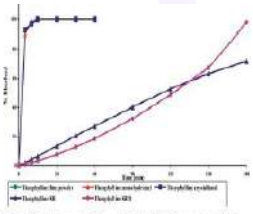

Figure 2: Dissolution study of theophylline batches (flow rate 30 mL/min, amount of drug 100 mg)

Ref. : Dissolution Study of Active Pharmaceutical Ingredients Using the Flow Through Apparatus USP 4, Dissolution Technologies | MAY 2005

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Dissolution ⟶ Surface Area

- Dissolution of Drug Substance depends on Surface Area
- Noyes-Whitney Equation

$$\frac{dm}{dt} = A\frac{D}{d}(C_s - C_b)$$

m = mass dissolved material
t = time
A = Surface area of interface
D = Diffusion coefficient
d = Boundary layer thickness
C_s = Concentration of substance on surface
C_b = Concentration of substance in solvent

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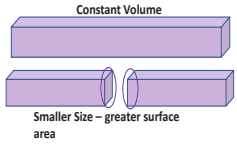
Surface Area ⟶ Particle Size

When a particle of a given volume is broken into two parts as shown in the figure, total volume does not Change. The total surface area, however, does change. It INCREASES by the amount of the two newly-exposed edges.

This simple illustration demonstrates relationship between surface area and particle size



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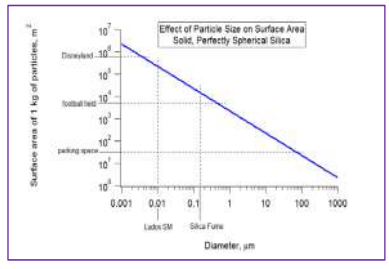
Surface Area ⟶ Particle Size



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Surface Area ⟶ Particle Shape

Shape		 (1:1:1)	 (2:1:1)	 (4:1:1)
Spherical Eq Diameter µm	10	10	10	10
Volume µm3	523.81	523.81	523.81	523.81
Length µm	-	8.06	12.80	16.12
Width µm	-	8.06	6.40	8.06
Height µm	-	8.06	6.40	4.03
Surface Area µm2	314.29	389.88	409.35	454.86
% Increase	-	24%	30%	45%

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DISRUPTIVE CAPABILITIES

Automated microscopic analysis

Convert any microscope to an Imaging Workstation

- Reduce particle analysis time by 50%
- Reduce development time by 30%
- From development, through formulation to release
- Improve product knowledge and process understanding
- Eliminate inefficient, error-prone and tedious data processing tasks

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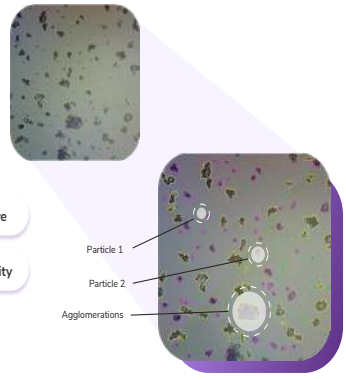
PARTICLE CLASSIFICATION

Based On

- Shape
- Texture
- Size
- Intensity
- Color



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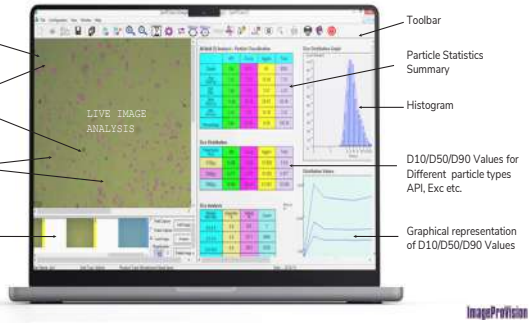
ipvPClass Main Screen



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PARTICLE SHAPE MORPHOLOGICAL PARAMETERS

- Length Dmax
- Width Dmax
- CED DCED
- Circularity
- Aspect Ratio
- Convexity
- Major Axis
- Solidity

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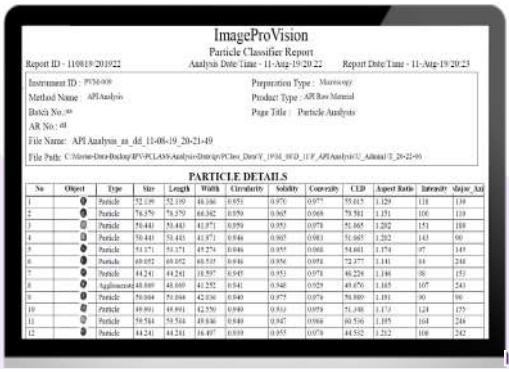
PARTICLE SHAPE - MORPHOLOGY



Compliance

US FDA 21CFR Part 11
EU Annex 11

Most Highlighted points

- Secured Access To The Application
- User Password Validity
- Audit Trail Log For Every Action Performed In The Software
- Different Levels Of Software Access Rights Based On Different User Types
- Analysis Data Records In Pdf Format For Print
- Digital Signature
- Integration With Other Systems

New Technology in Microscopic Particle Size & Shape Analysis powered by

MACHINE LEARNING & ARTIFICIAL INTELLIGENCE

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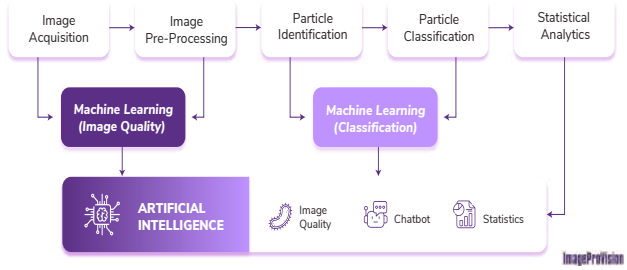
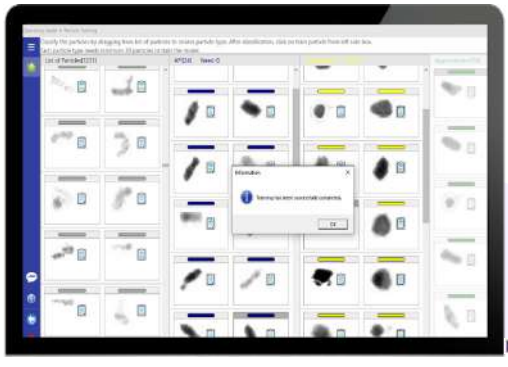
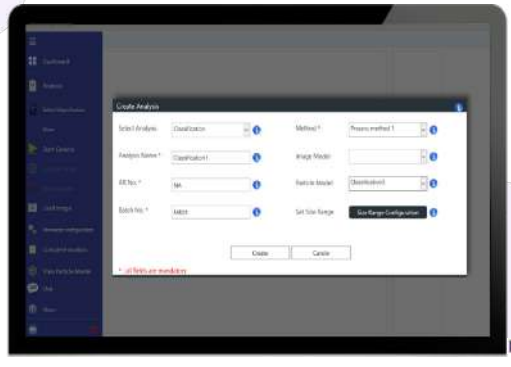
ARTIFICIAL INTELLIGENCE & MACHINE LEARNING FRAMEWORK ipvMorpho

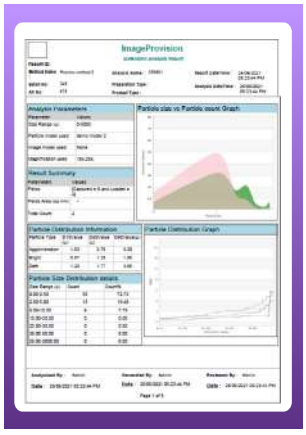


PARTICLE TRAINING



ANALYSIS BY SELECTING PARTICLE MODEL





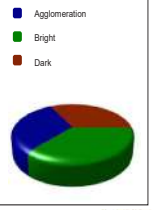
PARTICLE SHAPE DEFINITIONS

Particle Classification Information	
Particle Type	Count(%)
Agglomeration	36.36%
Bright	31.17%
Dark	32.47%
Total	100.00%

Particle Classification Graph:

Particle classification graph describes the classified particle types in Analysis. It also describes the particle count & it's percentage value in tooltip.

Particle Classification Graph



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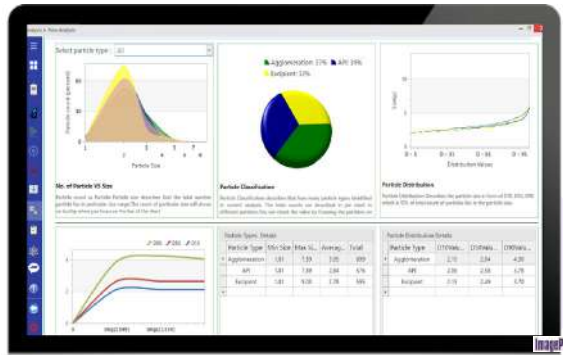
GRAPHICAL REPRESENTATION OF DATA



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AI & ML POWERED MorphoWiz

- Auto Scanning of Fields Image Quality Check through ML engine.
- Particle Identification and Classification through ML Engine
- Every analysis data goes to database as input to AI engine
- AI engine keeps records and makes the process intelligent on its own every time it is used.
  Fast, Accurate, Reliable.

ImageProVision

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THANK YOU

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sandeep@imageprovision.com

Status of Recognition and Acceptance of Indian Pharmacopoeia in Foreign Countries

As per the Second Schedule of the Drugs and Cosmetics Act 1940, Indian Pharmacopoeia (IP) is designated as the official book of standards for drugs imported and/or manufactured for sale, stock or exhibition for sale or distribution in India. In order to ensure the quality of medicinal products, the legal and scientific standards of IP are published at regular intervals by the Indian Pharmacopoeia Commission (IPC). Standards prescribed in the IP are authoritative in nature and are enforced by the regulatory authorities for quality control of medicines in India. IPC has been making sincere efforts towards recognition and acceptance of IP in foreign countries and proposals in this regard have been submitted to various countries through Ministry of Health & Family Welfare, Department of Commerce, Department of Pharmaceuticals, and Ministry of External Affairs.

It is a matter of delight to share that in pursuant to sincere efforts and guidance provided by the Hon'ble Union Minister of Health & Family Welfare to get IP recognized in foreign countries, IP has been accepted as a book of standards in a total of five countries with details as appended below:

o Afghanistan

IP has been recognised formally by the National Department of Regulation of Medicines and Health Products of the Ministry of Public Health of Islamic Republic of Afghanistan and also will be used based on the requirement as reputable pharmacopoeia in the laboratory of medicines and health products quality. With this, a new beginning has been made as Afghanistan has become the first country to recognize the IP. (Click here to view letter issued by Ministry of Foreign Affairs of Afghanistan) https://drive.google.com/file/d/1XTv8CaalRvDYuZYYdXQBnK7KYQh5gOkG/view

o Ghana

IP is considered as an approved reference when its monograph compares with the monographs in recognized pharmacopoeias in the Fourth Schedule of the Public Health Act. (Click here to view letter issued by Food & Drugs Authority of Ghana) https://drive.google.com/file/d/1h1NDW8hJq8Sfr_HzCeks-1DRD-s_p1OZ/view

o Nepal

IP is recognised as the book of standards in Drugs Category Rules 1986 of Nepal. As per the list of pharmacopoeia or encyclopedia related to the category of drugs under Schedule 1 (related to Rule 5) of the Drugs Category Rules 1986, "Pharmacopoeia of India" published by the Ministry of Health of Government of India has been included at Sr. No. 3. (Click here to view Drugs Category Rules 1986 of Nepal) https://drive.google.com/file/d/1kxfkBDHTvZgbb_xZdObmvsgzA7w1mqml/view

o Mauritius

In order to include IP in the standards of pharmaceuticals authorized in Mauritius, Section 2 of the Pharmacy Act 1983 has been amended through Section 50 of the legal supplement published in August 2020 and in the definition of "specified standards" of the Section 2 of the Pharmacy Act, the word "or European" has been deleted and replaced with the words "European or Indian". Accordingly, the amended section reads as: "specified standards" means such standards as are specified in the British, French, United States, Europoean or India Pharmacopoeia; (Click here to view Pharmacy Act 1983 of Mauritius and its amendment) https://drive.google.com/file/d/1qnC0wkazbeg25QHdI-V13sRrqeXqi6C6/view

o Suriname

A memorandum of understanding (MoU) has been signed between the IPC and Health Ministry of Republic of Suriname to recognize the importance of close cooperation and exchange of information in the field of regulation of medicine. IP is accepted as a book of standards for medicines in the Republic of Suriname so as to ensure quality of medicines being manufactured and/or imported in Suriname (Click here to view signed MoU) https://drive.google.com/file/d/1s1o2E4y19fArr_OHD8xEnSl88rgecAjQ/view

Efforts are on to add more countries in the list and stakeholders are encouraged to take advantage of these recognitions of IP in various countries.

Source: IPC website, www.ipc.gov.in, 13.06.2023

Pharma companies may have to switch to opaque bottles for eye drops packaging

Pharmaceutical Companies may have to switch to using opaque plastic bottles for packing eye drops to avoid microbial contamination. India's drug regulator is considering making amendments in the drugs rules for packaging of eye drops, said people with knowledge of the matter.

"Bacterial contamination in ophthalmic solution bottles are often reported and hence the need was felt to change its packaging to ensure that it remains free from any contamination," said one of the persons, who did not wish to be identified.

The Drugs Consultative Committee (DCC), a technical body of experts under the Drugs Controller General of India (DCGI), deliberated on the issue in their meeting last week and will take final decision soon, said the person.

Companies currently use non-transparent plastic bottles, which are prone to contamination. "The DCC suggested that transparent bottles be used so as to ensure that they are free from any contamination," said the person.

The drug regulatory authority may discuss the matter with the pharma industry to ascertain the feasibility of switching to opaque bottles before taking a final decision on the issue, said another person.

Complaints of contamination were received in the recent past and it was felt that ophthalmic drug product packaging was more crucial to product performance and safety than the packaging used for solid oral drug dosage forms. "Hence the discussion," said the person.

"It has been seen that bottles of eye drops are more likely to be contaminated with bacteria at the bottle tip and not within the solution. Many times patients use it without realising that there could be some bacterial contamination as the bottles are not transparent," he said.

Single-dose plastic bottles are widely used these days, while traditionally glass bottles with rubber teat droppers were used by companies.

Source: Teena Thacker, ET Bureau, 08.06.2023

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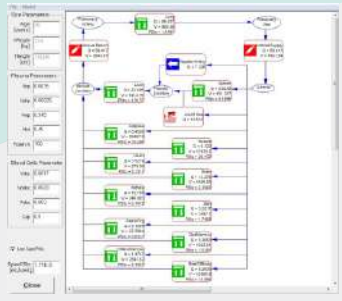

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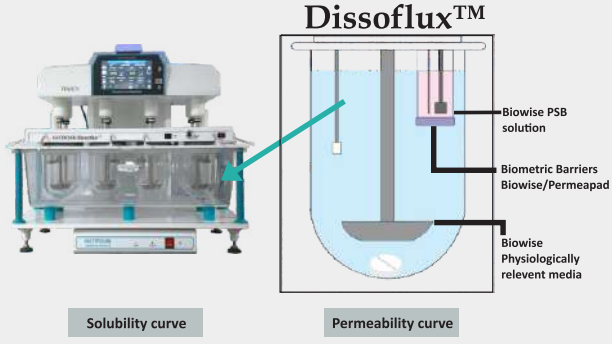

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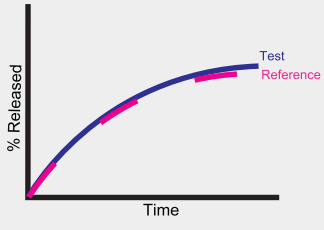

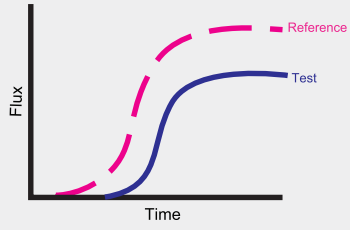

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