USP Workshop: Control of Nitrosamine and Other Mutagenic Impurities in Human Drugs

人用药中亚硝胺及基因毒性杂质控制

May 27, 2022 CST (Shanghai, China)

演讲者简介

Welcome Address

Edwin L. Gump, Ph.D.
Vice President of the Small Molecules Department
United States Pharmacopeia (USP)

Dr. Edwin L. Gump is currently the Vice President of the Small Molecules Department at the United States Pharmacopeia (USP) which develops USP documentary standards for prescription and Over-the-Counter (OTC) medicines. Prior to joining USP in 2018, Dr. Gump worked for Boehringer Ingelheim Pharmaceuticals for over 20 years primarily in the area of new drug development. During that time he contributed to the development and commercialization of both small molecule and biologic drugs. Dr. Gump is an analytical chemist by training and holds a Ph.D. in Analytical Chemistry from the University of California at Riverside and a B.S. in Chemistry from the University of California at Santa Barbara.

Edwin L. Gump, 博士
美国药典委员会 小分子部门副总裁

Edwin L. Gump 博士目前担任美国药典委员会小分子部门副总裁，该部门为处方药和非处方药制定 USP 书面标准。在 2018 年加入 USP 之前，Gump 博士在勃林格殷格翰制药公司工作了 20 多年，主要负责新药开发领域工作。在此期间，他为小分子和生物药的开发和商业化做出了贡献。Gump 博士拥有加州大学河滨分校分析化学博士学位。

Welcome Address

Jeff Moore, Ph.D.
Senior Director, Scientific Affairs & Strategy
United States Pharmacopeia (USP)

Dr. Jeff Moore is the head of Scientific Affairs & Strategy at US Pharmacopeia. He holds a PhD in food chemistry from the University of Maryland and a BS from Michigan State University. He leads a team of scientists responsible for growing USP scientific voice and presence globally and led USP's COVID-19 treatments initiative in 2020. He is the author of the most cited manuscript on food fraud and led the development of USP's Food Fraud Database in 2012. He has extensive experience in the areas of risk-based systems approaches to food safety, food authenticity testing, non-targeted testing, food fraud mitigation, food chemical safety, and international food additive regulations. He serves on the EU-China SAFE and EU Food Integrity advisory boards and University of Maryland's Global Leadership Council. He has authored more than 30 manuscripts in peer reviewed journals and book chapters. Prior to joining USP Jeff was a research scientist at Nestlè.

Jeff Moore 博士

美国药典委员会 科学事务与战略部门高级总监

Jeff Moore 博士是美国药典委员会科学事务与战略部门的负责人。他拥有马里兰大学食品化学博士学位和密歇根州立大学的理学士学位。他带领的科学团队负责在全球范围内提高 USP 的科学声音和影响力。他领导了 USP 2020 年 COVID-19 治疗计划，撰写的食品欺诈文章是迄今为止被引用次数最多的文章，并在 2012 年领导了 USP 食品欺诈数据库的开发。Jeff Moore 博士在基于风险的食品安全系统方法、食品真实性检测、非靶向检测、减少食品欺诈、食品化学安全和国际食品添加剂法规等领域拥有丰富的经验。他是中欧食品安全合作项目和欧盟食品完整性顾问组专家，马里兰大学全球领导者委员会委员。他撰写了 30 多篇学术期刊和书籍文章。加入 USP 之前，在雀巢公司担任研究科学家。

Jason D. Rodriguez, Ph.D.
Director, Division of Complex Drug Analysis
Office of Testing and Research, Office of Pharmaceutical Quality, FDA

Jason Rodriguez is the Director for the FDA Division of Complex Drug Analysis in St. Louis, MO. He has a Ph.D. in Chemistry from the University of Illinois Urbana-Champaign and B.S. in chemistry from the University of Texas-Pan American. Prior to serving in management roles, Dr. Rodriguez established a program in spectroscopic screening techniques using portable Raman and near infrared technologies with an emphasis on using these tools to enhance raw material screening and developing new methods to test finished drugs. Dr. Rodriguez leads a team of scientists that spans a broad cross-section of pharmaceutical research and testing projects including dissolution, chromatography, inhalation, transdermal and mass spectrometry. Dr. Rodriguez is also currently serving as the regulatory chair of the ICH expert working group (Q3E) on development of a technical guideline on extractables and leachables.

Presentation: Control of Nitrosamine Impurities in Human Drugs

ABSTRACT: This presentation provides a brief overview of the FDA laboratory response to the detection of nitrosamines in the pharmaceutical supply chain dating back to 2018. A timeline will be provided, starting with the detection of NDMA in valsartan and subsequent detection of other nitrosamines in other drugs. A high-level overview of the 2020 FDA guidance on nitrosamine impurities will be provided with an emphasis on the laboratory perspective of developing a fit for purpose method.

Jason D. Rodriguez 博士

美国食品药品监督管理局 检测与研究/药品质量办公室 复杂药物分析部门主任

Jason Rodriguez 博士是位于密苏里州圣路易斯市的 FDA 复杂药物分析部门总监。他拥有伊利诺伊大学香槟分校化学博士学位和德克萨斯大学泛美分校化学学士学位。Rodriguez 博士在担任管理职位之前，建立了一个使用便携式拉曼和近红外技术的光谱筛选技术项目，其重点是使用这些工具加强原料筛选，并开发新的方法来测试成品药物。Rodriguez 博士带领的科学家团队，涵盖了药物研究和测试项目的广泛领域，包括溶出、色谱、吸入、透皮和质谱。Rodriguez 博士目前还担任 ICH 专家工作组（Q3E）的监管主席，负责制定关于可提取物和可浸出物的技术指南。

演讲主题：人用药中亚硝胺杂质的控制

摘要：本次演讲将介绍 FDA 实验室对 2018 年药品供应链中亚硝胺检测的回应。本次演讲将提供亚硝胺问题时间轴，从检测缬沙坦中的 NDMA 开始，到检测其他药物中的其他亚硝胺。还将介绍 2020 年 FDA 亚硝胺杂质指南，着重于从实验室角度开发适用方法。

Edmond Biba, Ph.D.
Principal Scientist, General Chapters Department-Science Division
United States Pharmacopeia (USP)

Dr. Edmond Biba is a Principal Scientist in the General Chapters Department-Science Division at United States Pharmacopeial Convention. He serves as scientific liaison to the USP General Chapters-Chemical Analysis Expert Committee and USP General Chapters-Physical Analysis Expert Committee.
Since joining USP in 2001, Dr. Biba served as a scientist in the Research and Development Laboratory and in the Reference Standards Evaluation Department.
Prior to joining USP, Dr. Biba was a National Research Council-Walter Reed Army Institute of Research Postdoctoral Fellow in the Medicinal Chemistry Department of Experimental Therapeutic Division conducting drug discovery research on bioassay directed mechanism of action-based design and synthesis of new antimalarial drug candidates.
Dr. Biba received his Ph.D. in Chemistry-Synthetic Organic Chemistry from the American University, Washington DC, and a B.Sc. in Chemical Engineering/Chemistry from University of Tirana, Tirana, Albania.
Dr. Biba is member of Sigma Xi – The Scientific Research Honor Society, American Chemical Society, American Association of Pharmaceutical Scientists, International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) Q3C (R9) Working Group, and a member of Product Quality Technical Committee of the Product Quality Research Institute (PQRI).

Presentation: Highlights and key points of USP <1469> Nitrosamine Impurities

ABSTRACT: The nitrosamine presence in pharmaceutical products emerged as a public health concern in 2018 after reports that harmful levels of nitrosamine impurity, N-nitrosodimethylamine (NDMA), had been observed in Valsartan containing products. In response to this public health concern USP convened a Joint Subcommittee (membership from USP General Chapters-Expert Committee and from two Small Molecules Expert Committees) with a charge to develop a roadmap and guide USP for creating public standards to address it. The first product of the joint subcommittee work was the development of Chapter <1469> Nitrosamine Impurities, which was published for public comments in Pharmacopeial Forum Volume 46, Issue 5 available on-line since September 1st 2020, approved as public standard by the General Chapters-Chemical Analysis Expert Committee in the USP-NF 2021 ballot, and has been official since December 1st, 2021. This presentation discusses USP perspective for addressing nitrosamines in pharmaceuticals and the highlights of all sections of Chapter <1469> and the rationale of their content. The presentation briefly discusses the USP standards, their applicability and the public standards' development process. It also includes a short summary of regulatory landscape regarding nitrosamines in pharmaceuticals.

Edmond Biba 博士

美国药典委员会 科学部门通则首席科学家

Edmond Biba 博士是美国药典委员会科学部门通则首席科学家。他在 USP 化学分析通则专家委员会和物理分析通则专家委员会中担任科学事务联络官。自 2001 年加入 USP，Biba 博士在研发实验室和标准物质评估部门中担任科学工作。在加入 USP 之前，Biba 博士是美国国家研究委员会 Walter Reed 陆军研究所的博士后研究员，在实验治疗部药物化学部门从事药物发现研究，对基于行动设计的生物测试机制和合成新的抗疟潜在药物进行研究。Biba 博士在华盛顿特区美国大学获得化学合成有机化学博士学位，在阿尔巴尼亚地拉那大学获得化学工程/化学理学学士

学位。Biba 博士是美国科学研究荣誉学会（Sigma Xi）、美国化学学会、美国药物科学家协会成员，ICH Q3C（R9）工作组成员，以及药物质量研究所（PQRI）药物质量技术委员会成员。

演讲主题：USP <1469>亚硝胺杂质通则要点

摘要：2018 年有报道称，在含有缬沙坦的产品中发现了达到有害量的亚硝胺杂质 N-亚硝二甲胺（NDMA），药品中亚硝胺的存在成为一个公共卫生问题。为了应对这一问题，USP 召集了联合小组委员会（成员来自 USP 通则专家委员会和两个小分子专家委员会），他们负责制定计划，并指导 USP 制定公共标准来解决这一问题。联合小组委员会第一个工作成果是制定了通则<1469>亚硝胺杂质，该通则于 2020 年 9 月 1 日在药典论坛 PF46(5)在线发布供公众评议，并在 *USP-NF* 2021 投票中被化学分析通则专家委员会批准为公共标准，自 2021 年 12 月 1 日起正式生效。本次演讲将讨论 USP 对解决药品中亚硝胺问题的观点，以及通则<1469>的要点及基本原理。还将讨论 USP 标准及其适用性，公共标准的制定过程，以及关于药品中亚硝胺的监管概况的简短总结。

Naiffer Romero, MSc, MPH
Senior Scientific Affairs Manager
United States Pharmacopeia (USP)

Naiffer has more than 18+ years of pharmaceutical industry experience. In his 10 years tenure with USP, he has served several roles: Lead scientist in performance testing compendial reference standards development, Manager in charge of LATAM Compendial engagement and education with stakeholders and national regulatory bodies. Naiffer is also certified USP Education instructor.
Most recently, Naiffer joined USP's Scientific Affair performance cell where he leads scientific outreach and engagement for LATAM & US region on key national health priority topics. His combined pharmaceutical expertise includes Analytical development, salt and polymorph selection, Development of dissolution methods, IVIVC modelling, and impurity analytical strategy. Naiffer also serve as member of USP's Nitrosamine Steering Committee and community host to 'Nitrosamine Exchange', a knowledge community in All-things Nitrosamine.
Naiffer also liaise technical discussion on pharmacopeial collaboration including International meeting of World Pharmacopeias (part of WHO).

Presentation: Nitrosamine Impurities – The compendial Response & Resources

ABSTRACT: The nitrosamine impurities crisis prompted regulators worldwide to scrutinize drug manufacturing processes further. This greater scrutiny may lead to the discovery of nitrosamine impurities in other medicines in the future. For this reason, manufacturers need to understand which medicines are likely to form nitrosamines, how and at what levels nitrosamine impurities are forming, and how to control nitrosamines.

In the following seminar, we will explore how USP responded to the nitrosamine impurities crisis with a proposed general chapter on nitrosamine impurities that provides a risk assessment strategy and methods for detecting and measuring nitrosamine impurities with physical reference standards against which manufacturers can compare their test results. Additionally, USP has created a whole suite of resources and tools for stakeholders to face the challenges of Nitrosamine Impurities effectively.

Fan Wu, Ph.D.
Technical Director of Global Measurement Science, Ashland LLC

Dr. Fan Wu received his Ph.D. in organometallic chemistry from the University of Chicago in
2004. Following a postdoctoral fellowship at the Brookhaven National Laboratory in Upton, NY, he accepted a senior analytical scientist position in Ciba Specialty Chemicals in 2006, which was later acquired by BASF. In 2010, Dr. Wu joined Ashland, LLC as a group leader in Measurement Science and was appointed the technical director of global measurement science in 2018. Dr. Wu has the overall responsibility for providing comprehensive analytical characterizations and fundamental understanding of structure/property relationship to enable the creation of innovative and sustainable technologies, and to drive and accelerate profitable growth. Ashland is a global leader in providing specialty chemical solutions to customers in a wide range of consumer and industrial markets, including pharmaceutical, personal care, nutraceutical, beverage, nutrition, architectural coatings, construction and energy. In particular, Ashland is the leading global supplier for cellulose ether and vinyl pyrrolidone polymers for pharmaceutical excipient market. Dr. Wu has volunteered in the USP Povidone expert panel, excipient monograph expert committee and complex excipient expert committee since 2011.

Presentation: Industry challenges with sources of Nitrosamines in Excipients

ABSTRACT: This presentation is intended to stimulate global stakeholders' discussion on the industry challenges with the identification of the sources of nitrosamine impurities in pharmaceutical excipients and the corresponding risk assessment and control strategies. The engagement and inputs of all global stakeholders will enable USP's standard setting strategies and action plans for the nitrosamine impurities in excipients. In addition, as a representative from a key excipient manufacturer, Ashland's perspective of the challenges in identifying the sources and controlling the nitrosamine impurities in excipients are discussed.

Junichi Fukuchi, Ph.D.
Principal Technical Officer, Office of Review Management
Division of Pharmacopoeia and Standards for Drugs as a Japanese Pharmacopoeia secretariat
PMDA

Dr. Junichi Fukuchi, of PMDA, Office of Review Management, is Principal Technical Officer. He belongs to Division of Pharmacopoeia and Standards for Drugs as a Japanese Pharmacopoeia secretariat. He also participates in ICH-M7 topic as quality expert of Japan regulatory. Previously, he was responsible for reviewing the CMC of small molecules and biotechnological products. He obtained a Ph.D. in Pharmaceutical Science from Chiba University and completed post-doctoral work at University of Chicago studying in prostate cancer. He is a licensed pharmacist.

Presentation: Current status on control of nitrosamines in marketed products in Japan

ABSTRACT: In recent years, nitrosamines, which are carcinogens, have been detected in some pharmaceutical products in Japan and overseas. Possible causes of contamination of pharmaceuticals with nitrosamines include production in the synthetic process, contamination in recovered solvents and reagents, use of some packaging materials, and production during storage. It cannot be denied that nitrosamines may be contaminated in pharmaceutical products other than those in which nitrosamines have been detected so far, and it is important to reduce the risk of contamination as much as possible.
This presentation is intended to give an overview of the notification published by MHLW regarding the handling of self-inspection on the risk of contamination with nitrosamines in pharmaceutical products.

Junichi Fukuchi 博士

日本药品和医疗器械管理局 药典秘书处 药典与药物标准审评管理办公室 首席技术官

Junichi Fukuchi 博士是日本药品和医疗器械管理局 (PMDA)审评管理办公室首席技术官，隶属于药典与药物标准部门，日本药典秘书处。他也作为日本监管部门的质量专家参与了 ICH-M7 相关工作。在此之前，他负责小分子和生物技术产品的 CMC 审核。Junichi Fukuchi 博士拥有千叶大学药理学博士学位，并在芝加哥大学完成了前列腺癌研究博士后工作。他是职业药剂师。

演讲主题：日本上市药品中亚硝胺杂质控制现状

摘要：近年来，在日本和国外的一些药品中检测出致癌物质亚硝胺。亚硝胺污染药品的可能原因包括合成工艺生产、回收的溶剂和试剂的污染、一些包装材料的使用、以及存储期间的生产。不可否认，除了迄今已检测到亚硝胺的药品外，其他药品中也可能含有亚硝胺，因此，重要的是尽可能减少污染的风险。
本介绍旨在概述日本厚生劳动省发布的关于处理药品中亚硝胺污染风险的自检通知。

Ying Chen

Director, Pharmaceutical Excipients Department
Guangdong Institute for Drug Control and NMPA Key Laboratory for Quality Control and Evaluation of Pharmaceutical Excipients

Chen Yin is the director of Pharmaceutical Excipients Department of Guangdong Institute for Drug Control. She is also the member of the 11th Professional Committee of Pharmaceutical Excipients of the National Pharmacopoeia Commission and the director of the Key Laboratory of Quality Control and Evaluation of Pharmaceutical Excipients of the National Drug Administration. Over the 5 years, she has led and participated the establishment of the quality standard system for pharmaceutical excipients in the new version of National Pharmacopoeia and took the lead in drafting dozens of species standards, general methods and guidelines, etc., which were included in the 2020 edition of the National Pharmacopoeia; She has also been in charge of the quality evaluation studies of several national pharmaceutical excipient species.

Presentation: Study on Chloropropanol Impurities in Pharmaceutical Excipients

ABSTRACT：The presentation introduces the research on chloropropanol impurities in pharmaceutical excipients and the development of its verification, providing technical support for the risk assessment of chloropropanol in pharmaceutical excipients.

陈英 主任药师

广东省药品检验所辅料室负责人，国家药监局药用辅料质量控制与评价重点实验室主任

陈英主任药师，广东省药品检验所辅料室负责人，国家药典委员会第十一届药用辅料专业委员会委员、国家药监局药用辅料质量控制与评价重点实验室主任。近 5 年来，主持和参与新版国家药典药用辅料质量标准体系建设，主持完成数十项品种标准、通用方法和指导原则等的起草工作，收载于 2020 年版国家药典；主持多个国家药用辅料品种的质量评价研究。

演讲主题：药用辅料中氯丙醇杂质的控制研究

摘要: 介绍药用辅料中氯丙醇杂质研究情况以及测定方法的建立开发，为药用辅料中氯丙醇的风险评估提供技术支持。

BM Rao, Ph.D.
VP & Head - CQC, ASAT & EM QA
Dr. Reddy's Laboratories Limited, Hyderabad

Dr. BM Rao possess a Ph.D. degree in Chemistry and has about 32 years of work experience in pharmaceutical Analytical R&D, Quality Control & Assurance functions in reputed organizations includes Janssen (pharmaceutical companies of Johnson & Johnson, Novartis, Zydus Cadila, Nicholas Piramal, and Dr. Reddy's. He has extensive hands-on experience on analytical instruments related to chromatography, spectroscopy and thermal analysis. He has exposure to various regulatory audits includes USFDA, EMEA, TGA, Health Canada, CFDA etc. and worked with reputed International consultants in QC remediation. He has about 80 scientific publications in reputed peer reviewed national/ international journals and successfully guided eight part-time Ph.D. candidates.
During his professional career he has been recognized for his contributions at work and won awards including Chairman's Excellence Award from Dr. Reddy's Laboratories (Feb, 2018 & Jan, 2003), "Standards of Leadership" from J&J at Janssen, Mumbai site (year 2010) and Best New Leader Award at SAI Life Sciences Limited (year 2013). He has extensively travelled to USA, Mexico, Europe, Germany, Belgium, Singapore, Brazil, and Malaysia and interacted with several big and emerging biotech pharmaceutical analytical & quality experts.
Since September 2015, Dr. BM Rao is working as Head of Quality for Emerging Markets, Analytical Science & Technology (ASAT) & Corporate Quality control at Dr. Reddy's Laboratories and providing technical leadership to the Analytical method validations/transfers and Quality Control labs of APIs and Formulations.

Presentation: Nitrosamine impurities – Current Regulatory Status

ABSTRACT: Medicine Regulatory Authorities first became aware of the presence of the nitrosamine impurity, N-nitrosodimethylamine (NDMA), in products containing valsartan in July 2018. Valsartan is an Angiotensin II Receptor Blocker (ARB) and belongs to a family of analogue compounds commonly referred to as the sartans. Further nitrosamine impurities were subsequently detected in other medicines belonging to the sartan family, including: N-nitrosodimethylamine (NDEA), N-nitrosodiisopropylamine (NDIPA), N-nitrosoethylisopropylamine (NEIPA) and N -nitroso-N-methyl-4-aminobutyric acid (NMBA). More recently, nitrosamine impurities have been reported in pioglitazone and ranitidine containing products. FDA has been working diligently to address the concerns created by the presence of nitrosamines in DP's (Drug Product) and keeping the public informed. Recent actions have included the recall of certain lots of DP's, publication of acceptable daily exposure limits of nitrosamines in the DP's in question and the development and publication of sensitive analytical methods for the determination of nitrosamines. This situation has created uncertainty for FDA, industry, and consumers alike. It has shaken consumers' confidence in the safety of the medications they have come to trust and depend on to maintain the quality of their lives. This said, the impact on the generic pharmaceutical industry has been especially disconcerting, as most of the affected drugs are genericized. Generics represent, by volume, greater than 90% of all prescriptions dispensed in the U.S. Many of the global regulatory authorities, including WHO, EMA and Health Canada have provided directives regarding evaluation of nitrosamines in products including complete retrospective analysis of all approved DP's.
The current topic describes the suggested approaches to mitigate the regulatory risks with respect to nitrosamine impurities present the pharmaceutical products.

BM Rao 博士

瑞迪制药有限公司副总裁，CQC, ASAT & EM QA 负责人

BM Rao 博士拥有化学博士学位，他在知名企业例如杨森（强生旗下的制药企业）、诺华、Zydus Cadila、Nicholas Piramal 和 Dr.Reddy’s 拥有约 32 年的药物分析研发、质量控制和保证领域的工作经验。他在色谱、光谱和热分析相关的分析仪器方面拥有丰富的实践经验。他参与过各类监管审计，包括美国 FDA、EMEA、TGA、加拿大卫生部、CFDA 等，并与著名的国际顾问合作进行 QC 补救。他在著名国家/国际学术期刊上发表了约 80 篇科学文章，并成功指导了八名兼职博士候选人。

在职业生涯中，Rao 博士因工作中的出色贡献受到认可，2003 年 1 月和 2018 年 2 月获得了 Dr. Reddy’s 公司颁发的总裁卓越奖，2010 年获得了孟买杨森公司颁发的“领导力标准”奖，以及 2013 年 SAI 生命科学有限公司颁发的最佳领导新人奖。他曾广泛访问美国、墨西哥、欧洲、德国、比利时、新加坡、巴西和马来西亚，并与一些大型新兴生物技术公司的药物分析和质量专家进行交流。

自 2015 年 9 月起，Rao 博士担任 Dr. Reddy’s 公司新兴市场、分析科学与技术（ASAT）和企业质量控制部门负责人，并为原料药和制剂的分析方法验证/转移和质量控制实验室提供技术指导。

演讲主题：亚硝胺杂质 — 当前监管状态

摘要：2018 年 7 月，监管机构首次意识到含有亚硝胺的缬沙坦药物的存在。缬沙坦是一种血管紧张素 II 受体阻滞剂（ARB），属于一类类似化合物，通常被称为沙坦。随后，在沙坦家族的其他药物中检测到更多亚硝胺杂质，包括：N-亚硝二甲胺（NDEA）、N-亚硝二异丙胺（NDIPA）、N-亚硝乙基异丙胺（NEIPA）和 N-亚硝基-N-甲基-4-氨基丁酸（NMBA）。最近，有报道称含有吡格列酮和雷尼替丁的产品中含有亚硝胺杂质。FDA 一直在努力解决因药品中存在亚硝胺而引起的担忧，并向公众通报情况。最近的行动包括召回某些批次的药品，公布相关药品中亚硝胺的每日可接受的限值，以及开发和公布测定亚硝胺的敏感分析方法。这种情况给 FDA、行业和消费者都带来了不确定性。它动摇了消费者对他们信任和依赖、维持生活质量的药物安全性的信心。尽管如此，对非专利药行业的影响尤其令人不安，因为大多数受影响的药物都是非专利药。非专利药占美国处方总量的 90%以上。包括世界卫生组织、EMA 和加拿大卫生部在内的许多全球监管机构都提供了有关产品中亚硝胺评估的指导，包括对所有已批准的药品的完整回顾性进行分析。本次演讲将讨论减少药品中亚硝胺杂质监管风险的建议方法。

Raphael Nudelman, Ph.D., ERT
Senior Director Impurity Expert, R&D Operations
Teva Pharmaceutical Industries Ltd.

Raphael has over 20 years of pharmaceutical industry experience. He has a Ph.D. in organic chemistry from the Weizmann Institute of Science in Israel, a post-doctorate at the US Air Force Research Lab in Aberdeen Proving Ground, Maryland, and another post-doctorate at Duke University Medical Center, North Carolina. In 2003 Raphael joined the Medicinal Chemistry department at Teva Pharmaceuticals. In 2010 he established the Chemical & Computational Toxicology group in Teva, and now he is Senior Director Impurity Expert in R&D Operations. Raphael's main topics of expertise are impurity and excipient qualification in drug substances and drug products. Over the past few years he has specialized in nitrosamine evaluation and setting limits for nitrosamines.

Presentation: Setting Limits for Complex Nitrosamines

ABSTRACT: Nitrosamine impurities have been in the center of the stage of impurities in drug products for the past 3 years. Regulators and industry have been deliberating the methods for determining limits for this special class of mutagenic/carcinogenic impurities. Preliminary guidelines have been published by regulatory agencies, however, they lack guidance on how to set limits for API-related nitrosamines, also known as “Complex Nitrosamines”. My presentation will discuss the ongoing activities to come to a consensus between the regulatory agencies and the pharmaceutical industry on what is the adequate process to set acceptable intake limits for the complex nitrosamines.

Raphael Nudelman 博士

梯瓦制药工业有限公司研发运营部门高级总监，杂质专家

Nudelman 博士拥有超过 20 年的制药行业经验。他拥有以色列 Weizmann 科学研究所的有机化学博士学位、马里兰州 Aberdeen 试验场美国空军研究实验室的博士后学位、以及北卡罗来纳州杜克大学医学中心的博士后学位。2003 年，Nudelman 博士加入梯瓦制药工业有限公司药物化学部门。2010 年，他在梯瓦成立了化学和计算机毒理学组，现在他是研发部门的高级总监和杂质专家。Nudelman 博士主要专长是原料药和制剂中的杂质和辅料鉴定。在过去几年中，他专门从事亚硝胺评估和亚硝胺限值的设定。

演讲主题：复杂亚硝胺杂质限量的设定

摘要：近三年来，亚硝胺杂质一直是药品杂质阶段的关注重点。监管机构和行业一直在研究确定这类特殊诱变/致癌杂质限值的方法。监管机构已经发布了初步指南，但是，它们缺乏关于如何设定 API 相关亚硝胺（也称为“复杂亚硝胺”）限值的指导。此次演讲将讨正在进行的活动，旨在使监管机构和制药行业就制定复杂亚硝胺可接受摄入量限制的适当工艺达成共识。

Aloka Srinivasan, Ph.D.
Principal and Managing Partner of RAAHA LLC

Aloka Srinivasan, Ph.D., the Principal and Managing Partner of RAAHA LLC (www.raahallc.com) has more than two decades of experience in the pharmaceutical industry, including nine years of progressive experience with the U.S. FDA in the Office of Generic Drugs, Lupin Pharmaceuticals, Lachman Consultants and PAREXEL International. Dr. Srinivasan has supported the development of several new drugs and generics during her tenure in PAREXEL and Lachman. Dr. Srinivasan has worked closely with the industry and FDA related to development and approval of several complex 505(b)(2) applications as well as complex generic applications. Dr. Srinivasan spearheaded the foundation of a division in FDA related review of drug master files (DMF) for drug substances under GDUFA and played a pivotal role in writing of the FDA Guidance for Industry: Initial Completeness Assessments for Type II API DMFs Under GDUFA and a QbR document for drugs substance, which is part of FDA Mapp. 5015.10. Dr. Srinivasan was one of the main authors of the QbR-QOS (Question based Review-Quality Overall Summary) for ANDAs, which is the current basis of review of generis at CDER/FDA.
Dr. Srinivasan is one of the world class experts in the area of nitrosamine impurities based on her research background and has been supporting the industry in addressing these carcinogenic impurities in the drugs.
Dr. Srinivasan received her Ph.D. from University of Missouri, Columbia under Dr. Richard N. Loeppky of nitrosamine fame. Her thesis was titled “A study of putative intermediates involved in the activation of beta oxidized nitrosamines and nitrosation of N-substituted aziridines”. Dr. Srinivasan also spent seven years as a scientist in National Cancer Institute, working for Dr. Larry K. Keefer, researching on nitrosamines in potential nitric oxide donor drugs.
Dr. Srinivasan champions the regulatory efforts of RAAHA’s clients based on her extensive experience and in-depth knowledge of chemistry and U.S. FDA’s regulatory requirements.

Presentation: Current landscape in the US

Aloka Srinivasan 博士

RAAHA LLC 公司负责人兼管理合伙人

Aloka Srinivasan 博士是 RAAHA LLC 公司负责人兼管理合伙人。她在制药行业有超过 20 年的经验，包括 9 年美国 FDA 非仿制药办公室、Lupin 药业、Lachman 咨询和 PAREXEL 国际公司的先进经验。
Srinivasan 博士在 PAREXEL 公司 和 Lachman 咨询任职期间，支持开发了几种新药和仿制药。她与行业和 FDA 密切合作，开发和批准了多个复杂 505(b)(2)应用以及复杂仿制药应用。Srinivasan 博士领导了 FDA 一个部门的成立，该部门负责原料药 DMF 审查，并在撰写 FDA 行业指南（“GDUFA 下 II 类原料药 DMF 的初始完整性评估”、“作为 FDA Mapp 一部分的原料药 QbR 文件.5015.10.”）中发挥关键作用。Srinivasan 博士是 ANDAs QbR QOS（基于问题的审查质量总结）的主要作者之一，这是 CDER/FDA 目前对仿制药进行审查的基础。
因其出色的研究背景，Srinivasan 博士是亚硝胺杂质领域的世界级专家之一，并一直支持行业解决药物中的致癌杂质问题。

Srinivasan 博士在密苏里大学哥伦比亚分校获得博士学位，师从以亚硝胺闻名的 Richard N. Loeppky 博士。她的论文名为《β-氧化亚硝胺活化和 N-取代氮杂环胺的亚硝化过程中的假定中间体研究》。Srinivasan 博士还曾在美国国家癌症研究所担任科学家长达七年，为 Larry K.Keefer 博士工作，研究潜在一氧化氮供体药物中的亚硝胺。Srinivasan 博士凭借其丰富的经验和对化学和美国 FDA 监管要求的深入了解，负责 RAAHA 客户的监管工作。

演讲主题：美国亚硝胺杂质现况

Cristian Sampaolesi
Head of New Dossiers Section
Certification of Substances Department (DCEP), EDQM

Cristian Sampaolesi is the Head of New Dossiers Section since March 2017, the group in charge of the evaluation of new dossiers at the Certification of Substances Department (DCEP) of the EDQM. He holds an MSc in Regulatory Affairs Sciences for Medicines and a BSc in Industrial Chemistry. After 5 years working with the pharmaceutical industry he joined an EU National Competent Authority in 2009 as Quality Assessor, a position he held for 3 years. From 2010 to 2012, he was the nominated member within the Joint CHMP/CVMP Quality Working Party at the EMA. He works with the Certification of Substances Department of the EDQM since June 2012.

Presentation: The EDQM response to nitrosamines
ABSTRACT: Giving participants an overview on how the nitrosamines quality incident was managed in Europe, with emphasis on the role and measures taken by the European Pharmacopoeia and actions in the framework of the Certification Procedure.

Cristian Sampaolesi

欧洲药品质量管理局 原料药认证部门 新档案组负责人

Cristian Sampaolesi 自 2017 年 3 月起担任新档案部负责人，该团队负责评估 EDQM 原料药认证部门（DCEP）的新档案。他拥有医药监管事务科学硕士学位和工业化学学士学位。他在制药行业工作 5 年后，于 2009 年加入欧盟国家主管机构，担任了三年质量评估员工作。2010 年至 2012 年，他成为 EMA CHMP/CVMP 联合质量工作组成员。自 2012 年 6 月起，他在 EDQM 原料药认证部门工作。

演讲主题：欧洲药典应对亚硝胺杂质
摘要：该演讲将向与会者介绍欧洲如何管理亚硝胺质量事件，重点介绍欧洲药典的作用和采取的措施，以及认证程序框架下采取的行动。

Amanda Guiraldelli, Ph.D.
Scientific Affairs Manager
U.S. Pharmacopeia

Amanda Guiraldelli has been with USP since 2012 and holds the position of scientific affairs manager and principle scientist in the compendial science group-general chapters. She is the scientific liaison to the USP Measurement and Data Quality Expert Committee, where she works to develop and revise USP standards. Previously, Amanda worked as senior scientist at the USP reference standard laboratory for 8 years with characterization of compendial standards. She is visiting professor at the University of Campinas (UNICAMP) Brazil at the Institute of Chemistry and is a frequent speaker and instructor on topics related to analytical procedure life cycle and Analytical Quality by Design (AQbD). Amanda is specialist in chromatography, mass spectrometry and chemometrics and has more than 14 years of experience in pharmaceutical R&D areas. Prior to joining USP, she was R&D scientist in a pharmaceutical industry and visiting scientist at TU Berlin in Germany and Leiden University in Netherlands (Center for Proteomics and Metabolomics) working on proteins characterization by LC-HRMS and method development using UHPLC-HRMS. Amanda is graduated in pharmacy biochemistry and holds a Ph.D. in analytical chemistry from the University of São Paulo (metabolomics by UHPLC-HRMS, GC-MS and 1H NMR and chemometrics).

Presentation: Testing Methods for Nitrosamines Monitoring in Pharmaceuticals: Analytical Challenges
ABSTRACT: The presentation will cover an overview of the USP General Chapter <1469> Nitrosamines Impurities with focus on the sections related to analytical procedures for nitrosamines analysis by LC-MS and GC-MS based methods. This presentation includes a discussion on analytical challenges faced during nitrosamines monitoring in pharmaceutical including sample preparation, sensitivity & selectivity issues and matrix effect.

Amanda Guiraldelli 博士
美国药典委员会科学事务经理

Amanda Guiraldelli 博士自 2012 加入 USP 并工作至今，在药典科学通则组担任科学事务经理和首席科学家。她是 USP 测量和数据质量专家委员会的科学事务联络官，从事制定和修订 USP 标准工作。在此之前，Guiraldelli 博士作为高级科学家在 USP 标准物质实验室工作了 8 年，从事药典标准的表征工作。她是巴西 Campinas 大学化学研究所的客座教授，是分析方法生命周期和 AQbD 相关主题的讲师。Guiraldelli 博士是色谱、质谱和化学计量学方面的专家，在医药研发领域拥有超过 14 年的经验。在加入 USP 之前，她是制药行业的研发科学家，也是德国柏林大学和荷兰莱顿大学（蛋白质组学和代谢组学中心）的客座科学家，致力于通过 LC-HRMS 对蛋白质进行表征研究，并使用 UHPLC-HRMS 进行方法开发。她毕业于药学生物化学专业，拥有巴西圣保罗大学分析化学博士学位。

演讲主题：亚硝胺杂质分析方法的挑战
摘要：本次演讲将论述 USP 通则<1469>亚硝胺杂质，重点介绍通过 LC-MS 和基于 GC-MS 的方法进行亚硝胺分析的相关章节内容。本次演讲还将介绍药品中亚硝胺监测过程中面临的分析挑战，包括样品制备、灵敏度和选择性问题以及基质效应。

David Ponting, Ph.D.
Principal Scientist
Lhasa Limited

David completed his undergraduate degree in Natural Sciences at the University of Cambridge, specialising in Chemistry, and stayed to study for a PhD under the supervision of Professor Jonathan Goodman, investigating computational – principally quantum-mechanical modelling - approaches to the prediction of skin sensitisation. After successfully defending his thesis, David moved to the University of Gothenburg for postdoctoral research with Professor Ann-Therese Karlberg, applying the principles developed during his PhD to a series of chemical classes, as well as briefly returning to the experimental side of the lab.

Following this, David joined Lhasa Limited, where he has taken on a number of distinct roles utilising both aspects of his previous experience. David is a core member of the team continually improving the science in Derek Nexus, developing alerts for a wide variety of endpoints - including of course skin sensitisation, but also genetic toxicology endpoints from mutagenicity to carcinogenicity. David is applying his quantum-mechanics expertise to develop novel descriptors for aromaticity, reactivity, bond dissociation energy and photochemical parameters in order to improve predictions across Lhasa's range of products. David is heavily involved in Lhasa's response to the nitrosamine crisis, where he has been leading a major cross-industry working group addressing, and publishing on, aspects of nitrosamine carcinogenic potency and structure-activity relationships.

Presentation: How concerning is your nitrosamine? Using SAR to evaluate hazard and potency
ABSTRACT: "The inclusion of nitrosamines in the cohort of concern under ICH M7 was due to their extreme carcinogenic potency. Exposure to many nitrosamines at levels corresponding to the general threshold of toxicological concern (TTC) would lead to unacceptable carcinogenic risk; however, not all nitrosamines are this potent [Thresher et al (2020), Regul Toxicol Pharmacol, 116, 104749]. This presentation will review the applicability of the ICH M7 safety assessment process to nitrosamines, highlighting both areas where it works without modification and areas where the cohort of concern nitrosamines must be treated differently. Key SAR classes [Cross and Ponting (2021), Comput Toxicol, 20, 100186); Thomas et al (2021), Regul Toxicol Pharmacol, 121, 104875] and reasons why certain nitrosamines are potent and others not will be discussed. Methods for the calculation of class-specific TTCs will be discussed, as will suggested boundaries for the cohort of concern and strategies for determining compound-specific acceptable intake limits.

David Ponting 博士

Lhasa 公司首席科学家

Ponting 博士在剑桥大学获得自然科学学士学位，主修化学，并在 Jonathan Goodman 教授的指导下继续攻读博士学位，通过量子力学建模方式研究计算预测皮肤敏感性的方法。Ponting 博士成功完成论文答辩后到哥德堡大学与 Ann Therese Karlberg 教授进行博士后研究，将博士期间开发的原理应用于一系列化学课程。
在此之后，David 加入了 Lhasa 公司，凭借自己以往经验担任了许多不同的职位。David 是团队的核心成员，在 Derek Nexus 方面持续改进科学，为各种端点开发预警 — 包括皮肤过敏，也包括从诱变性到致癌性的遗传毒理学

端点。大卫运用量子力学的专业知识，开发芳香性、反应性、键离解能和光化学参数的新内容，以改进 Lhasa 系列产品的预测。Ponting 博士积极参与 Lhasa 公司应对亚硝胺危机的工作，他领导一个大型跨行业工作组，讨论并发表亚硝胺致癌强度和结构活性关系方面的内容。

演讲主题：您是否为产品中的亚硝胺杂质焦虑？ 使用 SAR 评估危害及活性

摘要： “根据 ICH M7，亚硝胺因具有极高的致癌效力引发关注。在与毒理学有关的一般阈值（TTC）对应的水平下暴露于许多亚硝胺会导致不可接受的致癌风险；然而，并非所有亚硝胺都具有这种效力【Thresher et al (2020), Regul Toxicol Pharmacol, 116, 104749】。本次演讲将就 ICH M7 对亚硝胺安全评估过程的适用性进行论述，重点介绍其在未经修改的情况下发挥作用的领域，以及必须对亚硝胺进行不同处理的相关领域。也将讨论主要 SAR 类别【Cross and Ponting (2021), Comput Toxicol, 20, 100186); Thomas et al (2021), Regul Toxicol Pharmacol, 121, 104875】和为什么某些亚硝胺有效力而其他亚硝胺无效力的原因。演讲中也将讨论特定类别 TTC 的计算方法，以及关注群体的界限和确定特定化合物可接受摄入量限值的策略。

Andrew Teasdale Ph. D.
Chair of AstraZeneca's Impurity Advisory Group, AstraZeneca

Andrew Teasdale PhD has over 25 years' experience in the pharmaceutical industry as an analytical chemist and within quality assurance and regulatory roles. In his current role he chairs AstraZeneca's Impurity Advisory Group. Dr Teasdale has published a number of papers relating to extractables and leachables, mutagenic impurities and other impurity related matters. He is currently the chair of the Extractables and Leachables safety Information exchange (ELSIE) and also led a number of industry expert groups; these include both safety and quality groups within Pharmaceutical Research and Manufacturers of America (PhRMA), European Federation of Pharmaceutical Industries and Associations (EFPIA), Product Quality Research Institute (PQRI) . Andrew has also represented EFPIA in ICH Q3C, Q3D and Q3E Expert working groups. He has also advanced a number of key scientific advancements in the control of impurities as the inventor of the purge factor concept and the instigator of the development of Elemental Impurities database for excipients.

With over 50 scientific papers, he has also written 3 books:

Genotoxic Impurities – Strategies for Identification and control. Editor A Teasdale. Publisher Wiley. ISBN 978-0-470-49919-1

ICH Quality Guidelines – An Implementation Guide. Editors A Teasdale, D Elder, R W Nims. Publisher Wiley. ISBN 978-1-118-97111-6.

Mutagenic Impurities – Strategies for Identification and Control Second Edition. Editor A Teasdale. Publisher Wiley. ISBN 978-1-119-55121-8

Presentation: N-Nitrosamines Light at the end of the Tunnel? or the end of the Road?

ABSTRACT: Since N-Nitrosamines were first identified as concern in Valsartan based products, we have been on a rollercoaster ride seeking to address arguably the biggest challenge the industry has ever faced in terms of an impurity-based concern. This presentation seeks to outline the journey to date and critically, the challenges we still face; both in the short term and the longer term. It examines both threats and opportunities as we seek to maintain access to vital medicines and the choices industry and regulators need to make.