

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

First Inventor: WRAIGHT, Christopher John Confirmation No.: 4050
Application No.: 15/887,388 Group Art Unit: 1628
Filed: February 2, 2018 Examiner: HEYER, Dennis
For: **PHARMACEUTICAL COMPOSITION COMPRISING BETAHISTINE**

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

DECLARATION UNDER 37 C.F.R. § 1.132

I, David P. Elder, Ph.D., declare as follows:

1. I hold a Ph.D. degree in solid-state chemistry and crystallography from the University of Edinburgh and I am a Fellow of the Royal Society of Chemistry (FRSC). I am a visiting professor at King's College, London where I teach a course in pharmaceuticals. I also have my own consultancy company. I have 41 years of experience in the pharmaceutical industry ranging from drug development, drug delivery, quality control, regulatory submission compilations (NDAs, MAAs) and CMC (Chemistry, Manufacturing, and Controls) aspects of pharmaceutical products. Prior to starting my consultancy company, I served in many roles at GlaxoSmithKline, PLC for 23 years. For the last 10 years I coordinated all aspects of CMC due diligence. This involved reviewing/critiquing many hundreds of drug product opportunities from external partners. Prior to that, I was a Director of New Chemical Entities Development at Glaxo where my team was involved in developing oral and intra-nasal products and we successfully developed and commercialized an intra-nasal suspension product for seasonal rhinitis. My curriculum vitae is attached (Exhibit 1).

2. I have advised Auris Medical, AG, the assignee of the present application on certain aspects of their intra-nasal betahistine product. I have no financial interests in the outcome of

Auris' intra-nasal betahistine product. Furthermore, I have no inventive or financial interest in the present application.

3. I have reviewed and understand the specification, claims, and pending Office Action in the present application, as well as the references cited therein. Specifically, I understand that claims 60 - 64, 67, 71 - 83 and 89 are rejected under 35 U.S.C. §103(a) as being unpatentable over Passarotti *et al.* (EP 0397025, hereinafter "Passarotti") in view of Bhise *et al.* (Asian Journal of Pharmaceutics, 201 - 215 (2008), hereinafter "Bhise") and Marx *et al.* (Intranasal Drug Administration - An Attractive Delivery Route for Some Drugs, Chapter 13, Drug Discovery and Development - From Molecules to Medicine, pages 299 - 320 (2015), hereinafter "Marx"); and claim 68 is rejected under 35 U.S.C. § 103(a) as being unpatentable over Passarotti in view of Bhise, Marx, and Haslwanter *et al.* (U.S. Patent No. 5,897,858, hereinafter "Haslwanter"). The "obviousness" standards under 35 U.S.C. § 103(a) have been explained to me by patent counsel.

4. I understand that the claimed composition is for intra-nasal delivery and comprises a solution or suspension of a therapeutically effective amount of betahistine dihydrochloride, a viscosity enhancing agent, a moisturizing agent, and a buffer, wherein the pH of the pharmaceutical composition is between about 4.4 to about 6.4. In my opinion, none of the cited references discloses or would have suggested the claimed composition to a person of ordinary skill in the art at the time the application was filed.

5. Passarotti is directed to polycarboxylic acid salts of betahistine and their use for pharmaceutical formulations (Abstract). Passarotti compared the effect of equimolar doses of betahistine dihydrochloride and betahistine fumarate with regard to toxicity and gastric erosions (p. 2, ll. 37-38). Passarotti observed that about 92% of the animals administered with the dihydrochloride salt of betahistine suffered severe gastric erosions whereas only 10% of the animals administered with the fumarate salt of betahistine suffered serious erosions (Table 2). In addition, the erosions experienced by the animals administered with the dihydrochloride salt were very severe compared to those experienced by the animals administered with the fumarate

salt (Table 2). Passarotti notes that the bioavailability of the dihydrochloride salt and the fumarate salt after oral administration is substantially the same (p. 3, ll. 23-24).

6. Overall, Passarotti teaches that the fumarate salt of betahistine is advantageous over the dihydrochloride salt as it does not lead to severe gastric erosions and at the same time provides similar oral bioavailability. *See* Passarotti at p. 2, ll. 26-28.

7. The Examiner takes the position that in view of Passarotti, a person of ordinary skill in the art would have considered betahistine fumarate and betahistine dihydrochloride to be functionally equivalent as the only difference between the two salts being the extent of gastric erosions caused by oral administration of the dihydrochloride salt at much lower pH and this difference would be relevant solely for oral administration. Office Action, p. 10.

8. In my opinion, one of ordinary skill in the art would not have considered betahistine dihydrochloride and betahistine fumarate to be functionally equivalent in view of the gastric erosion data in Passarotti. In my opinion, Passarotti's gastric erosion data is not only relevant for oral administration but is also highly relevant for intranasal administration as explained below.

9. As noted in my first declaration, it is known that the gastric mucosa can tolerate very acidic pH, a pH of about 1.2, whereas the nasal mucosa can only tolerate mildly acidic pH, a pH of about 5.5 to 7.0. Even after being capable of tolerating strongly acidic pH, the gastric mucosa suffered severe erosions upon exposure to betahistine dihydrochloride as shown in Passarotti. In view of this observation, in my opinion, a person of ordinary skill in the art would expect betahistine dihydrochloride to have a similar severe erosive effect, or more likely, even more severe erosive effect on the nasal mucosa. That is, a person of ordinary skill in the art would have considered the gastric erosion data in Passarotti to be predictive of nasal erosion. Therefore, I believe that one of ordinary skill in the art would not have considered betahistine dihydrochloride and betahistine fumarate to be functionally equivalent. Accordingly, in my opinion, at the time of invention, a person of ordinary skill in the art would not have used betahistine dihydrochloride for intra-nasal formulations.

10. Furthermore, one of ordinary skill in the art would not have selected the dihydrochloride salt of betahistine over the fumarate salt of betahistine due to their expected aqueous solubility at the pH range of 4.5 to 6.5 taught by Bhise and Marx as desired for intranasal formulations. Specifically, one of the important formulation challenges when developing a liquid formulation, i.e. a parenteral formulation, an oral liquid formulation or an intranasal formulation, is aqueous solubility. *See Dressman and Reppas 2007, Drug Solubility: How to measure it, how to improve it. Adv, Drug Deliv., Rev., 59, 531-532; and Akers, 2010, Chapter 11: Overcoming formulation Problems and Some Case Studies In: Sterile Drug Products, Formulation, Packaging, Manufacturing and Quality, M.J.Akers (Ed), Informa Press, New York and London, pp. 169-179 (attached here as Exhibits 2 and 3, respectively).* For intranasal liquid formulations, aqueous solubility is even more important and significant than parenteral or oral liquid dosage forms, because the optimal delivery volume for intranasal formulations is very small, only about 100 μ L (0.1 mL) per nostril; volumes higher than this cause nasal run-off (i.e. part of the delivered dose is lost from the nasal cavity without eliciting a pharmacological response). *See Bhise, p. 207, left column and Marx, p. 302, last paragraph.* As such, the pharmacologically active dose has to dissolve in 0.1mL, which requires significantly higher aqueous solubility than in other liquid dosage forms, i.e. oral liquid or parenteral. Therefore, any factor that affects the aqueous solubility of a drug will be taken into consideration by a person of ordinary skill in the art while formulating a liquid formulation for intranasal delivery.

11. It is known that the solubility profile of a drug at any given pH depends on the pKa of the drug and the pKa of the counterion, as the pKa determines the degree of ionization at that pH. *See also Bhise, p. 206, right column, first paragraph.* Betahistine has two pKa's (3.5 and 9.7); but only very strong acids e.g. hydrochloric acid can fully protonate the lower pKa, i.e. 3.5. As noted in Bhise, there is not much flexibility in adjusting the pH of the nasal formulations as "acidic pH causes nasal irritation followed by increase in the nasal mucociliary clearance rate, whereas alkaline pH leads to the microbial susceptibility and infection. Therefore, it is advised to maintain the nasal formulation pH in the physiological range of 4.5 to 6.5." Bhise, p. 206, right column. Unfortunately, the intrinsic pH of the dihydrochloride salt would be very acidic, about $\sim$ pH 1.5. In contrast, as the pKa of the fumarate counterion is much higher, about $\sim$ pH 3.55,

this counterion can only protonate the higher of betahistine's two pKa's i.e. 9.7. The intrinsic pH of the betahistine fumarate will be about pH 4.0-5.0 and this is much more aligned with the pH required for intranasal delivery, i.e, pH range of 4.5 to 6.5 taught by Bhise and Marx. In other words, a person of ordinary skill in the art would expect the dihydrochloride salt to be less soluble at the pH range of 4.5 to 6.5 as at this pH only the monohydrochloride salt would be expected to be present in solution. Thus, one of skill in the art would have two reasons not to substitute betahistine dihydrochloride for the betahistine fumarate in Passarotti's composition: (1) the dihydrochloride salt would be expected to cause nasal erosion, and (2), betahistine dihydrochloride salt would be less soluble at the pH range taught by Bhise.

12. In view of the expected nasal erosion and lower aqueous solubility of betahistine dihydrochloride at the pH range taught by Bhise and Marx, I believe that a person of ordinary skill in the art would not have been motivated to substitute the fumarate salt of betahistine taught in Passarotti with the dihydrochloride salt.

13. Betahistine is a known histamine receptor 1 (H1) agonist. In general, histamine receptor agonists are not administered intranasally as they mimic the inflammatory and/or allergic responses mediated by histamine. Passarotti contemplates intranasal formulations of betahistine fumarate; however, it does not provide any data on effects of these formulations upon intranasal administration.

14. Shelton and Eiser (*Clin. Otolaryngol.* 1994, 19, pp. 45-49, hereinafter "Shelton", attached here as Exhibit 4) tested the effects of intranasal administration of histamine, betahistine (H1 agonist), and impromidine (H2 agonist). Shelton notes that prior to their study, histamine agonists were never administered intranasally (p. 48, left column, last paragraph). Accordingly, Shelton was the first to test the effects of intranasal administration of histamine, betahistine, and impromidine.

15. Shelton performed unilateral nasal challenges with intranasal formulations of histamine, betahistine and impromidine, each given in random order, single-blind and at similar times on

separate days, using the same side of the nose (Shelton, p. 45, right column). Shelton demonstrates that this single administration of intranasal formulations of histamine and betahistine induced sneezing, itching, and rhinorrhea (Shelton, p. 47), all of which are considered the symptoms of allergy.

16. I believe that, in view of the undesirable side effects induced by intranasal formulation of betahistine as shown in Shelton and common knowledge in the art that histamine agonists are not administered intranasally, a person of ordinary skill in the art would not have been motivated to prepare intranasal betahistine formulations.

17. As noted in my first declaration, betahistine has a very short plasma half-life (3-4 h) (paragraph [006] of the present application). Such a short half-life, therefore, would likely require frequent administration, probably several times a day, due to its rapid rate of elimination. Moreover, because the claimed compositions are intended for treating chronic conditions such as Meniere's disease, it would be necessary to administer such compositions over an extended period of time, such as days or months.

18. As noted above, Shelton shows that a single administration of intranasal betahistine formulations induced undesirable side effects of sneezing, itching, and rhinorrhea. I believe that a person of ordinary skill in the art would therefore expect intranasal betahistine formulations to be even more irritating when administered multiple times a day over an extended period of time as would be necessary for treating chronic conditions. That is, in my opinion, a person of ordinary skill in the art would not consider intranasal formulations of betahistine to be tolerable and would expect such poor tolerability to have a significant and adverse impact on patient adherence/compliance. Therefore, in my opinion, a person of ordinary skill in the art would not have been motivated to prepare intranasal betahistine formulations. This, I believe, is also reflected from the fact that no intranasal betahistine product has been approved.

19. Furthermore, even if one of ordinary skill in the art would have considered formulating betahistine for intranasal administration for the sake of argument, the artisan would not have

been motivated to formulate betahistine dihydrochloride for intranasal administration as the artisan would expect betahistine dihydrochloride to be extremely erosive to the nasal mucosa in view of Passarotti's showing that betahistine dihydrochloride induces severe gastric erosions. The artisan would expect that the dihydrochloride salt of betahistine would further exacerbate the lack of tolerability of betahistine itself. Additionally, the artisan would have expected betahistine fumarate to show better solubility at the pH range desired for intranasal formulations than betahistine dihydrochloride. Accordingly, a person of ordinary skill in the art would not have been motivated to use betahistine dihydrochloride for intranasal delivery.

20. The Examiner had cited Anderson *et al.* (US 8,642,631, hereinafter "Anderson") in the last Office Action for disclosing betahistine dihydrochloride in the form of nose drops or nasal spray for treating Eustachian Tube (ET) dysfunction. As noted in my first declaration, in my opinion, Anderson provides a broad and generic disclosure on a variety of possible topical compositions of betahistine that may be applied to the nasopharynx or an opening of the ET for treating ET dysfunction; however, Anderson does not disclose any specific betahistine formulations other than the exemplified Vasomotal® formulation. Vasomotal® is a commercially available 8 mg/mL ethanol solution of betahistine dihydrochloride, from Solvay Pharma S.A. (col. 8, ll. 52-54), and is formulated **for oral delivery**. In Anderson, Vasomotal® was injected into the bulla of the rats (i.e. injected into the middle ear of the rats through the tympanic membrane) and then flushed through the ET, or applied to the nasopharynx or was injected peritoneally (col. 8, ll. 52-57). Thus, Anderson does not disclose intra-nasal administration of Vasomotal®, and accordingly cannot have evaluated the intra-nasal tolerability of Vasomotal®. As one of ordinary skill in the art, I believe that Anderson does not add anything more than Passarotti to the knowledge of an ordinarily skilled artisan, as Anderson does not exemplify intranasal administration. Therefore, in my opinion, at the time of invention, one of ordinary skill in the art would have considered Shelton's teachings as most relevant for the effects of intranasal betahistine formulations. Furthermore, as noted above, even if one of ordinary skill in the art would have considered formulating intranasal betahistine compositions for the sake of argument, the artisan would not have been motivated to formulate the

dihydrochloride salt of betahistine for intranasal administration as the artisan would expect betahistine dihydrochloride to be extremely erosive to the nasal mucosa in view of Passarotti.

21. The fact that histamine agonists are not generally formulated for intranasal administration is also evident from Haslwanter. Haslwanter is directed to nasal spray compositions and discloses a number of categories of therapeutic agents that could be included in the nasal sprays (col. 2, lines 36-49). The categories disclosed in Haslwanter include antihistamines (col. 2, line 44); however, they do not include histamine agonists as histamine agonists are generally not formulated for intranasal administration.

22. Taken together, in my opinion, one of ordinary skill in the art would not have considered formulating a histamine agonist such as betahistine for intranasal administration in view of the undesirable side effect profile shown in Shelton. Second, even if one of ordinary skill in the art would have decided to formulate betahistine for intranasal administration, the artisan would have opted for organic acid salts such as fumarate disclosed in Passarotti as the artisan would have considered these salts to have substantially more tolerability and solubility than the dihydrochloride salt of betahistine. Thus, I believe that prior to the present invention, one of ordinary skill in the art would not have been motivated to formulate compositions comprising betahistine dihydrochloride for intranasal administration. It is my understanding that the present invention is the first to show that a composition comprising betahistine dihydrochloride formulated for intranasal administration can be tolerated over the extended period of time.

23. I further declare that all statements made herein of my own knowledge are true, and that all statements made on information and belief are believed to be true, and further, that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

By:



Dated:

07th January 2017

EXHIBIT 1

CURRICULUM VITAE

NAME: David Philip Elder

ADDRESS: 110 Fordwich Rise
Hertford, SG14 2DE

TELEPHONE: 01992 302541 (Home)
07568490352 (Mobile)

DATE OF BIRTH: 10th June 1954

PLACE OF BIRTH: Newcastle upon Tyne

MARITAL STATUS: Married

UNIVERSITY QUALIFICATIONS

1992 PhD, University of Edinburgh - *Part Time*
"Physicochemical and Crystallographic Investigations into the Salt Formation of Two Heterocyclic Drugs".

1982 MSc, University of Northumbria - *Part Time*
Analytical Chemistry: *"Investigation into the Polymorphism of Various Drugs of Pharmaceutical Interest"*.

1977 BSc, University of Northumbria - *Full Time Sandwich Course*
Applied Chemistry: 2.1.

PROFESSIONAL MEMBERSHIP/AWARDS

2017 – Present Senior Visiting Research Fellow Department of Pharmacy, Pharmacology and Postgraduate Medicine, University of Hertfordshire

2016 Elected as 2016 Top Reviewer for *JPharmSci*

2015 - 2017 Chair of Joint Pharmaceutical Analysis Group (JPAG)

2014 - Present Member of IQ Consortium

2014 - 2020 Editorial Advisory Board Journal of Pharmaceutical Science (re-elected in 2017)

2014 – Present Visiting Professor, King's College, University of London (re-elected 2016)

2013 -2016 Pharmaceutical scientist member of Royal Pharmaceutical Society (SRPharmS)

2011 - Present Editorial Advisory Board European Pharmaceutical Review

2011 - 2017 Council member of Analytical Division, RSC (re-elected 2014)

2011 - Present *Ex officio* trustee of Analytical Chemistry Trust Fund (re-elected 2014)

2009 Certificate of Appreciation for outstanding work on the Genotoxic Impurities Work Group from Product Quality Research Institute (PQRI). April 08th 2009

2009 - Present Committee Member of Joint Pharmaceutical Analysis Group (JPAG). Re-elected in 2008, 2011 and 2014.

2008 - Present Member of Chartered Quality Institute (MCQI) and Chartered Quality Professional (CQP)

2008 Member of PhRMA sub-group on Genotoxic Impurities

2007 Member of EfPIA sub-group on Genotoxic Impurities

2007 Certificate from Journal of Chromatography A for "Top 20 Most Cited Review Articles, 2002-2007". For Overview of the status and applications of capillary electrophoresis to the analysis of small molecules, Journal of Chromatography A, Volume 1023, Issue 1 (2004), Pages 1-14

2006 Member of PASG sub-group on Genotoxic Impurities

2006 Diplome D'Honneur L'Academie Des Alpilles, Sep 2006

2006 - Present Member of Expert Advisory Group PCY: Pharmacy (Formerly Committee P: Pharmacy), July 2006, re-elected in 2009, 2012 and 2015.

2006 - 2008 Member of American Chemical Society

2005 - Present Member of Joint pharmaceutical Analysis Group (JPAG).

2004 - Present Chartered Scientist (C. Sci), Science Council

2003 - 2006 Member Pharmacy Committee (Committee P) of British Pharmacopoeia

2002 - 2010 RSC Industry Representative (23 September 2002)

2002 - Present Fellow Royal Society of Chemistry

2001 - 2007	Member Quality Group of the Association of British Pharmaceutical Industries (ABPI)
2001 - 2007	Member GSK Analytical Sciences Board
1987 - Present	Qualified Person (Category 4.2). 2005, 2006, 2007, 2008, 2009, 2010, 2011, 2012, 2013, 2014 (CPD)
1987 - 2008	Member Institute of Quality Assurance (MIQA).
1984 - Present	Chartered Chemist (C. Chem), Member Royal Society of Chemistry (MRSC).
1979	Graduate Royal Institute of Chemistry (GRIC).

WORK EXPERIENCE

2016-	Consultant
2014-2016	Due Diligence Director, Product Development, GSK Ware
2009-2014	Due Diligence Director, SCINOVO Group, GSK Ware/Stevenage
2007 -2009	Director Global Due Diligence, Pharmaceutical Development, GSK Ware
2003 - 2007	Director, UK Product Development, Pharmaceutical Development, GSK, Ware
2001 - 2003	Director, UK PLE, Pharmaceutical Development, GSK, Ware
1993 - 2000	Team Leader, Pharmaceutical Development, SB, Harlow
1993	Analytical Manager, Analytical Development, SB, Welwyn Garden City
1990 - 1993	QC Manager, Syntex, Edinburgh
1986 - 1990	Stability Supervisor, Syntex, Edinburgh
1983 - 1986	Pre-formulation Supervisor, Syntex, Edinburgh
1979 - 1983	Scientist II, QC/Pre-formulation, Sterling Winthrop, Alnwick
1977 - 1979	Scientist I, Radiochemist, Sterling Winthrop, Newcastle upon Tyne.

CURRENT ROLE: My current role is CMC consultant.

WORKSHOP/SESSION CHAIRS

1. Chaired JPAG session on the Role of MS in Impurity Monitoring and Control, BMSS Annual Conference, 12 September 2018, Churchill College, Cambridge.
2. Chaired JPAG session Harmonisation and application of BCS-based Guidance, 28 June 2018, RSC, London, UK.
3. Chaired BOS Conference, 19 June 2018, Conference Center, Basel, Switzerland.
4. Chaired Biopharma and Biotherapeutics Conference, 23-24 May, 2018, Montreal, Canada.
5. Chaired JPAG session (Challenges and triumphs: the analysis of biomolecules) at APS UKPharmSci meeting, 05 September 2017, University of Hertfordshire, UK.
6. Chaired JPAG meeting on The role of MS in impurity profiling, 11 May 2017, RSC, London, UK.
7. Chaired JPAG meeting on Data Integrity, 16th March 2017, RSC, London, UK.
8. Chaired JPAG meeting on Dissolution Testing: Current and future considerations, 09th February 2017, RSC, London, UK.
9. Chaired JPAG symposium on Counterfeit Medicines: Inevitable or Soluble? at 7th APS International PharmSci Conference, 05 September 2016, Technology Innovation Centre, University of Strathclyde, Glasgow
10. Chaired JPAG meeting on The use of in silico modelling in drug development, 17th March 2016, RSC, London, UK.
11. Chaired JPAG meeting on Solving Problems with Spectral Imaging, 04th February 2016, RSC, London, UK.
12. Chaired JPAG meeting Maximising Productivity in the Pharma QC and Stability Testing Laboratory, 10th December 2015, RSC, London, UK.
13. Chaired ChromSoc Meeting on Difficult to Analyse Molecules, 10-11th November 2015, GSK Ware, Hertfordshire, UK.
14. Chaired JPAG meeting What's New in the Approval and Conduct of Clinical Trials in Europe, 08th October 2015, RSC, London, UK.
15. Chaired JPAG session at UK APS Annual Meeting, 07th September 2015, Nottingham University, UK.
16. Chaired JPAG meeting Current Challenges in GMP, 25th June 2015, RSC, London, UK.
17. Jointly chaired APS meeting From Patient to Product, 19th May 2015, GSK Ware, UK.
18. Jointly chaired JPAG meeting on Risk Assessment, 05th February, 2015, GSK Ware, UK.
19. Jointly chaired APS/JPAG session on New Medicines 1: Future Benefits and Current Analytical Challenges, APS Annual Meeting, 08th September 2014, University of Hertfordshire, Hatfield, UK.
20. Jointly chaired Analytical Research Forum afternoon session, 07th July 2014, RSC, London, UK.
21. Chaired, Developments in analysis of orally inhaled and nasal drug products, In association with the European Pharmaceutical Aerosol Group (EPAG) and Joint Pharmaceutical Analysis Group (JPAG), 06th February 2014, RSC, London, UK.
22. Chaired, Prediction 1 session, APS Annual Conference, 12th September 2012, East Midlands Conference Centre, University of Nottingham, UK.

23. Chaired, In silico predictive tools: Beyond the solubility challenge, 8th Annual Improving Solubility Conference, 27th-28th June 2012, Munich, Germany.
24. Chaired Day 1, Advanced Physical Stability Testing of Commercial Pharma Products, 11th June 2012, Hotel NH Berlin, Friedrichstrasse, Germany.
25. Chaired Day 1 Challenges in Formulation Development in First in Human Strategies, Exploratory Clinical Development World Europe, 23rd-24th May 2012, Business Design Centre, London, UK.
26. Chaired Pre-Conference Session, 8th Annual Bioavailability/Bioequivalence and Biowaivers/Dissolution, 22nd -24th May 2012, Hotel Zara Budapest, Hungary.
27. Chaired Day 2, SMI Controlled Release 2012, 28th-29th March, Copthorne Tara, London, UK.
28. Chaired Day 2, Oligonucleotides: The Next Big Challenge for Analytical Sciences, The Chromatography Society, GSK Ware, 28th October, 2010, Ware, Hertfordshire, UK.
29. Chaired Day 1 of Improving Solubility for Pharmaceuticals and Biologics, CCT Venues, 22nd June 2010, Canary Wharf, London, UK.
30. Chaired Control Strategies to Detect, Control and Report Genotoxic Impurities, The Bentley Waldorf Hotel, 25th February 2010, London, UK.
31. Chaired Day 1, IQPC Solubility and Bioavailability, Dorrint Pallas, 22nd February, 2010, Wiesbaden, Germany.
32. Chaired Day 1 and 2 of Informa Solubility Enhancement and Crystallization symposium, 01st -02nd December 2009, Rubens Hotel, London, UK.
33. Chaired Day 1 of Informa Genotoxic Impurities conference, Hotel Danubius, 16th-June 2009, London, UK.
34. Chaired Day 1 of Informa Amorphous materials conference, Hotel Bloom, 19th-20th May 2009, Brussels, Belgium.
35. Chaired Day 2 of Informa Genotoxic Impurities Conference, Hotel Bloom, 17th-18th June 2008, Brussels, Belgium.
36. BPC 2007: The Medicines Maze. Balancing Risks and Benefits. Chaired Genotoxic Impurities Session, 12th September 2007, Manchester, UK.
37. Chaired IntraNasal Drug Development Session at Drug Delivery to the Lung (DDL-17), 01st December, 2006, Edinburgh, UK.

WEBINARS/PODCASTS

1. Safety based limits for non-mutagenic impurities for early phase clinical studies, www.europeanpharmaceuticalreview.com.
2. From Candidate to Clinic: Strategies to Select, Assess, Formulate, and Deliver the Right Drug Candidate in the Early Phase, Discovery Quality by Design, Dr David Elder, in association with Catelant and Pharmaceutical Technology, 10 October, 2017.
3. Examining How Quality by Design (QbD) can Aid Formulation and Controlled Release Delivery, Dr Dave Elder, in association with MA Business, 14th February, 2017.
4. Role of Biopharmaceutics in Early Development, Dr Dave Elder, in association with Catelant, 25th January 2017.

5. Microbial Risk Assessment for Non-Sterile Oral Dosage Forms, Dr Dave Elder, in association with Audio Educator, 24th January, 2017.
6. Oxford Global Webinar, Microbial Risk Assessment for Non-Sterile Oral Dosage Forms, Dr Dave Elder, 7th Annual Global Drug Delivery & Formulation Summit, 23-25 May 2016, Maritim ProArte Hotel, Berlin Germany
7. Oxford Global Webinar, Advances in small molecule drugs formulation research, Dr David Elder, 15th February 2016.
8. IQPC interview: Part 1: Benefits of employing early formulation testing, Dr David Elder, 15th February 2011.
9. IQPC interview: Part 2: Most critical unmet drug delivery needs, Dr David Elder, 15th February 2011.
10. IQPC interview: Part 3: New and emerging technologies, Dr David Elder, 15th February 2011.
11. IQPC interview: Part 4: Next breakthrough in your field, Dr David Elder, 15th February 2011.
12. IQPC interview: Part 5: Formulation screening and testing developments in the next 5-years, Dr David Elder, 15th February 2011.
13. Drug Discovery and the Market Today: Video Exclusive, IQPC, Dr David Elder, 06th November 2010,
14. Drug Discovery and the Market Today: IQPC (improving-solubility.co.uk), Part 1: An overview of Externalization in the Pharma Industry, Dr David Elder, 09th June 2010.
15. Drug Discovery and the Market Today: IQPC (improving-solubility.co.uk), Part 2: Critical Thoughts on Stability, Dr David Elder, 09th June 2010.
16. Drug Discovery and the Market Today: IQPC (improving-solubility.co.uk), Part 3: The Focus on Solubility, Dr David Elder, 09th June 2010.
17. Drug Discovery and the Market Today: IQPC (improving-solubility.co.uk), Part 4: Developing Amorphous Forms, Dr David Elder, 09th June 2010.
18. Drug Discovery and the Market Today: IQPC (improving-solubility.co.uk), Part 5: Considering Genotoxic and Carcinogenic Impurities, Dr David Elder, 09th June 2010.

PRESENTATIONS

1. Historical perspectives on the development of guidelines relating to mutagenic impurities and their reliance/relevance to ICH M7, Dr David Elder, PTI Course on Mutagenic Impurities, 01-02 October 2018, Grafton Hotel, London.
2. What does ICH M7 mean? Should I be worried? Reflection on potential impact of current guideline. Dr David Elder, PTI Course on Mutagenic Impurities, 01-02 October 2018, Grafton Hotel, London.
3. How to conduct a mutagenic impurity risk assessment. Dr David Elder, PTI Course on Mutagenic Impurities, 01-02 October 2018, Grafton Hotel, London.
4. Structural analysis of impurities and data interpretation. Dr David Elder, PTI Course on Mutagenic Impurities, 01-02 October 2018, Grafton Hotel, London.

5. Establishment of acceptable daily intakes for mutagenic carcinogens. Dr David Elder, PTI Course on Mutagenic Impurities, 01-02 October 2018, Grafton Hotel, London.
6. Safety testing – pre-clinical assessment of MI related risk. Dr David Elder, PTI Course on Mutagenic Impurities, 01-02 October 2018, Grafton Hotel, London.
7. Analysis of mutagenic impurities. Dr David Elder, PTI Course on Mutagenic Impurities, 01-02 October 2018, Grafton Hotel, London.
8. Sulfonate esters – How real is the risk? Dr David Elder, PTI Course on Mutagenic Impurities, 01-02 October 2018, Grafton Hotel, London.
9. Valsartan case study. Dr David Elder, PTI Course on Mutagenic Impurities, 01-02 October 2018, Grafton Hotel, London.
10. Purge calculations – The next step: Mirabilis. Dr David Elder, PTI Course on Mutagenic Impurities, 01-02 October 2018, Grafton Hotel, London.
11. Why Increasing Sensitivity isn't always the Answer Alignment with Safety Based Limits & Analytical Target Product Profile Considerations, Dr David Elder, BMSS Annual Conference, 12 September, 2018, Churchill College, Cambridge, UK.
12. Antibiotic Resistance: The Need for a Global Strategy, Dr David Elder, Health Economics, 15 September, 2018, Zurich, Switzerland
13. ICH M9: Permeability Issues, Dr David Elder, Harmonisation and application of BCS-based Guidance, 28 June 2018, RSC, London, UK.
14. Setting specifications in the early Development Phases (Phase I/II), Dr David Elder, BOS Conference, 20 June 2018, Conference Center, Basel, Switzerland.
15. Addressing the Challenges in Biopharmaceuticals and Biological products: Stability, Storage and Cold Chain Supply of Biologics, Dr David Elder, Biopharma and Biotherapeutics Conference, 24 May, 2018, Montreal, Canada.
16. Setting Impurity Specifications for Biologicals, Dr David Elder, Biopharma and Biotherapeutics Conference, 24 May, 2018, Montreal, Canada.
17. ICH M9 Biopharmaceuticals Classification System-Based Biowaivers: Challenges and Opportunities, Dr David Elder, Biopharma and Biotherapeutics Conference, 23 May, 2018, Montreal, Canada.
18. The Impact of Variability of GI Parameters on Design of Functional Film Coats, Dr David Elder, 22nd March 2018, SMI 15th Annual Controlled Release Symposium, Holiday Inn, Regents Park, London
19. HPLC Method Validation, Dr David Elder, 21 March 2018, BSC Lecture, University of Hertfordshire, Hatfield
20. Mutagenic Impurities (ICH M7), Dr David Elder, 14 March 2018, BSC Lecture, University of Hertfordshire, Hatfield
21. Modified Release: An Industrial perspective, Dr David Elder, 19th February 2018, MSc Lecture, King's College London.
22. Hard Capsules: Everything you wanted to know but were afraid to ask! Dr David Elder, 19th February 2018, MSc Lecture, King's College London.
23. Softgels and Liquid Filled Hard Shell Capsules (LFHC): Everything you wanted to know but were afraid to ask! Dr David Elder, 19th February 2018, MSc Lecture, King's College London

24. Transferable learnings from a decade of mutagenic impurity analysis, Dr David Elder, Trends in Chemical Production, 03-05 October 2017, Hotel Dubrovnik, Zagreb, Croatia.
25. Physicochemical and Functional Comparability between Innovator and Biosimilar, Dr David Elder, UKPharmSci Annual Meeting, The Challenges and Triumphs: The Analysis of Biomolecules, 05 September 2017, University of Hertfordshire, Hatfield campus, UK.
26. ICH M7 in Discovery/Early Development, Dr David Elder, Biotech Outsourcing Strategies Meeting, 28 June 2017, Conference Centre, Basel, Switzerland
27. Antibiotic Resistance: The Need for a Global Strategy, Dr David Elder, Progressive PharmSciences: Technology, Research and Development, 19 June 2017, Barcelo Valencia, Spain.
28. Excipients and their Effects on the Quality of Small Molecules, Dr David Elder, 8th Global DDF Summit, 28 March 2017, ProArte Hotel, Berlin
29. Analytical Testing, Specification Setting and Stability, Dr David Elder, APS Developability Workshop, 23 March 2017, Granta Science Park, Cambridge
30. Case Study 3: Oxidative Stability, Dr David Elder, APS Developability Workshop, 23 March 2017, Granta Science Park, Cambridge
31. Case Study 4: Food Effects, Dr David Elder, APS Developability Workshop, 23 March 2017, Granta Science Park, Cambridge
32. Development of Oligonucleotide Drugs, Dr David Elder, 22 March 2017, BSC Lecture, University of Hertfordshire, Hatfield
33. Development of Biological Drugs, Dr David Elder, 15 March 2017, BSC Lecture, University of Hertfordshire, Hatfield
34. Mutagenic Impurities (ICH M7), Dr David Elder, 08 March 2017, BSC Lecture, University of Hertfordshire, Hatfield
35. Modified Release: An Industrial perspective, Dr David Elder, 20th February 2017, MSc Lecture, King's College London
36. Hard Capsules: Everything you wanted to know but were afraid to ask! Dr David Elder, 20th February 2017, MSc Lecture, King's College London
37. Softgels and Liquid Filled Hard Shell Capsules (LFHC): Everything you wanted to know but were afraid to ask! Dr David Elder, 20th February 2017, MSc Lecture, King's College London
38. Dissolution: An Industry Perspective, Dr David Elder, Dissolution Testing: Current and future considerations, JPAG Meeting, 09th February 2017, RSC, London, UK.
39. Microbial Risk Assessment for Non-Sterile Oral Dosage Forms, Dr David Elder, 18th February 2017, SMI, Holiday Inn, Kensington, London,
40. Microbiological quality of non-sterile dosage forms (USP 1111 and 1115), Dr David Elder, 10th December 2016, Regulatory Hot Topics II, JPAG Meeting, RSC, London, UK.
41. How does a global pharma company manage non-harmonised excipient regulations? Dr David Elder, APV/IPEC Europe Excipient Conference, 20th September 2016, Prague, Czech Republic.
42. Building a Robust Analytical Data Set to Guide Early Drug Development and Attract Licensing Partners, Dr Dave Elder, Biotech Outsourcing Strategies, 27-28th June 2016, 2016, Conference Centre, Basel, Switzerland.

43. The importance of physical properties in decreasing drug attrition, Dr Dave Elder, 17th Annual Drug Discovery Summit Oxford Global, 13-14th June, 2016, Hotel Palace Berlin, Germany.
44. An overview of process analytical control (PAT), PharmaTalk, 13-14th June, 2016, Hotel Seminaris Berlin, Germany.
45. Exploring and practically implementing stability studies for drugs in suspension, Dr Dave Elder, 2nd Annual Formulation and Drug Delivery Congress Oxford Global, 18-19th May 2016, Kensington Court Hotel, London, UK.
46. Modified Release: An Industrial perspective, Dr David Elder, 01st March 2016, MSc Lecture, King's College London
47. Hard Capsules: Everything you wanted to know but were afraid to ask! Dr David Elder, 01st March 2016, MSc Lecture, King's College London
48. Softgels and Liquid Filled Hard Shell Capsules (LFHC): Everything you wanted to know but were afraid to ask! Dr David Elder, 01st March 2016, MSc Lecture, King's College London
49. Strategic Approaches to Analysing Mutagenic Impurities, Dr Dave Elder, ChromSoc Meeting on Difficult to Analyse Molecules, 10-11th November 2015, GSK Ware, Hertfordshire, UK
50. Co-Crystals (on behalf of IQ co-crystal group), Dr Dave Elder, UK APS Annual Meeting, 08th September 2015, Nottingham University, UK
51. ICH M7 Guideline, Dr Dave Elder, UK APS Annual Meeting, 07th September 2015, Nottingham University, UK
52. Quality of oral modified release products, Dr Dave Elder, UK APS Annual Meeting, 07th September, Nottingham University, UK
53. 10 Year Survey of GTI Impurities in the Scientific Literature, Dr Dave Elder, Informa 8th Annual Genotoxic Impurities Conference, 11th June 2015, Millennium, Gloucester Hotel, London
54. Evaluation of GMP: A personal reflection on progress since its inception, Dr Dave Elder, 25th June 2015, Current challenges in GMP, Joint Pharmaceutical Analysis, London
55. The Development of an Age Related Medicine (Oral Suspension). Challenges of Taste Masking, Bioequivalence and Stability, Dr Dave Elder, 18th May 2015, Formulation and Drug Delivery Congress, Oxford Global, London
56. The Development of an Age Related Medicine (Oral Suspension). Challenges of Taste Masking, Bioequivalence and Stability, Dr Dave Elder, 19th May, APS, From Patient to Product, GSK Ware, UK.
57. Pre-Competitive / Competitive Collaborations in the Pharmaceutical Industry, Dr Dave Elder, GSK, 10th-11th February 2015, Open Innovation Conference, Hotel Radisson, Heathrow Hotel, London. UK.
58. Update on ICH M7 and Case Study: Sharing Practical Experiences of Implementing M7 and a Second In-Silico Tool for GTI Assessment, Dr Mat Popkin and Dr Dave Elder, 05-07th November, 17th Annual APIC/CEFIC Conference on APIs, Park Royal Palace, Vienna, Austria.
59. Technologies to Address Poorly Soluble and Poorly Permeable Compounds, Dr Dave Elder, GSK, 17th-18th Sep 2014, Drug Delivery Partnerships, Radisson Blu Hotel, Hamburg, Germany

60. Pharmaceutical Design of Medicines for the Elderly, Dr Dave Elder, GSK, Use of Medicines in Older People: The Role of Pharmaceutical Sciences in the Forgotten Majority, 08th-10th Sep 2014, Univ. of Hertfordshire, Hatfield, UK.
61. Case Study: Sharing Practical Experiences of Implementing a Second In Silico Tool for GTI Assessment, Dr Dave Elder, 25th June 2014, Radisson Blu Hotel Berlin. 7th Annual Genotoxic Impurities Conference
62. Practical Issues with the Implementation of the Emerging ICH M7 Guidance: Use of Two In Silico Systems as part of Risk Assessment Process, Dr Dave Elder, 02nd June 2014, Hotel Intercontinental, Geneva. 15th Annual Drug Discovery Summit
63. Case study: Sharing practical experience of developing and validating dissolution testing methods for QC applications, Dr Dave Elder, 10th Annual Bioavailability / Bioequivalence, Dissolution Testing and Biowaivers, 14th-15th May 2014, Budapest, Hungary
64. The Importance of Physical Properties in Decreasing Drug Attrition, Dr Dave Elder, 7th annual global discovery & development innovation forum, 13th May 2014, Intercontinental Hotel, London
65. Setting Specifications for Controlled Release Products: A Statistically Based Approach, Dr Dave Elder, 11th Annual SMi Controlled Release Meeting, 12th-13th March 2014, Holiday Inn, Regents Park London
66. Development of a Novel IntraNasal Spray Product: A Case Study, Dr Dave Elder, JPAG Symposium, 06th February 2014, RSC, London
67. Development of metals guidelines, Dr Dave Elder, JPAG Symposium, 10th October 2013, RSC, London
68. Excipient Compatibility Workshop, Dr Dave Elder, 3rd Annual Formulation Strategies for Pharmaceuticals, Informa, 18th September 2013, Radisson Blu Hotel, Berlin, Germany
69. Outsourcing and the increased challenges of technology transfer, Dr Dave Elder, King's College University, 04th September 2013, London
70. Current status on Sulfonate esters (potential bi-products of sulfonate salt formation), Dr Dave Elder, PPD Knowledge Cafe, GSK global presentation, 17th July, 2013, Ware, UK
71. Evaluating the Changes and Practical Implications of ICH M7 (step 2) from a CMC Perspective, Dr Dave Elder, 6th Annual Genotoxic Impurities Conference, 19-20th June 2013, Berlin, Germany.
72. Bio-Enhancement Strategies for Poorly Soluble Drugs, Dr Dave Elder, Merck Millipore Pharma Forum 2013, 18th June 2013, Darmstadt, Germany.
73. The Importance of Physical Properties in Decreasing Drug Attrition, Dr Dave Elder, 14th Annual Drug Discovery Summit, 10-11th June 2013, Geneva, Switzerland.
74. Genotoxic Impurities: A review of recent international developments, Dr Dave Elder and Dr Andy Teasdale, Progress and Challenges in Harmonisation (A Joint symposium between JPAG and TOPRA), 21st March 2013, Royal Society of Chemistry, London, UK.
75. The impact of changing the site of manufacture for controlled release products, Dr Dave Elder, SMi Controlled Release Symposium, 18th March 2013, Copthorne Tara, London, UK.

76. QbD and the Impact of Externalisation on Lifecycle Management of Analytical Methods, Dr Dave Elder, 4th Evening Discussion Group, 25th October 2012, Islington, London, UK
77. Derivation of Toxicity Based Limits for Mutagenic/Genotoxic Impurities and Development of Sensitive Analytical Methods for these Impurities in APIs, Dr David Elder, 03rd October, 2012, King's College, London, UK.
78. Novel statistical approaches to the development of specifications for MR products, Dr David Elder, APS Annual Conference, 12th September 2012, East Midlands Conference Centre, University of Nottingham, UK.
79. Setting Specifications for Controlled Release Products: A Statistically Based Approach, Dr David Elder, Informa 2nd Innovations in Modified Release Meeting, 11-12th September 2012, Holiday Inn, Munich, Germany
80. Real Life Industry Case Study: Changing the Site of Manufacture for Modified Release Products, Dr David Elder, Informa 2nd innovations in Modified Release Meeting, 11-12th September 2012, Holiday Inn, Munich, Germany
81. Model Guided Formulation Development: Effective Predictive Modelling through *In Silico* Solubility Assessment, Dr David Elder, 8th Annual Improving Solubility Conference, 27th-28th June 2012, Munich, Germany.
82. Successful Strategies for Developing New Analytical Methods in Genotoxic Impurity Testing, Dr David Elder, 5th Annual Genotoxic Impurities Conference, 20-21 June 2012, Radisson Blu, Berlin, Germany.
83. Stability of the Drug in the Amorphous State, Dr David Elder, Advanced Physical Stability Testing of Commercial Pharma Products, 11th June 2012, Hotel NH Berlin, Friedrichstrasse, Germany.
84. Challenges in Formulation Development in First in Human Strategies, Dr David Elder, Exploratory Clinical Development World Europe, 23rd-24th May 2012, Business Design Centre, London, UK.
85. Methods for Improving Bioavailability, Solubility and Dissolution: Solubility/Permeability/BCS, Dr David Elder, 8th Annual Bioavailability/Bioequivalence and Biowaivers/Dissolution, 22nd -24th May 2012, Hotel Zara Budapest, Hungary.
86. Methods for Improving Bioavailability, Solubility and Dissolution: Formulation Strategies for Poorly Soluble APIs, Dr David Elder, 8th Annual Bioavailability/Bioequivalence and Biowaivers/Dissolution, 22nd -24th May 2012, Hotel Zara Budapest, Hungary.
87. Selecting the Right Counter-Ion during Salt Screening, Dr David Elder, IQPC Global Formulation and Drug Delivery Summit, 17th-18th April 2012, Amsterdam, The Netherlands.
88. Exploring best practice methods and novel approaches for overcoming the challenges of poor solubility and stability, Panel Discussion chaired by Dr Dave Elder (GSK, UK) and Prof. M.N.V. Ravi Kumar (Univ. Of Strathclyde, UK), IQPC Global Formulation and Drug Delivery Summit, 17th-18th April 2012, Amsterdam, The Netherlands.
89. Development of a Novel Intra-Nasal Steroid Product for Treatment of Seasonal Rhinitis, Dr David Elder, SMI Controlled Release 2012, 28th-29th March 2012, Copthorne Tara, London, UK.

90. Monitoring the Impact of Degradation Products on Stability, Dave Elder, Informa Stability Testing for Pharmaceuticals, 21-22nd March 2012, Radisson Blu Hotel, Berlin, Germany.
91. Characterisation and Quantifying Genotoxic Impurities and Implications in Stability Studies Dave Elder, Stability Testing for Pharmaceuticals, 21st-22nd March 2012, Radisson Blu Hotel, Berlin, Germany.
92. Genotoxic Degradation: Genotoxic Risk Assessments, Dr David Elder, Informa 6th Annual Forced Degradation for Pharmaceuticals, 18th-19th January 2012, Dexter House, London, UK.
93. *In Silico* Strategies for Assessing Solubility and Permeability, Dr David Elder, JPAG Predictive Tools in the Development of Solid Oral Dosage Forms, Thursday 08th December 2011, Royal Astronomical Society, London, UK.

94. Eliminating Problems before they Exist: Using Screening to Impact on Formulation Development: A Holistic Perspective, Dr David Elder, Molecular Profiles, Recent Advances in Early Drug Development, Monday, 05th December 2011, Belfry Hotel, Nottingham, UK.
95. Development of Paediatric Medicines – The Industrial Perspective, Dr David Elder, Children's Medicine Symposium, 22nd November 2011, LJMU, Liverpool, UK.
96. Realising the Practical Development Potential of Amorphous Solid Dispersions as Successful Drug Candidates, Dr David Elder, 5th Annual Amorphous Pharmaceutical Materials 2011, 28th September 2011, Crowne Plaza Hotel, Amsterdam, The Netherlands.
97. Setting Specifications for Genotoxic Impurities (GTIs) and Potentially Genotoxic Impurities (PGIs) in APIs, Dr David Elder, Informa Setting Specifications, Radisson Blu Hotel, 14th-15th September 2011, Amsterdam, The Netherlands.
98. Stress Testing and Degradation-Derived Genotoxic Impurities: Scientific, Practical and Regulatory Considerations, Dr Steve Baertschi (Lilly), Dr Dave Elder (GSK), Dr Mark Kleinman (GSK), Dr Alan McKeown (Pfizer), Dr Mark Mowery (Merck), Dr Daniel Norwood (BI), Dr Andrew Teasedale (AZ), Dr Linda Dow (Lilly), Dr Brian Pack (Lilly), Conference on Small Molecule Science, 02nd August 2011, UNC-Chapel Hill, North Carolina, US.
99. Outsourcing. Experiences of the Contract Giver: Due Diligence, Experiences (Good and Bad), Best Practices, Joint Pharmaceutical Analysis Group, 07th July 2011, Royal Astronomical Society, Piccadilly, London, UK.
100. In Silico Strategies for Assessing Solubility, Dr David Elder, PharmIQ, Improving Solubility Conference, America Square Conference Centre, 29th June 2011, London, UK.
101. Reviewing the theory and practical applications of chemical purging and spiking/purging, Dr Dave Elder, Informa Genotoxic Impurities Meeting, 28th June 2011, Berlin, Germany.
102. Eliminating Problems Before They Exist: Using Screening to Impact Formulation Development, Dr David Elder, IQPC Global Pre-Formulation and Formulation Summit, 12th April 2011, Mercure Hotel, Amsterdam, The Netherlands.
103. Generic Methods for Determining Genotoxic Impurities, Dr David Elder, Characterisation of Active Product Ingredients, Joint Pharmaceutical Analysis Group, 02nd December 2010, Royal Pharmaceutical Society, Lambeth, London, UK.
104. Setting Specifications for Controlled Release Products: A Statistically Based Approach, Dr David Elder, Informa Setting Specifications, 24th November, NH Amsterdam Centre Hotel, The Netherlands.

105. Stability Challenges of Amorphous Compounds, Dr David Elder, Visiongain 4th Annual Stability Testing, 22nd November, Shropshire House, London, UK.
106. Eliminating Problems Before They Exist: Using Screening to Impact Formulation Development, Dr David Elder, Pharmaceutical Stability Testing 2010, 14 - 16 September, 2010, CCT Venues-Smithfield, London, UK.
107. Characterisation of drug resin complexes, Dr David Elder as part of Analysis of Drug Inclusion Complexes at APS: The Science of Medicines, Nottingham, 01st September, 2010.
108. Industry Challenges in Controlling Structurally Similar Genotoxins , Dr David Elder and Dr Jim Harvey (GSK), Informa Genotoxic Impurities Conference, 29th June 2010, Renaissance Zurich Hotel, Switzerland.
109. Formulation Strategies for Poorly Soluble APIs to Ensure Efficient Development, Dr David Elder (GSK, Improving Solubility for Pharmaceuticals and Biologics, 22nd June 2010,CCT Venues, Canary Wharf, London, UK.
110. Determining the Appropriate Manufacturing Technique for your API, Dr David Elder (GSK, UK), Informa Amorphous Materials, 18th-19th May 2010, Hotel Lev, Ljubljana, Slovenia.
111. Developing Robust Methods to Detect and Resolve Genotoxic Impurities/Degradants on Stability, Drs David Elder (GSK, UK), Alireza Kord (GSK, US) and David Liu (GSK, US), Informa Stability Testing 2010, 15th March 2010, Hilton Olympia, London, UK.
112. Genotoxic Impurities/Degradants Workshop: An Overview of Industry Approaches, Dr David Elder (GSK, UK), Control Strategies to Detect, Control and Report Genotoxic Impurities, The Bentley Waldorf Hotel, London, 25th February 2010.
113. Genotoxic Impurities/Degradants Workshop: Method Development Strategies to Detect and Control Genotoxic Impurities/Degradants, Dr David Elder (GSK, UK), Informa Control Strategies to Detect, Control and Report Genotoxic Impurities, The Bentley Waldorf Hotel, London, 25th February 2010.
114. New Directions in Pharmaceutical Analysis, Dr David Elder (GSK, UK), Informa Pharmaceutical Analysis Course, The Bentley Waldorf Hotel, London, 24th February 2010.
115. Utility of Salts in Enabling Development of Poorly Soluble APIs, Dr David Elder (GSK, UK), IQPC Solubility and Bioavailability, Dorrint Pallas, Wiesbaden, Germany, 22nd February, 2010.

116. How to Formulate Poorly Soluble Drugs by Dr David Elder (GSK, UK), Informa Solubility Enhancement and Crystallization symposium, Rubens Hotel, London, 01st December 2009.
117. Developing Paediatric Medicines – The Industrial Perspective by Dr David Elder (GSK, UK), Annual Children's Medicines Symposium, LJMU, Liverpool, 10th November 2009.
118. Safety Assessment of Pharmaceuticals. Application of TTC to Genotoxic Impurities in Active Pharmaceutical Ingredients (API) by Dr David Elder (GSK, UK), 32nd European Meeting of The Toxicology Forum, Le Meridien, Brussels, Belgium, 20th October 2009.
119. Assessing Outsourcing Opportunities within the Solid State Arena by Dr David Elder (GSK, UK), Pharm IQ 3rd Annual Amorphous Pharmaceutical Materials 2009, Mövenpick Hotel Amsterdam, 21st-22nd September 2009
120. Overcoming Stability Challenges in Developing Oral Solid Dose Products by Dr David Elder, Advances in Oral Solid Dose Manufacturing Conference 1-3rd July 2009
121. Development of Paediatric Medicines – The Industrial Perspective presentation by Dr David Elder (GSK, UK), Gatefosse Foundation, St Remy de Provence, France, 20th June 2009
122. Experiences of Developing, Validation and Routine Use of a GRI Analytical Method in a Production Environment presentation by Dr David Elder (GSK, UK) at Informa Genotoxic Impurities conference, Hotel Danubius, London, 16th June 2009
123. Establishing Appropriate Strategies for Control of Genotoxic Impurities presentation by Dr David Elder (GSK, UK) (on behalf of PhRMA ATG Genotoxic Impurities Working Group) at Informa Genotoxic Impurities conference, Hotel Danubius, London, 17th June 2009
124. Introduction to Amorphous Materials presentation by Dr David Elder (GSK, UK), Hotel Bloom, Brussels, 19th-20th May 2009
125. Amorphous Dosage Forms: Opportunities and Challenges presentation by Dr David Elder (GSK, UK), Hotel Bloom, Brussels, 19th-20th May 2009
126. Externalization presentation by Dr David Elder (GSK, UK), Avantium Conference, Barcelona, 30th April 2009.
127. Informa Crystal Form Selection and Crystallisation of API, Sulphonate Salts: Pariahs or Messiahs? by Dr David Elder (GSK, UK), Hotel Marriott Brussels, 15th October 2008

128. The World Congress of Pharmacy and Pharmaceutical Sciences, 2008. 68th International Congress of FIP. Making Paediatric Medicines Work. Paediatric Medicines-The Industrial Perspective, presentation by Dr David Elder (GSK, UK), Basel, Switzerland, 01st September 2008.
129. Nanotechnology for Improving Drug Delivery across Biological Barriers, Gatefosse Industry Perspective: Bio-enhancement Strategies (nano-milling versus Lipidic Approaches, presentation by David Elder, Academie Des Alpillles, St. Remy de Provence, France, 27th June, 2008.
130. Informa Genotoxic Impurities Conference, Quality by Design Approach to Control Genotoxic Impurities: A Holistic Approach, presentation by Dr David Elder, Hotel Bloom, Brussels, 18th June 2008
131. Sulphonate Salts: Pariahs or Messiahs, presentation by Dr David Elder at PASG Genotoxins Sub-Group Meeting, AstraZeneca, Loughborough, 16th April 2008.
132. Genotoxic Degradants and Metabolites, presentation by Jon Sims and Dr David Elder at PASG Genotoxins Sub-Group Meeting, AstraZeneca, Loughborough, 16th April 2008.
133. Development of Paediatric Formulations. Just a Spoonful of Sugar? presentation by Terry Ernest and Dr David Elder at Child Health Symposium, Liverpool John Moore's University, Liverpool, 13th November 2007.
134. How Realistic is the Avoidance of Risk? The Challenges of Genotoxic Impurities,, presentation by Dr David Elder at BPC 2007: The Medicines Maze. Balancing Risks and Benefits, Manchester, 12th September 2007
135. Pre-Formulation and Formulation Development presentation by Dr Simon Mills and Dr David Elder, WHO Regulatory Training Meeting, Cape Town, South Africa, 16th-21st April, 2007.
136. Excipients, presentation by Dr Simon Mills and Dr David Elder, WHO Regulatory Training Meeting, Cape Town, South Africa, 16th-21st April, 2007.
137. Packaging Development, presentation by Dr Simon Mills and Dr David Elder, WHO Regulatory Training Meeting, Cape Town, South Africa, 16th-21st April, 2007.
138. Development of Paediatric Formulations. Just a Spoonful of Sugar? presentation by dr david Elder at Child Health Symposium, Liverpool John Moore's University, Liverpool, 14th November 2006.
139. How Safe is Safe? -The Challenge of Genotoxic Impurities and their Analysis, presentation by Dr David Elder at PASG Autumn Meeting, Milton Keynes, 02nd October 2006.

140. To Boldly Go Where No Analyst has Gone Before? New Technologies in Characterization and Control of Impurities, presentation by Dr David Elder at USP Annual Scientific Meeting, Denver, 26-29th September, 2006.
141. How Safe is Safe? The Challenges of Genotoxic Impurities. Genotoxic Impurities, presentation by Dr David Elder at USP Annual Scientific Meeting, Denver, 26-29th September, 2006
142. Impurity Specifications in the New Paradigm. Merging the Science and the Regulations. Genotoxic Impurities – Analytical Implications of Parts per Million Specifications, presentation by Dr David Elder at AAPS 2005, Gaylord Oprey Convention Centre, Nashville, Tennessee, 10th November, 2005.
143. Preservatives: An Uncertain Future? by Dr David Elder at Formula IV: Frontiers in Formulation Science, Kings College, London, 05th July 2005.
144. How Safe is Safe? Managing Genotoxic Impurities within GSK, presentation by Dr David Elder at the North Carolina Pharmaceutical Discussion Group, Raleigh, North Carolina, 15th September, 2004.
145. Bioavailability, Bioequivalence and Dissolution Testing symposium, "Application of BCS Concepts in the Development of New Drugs" by Dr David Elder at Le Meridien, London, 21st May 2002.
146. Global Specifications for Drug Substances and Dosage Forms symposium, "Setting Specifications for Oral Suspension Products", by Dr David Elder at the Simpon's in the Strand, London, 23rd January 2002.
147. Drug Dissolution Testing: Current Status and Future Challenges symposium "Setting Specifications for Extended Release Products" by Dr David Elder at Hotel Copthorne Tara, London, 18 June 2001.
148. The PASG Spring Meeting: Specifications for Quality- Discovery to Market symposium, "Specifications Setting: Immediate vs Controlled Release" by Dr David Elder at Burleigh Court, Loughborough University, 23 April 2001.
149. Ion Exchange at the Millennium International Conference symposium, "Development of a Palatable Liquid Formulation of a Bitter Tasting Drug Using Ion Exchange Resins for Taste Masking" by David Elder at Churchill College, Cambridge, 19 July 2000.
150. Annual lecture, "Aspects of QA in the Pharmaceutical Industry", by David Elder at MSc course at Kings College, London, 2000
151. Annual lecture, "Aspects of QA in the Pharmaceutical Industry", by David Elder at MSc course at Kings College, London, 1999

152. Annual lecture, "Aspects of QA in the Pharmaceutical Industry", by David Elder at MSc course at Kings College, London, 1998
153. Annual lecture, "Aspects of QA in the Pharmaceutical Industry", David Elder at MSc course at Kings College, London, 1997
154. Annual lecture, "Aspects of QA in the Pharmaceutical Industry", David Elder at MSc course at Kings College, London, 1996
155. Poster Presentation at APS Meeting in Boston, December 1997, "Investigation into New Salt Forms of Cimetidine", P Patel, G Buckton, D P Elder, D Eggleston.
156. Joint Pharmaceutical Analysis Group symposium, "Drug Excipient Compatibility", by Dr David Elder at the RPSGB, London, 19th January 1995.
157. Poster Presentation at XV Congress of International Union of Crystallography, Bordeaux, 24 July 1990, entitled: "Five Crystal Modifications of an Imidazole Substituted Piperazine", by D P Elder
158. Poster Presentation at British Crystallographic association Meeting, 6th April 1987, entitled: "Tautomerism, Conformation and Packing Studies in a Piperazine derivative" by D P Elder.

BOOK CHAPTERS - EDITING

1. Analytical Characterisation and Separation of Oligonucleotides and their Impurities, Eds: D.P. Elder, G. Okafo and M. Webb, The Chrom. Soc. Separation Science Series, ILM Publications, ISBN 978-1-906799-14-4, April 2013.
2. ICH Guidelines: Opportunities and Challenges, Eds: A. Teasdale, D P Elder, R.W. Nims, John Wiley, ISBN: 978-1-118-97111-6 .

BOOK CHAPTERS - AUTHORIZING

1. ICH Q2(R1) Validation of Analytical Procedures: Text and Methodology, D.P.Elder and P. Borman *In* ICH Guidelines: Opportunities and Challenges, Eds: A. Teasdale, D P Elder, R.W. Nims,, John Wiley, pp. 127-166.
2. Impurities in New Drug Substances and New Drug Products: ICH Q3A/B: Key Guidelines in the General Impurity Management Process. J.Harvey, A. Teasdale, D.P.Elder *In* ICH Guidelines: Opportunities and Challenges, Eds: A. Teasdale, D P Elder, R.W. Nims, John Wiley, pp. 167-198.
3. ICH Q4: Pharmacopeial Harmonization and Evaluation and Recommendation of Pharmacopeial Texts for Use in the ICH Regions. D.P.Elder *In* ICH Guidelines: Opportunities and Challenges, Eds: A. Teasdale, D P Elder, R.W. Nims, John Wiley, pp. 281-310.
4. ICH Q6A Specifications: Test Procedures and Acceptance Criteria for New Drug Substances and New Drug Products: Chemical Substances. D.P.Elder *In* ICH Guidelines: Opportunities and Challenges, Eds: A. Teasdale, D P Elder, R.W. Nims, John Wiley, pp. 433-466.

5. ICH Q9 Quality Risk Management. D.P.Elder, A.Teasdale *In* ICH Guidelines: Opportunities and Challenges, Eds: A. Teasdale, D P Elder, R.W. Nims, John Wiley, pp. 579-610.
6. Quality by Design, Chapter 12: Genotoxic Impurities/Degradants, D.P.Elder, A. Kord and Z. Cimarosti, Eds. V. Novack, R. Leak and L. Wiley, John Wiley and Sons Ltd
7. Introduction to oligonucleotides, M.Webb, D.P.Elder and G.Okafo *In* Analytical Characterisation and Separation of Oligonucleotides and their Impurities, Eds: D.P. Elder, G. Okafo and M. Webb, The Chrom. Soc. Separation Science Series, ILM Publications, ISBN 978-1-906799-14-4, February 2013.
8. Analytical characterisation of oligonucleotides using thermal melting curves, D.P.Elder, G.Okafo and M.Webb, *In* Analytical Characterisation and Separation of Oligonucleotides and their Impurities, Eds: D.P. Elder, G. Okafo and M. Webb, The Chrom. Soc. Separation Science Series, ILM Publications, ISBN 978-1-906799-14-4, February 2013.
9. Principles, Methodology and Emerging Challenges, Chapter 1, Outsourcing and Technology Transfer, David Elder, pp. 1-26, Eds: Marco Rossi and Santina Bertone, Nova publishers, ISBN 978-1-62417-790-3.
10. Drug Development: Genetic Toxicology, Chapter 7: *In Vitro* Approaches for Medicinal Chemists, R.M. Walmsley and D.P.Elder in *ADMET for Medicinal Chemists: A Practical Guide* (pp. 315-352), Editors: K.Tsaoun and S.A. Kates. ISBN 978-0-470-48407-4, Published by Wiley, London, 2010.
11. Genotoxic Impurities, Chapter 10 Analysis of Genotoxic Impurities, Review of Approaches (pp. 249-280), D.P.Elder, *In* Genotoxic Impurities: Strategies for Identification and Control, Edited by Andrew Teasedale, ISBN 978-0-470-49919-1, Published by Wiley, London,.
12. Genotoxic Impurities, Chapter 8: A Risk in Perspective (pp. 193-218), D.P.Elder and J.Harvey, *In* Genotoxic Impurities: Strategies for Identification and Control, Edited by Andrew Teasedale, ISBN 978-0-470-49919-1, Published by Wiley, London.
13. Genotoxic Impurities, Chapter 9: Strategies for Evaluating Genotoxic Impurity Risk (pp. 221-247), A.Teasedale, S. Fenner and D.P.Elder in Genotoxic Impurities: Strategies for Identification and Control, Edited by Andrew Teasedale, ISBN 978-0-470-49919-1, Published by Wiley, London.
14. Chapter 2: Organic Impurities in Drug Products: Origin, Control and Measurement (pp. 21-46), D P Elder, *In* Drug Impurities, Edited by Richard J Smith and Michael Webb, ISBN 978-14051-3358-6, Published by Blackwell Publishing Oxford, 2007.
15. Development of a Palatable Liquid Formulation of a Bitter Tasting Drug Using Ion Exchange Resins for Taste Masking (pp. 306-313), D P Elder, A Park, N Marzolini and P Patel, *In* Proceedings of IEX2000, Editor J.A. Greig, Imperial College Press, London, 2000.

SUBMITTED FOR PUBLICATION

PUBLICATIONS

1. Foreward: Understanding the importance of Analytical Target Profile: The key questions to ask. D P Elder, Eur. Pharm. Rev., 23(4), 2018, 9.
2. Specifications and method/process capability: Two sides of the same coin. Eur. Pharm. Rev., 23(4), 2018, 42-44.
3. Foreward: Safety based limits for non-mutagenic impurities for early phase clinical studies, D P Elder, Eur. Pharm. Rev., 23(3), 2018, 7.
4. Continuous Manufacturing Symposium: the topics under discussion at the JPAG meeting, C. Reddington, R. Ogilvie, P. Moree, C. Clarke, M. Casadevall-Callis, R. Hart, D. Littlejohn, P. Wahl, D P Elder, Eur. Pharm. Rev., 23(3), 2018, 7.
5. Foreward: Data Integrity, D P Elder, Eur. Pharm. Rev., 23(2), 2018, 7.
6. Foreward: ICH M10: Guideline on bioanalytical method validation. D P Elder, Eur. Pharm. Rev., 23(1), 2018, 7.
7. Stability testing, D P Elder, Eur. Pharm. Rev., 23(1), 2018, 52-54.
8. Antimicrobial preservatives Part Three: Challenges facing preservative systems. D P Elder, P J Crowley, Amer. Pharm. Rev. 20(7), 2017, 26-33.
9. Biopharmaceuticals/Biosimilars Roundtable. R. Savla, D P Elder, D Peckman, M. Merges. Amer. Pharm. Rev. 20(7), 96-98, 2017.
10. Foreward: Objectionable organisms in non-sterile medicinal products, D P Elder, Eur Pharm Rev, 22(6), 7, 2017.
11. The importance of particle size analysis, D.P.Elder, S. Tindal, P. Nielson, G. Pacowski, Eur Pharm Rev, 22(6), 58-61, 2017.
12. Analytical Control Strategies for Mutagenic Impurities: Current Challenges and Future Opportunities? A. Teasdale, D.P.Elder, TRAC Trends in Analytical Chemistry. 2017. <https://doi.org/10.1016/j.trac.2017.10.027>.
13. Industry's View on Using Quality Control, Biorelevant and Clinically Relevant Dissolution Tests for Pharmaceutical Development, Registration and Commercialization, H. Grady, D.P. Elder, G. K. Webster, Y. Mao, Y. Lin, T. Flanagan, J. Mann, A. Blanchard, M. J. Cohen, J. Lin, F. Kesisoglou, A. Hermans, A. Abend, L. Zhang, D. Curran. J. Pharm. Sci., 107(1), 2018, 34-41.
14. Excipients and their Effects on the Quality of Small Molecules, D.P.Elder, Pharma Horizon, 1(3), 48-51, 2017.
15. Antimicrobial preservatives Part Two: Choosing a preservative. D.P.Elder, P. Crowley. American Pharmaceutical Review, 20(6), 74-58, 2017.
16. Drug delivery roundtable. Y. Qiu, D. Kelemen, C. Stanmorán, D.P.Elder, C. Cassidy, H. Terefe, N. Grasman, M. Shaffer. American Pharmaceutical Review, 20(6), 74-58, 2017.
17. Foreward: The Use of Preservatives in Multi-Dose products: Balancing Efficacy and Safety. D.P.Elder, European Pharmaceutical Review, 22(5), 2017, 7.

18. Design, Formulation and Manufacture of Film Coated Drug Products. D.P.Elder, European Pharmaceutical Review, 22(5), 2017, 38-41.
19. Modernization of the Drug Supply Chain using Continuous Manufacturing. D.P.Elder, European Pharmaceutical Review, 22(5), 2017, 51-54.
20. A consortium-driven framework to guide the implementation of ICH M7 Option 4 control strategies, C. Barber, V. Antonucci; J.-C. Baumann; R. Brown; E. Covey-Crump; D. Elder; E. Elliott; J. W. Fennell; F.E Gallou; N. D. Ide; G. Jordine; J. Kallemeyn; D. Lauwers; A. R. Looker; L. E. Lovelle; M. McLaughlin; R. Molzahn; M. Ott; D.R. Schils; R. S. Oestrich; N. Stevenson; P. Talavera; A. Teasdale; M. W. Urquhart; D. L. Varie; D. Welch, Reg Pharm Toxicol, 90, 2017, 22-28.
21. Foreward: Extractables and leachables – safety based limits, D.P. Elder, European Pharmaceutical Review, 22(4), 7, 2017.
22. Antimicrobial preservatives Part One: Choosing a preservative system. D.P.Elder, P. Crowley. American Pharmaceutical Review, 20(5), 44-52, 2017.
23. Meeting Report: Dissolution Testing: Current and Future Considerations, M.Santillo, S. Young, K. Bracht, D. Elder, A. Zeitler, J. Butler, K. Box, E. Kostewicz, J. Mann. Dissolution Technologies. 2017. [dx.doi.org/10.14227/DT240317P62](https://doi.org/10.14227/DT240317P62).
24. Continuous manufacturing: Regulatory and quality assurance challenges, D. P. Elder, S. Tindall, R. Savia, European Pharmaceutical Review, 22(4), 60-64, 2017.
25. Foreward: Good manufacturing practice and mutual recognition, D.P. Elder, European Pharmaceutical Review, 22(3), 7, 2017.
26. Separation and purification applications for mutagenic impurities, D.P. Elder, European Pharmaceutical Review, 22(3), 64-67, 2017.
27. Exposure based limits for controlling impurities, D.P.Elder, American Pharmaceutical Review, 20(4), 10-15, 2017.
28. Controlled release roundtable, J. Tillotson, S.Ali, J. Cape, M.Bayru, N. Grassman, A.Bulpin, G. Servant, D.P.Elder, I. Ellis. American Pharmaceutical Review, 20(4), 22-30, 2017
29. ICH M9: Biopharmaceutics Classification System- Biowaiver, D.P.Elder S Tindall, American Pharmaceutical Review, 20(3), 20-25, 2017.
30. Raw Materials/Functional Excipients Round Table, J.M. LePree, D.P.Elder, N. Sloane, J. Zeleznik, K. Bracquiné, S. Ali, American Pharmaceutical Review, 20(3), 46-51, 2017.
31. Foreward: The Role of Packaging in the Stabilisation of Drug Products, D.P.Elder, European Pharmaceutical review, 22(2), 7, 2017.
32. GC-MS Applications in Pharmaceutical Analysis, D.P.Elder, European Pharmaceutical review, European Pharmaceutical review, 22(2), 48-52, 2017.
33. Medicines for Pediatric Patients—Biopharmaceutical, Developmental, and Regulatory Considerations, D.P.Elder, M.Kuentz, R. Holm, J. Pharm. Sci., 106(4); 950-960, 2017.
34. Foreward: ICH M9: BCS-Based Biowaivers, D.P.Elder, European Pharmaceutical Review, 22(1), 2017, 7.

35. Monitoring and controlling drug products and manufacturing processes with NIRS. D.P.Elder, European Pharmaceutical Review, 22(1), 2017, 40-43.
36. Medicines for Pediatric Patients - Biopharmaceutical, Developmental, and Regulatory Considerations. D.P.Elder, R. Holm, M.Kuentz, J. Pharm. Sci. 2017. DOI: <http://dx.doi.org/10.1016/j.xphs.2016.12.018>
37. Safety based limits for the control of impurities in drug substances and drug products: A review. D.P.Elder. Glob. J. Pharm. Pharm. Sci., 1(4), 1-7, 2017.
38. Foreward: More efficient management of post-approval change control, D. P.Elder, European Pharmaceutical Review, 21(6), 2016, 7.
39. Excipients and their Effects on the Quality of Small Molecules, D.P.Elder, BioPharm Asia, November/December 2016, 6-11.
40. Excipients: Current perspectives, D.P.Elder, Chimica Oggi- Chemistry Today, 34(5), 2016, 16-20.
41. Excipient quality and supplier inter-changeability, M. Kuentz, D.P.Elder, European Pharmaceutical Review, 21(5), 2016, 24-28.
42. Interpreting ICH's evolving residual solvents guideline, D.P.Elder, European Pharmaceutical Review, 21(5), 2016, 30-33.
43. Foreward: Modernising Pharmaceutical Manufacturing, D.P.Elder, European Pharmaceutical Review, 21(5), 2016, 7.
44. Foreward: EPR health-based exposure limits for cleaning qualification, D.P.Elder, European Pharmaceutical Review, 21(4), 2016, 7.
45. Antibiotic Resistance: The Need for a Global Strategy, D.P.Elder, M. Kuntz, R. Holm. J. Pharm. Sci. 105(8), 2016, 2278-2287.
46. Foreward: Biosimilars: Future Prospects, D.P.Elder, European Pharmaceutical Review, 21(3), 2016, 7.
47. Risk-Based Microbiological Testing, D.P.Elder, P.Newby, European Pharmaceutical Review, 21(3), 2016, 36-40.
48. Foreward: New Regulatory Strategies to Address Unmet Clinical Needs, D.P.Elder, European Pharmaceutical Review, 21(2), 2016, 7.
49. The Role of Complimentary Methods in Analytical Quality Control, J. Mitchell, D.P.Elder, American Pharmaceutical Review, Jan/Feb 2016, 1-3.
50. Foreward: The Evolving Pharmacopoeia, European Pharmaceutical Review, 21(1), 7.
51. Dissolution Testing in the Modern World, J. Symonds, D.P.Elder, European Pharmaceutical Review. European Pharmaceutical Review, 21(1), 40-43, 2016.
52. Pharmaceutical excipients – regulatory and biopharmaceutical considerations, D.P.Elder, R. Holm, M. Kuentz, European Journal of Pharmaceutical Sciences, 87, 88-89, 2016.
53. Analytical Advances in Pharmaceutical Impurity Profiling, R. Holm, D.P.Elder, European Journal of Pharmaceutical Sciences, 87, 118-135.
54. Methodology of oral formulation selection in the pharmaceutical industry, M. Kuentz, R. Holm, D.P.Elder, European Journal of Pharmaceutical Sciences, 87, 136-163, 2016.

55. Recent advances and potential applications of modulated differential scanning calorimetry (mDSC) in drug development, M.M. Knopp, K. Löbmann, D. P. Elder, T. Rades, R. Holm, *European Journal of Pharmaceutical Sciences*, 87, 164-173, 2016.
56. Foreward: The Purge Tool: An In Silico Approach to Assessing Likely Purging of Mutagenic Impurities, D.P.Elder, *European Pharmaceutical Review*, 20(6), 5.
57. Process Analytical Control: An Overview, D. P.Elder, *European Pharmaceutical Review*, 20(6), 44-47.
58. Foreward: Importation testing: an unnecessary burden on industry? *European Pharmaceutical Review*, 20(5), 2015, 5.
59. Meeting Commentary: Parkinson's Disease: From Patient to Product, J. Wahlich, D.P.Elder, F. Liu, C. Hughes, M. O. Gul, *Int. J.Pharm.*, 494, 2015, 167-171.
60. Is Avoidance of Genotoxic Intermediates/Impurities Tenable for Complex, Multi-Step Syntheses? D.P.Elder, A. Teasdale, *Org. Proc. R.D.*, 2015, 19, 1437-1446.
61. Solubility concerns: API and excipient solutions, J. Mitchell, D.P.Elder, *American Pharmaceutical Review*, 18(6), 2015, 28-32.
62. Foreward: The importance of good distribution practice, *European Pharmaceutical Review*, 20(4), 2015, 5.
63. Computational Approaches to Mutagenicity Assessments of Impurities: In Silico Methods, D.P.Elder, *European Pharmaceutical Review*, 20(4), 2015, 23-26.
64. Universal Detection in High Performance Liquid Chromatography. *European Pharmaceutical Review*, 20(3), 2015, 47-51.
65. Foreward: Drug Shortages are Finally Being Addressed. *European Pharmaceutical Review*, 20(3), 2015, 5.
66. Mutagenic Impurities: Precompetitive/Competitive Collaborative and Data Sharing Initiatives, David P Elder, Angela White, Jim Harvey, Andrew Teasdale, Liz Covey-Crump, Richard Williams, *Org. Proc. R.D.*, 2015, 19, 1486-1494.
67. Strategies to Address Mutagenic Impurities Derived from Degradation in Drug Substances and Drug Products, Mark H. Kleinman, David Elder, Andrew Teasdale, Mark D. Mowery, Alan P McKeown , and Steven W. Baertschi. *Org. Proc. R.D.*, 2015, 19, 1447-1457.
68. Do carboxylic/sulfonic acid halides really present a mutagenic and carcinogenic risk as impurities in final drug products? Alexander Amberg, James S. Harvey, Andreas Czich, Hans-Peter Spirkli, Sharon Robinson, Angela White, David P. Elder, *Org. Proc. R.D.*, 2015, 1495-1506.
69. Meeting Report- Quality Risk Management. Joint Pharmaceutical and Analysis Group Meeting: Quality Risk Management, *Regulatory Rapporteur*, 12(6), 30-32, 2015.
70. Meeting Report- Stability Requirements. Joint Pharmaceutical and Analysis Group Meeting: Stability Challenges Part II, *Regulatory Rapporteur*, 12(5), 30-32, 2015.
71. HPLC Mass Spectral Analysis of Glycans, D. P. Elder, Phil Borman, G. Okafo, W. McDowell, *European Pharmaceutical Review*, 20(2), 2015, 45-51.
72. In-Depth Focus: LC-MS Roundtable, K. Ray, S. Morea, I. Gibb, McCarthy S.M., Moderator D. P.Elder, *European Pharmaceutical Review*, 20(2), 2015, 58-60.

73. Foreword: Precompetitive collaborations in the pharmaceutical industry. European Pharmaceutical Review, 20(2), 2015, 7.
74. Solubility in Pharmaceutical R&D: Predictions and Reality, D.P.Elder, C. Saal, Pharmaceutical Outsourcing, 16(1), 2015, 36-41.
75. Foreword: The cost of drug counterfeiting, D. P. Elder, European Pharmaceutical Review, 20(1), 2015, 5.
76. Analytical Methods and Control Strategies: The Forgotten Interface? P. Borman, M. Popkin, N. Oxby, M. Chatfield, D. P. Elder, Pharmaceutical Outsourcing, 16(1), 2015, 1-4.
77. Foreword: Cocrystals: Defining the opportunity, D. P. Elder, European Pharmaceutical Review, 19(6), 2014, 7.
78. Foreword: Crystallography: A Core Science, D. P. Elder, European Pharmaceutical Review, 19(5), 2014, 5.
79. Foreword: Can HPLC assay methods really be considered quality critical test? D. P. Elder, European Pharmaceutical Review, 19(4), 2014, 5.
80. Pharmaceutical equivalence, therapeutic equivalence and the role of analytical science. D. P. Elder, Richard Kaye, Regulatory Rapporteur, Sep. 2014, 29-32.
81. The solid-state continuum: a perspective on the interrelationships between different solid-state forms in drug substance and drug product. D.P.Elder, J. Patterson, R. Holm, Journal of Pharmacy and Pharmacology, 2014, doi: 10.1111/jphp.12293
82. Foreword: What does quality mean to you? D.P.Elder, European Pharmaceutical Review, 19(3), 2014, 5.
83. Are HPLC-UV methods fit for purpose as true arbiters of Quality for APIs? D.P.Elder, American Pharmaceutical Review, 17(4), 2014, 68-72.
84. Foreword: Is risk in the eye of the beholder? D.P.Elder, European Pharmaceutical Review, 19(2), 2014, 7.
85. Meeting Report –ICH Q3D (Residual Metals): Challenges and Opportunities, D.P.Elder, A. Teasdale, Regulatory Rapporteur, April 2014, 25-29.
86. Solubility in pharmaceutical R&D: Predictions and reality, D.P.Elder, C. Staal, American Pharmaceutical Review, 17(1), 2014, 1-6.
87. Foreword: ICH M7: Mutagenic impurities: A critical evaluation, D. P.Elder, European Pharmaceutical Review, 19(1), 2014, 6.
88. Foreword: ICH Q6A: Specifications: Test procedures and acceptance criteria for new drug substances and new drug products: chemical substances, D.P.Elder, European Pharmaceutical Review, 18(6), 2013, 7.
89. Foreword: ICH Q3D Metal impurities: A critical evaluation, D.P.Elder, A. Teasdale, European Pharmaceutical Review, 18(5), 2013, 7.
90. Foreword: ICH Q2(R1) Validation of Analytical Procedures – Challenges and Opportunities, D.P.Elder, European Pharmaceutical Review, 18(4), 2013, 7.
91. Improving analytical method reliability across the entire product lifecycle using QbD approaches, D.P.Elder, P. Borman, Pharmaceutical Outsourcing, 14(4), 2013, 14-19.

92. Assessment of Predictivity of Semiquantitative Risk Assessment Tool: Pazopanib Hydrochloride Genotoxic Impurities, D.P.Elder, G. Okafo, M.McGuire, Organic Process Research Development, 17(8), 2013, 1036-1041.
93. Review: Use of pharmaceutical salts and cocrystals to address the issue of poor solubility, D. Elder, R. Holm, Int. J. Pharmac. 453 (2013) 88-100.
94. Review: Aqueous solubility: Simple predictive methods (in silico, in vitro and bio-relevant approaches), D. Elder, R. Holm, Int. J. Pharmac. 453 (2013) 3-11
95. Progress and challenges in pharmaceutical harmonisation, D.P.Elder, Regulatory Rapporteur, 10 (7/8), July/August 2013, 23-27.
96. Genotoxic/Mutagenic Impurities Part 3: CMC (Chemistry, Manufacturing and Controls) Overview, D.P.Elder, D.Snodin, Pharmaceutical Outsourcing, May 21st 2013.
97. Development of a novel intra-nasal spray product: A case history, D.P.Elder, A.C.Grant, J.Godfrey, A. Slater, G.Bone, G.Cannon, Industrial Pharmacy, 36, 2013, 12-14
98. Foreword: Towards global stability protocols: A decade of lost opportunities? D.P.Elder, European Pharmaceutical Review, 18(2), 2013, 7.
99. Risk assessment of genotoxic impurities (GTIs) in new chemical entities- strategies to demonstrate control, A. Teasdale, D. P.Elder, S-J.Chang, S.Wang, R.Thompson, I.Sanchez, Organic Process Research Development, 17(2), 2013, 221-230.
100. An approach to control strategies for sulfonate ester formation in pharmaceutical manufacturing based on recent scientific understanding, D.Elder, K.Facchine, J.N. Levy, R. Parsons, D. Ridge, L. Semo, A. Teasdale, Organic Process Research Development, 16, 2012, 1707-1710.
101. Genotoxic Impurities Part II: Toxicology Overview, D.Snodin and D.P.Elder, Pharmaceutical Outsourcing, 13(5), 2012, 38-50.
102. Genotoxic Impurities Part I: General Overview, D.P.Elder and D.Snodin, Pharmaceutical Outsourcing, 13(3), 2012, 44-59.
103. Review: Quality in the manufacture of medicines and healthcare products (2nd Edition), D.P.Elder, Chemistry World, 9(6) 2012 63.
104. Antimicrobial Preservatives Part One: Choosing a Preservative System, David Elder and Patrick Crowley, American Pharmaceutical Review, published on-line 01st January 2012.
105. Antimicrobial Preservatives Part Two: Choosing a Preservative, David Elder and Patrick Crowley, American Pharmaceutical Review, published on-line 01st January 2012.
106. Antimicrobial Preservatives Part Three: Challenges Facing a Preservative System, David Elder and Patrick Crowley, American Pharmaceutical Review, published on-line 01st January 2012.
107. Solubility Round Table, C. Saal (Merck KGaA), Stephan Tindal (Catelant Pharma Solutions), Vivian Bi (ISP Pharmaceuticals), David Elder (GSK), American Pharmaceutical Review, June 2011.
<http://www.americanpharmaceuticalreview.com/ViewArticle.aspx?ContentID=7355>

108. Effective Formulation Development Strategies for Poorly Soluble Active Pharmaceutical Ingredients (APIs), D P Elder, *Pharmaceutical Outsourcing*, 12(2), 2011, 1-7.
109. Oligonucleotide Biopolymers – Future Challenges for Chromatography, G. Okafo, D.S. Levin and D.P.Elder, *International Labmate*, 36(3) (2011) 4-7.
110. Oligonucleotide Biopolymers – Future Challenges for Chromatography, G. Okafo, D.S. Levin and D.P.Elder, *Chromatography Today*, 4(1) (2011) 4-8.
111. Control and Analysis of Hydrazine, Hydrazides and Hydrazones – Genotoxic Impurities in Active Pharmaceutical Ingredients (APIs) and Drug Products, D P Elder, D Snodin, A Teasdale, *Journal of Pharmaceutical and Biomedical Analysis*, 54 (2011) 900-910.
112. Effective Formulation Development Strategies for Poorly Soluble Active Pharmaceutical Ingredients (APIs), D P Elder, *American Pharmaceutical Review*, 13 6(1) (2010) 28-34.
113. Is there A Real Case for the Cumulative Control of Structurally Related Genotoxic Impurities? D. P. Elder and J.S.Harvey, *Organic Process Research and Development*, 14, 2010, 1037-1045.
114. A Detailed Study of Sulfonate Ester Formation and Solvolysis Reaction Rates and Application towards Establishing Sulfonate Ester Control in Pharmaceutical Manufacturing Processes, A Teasdale, S Eyley, E Delaney, K.Jacq K Taylor-Worth, A Lipczynski, V D Reif, D P Elder, K Facchine, S Golec, R S Oestrich, P Sandra and F David, *Organic Process Research and Development*, 14, 2010, 999-1007.
115. Review: The Utility of Sulfonate Salts in Drug Development, D.P.Elder, E.Delaney, A.Teasdale, S.Eyley, Van D.Reif, K.Jacq, K.L.Facchine, R.Oestrich, P.Sandra, F.David, *J.Pharm.Sci*, 2010, 99(7), 2948-2961.
116. Development of Paediatric Medicines – The Industry Perspective, D.P.Elder, *Bulletin Technique Gatefosse*, 102 (2009) 75-80.
117. Review: Analytical approaches for the detection of epoxides and hydroperoxides in active pharmaceutical ingredients, drug products and herbals, by D.P. Elder, D. Snodin and A. Teasdale, *Journal of Pharmaceutical and Biomedical Analysis*, 51(5) (2010) 1015-1023
118. Drug Substances Presented as Sulfonic Acid Salts: Overview of Utility, Safety and Regulation, D.P.Elder and D.J.Snodin, *J.Pharm.Pharmac*, 61 (2009) 1-10.
119. Detection and Assessment of Co-Association in Inhalable Drug Particles using Aerosol Time-of-Flight Mass Spectrometry, A.New, D.Prime, S.Zomer, D.Elder, R.Donovan and E.Freney, *Rap. Comm. Mass Spec.*, 22 (2008) 3873-3882.
120. Mechanism and Processing Parameters Affecting the Formation of Methyl Methanesulfonate from Methanol and Methanesulfonic Acid, An Illustrative Example for Sulfonate Ester Impurity Formation, A Teasdale, S Eyley, E Delaney, K.Jacq K Taylor-Worth, A Lipczynski, V D Reif, D P Elder, K Facchine, S Golec, R S Oestrich, P Sandra and F David, *Organic Process Research and Development*, 13, 2009, 429-433.
121. Development and Validation of an Automated Static Headspace Gas Chromatography-Mass Spectrometry (SHS-GC-MS) Method for Monitoring the

- Formation of Ethyl Methane Sulfonate from Ethanol and Methane Sulphonic Acid, K.Jacq, E Delaney, A Teasedale, S Eyley, K Taylor-Worth, A Lipczynski, V D Relf, D P Elder, K Facchine, S Golec, R S Oestrich, P Sandra and F David, J Pharm Biomed Anal 48 (2008) 1339-1344.
122. Development, Validation and Transfer into a Factory Environment of a Liquid Chromatography Tandem Mass Spectrometry Assay for the Highly Neurotoxic Impurity FMTP (4-(4-Fluorophenyl)-1-Methyl-1,2,3,6-Tetrahydropyridine) in Paroxetine Active Pharmaceutical Ingredient (API), P J Borman, M J Chatfield, E L Crowley, C Eckers, D P Elder, S W Francey, A M-F Laures and J-C Wolff, J Pharm Biomed Anal 48, 1082-108, 20089.
 123. Industry Perspective: BioEnhancement Strategies (Nanomilling vs. Lipidic Approaches), D.P.Elder, H.M.Gorton, R.J.Mackey and R.S.Lloyd, Bulletin Technique Gatefosse, 101,) 53-56, 2008.
 124. The Control and Analysis of Alkyl and Benzyl Halides and Other Related Reactive Organohalides as Potential Genotoxic Impurities in Active Pharmaceutical Ingredients (APIs), D. P. Elder, A. Teasedale and A.M. Lipczynski, J. Pharm. Biomed. Anal, 48, 497-507, 2008.
 125. The Control and Analysis of Alkyl Esters of Alkyl and Aryl Sulphonic Acids in Novel Active Pharmaceutical Ingredients (APIs), D. P. Elder, A. Teasedale and A.M. Lipczynski, J. Pharm. Biomed. Anal, 46, 1-8, 2008.
 126. Developing Paediatric Medicines: Identifying the Needs and Recognising the Challenges, Terry B Ernest, David P Elder, Luigi G Martini, Matthew Roberts and James L Ford, J. P. J. Pharm. Pharmac., 59, 1043-1055, 2007.
 127. The use of a Gastro-Intestinal model and GastroPLUS™ for the prediction of *in-vivo* performance, T. A. Naylor, P.C. Connolly, L.G. Martini, D. P. Elder, M Minekus, R. Havanaar and E. Zeijdner, Ind. Pharm., 12, 9-12, 2006.
 128. The use of a Gastro-Intestinal model and GastroPLUS™ for the prediction of *in-vivo* performance, T. A. Naylor, P.C. Connolly, L.G. Martini, D. P. Elder, M Minekus, R. Havanaar and E. Zeijdner, Appl. Therap. Res., 6(1) (2006) 15-19.
 129. The Use Of Surface Analysis Techniques To Determine The Route Of Manufacture Of Tablet Dosage Forms, R. Mitchell, N. L. Marzolini, S. A. Hancock, A.M.Harridance and D.P.Elder, Drug Dev.Ind. Pharm., 32, 2006, 253-261.
 130. Pharmaceutical Applications of Ion Exchange Resins, J. Chem. Ed., 82, 575, 2005.
 131. Overview of the Status and Applications of Capillary Electrophoresis, K D Altria and D P Elder, J. Chromatogr. (A), 1023, 1-14, 2004.
 132. Review: Never Ending Battle, D P Elder, Chem.Ind., 768-769, 03 December 2001.
 133. Review: A Complex Solution, D P Elder, Chem. Ind., 209-214, 02 April 2001.
 134. Stability of Medicines (PAG), Excipient Compatibility, D. P. Elder, Pharm. J., 255, October 14th (1995), 518.
 135. Structure of *N*²-(3,5-Dichlorophenyl)-4-(4-Hydroxy-2-Methoxyphenyl)-1-Piperazine-Carboxamide Monohydrate, D P Elder, I A Selby, R O Gould and P Taylor, Acta. Cryst, Section C, 48, 871-873, 1992.

136. Synthesis of [4 - ^{14}C] and [6,7 D_2] Trilostane, D Johnston and D P Elder, J. Lab.Comp. Radiopharm., Vol. XXVII, 1, 1989.
137. Synthesis of [carbonyl - ^{14}C] Hexopal, D Johnston and D P Elder, J. Lab. Comp.Radiopharm., Vol. XXVII, 1, 1989.
138. Synthesis of [D_4] - Acetaminophen, D Johnston and D P Elder, J. Lab.Comp. Radiopharm., Vol. XXVI, 12, 1988.

POSTER PRESENTATIONS

1. Process Optimization of Aqueous Ethylcellulose (Surelease) film coated Paracetamol Pellets With and Without a Hypromellose Pore Forming Agent (Opadry) Assessed Using Accelerated Stability Testing, S.David and D Elder, J.Pharm. Pharmac., Science Proceedings 2008, British Pharmaceutical Conference, 60 Supplement 1, A-26, Abstract 65.
2. Process for the Development and Validation of a Near Infra Red Spectroscopic Whole Tablet Assay, K. Smith, D. P. Elder, N.C. North, J. Pharm. Pharmac, Science Proceedings 2007, British Pharmaceutical Conference, 59, Supplement 1, Abstract 71, A-27, 2007.
3. The Diversity of Alginates as a Drug Delivery System, F. Stops, J. Collett, J. Fell, L. Martini, D. P. Elder, C. Wilson and P. Meneaud, J. Pharm. Pharmac, Science Proceedings 2007, British Pharmaceutical Conference, 59, Supplement 1, Abstract 34, A-14, 2007.
4. The Influence of Spray Drying on the Physical Properties of Hydroxypropylcellulose and Hypromellose, T.B. Ernest, L.G. Martini, D. P. Elder, M. Robersts and J.L. Ford, J. Pharm. Pharmac, Science Proceedings 2007, British Pharmaceutical Conference, 59, Supplement 1, Abstract 110, A-41, 2007.
5. How Realistic is the Avoidance of Risk? The Challenges of Genotoxic Impurities, D. P. Elder, J. Pharm. Pharmac, Science Proceedings 2007, British Pharmaceutical Conference, 59, Supplement 1, Abstract 217, A-78, 2007.
6. A Quality by Design Approach for the Development of a Next Generation Nasal Spray Delivery System, A.L. Slater, D. P. Elder, C.A. Fisher, S. Charles and S. Broughton. XXVI Congress of European Academy of Allergy and Clinical Immunology, Goteborg, Sweden. Allergy, European Journal of Allergy and Clinical Immunology, 62, Supplement 83 (Abstract No. 1405), (June 2007) 488.
7. Setting Meaningful Specifications for MR Products, D. P. Elder, J. Pharm. Pharmac, Science Proceedings 2006, British Pharmaceutical Conference, 58, Supplement 1, Abstract S096, 2006.
8. Genotoxic Impurities: Strategies for Balanced Approach, D. P. Elder, J. Pharm. Pharmac, Science Proceedings 2006, British Pharmaceutical Conference, 58, Supplement 1, Abstract S097, 2006.
9. An Initial Assessment of Process Conductivity Profiles in Pharmaceutical Manufacturing, A. P. New, D. P. Elder, D. Rudd, and D. Taylor, J. Pharm. Pharmac, Science Proceedings 2006, British Pharmaceutical Conference, 58, Supplement 1, Abstract S098, 2006.
10. The Development of MS Compatible HPLC Method for the Analysis of 2,4-DNPH Derivatised Aldehydes Present as Secondary Oxidative Degradants in Non-Ionic Excipients, R. Marshall and D. P. Elder, J. Pharm. Pharmac, Science Proceedings

- 2006, British Pharmaceutical Conference, 58, Supplement 1, Abstract S103, 2006.
11. The Application of Ferric Oxide (FOX) Assay for the Analysis of Peroxides Present as Primary Oxidative Degradants in Non-Ionic Excipients, R. Marshall and D. P. Elder, J. Pharm. Pharmac, Science Proceedings 2006, British Pharmaceutical Conference, 58, Supplement 1, Abstract S104, 2006.
 12. Ion Exchange Resins: Improving Palatability without Compromising Bioequivalence, T.B. Ernest, D. P. Elder, L.G.Martini, M. Roberts, J.L. Ford, J. Pharm. Pharmac, Science Proceedings 2006, British Pharmaceutical Conference, 58, Supplement 1, Abstract S211, 2006.
 13. Preservatives: An Uncertain Future? D. P. Elder, A. Slater and T. Shreeves J. Pharm. Pharmac, Science Proceedings 2006, British Pharmaceutical Conference, 58, Supplement 1, Abstract S240, 2006.
 14. The use of the TNO intestinal model (TIM-1) and GastroPLUS for the prediction of *in-vivo* performance of immediate release tablets, T. A. Naylor, L.G. Martini, P.C. Connolly, D. P. Elder, R. Havanaar, M Minekus and E. Zeijdner, J. Pharm. Pharmac, Science Proceedings 2004, British Pharmaceutical Conference, 56, Abstract 200, S-74 – S-75, 2004.

PATENTS

Novel Formulations Containing Paroxetine, G S Leonard and D P Elder, GB/20.07.95/GBA 9514842, 20 July 1995.

A Controlled Release or Delayed release Formulation Containing a Selective Serotonin Reuptake Inhibitor (SSRI) such as Paroxetine, G S Leonard and D P Elder, US20020090394, 11 July 2002.

Pharmaceutical Compositions Containing Paroxetine Mesylate, A K Al-Ghazawi, A Craig, D P Elder, V Jacewicz, D Jones, D O'Keeffe, P Patel, M Urquhart, and Neal Ward, GB9814316, 02 July 1998.

Pharmaceutical Compositions Containing Paroxetine Mesylate, A K Al-Ghazawi, A Craig, D P Elder, V Jacewicz, D Jones, D O'Keeffe, P Patel, M Urquhart, and Neal Ward, US2001002352, 20 September 2001.

Pharmaceutical Compositions Containing Paroxetine Mesylate, A K Al-Ghazawi, A Craig, D P Elder, V Jacewicz, D Jones, D O'Keeffe, P Patel, M Urquhart, and N Ward, US20030203937, 30 September 2003.

Water Dispersible Formulations of Paroxetine, A K Al-Ghazawi, D P Elder and P Meneaud, WO2001GB569, 09 February 2001.

Water Dispersible Formulations of Paroxetine, A K Al-Ghazawi, D P Elder and P Meneaud, US20030186938, 02 October 2003.

EXHIBIT 2



Preface

Drug solubility: how to measure it, how to improve it[☆]

Solubility of active pharmaceutical ingredients (API) has always been a concern for formulators, since inadequate aqueous solubility may hamper development of parenteral products and limit bioavailability of oral products. In recent years, the problem has become more acute and more common as pharmaceutical companies cast the drug discovery net ever wider in the anticipation of finding new therapeutic approaches and improving drugs for existing therapeutic areas.

With the advent of high throughput screening for receptor activity, throughput requirements for physicochemical characterization of new APIs have increased commensurately. This challenge has been met by the pharmaceutical industry by improving *in silico* predictions of important physicochemical characteristics such as solubility, ionization constants and partition coefficients and by developing high throughput characterization methods to enhance predictions with experimental data. Additionally, new medium throughput methods have also been developed to more accurately characterize solubility of new APIs before they are taken forward into animal and human studies.

All these developments are described in the first three contributions to this issue. Faller and Ertl review computational models to predict water solubility, with emphasis on the accuracy of the various prediction methods. They also stress the importance of comparing calculated and measured solubility, and provide guidelines as to when to trust the computed value. Alsenz and Kansy summarize current experimental approaches to solubility determination, with emphasis on recent advances in the experimental methods used to determine drug solubility in drug discovery and early development. Methods for both kinetic and thermodynamic (equilibrium) solubility with both high throughput and traditional methods are presented. Avdeef reviews the experimental and computational basis of the pH-dependent measurement of solubility of sparingly-soluble ionizable drugs. Recently described compound-sparing (but still accurate) approaches, suitable for application in preclinical development, and appropriate for the analysis of solubility of “problematic” molecules, are critically examined. A number of useful experimental methods are reviewed, including the miniaturized shake-flask microtitre plate, the micro solubility self-

calibrating direct UV, the potentiometric, and the micro dissolution methods.

Rounding out the discussion on assessing solubility is a contribution by the editors on the subject of gastrointestinal (GI) solubility of APIs, since GI solubility may be far greater than the solubility measured in water. The use of aqueous solubility to predict oral drug absorption can therefore lead to very pronounced underestimates of the oral bioavailability, typically for drugs which are poorly soluble and lipophilic. Various methods for estimating intra-luminal solubilities are presented, with emphasis on the two most widely implemented methods: determining solubility in fluids aspirated from the human gastrointestinal tract, and determining solubility in so-called biorelevant media, composed to simulate these fluids.

Despite the relatively favorable environment, API solubility in the GI tract can, and often does, limit its oral bioavailability by affecting dissolution rates and/or the maximum amount that can be dissolved intra-lumenally. Similarly, for intravenous application, the API must be dissolved in a vehicle in order to meet tolerance and safety demands. In the second part of the issue, the focus is shifted from estimation of solubility to improvement of API solubility and/or dissolution by both chemical (salts and prodrugs) and formulation (crystal engineering, nanosizing, lipid formulation and cyclodextrin complexation) approaches.

Salt formation is a common and effective method of increasing solubility and dissolution rates of acidic and basic drugs. Serajuddin presents the physicochemical principles of salt solubility. Whether certain acidic or basic drugs would form salts and, if salts are formed, how easily they would dissociate back into their free acid or base forms depend on interrelationships of several factors, such as S_0 (intrinsic solubility), pH, pK_a , K_{sp} (solubility product) and pH_{max} (pH of maximum solubility) and these issues are illustrated with practical examples. Non-ideality of salt solubility due to self-association in solution is also discussed.

Crystal engineering offers a number of routes to improved solubility and dissolution rate, which can be adopted through an in-depth knowledge of crystallization processes and the molecular properties of active pharmaceutical ingredients. The article by Blagden and colleagues covers the concept and theory of crystal engineering and discusses the potential benefits, disadvantages and methods of preparation of co-crystals,

[☆] This preface is part of the *Advanced Drug Delivery Reviews* theme issue on “Drug solubility: How to measure it, how to improve it”.

metastable polymorphs, high-energy amorphous forms and ultrafine particles. Nanosizing refers to the reduction of the active pharmaceutical ingredient (API) particle size down to the sub-micron range, with the final particle size typically being 100–200 nm. The reduction of particle size leads to a significant increase in the dissolution rate of the API, which in turn can lead to substantial increases in bioavailability. Kesisoglou and colleagues describe the principles behind nanosizing, the production and characterization of nanoformulations as well as the current experience with utilization of such formulations *in vivo*.

Cyclodextrins can form non-covalent dynamic inclusion complexes with a wide variety of APIs in solution, resulting in large increases in solubility and thus improvements in parenteral application on the one hand and in oral bioavailability of poorly soluble APIs on the other hand. A number of cyclodextrin-based products have reached the market based on their ability to (temporarily) camouflage undesirable physicochemical properties. The review by Brewster and Loftsson provides a general background to the use of cyclodextrin as solubilizers as well as discussing in detail the kinetic and thermodynamic tools and parameters useful in the study of drug solubilization by cyclodextrins.

The ability of lipid-based formulations to facilitate gastrointestinal absorption of many poorly soluble drug candidates has been thoroughly documented in the published literature. However, a considerable gap exists between our knowledge of this technology and the know-how required for its application. Hauss provides a comprehensive summary of the development, characterization, and utilization of oral lipid-based formulations, from both physicochemical and biopharmaceutical perspectives.

In the closing contribution, Stella and Nti-Addae review the use of prodrugs to effect improved oral and parenteral delivery of

poorly water-soluble problematic drugs, using both marketed as well as investigational prodrugs as examples. Data are presented to illustrate that an increasing percentage of new drug approvals in fact contain prodrugs. They emphasize that prodrug interventions should be considered early in the drug discovery paradigm rather than as a technique of last resort.

The editors wish to thank all the contributors for their excellent and very current synopses of solubility-related research in the pharmaceutical arena. It is clear that pharmaceutical research and researchers are responding extremely well to the challenge of poorly soluble APIs and that we may expect continued rapid progress in the prediction, measurement and improvement of solubility in the years to come.

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EXHIBIT 3

11 Overcoming formulation problems and some case studies

Challenges and problems to solve when developing sterile dosage forms are innumerable. However, while not claiming to be totally comprehensive, Table 11-1 summarizes the formulation problems to overcome in sterile product development. This chapter is intended to provide some practical guidance on approaching and solving common formulation problems in sterile product development on the basis of actual experiences of the author.

OVERCOMING SOLUBILITY PROBLEMS

There are seven general approaches to overcome solubility problems (1).

The first approach is to determine if the optimal salt form of the drug can be used, provided the drug is an electrolyte (can be ionized at different pH values) and depending on properties of the salt form, especially drug stability. Often the most soluble form is too unstable for further development so a compromise must be made between acceptable solubility and stability. It is beyond the scope of this book to discuss optimal drug molecular structure for optimal solubility, but before a formulation scientist begins to develop the final product formulation, he/she should be using the optimal salt form of the drug (Table 11-2).

The next approach that can be tried to render drugs more soluble in aqueous solution is to adjust solution pH. This is a relatively simple approach that is widely used. Either the drug salt form is isolated and used, which when dissolved in solution, solubilizes the drug without adjustment of pH, or the drug is added to water to form a slurry (drug in suspension). The pH is then adjusted by adding the appropriate acid or base form to reach the pH at which the drug will dissolve and remain in solution.

The relationship of drug solubility and solution pH is described by the following equation:

$$\text{pH} = \text{p}K_a + [\log(S - S_o)/S_o] \text{ Henderson-Hasselbalch Equation.}$$

Where S is the total solubility in water, S_o is the solubility of the drug in its natural (undissociated) form, and $\text{p}K_a$ is the dissociation constant of the drug. A simple example will demonstrate the use of this equation. A drug has a natural solubility of 0.61 mg/mL and a $\text{p}K_a$ of 7.12. A total solubility of 50 mg/mL is required for the final dosage form. What must the solution pH be adjusted to in order to obtain this concentration?

$$\text{pH} = \text{p}K_a + [\log(S - S_o)/S_o] = 7.12 + [\log(50 - 0.61)/0.61] = 9.03.$$

Typically, increasing drug solubility will also increase its instability in water. Figure 8-2 presented the classic example of the solubility and stability of penicillin as a function of pH.

Adjustment of pH *in situ* can render insoluble drugs soluble in water. Vancomycin-free base is relatively insoluble in water. A slurry of vancomycin-free base in water is prepared and then the slurry is slowly titrated with hydrochloric acid. As the hydrochloride salt of vancomycin is formed *in situ*, vancomycin hydrochloride dissolves completely in solution.

If a salt form of the drug cannot be used (or is still insufficiently soluble) or pH adjustment does not increase drug solubility sufficiently, then slightly more complicated, albeit still relatively simple, formulation approaches are possible. These approaches, using co-solvents or complexing agents or surface-active agents, are presented in chapter 6.

If the addition of co-solvents or solubilizing solutes do not solve the solubility problem for a particular drug, or there are safety/toxicologic issues using these additives for a particular product and/or route of administration and/or clinical indication, then an alternative dosage form must be developed. In such dosage forms the drug is not in a true solution but can be formulated and processed where the mean particle (micro- or nanosuspension) or globule (microemulsion or liposome) size is 1 μm or less, allowing for intravenous (IV) administration. If the route of administration does not include IV, then the dosage form can be a conventional (macro) suspension (size ranges $> 5 \mu\text{m}$) or an emulsion.

Table 11-1 Summary of Sterile Product Formulation Challenges

-
1. Overcoming solubility problems, especially for aqueous insoluble drugs intended for IV administration.
 2. Overcoming stability problems, the greatest area of challenges and opportunities for development scientists. The major stability issues include:
 - a. Instability in water, influence by pH and ionic strength.
 - b. Oxidation stability problems
 - c. Photolytic stability problems
 - d. Stability problems during processing, e.g.,
 - i. During freeze-drying, especially for biomolecules
 - ii. During processing of time/temperature sensitive molecules
 - iii. During processing of dispersed systems where significant physical instability problems can arise
 3. Overcoming compatibility problems between drug and added substance, between one or more added substances, between drug and/or added substance and packaging. This is especially significant when formulating biomolecules because of their high reactivity with almost any other component in the formulation.
 4. Overcoming problems that formulations may cause, with pain and tissue irritation upon injection.
 5. Overcoming homogeneity problems with dispersed systems, especially suspensions.
 6. Overcoming drug delivery problems when targeting a certain dose to be delivered at or over a certain time and depending on the formulation matrix to achieve this goal consistently.
-

For first human dose studies for cancer drugs typically, “heroic” approaches are taken to render drugs soluble for IV administration. These approaches may be suitable for very early clinical phase studies of life-saving drugs to patients who otherwise may die, but are not suitable for commercial injectable formulations. Examples of heroic approaches for drug solubilization include:

- Using relatively toxic solvents such as dimethyl sulfoxide (DMSO)
- The vehicle being 100% ethanol
- High concentrations of surface-active agents or other solubilizing agents whose concentrations exceed what is known to be safe for injectable administration

Table 11-2 Examples of Salt Forms Used To Improve Drug Solubility (in order of frequency of appearances in the United States Pharmacopeia)

Cationic salts	Anionic salts
Sodium	Hydrochloride
Potassium	Sulfate
Calcium	Acetate
Aluminum	Phosphate/diphosphate
Zinc	Chloride
Meglumine	Maleate
Benzathine	Citrate
Tromethamine	Tartrate/Bitartrate
Magnesium	Mesylate
Lysine	Nitrate
Procaine	Succinate
Ethylenediamine	Gluconate
	Bromide
	Fumarate
	Hydrobromide
	Carbonate
	Iodide
	Benzoate
	Pamoate
	Valerate

Source: From Ref. (2).

OVERCOMING STABILITY PROBLEMS

Because pharmaceutical dosage form stability is perhaps the most important property and one requiring the most effort from formulation development scientists, overcoming stability problems and formulating stable products, especially for proteins, has been covered in chapters 8, 9, and 10 for the specific type of dosage form.

OVERCOMING COMPATIBILITY PROBLEMS

Compatibility problems with injectables cover a wide range of possible problems.

- Drug and additive incompatibilities that result in inactivation of the drug or precipitation of an insoluble complex.
- Drug or additive interacting with packaging components such as
 - binding to glass
 - adsorption to rubber
 - adsorption to plastic
 - binding to silicon coatings from glass syringes or cartridges or rubber closures or plungers
 - reactions with needle components
- Leachates from the packaging system caused by certain properties of the formulation.
- Drug binding to the surfaces of devices used to deliver the product, such as syringes, IV sets, and catheters

OVERCOMING PAIN AND TISSUE IRRITATION PROBLEMS

Injections are painful, either for real or imaginary. Pain is associated with the needle primarily, but besides the needle, the properties of the drug product can cause pain and irritation. Obviously the pharmaceutical product formulation scientist cannot help to avoid needle pain, but can do some things to minimize the pain caused by the product.

Both in vitro and in vivo methods exist (Table 11-3) to study pain and irritation potential of drug products (3). These methods can be used to pinpoint one or more of the component of the product, be it drug, additive, or solvent and properties therein, that might be causing or contributing to the pain sensation. Data from these studies can help to determine whether a component can be reduced or eliminated or a property such as pH, tonicity, volume percent of co-solvent, ionic strength, or particle size, whatever the case, be changed.

There is precedence for altering the amino acid sequence of polypeptide drugs in order to minimize the self-aggregation of the protein at the site of injection, the aggregation of which caused patients to complain of injection pain.

Once everything has been done to optimize the formulation to minimize or eliminate the pain, yet pain response still results, the main approach that can be used is to minimize the rate of drug product injection or infusion. Other possible aids, although not as effective as injection/infusion rate, include dilution of the drug product prior to injection and use of an

Table 11-3 In Vitro and In Vivo Methods for Determination of Formulation Potential for Pain, Irritation, and/or Other Problems Following Intravenous Administration of the Dosage Form

Method type	Specific description of method	What potential problem is determined?
In Vitro	Mixing formulation and blood (1:10 ratio)	Hemolysis
	Slow addition and mixing of formulation with blood or isotonic Sorensen's phosphate buffer	Precipitation in blood
	Depletion of creatine phosphokinase when formulation mixed with muscle cells	Pain
	Precipitation studies	Phlebitis
In Vivo	Rabbit ear vein model	Phlebitis, precipitation
	Blood level of hemoglobin	Hemolysis
	Rat or rabbit paw lick	Pain
	Serum levels of creatine phosphokinase	Pain, cell damage

Source: From Ref. (3).

in-line filter if there's a possibility that particulate load, however small, might be contributing to the problem.

OVERCOMING HOMOGENEITY PROBLEMS

Dispersed system homogeneity problems, manifested typically through nonuniformity of active ingredient dose from container to container, are almost always the result of poor formulation design and/or nonuniform particle size distribution of the suspended drug particles.

Well-designed parenteral suspensions are formulated according to the principles described in chapter 9. Perhaps the overriding key factor to good homogeneous suspension formulations is adequate wetting of all drug particles and particle size reduction of particles within a very narrow size distribution range.

OVERCOMING DRUG DELIVERY PROBLEMS

Drug release from microspheres or other polymer delivery devices must be constant as a function of time. If zero-order rates of release and availability of drugs from depot injections does not occur, serious therapeutic problems will occur.

There are three approaches used to help assure that drug delivery problems from depot injections do not occur:

1. Understand polymer chemistry. This includes understanding the following factors:
 - a. How the active ingredient is entrapped within the polymer matrix
 - b. Understanding how the polymer degrades in vivo
 - c. Knowing the safety profile of the polymer
 - d. Understanding how the polymer used is itself manufactured
 - e. Knowing the polymer physical properties
2. Understanding the engineering of microsphere or other delivery formulation
 - a. What is the process used in fabricating the microspheres and how is each step controlled and characterized.
3. Understanding the stability of the active ingredient in the polymer matrix:
 - a. During encapsulation
 - b. Shelf life in microsphere
 - c. After administration
 - d. Verification of protein conformation in microsphere
 - e. Protein-polymer interactions

CASE STUDIES IN FORMULATION DEVELOPMENT OF STERILE DOSAGE FORMS

These case studies are based on actual problems encountered by the author or problems that have been published elsewhere. The case study problems will be presented first with the idea that the reader will think about how to approach solving the problem. The answers are given starting on page 174.

Case Study 1

Stability samples of a ready-to-use sterile solution show visible evidence of extremely small particulates after storage for 1 month at ambient temperature. What are possible causes or sources of these particulates? For each cause or source, what can be done to eliminate the problem?

Case Study 2

A new small molecule you are to formulate contains a phenolic functional group that you know will be sensitive to oxidation. What should be done to minimize its oxidation potential in solution? What do you do if your new product shows discoloration during storage?

Case Study 3

During initial dosing of a phase I clinical study, patients experience a high incidence of thrombophlebitis after IV injection of your formulation. What can you do or suggest that will minimize or eliminate this problem?

Case Study 4

A new drug has been assigned to you that has significant water insolubility yet the clinic desires an IV dosage form. What can be done to provide a soluble IV dosage form?

Case Study 5

During initial freeze-drying experiments, you find that your protein undergoes some degradation including aggregation. What causes this during freeze-drying? What can you do to solve this problem?

Case Study 6

Your newly developed drug suspension tends to clog within a 24-gauge needle. Manufacturing also has reported some problems with filling needles not dosing properly. The product can be difficult to resuspend. How do you solve these problems?

Case Study 7

A new protein product is being developed. Marketing has requested that the product be a multi-dose product. You will be attending a project team meeting to discuss the issues with multidose formulations containing proteins. What would you share? What antimicrobial preservative choices do you have to develop a multidose parenteral solution or suspension that can be used globally?

On a separate note, discuss potential of using antimicrobial preservatives in single use injections that are aseptically processed.

Case Study 8

You are developing a new product containing a drug that must be freeze-dried. Freeze-drying will produce the amorphous form of the drug initially, but the drug will tend to crystallize over time after freeze-drying. What formulation and process approaches can you try to minimize the crystallization of the drug? What are some of the potential problems if the freeze-dried drug crystallizes over time? When is it preferable to have the drug in the crystalline form?

Case Study 9

Your product is a protein formulated with phosphate buffer (10 mM), sodium chloride (0.9%), EDTA (0.01%), and pH = 6.5. Normal storage is at refrigeration. At 3 months, visual inspection showed small (1–2 mm), gray-whitish particles at 25°C storage while no particles seen with the refrigerated vials. However, at 6 months, the refrigerated vials showed these same types of particles. What could have happened to this product? What methods would you use to support your conclusion(s) with data? What recommendations would you make to your management?

Case Study 10

You are the formulation development scientist of a protein that significantly self-associates in solution, adversely affecting in vivo bioavailability and efficacy. This protein does not have any significant chemical stability problems and does not bind to glass. What analytical techniques might be useful? What formulation approaches might inhibit aggregation?

Case Study 11

A drug product intended for IV bolus injection is formulated in aqueous solution containing a buffer, tonicity adjuster, and nonionic surface-active agent. The drug is stable to hydrolysis, but degrades by an oxidative mechanism at ambient temperature. Because of rapid loss of solubility at pH > 3 and its sensitivity to light and oxygen, the pH is adjusted to 2.5. It also loses some activity after 1 month when stored in Type I tubing glass containers. What kinds of problems would you anticipate is this drug product experiencing and what can be done to solve these problems?

Case Study 12

The manufacturer of a commercial product filled in a 1 mL glass syringe begins to receive complaints from the marketplace that the product contains particles or haze or “something

floating.” The product is a polypeptide formulated in water containing mannitol with pH adjusted in the range of 5.0 to 6.5 (no buffer). What could be the causes and possible solutions for this problem?

Case Study 13

How do you determine what kind and how much buffer component to incorporate into your final formulated product? What choices are available if preformulation API stability indicates that pH 5.5 to 6.3 is desirable? What about pH 6.8 to 7.6?

Case Study 14

An anesthetic drug is to be administered by IV bolus injection. It is very soluble at very low pH, but solubility rapidly declines at pH 3 and virtually insoluble at pH > 5. It is stable in solution to hydrolysis, but susceptible to oxidation at room temperature at pH > 3.5. The formulation consists of active, buffer, tonicity adjuster, nonionic surfactant, and WfI.

- Phase I clinical trial was conducted with a dose of 10 mg/mL active. No problems reported. A Phase Ia clinical trial was conducted using a dose of 20 mg/mL, no changes in the formulation. There was a problem. What might this have been and what was the solution?
- The filter integrity test (bubble point) after filtration was lower than the prefiltration integrity test. Why?
- For long-term stability a freeze-dried product was developed. However, reports from the market complained of a haze appearing within the walls of the vials. Production personnel also had observed and reported a film or haze upon the interior door of the lyophilizer at the completion of the cycle. The shelf temperature of the secondary drying cycle is +58°C for 11 hours at a pressure of 20 μ m. Review of the thermogram from DSC shows an exotherm at +20°C. What caused the haze and what was the solution?

ANSWERS AND SOME DISCUSSION OF CASE STUDIES

Case Study 1

What is the first thing to do? Isolate and attempt to identify the composition of the particulates. This is much easier stated than done. However, if the particle can be identified, corrective and preventative actions can much more easily be enacted.

Table 11-4 lists possible causes and potential elimination or, at least, minimization of the source of particles found in injectable solutions:

Case Study 2

It has been emphasized in this text that overcoming oxidation problems involves more than developing an optimal formulation. This problem must be attacked simultaneously:

- Evaluate packaging choices. Does the rubber closure used have an acceptable air transmission coefficient (to discuss with the rubber closure vendor)? If plastic packaging is used, what are its oxygen transmission properties? How tight is the container closure integrity? Is there a need to use better secondary packaging? Would the use of oxygen scavengers in the secondary package help?
- Eliminate all sources of oxygen exposure during manufacturing:
 - Inert gassing of water
 - Inert gas flushing of final solution and container prior to filling
 - Inert gas overlay in container prior to sealing
- Other manufacturing precautions
 - Use lowest temperatures possible in room and solution preparation
 - Protect from light
- Use as low a pH as possible
- Use of antioxidants and chelating agents
- Use excipients free from peroxide contamination, metal impurities

Table 11-4 Possible Causes and Solutions of Particles in Solution

Cause/source of particles in solution	Minimization/elimination of source of particles
Degradation product	Understand mechanism of drug degradation and use approaches to minimize such degradation
Change in pH causing particle formation	Increase buffer capacity although beware of salting out effect or potential for injection pain if pH not physiologic. Also could try a different buffer system
Low solubility of salt form	Try different salt Increase dilatation Use a co-solvent, surfactant, or a cyclodextrin
Exposure to lower temperature caused drug to irreversibly fall out of solution	Use better temperature controls and monitors
Interaction with container/closure system	Use coated rubber closure Use treated Type I glass
Extractables and leachables from any kind of product contact surface (manufacturing equipment, packaging components)	Cleaning methods Impeccable handling and proper functioning of equipment, especially fillin machines
Personnel	Proper hygiene, gowning, and aseptic practices and techniques
Complexation with formulation component	Need to do empirical studies to determine source of interaction
Impurity	Identify impurity, modify API manufacturing process
If a protein product, aggregation	Optimize formulation using surfactants Reduce sources of particles coming from contact surfaces by improving cleaning methods and adequate rinsing Minimize shear effects during processing and distribution

Case Study 3

Factors that can affect potential for phlebitis during/after injection include:

1. pH
2. Tonicity
3. Infusion rate
4. Concentration of infused drug
5. Inherent irritation properties of the drug molecule
6. Impurities in bulk drug substance
7. Precipitation at injection site due to loss of solubility
8. Extractable material from rubber closures
9. Particulate matter

The review article by Yalkowsky et al. (3) can be helpful in understanding how problems with pain and irritation upon injection can be tackled and solved.

Case Study 4

The approaches discussed in this chapter can be applied in solving this solubility problem

1. Use the optimal salt form of the API
2. Solution pH adjustment *in situ* or via modest reformulation
3. Use of co-solvent (PEG, PG, glycerin, alcohol)
4. Use of surface-active agents (polysorbate 80, Pluronic)
5. Use of complexing agents (Beta cyclodextrins)
6. Going to an alternative dosage form (emulsion, liposome, nanosuspension)

The article by Sweetana and Akers (1) can be a helpful reminder in dealing with solubility problems for drugs intended for IV administration.

Case Study 5

Freezing and drying will denature some proteins. Freezing will concentrate solutes such as salts, which will unfold some proteins. Drying may cause excessive loss of water within the structure of the protein causing distortion of the protein.

1. Use cryoprotectants (amino acids, polyols, sugars, PEG) that stabilize the native conformation of the protein by being excluded from the surface of the protein, thereby inducing "preferential hydration" of the protein.
2. Freeze as rapidly as possible in order to keep solute stabilizer in the amorphous state, for example, mannitol, glycine.
3. Use more than one cryoprotectant in order to inhibit one cryoprotectant from crystallizing

Case Study 6

1. Mill or micronize the drug. This will require sterile milling and the issue of validation of sterility assurance of the particle size reduction operation(s).
2. Modify the method(s) of drug crystallization in order to produce a smaller particle size distribution of the drug
3. Use surface-active agents to help disperse the drug
4. Develop a syringe/needle handling technique that will minimize bridging of the suspension particles in the needle.
5. Use a larger gauge needle, for example, 21-G (although impossible if infants are included in indication for use of drug product)
6. Since the suspension is likely to have some elegance problems if it is clogging needles, use silicon to coat the glass walls and a slotted stopper to minimize drug deposits.

The article by Akers et al. (4) can be helpful in dealing with suspension formulation problems.

Case Study 7

Discussion points to share with the team would include:

1. Examples of incompatibilities of proteins and preservatives
2. Lack of ideal preservative; many problems including odor, stability, solubility, purity, effectiveness, interaction with closures, and tubing
3. Problems in passing EP preservative challenge test
4. Limitations in choice of preservatives and maximum dose

1. Phenol	0.5%
2. Meta-cresol	0.3%
3. Benzyl alcohol	1.0%
4. Methylparaben	0.2%
5. Propylparaben	0.02%
6. Combinations of the above	
7. Chlorobutanol	0.5%
8. Thimerosal	0.02%
9. Benzalkonium chloride	0.01%

(for topical ophthalmics)

In general, preservatives are not to be used for single-dose products. Only a couple of marketed examples and these are older products where a preservative is in the formulation of a single dose product.

See Ref. (5) for further review.

Case Study 8

1. Use high ratios of excipient to drug to cause preferential crystallization of excipient while keeping drug in amorphous state
2. Primary drying step conducting in very cold ($< -30^{\circ}\text{C}$) temperature conditions
3. Storage of finished product in refrigerator

Crystallization over time can create problems both in solubilization of reconstituted freeze-dried product (rate and extent) and/or in solid state stability.

Crystalline form is usually preferable as long as crystalline form is in a sufficient soluble and stable. Crystalline form is usually more stable than amorphous form. Changes over storage time are less likely to occur. Crystalline mannitol preferred because amorphous mannitol will want to crystallize over time anyway and crystallization process can cause vial breakage.

Crystalline powder is usually more elegant and the collapse temperature is usually higher, thus shortening freeze-dry cycles.

Case Study 9 (6)

Potential causes include:

- protein denaturation, precipitation
- bacterial contamination
- leachates from glass vial
- silicon interactions
- impurities in packaging or raw materials

Refer to preformulation studies:

- particulates should be known via elemental analysis using SEM and energy-dispersive X-ray technology
- known routes of degradation

Use SDS-PAGE to investigate potential unfolding.

Use ICP-MS and Electron Microscopy to determine possible inorganic leachates.

Case Study 10

Summary of Analytical Techniques (7–9)

1. Measuring changes in secondary structure: Far UV CD, FTIR, Raman
2. Measuring changes in tertiary structure: Intrinsic fluorescence spectroscopy, near UV CD, near UV absorbance, Raman
3. Measuring changes in quaternary structure: SEC, light scattering, sedimentation

Measuring Aggregation:

For Aggregate Size up to 0.05 μm

1. Size-exclusion chromatography—Can be a stability-indicating assay for soluble aggregation, not for insoluble aggregation.
2. Analytical ultracentrifugation—Can measure large changes in molecular weight and can distinguish between reversible and irreversible aggregation.
3. Field flow fractionation—Characterizes both soluble and insoluble aggregation. Can be used with MALLS detector to determine molecular weight.
4. Electrophoresis (CE, gel, CE-SDS)—More useful for protein purity and quantity, especially at extremely low concentrations.
5. Light scattering (DLS, MALLS, SEC-MALLS)—Measures diameter and molecular weight of protein in solution, but cannot quantify insoluble aggregates.
6. Spectroscopy:
 - a. Absorption—If protein contains aromatic amino acids (Phe, Try, Trp). Can detect unfolding since aromatic amino acids are folded into the protein interior.
 - b. Fluorescence—Aromatic amino acids (tryptophan) also can fluoresce (excited at one wavelength; fluoresce at another). Reveals information about microenvironment generated by folding of protein.
 - c. Circular Dichroism—Measures alterations in side chain absorption due to alpha helices and β sheets. β sheets indicative of aggregation. Changes in secondary structure changes CD shape and signal intensity.

- d. IR Spectroscopy—Normal IR; also FTIR for evaluation of solid state protein structure (e.g., bulk lots)
7. Mass spectroscopy
8. Calorimetry

For Aggregate Size Greater Than 0.5 μm

1. Light obscuration
2. Turbidity
3. Microscopy
4. Visual testing

Formulation and Other Approaches

1. Surface-active agents: Polysorbates 20 and 80; Pluronics
2. Reduce ionic strength: Reduce buffer concentration
3. Co-solvents: Glycerol, ethanol (usually too high concentrations are required)
4. Reduce temperature
5. Optimize the protein structure: LysPro Insulin, an example

Case Study 11

Potential problems:	Potential solutions:
1. Peroxide impurities in surfactant	1. Work with vendor to use peroxide-free surfactant raw material
2. Leachates from rubber	2. Use coated rubber closures
3. Delamination of glass	3. Consider coated glass (e.g., Schott Plus)
4. Activity loss may be due to heavy metal contaminants	4. See if adding chelating agent helps to stabilize the drug against metal-catalyzed oxidation
5. Too much oxygen in headspace solution and/or water	5. Overlay with inert gas, purge in with inert gas; add antioxidant (Sodium metabisulfite best at low pH)

Case Study 12

The particles or haze or whatever is floating needs to be identified first. If it is nonproteinaceous, then it is likely a particle coming from the glass or rubber components of the syringe. It could also be some excess silicon that looks like a foreign particle.

If the particles are proteinaceous, then the protein is self-aggregating due to one or more of the following:

1. Air-liquid interfacial interactions: Need a surface-active agent
2. Mechanical shear during manufacturing and/or distribution and use—Need a surface-active agent, gentler handling
3. Interactions with silicon on glass—reduce silicon amount, improve the bonding and silicization process
4. pH shift might cause protein to be close to pI—need a buffer

Case Study 13

1. Must know pH-solubility and pH-stability profile and choose a target pH range that provides overall the best solubility and stability properties for the drug product.
2. Use the literature to be reminded of what buffer systems have dissociation constants (pK_a) that fall well within the desired pH range, preferably as close to the mid-point as possible. Also search the literature for what buffer systems have been approved in marketed products within the same pH region.

3. The amount of buffer component can be determined by asking the following questions:
 - a. How much does the solution pH drift in solution without a buffer?
 - b. What is the route of product administration?
 - c. What is generally known about concentration levels of preferred buffer?
 - d. What are concentrations of similar buffer components in other products?
4. Start with the lowest amount of buffer that you believe will control pH, then perform short-term accelerated stability studies to determine if concentration needs to be increased.

Case Study 14

- a. Increasing concentration without modifying ratios with stabilizing excipients could lead to stability issues, both chemical and physical. Control of pH can be affected by changing the ratio of drug to buffer and hydrophobic surface interactions can be affected by changing the ratio of drug to surfactant.
- b. Typically, the presence of a surfactant or any amphiphilic compound (e.g., proteins) will affect the surface tension property of filter surfaces.
- c. Some (perhaps many) drugs and solutes can exist both as amorphous or crystalline solids. Conversion of amorphous to crystalline solid state structure can lead to changes in rate and extent of drug solubility. Also the combination of relatively high temperature and very low pressure during secondary drying could lead to rapid crystallization and even degradation.

REFERENCES

1. Sweetana S and Akers MJ. Solubility principles and practices for parenteral drug dosage form development. *PDA J Pharm Sci Technol* 1996; 50:330–342.
2. Kumar L, Amin A, Bansal AK. Salt selection in drug development. *Pharm Tech* 2008; 32:128–146.
3. Yalkowsky SH, Krzyzaniak JF, Ward GH. Formulation-related problems associated with intravenous drug delivery. *J Pharm Sci* 1998; 87:787–796.
4. Akers MJ, Fites AL, Robison RL. Formulation Design and Development of Parenteral Suspensions, " *J Parenter Sci Technol* 1987; 41:88–96.
5. Akers MJ, Vasudevan V, Stickelmeyer M. Protein dosage form development. In Nail SL and Akers MJ, eds. *Development and Manufacture of Protein Pharmaceuticals*. New York: Kluwer Academic/Plenum, 2002:80–84.
6. Scatt C. Formulation case studies: a tutorial. *BioPharm* 2001; 14:34–35.
7. Nguyen LT, Wiencek JM, Kirsch LE. Characterization methods for the physical stability of biopharmaceuticals. *PDA J Pharm Sci Technol* 2003; 57:429–445.
8. Chan CP. Biochemical and biophysical methods currently used for therapeutic protein development. *Amer Pharma Rev* 2008; 11:48–54.
9. Cordoba-Rodriguez RV. Aggregates in MAbs and recombinant therapeutic proteins: A regulatory perspective. *BioPharm Int* 2008; 21:44–53.

EXHIBIT 4

Histamine receptors in the human nose

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Histamine receptors in the human nose

The aim of this study was to determine the role of histamine receptors in the nose. The effects of intranasal histamine challenge were compared with those of a specific H1-receptor agonist, betahistine and a specific H2-receptor agonist, impromidine, in 11 normal individuals and four with rhinitis. Sneezing, nasal irritation and hypersecretion were induced by histamine and the H1-receptor agonist, betahistine only. Nasal airway resistance (Rna) was measured by passive anterior rhinomanometry. Histamine, betahistine and impromidine all induced rises in Rna in both normal individuals and those with rhinitis but histamine had the most potent effect; the H2-receptor effect on Rna was predominant over that of the H1-receptor. The sensitivity to all three agonists was greater in the individuals with rhinitis.

Keywords *nasal mucosa histamine receptors allergic rhinitis*

The principal symptoms of allergic rhinitis — sneezing, rhinorrhoea and nasal obstruction — can be reproduced by intranasal application of histamine.^{1,2} Although histamine acts on two classes of receptors,^{3,4} it is only the H1-receptor antagonists which are widely used in the treatment of allergic nasal disease. They alleviate sneezing and hypersecretion but have little effect on nasal obstruction which is due to vascular congestion and mucosal oedema.⁵ Evidence for a role for histamine H2-receptors in the human nose is inconclusive. Clinical studies in seasonal rhinitis suggested that treatment with an H2-receptor antagonist produced some symptomatic benefit^{6,7} but pre-treatment with an oral H2-receptor antagonist did not prevent the measured rise in nasal airway resistance (Rna) induced by allergen challenge.⁸ During intranasal histamine challenge studies, topical H2-receptor antagonists had no effect on sneezing and hypersecretion in contrast to the marked inhibitory effect by an H1-receptor antagonist. Histamine-induced rises in Rna were only partly prevented by the two classes of histamine antagonists.^{9,10}

The aim of this study was to determine the function of H1- and H2-receptors in the nose by comparing the effects of intranasal challenges with histamine, betahistine, a specific H1-receptor agonist and impromidine, a specific H2-receptor agonist.

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Methods

SUBJECTS

Fifteen subjects gave informed consent to the study which was approved by the Ethical Committee of Guys Hospital. There were seven men and eight women with a mean age of 29 years (range 20–42 years). Eleven patients had no symptoms or past history of nasal disease and were non-atopic while four patients had experienced mild symptoms of rhinitis and were atopic (two or more positive skin-prick allergy tests). None was taking any medication nor had had a recent respiratory infection.

PROTOCOL

Prior to the study the subject rested in the laboratory for at least 15 min. Unilateral nasal challenges were performed with histamine, betahistine and impromidine, each given in random order and single-blind. All challenges were at similar times on separate days, using the same side of the nose.

CHALLENGE PROCEDURES

Two sets of baseline Rna measurements were taken 10 min apart. The challenge solutions were diluted in phosphate buffered saline and a dose of 0.13 ml was sprayed into one nostril, using a metred dose device (Rynacrom-M Bottle, Fisons Pharmaceuticals, Loughborough, Leicestershire).

Each challenge consisted of buffered saline as control followed by doubling concentrations of agonist until either Rna had doubled or the highest concentration had been given. The concentrations used were 0.5–32 mg/ml for histamine, 5–160 mg/ml for betahistine and 1.25–40 mg/ml for impromidine. Ipsilateral Rna measurements were made at 2 min after each dose of agonist and also at 5 min after impromidine, since these had been shown to be the times of maximum response in preliminary studies. In addition, Rna of the contralateral (non-challenged) nostril was measured at the beginning and end of each challenge.

MEASUREMENTS

The response to a challenge was assessed by (a) measurement of Rna by passive anterior rhinomanometry, (b) recording number of sneezes and occurrence of irritation and (c) subjective assessment of the volume of nasal secretion on a scale of 0 to 3. Pulse rate and blood pressure were recorded before and after each challenge and in the four atopic patients forced expiratory volume in 1 second (FEV₁), vital capacity (VC) and peak expiratory flow rate (PEFR) were also measured.

Passive anterior rhinomanometry was performed using a P.K.Morgan Nasal Airways Resistance Tester, P.K.Morgan, Chatham, Kent, UK.^{11,12} This technique determined unilateral nasal airways resistance by measurement of the pressure resulting from the passage of air at a controlled low flow rate into one side of the nose. A nasal adaptor was inserted just inside the nostril to be measured and sealed by an inflatable cuff. Air from a compressed source was passed via a flow control device to produce a smooth acceleration of flow from 0 to 0.08 l/s⁻¹, through the nasal adaptor and then through the open mouth and contralateral patent nostril while the patient held his/her breath. A small bore tube, connected to a Validyne pressure transducer, passed through the nasal adaptor to just inside the external nares to record pressure. Resistance was calculated at a reference flow rate of 0.05 l/s⁻¹. Mean unilateral Rna was calculated from six consecutive measurements.

ANALYSIS OF DATA

A dose-response curve was constructed for each challenge. Rna was plotted against the cumulative log dose of agonist. From these curves the PD values (the doses of agonists required to produce 40, 50, 75 and 100% rises of Rna above basal value) were calculated. Log PD values were used for all inter-subject comparisons. A 40% increase above basal value was chosen as the lowest point on the dose response curve for analysis because this is twice the intra-subject co-efficient of variation of Rna measurements during histamine challenge.¹³

Paired *t*-tests were used to compare baseline Rna values of

Table 1. Baseline nasal airways resistance (kPa/s⁻¹) before challenge

Agonist	Normal patients		Rhinitic patients	
	Mean	SD	Mean	SD
Histamine	0.43	0.14	0.74	0.39
Betahistine	0.37	0.08	0.55	0.13
Impromidine	0.41	0.12	0.48	0.22

all the challenges. Comparison of corresponding PD values for the three agonists were made by analysis of variance.

Results

EFFECTS OF HISTAMINE RECEPTOR AGONISTS ON Rna

There was no significant difference in mean basal Rna prior to challenge with the different agonists (Table 1). Although mean basal Rna was higher in the patients with rhinitis than in the normal group (0.59 compared with 0.40 kPa l/s⁻¹), this difference was not statistically significant ($P < 0.08$).

All three histamine receptor agonists produced dose-dependent increases in Rna in both normal and patients with rhinitis (Figures 1 and 2). In normal patients all mean PD values for histamine were lower than those for impromidine but this did not attain statistical significance. Betahistine had the least effect on Rna in normal patients and PD values were significantly different from both histamine and impromidine ($P < 0.001$) (Table 2). There was considerable variation in responsiveness to the three histamine agonists between subjects. The responses of the patients with rhinitis to the three agents were greater than those of normal patients but they exhibited a similar pattern of dose-dependent increase in Rna for each agonist. Figure 3 demonstrates the increased sensitivity of the patients with rhinitis compared with the normal subjects to the same dose of each agonist (5 μ mol).

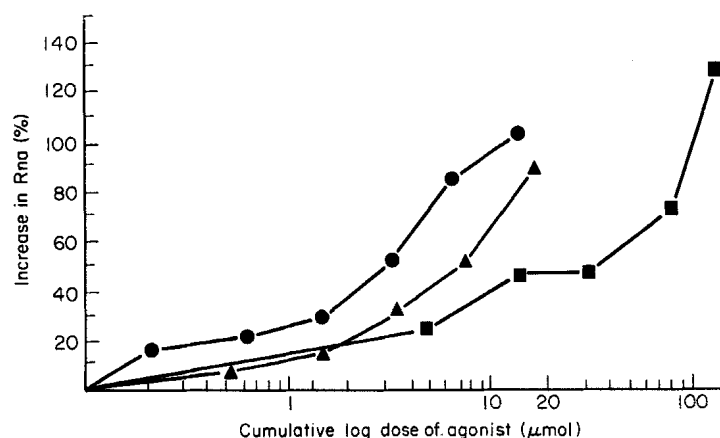


Figure 1. Mean dose response curves for ●, Histamine; ■, Betahistine; ▲, Impromidine, in 11 normal patients.

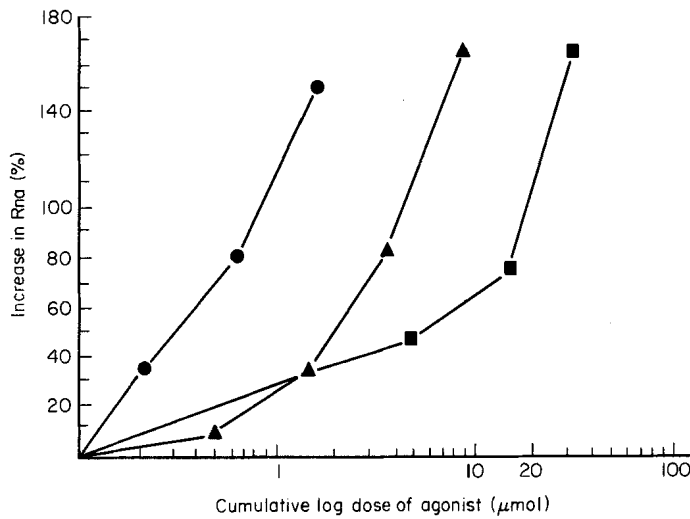


Figure 2. Mean dose response curves for ●, Histamine; ■, Betahistine and ▲, Impromidine in four rhinitic patients.

The effects of the agonists on the Rna of the non-challenged side of the nose varied from no change to 300% increase, with mean changes of 57% for histamine, 56% for impromidine and 33% for betahistine.

EFFECTS OF HISTAMINE AGONISTS ON NASAL SECRETION AND SNEEZING (TABLE 3)

Sneezing, itching and rhinorrhoea occurred only with histamine and betahistine. The onset of sneezing was

Table 2. Comparison of the doses (PD) in μmol of histamine, impromidine and betahistine which produced a rise in Rna of 40, 50, 75 and 100% in normal patients

	PD40	PD50	PD75	PD100
<i>Histamine</i>				
Mean	3.6	5.9	8.3	10.3
Min.	0.4	0.5	0.7	1.8
Max.	10.0	28.0	33.0	40.0
Median	3.2	4.9	7.6	8.3
No.	21.0	21.0	20.0	18.0
<i>Impromidine</i>				
Mean	5.7	7.3	13.3	18.0
Min.	0.9	1.3	2.4	4.8
Max.	12.5	24.0	35.0	40.0
Median	12.5	6.6	11.0	14.0
No.	21.0	20.0	17.0	12.0
<i>Betahistine</i>				
Mean	44.7	64.2	69.1	94.7
Min.	1.6	1.8	2.4	4.0
Max.	320.0	300.0	190.0	220.0
Median	23.0	33.0	58.0	82.0
No.	21.0	19.0	17.0	15.0

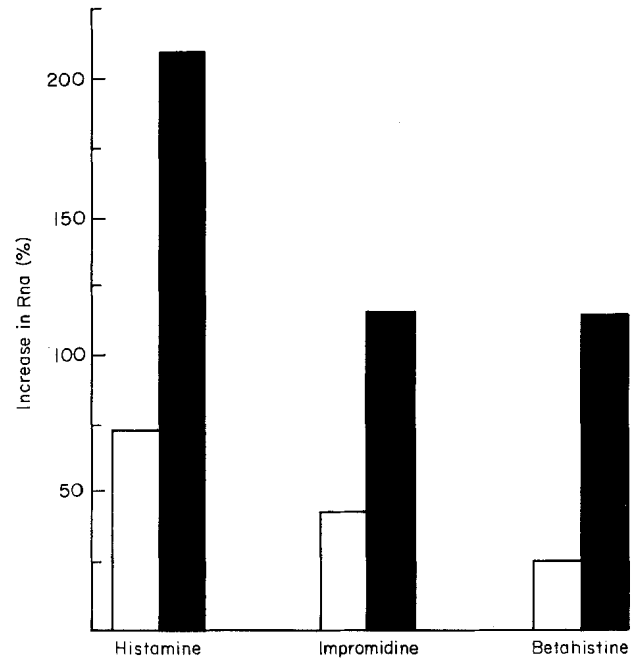


Figure 3. Mean percentage increase in Rna at a cumulative dose of 5 μmol for each agonist in 11 normal (□) and four rhinitic (■), patients.

rapid — within 1 min of application of the provoking dose. Tachyphylaxis occurred in some patients. In the impromidine challenges sneezing occurred only once, at the lowest concentration and ceased on subsequent doses. There was considerable inter-patient variation in awareness of irritation and propensity to sneeze and so counting the number of sneezes was found to be a poor quantitative index. Increase in nasal secretions followed a similar pattern to sneezing in all patients.

OTHER EFFECTS OF HISTAMINE AGONISTS

There was no change in lung function (FEV_1 , FVC, PEFR) in the atopic patients during any of the challenges. Histamine

Table 3. Effects of Histamine Agonists

	Number of patients who experienced:-	
	Sneezing/itching	Rhinorrhoea
Normal patients ($y = 11$)		
Histamine	10	8
Betahistine	7	9
Impromidine	1	0
Rhinitic patients ($y = 4$)		
Histamine	4	4
Betahistine	4	4
Impromidine	0	0

and betahistine produced no change in pulse rate or blood pressure. No patient experienced headaches although two noticed mild facial flushing after a cumulative dose of 27 μmol of histamine. At the highest concentration of betahistine some patients felt a mild intranasal stinging sensation. Impromidine produced facial flushing in 10 patients, starting 4 min after a cumulative dose of 16 or 32 μmol which lasted up to 30 min. At these doses flushing was not associated with any appreciable change either in pulse rate or in blood pressure. However, two patients who had 64 μmol of impromidine developed marked facial flushing, a rise in pulse rate of 16 to 20 beats/min and a fall in systolic blood pressure of 10 mm but with no change in diastolic pressure. There were no other systemic effects.

Discussion

Our results provide one explanation why H₁-receptor antagonists are only partially successful in the treatment of allergic rhinitis. These conventional 'antihistamines' control sneezing and nasal hypersecretion — symptoms which could be reproduced in our study by intranasal application of histamine and the H₁-receptor agonist, betahistine but not by the H₂-receptor agonist. It seems likely, therefore, that in rhinitis these symptoms are due to the released histamine acting at the H₁-receptor. In contrast, H₁-receptor antagonists alone are ineffectual against nasal obstruction. One previous study has demonstrated that topical H₁-receptor antagonists have no effect on histamine-induced rises in Rna but that the addition of a topical H₂-receptor antagonist will provide protection against this response.⁹ Histamine produces nasal obstruction mainly by dilating nasal capacitance vessels. The results from our study support the view that, while this effect is mediated by both H₁- and H₂-receptors, the effect of the H₂-receptor is predominant.

Previous studies have indicated that patients with rhinitis were more sensitive than normal patients to the effects of intranasal histamine.^{14,15} Our results confirmed this and showed that the increased sensitivity was at both H₁- and H₂-receptor sites.

The differing time-responses for the various effects of the histamine agonists suggested that different mechanisms mediated these responses. Since sneezing occurred within 1 min and tachyphylaxis was noted in some subjects, it is likely that it was mediated directly via local H₁-receptors. The effects of the histamine agonists on Rna were slower to develop. The maximum response was at 2–3 min for betahistine and at 5 min for impromidine and no tachyphylaxis developed. The possible explanation is that the control of nasal mucosa and vasculature is complex, involving axon, ganglion and central reflexes.¹⁶

To our knowledge histamine agonists have never previously been administered by the intranasal route. We were especially concerned with preventing cardiovascular

side-effects due to systemic absorption from the nasal mucosa. In order to minimize the total dose of histamine agonists we chose to perform unilateral nasal challenges, even though they are considered less physiological than bilateral challenges. The non-challenged side could not be used as a control because of the possibility that local absorption or local reflexes might have affected its resistance. Nevertheless, the overall resistance change in the non-challenged side was only about half that of the challenged side.

Conclusions

The effects of histamine on the human nose are mediated via both H₁- and H₂-receptors. The dilatation of nasal capacitance vessels responsible for the increase in nasal airways resistance is mediated via both types of histamine receptor but the effect of the H₂-receptor predominates. Sneezing irritation and possibly hypersecretion are a result of stimulation of H₁-receptors only. A combination of H₁- and H₂-receptor antagonists may be more effective in the control of the symptoms of rhinitis than an H₁-receptor antagonist alone.

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References

- OKUDA M. & MYGIND N. (1980) Pathophysiological basis for topical steroid treatment in the nose. In *Topical steroid treatment for asthma and rhinitis* Mygind N., Clark T.J.H., eds, pp. 22–25, Balliere Tindall, London
- NACLERIO R.M., MEIER H.L., ADKINSON N.F., KAGEY-SOBOTKA A., MEYERS D.A., NORMAN P.S. & LICHTENSTEIN L.M. (1983) *In vivo* demonstration of inflammatory mediator release following nasal challenge with antigen. *Eur. J. Respir. Dis. (Suppl 128)* **64**, 26–32
- BLACK J.W., DUNCAN W.A.M., DURANT C.J., GANELLIN C.R. & PARSONS M.E. (1972) Definition and antagonism of histamine H₂-receptors. *Nature* **236**, 385–390.
- GANELLIN C.R. (1980) Agonists and antagonists at histamine receptors. In *H₂-receptor antagonists in peptic ulcer disease and progress in histamine research*. Torsoli A., Lucchelli PE, Brimblecombe RW, eds, pp. 231–241, European Symposium, Capri. Excerpta Medica, Amsterdam
- DOUGLAS W.W. (1985) Histamine and 5-hydroxytryptamine (serotonin) and their antagonists. In *The pharmacological basis of therapeutics 7th edn*, Goodman L., Gilman A., eds, p. 623. Macmillan Publishing Co., New York
- CARPENTER G.B., BUNKER-SOLER A.L. & NELSON H.S. (1983) Evaluation of combined H₁- and H₂-receptor blocking agents in the treatment of seasonal allergic rhinitis. *J. Allergy Clin. Immunol* **71**, 412–417

- 7 TESTA B., MAZZEI F., MESOLELLA M., MAIONE A., TESTA D. & MESOLELLA C. (1989) Histamine-2 antagonists in allergic rhinitis. *Arch. Otolaryngol. Head Neck Surg.* **115**, 950-953
- 8 BROOKS C.D., BUTLER D. & METZLER C. (1982) Effect of H₂ blockade in the challenged allergic nose. *J. Allergy Clin. Immunol.* **70**, 373-376
- 9 SECHER C., KIRKEGAARD J., BORUM P., MAANSSON A., OSTERHAMMEL P. & MYGIND N. (1982) Significance of H₁- and H₂-receptors in the human nose: rationale for topical use of combined antihistamine preparations. *J. Allergy Clin. Immunol.* **70**, 211-218
- 10 MYGIND N., SECHER C. & KIRKEGAARD J. (1983) Role of histamine and antihistamines in the nose. *Eur. J. Respir. Dis. (Suppl 128)* **64**, 16-20
- 11 ROTH R.P., CANTEKIN E.I., BLUESTONE C.D., WELCH R.M. & CHO Y.W. (1977) Nasal decongestant activity of pseudoephedrine. *Ann. Otol. Rhinol. Laryngol.* **86**, 235-242
- 12 BRITTON M.G., EMPEY D.E., JOHN G.C., McDONNELL K.A. & HUGHES D.T.D. (1978) Histamine challenge and anterior nasal rhinomanometry: their use in the assessment of pseudoephedrine and triprolidine as nasal decongestants in subjects with hayfever. *Br. J. Clin. Pharmacol.* **6**, 51-58
- 13 SHELTON D.M., FARQUHARSON M., LOSEWICZ S., YOULTEN L., PARRY D. & EISER N.M. (1986) Reproducibility of nasal airways resistance response to intranasal histamine challenge in normal subjects. *Bull. Europ. Physiopath. Resp.* **22 (S8)**, 173
- 14 BORUM P., GRONBORG H., BROFELDT S. & MYGIND N. (1983) Nasal reactivity in rhinitis. *Eur. J. Respir. Dis.* **64 (Suppl 128)**, 65-71
- 15 CORRADO O.J., GOULD C.A.L., KASSAB J.Y. & DAVIES R.J. (1986) Nasal response of rhinitic and non-rhinitic subjects to histamine and methacholine: a comparative study. *Thorax* **41**, 863-868
- 16 WIDDICOMBE J.G. (1986) The physiology of the nose. *Clin. Chest Med.* **7**, 159-170