IN THE UNITED STATES DISTRICT COURT
FOR THE SOUTHERN DISTRICT OF FLORIDA

UCB, INC. and UCB BIOPHARMA SPRL, Plaintiffs, v. APOTEX INC., Defendant.	C.A. No. 18-CV-60846 **RESTRICTED CONFIDENTIAL INFORMATION – SUBJECT TO PROTECTIVE ORDER**

OPENING EXPERT REPORT OF SARFARAZ K. NIAZI, PH.D.

CONTENTS

I, Sarfaraz K. Niazi, submit this report on behalf of Plaintiffs UCB, Inc. and UCB Biopharma, Sprl (collectively, "Plaintiffs") in this action. This report sets forth opinions related to unexpected and surprising properties of the claimed inventions of the '194 patent.

I. INTRODUCTION

A. Qualifications

1. I am currently Adjunct Professor of Biopharmaceutical Sciences at the University of Illinois, College of Pharmacy. I am also Visiting Professor at the University of Houston College of Pharmacy.

2. In addition to my academic positions, I am also the founder and Executive Chairman of Pharmaceutical Scientist, LLC—a pharmaceutical and biological products consulting company that is also assisting in the development of biosimilar products. In 2003, I also founded what is now known as Adello Biologics, LLC and served as Executive Chairman until 2017. I no longer have any equity interest in Adello. Additionally, I served as Director Technical Affairs for Abbott International from 1988-1995.

3. My formulation experience dates back to my teaching tenure at the University of Illinois when I taught formulation sciences and supervised dozens of graduate theses, several of which comprised creating new formulations and methods of testing and evaluation. At Abbott International, I was the first to suggest and initiate a generic line of pharmaceutical formulations that resulted in several formulations including topical analgesics, and over 10 other narrow therapeutic index drugs. I formulated, evaluated in humans, and created regulatory dossiers. Additionally, in my consulting capacity, I have assisted major pharmaceutical companies in developing complex generic dosage forms and in April I am invited by the FDA to teach the science of formulation of complex generics. I have also developed several biologic drug

formulations including PEGylation products, and sustained delivery of proteins. I own dozens of United States patents on topical formulations, combination formulations, drug delivery modalities, and new chemical entities.

4. I received my B.Sc. in Chemistry from Karachi University, Pakistan in 1966. In 1969, I received my B. Pharm, also from Karachi University. I then received my M.S. in Pharmaceutical Sciences from Washington State University in 1970, followed by my Ph.D. in Pharmaceutical Sciences from the University of Illinois in 1974.

5. I am the sole author of 74 books, including the series "Handbook of Pharmaceutical Manufacturing Formulations." This series teaches the principals of pharmaceutical formulations and manufacturing and is broken into six categories: Over the Counter Products; Semisolid Products; Liquid Products; Uncompressed Solids; Compressed Solids; and Sterile Products. In addition, I have also authored key handbooks on preformulation and bioequivalence testing. I am the author of over 100 research articles and have been invited to hundreds of speaking engagements worldwide. I am also a named inventor on over 80 patents. I have been a licensed patent agent with the United States Patent and Trademark Office since 2002.

6. A copy of my curriculum vitae, which contains more detail on my educational background and professional career, is attached as Exhibit A.

B. Compensation

7. I am being compensated for my work in this case at my usual rate of $500 per hour. My per diem rate is $4,000.

C. Cases in the Past Four Years

8. During the past four years I have testified in 2016 in a case involving formulation of products with oxygenation (*Cadence Pharmaceuticals Inc., et al v. InnoPharma Licensing LLC et al,* 14-cv-01225 (D. Del.).

D. Materials Relied Upon

9. A list of the materials that I have considered in forming my opinions is attached as **Exhibit B**. In addition to the materials listed in my Exhibit B, I have also relied on my education, training, general knowledge, and experience.

10. The opinions that I express in this report are based on the information and evidence currently available to me. I understand from counsel that I may be asked to revise or supplement my opinions as additional information becomes available. I further understand from counsel that I may be asked to respond to any assertions or additional arguments that Apotex or its experts raise during the course of this litigation.

11. If called at trial, I expect to explain the opinions and analyses described in this report. I have not yet prepared any demonstratives for use at trial to support my testimony, but may do so should I be called to testify. Further, I may provide background testimony or a tutorial at trial regarding pharmaceutical formulating.

II. LEGAL STANDARDS

12. I have been retained by Plaintiffs as an expert witness in the above-captioned matter. I understand that Apotex Inc. ("Apotex") has filed an Abbreviated New Drug Application ("Apotex's ANDA") seeking FDA approval to sell a generic version of Xyzal Allergy 24HR®, which contains levocetirizine as its drug substance. I understand that Plaintiffs have brought this litigation against Apotex in response to Apotex's filing of its ANDA.

13. I understand that this litigation involves U.S. Patent No. 8,633,194 (the "'194 patent").

14. I understand that the earliest priority date to which the '194 patent is entitled is July 14, 2004, and that Apotex has not challenged whether the '194 patent is entitled to this priority date. Therefore, I have used this date as the relevant date for assessing what was known in the field at the time of the invention.

15. I understand that Apotex alleges that the asserted claims of the '194 patent are invalid because the inventions claimed therein would have been obvious to a person of ordinary skill in the art. I understand that an obviousness analysis requires an assessment of (1) the level of ordinary skill in the art; (2) scope and content of the prior art; (3) differences between the prior art and the claimed invention; and (4) objective indicia of nonobviousness.

16. I understand that Apotex bears the burden of proving invalidity in this litigation, including obviousness, and that Apotex may submit a report from one or more experts to support Apotex's views on those issues; in particular, items (1)-(3) in the paragraph above. I have been informed by counsel that I may be asked to consider any expert report submitted on behalf of Apotex and to potentially submit a report in response.

17. For purposes of this report, I have been asked by counsel to focus on item (4) in the paragraph above, objective indicia of nonobviousness. In particular, I have been asked to focus on the unexpected or surprising properties, or the unexpected benefits, of a claimed invention, which I understand may be objective indicia of nonobviousness relevant to the obviousness analysis. Specifically, I understand that if an experiment demonstrates an unexpected or surprising result, then the result would likely not be obvious to a person of ordinary skill in the art. I further

understand that if a claimed invention exhibits a surprising or unexpected result in comparison to the closest comparators in the prior art, that such a result may demonstrate nonobviousness.

18. As further context for my opinions, I understand that in considering obviousness, what the prior art teaches and, in particular, if the prior art teaches away from the claimed invention, then a person of ordinary skill would be discouraged from following the path of the claimed invention or would otherwise be led in a divergent direction. Further, I understand that the level of predictability or complexity in a field, or any serendipity in arriving at the claimed invention, may be relevant to the nonobviousness of an invention.

III. PERSON OF ORDINARY SKILL IN THE ART

19. My understanding is that the term "person of ordinary skill in the art" (POSA) refers to a typical scientist or researcher having average skill in the technical field to which the patented inventions relate. It is my view that a person having ordinary skill in the art to which the '194 patent relates would have a Ph.D. or equivalent degree in Pharmaceutical Sciences, Industrial Pharmaceutics, or a related field and have at least three years of experience working with liquid, particularly aqueous, pharmaceutical formulations. Alternatively, the individual would be a highly skilled scientist lacking a Ph.D. or equivalent degree, but would have more than five years of experience working with liquid, particularly aqueous, pharmaceutical formulations.

20. Further, it is my opinion that a person of ordinary skill in the art would be part of a team comprising persons of ordinary skill in the art that are physicians with experience in the treatment of allergies. Such a physician would have an M.D. or a D.O., at least three years of experience in the treatment of allergies, including any residency, and be Board Certified in an area applicable to the treatment of allergies.

IV. SUMMARY OF OPINIONS

21. I have been asked by Plaintiffs to assess the scope and content of the prior art and opine on whether the claimed invention of the '194 patent exhibits any unexpected or surprising properties. It is my opinion that nothing in the prior art taught or predicted that levocetirizine would have antimicrobial properties. In fact, as of the priority date, publications regarding predicting antibacterial properties had classified cetirizine—the racemic mixture of levocetirizine and its dextrorotary enantiomer—as a compound that lacked antimicrobial effects, although this was later disproven. Thus, the discovery of levocetirizine's antimicrobial effects was unexpected and surprising.

22. It is also my opinion that nothing in the prior art would have taught a person of ordinary skill that they could use the low amount of parabens present in the liquid pharmaceutical composition claimed in the '194 patent and obtain a formulation that is substantially free of bacteria. On the contrary, the prior art taught the importance of using significantly higher amounts of parabens in liquid, and particularly aqueous, pharmaceutical formulations due to their high risk of bacterial contamination. Thus, it was surprising and unexpected that the inventors of the '194 patent were able to obtain an aqueous pharmaceutical formulation with substantially lower amounts of paraben yet substantially free of bacteria.

23. I am prepared to testify, if asked, on the '194 patent and how a pharmaceutical formulator would interpret the information claimed in the patent. I am also prepared to testify as to how a pharmaceutical formulator would develop formulations as of the '194 patent's priority date. Finally, I have considered the claims of the '194 patent and, in my opinion, Xyzal Allergy 24HR® and Xyzal®, are both embodiments of the claims.

V. BACKGROUND

24. Below I have provided a general discussion of background information that is applicable to my opinions. As I understand that I may be asked to prepare a second, rebuttal, report, I may provide additional background information there that is relevant to any additional opinions I may offer.

A. General Principles of Formulation

25. Below, I have provided a brief background on the principles of formulation. While I have tried to present this background in a concise, clear fashion, the exercise of formulation is rarely as routine or linear as I have presented it, and is instead generally riddled with trial-and-error. *See, e.g.,* I. Rácz, *Drug Formulation* at Ch. 3.1 (1989). Further, the considerations described below co-depend on each other and must be balanced as, for example, a modification in excipients can have significant effects on a formulation. *See, e.g.,* I. Rácz, *Drug Formulation* at Ch. 3.3 (1989).

26. One of the first things a POSA must consider is the active pharmaceutical ingredient (API) or drug substance itself. In particular, the POSA must consider the properties of the API that commonly affect formulation, including its physical and chemical stability, taste, and appearance. *See, e.g.,* I. Rácz, *Drug Formulation* at Ch. 1.1, Ch. 1.1.1.1, Ch. 1.2 (1989). All of these factors may affect development of the ultimate drug product and are routinely considered by formulators at the outset of formulation work. *See id*.

27. As the ’194 patent focuses on the use of preservatives to combat microbial and fungal growth, I note here, and describe further below at §V.B, that the API’s own ability to act as a preservative is generally not considered because it is uncommon that the API possesses such properties.

28. The POSA must also consider the route of administration. *See id*. at Ch. 1.1.1. Routes of administration include, among others, injection (*e.g.*, subcutaneous, intravenous, intradermal, parenteral, or intramuscular), inhalation, ophthalmic, oral, rectal, topical, and vaginal. *See id*. Each route of administration presents different formulation challenges particular to that route. *See id*. For example, a single-use intravenous injection faces much different challenges than a topical gel.

29. As the '194 patent focuses on the use of preservatives to combat microbial and fungal growth, it is worth nothing that certain routes of administration may require that the product be prepared in a "clean" environment (*e.g.*, certain injectables) to avoid microbial and fungal growth, or the POSA should anticipate that the product will be directly exposed to substantial amounts of external contaminants during normal patient use (*e.g.*, oral liquid solutions used in a multi-use formulation). Each different route of administration may present different challenges with respect to microbial and fungal growth.

30. The POSA must also consider the type of preparation to use for that route, such as whether to use a solid, liquid, suspension, emulsion, coacervate, or gel form. Again, the type of preparation presents vastly different challenges including, chemical interactions that may inactivate a preservative, binding of preservatives to inactive and active components, unbalanced biphasic distribution in emulsions, precipitation of solutes at different storage conditions, and risk of contamination based on the length for which a packaged product is used. For example, many non-ionic surfactors are known to inactivate preservatives. *See* W. P. Evans, *The solubilization and inactivation of preservatives by non-ionic detergents*, 16 Journal of Pharmacy and Pharmacology 323 (1964).

31. Again, as the '194 patent focuses on the use of preservatives to combat microbial and fungal growth, I note that the need for preservatives in different types of preparations vary widely. For example, oral tablets, as a solid form, are not nearly as susceptible to bacterial growth as an oral solution, especially aqueous oral solutions where water is present. *See, e.g.,* The European Agency for the Evaluation of Medicinal Products, Evaluation of Medicines for Human Use, *Draft Note for Guidance on Excipients, Antioxidants and Antimicrobial Preservatives in the Dossier for Application for Marketing Authorisation of a Medicinal Product*, at 8 (2003), available at https://www.ema.europa.eu/en/documents/scientific-guideline/draft-note-guidance-excipients-antioxidants-antimicrobial-preservatives-dossier-application_en.pdf (last accessed Mar. 21, 2019).

32. As the claims of the '194 patent focus on "a liquid pharmaceutical composition," (*see* claim 1), I will focus the rest of my background discussion on liquid pharmaceutical compositions. Assuming that a POSA has chosen to develop a liquid pharmaceutical composition, they still face numerous challenges, as he or she must balance a number of factors such as solubility, viscosity, taste, microbial growth, appearance, chemical stability, physical stability, packaging (*e.g.*, single-use v. multi-use formulations), and manufacturability of the formulation itself. *See, e.g.,* I. Rácz, *Drug Formulation* at Ch. 4.5 (1989). While many of these factors are the same types of factors that must be considered in the context of the API by itself, it is important to consider these factors in the context of the overall drug product, which includes the API and all other ingredients/excipients, as well.

33. As the '194 patent focuses on the use of preservatives to combat microbial and fungal growth, it is important for the POSA to consider that liquid pharmaceutical compositions are particularly susceptible to microbial and fungal growth. *See Draft Note for Guidance on*

Excipients, Antioxidants and Antimicrobial Preservatives in the Dossier for Application for Marketing Authorisation of a Medicinal Product, at 8. In particular, aqueous products (*i.e.*, products with water present) are particularly susceptible to microbial and fungal growth because water itself is a source of microbes and potential contamination. Thus, when working with liquid, and particularly, aqueous products, the POSA expects that the formulation will be exposed to substantial amounts of bacteria.

34. With these considerations in mind, a POSA has a number of options to control microbial and fungal growth in liquid pharmaceutical products. For example, a formulator may choose to pursue any of the below options:

- A single-use product may be chosen because multi-use products are more susceptible to microbial and fungal growth because the patient exposes the product to the environment where contamination may occur;
- Sugars and other excipients not typically classified as "preservatives" may have an antimicrobial and/or antifungal effect and therefore may be used as a substitute or compliment to ingredients typically classified as "preservatives";
- Within the field of "preservatives," the POSA may choose between a wide range of classes of preservatives, and preservatives within those classes; and
- A POSA working with preservatives may choose to combine different preservatives or classes of preservatives and has discretion over the amount of preservatives to use. The quantity or concentration of preservatives is inevitably linked to the risk of contamination that is proportional to the length of time a product will be used. For example, a drug product containing a large amount of API (e.g., 500 ml) may require more preservative in concentration than a single-dose packaging.

See, e.g., Dániel Nemes, *Interaction between Different Pharmaceutical Excipients in Liquid Dosage Forms—Assessment of Cytotoxicity and Antimicrobial Activity*, 23 Molecules 1827, 1827 (2018); Hang Guo and Chris Knutsen, *Preservative Formulation and Effectiveness in Oral Solutions and Suspensions*, PDA Metro Meeting at 5 (Feb. 15, 2011).

35. Given that preservatives have been used for decades in pharmaceutical products and for centuries in other types of products, there is a large volume of data regarding the usage of

preservatives that predates the '194 patent, and a POSA would be comfortable with the general use of preservatives in such formulations. *See, e.g.,* Graham W. Gould, *Preservation: past, present and future*, 56 Br. Med. Bull. 84-96 (2000); Sally L. Buck, et al., *Methods used to evaluate the effectiveness of contact lens care solutions and other compounds against Acanthamoeba: a review of the literature*, 26 CLAO J. 72-84 (2000); S. Brul and P. Coote, *Preservative agents in foods. Mode of action and microbial resistance mechanisms*, 50 (Int. J. Food. Microbiol. 1-2 (1999); Graham W. Gould, *Methods for preservation and extension of shelf life*, 33 Int. J. Food Microbiol. 51-614 (1996); S.J. Lehner, et al., *Effect of hydroxypropyl-beta-cyclodextrin on the antimicrobial action of preservatives*, 46 J. Pharm. Pharmacol.,186-91 (1994); M. R. W. Brown and R. M. E. Richards, *Effect of Polysorbate (Tween) 80 on the Resistance of Pseudomonas Aeruginosa to Chemical Inactivation*, 16 J. Pharm. Pharmacol. Suppl. 51-5T (1964); W. P. Evans, *The Solubilisation and Inactivation of Preservatives by Non-Ionic Detergents*, 16 J. Pharm. Pharmacol. 323-31 (1964).

36. A POSA would also consider formulations that have been successful in the past, and use these successful formulations as reference or comparison points. These reference points may be identified through the publication of data that shows inhibition of microbial and fungal growth in particular formulations, or by the fact that a formulation was approved by regulatory authorities such as the U.S. FDA or European EMEA. A POSA would place little weight in formulations that have been suggested by others, but where there is no testing presented or indication that a regulatory authority considered and approved the formulation.

B. Active Pharmaceutical Ingredients Are Not Expected to Possess Preservative or Antimicrobial Properties

37. Except in the situation where a POSA is working with an API intended to be antimicrobial or antifungal – for example, an antibiotic like penicillin – a POSA would not expect

the API itself to have antimicrobial or antifungal properties. In fact, while as noted above, the POSA must consider the properties of the API in designing a formulation, it is not typical or routine for a POSA, or anyone involved with the formulation, to test whether the API itself is antimicrobial or has antifungal properties.

38. Further, APIs are often selected for pharmaceutical development because they do not interact with other substances in the body, which therefore minimizes the risk of side effects or drug-drug interactions. *See, e.g.,* I. Rácz, *Drug Formulation* at Ch. 3.1 (1989). Consequently, in the abstract, a POSA would actually expect that the API *does not* have an antimicrobial or antifungal effect because they would expect that the API was selected for development precisely because it only acts on the particular target in the body of interest.

39. In fact, in 2011, years after the discovery of levocetrizine's antimicrobial effect in the early 2000s (*see infra,* §V.II.B), researchers conducted a study on the antimicrobial effects of antihistamines because, as they described:

> The use of antihistaminics in the drug regimen for patients who acquire microbial infection is inevitable and that gave rise to the need to assess the antimicrobial activity of antihistaminics. ***Few studies were previously carried out to demonstrate the antimicrobial activity of a number of antihistaminics*** which belonged mainly to the first generation especially the ethanolamine and phenothiazine antihistaminics; however, ***the published results are rather controversial***.

Moustafa A. El-Nakeeb, et al., *In vitro Antibacterial Activity of Some Antihistamines Belonging to Different Groups Against Multi-Drug Resistant Clinical Isolates*, 42 Braz. J. Microbiol. 980-991 (2011) at 980. The researchers then elaborated on the controversial prior results, by explaining that prior research teams had published data showing varying minimum inhibitory concentrations ("MICs")[1] for the same antihistamines, and varying results even within a given study. *Id.* The

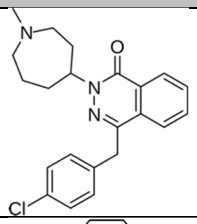
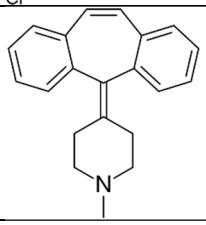
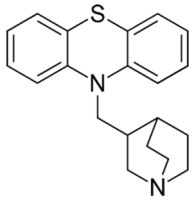
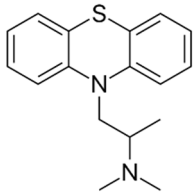
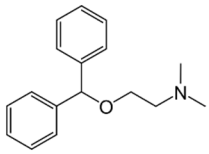
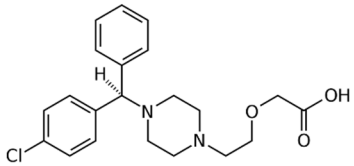
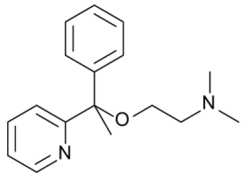
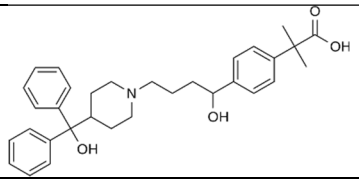
[1] MIC is the number that is the "lowest concentration of an antimicrobial that will inhibit the visible growth of a microorganism after overnight incubation." Jennifer M. Andrews, *Determination of minimum inhibitory*

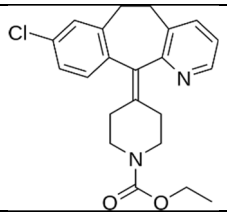
researchers also noted that prior studies predominantly focused on first-generation antihistamines, and that second- or third- generation antihistamines, such as levocetirizine, had "almost received no attention from the microbiological point of view." *Id*. Thus, there was still a need, ***seven years after the priority date***, to assess whether antihistamines, particularly second- and third-generation antihistamines like levocetirizine, possess antimicrobial properties. *Id.*

40. The El-Nakeeb publication also shows that there is no apparent correlation between antihistaminic and antibacterial properties. For example, the antihistamines azelastine, cyproheptadine, mequitazine, and promethazine were found to be active antibacterials, while diphenhydramine and cetirizine possessed weaker activity, and doxylamine, fexofenadine and loratadine were inactive even at the highest tested concentration (1 mg/ml). *Id.* at 983, Table 1.

41. Moreover, as shown in the table below, there is no apparent chemical structural feature common to those antihistamines that possess antibacterial properties; therefore, one cannot predict from the chemical structure alone that an API would have antibacterial properties.

concentrations, 48 J. Antimicrobial Chemotherapy Suppl. S1 5, 5 (2001). MICs are considered the "gold standard" for determining effectiveness of a preservative against a microorganism. *See id*.

Compound	Chemical Structure	Chemical Class	Antimicrobial Activity
Azelastine		Phthalazine derivative	High activity
Cyproheptadine		Tricyclic benzocycloheptene	High activity
Mequitazine		Phenothiazine	High activity
Promethazine		Phenothiazine	High activity
Diphenhydramine		Diphenylmethane	Low activity
Cetirizine		Piperazinyl derivative	Low activity
Doxylamine		Ethanolamine	No activity
Fenofexidine		Benzeneacetic acid	No activity

Loratidine		Benzocycloheptene	No activity

42. The researchers attempted to find a structural correlation because they noted, "[t]he variation in the magnitude of antibacterial effects among different antihistaminics is however difficult to explain since screening the literature revealed that no extensive studies were published on the antibacterial activity of the different classes of antihistaminics." *Id.* at 985. In other words, the authors concluded, prior to their 2011 publication, there had been no extensive study of structural correlations between antihistaminic and antibacterial properties.

43. Ultimately, the researchers concluded that the best predictor they could determine of antibacterial activity in antihistamines is activity at the bacterial cell surface. *Id.* However, this is a biological feature that cannot be readily determined without testing. While certain chemical structures may be more readily associated with surface activity, as the authors note, biological testing must occur before it could be determined that a chemical compound has such surface activity. This conclusion, ***from seven years after the priority date***, reinforces that it was unpredictable in 2004 whether a particular antihistamine, such as levocetirizine, would have antibacterial properties.

C. The Mechanisms of Actions of Antimicrobials Are Not Well Understood

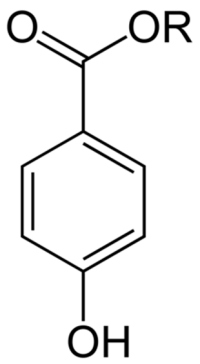
44. A person of ordinary skill would additionally not expect a particular chemical compound to possess antimicrobial activity because the mechanisms of action underlying antimicrobial activity are not well-understood.

45. As an example, the antibacterial mode of action for the class of preservatives known as "parabens," which are discussed in the '194 patent and used in Xyzal®, is not well understood.

There are a number of prevailing views, including that parabens act by disrupting membrane transport processes, or by inhibiting synthesis of DNA or RNA of various key enzymes, such as ATPases and phosphotransferases. *See* Ernst Freese, et al., *Function of lipophilic acids as antimicrobial food additives*, 241 Nature 321-5 (1973); Ingolf F. Nes and Trygve Eklund, *The effect of parabens on DNA, RNA and protein synthesis in Escheria coli and Bacillus subtilis*, 54 The Journal of Applied Bacteriology 237-42 (1983); Y. Ma and R. E. Marquis, *Irreversible paraben inhibition of glycolysis by Streptococcus mutans GS-5*, 23 Letters in Applies Microbiology 329-33 (1996); Nelly Valkova,, et al., *Hydrolysis of 4-Hydroxybenzoic Acid Esters (Parabens) and Their Aerobic Transformation into Phenol by the Resistant Enterobacter cloacae Strain EM*, 67 Applied and Environmental Microbiology 2404-09 (2001).

46. Further, certain paraben types are more active than other types, and it is speculated that stronger antibacterial action may be associated with greater solubility in the bacterial membrane, which may allow the paraben to reach cytoplasmic targets in greater concentrations. *See* John J. O'Neill and Catherine A. Mead, *The parabens: Bacterial adaptation and preservative* capacity, 33 J. Soc. Cosmet. Chem 75-84 (1982). However, since a majority of the studies on the mechanism of action of parabens suggest that their antibacterial action is linked to the membrane, it is possible that its greater lipid solubility disrupts the lipid bilayer, thereby interfering with bacterial membrane transport processes and perhaps causing the leakage of intracellular constituents. *See Function of lipophilic acids as antimicrobial food additives*; *The effect of parabens on DNA, RNA and protein synthesis in Escheria coli and Bacillus subtilis*; *Irreversible paraben inhibition of glycolysis by Streptococcus mutans GS-5*; *Hydrolysis of 4-Hydroxybenzoic Acid Esters (Parabens) and Their Aerobic Transformation into Phenol by the Resistant Enterobacter cloacae Strain EM*.

47. All of this uncertainty comes despite the fact that parabens have an extremely simple chemical structure, as depicted below. In the below image, the R is replaced with an appropriate chemical substituent: -CH3 for methyl, and -CH2CH2CH3 for propyl paraben



D. Levocetirizine

48. Levocetirizine is the levorotary or R-enantiomer of cetirizine, the chemical compound depicted in the above table in paragraph 41. *See* James H. Day, Anne K. Ellis, Elizabeth Rafeiro, *Levocetirizine: a new selective H1 receptor antagonist for use in allergic disorders*, 40 Drugs Today 415, 415 (2004). Levocetirizine is derived from the chemical compound cetirizine and is typically characterized as either a second or third-generation H_1 antihistamine.

49. As of the priority date, there was minimal public information available regarding levocetirizine, and I am aware of no public reference that described, or predicted, that levocetirizine, or its related compound cetirizine, would have antimicrobial properties. In making this statement, I have considered Apotex's interrogatory responses and the documents cited, including its petition for *inter partes* review and the associated expert declaration of Dr. Paul Laskar. I have reviewed these documents and the prior art cited therein, and I am aware of no prior art disclosure that would teach a person of ordinary skill in the art that levocetirizine has antimicrobial properties. Additionally, none of these prior art references teach that using the lower

amount of parabens claimed by the '194 patent would result in an aqueous pharmaceutical formulation that would remain substantially free of bacteria.

50. In fact, as of the priority date, researchers investigating whether antibacterial activity could be predicted had classified cetirizine as a compound that lacked antibacterial properties. *See* Mark. T. D. Cronin, *et al*., *Structure-Based Classification of Antimicrobial Activity*, 42 J. Chem. Inf. Comput. Sci. 869, 871 (2002); Miguel Murcia-Soler, *et al*., *Discrimination and selection of new potential antibacterial compounds using simple topological descriptors*, 21 J. Mol. Graphics and Modelling 375, 382 (2003). While this conclusion was later disproven, even just two years ago, ***over a decade after the priority date***, researchers were still conducting extensive studies into the antimicrobial activity of cetirizine. H. S. Maji, et al., *An Exploratory Study of the Antimicrobial Activity of Cetirizine Dihydrochloride*, Indian J. Pharm. Sci., 79(5):751-757 (2017). In sum, it is clear that even for the earlier-known racemate, cetirizine, its antibacterial activity was not recognized as of the priority date, and was debated even well after that date.

VI. THE '194 PATENT AND ITS PROSECUTION

51. I have reviewed the '194 patent, and understand Plaintiffs assert Claims 1-11 against Apotex (the "Asserted Claims"). The language of those claims is provided in the table below in §VII.A.

52. The specification of the '194 patent explains that the surprising self-preservative effect of levocetirizine was the source of the invention, which is a formulation that was unexpectedly able to be prepared with less amounts of parabens than is typical. For example, the specification states:

- It has now ***surprisingly been found*** that the active substances belonging to the family of substituted benzhydryl piperazines ***possess a preservative effect in aqueous solutions***. (Col. 1, ll. 51-54 (emphasis added)).

- The ***purpose of the invention concerns a liquid pharmaceutical composition containing an active substance*** belonging to the family of substituted benzhydryl piperazines chosen among cetirizine, levocetirizine and efletirizine, ***and a reduced amount of preservatives***. (Col. 1, ll. 55-59 (emphasis added)).

- ***The present invention is based on the unexpected recognition*** that a pharmaceutical composition comprising an active substance belonging to the family of substituted benzhydryl piperazines and ***a reduced amount of preservatives is stable during a long period of time. Stability means the capacity to resists to [sic] microbial contamination***. (Col. 1, ll. 60-65 (emphasis added)).

53. The patent provides data to support these conclusions. Example 2, and Tables 4-6 cited therein, demonstrate that in studies across three bacterial and two fungal species, levocetirizine possesses a preservative effect. Col. 6, l. 40- col. 7, l. 35. In particular, Table 4 shows that the levocetirizine oral solution formulation has no parabens or sorbitol, two known preservatives. Col. 6, ll. 40-58. As Example 3 concludes, this formulation resulted in the "rapid disappearance" of the three bacterial species, and my review of the data in Table 5 shows that the formulation also inhibited the growth of the two antifungal species. Col. 7, ll. 1-35.

54. Example 4, and Tables 15-20 cited therein, shows the results of testing various amounts of parabens on formulations containing levocetirizine. Col. 9, l. 37 – 11, l. 9. The inventors took the formulation of Table 4, discussed above, and added various paraben mixtures. *Id.* These data demonstrate that even formulations with as little as 0.375 mg/ml total parabens successfully inhibited bacterial and fungal growth, as Example 4 concludes. *Id.*

55. I have also reviewed the prosecution history of the '194 patent, including a declaration submitted by one of the inventors to the patent office in response to an obviousness rejection. *See* UCB_AP00000677-704. More specifically, the inventor, Domenico Fanara,

explained how it was surprising and unexpected that the inventors had been able to invent a formulation of levocetirizine containing only 0.75 mg/ml total amount of parabens yet remains substantially free of bacteria. *See id*. at UCB_AP00000678-79.

56. Mr. Fanara explained how, at the time of the invention, it was typical for pharmaceutical preparations to contain at least 2 mg/ml of combined parabens. *See id*. To support this explanation, Mr. Fanara included excerpts of *Remington's*, a treatise commonly used by formulators, which shows that the "typical usage level (%w/w)" of methylparabens is 0.1-0.25% and of propylparabens is 0.1-0.25%. *See id*. at UCB_AP00000693-94. When the two paraben types are added together, the typical usage level, as Mr. Fanara noted, is above 0.2%, or 2 mg/ml.

57. Mr. Fanara explained how the tables in the patent application and additional data submitted with the declaration showed how levocetirizine had an antimicrobial effect. *See id*. at UCB_AP00000678-79, -702-704. First, Mr. Fanara explained how the data presented in Tables 5 and 6 of what would issue as the '194 patent demonstrates levocetirizine's antimicrobial effect and how this property was unexpected. *Id*. at UCB_AP0000678. Next, Mr. Fanara submitted, and explained, Exhibits C and D to his declaration which provide a detailed summary of efficacy of antimicrobial preservation testing. *Id*. at UCB_AP0000678-79. The exhibits explain that testing was conducted pursuant to the European Pharmacopeia 5.1, which provides detailed test procedures to test whether bacterial contamination occurs in a formulation and with which I am familiar. *Id*. at UCB_AP0000695-703. [redacted]

58. Upon review of Mr. Fanara's declaration, the Examiner initiated an interview and agreed that "compositions containing levocetirizine and MP/PP with ratio of 9/1 and total

concentration of 0.675 mg/ml and 0.375 hav[ing] antimicrobial effects" was surprising and unexpected. *See* UCB_AP00000712-713 at -713. The Examiner explained that in order for the claims to be allowed, the upper limit of parabens would need to be adjusted to 0.75 mg/ml. *Id*. After agreeing to this amendment, the patent application was allowed. *See id*. at UCB_AP00000724-731.

VII. OPINIONS

A. Xyzal® and Xyzal Allergy 24HR® are Embodiments of Claims 1-11 of the '194 Patent

59. I have reviewed the '194 patent and its claims, and I have reviewed documents that describe the formulation of Xyzal® and Xyzal Allergy 24HR®. In my opinion, Xyzal® and Xyzal Allergy 24HR® are embodiments of Claims 1-11 of the '194 patent, as shown below.

60. [redacted]

[redacted]

[redacted]

61. [redacted]

62. [redacted]

63. [redacted]

[redacted]

	The Xyzal® formulations are FDA-approved for sale in the United States and, for at least this reason, are "substantially free of bacteria," as the claim requires.

[redacted]

[redacted]

B. It was Unexpected that Levocetirizine Would Have Antimicrobial Properties

64. As described in §V.B-C above, as of the 2004 priority date, a person of ordinary skill would not expect that a particular API would have antimicrobial or antifungal properties, unless that API was prepared for that very purpose, such as an antibiotic.

65. The mere fact that a compound was known in 2004 to be an antihistamine would not change that conclusion. For example, the 2011 El-Nakeeb publication described the varying and conflicting reports regarding antibacterial activity in antihistamines, even as of 2011. Further, El-Nakeeb detailed how second- and third-generation antihistamines, like levocetirizine, had not been publicly evaluated prior to that 2011 publication. *See supra*, §V.B. Consequently, it was not predictable, at the priority date in 2004 or today, that levocetirizine would have antibacterial properties based merely on the fact that it was known to be an antihistamine.

66. Further, the data presented by the El-Nakeeb group shows that there is no common chemical structure associated with both antihistaminic and antibacterial activities, which is likely why the researchers concluded that a biological property (not a chemical structure) may underlie any such correlation. *See supra*, §V.B. Consequently, it was not predictable, at the priority date in 2004 or today, that levocetirizine would have antibacterial properties based merely on its chemical structure either.

67. In addition, as described above at §V.C, the mechanism of action underlying antibacterial compounds was in 2004, and remains, unknown and unclear. In fact, the mechanism of action of cetirizine's antibacterial properties remains under assessment with a research team as recently as 2017 publishing its studies. *Id.* The lack of knowledge surrounding the antibacterial mechanism of action reinforces that it would not have been predictable that levocetirizine would have antibacterial properties.

68. Further, while I understand that later publications (from after the 2004 priority date) discuss that cetirizine, in fact, does have an antimicrobial effect, I understand from counsel that the assessment of whether a property is unexpected or surprising should be made based on the state of knowledge at the priority date. As of that date, cetirizine was publicly believed to lack

antibacterial effects, as demonstrated through contemporaneous publications seeking to predict antibacterial effects by analyzing chemical structures. *Id.* As the racemate of levocetirizine, this conclusion or belief taught away from any expectation that levocetirizine itself would have antibacterial effects and would have instead created an expectation that levocetirizine, in fact, would not have antibacterial properties.

69. Relatedly, the existence of the dextrorotary enantiomer provides no suggestion that levocetirizine would possess antimicrobial properties because I have found no publication that indicates that either at the time of the invention or today that this enantiomer is known to have, or not have, any such effect.

70. In sum, as of the '194 patent's 2004 priority date, scientists knew that levocetirizine was an antihistaminic drug, but nothing in the literature available at the time indicated that levocetirizine possessed antimicrobial properties as well or would have taught toward such a conclusion. Even today, scientists are uncertain as to the mechanism of action surrounding levocetirizine's antimicrobial properties. *See supra* §V.C. Levocetirizine's antimicrobial effects are also not believed to be tied to its antihistaminic effects.

C. The '194 Patent and the Fanara Declaration Demonstrate that Levocetirizine Possesses Antimicrobial Properties

71. As described above in §VI, the '194 patent provides detailed testing and results that demonstrate that levocetirizine possesses antimicrobial properties. Based on this data, it is my opinion that a POSA would conclude that levocetirizine possesses such unexpected properties.

72. Further, as also described above in §VI, during prosecution, one of the inventors, Domenico Fanara, submitted a declaration that described testing that, according to Mr. Fanara, further demonstrated that levocetirizine has antimicrobial and antifungal properties. *See* UCB_AP00000677-704. Based on my review of the data, I agree with Mr. Fanara's conclusion

that the data demonstrates the antimicrobial efficacy of levocetirizine itself because the formulations were able to be prepared with unexpectedly low amounts of parabens. Thus, I agree with Mr. Fanara's conclusion and it is my opinion that it was both surprising and unexpected that levocetirizine possessed antimicrobial properties as established by the data Mr. Fanara submitted to the PTO. This conclusion is reinforced by the fact that, as discussed below, regulatory agencies approved the Xyzal® formulations for sale despite the unexpectedly low amounts of preservatives present in the formulation.

D. Based on the Unexpected Self-Preservative Effect of Levocetirizine, The Inventors Were Able to Prepare a Formulation with Unexpectedly Low Amounts of Parabens That Would Remain Substantially Free of Bacteria

73. Prior to the time of the invention, it would have been unexpected that an aqueous pharmaceutical formulation containing only 0.75 mg/ml (or 0.075%) total amount of parabens would remain substantially free of bacteria, such as what is claimed in claim 1 of the '194 patent.

74. The '194 patent provides more than sufficient data to show that such a formulation was successful. *See e.g.* '194 patent, tables 15-20. [redacted]

75. As described above, there was no reason to believe in 2004 that levocetirizine would have an antibacterial effect. Given that an oral liquid product is dispensed in a multi-use container that is frequently opened and closed by patients, a POSA would understand that the risk of contamination is high. *See* Dániel Nemes, *Interaction between Different Pharmaceutical Excipients in Liquid Dosage Forms—Assessment of Cytotoxicity and Antimicrobial Activity*, 23 Molecules 1827, 1827 (2018). Therefore, even mild antimicrobial properties would not have been sufficient to protect the product.

76. [redacted]

77. These findings demonstrate the non-obviousness of the invention – the combination of levocetirizine, only a mild antimicrobial on its own, with trace amounts of parabens afforded full antimicrobial protection. This conclusion could not have been reached based on any teaching in the prior art.

78. In fact, prior art at the time of the invention taught that pharmaceutical formulations should use at least a combined total of 2 mg/ml of parabens to maintain stability. For example, I have reviewed the prior art that Apotex has cited in its interrogatory responses and note that each prior art reference, to the extent Apotex relies upon it because it purportedly presents a relevant formulation with parabens, teaches that the amount of parabens should be significantly higher than the 0.75 mg/ml amount claimed by the '194 patent:

- EP 0605203: Apotex cites Example 5 (p. 11 of EP '203), which teaches 0.2 g of methylparaben and 0.1 g of propylparaben in 100 ml of water, which would total 3 mg/ml parabens.

- Handbook: Apotex cites a parenteral formulation which, to the extent it is relevant at all to the claims of the '194 patent, teaches a formulation with 0.18% (*i.e.*, 1.8 mg/ml) methylparaben and 0.02% (*i.e.*, 0.2 mg/ml) propylparaben, which totals 2 mg/ml parabens.

- WO2004/050094: Apotex cites an example composition at page 4, ll. 33-35, but this example does not provide the relative amounts of the two parabens and therefore teaches nothing about how much of the parabens to use.

79. Further, other references provide similar teachings. For example, Remington's, as Mr. Fanara explained, teaches using 2 mg/ml of parabens. *See* UCB_AP00000690-94. Similarly, the below table of MICs for methylparaben and propylparaben for various molds, yeasts, and bacteria shows that a POSA should use at least 0.2% methylparaben and 0.025% propylparaben to control all of the species shown, or a total of 0.225% or 2.25 mg/ml.

PARABENS' MICROBACTERIAL EFFECTS

Minimum Inhibitory Concentration of Parabens (%)

Microorganism		MIC			
		MP	EP	PP	BP
Molds	*Aspergillus niger* ATCC 10254	0.1	0.04	0.02	0.02
	Penicillium digitatum ATCC 10030	0.05	0.025	0.0063	0.0032
Yeasts	*Candida albicans* ATCC 10331	0.1	0.1	0.0125	0.0125
	Saccharomyces cerevisiae ATCC 9763	0.1	0.05	0.0125	0.0063
Bacteria	*Bacillus subtilis* ATCC 6633	0.2	0.1	0.025	0.0125
	Bacillus cereus var. mycoides ATCC 6462	0.2	0.1	0.0125	0.0063

MP:Methylparaben
EP:Ethylparaben
PP:Propylparaben
BP:Butylparaben

Aalto,T.R., Firman,M.C., Rigler,N.E.,
p-Hydroxybenzoic acid esters as preservatives Ⅰ,
J.Am.Pharm.Assoc.Sci.Ed.,**42**,449-457 (1953)

See Ueno Fine Chemicals Industry, *Parabens as Preservatives*, *available at* (https://www.ueno-fc.co.jp/english/pdf/PARABEN2013.pdf) (last accessed Mar. 21, 2019) (citing Aalto, T.R., *et al*., *p-Hydroxybenzoic acid esters as preservatives I*, 42 J. Am. Pharm. Assoc. Sci. Ed. 449-457 (1953)).

80. It was also known that out of the organisms tested in the European Pharmacopoeia Antimicrobial Efficacy Testing, *Psueodomonas aeruginosa* had the highest MIC required for methylparaben and propylparaben (4 mg/ml and 1 mg/ml respectively). *See* Arthur H. Kibbe, *Handbook of Pharmaceutical Excipients, 3d ed.* at 341, 451 (2000). Therefore, in order to satisfy the European Pharmacopoeia requirements, a POSA would expect to need at least this amount of methylparaben or propylparaben (4 mg/ml and 1 mg/ml respectively).

81. Therefore, the fact that the Xyzal® formulations, which are embodiments of the '194 claims, were able to meet the criteria for the European Pharmacopoeia Antimicrobial Efficacy Testing and were approved by the U.S. FDA with only 0.75 mg/ml combined total of parabens would have been completely unexpected.

VIII. CONCLUSION

82. The inventors of the '194 patent found that levocetirizine unexpectedly had antimicrobial properties. The inventors of the '194 patent developed a new, optimized formulation of levocetirizine that was able to be remain substantially free of bacteria with a significantly lower amount of methylparaben and propylparaben than would typically be used as of the time of the invention. This finding was completely surprising and unexpected.

IX. TRIAL EXHIBITS

83. I have not yet selected or prepared any exhibits for use at trial but may do so in accordance with any schedule ordered by the Court.

X. SUPPLEMENTAL OPINIONS

84. All opinions that I have rendered in this report are true to the best of my knowledge and belief. As it is my understanding that additional evidence may be produced in this matter, I reserve the right to modify, supplement, or otherwise amend or refine this report after having

reviewed such additional evidence or information as I may become aware of prior to, or at trial. To the extent that trial evidence may differ from that which I have become aware prior to trial, I may be required to reevaluate one or more of the aspects of this report.

I hereby 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. I reserve the right to revise or supplement my opinions as additional information becomes available. I declare under penalty of perjury that the foregoing expert report is true and correct.

Dated: March 22, 2019

Sarfaraz K. Niazi, Ph.D.

EXHIBIT A

Sarfaraz K. Niazi, Ph.D., SI, FRSB, FPAMS, FACB.

Biosimilars Pioneer | Inventor | Teacher | Researcher | Scientist | Author | Speaker |Entrepreneur | Patent Law Practitioner | Radio Host | Consultant

Sarfaraz K. Niazi[1] is a globally recognized pioneer of biosimilars; in 2014, the Forbes Magazine's highlighted him as "The Most Interesting Man Revolutionizing The Health World,"[2] for his lifetime efforts in making high cost essential drugs, biosimilars and complex generics, accessible across the globe. In 2018, the Forbes magazine reported him as "Scientist Invented A New Pathway To Approve Biosimilars, And The FDA Is Listening,"[3] for his efforts to force the US FDA adopt a more rational approach to approval of biosimilars to allow faster approval and lowered cost of development. He is now advising the US FDA in defining the structure of its new Biosimilars Action Plan (BAP)[4] that was issued by the US FDA after Niazi filed a citizen petition against the FDA[5] (FDA-2018-P-1876). The current BAP is entirely based on the recommendations made by Niazi in the citizen petition. The FDA has also shared the progress by posting Niazi recommendations on the US government portal[6].

Dr. Niazi's efforts in changing the FDA approval process are widely acclaimed to be the most pivotal move to make biological drugs affordable.[7] To promote faster adoption of biosimilars, he

[1] www.niazi.com
[2] https://www.forbes.com/sites/nicolefisher/2014/08/30/the-most-interesting-man-revolutionizing-the-health-world/#4fad94cd20ba
[3] https://www.forbes.com/sites/nicolefisher/2018/07/25/one-mans-mission-to-fix-the-fdas-biosimilar-problem/#7945680b2380

[4] https://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/TherapeuticBiologicApplications/Biosimilars/UCM613761.pdf

[5] http://www.fdalawblog.net/2018/05/biosimilar-approval-better-stronger-faster/

[6] https://www.regulations.gov/document?D=FDA-2018-P-1876-0003

[7] https://www.prnewswire.com/news-releases/fda-withdraws-its-pivotal-biosimilar-products-testing-guideline-after-sarfaraz-niazi-founder-of-pharmaceutical-scientist-files-the-first-citizen-petition-challenging-its-clinical-relevance-300675168.html; https://www.biospace.com/article/fda-withdraws-draft-guidance-on-biosimilar-development/; https://seekingalpha.com/news/3367537-fda-withdraws-draft-guidance-related-biosimilar-development; https://www.forbes.com/sites/nicolefisher/2018/07/25/one-mans-mission-to-fix-the-fdas-biosimilar-problem/#402daf2e2380; https://www.biosimilardevelopment.com/doc/fda-withdraws-its-pivotal-biosimilar-products-testing-guideline-after-sarfaraz-

has written dozens of major books,[8] including the first-ever book on biosimilars and coined the phrase "biosimilar" in his first biosimilars guidance advise to FDA. Other major books of Niazi include the first book on single-use bioprocessing, a textbook on bioprocessing, a two-volume book on biosimilars, a six-volume set of cGMP manufacturing encyclopedia. He has also authored 100+ research papers and hundreds of blogs. His most recent book, Biosimilarity: The FDA Perspective, published July 2018 is dedicated to Dr. Janet Woodcock, Director, CDER at the FDA. His other books have been dedicated to Dr. James Watson, Nobel Laureate, who discovered DNA structure and President Barack Obama with White House approval, among other notable personalities.

Dr. Niazi has also authored a large number of internationally published blogs on topics ranging from contemporary scientific ideas to philosophy, poetry and ironies of life.

Dr. Niazi has been a keynote speaker on the topic of biosimilars including presenting the FDA viewpoints before the industry audience.[9]

From Left to Right: Dr. Niazi will Dr. Janet Woodcock, Director, CDER, FDA; announcement by FDA appointing Dr. Niazi as the spokesperson for the FDA 2018 plans; The Nobel Laureate Dr. James Watson, the discoverer of the structure of DNA and author of the famous book, The Double Helix, visiting Dr. Niazi to tell "how his dreams are played out." With Dr. Leah Christl, Deputy Director and Head of FDA Biosimilars Program at the FDA invitation to teach the scientists on rational method of complying with safety evaluation of bniosimilars.

niazi-0001; http://www.fdalawblog.net/2018/05/biosimilar-approval-better-stronger-faster/; https://www.europeanpharmaceuticalreview.com/article/70987/obstacles-success-biosimilars-us-market/; https://www.bigmoleculewatch.com/wp-content/uploads/2018/05/Citizen_Petition_from_UIC_College_of_Pharmacy.pdf; http://www.erienewsnow.com/story/38684328/fda-issues-new-biosimilar-action-plan-bap-accepting-recommendations-made-by-sarfaraz-niazi-ceo-of-pharmaceutical-scientist-to-modernize-regulatory; https://www.mmm-online.com/home/channel/regulatory/pfizer-petitions-fda-for-biosimilar-communications-guidelines/; https://www.jdsupra.com/legalnews/fda-to-hold-public-hearing-on-67759/; http://gabi-journal.net/potential-changes-to-the-fda-approach-to-biosimilars-have-a-global-impact.html; https://static1.squarespace.com/static/5891331d8419c227312ee2ca/t/5a60d138e2c483a5c287ab56/1516294469587/16-1-Biosimilars-eBook.pdf; https://exlevents.com/fda-withdraws-biosimilar-draft-guidance-after-public-outcry/; https://www.epmmagazine.com/news/fda-is-asking-for-public-comments-on-bioequivalence-testing-/; https://www.rdmag.com/article/2014/10/biosimilars-market; http://www.smartbrief.com/branded/D4C8EBAD-9C67-4D55-869C-CC2C8F893F9E/8F6CA12E-FE53-449F-B181-D9E3E11EEDCF

[8] https://www.niazi.com/scholar/

[9] https://karyobio.com/news/2017/11/6/dr-niazi-invited-as-keynote-speaker-at-the-fdacms-conference

Dr. Niazi's is Executive Chairman of Pharmaceutical Scientist, LLC (www.pharmsci.com), a consulting company that has helped approval of dozens of products by FDA and EMA.

Dr. Niazi is a fellow of several learned societies including the Royal Society; a widely sought-after speaker with over 500 talks across the globe.

In his capacity as an academician, he has trained 50+ Ph.D. students and scores of FDA inspectors.

A few recent notable contributions of Dr. Niazi include:

- First book on the subject of bioequivalence testing; coined the word, "bioequivalence." Wrote BE testing guidance for FDA, organized and established dozens of bioequivalence testing facilities across the globe. Authored the most widely used handbook on testing of BE[10]. Trained scientists and statisticians on designing and analyzing study results, protocol writing; provided GLP/GMP compliance of laboratory testing, clinical site management, study safety oversight (Form 1572-FDA).
- First Citizen's Petition partially approved by FDA (FDA-2007-P-0055-0002, 2007-P-0003) to substitute human testing of bioequivalence with *in vitro* methods to reduce the cost of generic drug approval.
- Contributor to BPCIA as advisor to US Congress.
- Contributor to FDA and EMA biosimilar guidance.
- First acceptance by FDA of a biosimilar product without testing in patients.
- First acceptance of a non-inferiority testing protocol for immunogenicity in healthy subjects and in patients, saving millions of dollars.
- First *in vitro* immunogenicity testing protocol for biosimilars, currently under review by the FDA.
- First fourth-dimension analytical similarity testing to achieve fingerprint-like similarity.
- First BLA accepted by FDA using a proprietary single-use bioreactor patented by Niazi.
- First book authored by Dr. Niazi and FDA on the topic of biosimilarity[11] and dedicated to Dr. Janet Woodcock, Head, CDER, FDA.
- First published advise to the US FDA and the industry to identify and obviate the impediments to slow entry of biosimilars in the US markets[12],[13].

[10] https://www.amazon.com/Handbook-Bioequivalence-Testing-Pharmaceutical-Sciences/dp/1482226375/ref=dp_ob_title_bk?dpID=41GrUD9hA7L&preST=_SY291_BO1,204,203,200_QL40_&dpSrc=detail

[11] https://www.barnesandnoble.com/w/biosimilarity-sarfaraz-k-niazi/1125939292

[12] http://www.bioprocessintl.com/wp-content/uploads/2018/01/16-1-Biosimilars-eBook.pdf?submissionGuid=ba89dcc5-a456-4ef0-849d-bceda94f16a3

[13] https://www.europeanpharmaceuticalreview.com/article/70987/obstacles-success-biosimilars-us-market/

- First citizen petition on the subject of changing evaluation of biosimilars by the FDA[14].
- Trained FDA inspects on cGMP compliance.
- Coordinated dozens of FDA audits of generic and biological manufacturers, particularly managing consent decrees.
- Consultants to investment bankers, VC groups and private investors on value proposition analysis in the field of pharmaceutical and biopharmaceuticals.
- Expert witness in IP and pharmaceutical cases.
- Trainer on behalf of the USP.

Dr. Niazi is the largest solo inventor of bioprocessing inventions with over 100 inventions[15], additionally including new drugs, new dosage forms, bioequivalence testing methods and a large number of other patient-related inventions that are widely used across the globe. His patented invention of demonstrating analytical similarity methods[16] was accepted by the FDA to allow waiver of patient trials of biosimilar products. In recognition of his inventive contributions, Dr. Niazi was awarded the highest civil award of Pakistan, Star of Distinction.

Dr. Niazi is also a licensed practitioner of the patent law at the United States Patent Office, an expertise he has used to create the FTO boundaries for biosimilars to avoid litigation under the BPCIA[17]. Dr. Niazi provides this service free of charge to the Third World scientists and has secured over 200 patents for his clients.

The President of Pakistan conferred the high civil award, Start of Distinction[18], upon him in the field of engineering sciences, as his 100+ inventions are helping a large population around the world with more affordable drugs, clear water, new drugs, new devices, and novel disease management systems.

Dr. Niazi holds a MS degree in pharmacy from the Washington State University, and a PhD in pharmaceutical sciences from the University of Illinois, where he began his academic career—he continues as Adjunct Professor at the University of Illinois and additionally at the University of Houston in the US and other academic institutions around the world. Dr. Niazi became a tenured professor at the age of 27, a position he left to join Abbott Laboratories International, where he was tenured as Volwiler Fellow. He left Abbott to develop biosimilars to make them accessible globally.

Dr. Niazi is an avid photographer, a musician, a poet, a radio broadcaster (Voice of America, awarded by the Obama White House) with audience of over a billion, on literary and philosophic topics. He is also a translator of Asian love poems into English; he resides in Deerfield, Illinois.

Contact: niazi@niazi.com; Consulting Web: www.pharmsci.com; Author Web: www.niazi.com; Phone: +1-312-297-0000; Fax: +1-312-297-1100; SKYPE: sarf.niazi; Twitter: @moustaches and @sarf.niazi; LinkedIn: https://www.linkedin.com/in/skniazi/

[14] http://www.fdalawblog.net/2018/05/biosimilar-approval-better-stronger-faster/

[15] https://sarfaraz-niazi.squarespace.com/s/biomolecule-patent.pdf
[16] https://patents.google.com/patent/US20180024137A1/en?oq=US20180024137A1
[17] https://www.law.cornell.edu/uscode/text/42/262
[18] https://en.wikipedia.org/wiki/Category:Recipients_of_Sitara-i-Imtiaz

Sarfaraz K. Niazi, Ph.D., SI, FRSB, FPAMS, FACB, USPA
20 Riverside Drive, Deerfield, Illinois 60015. USA
Phone: +1-312-298-0000; Fax: +1-312-297-1100; email: niazi@niazi.com

Education:

- 1974: Ph.D., Pharmaceutical Sciences, University of Illinois, Chicago, IL
- 1970: MS, Pharmaceutical Sciences, Washington State University, Pullman, Washington
- 1969: B. Pharm., Karachi University, Pakistan
- 1968: Diploma Marketing, Institute of Business Administration, Karachi, Pakistan
- 1966: BSc., Karachi University, Pakistan

Positions:

Academic:

- 2015-Present: Adjunct Professor of Biopharmaceutical Sciences, University of Illinois College of Pharmacy
- 2012-Present: Visiting Professor, University of Houston College of Pharmacy.
- 2000-Present: Visiting and Foreign Professor, HEJ Research Institute, Karachi, Pakistan.
- 2004-present: Visiting Professor, National University of Science and Technology, Islamabad, Pakistan.
- 1995-present: Founder and Executive Chairman, Pharmaceutical Scientist, LLC, a biological products consulting company established in 1995. 50+ global clients.
- 1972-1988: Instructor to Tenured (at age 28) professor at University of Illinois College of Pharmacy, Chicago, Illinois.

Corporate:

- 2017-present: Founder and Executive Chairman, Karyo Biologics, LLC, a biosimilar products development company with several products in clinical approval stage with FDA.
- 2003-2017: Founder and Executive Chairman, Adello Biologics, LLC (formerly Therapeutic Proteins Inc.), a fully integrated biosimilar products company with cytokines and monoclonal antibodies in approval stages with the US FDA.
- 1988-1995: Director Technical Affairs, Abbott International.
- 1995-Present: Founder and Executive Chairman, Pharmaceutical Scientist, LLC, Chicago, IL.
- 1995-1999: Director Quality Affairs, Gulf Pharmaceutical Industries, Ras Al Khaimah UAE.

Professional

- 2002-present: United States Patent and Trademark Office, Patent Agent.

Recognitions, Awards, and Contributions

- Highest Civil Award by the President of Pakistan for contribution to biotechnology.

- Fellowship if Royal Society of Biology, Pakistan Academy of Medical Sciences, American Society of Clinical Biochemistry.
- Forbes Magazine's "The Most Interesting Man Revolutionizing The Health World" and "Scientist Invented A New Pathway To Approve Biosimilars, And The FDA Is Listening."
- Invited contributor to BPCIA as advisor to the US Congress
- Invited advisor to President Obama.
- Advisor to US FDA on Biosimilars Guidance
- Volwiler Fellow Abbott Laboratories (tenured)
- Advisor to US Pharmacopoeia on Biosimilar Monographs
- Inducted into Entrepreneur Hall of Fame.
- University of Illinois Alumni of the Year
- TOKTEN Fellow to assist Indian government institutions.
- March of Dimes grant reviewer.
- Editorial boards of scientific journals.
- Radio host for Voice of America since 2008.
- Advisor to Higher Education Commission of Pakistan on intellectual property management.
- Pro bono service to scientist in the developing countries to secure US patents.
- Invited speaker 500+ engagements worldwide.
- Innovation of the Year, Sponsored by Honeywell; Global Generics and Biosimilars Awards 2014: https://www.generics-bulletin.com/media/19636/Winners-for-Website1.jpg
- Finalists Best Upstream Technology Application 2012: TPI Single-use technology for production of bacterial proteins, Bioprocess International (http://www.bioprocessintl.com/bioprocess-international-2016-awards/past-winners-of-bioprocess-international-awards/).

Achievements

- Assisted 10+ companies worldwide to establish biosimilar development and manufacturing.
- Challenged and forced FDA to withdraw its Biosimilars Guidance and suggested replacement with a rational approach.
- Taught FDA inspectors in cGMP compliance.
- Trained 46 graduate students: MS. Ph.D.
- 100+ patented inventions: bioprocessing, NCE, NBE, drug delivery, natural products, drug testing, wine aging, automobile safety, disease management, etc.
- Received first waiver of in-patient testing of a biosimilar candidate under 351(k).
- Developed a fourth-dimension analytical similarity testing to achieve fingerprint-like similarity for biosimilars.
- Developed an ISO 9 bioreactor used to file the first BLA of a biosimilar.
- First handbook authored on biosimilars. Largest number of books on biosimilars.
- First book on FDA views on biosimilarity; dedicated to Dr. Woodcock.

- Coordinated dozens of FDA audits of generic and biological manufacturers, particularly managing consent decrees; secured first FDA approval of a product from ME countries.
- Wrote the core document for establishment of Pakistan's Drug Regulatory Authority.
- Assisted Indonesia, Canada, Japan and Australia in writing biosimilars guidance policies.
- Consultant to investment bankers, VC groups and private investors on value proposition analysis in the field of pharmaceutical and biopharmaceuticals.
- Served as expert witness in IP and pharmaceutical cases.
- Trained scientists on behalf of the US Pharmacopeia.
- Taught physicians in the US on the regulatory pathways and safety features of biosimilars on behalf of large pharma companies.
- Largest solo inventor of bioprocessing patents; 100+ patents.
- Founded the first US biosimilars company—raised $500 Million [largest funding of startup biotech in US history].
- Solo-authored the first biosimilars monographs for US Pharmacopoeia.
- Chicago Marathon runner 2014.

Publications

Books:

- Textbook of Biopharmaceutics and Clinical Pharmacokinetics, J Wiley & Sons, New York, NY, 1979; ISBN-13: 9789381075043
- The Omega Connection, Esquire Press, Illinois, 1982; ISBN-13: 9780961784102
- Adsorption and Chelation Therapy, Esquire Press, Illinois; 1987. ISBN-9780961784140
- Attacking the Sacred Cows: The Health Hazards of Milk, Esquire Press, Illinois; 1988; ISBN-13: 9780961784119
- Endorphins: The Body Opium, Esquire Press, Illinois; 1988; ISBN 9780961784126
- Nutritional Myths: The Story No One Wants to Talk About, Esquire Press, Illinois. ISBN 9780961784133
- Wellness Guide. Ferozsons Publishers. Pakistan 2002. ISBN 9789690017932
- Love Sonnets of Ghalib: Translations, Explication and Lexicon, Ferozsons Publishers, Lahore, Pakistan 2002 and Rupa Publications, New Delhi, India 2002; ISBN-13: 9788171675968
- Filing Patents Online, CRC Press, Boca Raton, Florida, 2003; ISBN-13: 9780849316241
- Pharmacokinetic and Pharmacodynamic Modeling in Early Drug Development in Charles G. Smith and James T. O'Donnell (eds.), The Process of New Drug Discovery and Development (2nd ed.). New York: CRC Press, 2004; ISBN-13: 978-0849327797.
- Handbook of Biogeneric Therapeutic Proteins: Manufacturing, Regulatory, Testing and Patent Issues, CRC Press, Boca Raton, FL, 2005; ISBN-13: 9780971474611
- Handbook of Preformulation: Chemical, Biological and Botanical Drugs, Informa Healthcare, New York, NY, 2006; ISBN-13: 9780849371936
- Handbook of Bioequivalence Testing. New York: Informa Healthcare, 2007; ISBN-13: 978-0849303951

- Handbook of Pharmaceutical Manufacturing Formulations, Volume 6 Second Edition: Sterile Products, Informa Healthcare, New York, NY, 2009; ISBN-13: 9781420081305
- Handbook of Pharmaceutical Manufacturing Formulations, Volume 1 Second Edition: Compressed Solids, Informa Healthcare, New York, NY, 2009; ISBN-13: 9781420081169
- Handbook of Pharmaceutical Manufacturing Formulations, Volume 2 Second Edition: Uncompressed Solids, Informa Healthcare, New York, NY, 2009; ISBN-13: 9781420081183
- Handbook of Pharmaceutical Manufacturing Formulations, Volume 3 Second Edition: Liquid Products, Informa Healthcare, New York, NY, 2009; ISBN-13: 9780849317484
- Handbook of Pharmaceutical Manufacturing Formulations, Volume 4 Second Edition: Semisolid Products, Informa Healthcare, New York, NY, 2009 ISBN-13: 9781420081268;
- Handbook of Pharmaceutical Manufacturing Formulations, Volume 5 Second Edition: Over the Counter Products, Informa Healthcare, New York, NY, 2009; ISBN-13: 978-1420081282
- Textbook of Biopharmaceutics and Clinical Pharmacokinetics. Hyderabad, India: The Book Syndicate, 2010. ISBN 978-93-8107-504-3
- Wine of Passion: Love Poems of Ghalib, Ferozsons (Pvt) Ltd., Lahore, Pakistan, 2010; ISBN-13: 9780971474611
- Disposable Bioprocessing Systems, CRC Press, Boca Raton, FL, 2012; ISBN-13: 9781439866702
- Handbook of Bioequivalence Testing. Second Edition, New York, NY: Informa Healthcare, 2014 ISBN-13: 9781482226379
- There is No Wisdom: Selected Love Poems of Bedil. Translations from Darri Farsi, Sarfaraz K. Niazi and Maryam Tawoosi, Ferozsons Private (Ltd), Lahore, Pakistan, 2015 ISBN 978969025036
- Wine of Love: Complete Translations of Urdu Persian Love Poems of Ghalib, Sarfaraz K. Niazi, Ferozsons Private (Ltd), Lahore, Pakistan, 2015. ISBN: TBA
- Biosimilars and Interchangeable Biologicals: Strategic Elements. CRC Press, 2015; ISBN 9781482298918
- Biosimilars and Interchangeable Biologics: Tactical Elements. CRC Press, 2015; ISBN 9781482298918
- Fundamentals of Modern Bioprocessing, Sarfaraz K. Niazi and Justin L. Brown, CRC Press, 2015; ISBN 9781466585737

Research Papers:

- 100+: https://www.ncbi.nlm.nih.gov/pubmed/?term=niazi+s

Inventions:

Published inventions; pending and unpublished not included.

PUBLICATION	TITLE

US2018147552 (A1)	ZERO GRAVITY PROCESS DEVICE
US2018143754 (A1)	VEHICLE STEERING AND CONTROL DEVICE (VSCD)
US2018024137 (A1)	METHODS FOR COMPARING A STRUCTURE OF A FIRST BIOMOLECULE AND A SECOND BIOMOLECULE
WO2017123788 (A2);	MULTIPURPOSE BIOREACTOR
US2017198246 (A1)	MULTIPURPOSE BIOREACTOR
US2017191015 (A1)	GAS HEATING APPARATUS FOR DISPOSABLE BIOREACTOR
US2017136800 (A1)	ANGLED PRINTED BOUND BOOK
US2017101435 (A1)	HARVESTING AND PERFUSION APPARATUS
US2017051243 (A1)	RECIRCULATING BIOREACTOR EXHAUST SYSTEM
HK1194105 (A1)	SINGLE-CONTAINER MANUFACTURING OF BIOLOGICAL PRODUCT
US2017008751 (A1)	WINE PRESERVING PACKAGING
US2017008747 (A1)	WINE PRESERVING AND AERATING CONTAINER
US2016376538 (A1); US9745545 (B2)	FASTER AGING OF ALCOHOLIC BEVERAGES
US2016301828 (A1)	VISUAL AXIS OPTIMIZATION FOR ENHANCED READABILITY AND COMPREHENSION
US2016264930 (A1)	CONCENTRATOR FILTER
US2016237111 (A1)	DOWNSTREAM BIOPROCESSING DEVICE
US2016200761 (A1)	BUOYANT PROTEIN HARVESTING DEVICE
US2016166949 (A1)	PREPARATIVE CHROMATOGRAPHY COLUMN AND METHODS
US2016097073 (A1)	PURIFICATION AND SEPARATION TREATMENT ASSEMBLY (PASTA) FOR BIOLOGICAL PRODUCTS
WO2016044758 (A1)	HARVESTING AND PURIFICATION OR PERFUSION YIELDER (HAPPY) DEVICE
US2015371120 (A1)	VISUAL AXIS OPTIMIZATION FOR ENHANCED READABILITY AND COMPREHENSION
WO2015157494 (A1)	AERATION DEVICE FOR BIOREACTORS
HK1201869 (A1)	CLOSED BIOREACTORS
US2015275318 (A1); US9587283 (B2)	INTERCONNECTED BIOREACTORS
US2015253022 (A1); US9593859 (B2)	CLEAN ZONE HVAC SYSTEM

HK1201078 (A1)	NONINVASIVE BIOREACTOR MONITORING
EP3096744 (A1); EP3096744 (A4)	THERMODYNAMIC EQUIVALENCE SURROGATE TEST (TEST) FOR BIOEQUIVALENCE
US2015210974 (A1); US9587214 (B2)	BIOREACTOR EXHAUST
US2015099293 (A1); US9290732 (B2)	BUOYANT PROTEIN HARVESTING DEVICE
EP3030263 (A1)	COMPARING THE STRUCTURES OF TWO BIOMOLECULES
CN104169426 (A)	PURIFICATION AND SEPARATION TREATMENT ASSEMBLY (PASTA) FOR BIOLOGICAL PRODUCTS
US2014225727 (A1)	TURNING SIGNAL
WO2014018374 (A1)	BAFFLED SINGLE-USE BIOREACTOR
WO2013188649 (A1)	PNEUMATICALLY AGITATED AND AERATED SINGLE-USE BIOREACTOR
US2013220923 (A1); US8663474 (B2)	NON-BLOCKING FILTRATION SYSTEM
US2012258519 (A1)	PROTEIN HARVESTING
US2012198600 (A1)	WINDY CITY HAT
US2012164300 (A1)	ACCELERATED AGING OF WINES AND SPRITS
US2011287404 (A1); US9499290 (B2)	STATIONARY BUBBLE REACTORS
US2011117538 (A1)	BIOREACTORS FOR FERMENTATION AND RELATED METHODS
US2010316534 (A1); US8066947 (B2)	AIR SCRUBBING SYSTEM
US2010261226 (A1); US9550971 (B2)	UNIVERSAL BIOREACTORS AND METHODS OF USE
AU2002327646 (A1)	COMPOSITION AND METHOD FOR THE TREATMENT OF HYPERCHOLESTEROLEMIA AND HYPERLIPIDEMIA IN MAMMALS
AU2002248319 (A1)	PHARMACEUTICAL COMPOSITION FOR THE PREVENTION AND TREATMENT OF SCAR TISSUE
AU2001268731 (A8)	A COMBINATION OF APPETITE CONTROLLING AGENTS WHICH CREATE A SYNERGY AND PRODUCE A SATIATING RESULT
WO2006086065 (A2); WO2006086065 (A3)	FORMULA, SYSTEM AND METHOD FOR TREATING URUSHIOL INDUCED CONTACT DERMATITIS
US2003054020 (A1)	METHOD AND COMPOSITION FOR REDUCING SEBUM SECRETION IN MAMMALS
US4639368 (A)	CHEWING GUM CONTAINING A MEDICAMENT AND TASTE MASKERS
US6419963 (B1)	COMPOSITION AND METHOD FOR THE TREATMENT OF DIAPER RASH USING NATURAL PRODUCTS

US6338862 (B1)	COMPOSITION AND METHOD OF USE IN TREATING SEXUAL DYSFUNCTION USING CGMP-SPECIFIC PHOSPHODIESTERASE TYPE 5 INHIBITORS
US6555118 (B1)	PHARMACEUTICAL PREPARATION FOR THE TREATMENT OF TOPICAL WOUNDS AND ULCERS
US6495174 (B1)	HERBAL COMPOSITION FOR THE TREATMENT OF ALOPECIA
US6312735 (B1)	METHOD FOR INSTANTANEOUS REMOVAL OF WARTS AND MOLES
US6365198 (B1)	PHARMACEUTICAL PREPARATION FOR THE TREATMENT OF GASTROINTESTINAL ULCERS AND HEMORRHOIDS
US6251421 (B1)	PHARMACEUTICAL COMPOSITION CONTAINING PSYLLIUM FIBER AND A LIPASE INHIBITOR
US6235314 (B1)	ANALGESIC, ANTI-INFLAMMATORY AND SKELETAL MUSCLE RELAXANT COMPOSITIONS
US2005013871 (A1)	PHARMACEUTICAL COMPOSITION FOR THE TREATMENT OF ITCH
US6235796 (B1)	USE OF FLUOROCARBONS FOR THE PREVENTION OF SURGICAL ADHESIONS
US4530936 (A)	COMPOSITION AND METHOD FOR INHIBITING THE ABSORPTION OF NUTRITIONAL ELEMENTS FROM THE UPPER INTESTINAL TRACT
US2007141182 (A1)	COMBINATION OF MULTIPLE NON-STEROIDAL ANTI-INFLAMMATORY DRUGS AND MUSCLE RELAXANTS FOR LOCAL TREATMENT OF MUSCULOSKELETAL PAIN
US2007142480 (A1)	ALLEVIATION OF PAIN IN OSTEOARTHRITIS BY MEANS OF INTRA-ARTICULAR IMPLANTATION OF PERFLUORODECALIN.
US2004253327 (A1)	COMPOSITIONS AND METHODS FOR REDUCING OR CONTROLLING BLOOD CHOLESTEROL, LIPOPROTEINS, TRIGLYCERIDES, AND SUGAR AND PREVENTING OR TREATING CARDIOVASCULAR DISEASES
US2002183297 (A1)	PHARMACEUTICAL COMPOSITION FOR THE TREATMENT OF ALOPECIA
US6462083 (B1)	SUPPOSITORY BASE
WO02085390 (A1)	COMPOSITION AND METHOD FOR THE PREVENTION AND TREATMENT OF ACNE
AU2002310047 (A1); AU2002310047 (A8)	COMPOSITION AND METHOD FOR THE TREATMENT OF DIAPER RASH USING NATURAL PRODUCTS
AU2002254428 (A1)	PHARMACEUTICAL PREPARATION FOR THE TREATMENT OF GASTROINTESTINAL ULCERS AND HEMORRHOIDS

EXHIBIT B

List of Materials Considered: Opening Expert Report of Sarfaraz K. Niazi, Ph.D. on Secondary Considerations dated March 22, 2019				
Description		**Begin Bates**		**End Bates**
2018-09-17 Apotex (Levocetirizine) - Responses to First Set of Interrogatories and Documents cited Therein				
2018-11-16 Apotex (Levocetirizine) - Supplemental Responses to First Set of Interrogatories Nos. 1-8 and Documents Cited Therein				
2019-02-22 Apotex (Levocetirizine) – Supplemental Responses to Interrogatory No. 6 and Documents Cited Therein				
Arthur H. Kibbe, Handbook of Pharmaceutical Excipients, 3d ed. (2000)				
Brown MR and Richards RM, *Effect of Polysorbate (Tween) 80 on the Resistance of Pseudomonas Aeruginosa to Chemical Inactivation*, 16 J. Pharm. Pharmacol. Suppl. 51-5T (1964)				
Brul S. and Coote P., *Preservative agents in foods. Mode of action and microbial resistance mechanisms*, 50 Int. J. Food. Microbiol. 1-2 (1999)				
Buck SL et al, *Methods used to evaluate the effectiveness of contact lens care solutions and other compounds against Acanthamoeba: a review of the literature*, 26 CLAO J. 72-84 (2000)				
Cronin, Mark T.D., et al., *Structure-Based Classification of Antimicrobial Activity*, 42 J. Chem. Inf. Comput. Sci. 869, 871 (2002)				
Day JH, Ellis AK, Rafeiro E, *Levocetirizine: a new selective H1 receptor antagonist for use in allergic disorders*, 40 Drugs Today 415, 415 (2004)				
El-Nakeeb, Moustafa A., et al., *In vitro Antibacterial Activity of Some Antihistamines Belonging to Different Groups Against Multi-Drug Resistant Clinical Isolates*, 42 Braz. J. Microbiol. 980-991 (2011)				
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Evans WP, *The Solubilisation and Inactivation of Preservatives by Non-Ionic Detergents*, 16 J. Pharm. Pharmacol. 323-31 (1964).				

FDA's website of approved products (https://www.accessdata.fda.gov/scripts/cder/iig/)				
Freese, E. et al., *Function of lipophilic acids as antimicrobial food additives*, 241 Nature 321-5 (1973)				
Gould GW, *Methods for preservation and extension of shelf life*, 33 Int. J. Food Microbiol. 51-614 (1996)				
Gould GW, *Preservation: past, present and futur*e, 56 Br. Med. Bull. 84-96 (2000)				
Hang Guo and Chris Knutsen, *Preservative Formulation and Effectiveness in Oral Solutions and Suspensions*, PDA Metro Meeting at 5 (Feb. 15, 2011)				
I. Rácz, *Drug Formulation* (1989)				
Jennifer M. Andrews, *Determination of minimum inhibitory concentrations*, 48 J. Antimicrobial Chemotherapy Suppl. S1 5 (2001)				
John J. O'Neill and Catherine A. Mead, *The parabens: Bacterial adaptation and preservative capacity*, 33 J. Soc. Cosmet. Chem 75-84 (1982)				
Lehner SJ et al, *Effect of hydroxypropyl-beta-cyclodextrin on the antimicrobial action of preservatives*, 46 J. Pharm. Pharmacol.,186-91 (1994)				
Ma, T and Marquis, RE, *Irreversible paraben inhibition of glycolysis by Streptococcus mutans GS-5*, 23 Letters in Applies Microbiology 329-33 (1996)				
Maji, H.S., et al, *An Exploratory Study of the Antimicrobial Activity of Cetirizine Dihydrochloride*, Indian J. Pharm. Sci., 79(5):751-757 (2017)				
Murcia-Soler, Miguel, et al., *Discrimination and selection of new potential antibacterial compounds using simple topological descriptor*s, 21 J. Mol. Graphics and Modelling 375, 382 (2003)				
NDA 22-157 - 1.13.5 Summary of Manufacturing Changes		UCB_AP00006060		UCB_AP00006080
Nemes, Dániel, *Interaction between Different Pharmaceutical Excipients in Liquid Dosage Forms—Assessment of Cytotoxicity and Antimicrobial Activity*, 23 Molecules 1827 (2018)				
Nes, IF and Eklund, T, *The effect of parabens on DNA, RNA and protein synthesis in Escheria coli*				

and Bacillus subtilis, 54 The Journal of Applied Bacteriology 237-42 (1983)				
Petition for *inter partes* Review and the Associated Expert Declaration of Dr. Paul Laskar				
The European Agency for the Evaluation of Medicinal Products, Evaluation of Medicines for Human Use, *Draft Note for Guidance on Excipients, Antioxidants and Antimicrobial Preservatives in the Dossier for Application for Marketing Authorisation of a Medicinal Product, at 8 (2003)*, available at https://www.ema.europa.eu/en/documents/scientific-guideline/draft-note-guidance-excipients-antioxidants-antimicrobial-preservatives-dossier-application_en.pdf				
U.S. Patent No. 8,633,194				
U.S. Patent No. 8,633,194 Certified File History		UCB_AP00000009		UCB_AP00000755
Ueno Fine Chemicals Industry, *Parabens as Preservatives*, available at (https://www.ueno-fc.co.jp/english/pdf/PARABEN2013.pdf)				
Valkova, N, et al, *Hydrolysis of 4-Hydroxybenzoic Acid Esters (Parabens) and Their Aerobic Transformation into Phenol by the Resistant Enterobacter cloacae Strain EM*, 67 Applied and Environmental Microbiology 2404-09 (2001)				
WO2004/050094				
Xyzal Oral Solution 3.2.P.1 Description and Composition of the Drug Product US		UCB_AP00006015		UCB_AP00006015
Xyzal Oral Solution 3.2.P.5.1 Specification(s) SFP-157-03		UCB_AP00006052		UCB_AP00006053
All references cited in Opening Expert Report of Sarfaraz K. Niazi, Ph.D.				