IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE

MEDA PHARMACEUTICALS INC. and CIPLA LTD.,	)	
Plaintiffs,	)	
v.	)	C.A. No. 14-1453-LPS
APOTEX INC. and APOTEX CORP.,	)	
Defendants.	)	

PLAINTIFFS MEDA AND CIPLA'S RESPONSE TO
DEFENDANTS' CLAIM CONSTRUCTION TUTORIAL

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I. Introduction

Plaintiffs Meda Pharmaceuticals Inc. and Cipla Ltd. (together, "Plaintiffs") submit this Response to the Claim Construction Tutorial of Defendants Apotex Inc. and Apotex Corp. (together, "Apotex") to address certain inaccuracies and improper arguments related to invalidity and claim construction in Apotex's tutorial.

II. Apotex's Tutorial Provides a Selective Recitation of the Technology to Advance Improper Invalidity Arguments

Apotex provides a selective view of the history of the active ingredients of the claimed product, as well as their mechanism of action[1] to advance its invalidity positions before expert discovery. Plaintiffs will briefly clarify Apotex's misleading statements here and will provide more detail during expert discovery and at trial. For example, Apotex's "History of Drug Substances at Issue" provides only a selective list of the alleged dates of discovery of the class of antihistamines and corticosteroids and the use, publication, and sale of two particular types. This leaves the false impression that the active ingredients in the claimed formulation have been known and used for decades. (Apotex Tutorial at 9-16.)

As an initial matter, the summary conflates the many different types of corticosteroids and antihistamines that have undergone substantial evolution over time, such as the reduction in sedative side effects achieved by new chemical structures of second-generation antihistamines compared to first-generation antihistamines. The summary also ignores the development of various dosage forms of antihistamines and corticosteroids (*e.g.* oral, nasal). Finally, the

[1] On slide 18, Apotex identifies histamine as being "shown in purple" but Plaintiffs assume this is an inadvertent error as the mast cell is shown in purple and histamine is shown in green-blue.

summary fails to distinguish the conditions treated by the various dosage forms or the knowledge and understanding required to treat these different conditions.

Apotex also oversimplifies the operation of fluticasone, a corticosteroid, in its slide titled "Fluticasone Mechanism of Action." (*Id.* at 21.) While Apotex correctly states that fluticasone works by reducing inflammation, Apotex incorrectly attributes this effect to "reducing the activity" of three cell types: mast cells, eosinophils, and basophils, "thus reducing the amount of histamine or other related substances released." Apotex confuses the science in order to advance improper invalidity arguments that "the mechanism of action for corticosteroids complements the mechanism of action of antihistamines" and that "the patents at issue involve the combination of two well-known drug substances." (*Id.* at 22.)

The literature published by the priority date and even after, however, demonstrates that the mechanism of action of fluticasone propionate is more complicated and less well understood than Apotex suggests. While mast cells, eosinophils, and basophils, among others cells and molecules, are involved in the inflammatory response, the exact mechanism of action of fluticasone and other corticosteroids is unknown. For example, a 2001 publication observes that although the exact mechanism of action of intranasal steroids are not known, the major pathway involves binding of the steroid molecule to a cytoplasmic receptor that is then transported to the nucleus where it binds to the DNA at the glucocorticoid response element. This results in inhibition of a variety of pro-inflammatory cytokines that decrease the inflammatory response. *See*, *e.g.*, Joint Claim Construction Ex. 39, Galant and Wilkinson, *Clinical Prescribing of Allergic Rhinitis Medication in the Preschool and Young School-Age Child*, BioDrugs Vol. 15, No. 7, 453-463 (2001). Further, the label for Flonase®, GlaxoSmithKline's fluticasone propionate nasal spray which received FDA approval in 1994, states that "[t]he precise

mechanism through which fluticasone propionate affects allergic rhinitis symptoms is not known." Product Information for Flonase® (fluticasone propionate) Nasal Spray, 50 mcg, at Apotex's Opening Claim Construction Brief at Ex. G, APOTEX_AZFL 0060187.

Finally, on the last slide of Apotex's tutorial, it appears that Apotex is arguing its validity case when it states that "nasal sprays containing both antihistamines and corticosteroids were also specifically known in the prior art to the asserted patents" citing "EP 0780127 A1 (1997)." (Apotex Tutorial at 22.) Apotex's statement is wholly unrelated to the background of the technology at issue, and it also omits that the USPTO Examiner thoroughly considered the cited reference and similar arguments during prosecution of the asserted U.S. Patent No. 8,168,620 ("the '620 patent"). The patentee overcame these arguments and the reference, and the USPTO found the claims to be patentable and issued both asserted patents.[1] During expert discovery, Plaintiffs will provide a more thorough overview of the state of the art, but until that time, Apotex's presentation of its invalidity arguments is inappropriate.

III. Apotex's Tutorial Advances Claim Construction Arguments

Throughout the tutorial, Apotex bases its presentation on its proposed construction of the terms "administration" and "condition," which results in a tutorial that reflects Apotex's litigation position, rather than the facts of a technology tutorial. For example, in the "Nature of this Action" slide Apotex recites an argument raised repeatedly in the "administration" section of its claim construction brief, that "[a]s discussed in the patents, the active ingredients azelastine and fluticasone 'can be administered simultaneously, … separately or sequentially.'" (Apotex

[1] In addition, Apotex fails to mention that the European Patent Office (EPO) also considered this reference during a post-grant review initiated by a third party against a European counterpart to the '620 patent. The EPO also found the claims patentable over this reference. *See In re EP 1519 731 B1* (Eur. Pat. Off., Jan. 19, 2012).

Tutorial at 3.) Likewise Apotex repeatedly pushes its construction of "condition" without providing any background on how the technology works or noting the conditions set forth in the patent and file history.

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