

UNITED STATES DISTRICT COURT  
SOUTHERN DISTRICT OF INDIANA  
INDIANAPOLIS DIVISION

ELI LILLY AND COMPANY, )  
ELI LILLY EXPORT S.A., )  
ACRUX DDS PTY LTD., )

Plaintiffs, )

1:13-cv-00851-SEB-DKL

vs. )

PERRIGO COMPANY, )  
PERRIGO ISRAEL )  
PHARMACEUTICALS LTD., )  
ACTAVIS LABORATORIES UT, INC. )  
formerly known as WATSON )  
LABORATORIES INC., )  
AMNEAL PHARMACEUTICALS LLC, )  
LUPIN PHARMACEUTICALS, INC., and )  
LUPIN LTD., )

Defendants. )

**FINDINGS OF FACT AND CONCLUSIONS OF LAW AND FINAL JUDGMENT  
BASED THEREON**

This matter is before the Court for decision on the issues of validity, enforceability, and infringement of three patents owned by Plaintiff Acrux DDS PTY Ltd. (“Acrux”). Plaintiff Eli Lilly Export S.A. is the exclusive worldwide licensee of the patents at issue in this litigation and has licensed its rights in the United States to Plaintiff Eli Lilly and Company (“Lilly”). Plaintiffs hold an approved New Drug Application (“NDA”) No. 022504 for the manufacture and sale of testosterone metered transdermal solution, 30 mg/1.5mL used to treat males for conditions associated with a deficiency or absence of endogenous testosterone. Lilly markets the product disclosed in NDA No.

022504 under the tradename Axiron®. Axiron® was approved by the Food and Drug Administration (“FDA”) on November 23, 2010. In connection with the NDA, Lilly listed nine patents in the Orange Book, including: U.S. Patent Nos. 6,299,900 (“the ‘900 patent”); 6,818,226 (“the ‘226 patent”); 6,923,983 (“the ‘983 patent”); 8,071,075 (“the ‘075 patent”); 8,419,307 (“the ‘307 patent”); 8,435,944 (“the ‘944 patent”); 8,177,449 (the ‘449 patent”); 8,807,861 (“the ‘861 patent”); and 8,993,520 (“the ‘520 patent”).

This action arises out of the Abbreviated New Drug Applications (“ANDA”) for the commercial manufacture, use, and sale of generic versions of Axiron® filed by Defendants Perrigo Company and Perrigo Israel Pharmaceuticals Ltd. (collectively, “Perrigo”); Actavis Laboratories UT, Inc. (“Actavis”); Amneal Pharmaceuticals LLC (“Amneal”); and Lupin Pharmaceuticals, Inc. and Lupin Ltd. (collectively, “Lupin”), respectively. As will be described in more detail below, each Defendant sought FDA approval to market its generic transdermal testosterone product before expiration of the patents Lilly listed in the Orange Book, and, pursuant to 21 U.S.C. § 355(j)(2)(A)(vii)(IV), each ANDA includes a “paragraph IV certification” to Plaintiffs’ patents, in which each Defendant has certified that certain patents are invalid and/or would not be infringed by Defendants’ manufacture, use, or sale, of their generic testosterone products.

Plaintiffs proceeded to trial on the following representative patent claims: claim 13 of the ‘075 “formula” patent against Actavis; claim 20 of the ‘944 “axilla” patent against all defendants; and claims 9 and 10 of the ‘861 “applicator” patent against all defendants. Defendants contend that their proposed ANDA products would not infringe the asserted

claims of the '861 patent and that each of the asserted claims of the '861 patent and the '944 patent are invalid. Actavis also contends that the asserted claim of the '075 patent is invalid.

A bench trial on these issues was conducted over nine (9) days, the first eight of which ran from June 16, 2016 to/through June 28, 2016, and a final day of trial occurred on July 21, 2016. Having now considered the evidence adduced at trial and the parties' post-trial submissions, we hold, for the reasons set forth in detail below, as follows: (1) claim 13 of the '075 patent is invalid for lack of written description and enablement; (2) claim 20 of the '944 patent is invalid for obviousness; (3) the asserted claims of the '861 patent are not infringed by Actavis's, Perrigo's or Lupin's accused products; (4) claims 9 and 10 of the '861 patent are neither anticipated nor obvious and are therefore valid and enforceable; and (5) Amneal's applicator product and/or its use will directly and indirectly infringe the asserted claims of the '861 patent.

### **Findings of Fact**

#### **I. The Parties**

##### **A. Plaintiffs**

Lilly is an Indiana corporation that has its corporate offices and principal place of business in Indianapolis, Indiana. Lilly is engaged in the business of research, development, manufacture, and sale of pharmaceutical products throughout the world. Eli Lilly Export S.A. is a Swiss corporation and wholly-owned subsidiary of Lilly. Its corporate offices and principal place of business are located at 16 Chemin des Coquelicots, The Air Centre, 1214 Vernier/Geneva, Switzerland. Acrux is an Australian

corporation and its corporate offices and principal place of business are located at 103-113 Stanley Street, West Melbourne VIC 3003, Australia. Acrux is engaged in the development and commercialization of pharmaceutical products.

## **B. Defendants**

Perrigo Company is a Michigan corporation with its principal place of business in Allegan, Michigan. Perrigo Israel Pharmaceuticals is an Israeli corporation with a principal place of business at 29 Lehi Street, Bnei Brak 51200, Israel. The Perrigo Defendants are engaged in the business of making and selling generic drugs, which they distribute in Indiana and throughout the United States. On April 3, 2012, Perrigo Israel submitted ANDA No. 204255, pursuant to 21 U.S.C. § 355(j), seeking approval from the FDA to sell “Testosterone Metered Transdermal Solution, 30 mg/1.5 mL.” By letter dated October 16, 2015, the FDA informed the Perrigo Defendants of its tentative approval of ANDA No. 204255.

Actavis (formerly known as Watson Laboratories, Inc.) is a Delaware corporation with its principal place of business in Salt Lake City, Utah. Actavis is engaged in the business of making and selling generic drugs, which it distributes in Indiana and throughout the United States. On January 29, 2013, Actavis filed ANDA No. 205328, pursuant to 21 U.S.C. § 355(j), seeking approval from the FDA to sell “Testosterone Topical Solution, for Topical Use, 30 mg of Testosterone per Pump Actuation.” By letter dated July 29, 2015, the FDA informed Actavis of its tentative approval of ANDA No. 205328.

Amneal is a Delaware corporation with its principal place of business in Bridgewater, New Jersey. Amneal is engaged in the business of making and selling generic drugs, which it distributes in Indiana and throughout the United States. On March 14, 2014, pursuant to 21 U.S.C. § 355(j), Amneal filed ANDA No. 206998, seeking approval from the FDA to sell “Testosterone Topical Solution, 30 mg/1.5 mL.”

Lupin Pharmaceuticals is a Delaware corporation with its principal place of business in Baltimore, Maryland. Lupin Ltd. is an Indian corporation with its principal place of business located at B/4 Laxmi Towers, Bandra-Kurla Complex, Bandra (E), Mumbai 400 051, India. Lupin Pharmaceuticals is a wholly-owned subsidiary of Lupin Ltd. The Lupin Defendants are engaged in the business of making and selling generic drugs, which they distribute in Indiana and throughout the United States. On April 13, 2015, Lupin submitted ANDA No. 208061, pursuant to 21 U.S.C. § 355(j), seeking approval from the FDA to sell “Testosterone Topical Solution, 30 mg/1.5 mL.”

Each of Defendants’ ANDA filings references Plaintiffs’ NDA No. 022504 for Axiron® (testosterone) Metered Transdermal Solution 30 mg/1.5 mL as the referenced listed drug.

## **II. The Patents-In-Suit**

### **A. The ‘075 Patent**

U.S. Patent No. 8,071,075, entitled “Dermal penetration enhancers and drug delivery systems involving the same,” issued on December 6, 2011, to named inventors Barry Leonard Reed, Timothy Mathias Morgan, and Barrie Charles Finnin. PTX-1 at 2. The ‘075 patent was assigned to Acrux DDS Pty Ltd. upon issuance. *Id.*

The '075 patent issued from U.S. Patent Application No. 11/905,926 filed on October 5, 2007. PTX-1 at 2. The '926 application is a continuation of U.S. Patent Application No. 10/759,303 filed on January 20, 2004, which issued as U.S. Patent No. 7,438,203. *Id.* The '303 application is a continuation-in-part of U.S. Patent Application No. 09/910,780 filed on July 24, 2001, which issued as U.S. Patent No. 6,818,226. *Id.* The '780 application is a divisional of U.S. Patent Application No. 09/125,436, which was filed as International Patent Application No. PCT/AU97/00091, filed on February 19, 1997, which issued as U.S. Patent No. 6,299,900. *Id.* The '075 penetration enhancer patent claims priority to Australian Provisional Patent Application No. 8144 filed on February 19, 1996.<sup>1</sup> *Id.*

Plaintiffs are asserting claim 13 of the '075 patent against Actavis.<sup>2</sup> Claim 13 depends from claims 1, 5, 9, 10, and 11. Claim 13 and the claims from which it depends recite as follows:

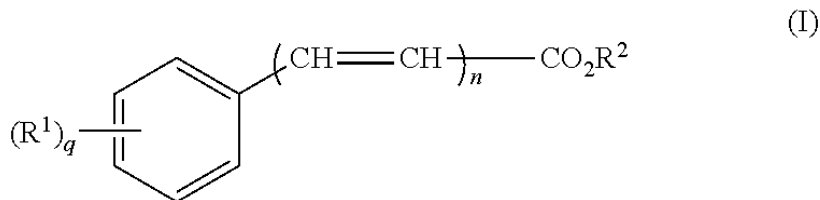
1. A transdermal drug delivery system comprising:
  - (a) a therapeutically effective amount of testosterone;

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<sup>1</sup> Plaintiffs contend that the '075 patent is entitled to priority back to the Australian provisional application filed in February 1996. Actavis initially challenged the priority date of 1996, but conceded that if the priority date were February 19, 1997, the date of the PCT filing and the date Actavis contends is the priority date, the prior art would remain the same. This dispute was mainly relevant for purposes of Actavis's obviousness challenge to the '075 patent, which it withdrew before the bench trial commenced. Accordingly, we need not make a definitive determination on this issue and will assume only for purposes of this ruling that the priority date is February 19, 2006, as it does not affect our written description and enablement analysis, which are the only two validity issues remaining in dispute.

<sup>2</sup> Plaintiffs asserted claims 1-13 of the '075 patent against Actavis. By stipulation, the parties proceeded to trial only on claim 13 of the '075 patent. They agree that disposition of claim 13 controls the disposition of the remaining asserted claims.

(b) at least one dermal penetration enhancer present in an amount of from 10 to 10,000 wt % based on the weight of the testosterone; wherein the dermal penetration enhancer is at least one ester of formula (I):



wherein  $R^1$  is hydrogen, lower alkyl, lower alkoxy, halide, hydroxy or  $\text{NR}^3\text{R}^4$ ;  $R^2$  is a  $\text{C}_8$  to  $\text{C}_{18}$  alkyl;  $R^3$  and  $R^4$  are each independently hydrogen, lower alkyl or  $R^3$  and  $R^4$  together with the nitrogen atom to which they are attached form a 5- or 6-membered heterocyclic ring;  $n$  is 0 or 1, and  $q$  is 1 or 2, wherein, when  $n$  is 0 and  $R^1$  is  $\text{NR}^3\text{R}^4$ , then  $\text{NR}^3\text{R}^4$  is para-substituted; and

(c) at least one volatile liquid present in an amount to act as a vehicle for the testosterone and penetration enhancer.

**5.** A method for the treatment of a testosterone deficient hypogonadal man which comprises administering to a dermal surface of said man in need of such treatment a therapeutically effective amount of the drug delivery system according to claim **1**.

**9.** The method according to claim **5**, wherein said ester is a  $\text{C}_8$  to  $\text{C}_{18}$  alkyl para-aminobenzoate,  $\text{C}_8$  to  $\text{C}_{18}$  alkyl dimethyl-para-aminobenzoate,  $\text{C}_8$  to  $\text{C}_{18}$  alkyl cinnamate,  $\text{C}_8$  to  $\text{C}_{18}$  alkyl methoxycinnamate or  $\text{C}_8$  to  $\text{C}_{18}$  alkyl salicylate.

**10.** The method according to claim **9**, wherein said ester is octyl dimethyl-para-aminobenzoate, octyl para-methoxycinnamate, or octyl salicylate.

**11.** The method according to claim **10**, wherein said ester is octyl salicylate.

**13.** The method according to claim **11**, wherein said volatile liquid is selected from the group consisting of ethanol, isopropanol, and a mixture thereof.

PTX-1 at 27.

Actavis has stipulated that it infringes the '075 patent, if the patent is upheld as valid. Dkt. 264 at ¶¶ 1-3.

**B. The '944 Patent**

U.S. Patent No. 8,435,944, entitled "Method and composition for transdermal drug delivery," issued on May 7, 2013, to named inventors Tony Dipietro, Andrew Humberstone, Igor Gonda, Adam Watkinson, Kerrie Setiawan, and Nina Wilkins. PTX-4 at 2. The '944 patent was assigned to Acrux DDS Pty Ltd. upon issuance. *Id.*

The '944 patent issued from U.S. Patent Application No. 11/445,463 filed on June 2, 2006. PTX-4 at 2. The '944 patent claims priority to U.S. Provisional Application No. 60/752,884 filed on December 23, 2005, and Australian Application No. 2005902902 filed on June 3, 2005. *Id.* The earliest date to which the '944 patent may claim priority is June 3, 2005. *Id.*; Hadgraft Tr. 359:23-25.

Plaintiffs assert that defendants Perrigo, Actavis, Amneal, and Lupin infringe asserted claim 20 of the '944 patent.<sup>3</sup> Hadgraft Tr. 355:2-9. The asserted claim of the '944 axilla patent and the claims to which it depends recite as follows:

**13.** A method of increasing the testosterone blood level of an adult male subject in need thereof comprising applying to at least one axilla of the subject, without occlusion by a patch device, a non-occlusive transdermal drug delivery composition consisting of: (a) a pharmaceutically effective amount of testosterone; (b) one or more lower alkyl alcohols, wherein the combined volume of the lower alkyl alcohol(s) is more than 60% (v/v) of the

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<sup>3</sup> Plaintiffs asserted claims 1-10 and 12-21 of the '944 patent and claims 1-19 of the '520 patent against Defendants. By agreement, the parties proceeded to trial only on claim 20 of the '944 patent as a representative claim for the asserted claims of these two patents. They agree that disposition of claim 20 controls the disposition of the remaining asserted claims.



composition; (c) one or more penetration enhancers selected from the group consisting of octisalate, octyldimethyl-para-aminobenzoate and octyl para-methoxycinnamate; (d) one or more viscosity modulating agents, in an amount effective to increase the viscosity of the composition to within the range of from greater than the viscosity of water to less than 300 centipoise; and (e) optionally, water, wherein the composition is applied in an amount effective to achieve a testosterone blood level in the subject of at least 200 ng/dL.

**14.** The method of claim **13** wherein the penetration enhancer is present in an amount of from 0.01% to 15% (w/v) of the composition.

**15.** The method of claim **14** wherein the penetration enhancer is octisalate.

**16.** The method of claim **15**, wherein the lower alkyl alcohol is selected from the group consisting of ethanol, isopropanol, and mixtures thereof.

**17.** The method of claim **16** wherein the combined volume of lower alkyl alcohol(s) is more than 70% (v/v).

**18.** The method of claim **17** wherein the combined volume of lower alkyl alcohols(s) is more than 80% (v/v).

**19.** The method of claim **18** wherein the viscosity modulating agent is polyvinyl pyrrolidone.

**20.** The method of claim **19** wherein the polyvinyl pyrrolidone is present in an amount of from 1% to 3% (w/v) of the composition.

PTX-4 at 18.

Defendants stipulate that they infringe the '944 patent, if the patent is upheld as valid. Dkt. 263, Joint Stipulation Between Plaintiffs and Perrigo Defendants, at ¶¶ 1-3; Dkt. 264, Joint Stipulation Between Plaintiffs and Defendant Actavis, at ¶¶ 1-3; Dkt. 272, Joint Stipulation Between Plaintiffs and Lupin Defendants as to U.S. Patent Nos. 8,435,944, 8,993,520, 8,177,449, and

8,419,307, at ¶ 13; Dkt. 284, Joint Stipulation Between Plaintiffs and Amneal as to U.S. Patent Nos. 8,435,944, 8,993,520, 8,177,449, and 8,419,307, at ¶¶ 1-3.

The use of Axiron® is an embodiment of claim 20 of the '944 patent.

### **C. The '861 Patent**

U.S. Patent Application No. 13/836,056 was filed on March 15, 2013, as a continuation of application No. 13/464,556 (now the '307 patent) and issued as the '861 patent," entitled "Spreading Implement," on August 19, 2014. PTX-5, '861 patent, at 2. The '861 patent names Peter Bayly, Mark Simon Bayly, Magnus Ahlstrom, and Adam Charles Watkinson as inventors. PTX-5, '861 patent, at 2; Dkt. 359, Stipulated Facts, at ¶ 16.

The '861 patent issued from U.S. Patent App. No. 13/836,056, filed on March 15, 2013, which is a continuation of U.S. Patent App. No. 13/464,556 filed on May 4, 2012, which is a continuation of U.S. Patent App. No. 11/678,673, filed on February 26, 2007, which claims priority to U.S. Provisional App. No. 60/884,482, filed on January 11, 2007.

Plaintiffs contend that Defendants' applicators infringe dependent claims 9 and 10 of the '861 patent.<sup>4</sup> These claims (and those from which they depend) recite as follows:

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<sup>4</sup> Plaintiffs asserted against Perrigo the following claims: 1, 10, 17-20, 23, and 25 of the '449 patent; 1-4 and 6-23 of the '307 patent; and 1, 9-11 and 19 of the '861 patent. Plaintiffs asserted against Actavis and Amneal claims 1 and 9-11 of the '861 patent and claims 1 and 9-10 of the '861 patent against Lupin. By agreement, the parties proceeded to trial on claims 9 and 10 of the '861 patent as the representative claims for the asserted Applicator Patents. Disposition of

**1.** A system for transdermal administration of a physiologically active agent from a liquid composition, the system including a container containing the liquid composition including the physiologically active agent, a dispensing device for delivering liquid composition from the container; and an applicator for applying the liquid to an area of skin for transdermal administration said applicator including a support detachably contactable to the dispensing device or container being adapted to detach to permit said dispensing device to deliver said liquid composition, a receptacle mounted on the support defining a reservoir space which receives a volume of the liquid composition from the container, the receptacle having a base and a resiliently deformable wall, the wall being substantially transverse to the base and having a working surface that is used to spread the liquid composition over the area of the skin surface, the base having a surface such that the liquid composition cannot pass through the base.

**9.** A method of transdermal administration of a physiologically active agent to a subject including providing a system according to claim **1**; applying the liquid composition including the physiologically active agent to the reservoir space; and deforming the wall of the receptacle containing the liquid composition against the skin of the subject and spreading the liquid composition over the area of the skin surface in at least one axilla.

**10.** A system according to claim **1** wherein the receptacle defining the reservoir space has an open top being configured to receive the liquid composition from the dispensing device through the open top.

(*Id.* at claims 1, 9, 10.)

Plaintiffs assert that Actavis and Perrigo indirectly infringe the '861 patent.

Dkt. 142-1, Second Consolidated Amended Complaint for Patent Infringement, at ¶¶

129-35, 180-90, 283-89, 378-88; Dkt. 264, Joint Stipulation Between Plaintiffs and

Defendant Actavis, at ¶¶ 4-6; Dkt. 263, Joint Stipulation Between Plaintiffs and Perrigo

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claims 9 and 10 of the '861 patent controls the disposition of the remaining asserted claims. *See, e.g., Scanner Techs. Corp. v. ICOS Visions Sys. Corp.*, 528 F.3d 1365, 1383-84 (Fed. Cir. 2008).

Defendants, at ¶¶ 4-6. Plaintiffs assert that Amneal and Lupin directly and indirectly infringe the '861 patent. Dkt. 142-1, Second Consolidated Amended Complaint for Patent Infringement, at ¶¶ 433-43, 488-98; Case No. 1:15-CV-1047, Dkt. 1, Complaint for Patent Infringement, at ¶¶ 73-83, 128-38.

### **III. The Experts**

#### **A. Plaintiffs' Experts**

At trial, Plaintiffs offered the testimony of the following experts: (1) Dr. Jonathan Hadgraft, an expert in transdermal formulation and skin barrier function; (2) Dr. Irwin Goldstein, an expert in urology and hypogonadism; and (3) Dr. Alexander Slocum, an expert in the field of mechanical engineering and the design of medical devices.

#### ***Jonathan Hadgraft, D.Sc.***

Dr. Jonathan Hadgraft, Plaintiffs' transdermal formulation and skin barrier function expert, has worked in the field of dermal and transdermal drug delivery for more than thirty-five years. Dr. Hadgraft testified that in his opinion the asserted claims of the '075 and '944 patents are valid.

In 1973, Dr. Hadgraft received a B.A. and M.A. in Chemistry, with an emphasis on Chemical Pharmacology, from the University of Oxford. In 1975, he earned a doctorate in Physical Chemistry from the University of Oxford. In 1992, he was awarded a D.Sc. from the Faculty of Medicine at the University of Oxford in recognition of his

research in dermal drug delivery. PTX-220; Hadgraft 102:2-104:17, 106:12-114:22, 116:20-123:23, 126:24-127:21.

Dr. Hadgraft founded the Prediction of Percutaneous Penetration Conference and Skin Forum, which is comprised of multiple academic and industrial research groups. In recognition of his contributions, he was named a Fellow of the American Association of Pharmaceutical Scientists, Academy of Pharmaceutical Sciences, and the Controlled Release Society. PTX-220; PDX-3001; Hadgraft 102:2-104:17, 106:12-114:22, 116:20-123:23, 126:24-127:21.

Dr. Hadgraft has conducted research, lectured extensively on skin barrier function and dermal and transdermal drug delivery, and published more than 500 peer-reviewed articles. Dr. Hadgraft currently holds the rank of Emeritus Professor of Biophysical Chemistry at the School of Pharmacy, the University of London. Prior to assuming Emeritus status, Dr. Hadgraft was a full-time Professor of Biophysical Chemistry at the School of Pharmacy. Since the 1980s, Dr. Hadgraft has served as an industry consultant for SmithKline Beecham, Eastman Kodak, Shire and others on formulations for dermal and transdermal therapies. Dr. Hadgraft worked on approved transdermal products, such as nitroglycerin, clonidine, estradiol, fentanyl, and nicotine. PTX-220; PDX-3000; PDX-3002; Hadgraft 102:2-104:17, 106:12-114:22, 116:20-123:23, 126:24-127:21; 142:25-143:5. However, he has never been the lead formulator of a transdermal product that has been approved by the FDA and has never worked on any actual experiments with

testosterone or conducted any research and development of a transdermal testosterone product. Hadgraft 306:10-12, 307:23-308:6.

***Irwin Goldstein, M.D.***

Dr. Irwin Goldstein is a Board-certified urologist. The field of urology focuses on the organs associated with the urinary system and male reproduction. At trial, Dr. Goldstein opined that the asserted claim of the '944 patent would not have been obvious.

Dr. Goldstein received his M.D.C.M. from McGill University Faculty of Medicine in 1975. He served as a surgical resident and fellow at University Hospital in Boston. In 1982, Dr. Goldstein joined the faculty of Boston University School of Medicine, teaching courses in urology and gynecology until 2005. PDX-7000; PDX-7001; Goldstein 604:9-610:10.

Dr. Goldstein has been treating patients for more than forty years. He has taught and lectured widely and published in excess of 300 peer-reviewed papers. Dr. Goldstein currently holds the position of Clinical Professor of Surgery at the University of San Diego and Director of San Diego Sexual Medicine, where he diagnoses and treats patients with hypogonadism. He also serves as a consultant in the Surgical Service of the San Diego Veterans Administration Hospital. PDX-7000; PDX-7001; Goldstein 604:9-610:10.

Dr. Goldstein was a principal investigator or co-investigator for various clinical trials, and was a consultant on a clinical trial involving the FDA's consideration of undecanoate as an oral testosterone therapy. Dr. Goldstein has been granted funding by

the National Institutes of Health to study urologic complications of diabetes and sexual dysfunction. PDX-7000; PDX-7001; Goldstein 604:9-610:10.

***Alexander H. Slocum, Ph.D.***

Dr. Alexander Slocum is an expert in the field of mechanical engineering. He conducts research, has published in excess of 100 academic peer-reviewed journal papers, and lectures extensively in the field. PTX-222 at 2, 4-5; Slocum 525:22-24, 526:21-527:11, 532:3-8. Dr. Slocum opined at trial that the asserted claims of the '861 patent are valid and infringed by Defendants' products.

Dr. Slocum received his Bachelor of Science degree in mechanical engineering in 1982, a Master of Science degree in 1983, and a Ph.D. in mechanical engineering in 1985, all from the Massachusetts Institute of Technology ("MIT"). PTX-222 at 1; Slocum 526:13-15. He is currently the Pappalardo Professor of Mechanical Engineering at MIT. PTX-222 at 3; Slocum 527:10-11. He teaches and conducts research in the field of precision machine design. PTX-222; Slocum 527:12-19, 531:2-8, 533:15-535:2. He has a particular research focus on machine tools and manufacturing equipment, medical devices, renewable energy machines, and tools for the petroleum industry. PTX-222; Slocum 535:13-536:7. He has extensive experience studying and working with fluids and seals. Slocum 527:12-19.

From 1983 until 1986, he served as a mechanical engineer with the National Institute of Standards & Technology ("NIST"). PTX-222 at 2; Slocum 526:17-21. During his tenure at NIST, he assisted with the Charters of Freedom project to create the

encasements to house and protect the Bill of Rights, Constitution, and Declaration of Independence in the National Archives. Slocum 527:24-528:14. In 1986, he received the U.S. Department of Commerce Bronze Medal Award for Outstanding Federal Service. PTX-222 at 3.

Dr. Slocum has been awarded more than 100 patents and has developed an important precision alignment standard for the semiconductor industry. PTX-222 at 1; Slocum 533:10-535:12. He has helped to create eleven products that have been awarded “R&D 100” awards, each for being one of the one hundred most technologically significant new products of the year. PTX-222 at 2-3; Slocum 533:1-8.

Dr. Slocum is the author of the books “Precision Machine Design” (Dearborn, MI, SME 1985) and “FUNdaMENTALS of Design” (Cambridge, MA, MIT 2005), <http://pergatory.mit.edu/resources/FUNdaMENTALS.html>. PTX-222 at 2; Slocum 530:22-531:18. He has also received the SME Frederick W. Taylor Research Medal and the ASME Leonardo da Vinci and Machine Design Awards, which are the two most prestigious awards for machine design bestowed by the American Society for Mechanical Engineers. PTX-222 at 2-3; Slocum 533:9-535:2.

## **B. Defendants’ Experts**

At trial, Defendants presented the testimony of the following experts, each of whom appeared in person: (1) Dr. Russell Potts, an expert in the field of research and development for the transdermal delivery of active pharmaceutical ingredients into and through the skin; (2) Dr. Walter Chambliss, an expert in the field of pharmaceutical



sciences and pharmaceutical formulations and related fields; (3) Dr. Peter Snyder, an expert in the field of endocrinology and the treatment of hypogonadism with testosterone; (4) Dr. Sher Singh, an expert in the field of the design and manufacturing of products and packaging for cosmetic, health and beauty aids and pharmaceutical applications; and (5) Dr. Steven MacLean, an expert appearing on behalf of Lupin regarding the fields of polymer science and mechanical engineering. Amneal offered the additional expert testimony of Mr. Hermann Plank, an expert in design and manufacture of products and packaging for cosmetic, health and beauty aids, and pharmaceutical applications, who appeared and testified through written submission.

***Russell Potts, Ph.D.***

Dr. Potts's expertise relates to research and development for the transdermal delivery of active pharmaceutical ingredients into and through the skin. Potts 1304:13-16, 1306:2-9. He testified that, in his opinion, the asserted claims of the '075 and the '944 patents are invalid.

Dr. Potts received his Bachelor of Science degree in Chemistry at Michigan State University in 1968, his Masters of Science degree in Physical Chemistry at Cornell University in 1970, his Ph.D. in Biochemistry at the University of Massachusetts in Amherst in 1978, and undertook post-doctoral training in Chemistry at Yale University in 1979. DTX-1122 at 2. Dr. Potts accrued more than 30 years of professional experience relating to drug delivery into and through the skin, including conducting and leading research at Gillette Research Institute, Pfizer Central Research, and Cygnus Therapeutic

Systems. Potts 1301:3-23. His industry work has led to several FDA-approved transdermal drug products, including a nicotine patch and contraceptive patch. *Id.* at 1301:24-1302:11. In 2002, Dr. Potts retired from full-time work in the pharmaceutical industry to become a full-time consultant.

Dr. Potts has published more than 115 papers in the area of skin transport and has been awarded 35 U.S. patents. *Id.* at 1302:12-19. He is a recognized leader in the field of transdermal drug delivery, having served on the board of several prominent journals and was elected a fellow of significant industry organizations in the field of pharmaceutical sciences. *Id.* at 1302:23-1303:22. Most notably, in 1991, Dr. Potts served as the Chairman of the Gordon Conference on topical and transdermal drug delivery. *Id.*

***Walter Chambliss, Ph.D.***

Dr. Chambliss is an expert in the field of pharmaceutical sciences and pharmaceutical formulations and related areas. Chambliss 1529:11-17; 1535:5-1536:7. At trial, he testified that in his opinion claim 20 of the '944 patent is invalid. He also testified regarding certain aspects of the asserted claims 9 and 10 of the '861 patent.

Dr. Chambliss accrued 30 years of experience in pharmaceutical research and development, both in industry and academia, including extensive experience in the formulation, development, and manufacturing of a variety of types of formulations that are applied to the skin for topical and/or transdermal use, including hydroalcoholic solution, lotion and gel formulations. Chambliss 1530:21-1535:4; PGO DX 2-2, 2-3;

PTX-224. Dr. Chambliss received a Bachelor of Science degree in Pharmacy in 1977, a Masters of Science degree in Pharmaceutics in 1980, and a Ph.D. in Pharmaceutics in 1982, all from the University of Mississippi. Chambliss 1529:18-1530:16; PTX-224. For seventeen years, Dr. Chambliss researched and developed various pharmaceutical products for G.D. Searle, Bristol-Myers, and Schering-Plough. Overall, he was involved in the formulation development and/or process development of more than 300 products. Chambliss 1530:21-1535:4; PGO DX 2-2, 2-3; PTX-224. In 1998, Dr. Chambliss retired from full-time work in the pharmaceutical industry, following which he has worked as a consultant. Currently, he is a professor of pharmaceutics at the University of Mississippi. Chambliss 1531:9-21; PTX-224.

***Peter Snyder, M.D.***

Dr. Snyder testified as an expert in the field of endocrinology and the treatment of hypogonadism with testosterone. Snyder 912:25-913:8. He opined that the asserted secondary considerations do not provide compelling evidence of the nonobviousness of asserted claim 20 of the '944 patent.

Dr. Snyder received his Bachelor's degree from Williams College in 1961 and his M.D. from the Harvard Medical School in 1965. DTX-1121 at 2. He completed his residency in internal medicine at Beth Israel Hospital in Boston and received a fellowship in endocrinology at the University of Pennsylvania in 1971. *Id.* Following his fellowship, Dr. Snyder has been a member of the faculty at the University of Pennsylvania in the field of endocrinology, specializing in reproductive endocrinology, which is the study of conditions affecting reproductive organs. Snyder 909:3-13.

Dr. Snyder has conducted extensive research in the area of reproductive endocrinology, including the treatment of male hypogonadism with transdermal testosterone replacement therapies. *Id.* at 910:3-7, 911:20-22, 912:6-16. He was involved with the pivotal clinical trials leading to FDA approval for Testoderm®, Testoderm® TTS, and AndroGel®. *Id.* at 912:6-16. Dr. Snyder is currently heading up the largest clinical trial of testosterone replacement therapy, which involves approximately 800 patients located at 12 centers across the United States. *Id.* at 910:24-911:15.

***Sher Paul Singh, Ph.D.***

Dr. Singh's expertise is the design and manufacturing of products and packaging for cosmetic, health and beauty aids and pharmaceutical applications. *See Singh* 1010:5-7. At trial, he testified that in his opinion Defendants' applicator products did not infringe on the '861 patent. He also testified as to the invalidity of the '861 patent.

Dr. Singh received a Bachelor of Science degree in Mechanical Engineering with Honors at Punjab University in Chandigarh, India in 1982, a Masters of Science degree in Packaging from Michigan State University in 1983, and a Doctorate in Agricultural Engineering from Michigan State University in 1987. *See Singh* 1006:23-1007:3. Dr. Singh is currently Professor Emeritus at Michigan State University and President of Packaging Forensics Associates Inc., a Michigan consulting company providing consulting services and expert testimony for transportation, packaging, and personal injury litigations. *See Singh* 1004:12-15. Dr. Singh has authored more than 150 peer-

reviewed papers, and participated as a contributing author of two text books and eight book chapters in the areas of packaging, machinery, and forensics. *See Singh 1008:21-23.*

Dr. Singh has served as a consultant for various companies, including leading suppliers of health and beauty aids, pharmaceuticals, and medical device packaging systems, for whom he has designed, tested, and evaluated various products and packaging systems. *See Singh Tr. 1008:11-16.* Dr. Singh currently serves as a member of several professional societies and associations representing the manufacturers of consumer products and packaging, including the International Association of Packaging Research Institutes and the American Society of Testing and Materials. *See Singh Tr. 1009:15-20.*

***Steven MacLean, Ph.D., P.E.***

Dr. MacLean is Lupin's expert based on his knowledge and experience in polymer science and mechanical engineering. *MacLean 1657:5-13.* He opined at trial that asserted claims 9 and 10 of the '861 applicator patent are invalid for indefiniteness. He further testified that Lupin's applicator does not infringe claims 9 and 10 of the '861 patent.

Dr. MacLean received his Ph.D. in Materials Science from the University of Rochester in 2007, following his completion of his Master of Science degree in Materials Science and Engineering from Rochester Institute of Technology in 2001. *DTX-3002\_001; MacLean 1645:7-13; DDX-502.* His Master's degree and Ph.D. were concentrated on the field of polymers. *MacLean 1645:14-20.* Dr. MacLean also received

a Bachelor of Sciences degree and a Master of Engineering degree in Mechanical Engineering from Rensselaer Polytechnic Institute in 1993 and 1997, respectively. DTX-3002\_001; MacLean 1645:7-13; DDX-502.

Dr. MacLean is a licensed, registered Professional Engineer in Mechanical Engineering in the States of New York and Maryland and a certified Six Sigma Black Belt. DTX-3002\_002; MacLean 1646:1-1647:10; DDX 503. Currently, Dr. MacLean is a Principal Engineer in the Polymer Science and Materials Chemistry Practice at Exponent Failure Analysis Associates, Inc., which is an engineering and scientific consulting firm. MacLean 1649:23-1650-6. Dr. MacLean conducts proactive as well as reactive investigations, assisting clients in developing or designing products and providing product failure analyses in areas including intellectual property matters. MacLean 1650:8-21. He has sixteen years of experience in materials selection as well as designing, testing, and manufacturing polymeric raw materials. MacLean 1648:16-1649-14; DDX 504. In his 20 years in the polymer industry, Dr. MacLean concentrated his work on numerous medical devices, including trocar tubes, syringes, surgical scalpels, vaginal speculums, tongue retractor implants, pelvic mesh implants, sleep apnea masks and devices. MacLean 1651:2-9.

Dr. MacLean is a voting member of the American Society for Testing Materials (“ASTM”), a professional organization that develops test standards for materials, and is a senior member of the Society of Plastics Engineers. MacLean 1651:12-1652:9; DDX-505; DTX-3002\_004. Dr. MacLean has authored and presented approximately 25 publications and presentations in the fields of polymer science and polymer mechanics,

including *Designing for injection molded parts*, General Electrics Plastics Customer Design Workshop (1998, 1999); *Mechanical behavior of polymeric materials*, General Electrics Plastics Engineering Workshop (1997); and *The importance of polymer structure-property relationships in preventing failure in medical devices*, Medical Grade Polymers Conference (2015). MacLean 1652:11-1653:20; DDX-506; DTX-3002\_002-3.

***Hermann Plank, MSc.***

Mr. Plank, MSc. is Amneal's expert in the design and manufacture of products and packaging for cosmetic, health and beauty aids, and pharmaceutical applications. He received his Masters of Science degree in Plastics Technology from Leoben University in Austria in 1985. He presently is the President of TecnoKal LLC. For thirty years, he has been engaged in Plastics Technology, including product development and execution as well as plastics, thermoplastics, thermoset, composite materials, injection molding, extrusion, thermoforming, blow molding, and defining prototyping methods. Mr. Plank is credited for his work in designing several applicators for delivery of cosmetic and other products to the body, including underarm applicators. In his opinion, Amneal's proposed applicator does not infringe any of the asserted claims of the '861 patent.<sup>5</sup>

**IV. The '075 Formula Patent**

The '075 formula patent claims a transdermal drug delivery system comprising a therapeutically effective amount of testosterone and at least one dermal penetration

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<sup>5</sup> By stipulation, in lieu of live testimony from Mr. Plank at trial, the parties admitted the Expert Report of Hermann Plank MSc., dated February 19, 2016 ("Plank Report"), including Exhibits 1 and 2 of the Plank Report as his direct testimony. See ECF No. 411. Mr. Plank's report was admitted as DTX-2082.

enhancer selected from safe ester sunscreens. PTX-1 at 2. The drug delivery system claimed in the '075 patent is used to treat various medical conditions, including testosterone deficiency in hypogonadal men. *Id.* at col. 28, ll. 32-26.

### ***Definition of a Person of Ordinary Skill in the Art for the '075 Patent***

A person of ordinary skill in the art (“POSA”) for the '075 formula patent would have been a pharmaceutical formulator with a doctorate or master’s degree and with at least two years of experience in transdermal or topical formulation, working together with, or able to rely on, the expertise of a clinician or physician. Hadgraft 250:23-251:5; 251:14-16. Both sides’ experts agree that their opinions on validity of the '075 patent are the same regardless of which expert’s precise POSA definition is adopted. Hadgraft 219:1-5; Potts 1309:17-1310:9.

### ***Hypogonadism***

Hypogonadism is the medical term for the physical condition of low levels of testosterone in men. Goldstein 616:14-19. Testosterone is a 19 carbon sex-steroid that is a male hormone circulating in human blood that affects male androgen dependent tissues, e.g., the prostate, scrotum, and apocrine glands. PDX-7003; Goldstein 613:15-614:8. Testosterone also forms and develops secondary sex characteristics such as facial hair, muscle strength, deepening of the voice, bone growth, sperm maturation, and sexual desire. Goldstein 614:9-14. There are several organs involved in the production and secretion of testosterone, including the hypothalamus, pituitary gland, and testicles. PDX-7003; Goldstein 615:8-616:13.



Hypogonadism is generally classified as primary or secondary hypogonadism. Primary hypogonadism is a lack of function of the testes; anorchism, orchitis, cancer of the testicles, and Klinefelter syndrome are examples. PTX-390 at 1; PDX-7004; Goldstein 617:3-12. Secondary hypogonadism involves a breakdown of the regulatory system that governs the hypothalamus and pituitary glands which regulates the production of testosterone. Tumors, diabetes, hypertension, high cholesterol, and HIV exemplify conditions that can lead to secondary hypogonadism and interfere with or limit testosterone production. PDX-7006; Goldstein 618:5-22.

A hypogonadal male may suffer physical, metabolic, cognitive, psychological, and sexual symptoms, e.g., decreased bone density, impaired memory, and reduced libido. PDX-7007; Goldstein 619:8-620:15. In 2005, it was estimated that approximately 13 million men were hypogonadal. Goldstein 621:1-15.

### ***The Invention and '075 Patent***

Although testosterone treatments have been available for many years, early treatment modalities involved the administration of drugs by intramuscular injection or oral administration, both of which had significant drawbacks. Transdermal delivery of testosterone, by contrast, offered a number of advantages, including reduced pain, ease of administration, and better bioavailability. PTX-390 at 1; PTX-253 at 1, 3; PDX-7008; Hadgraft 132:11-21; Goldstein 621:16-24.

In the 1980s, Drs. Reed and Finnin, professors in Melbourne, Australia, were engaged in transdermal formulation research, studying formulations containing

hydroquinone, a compound that causes depigmentation in the skin. Because they were concerned that the effects of sun exposure on skin would interfere with the effects of the hydroquinone formulations, they decided to add a sunscreen agent to the formulation. Upon adding the sunscreen agent, they were surprised to observe that a formulation without the normal penetration enhancer but with sunscreen substantially enhanced transdermal penetration of hydroquinone. PTX-1 at co. 11:41-45 (“Additionally the group of compounds of the invention surprisingly exhibited appreciable penetration into and substantivity for the outer layers of the skin, namely the stratum corneum which has previously presented a formidable barrier to percutaneous drug absorption.”).

Following this discovery, Drs. Reed and Finnin continued their research with Tim Morgan, then a Ph.D. student. Together, these inventors of the ‘075 patent discovered that sunscreen compounds in combination with testosterone showed a significant improvement in skin penetration, and that the penetration enhancer, octyl salicylate, in particular, showed a substantial improvement in testosterone absorption through the skin. PTX-1 at col. 23, ll. 15-41; Hadgraft 165:14-24.

In 1998, the inventors of the ‘075 patent along with a small group of founding members formed the company Acrux to develop pharmaceutical treatment based on their discovery. Their development work led to FDA approval of two products that include octyl salicylate as the dermal penetration enhancer – Evamist®, an estrogen product sold

in the United States, and Axiron®, which is a transdermal testosterone formulation used to treat hypogonadal men. Axiron® is the product at issue in this litigation.<sup>6</sup>

### ***Contemporaneous Transdermal Drug Formulations***

By February 1996, when the priority application for the '075 patent was filed, several compounds were in use or otherwise known that delivered transdermally into systemic circulation: scopolamine, nitroglycerin, fentanyl, nicotine, estradiol, isosorbide dinitrate, clonidine, norethisterone, and testosterone. PTX-531 at 17; PTX-253 at 3; PDX-3004; Hadgraft 141:20-143:18. As of 1996, transdermal testosterone formulations were commercially available and known to be therapeutically effective in increasing testosterone blood levels. PDX-2064. These formulations included the marketed drugs Testoderm®; Androderm® (PTX-630); Percutacrine Androgenique Forte (PTX-576 at 2); Testogel®; and a formulation that was not marketed but had been tested by Heiber *et al.* PTX-409 at 21-22; Dkt. 367 ¶ 88.

### ***Claim 13 of the '075 Patent***

Claim 13 of the '075 patent claims a method for the treatment of a testosterone deficient hypogonadal man which comprises administering to a dermal surface of said man in need of such treatment a therapeutically effective amount of a transdermal drug delivery system comprising: (a) a therapeutically effective amount of testosterone, (b)

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<sup>6</sup> Each metered dose of Axiron® contains 30 mg of testosterone in 1.5 mL of solution. PTX-44 at 8. The solution is 2% w/v testosterone (2.44% w/w); 5% w/v octisalate (6.1% w/w); 2% w/v povidone (2.44% w/w); 30% v/v isopropyl alcohol (28.76% w/w); and the remainder is ethanol alcohol (60.25% w/w). PTX-75 at 211.

octyl salicylate as a dermal penetration enhancer present in an amount of from 10 to 10,000 wt % based on the weight of the testosterone,<sup>7</sup> and (c) at least one volatile liquid selected from the group consisting of ethanol, isopropanol, and a mixture thereof present in an amount to act as a vehicle for the testosterone and penetration enhancer. PTX-1 at claims 1, 5, 9-11, 13. This description is consistent with Plaintiffs' proffered description of the scope of claim 13 in their opening statement as well as their pre-trial submissions. See PDX 2019; Dkt. 364 at 51-53; 227-228.

A POSA would understand that the transdermal drug delivery system recited in asserted claim 13 must include the penetration enhancer octyl salicylate in an amount ranging from 10% to 10,000% relative to the weight of testosterone. Potts 1307:22-1308:11; 1310:16-1311:3; see Hadgraft 340:21-341:15. The claimed upper limit of 10,000% corresponds to 100 times more octyl salicylate than testosterone by weight. Potts 1310:16-1311:3.

### ***The Testosterone Formulation Examples in the '075 Patent Specification***

The specification of the '075 penetration enhancer patent includes no exemplary testosterone formulation having 100-times more octyl salicylate than testosterone. Hadgraft 324:16-325:4; Potts 1321:11-1322:6. The parties' experts are not aware of any transdermal formulation that includes 100 times more penetration enhancer than active

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<sup>7</sup> This range is greatly expanded from that disclosed in the Australian provisional application. The disclosed range of penetration enhancer in the Australian provisional application was an amount of up to only 1,000% weight percent based on the weight of the active agent, which equates to 10 times more penetration enhancer than active. In the '075 patent, the 10,000 weight percent is claimed. We discuss this expansion in detail below.

ingredient and there is no evidence that the inventors ever made or tested such a formulation. Hadgraft 325:5-12. The specification instructs that “[t]he concentration of absorption/penetration enhancer may be in the range from 10-10,000 weight percent of absorption/penetration enhancer based upon the weight of the active ingredient.” PTX-1 at col. 12, ll. 35-45. But “[t]he ratio of penetration enhancer to active ingredient may vary considerably and will be governed as much as anything, by the pharmacological results that are required to be achieved.” *Id.* “In principle, it is desirable that as little absorption enhancer as possible is used,” but, “for some actives, it may well be that the upper range of 10,000% by weight will be required.” *Id.* The specification lists approximately 700 active ingredients. Hadgraft 341:23-342:20; PTX-1 at col. 5, l. 23 – col. 9, l. 60. The specification does not name testosterone as an active ingredient for which the inventors believed 10,000% of penetration enhancer may be required. Potts 1319:13-22; PTX-1 at col. 12, ll. 35-45.

The specification contains five examples disclosing transdermal formulations with testosterone, and all five have 12% w/v testosterone and 8% v/v of penetration enhancer—including Example 10 reciting 12% w/v testosterone and 8% v/v of octyl salicylate. PTX-1 at Examples 6, 10, 12, 13, and 15; Potts 1320:8-17, 1321:11-1322:6; Hadgraft 348:5-8; DDX 212. This ratio in all of the testosterone examples corresponds to approximately 0.67-times (or 67%) of the penetration enhancer by weight of testosterone. Potts 1320:18-1321:10. Accordingly, the examples illustrate that a formulation comprising less octyl salicylate than testosterone is effective. There is no other indication

in the specification that testosterone is an active ingredient that may require 10,000% of penetration enhancer. *Id.* at 1319:10-1322:6.

***Composition of Formula with 100 Times More Penetration Enhancer than Testosterone***

Defendants' expert, Dr. Potts, testified as to one way in which a POSA might make the claimed formulation with 100 times more penetration enhancer than testosterone. The first ingredient of the claimed formulation is a therapeutically effective amount of testosterone for treatment of a testosterone deficient hypogonadal man. PTX-1 at claim 13. The patent specification teaches that in hormone replacement therapy, for example with the Androderm® testosterone patch, the goal is to deliver 5 to 6 mg of testosterone per day to a testosterone deficient hypogonadal man. PTX-1 at col. 24, ll. 25-35; Potts 1327:14-1328:1. To deliver this amount of testosterone across the skin, Androderm® included 12.5 mg testosterone in its patch reservoir. Potts 1328:2-1329:14. The second ingredient of the claimed formulation is 100-times more octyl salicylate than testosterone at the upper claimed limit. PTX-1 at claim 13. If a POSA were to prepare a formulation having the same amount of testosterone as Androderm® and 100-times more octyl salicylate than testosterone, then the formulation would have 12.5 mg testosterone and 1,250 mg octyl salicylate. Potts 1330:2-1331:5. The third ingredient of the claimed formulation is ethanol, isopropanol, or a mixture thereof in an amount sufficient to act as a vehicle for the testosterone and penetration enhancer. PTX-1 at claim 13. The testosterone examples of the '075 penetration enhancer patent include a volatile liquid in an amount of four times the combined amount of testosterone and penetration enhancer

(or 80% by weight of the final formulation). *Id.* at Examples 6, 10, 12, 13, 15.

Accordingly, a POSA following the teachings of the '075 penetration enhancer patent would add 5,050 mg of volatile liquid to the formulation containing 12.5 mg testosterone and 1,250 mg octyl salicylate, for a total of 6,312.5 mg of material. Potts 1330:2-1331:5.

In transdermal drug delivery, typically only a few milligrams of material per square centimeter is spread across the skin. *Id.* Therefore, a formulation amounting to over 6,300 mg would need to be spread over thousands of square centimeters of the skin.

*Id.*

#### ***Concerns Identified in the '075 Patent Specification Related to Skin Irritation and Application Time***

The '075 patent specification identifies the minimization of skin irritation and drying time following application of the testosterone composition as two objectives of the invention. At the time of the invention, it was well-known that effective dermal penetration enhancers may be irritating to the skin, and the potential for skin irritancy increases as the concentration of the dermal penetration enhancers increases. Potts 1322:7-1324:18; Hadgraft 148:8-21. Dr. Hadgraft testified that in some cases, effective penetration enhancers can be too irritating to the skin to be tolerated. Hadgraft 323:18-21. To address the potential for skin irritation, the patent specification teaches that it is desirable to use as little enhancer as possible. Potts 1322:16-22 (referring to PTX-1 at col. 2, ll. 51-53, col. 4, ll. 13-15, col. 12, ll. 41-42). The patent specification further teaches that it is desirable for the claimed invention to have a convenient application time. Potts 1323:4-1324:5 (referring to PTX-1 at col. 4, ll. 1-6, col. 10, ll. 50-56).

Preparing a formulation that has 100 times more penetration enhancer than testosterone is at odds with the invention's purposes of minimizing skin irritation and applying a formulation that dries quickly. *Id.* at 1322:7-1324:18, 1325:8-18.

***Testing Required to Ensure Efficacy of Formula Using 100 Times More Penetration Enhancer than Testosterone***

Even if a POSA prepared a formulation having 100-times more octyl salicylate than testosterone, he would not know whether a formulation with such an extreme ratio of low active ingredient to high permeation enhancer would work without testing it first. Hadgraft 319:21-320:3. Dr. Potts is not aware of any evidence that anyone has ever made a formulation with 100 times more octyl salicylate than testosterone. Potts 1334:10-13. Dr. Hadgraft also is not aware of any indication that the inventors had actually made or tested a formulation that had 100 times more penetration enhancer than testosterone. Hadgraft 325:9-12. Nor is he aware of any person who has ever made a transdermal formulation that had 100 times more penetration enhancer than testosterone. Hadgraft 319:8-18. In the absence of this information in the patent specification, a POSA would need to conduct further testing, such as skin penetration studies, stability studies, and skin irritancy studies. *Id.* at 320:4-23.

As discussed above, more effective penetration enhancement typically correlates with increased skin irritation, and the potential for skin irritancy increases as the concentration of the dermal penetration enhancers increases. Potts 1322:16-22; Hadgraft 148:8-21. Octyl salicylate was generally recognized as safe for application to the skin in a concentration of up to 5%, but in Dr. Potts's hypothetical formulation, the octyl



salicylate is present in an amount of about 19.8%—equivalent to 1,250 mg out of 6,312.5 mg. Potts 1330:2-1331:5, 1439:2-15. Accordingly, a POSA would be particularly concerned that using 100 times more octyl salicylate than testosterone in a formulation that is spread across a very large area of the skin would be highly irritating to the skin. Potts 1336:3-9.

Dr. Hadgraft further explained that transitioning from these *in vitro* experiments to *in vivo* experiments can be an unpredictable process. Hadgraft 323:14-21. Therefore, according to Dr. Hadgraft, even if a POSA knew how much testosterone he wanted to deliver into a patient’s bloodstream, such a person would not be able to formulate a transdermal product to deliver that amount of testosterone with any degree of certainty without further testing. *Id.* at 324:11-15.

## **V. The ‘944 Axilla Patent**

The ‘944 axilla patent claims a method of treating hypogonadism by application of a non-occlusive (non-patch) transdermal testosterone formulation to the axilla. PTX-4 at claims 13-20. The relative time period for the validity analysis of the ‘944 patent is June 2005.

### ***Definition of a Person of Ordinary Skill in the Art for the ‘944 Patent***

A person of ordinary skill in the art (“POSA”) for the ‘944 axilla patent would have been a pharmaceutical formulator with a doctorate or master’s degree in pharmaceutical sciences or a similar degree and with at least two years of experience in transdermal or topical pharmaceutical formulation, working together with, or able to rely

on, the expertise of a clinician or physician. Hadgraft 250:23-251:5; 251:14-16. Both sides' experts agree that their opinions on validity of the '944 patent are the same regardless of which expert's specific POSA definition is adopted. Hadgraft 219:1-5; Potts 1339:14-1340:13; Chambliss 1538:22-1540:12.

### ***General Background of the Invention***

As of 2005, there were two types of transdermal testosterone replacement therapies on the market: patches and gels. The patches were associated with skin irritation, and the scrotal patch in particular was associated with elevated dihydrotestosterone ("DHT") levels. PTX-511 at 3; PTX-92 at 4; PTX-93 at 33; PTX-264; PTX-587; Hadgraft 197:19-22; Goldstein 622:20-23, 623:1-8, 635:9-636:22. Elevated DHT levels were associated with an increased risk of developing prostate cancer or enlarged prostate and because of the chronic or long-term nature of testosterone replacement therapy, such elevated DHT levels were of particular concern. PTX-511 at 3; PTX-92 at 4; Hadgraft 197:19-22; Goldstein 622:20-23; 636:23-637:16. The scrotal patch was withdrawn from the market in 2002 at least in part because of these concerns. PTX-587 at 4; Goldstein 623:12-15. The gels were applied to large areas, such as the upper arms, back, abdomen, thighs, buttocks, or shoulders. PDX-2064. Although gels were not associated with elevated DHT levels, it was reported that there was a risk of inadvertent transfer to a spouse or child by patients using the gels. Hadgraft 209:14-17.

Acrux sought to develop an improved testosterone replacement therapy with its sunscreen penetration enhancer formulation. In 2004, Acrux began clinical trials to

assess the safety, efficacy, and feasibility of administering testosterone through the axilla. *See, e.g.*, PTX-96; PTX-100; PTX-154; DTX-69; PTX-4, col. 20, ll. 32-67; Goldstein 668:23-669:20. The initial pilot study was conducted in women, and the follow-up study was conducted in healthy men with compressed testosterone. PTX-4 at 16, col. 20, l. 32-col. 23, l. 9; PTX-96; PTX-117. The results of the studies showed that applying testosterone to the axilla was effective at increasing testosterone blood levels and did not lead to abnormally high DHT levels or increase sweat or odor despite the increased perspiration usually associated with the use of testosterone. Hadgraft 296:10-300:15; Goldstein 612:17-613:8, 671:3-674:25, 682:17-683:17; PTX-4 at col. 22, l. 65-col. 23, l. 8. Based on the results of these studies, the inventors conceived of treating hypogonadism by application of transdermal testosterone to the axilla, which is the invention of the '944 patent. PTX-1109 at 3.

***Claim 20 of the '944 Patent***

Asserted claim 20 of the '944 patent depends upon independent claim 13 and each of dependent claims 14-19. PTX-4 at Claims 13-20. The chart below maps each of the limitations of asserted claim 20, including each of the limitations of the claims from which it depends. *Id.*; Potts 1347:8-1348:24 (discussing demonstratives DDX 234-36); *see also* PDX 2022.

Claim 13 of the Axilla Patent	Dependent Claims 14-20 of the Axilla Patent	Compilation of Claim 20 of the Axilla Patent
A method of increasing the testosterone blood level of an adult male subject in need thereof comprising applying to at least one axilla of the subject, without occlusion by a patch device, a non-occlusive transdermal drug delivery composition consisting of:		A method of increasing the testosterone blood level of an adult male subject in need thereof comprising applying to at least one axilla of the subject, without occlusion by a patch device, a non-occlusive transdermal drug delivery composition consisting of:
(a) a pharmaceutically effective amount of testosterone;		(a) a pharmaceutically effective amount of testosterone;
(b) one or more lower alkyl alcohols, wherein the combined volume of the lower alkyl alcohol(s) is more than 60% (v/v) of the composition;	'944 claim 16 – The method of claim 15, wherein the lower alkyl alcohol is selected from a group consisting of ethanol, isopropanol, and mixtures thereof.  '944 claim 17 – The method of claim 16, wherein the combined volume of lower alkyl alcohol(s) is more than 70% (v/v).  '944 claim 18 – The method of claim 17, wherein the combined volume of lower alkyl alcohol(s) is more than 80% (v/v).	(b) one or more lower alkyl alcohols selected from a group consisting of ethanol, isopropanol, and mixtures thereof, wherein the combined volume of the lower alkyl alcohol(s) is more than 80% (v/v) of the composition;
(c) one or more penetration enhancers selected from the group consisting of octisalate, octyldimethyl-para-aminobenzoate and octyl para-methoxycinnamate;	'944 claim 14 – The method of claim 13 wherein the penetration enhancer is present in an amount of from 0.01% to 15% (w/v)  '944 claim 15 – The method of claim 14 wherein the penetration enhancer is octisalate.	(c) the penetration enhancer octisalate in an amount of from 0.01% to 15% (w/v)

Claim 13 of the Axilla Patent	Dependent Claims 14-20 of the Axilla Patent	Compilation of Claim 20 of the Axilla Patent
(d) one or more viscosity modulating agents, in an amount effective to increase the viscosity of the composition to within the range of from greater than the viscosity of water to less than 300 centipoise; and	'944 claim 19 – The method of claim 18 wherein the viscosity modulating agent is polyvinyl pyrrolidone. '944 claim 20 – The method claim 19 wherein the polyvinyl pyrrolidone is present in an amount from 1% to 3% (w/v) of the composition.	(d) the viscosity modulating agent polyvinyl pyrrolidone present in an amount from 1% to 3% (w/v) of the composition, in an amount effective to increase the viscosity of the composition to within the range of from greater than the viscosity of water to less than 300 centipoise
(e) optionally, water		(e) optionally, water
wherein the composition is applied in an amount effective to achieve a testosterone blood level in the subject of at least 200 ng/dL.		wherein the composition is applied in an amount effective to achieve a testosterone blood level in the subject of at least 200 ng/dL.

***Occlusive and Non-Occlusive Transdermal Testosterone Treatments for Hypogonadism Were Well-Known in the Prior Art***

By June 2005, a number of transdermal testosterone products were commercially available in the United States as testosterone therapies to treat males experiencing a deficiency or absence of endogenous testosterone, as characterized by the condition known as hypogonadism. Snyder 915:19-917:22. Such products included occlusive (patch) treatments Testoderm® (PTX-511) and Androderm® (PTX-512), and non-occlusive (non-patch) treatments AndroGel® (PTX-1059), and Testim® (PTX-641). Other transdermal testosterone formulations were disclosed in the prior art literature, including U.S. Patent Application Publication No. 2004/0028725 (“Morgan ‘725 Publication”) (PTX-483); U.S. Patent No. 6,299,900 (“Reed ‘900 Patent”) (PTX-19);

U.S. Patent No. 6,211,250 (“Tomlinson ‘250 Patent”) (PTX-592); U.S. Patent No. 6,319,913 (“Mak ‘913 Patent”) (PTX-453); and U.S. Patent Application Publication No. 2005/0042268 (“Aschkenasy ‘268 Publication”) (PTX-243). These products and formulations are all § 102(b) prior art to the ‘944 axilla patent. We describe each in greater detail below:

**A. Testoderm®**

Testoderm® was first approved by the FDA in 1993 and was commercially sold in the United States prior to June 2005. PTX-511 at 2. Testoderm® was a commercially available patch for the transdermal delivery of testosterone for testosterone replacement therapy in hypogonadal men. *Id.* at 3. The Testoderm® system is a thin film about the size of a business card containing testosterone that was designed to be worn on the scrotum for 22 to 24 hours daily. *Id.*; Hadgraft 197:19-22; Goldstein 622:20-23. Testoderm® was later withdrawn from the market because of concerns related to elevated DHT levels associated with use of the product. Goldstein 623:12-15.

**B. Androderm®**

Androderm®, another transdermal testosterone patch product, was first approved by the FDA in 1995 and was commercially sold in the United States prior to June 2005. PTX-512 at 2. Androderm® is a commercially available testosterone patch for testosterone replacement therapy in men with conditions associated with a deficiency or absence of endogenous testosterone, such as hypogonadism. *Id.* at 3. The suggested

starting dosage is two Androderm<sup>®</sup> patches applied to the back, abdomen, upper arm, or thigh, providing a total dose of 5 mg/day of testosterone. *Id.* at 4.

**C. AndroGel<sup>®</sup> and U.S. Patent No. 6,503,894**

AndroGel<sup>®</sup> was first approved by the FDA in 2000 and was commercially sold in the United States prior to June 2005. PTX-1059 at 1; Potts 1342:6-12. AndroGel<sup>®</sup> is § 102(b) prior art to the axilla patent. AndroGel<sup>®</sup> is a non-occlusive hydroalcoholic gel containing 1% testosterone as the active ingredient. PTX-1059 at 1. AndroGel<sup>®</sup> is a testosterone replacement therapy for males with a deficiency or absence of endogenous testosterone, as characterized by the condition known as hypogonadism. *Id.* at 11-12. An appropriate starting dosage of AndroGel<sup>®</sup> 1% is 5 grams applied once daily to clean, dry, intact skin of (i) the shoulders and upper arms (ii) and/or abdomen. *Id.* at 22.

U.S. Patent No. 6,503,894 (“Dudley ‘894 patent”) (PTX-319), entitled “Pharmaceutical composition and method for treating hypogonadism,” issued on January 7, 2003. PTX-319 at 1; Potts 1342:6-12. The Dudley ‘894 patent is § 102(b) prior art to the axilla patent. The Dudley ‘894 patent discloses the AndroGel<sup>®</sup> composition and teaches a method for treating hypogonadism by applying the AndroGel<sup>®</sup> composition to the skin. PTX-319 at Abstract, col. 13, ll. 22-35, col. 14, ll. 25-28.

**D. Testim<sup>®</sup> and International Patent Application Publication No. WO 2003/088974**

Testim<sup>®</sup> was first approved by the FDA in 2002 and was commercially sold in the United States prior to June 2005. PTX-641 at 1, 18; Potts Tr. 1342:6-12. Testim<sup>®</sup> is §

102(b) prior art to the axilla patent. Testim® is a non-occlusive hydroalcoholic gel containing 1% testosterone as the active ingredient. PTX-641 at 1. Testim® is a testosterone replacement therapy for males with a deficiency or absence of endogenous testosterone, as characterized by the condition known as hypogonadism. *Id.* at 10. The recommended starting dosage of Testim® is “5 g of gel (one tube) containing 50 mg of testosterone applied once daily (preferably in the morning) to clean, dry intact skin of the shoulders and/or upper arms.” *Id.* at 17.

International Patent Application Publication No. WO 2003/088974 (“Gyurik ’974 publication”) (PTX-382), entitled “Pharmaceutical Composition,” was published on October 30, 2003. PTX-382 at 1; Potts 1342:6-12. Gyurik ’974 publication is § 102(b) prior art to the axilla patent. Gyurik ’974 publication discloses a variation of the Testim® formulation and teaches a method for treating hypogonadism by applying the formulation to the skin. PTX-382 at Abstract, Example 1, Comparative Example C-1.

#### **E. Morgan ’725 Publication**

U.S. Patent Application Publication No. US 2004/0028725 (“the Morgan ’725 publication”), entitled “Transdermal Delivery Of Hormones,” is a patent application that was filed by Morgan, *et al.*, no later than May 2, 2003, and was published on February 12, 2004. PTX-483. The Morgan ’725 publication issued as the Morgan ’983 patent. PTX-21.

The Morgan ’725 publication teaches a method of increasing testosterone blood levels of an adult male subject in need thereof. Potts 1349:4-23. The Morgan ’725



publication discloses a “transdermal drug delivery system which comprises: a therapeutically effective amount of a hormone; at least one dermal penetration enhancer, which is a safe skin-tolerant ester sunscreen ester; and at least one volatile liquid.” PTX-483 at Abstract. It further provides “a method for administering at least one systemic acting hormone to an animal which comprises applying an effective amount of the hormone in the form of the drug delivery system of the present invention.” *Id.* Specifically, it teaches that the transdermal drug delivery system may be used as “male hormone therapy in testosterone deficient hypogonadal men.” *Id.* at [0057].

A POSA would understand that the Morgan '725 publication's teaching that its transdermal drug delivery system may be used as male hormone therapy in testosterone deficient hypogonadal men inherently discloses raising the testosterone blood levels of that hypogonadal male to at least 200 ng/dL. Potts 1349:4-23; Chambliss 1559:20-1560:17. By June 2005, methods for treating hypogonadal adult males by applying a non-occlusive transdermal testosterone composition with the objective of increasing testosterone blood levels to normal physiologic ranges were well-known in the art. Potts 1341:22-1342:12. For instance, AndroGel<sup>®</sup> and Testim<sup>®</sup> were FDA-approved transdermal testosterone compositions used to treat hypogonadism in adult males by transdermally delivering testosterone to maintain therapeutically effective testosterone blood levels. PTX-1059 at 11-12; PTX-641 at 10. AndroGel<sup>®</sup> and Testim<sup>®</sup> deliver a therapeutically effective amount of testosterone across the skin to produce testosterone blood levels that approximate normal adult male blood levels of about 300 ng/dL to 1000

ng/dL. PTX-1059 at 2; PTX-641 at 1; Snyder 913:22-914:6. A POSA would have sought to return the testosterone blood levels of a hypogonadal man to the normal adult male levels, which is greater than 200 ng/dL. *Id.*; Chambliss 1559:20-1560:17.

Composition 13A of the Morgan '725 publication expressly teaches a non-occlusive transdermal drug delivery composition consisting of: (a) testosterone in an amount of 1% w/v, (b) 90% w/v aqueous ethanol, (c) the penetration enhancer octyl salicylate in an amount of 2.5% w/v, and (d) the viscosity modulating agent hydroxyl propyl cellulose in an amount of 1.5% w/v. PTX-483 at Example 13. Composition 13B of the Morgan '725 publication discloses a similar formulation containing the viscosity modulating agent ethyl cellulose in an amount of 1.5% w/v. *Id.* The Morgan '725 publication teaches that the viscosity modulating agents in Compositions 13A and 13B are interchangeable with the claimed viscosity modulating agent polyvinyl pyrrolidone (also known as povidone). PTX-483 at [0024]; Potts 1350:23-1352:6. The Morgan '725 publication also discloses that the preferred range of the thickening agent in such formulations is 0.5 to 5%. PTX-483 at [0027].

The Morgan '725 publication also states that “[p]referably the drug delivery system is applied to the skin of the animal covering a delivery surface area between about 10 and 800 cm<sup>2</sup>, more preferably between about 10 and 400 cm<sup>2</sup>, and most preferably between about 10 and 200 cm<sup>2</sup>.” PTX-483 ¶¶ 23, 30, 58; *id.* at claims 17-19. The Morgan '725 publication further discloses that the claimed transdermal testosterone

formulation may be applied to an area of the body on which it would be useful to use an applicator. PTX-483 ¶ 58; Chambliss 1564:11-1565:1.

#### **F. Morgan ‘983 Patent**

U.S. Patent No. 6, 923, 983 (“Morgan ‘983 patent”), entitled “Transdermal Delivery Of Hormones,” issued to Morgan, *et al.*, on August 2, 2005, from an application filed no later than May 2, 2003. PTX-21. The Morgan ‘983 patent is prior art to the axilla patent under 35 U.S.C. § 102(e). Dkt. 208, ¶ 19. The Morgan ‘983 patent issued from the Morgan ‘725 publication and contains the same disclosures. *See, e.g.*, Hadgraft 282:13-283:19, 486:10-16; Chambliss 1541:1-1542:8.<sup>8</sup>

#### **G. Reed ‘900 Patent**

The Reed ‘900 patent, entitled “Dermal penetration enhancers and drug delivery systems involving same,” issued on October 9, 2001. PTX-19 at 1. The Reed ‘900 patent is the grandparent of the ‘075 penetration enhancer patent. Hadgraft Tr. 271:18-20. The Reed ‘900 patent teaches a testosterone transdermal formulation. Potts 1342:16-1343:16; PTX-19 at Abstract, col. 4, ll. 20-45, col. 7, ll. 1-5, Example 15.

#### **H. Tomlinson ‘250 Patent**

The Tomlinson ‘250 patent, entitled “Percutaneous delivery system,” issued on April 3, 2001. PTX-592 at 1. The Tomlinson ‘250 patent teaches a testosterone

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<sup>8</sup> Because the disclosure of the Morgan ‘983 patent is the same as the Morgan ‘725 publication, we will hereinafter refer only to the ‘725 publication. However, reference to that publication incorporates the same disclosures of the ‘983 patent.

transdermal formulation. Potts 1342:16-1343:16; PTX-592 at Abstract, col. 4, ll. 39-48, col. 5, ll. 35-40, col. 6, ll. 39-40.

### **I. Mak '913 Patent**

The Mak '913 patent, entitled "Penetration enhancing and irritation reducing systems," issued on November 20, 2001. PTX-453 at 1. The Mak '913 patent teaches a testosterone transdermal formulation. Potts 1342:16-1343:16; PTX-453 at col. 2, ll. 40-45, col. 4, ll. 1-9, Example 9.

### **J. Aschkenasy '268 Publication**

The Aschkenasy '268 publication, entitled "Pharmaceutical composition and method for transdermal drug delivery," was published on February 24, 2005, from U.S. Patent Application No. 10/891,489 filed on July 15, 2004. PTX-243 at 1. The Aschkenasy '268 publication is § 102(a) and (e) prior art to the '944 axilla patent. *See* Dkt. 208 ¶ 31.

The Aschkenasy '268 publication teaches a testosterone transdermal formulation. Potts 1364:13-1366:6. The Aschkenasy '268 publication discloses "[a] pharmaceutical composition for transdermal administration of a hormone (*e.g.*, testosterone), which includes urea and/or a derivative thereof as a penetration enhancer, and methods utilizing same for treating medical conditions in which elevating a hormone serum level is beneficial." *Id.*; PTX-243 at Abstract.

The Aschkenasy '268 publication teaches that applying the pharmaceutical composition, such as testosterone and a penetration enhancer, to a biological surface can “elevat[e] a blood serum concentration of the hormone in the subject from a subpotent concentration to a potent concentration within about 24 hours after application. For testosterone, in a human male, a potent concentration ranges between about 300 ng/dl and 1100 ng/dl in serum.” PTX-243 at [0065]; Potts 1365:6-15.

The PT considered the Aschkenasy '268 publication prior to allowance of the '944 patent. PTX-4 at 2.

Based on at least these afore-mentioned prior art references, a POSA would have understood that transdermal testosterone formulas to treat hypogonadal men were well-disclosed in the prior art to the '944 axilla patent.

### ***Characteristics of the Axilla***

The axilla is the area of the body commonly referred to as the “armpit.” Hadgraft 362:8-10. The axilla is a region located under the shoulder joint that forms a depressed or hollow region, *i.e.*, a bowl, that contains, *inter alia*, apocrine and eccrine glands, lymph nodes, fat, loose connective tissue, skin folds, and the brachial plexus. There are both hairy and non-hairy portions of the axilla. Hadgraft 362:14-17; 364:17-365:5. The axilla is known to be sweaty and is often treated with antiperspirants and deodorants to offset odors. Hadgraft 177:23-25, 178:1-5.

### ***Known Permeability Studies of Various Anatomical Sites, Including the Axilla***

By June 2005, it was well-known in the art that the speed and extent of transdermal drug delivery varies by the surface area of application, the anatomical site upon which the drug formulation is applied, as well as the nature of the compound being applied to the skin. Potts 1355:20-1358:1; 1505:6-10; Hadgraft 136:22-24; 229:22-230:6, 236:17-237:6, 499:10-501:7. In studies comparing the relative permeability of different areas of skin for transdermal drug delivery, such as Feldmann (1967) and Maibach (1971), the axilla was consistently found to be a site of high permeability for various compounds in comparison to other potential application sites, including the back, shoulders, abdomen, and forearms. Potts 1354:16-1355:4; PTX-340; PTX 449. At the time of the invention of the '944 patent, the axilla was also known to have reduced barrier properties. PTX-607 at 1; *see* Potts 1361:18-22.

**A. Feldmann (1967)**

Feldmann *et al.*, *Regional Variation in Percutaneous Penetration of <sup>14</sup>C Cortisol in Man*, *The Journal of Investigative Dermatology*, 48(2):181-83 (1967) (“Feldmann (1967)”) was published in 1967. PTX-340 at 1. Feldmann (1967) is § 102(b) prior art to the axilla patent.

Feldmann (1967) conducted a study that “quantitates the effect of regional variation on percutaneous penetration of hydrocortisone.” PTX-340 at 1; Potts 1355:20-23. The study authors delineated a 13 cm<sup>2</sup> area on different skin sites for application of hydrocortisone and measured the amount of drug delivery per unit area. PTX-340 at 1; Potts 1355:24-1356:18. By pre-marking the exact size of the application site, the

Feldmann study accurately determined the amount of drug delivery per unit area. *Id.* As shown in table 1 of Feldmann (1967), the absorption of hydrocortisone is 3.6-fold greater across the axilla than the forearm (ventral). PTX-340 at 2; Potts 1356:19-1357:2; Hadgraft 228:9-229:2. The permeability of the axilla was the second greatest among the sites tested, with the scrotum having the highest permeability, which was 42 times more permeable than the forearm.<sup>9</sup>

The PTO considered Feldmann (1967) prior to allowing the '944 patent. PTX-4 at 3.

#### **B. Maibach (1971)**

Maibach HI *et al.*, *Regional Variation in Percutaneous Penetration in Man*, Arch Environ Health, 23:208-211 (1971) (“Maibach (1971)”) was published in 1971. PTX-449 at 2. Maibach (1971) is § 102(b) prior art to the axilla patent.

Maibach (1971) conducted a study of the systemic absorption of the pesticides parathion and malathion when topically applied to different anatomical regions. PTX-449 at 3-4. As shown in Tables 1-3 of Maibach (1971), the axilla demonstrated greater absorption than many of the anatomical regions tested, including a 7.4-fold greater absorption of parathion than the forearm and a 4.2-fold greater absorption of malathion than the forearm. *Id.* at Tables 1-3; Potts 1357:3-20; Hadgraft 231:20-232:4.

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<sup>9</sup> A later study conducted by Feldmann and Maibach comparing absorption of steroids across the skin of the forearm demonstrated that testosterone was better absorbed at that site than hydrocortisone. DTX-188 at 2; Hadgraft 473:20-475:15.

Maibach (1971) was considered by the PTO prior to allowance of the '944 patent. PTX-4 at 2-3.

**C. Watkinson (2002)**

Watkinson A *et al.*, *Reduced Barrier Efficiency in Axillary Stratum Corneum*, International Journal of Cosmetic Science 24:151-161 (2002) (“Watkinson 2000”) was published in 2002. PTX-607 at 1. Watkinson (2002) is § 102(b) prior art to the axilla patent.

Watkinson (2002) reports a study to characterize the axillary skin and evaluate its composition and function, particularly its barrier properties, as compared to other body sites. PTX-607 at 2. Watkinson (2002) conducted a study of transepidermal water loss (“TEWL”), which is a measure of how rapidly water is released from the skin and reflects the strength of the skin site to act as a barrier to drug delivery. *Id.*; Potts 1360:15-25. As illustrated in Figure 1 of Watkinson (2002), in a head-to-head comparison of the same subjects serving as their own control, the “axillary TEWL measurements were significantly greater than those of the volar forearm (Fig. 1).” PTX-607 at 5; Potts 1361:1-13. Watkinson (2002) ultimately concluded that the study “revealed a reduced barrier function in the axilla.” PTX-607 at 1.

Watkinson (2002) also described the axilla as a “major recipient tissue for sweat secretion,” a factor in providing the “ideal growth conditions for the commensal skin bacteria.” PTX-607 at 2. Watkinson (2002) further reported that “we know virtually



nothing about axillary skin or how antiperspirant (AP) use impacts upon it.” PTX-607 at 1.

**D. Berti (1995)**

Citing the data from Feldmann (1967) and Maibach (1971), Berti *et al.*, *Transcutaneous Drug Delivery: A Practical Review*, Mayo. Clin. Proc., Vol. 70:581-586 (1995) (“Berti 1995”), reported that the axilla is approximately four times more permeable than the forearm to transcutaneous absorption of the active ingredient hydrocortisone. PTX-264 at Fig. 3. Berti (1995) further reported that “[a]lthough not all drugs have the same degree of absorption as hydrocortisone, the relative ratio of absorption at various skin sites (Fig. 3) is likely similar and correlates with the thickness and lipid content of the stratum corneum.” PTX-264 at Fig. 3. Berti (1995) also noted that “the areas of greatest transcutaneous absorption” (including the axilla) were “also those subjected to the greatest application of cosmetics, antiperspirants, and deodorants.” PTX-264 at 4.

Berti (1995) was considered by the USPTO prior to allowance of the ‘520 patent (related to the ‘944 patent). PTX-6 at 4.

***Potential Application Sites for Transdermal Testosterone Formulations Known in the Art***

In June 2005, there were no transdermal testosterone products that were applied to the axilla. Rather, transdermal treatments as of 2005 were applied to the following sites: (1) scrotum (Testoderm®); (2) upper buttocks, upper arms, back (Testoderm® TTS); (3)

abdomen, upper arms, back, thighs (Androderm®); (4) abdomen, shoulders, upper arms (AndroGel®); (5) shoulders, upper arms, upper torso (Testim®); and (6) abdomen and trunk (Percutacrine Androgenique Forte (“PAF”)). Axiron® is currently still the only transdermal testosterone product that is applied through the axilla. Hadgraft 218:1-9.

The armpit or axillary area was, however, recognized as a potential application site for transdermal testosterone treatment in the prior art, and as of June 2005 a POSA would have been aware of the following references that teach administration of testosterone to the axilla for delivery of testosterone into the systemic bloodstream:

**A. Aschkenasy ‘268 Publication**

As discussed above, the Aschkenasy ’268 publication discloses pharmaceutical compositions for transdermal drug delivery, including testosterone. Potts 1365:2-15.

The Aschkenasy ’268 publication is directed to “a pharmaceutical composition for topical application, which comprises a pharmaceutically active ingredient, a penetration enhancer, and a pharmaceutically acceptable carrier, wherein the pharmaceutically active ingredient is a hormone, and the penetration enhancer is urea and/or a derivative thereof.” PTX-243 at [0048]. This transdermal drug delivery composition may be used to deliver a therapeutically effective amount of testosterone across a biological surface of the subject to raise testosterone blood levels within the normal adult male range of 300-1100 ng/dL testosterone:

[0065] The pharmaceutical composition of the present invention is capable, upon application of an amount of the composition onto at least one biological surface of a subject, of

elevating a blood serum concentration of the hormone in the subject from a subpotent concentration to a potent concentration within about 24 hours after application. For testosterone, in a human male, a potent concentration ranges between about 300 ng/dl and 1100 ng/dl in serum.

*Id.* at [0065]; Hadgraft 431:2-18. One of the express objectives of the Aschkenasy '268 publication is the topical administration of a testosterone gel for use in hormone replacement therapy in hypogonadal males. Hadgraft Tr. 428:4-429:2, 429:23-431:1; PTX-243 at [0024]-[0027], [0047], [0057].

The Aschkenasy '268 publication further teaches that its topical formulations (which include testosterone formulations) may be applied to one of seven biological surfaces of the skin, including the armpit:

[0066] The biological surface can be, for example, the abdomen, *an armpit*, an inside arm, the back, a thigh, a shoulder, or the scrotum.

PTX-243 at [0066] (emphasis added); Hadgraft 431:19-432:4, 447:5-12. The Aschkenasy '268 publication also claims application of the testosterone formulation to only these seven biological surfaces. PTX-243 at claims 88, 93, 113, 142, 147, 167. A POSA would understand that the Aschkenasy '268 publication teaches application of testosterone to the axilla for transdermal drug delivery. Potts 1365:2-1366:6.

A POSA would understand that the Aschkenasy '268 publication provides a curated list of appropriate sites for transdermal delivery of testosterone. Potts 1365:2-1366:6. A POSA also would have known that the FDA-approved testosterone products prior to June 2005 were applied to several of the biological surfaces listed in Aschkenasy

'268 publication—namely, the abdomen (Androderm® and AndroGel®), an inside arm (AndroGel® and Testim®), the back (Androderm®), a thigh (Androderm®), a shoulder (AndroGel® and Testim®), or the scrotum (Testoderm®). Hadgraft 447:5-452:16 (discussing DDX 1001). If a POSA wanted to apply a testosterone topical formulation to a biological surface listed in Aschkenasy '268 publication that would be commercially differentiated from the FDA-approved transdermal testosterone products, as Drs. Potts and Chambliss explained that a POSA would have been motivated to do, the only choice for application site would have been the armpit. Hadgraft 452:11-16; *see* Potts 1473:5-14; Chambliss 1611:10-1612:10.

The Aschkenasy '268 publication further teaches that the topical testosterone formulation may contain additional additives, including humectants, deodorant agents, antiperspirants, pH adjusting agents, preservatives, emulsifiers, occlusive agents, solubilizing agents, colorants, and surfactants. PTX-243 at [0139]. The axilla patent identifies these same inactive ingredients in the same order as the Aschkenasy '268 publication. PTX-243 at [0139]; PTX-4 at col. 18, ll. 14-23; Hadgraft 438:19-439:4. The Aschkenasy '268 publication also provides an extensive list of deodorant agents and antiperspirants (agents that are commonly applied to the axilla) for addition to the topical testosterone formulation. PTX-243 at [0141], [0142]; Hadgraft 433:10-434:18.

The Aschkenasy '268 publication was considered by the PTO prior to allowance of the '944 patent. PTX-4, '944 patent, at 2; PDX-3031, Aschkenasy '268 Publication (2005); PTX-243; Hadgraft 267:24-268:1.

**B. Cutter (2000)**

Cutter CB, *Compounded Testosterone Gels: A Guide for Clinicians and Pharmacists*, Int'l J. of Pharm. Compounding, 4(6):432-437 (2000) ("Cutter 2000") published in 2000. PTX-301 at 3. Cutter (2000) is § 102(b) prior art to the axilla patent.

Cutter (2000) reviews the role of compounding pharmacists in developing testosterone replacement therapies for the care of patients with hypogonadism. PTX-301 at 3. Cutter (2000) teaches that when administering testosterone gel for transdermal delivery, "the choice of the application site is quite important." *Id.* at 6. Cutter (2000) recommends administering testosterone replacement therapies to the trunk or "axillary area" to provide the normal physiologic balance of testosterone, DHT, and estradiol:

When the gel is applied to the trunk or axillary area, the resulting balance of testosterone, DHT, and E<sub>2</sub> will be very much in the normal physiologic range. However, when the gel is applied to the scrotum, the level of DHT becomes much higher because of the presence of a much higher level of the enzyme 5-alpha reductase.

*Id.* A POSA would understand that Cutter (2000)'s discussion of the axillary area is a reference to a part of the axilla. Potts 1380:21-1381:22, 1486:12-1487:25; 1489:5-17; Chambliss 1569:6-17, 1614:4-24.

**C. Cutter (2001)**

Cutter CB, *Compounded Percutaneous Testosterone Gel: Use and Effects in Hypogonadal Men*, J. of the Am. Board of Family Practice, 14(1):22-32 (2001) ("Cutter 2001") was published in 2001. (PTX-302 at 1.) Cutter (2001) is § 102(b) prior art to the axilla patent.

Cutter (2001) reports the results from administering compounded percutaneous testosterone gel to ten hypogonadal men (characterized as “a testosterone level of less than 300 ng/dL on repeat morning serum testing”). PTX-302 at 1, 4. Patients were provided a “testosterone gel in a dosing syringe and instructed on administration, the site of application (either *the upper inner arm or chest near the axilla* or the inner thigh and scrotum), and the amount of gel (1-3 mL).” *Id.* at 3. A POSA would understand that Dr. Cutter is describing application of the testosterone gel to a portion of the axilla as one of the sites of application. Potts 1367:21-1368:24; Snyder 966:20-967:7. A POSA would understand that the armpit or axilla includes areas above and below the hairline of the axilla. Chambliss 1614:4-1615:19; *see also* Hadgraft 419:1-420:9. A POSA would understand that Dr. Cutter’s site of application represents the non-hairy area of the axilla. *Id.* Indeed, consistent with his description of the study design, Dr. Cutter later identifies the site of application as the “axilla” when presenting the results from the study. PTX-302 at 4; Potts 1367:21-1368:24, 1487:3-25; Chambliss 1569:12-17.

Cutter (2001) further explains that he has “treated many men since the beginning of this study.” PTX-302 at 9. In describing his clinical practice beyond the ten men treated in his study, Dr. Cutter recommends that “the most useful starting dose for most men is a 6% gel, 2.5 mL applied to the *nonhairy area of the axilla*.” *Id.*; Hadgraft 420:18-421:4. A POSA would understand that the axilla has both hairy and nonhairy areas. Hadgraft 362:14-17. The nonhairy area of the axilla, where Dr. Cutter

recommends administering testosterone gel based on his clinical practice, is a part of the axilla. Potts 1368:25-1369:20; Snyder 938:14-17; Chambliss 1614:4-1615:19.

Cutter (2001) further warns that “inadvertent transmission of the gels could occur if the patient did not exercise caution in application and usage.” PTX-302 at 10.

Inadvertent transmission of testosterone is a particular concern for any children, sexual partners, or pregnant women who may come into contact with the patient. *Id.* Cutter (2001) recommends that “[b]y using the gel in the *axillary area*, at bedtime, transmission can be avoided.” *Id.* (emphasis added). A POSA would understand that Cutter (2001) teaches administration of testosterone gel to the remote area of the axilla to avoid inadvertent transmission of testosterone to others. Potts 1376:1-14.

Cutter (2001) was considered by the PTO prior to allowance of the '944 patent. PTX-4, '944 patent, at 2; PDX-3037, Cutter (2001): PTX-302; Hadgraft 255:17-18.

#### **D. Chein '790 Patent**

U.S. Patent No. 6,562,790 (“Chein '790 patent”), entitled “Hormone therapy methods and hormone products for abating coronary artery blockage,” issued on May 13, 2003. (PTX-283 at 1.) The Chein '790 patent is § 102(b) prior art to the axilla patent.

The Chein '790 patent discloses “methods and products to abate coronary artery blockage in men and in women” by “administering a combination of natural hormones, including human growth hormone or recombinant human growth hormone, one or more sex hormones, such as testosterone, estrogen or progesterone and other naturally occurring hormones, as appropriate.” PTX-283 at col. 1, ll. 5-11. For those men “with below optimal testosterone levels, these methods call for administering natural

testosterone in gel form, preferably applied topically to under arm pits.” *Id.* at col. 1, ll. 22-25. A POSA would understand the Chein ‘790 patent’s instruction to apply the testosterone composition to the “under arm pits” to refer to application to the axilla. Potts 1371:2-21.

The Chein ‘790 patent was considered by the USPTO prior to allowance of the related ‘520 axilla patent. PTX-6, ‘520 patent, at 2; PDX-3034, Chein ‘790 Patent (2003): PTX-283.

#### **E. Ben-Galim (1980)**

Ben-Galim E *et al.*, *Topically Applied Testosterone And Phallic Growth*, Am. J. Dis. Child, Vol. 134:296-298 (1980) (“Ben-Galim (1980)”) was published in 1980. (PTX-263 at 1.) Ben-Galim (1980) is § 102(b) prior art to the axilla patent.

Ben-Galim (1980) reports the results of a study of “the effect of topical application of testosterone cream in five boys with micropenis and hypopituitarism.” PTX-263 at 1. In this study, “all subjects were treated with 5% testosterone propionate in hydrophilic ointment USP. Average dosage was between 2.5 and 4.0 mg of testosterone (50 to 75 mg of ointment) applied three times a day for three weeks, on an approximate area of 9 sq cm. In four patients (1 through 4), the ointment was applied directly to the phallus, and in one patient (5) to his right axilla.” *Id.* For the patient that administered the testosterone propionate to his right axilla, the total plasma testosterone increased from < 20 ng/dL before treatment to 573 ng/dL on the last day of treatment. *Id.* at 2. A POSA would understand that Ben-Galim (1980) reports an example of administering



testosterone to the skin of the axilla to elevate systemic testosterone blood levels. Potts 1372:5-18; Hadgraft 403:25-404:21, 405:7-25, 407:9-15, 408:4-16.

Ben-Galim (1980) was considered by the PTO prior to allowance of the '944 patent. PTX-4, '944 patent, at 3; Hadgraft 225:23-226:1.

**F. Papa (1967)**

Papa CM *et al.*, *Effect of Topical Hormones on Aging Human Skin*, Journal of the Society of Cosmetic Chemists, 18(8):549-62 (1967) was published in 1967 (“Papa (1967)”). PTX-502 at 1. Papa (1967) is § 102(b) prior art to the axilla patent.

Papa (1967) reviews the effect of administering topical hormones, including testosterone propionate (a testosterone derivative) to aging human skin. PTX-502 at 1-2. Papa (1967) applied the topical hormones to the “face, extensor forearm, and back of the hand” and “axilla,” using “hydrophilic ointment base or alcoholic solution” formulations. *Id.* at 2. Papa (1967) found that administering testosterone propionate to the axilla of elderly men and women had a noticeable rejuvenating effect on the appearance of the axilla skin. *Id.* at 3-5.

Papa (1967) is directed to studying the effectiveness of hormones, like testosterone propionate, “to ameliorate the degradative changes” in aging human skin. PTX-502 at 12. Papa (1967) explains that the observed rejuvenating effect is limited to the local areas of the skin topically treated with hormones, and that the systemic administration of hormones (*i.e.*, drug delivery to the entire body through the bloodstream) has been found to be ineffective in rejuvenating the appearance of aging skin. *Id.* Papa (1967) does not suggest that transdermal delivery of testosterone into systemic circulation would be

ineffectual through the axilla, however. *Id.* Instead, a POSA would have known that to even have a local rejuvenating effect on the skin, the testosterone propionate must bypass the stratum corneum (the main barrier to transdermal drug delivery) to reach the deeper layers of the skin—in other words, it must penetrate the skin. Potts Tr. 1373:3-21) A POSA would understand that topical administration of testosterone propionate to the axilla was effective in delivering the drug across the skin for a local effect and would have expected that applying a greater amount of testosterone propionate would have increased the amount of testosterone delivered into the bloodstream. *Id.*

Papa (1967) was considered by the PTO during prosecution of the '944 patent.

***Known Concern Regarding Inadvertent Transference of Testosterone***

By June 2005, the inadvertent transference of testosterone was a known risk associated with transdermal testosterone formulations. Both the AndroGel® and Testim® labels cautioned that pregnant and nursing women should avoid skin contact with the testosterone gels and warned of the risk of inadvertent transference of testosterone. PTX-1059 at 12; PTX-641 at 10; Potts 1376:15-1377:8. Cutter (2001) further warned that inadvertent transmission of the testosterone gels could occur if patients did not exercise caution in application and usage. PTX-302 at 10; Potts 1375:23-1376:14; Hadgraft 421:23-422:22. A 2-year old boy experienced serious virilization symptoms after coming into contact with his father who was using a testosterone gel on his arms and back. *Id.* Cutter (2001) recommended that “by using the gel in the axillary area, at bedtime, transmission can be avoided.” *Id.* A POSA would have understood that

application of a testosterone gel to the axilla—an area that infrequently comes into contact with others—would avoid inadvertent transference of testosterone from the user to other individuals. *Id.*

***Elevated DHT Levels Associated With Transdermal Testosterone Treatment Applied to Scrotum***

Testosterone is converted in the body to DHT via the enzyme 5-alpha reductase. Goldstein 626:11-13; PDX-7010. The metabolite, DHT, is a potent androgen that targets androgen-dependent tissues: testes, prostate, apocrine glands, and hair follicles. Goldstein 627:3-629:24. The enzyme 5-alpha reductase catalyzes the conversion of testosterone to DHT. The relevant measurement is the DHT-to-T (DHT to testosterone) ratio. Goldstein 628:15-629:24.

Exogenous testosterone permeating across the skin is metabolized to DHT prior to reaching the dermal capillaries. PTX-464 at 12; Goldstein 627:3-12, 629:17-24. Once reaching the dermal capillaries, DHT travels to the prostate via systemic circulation. PTX-462 at 5; Goldstein 629:17-24; Snyder 965:13-18. The prior art recognized that elevated DHT levels were found in men using scrotal patches. It was theorized in the prior art that exogenous application of testosterone to a site rich in 5-alpha reductase activity, like the scrotum, was what caused the abnormally high DHT levels. PDX-7013; Goldstein 632:4-15. The prior art further recognized a concern regarding the possible link between elevated DHT and DHT-to-T levels and negative side effects such as benign prostatic hypertrophy (“BPH”) (enlargement of the prostate that can lead to kidney failure and morbidity) and prostate cancer. Goldstein 628:21-629:16.

Despite the prior art recognizing a concern regarding elevated DHT levels associated with transdermal application of testosterone to the scrotum, the FDA approved the Testoderm® scrotal patch in 1993 as safe and effective for replacement therapy in males for conditions associated with a deficiency or absence of endogenous testosterone. *Id.* at 622:20-623:8; PTX-511 at 3. The FDA approved Testoderm® even though the literature prior to 1993 (which Dr. Goldstein relied on) reported that administration of the scrotal patch resulted in elevated DHT levels. Goldstein Tr. 635:9-636:14. Even after the Testoderm® patch was discontinued,<sup>10</sup> the prior art still recommended administration of testosterone to the scrotum for transdermal drug delivery. *See, e.g.*, PTX-431 (“Kryger ‘448 patent”) at col. 4, ll. 36-50 (patent issued on June 1, 2004, teaching the application of a testosterone formulation “to the scrotal skin” in order to “achieve a serum testosterone level of from about 600 ng/dl to about 1200 ng/dl”); PTX-243 (Aschkenasy ’268 publication, which published on February 24, 2005, teaching topical administration of a testosterone composition to the scrotum to achieve potent testosterone compositions in men.). Indeed, the ’944 axilla patent itself lists the scrotum as a preferred area of skin where the claimed composition may be applied; nowhere states to avoid application of the disclosed formulation to the scrotum; and nowhere purports to solve any alleged problem with DHT levels. PTX-4 at col. 7, ll. 39-42.

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<sup>10</sup> Dr. Goldstein suggested that the Testoderm® patch was discontinued in 2002 due to DHT concerns. Goldstein 623:12-15, 716:3-15. But he presents no evidence that DHT levels had any bearing on the manufacturer’s decision to discontinue production. *Id.* Indeed, the manufacturer had developed a follow-on Testoderm® TTS product. *Id.* at 623:16-21. Further by 2002, two additional non-patch testosterone products, AndroGel® and Testim®, became commercially available in the United States. *Id.* at 624:1-14 (discussing PDX-7008).

At most, by June 2005, the clinical significance of elevated DHT levels on the prostate gland was the subject of debate among physicians. Snyder 921:6-22. In its normal function, the prostate converts testosterone taken from the bloodstream to DHT. *Id.* There is a distinction between DHT levels in the prostate and DHT blood levels, with levels in the prostate gland being far higher than those in the bloodstream. *Id.* Diseases of the prostate, like BPH, depend on the conversion of testosterone to DHT that occurred in the prostate. *Id.* To a physician in 2005, therefore, there was no particular reason to believe that the blood concentrations of DHT had any clinical effect or medical significance on prostate disease. *Id.*

The teachings of the prior art relevant to elevated DHT levels associated with transdermal testosterone treatment applied to the scrotal skin are summarized below. Each of the references cited is prior art to the '944 patent.

**A. Ahmed (1988)**

Ahmed et al., "Transdermal Testosterone Therapy in the Treatment of Male Hypogonadism," *J. Clin. Endocrin. & Metab.*, Vol. 66(3):546-51 (1988) ("Ahmed (1988)") reported on a study testing the efficacy of using a testosterone patch on the scrotal skin. PTX-235 at Abstract. Ahmed (1988) found a "disproportionate increase in serum DHT levels" which "probably resulted from the conversion of testosterone to DHT in the scrotal skin" related to 5 $\alpha$ -reductase activity known to be present there. *Id.* at 6-7. Ahmed (1988) recognized that while short-term DHT elevations were not known to be related to adverse clinical effects, "the effects of chronically elevated serum DHT

concentrations coupled with normal serum testosterone levels are unknown.” *Id.* at 7.

Although Ahmed (1988) noted that the long-term effects of increased serum DHT concentrations on the prostate “need to be systematically studied,” the authors concluded that transdermal testosterone therapy using a scrotal patch was “an effective long term treatment for hypogonadism in men.” *Id.* at 7-8.

### **B. Findlay (1989)**

Like Ahmed (1988), Findlay *et al.*, “Treatment of Primary Hypogonadism in Men by the Transdermal Administration of Testosterone,” *J. Clin. Endocrin. & Metab.*, Vol. 68(2):369-73 (1989) (“Findlay (1989)”) reported on a study testing the efficacy of using a scrotal patch for the long term treatment of hypogonadal men. PTX-343 at Abstract. Findlay (1989) stated that an “unexpected finding” following the study was “the increase in the serum [DHT] concentration in each of the 10 men from subnormal or low normal to supranormal during transdermal testosterone administration.” *Id.* at 7. Findlay (1989) speculated that “the reason for this increase is the high concentration in the scrotal skin of  $5\alpha$ -reductase, the enzyme that catalyzes the conversion of testosterone to [DHT].” *Id.* Findlay (1989) recognized that such abnormally high levels of DHT “raise the issue as to whether transdermal administration of testosterone would be more likely than other methods of replacement to accelerate the development of [BPH], since BPH is probably dependent on [DHT] formation.” *Id.* However, Findlay (1989) observed that the DHT upon which BPH is dependent “is normally formed within prostatic cells from testosterone taken up from the systemic circulation.” *Id.* Findlay (1989) advised that in

the absence of definitive information about the “hormonal mechanisms of BPH development,” prostatic examination of subjects should be performed before starting and annually during transdermal testosterone treatment. Findlay (1989) nonetheless concluded that the transdermal administration of testosterone via scrotal patch “is an effective means of treating testosterone deficiency in hypogonadal men, except in those who have a very small or irregular scrotal surface.” *Id.*

### **C. McClure (1991)**

McClure et al., “Hypogonadal Impotence Treated by Transdermal Testosterone,” *Urology*, Vol. 37(3):224-28 (1991) (“McClure (1991)”) reported the results of a clinical study of Testoderm® with four men in which the DHT:T ratio was more than double the upper value in normal men. PTX-468. McClure concluded that high concentration of 5-alpha reductase in scrotal skin was likely the reason for this increase. However, despite observing elevated DHT levels, McClure (1991) reported that “[n]one of our patients, 2 of whom were older than fifty-five, had any subjective evidence of changes in urine flow or frequency or an increase in the size of the prostate.” *Id.* at 4. McClure (1991) noted that the “etiology of the supposed large increases in DHT in BPH became a major focus of research during the last decade,” and that, following that research, “[t]oday, less credence is given to the simple concept that elevated DHT levels may be a factor in BPH ...” *Id.* McClure (1991) concluded that transdermal testosterone therapy applied to the scrotal skin “is convenient, reliable, and more closely mimics normal physiology than do conventional methods of testosterone replacement for hypogonadal men.” *Id.* at 5.

**D. Confrancesco (1996)**

Confrancesco & Dobs., “Transdermal Testosterone Delivery Systems,” *The Endocrinologist* 6(3): 207-13 (1996) (“Confrancesco (1996)”) compares studies of patients using the Testoderm® and Androderm® transdermal testosterone patches. PTX-290. Confrancesco (1996) reports that patients using Testoderm® (applied to the scrotal skin), unlike patients using Adroderm® (applied to nonscrotal skin), were found to have elevated serum DHT levels following treatment. Confrancesco (1996) concluded this was “likely due to the high level of 5  $\alpha$ -reductase activity in scrotal skin,” noting that “[t]he clinical significance of the increased DHT is unknown.” *Id.* at 3.

**E. Amory (1998)**

Amory & Matsumoto, “The therapeutic potential of testosterone patches.” *Exp. Opin. Invest. Drugs* 7(11) (1998) (“Amory (1998)”) is a review of various transdermal testosterone patches. PTX-238. Amory (1998) reported that in a study of Testoderm® treatment for an extended period of time DHT-to-T ratios were elevated but “[i]mportantly, there were no adverse effects such as gynaecomastia, *prostatic hypertrophy*, or oedema.” *Id.* at 4 (emphasis added).

**F. Cutter (2001)**

Cutter 2001 reported that long-term studies with Testoderm® do not support the concerns that DHT may be linked to increased prostate growth:

The published findings on the long-term use of the scrotal application of the Testoderm patch (ALZA Corporation, Palo Alto, California) indicate that the



level of DHT was several-fold higher in subjects who used the patch than it was in those treated with nonscrotal patches. *However, the incidence of prostate problems in those who wore scrotal patches was no greater than that in subjects given placebo.* Additional studies have indicated a 15% decrease in size of the prostate in men treated with pure DHT gels, probably as a result of an inhibition of the normal production of DHT and E<sub>2</sub> that occurs in the prostate itself.

PTX-301 at 7 (emphasis added).

***Prior Art Related to Connection Between Application of Testosterone to the Axilla and Elevated DHT Levels***

As discussed above, the prior art attributed the elevated DHT levels and DHT:T ratio associated with use of transdermal testosterone treatments applied to scrotal skin to the high 5-alpha reductase activity in that area. It was known at the time of the invention of the '944 patent that high concentrations of 5-alpha reductase are predominately found in skin where there are apocrine sweat glands, such as the scrotum and axilla. Goldstein 632:16-634:17, 711:16-25. Apocrine glands have highly regionalized locations and are found only in the axillae (armpits), in anogenital regions, and around the nipples.<sup>11</sup> Goldstein 625:15-626:7; Potts 1481:8-1482:6.

Dr. Goldstein opined that the prior art taught away from the application of testosterone to the axilla due to concerns of increases in DHT levels and increased DHT-to-T ratios to above supraphysiologic levels. Goldstein 632:4-15. Yet, in arriving at his

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<sup>11</sup> Dr. Snyder, Defendants' expert endocrinologist and only medical expert, did not contest Dr. Goldstein's testimony regarding high concentrations of 5-alpha reductase in apocrine glands in the axilla. Dr. Snyder did not know whether apocrine glands are predominant in the axilla. Snyder 946:1-948:9. Dr. Snyder also had no knowledge of whether apocrine glands produce 5-alpha reductase. Snyder 948:22-25.

opinion, Dr. Goldstein relied on no prior art data showing that the administration of testosterone to the axilla actually resulted in elevated DHT levels or elevated DHT-to-T ratios. *Id.* at 692:11-693:5. Nor did he rely on any prior art reference describing that administration of testosterone to the axilla would result in elevated DHT levels. *Id.* at 694:3-11. To the contrary, the Cutter (2000) and Cutter (2001) references disclose that application of testosterone to the “axillary area” did not result in elevated DHT levels. PTX-301 at 6; PTX-302 at 4.

Likewise, Dr. Goldstein presented no data or experimental results showing that administration of testosterone to the axilla would result in increased risk of prostate cancer. *Id.* at 694:12-22. Dr. Goldstein conceded that for his opinion on teaching away he did not rely on any prior art reference that actually criticizes the administration of testosterone to the axilla. *Id.* at 703:1-5. He is not aware of any prior art literature stating that the axilla would not be a good site for transdermal delivery of testosterone. *Id.* at 701:4-20.

In the absence of any prior art reference that actually criticizes the administration of testosterone to the axilla due to concerns of elevated DHT levels (Goldstein 703:1-5), Dr. Goldstein’s opinion relied upon only one study that concerned axilla skin—the *in vitro* study described in Takayasu (1980). *Id.* at 705:13-15. None of the studies Dr. Goldstein relied on studied application of testosterone to the axilla of a living human. Goldstein 704:11-24. None of the other prior art references that Dr. Goldstein relied upon for his opinion studied or otherwise discussed DHT levels after application of

testosterone to the axilla of a human, or activity of the enzyme 5 $\alpha$ -reductase in the axilla. *Id.* at 726:14-24 (referring to demonstrative PDX 7013).

The prior art relevant to this issue includes the following references:

**A. Takayasu (1980)**

Takayasu S. *et al.*, *Activity of Testosterone 5 $\alpha$ -Reductase in Various Tissues of Human Skin*, *Journal of Investigative Dermatology*, 74:187-91 (1980) reports a study of 5 $\alpha$ -reductase activity—the enzyme involved with converting testosterone to DHT—in various skin components derived from various human skin sites. PTX-583 at 1. In this study, samples of skin were collected from surgery and the authors collected a 5 mm punch biopsy. Potts 1389:16-1390:7; PTX-583 at 1. The punch biopsy was further dissected under a microscope into separate components—*i.e.*, glands, hair follicles, dermis, and epidermis. *Id.* Each individual component (but not the whole, intact skin samples) was tested for 5 $\alpha$ -reductase activity. *Id.* In total, Dr. Takayasu evaluated components of axillary skin taken from two patients—Subject I, a 22-year-old female and Subject J, a 41-year-old female. Potts Tr. 1391:8-22; PTX-583 at 4. No skin samples were collected from any anatomical region other than the axilla for these two patients. *Id.* Table II of Takayasu (1980) reports that the 5 $\alpha$ -reductase activity of the sebaceous glands or the dermis obtained from the axilla was in about the middle of the range for these components obtained from other skin samples of other patients, whereas the 5 $\alpha$ -reductase activity of the sweat gland obtained from the axilla was higher than the sweat

glands obtained from the scalp and forehead of other patients. Potts Tr. 1391:23-1392:5; Watkinson Dep. Tr. 152:10-24; PTX-583 at 4.

In the Takayasu study, only two subjects provided axillary skin samples, and no skin samples from other anatomic regions from these subjects were studied. Potts 1391:8-22; PTX-583 at 4. The study collected a 5 mm punch biopsy from the skin samples, which is about the diameter of a pencil eraser, representing less than 0.1% of the total area of the axilla. Potts Tr. 1389:16-1390:7; PTX-583 at 1. The  $5\alpha$ -reductase activity, as reported by Dr. Takayasu, was then adjusted by dry weight of the sample of the component studied. PTX-583 at 2, 4. Dr. Takayasu does not provide data regarding the relative abundance of the components in the skin samples—*i.e.*, how much sweat gland was in the skin sample relative to the total amount of all components in the punch biopsy. Potts 1392:6-16; Goldstein 715:24-716:2. In the absence of this information, a POSA would not be able to determine the level of  $5\alpha$ -reductase activity in the entire axillary skin sample. *Id.* Dr. Goldstein attempts to fill in this missing information regarding the composition of the skin by offering his opinion that the “majority” of the skin of the axilla is comprised of sweat glands, but this opinion was not included in his expert report nor did it rely upon any prior art for corroboration. Goldstein 711:16-712:4, 715:9-23.

Takayasu (1980) is the only prior art reference upon which Dr. Goldstein relied for his opinion regarding the level of  $5\alpha$ -reductase activity in the axilla. Goldstein Tr. 705:13-15. Dr. Goldstein’s opinion assumes that the axilla has similar  $5\alpha$ -reductase

activity as the scrotum. *Id.* at 701:21-702:14; 717:8-13, 723:9-19. Takayasu (1980) did not measure the 5 $\alpha$ -reductase activity of the scrotum, however. Potts 1396:10-14; Goldstein 706:17-21. Instead, Takayasu (1980) discloses that “[o]ur knowledge of the localization of 5 $\alpha$ -reductase activity in the skin largely depends upon indirect evidence obtainable from a study with whole skin: the activity is high in genital [2] and axillary skin [4].” PTX-583 at 2; Potts 1480:5-1481:3. Takayasu (1980) plainly cites to one study for genital skin and another study for axillary skin. *See* PTX-583 at 2. Dr. Potts is not aware of any reference that directly compares the 5 $\alpha$ -reductase activity of the axilla and that of the scrotum. Potts at 1397:6-25. Dr. Goldstein also is not aware of any data in the prior art literature that directly compares the 5 $\alpha$ -reductase activity of the axilla and that of the scrotum. Goldstein 702:16-20; *see also* Watkinson Dep Tr. 161:6-10, 161:12-14, 161:22-162:3.

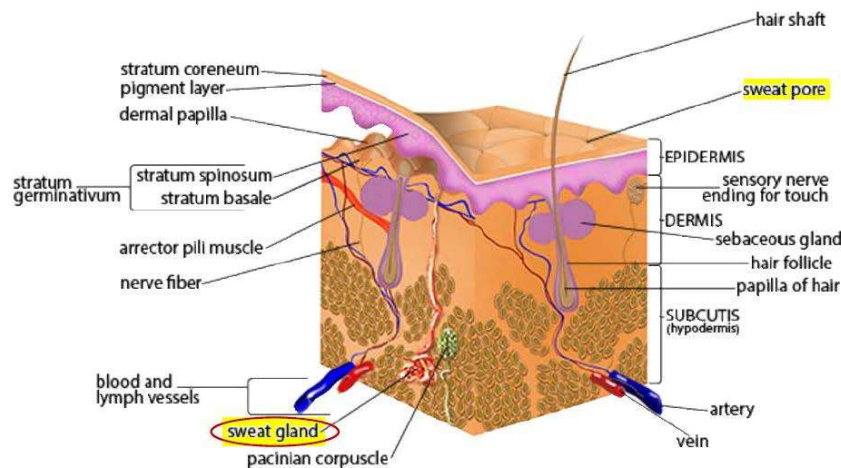
Since there is no study directly comparing those two skin sites, there is no way to evaluate what “high” activity in genital skin means versus in axillary skin. Potts 1480:5-1481:3. Indeed, Dr. Takayasu warned against drawing this parallel between 5 $\alpha$ -reductase activity of the axilla and scrotum from two different studies. *Id.*; PTX-583 at 2. Specifically, he stated that, “in addition to complexity of the skin constituents, different experimental conditions used in these studies, which may possibly have affected the *in vitro* testosterone metabolism, *does not permit us to draw a parallel between various components of the skin from different regions* or those in diseased state in terms of 5 $\alpha$ -reductase activity. PTX-583 at 2 (emphasis added).) A POSA would understand that Dr.

Takayasu cautions against making comparisons between two studies because of these methodological difficulties. Potts 1480:5-1481:3.

**B. Scheuplein (1971)**

Takayasu (1980) does not address whether the  $5\alpha$ -reductase activity of isolated axillary sweat glands is representative of the  $5\alpha$ -reductase activity of intact living human axilla. As Dr. Potts explained with Scheuplein & Blank, “Permeability of the Skin,” *Physiological Reviews*, Vol. 51 (1971) (“Scheuplein (1971)”) and his demonstrative exhibit DDX 248 (which was admitted into evidence), there are different routes of drug transport through the skin, including drug delivery directly through the outermost layer of skin (the stratum corneum) and through skin appendages that pierce the stratum corneum (the hair follicles and sweat ducts).

## Anatomy of the Skin



NIH, National Cancer Institute. *Anatomy Of The Skin*, <http://training.seer.cancer.gov/melanoma/anatomy/>

DDX248

*Id.* at 1393:7-20, 1394:18-1395:13 (referring to demonstrative DDX 248); Watkinson Dep Tr. 154:9-15, 156:1-9, 156:16-21; PTX-563 at 7.) For a drug applied to the top of the skin to reach the sweat glands in intact skin, the drug must go through the skin appendage route by diffusing through a sweat pore and down the sweat duct to reach the sweat gland. *Id.* As was well-known, drug delivery through the skin appendages is minimal due to the relatively small total surface area of these appendages, with total transport through the sweat glands and hair follicles on the order of about  $10^{-3}$  (0.1%). *Id.* Scheuplein (1971) in Table 6 compared the fractional diffusional volume of these separate pathways as reported in the literature. Potts 1393:21-1394:10; PTX-563 at 22. There are about 200-250 sweat ducts/cm<sup>2</sup> of the skin and the fractional diffusion volume of the collective sweat ducts is about  $3-5 \times 10^{-4}$  (0.03-0.05%) of the skin. *Id.* Even

accounting for regional variations of areas of high sweat—such as the palms of the hands and soles of the feet that have about two to four times greater the amount of sweat ducts than the average body surface—the fractional diffusion volume of the collective sweat ducts in these areas of high sweat remains small. Potts 1483:21-1484:12; PTX-563 at 22.

A POSA with an understanding of the structure of the skin and the routes of drug delivery through the skin would not extrapolate the data reported in Takayasu (1980) for individual components of the skin to draw conclusions about the 5 $\alpha$ -reductase activity of intact living human axilla. Potts Tr. 1395:14-1396:22. Dr. Takayasu harvested individual sweat glands away from the skin. *Id.* at 1395:14-21. His study was not designed to take into account the amount of testosterone that would follow the narrow pathway through the sweat pores and sweat ducts to reach the sweat glands. *Id.* at 1396:3-22. A POSA would know that drug delivery through the sweat ducts into the sweat glands comprises a minor fraction of the total volume and is not a major route for drug delivery through the skin. *Id.* at 1394:11-17; *see also* Hadgraft Tr. 183:6-184:10 (explaining that drug delivery through the hair follicle is “really insignificant”).

### C. Cutter (2000) and Cutter (2001)

Cutter (2000) teaches a POSA that applying a testosterone gel to the axillary area, unlike the scrotum, will result in a balance of testosterone, DHT, and estradiol that is very much in the normal physiologic range:

The choice of application site is quite important. When the gel is applied to the trunk or *axillary area, the resulting balance of testosterone, DHT, and E<sub>2</sub> will be very much in the normal physiologic range.* However, when the



gel is applied to the scrotum, the level of DHT becomes much higher because of the presence of a much higher level of the enzyme 5-alpha reductase.

PTX-301 at 6 (emphasis added); Potts 1380:17-1381:7. A POSA would understand that Dr. Cutter's reference to the "axillary area" would by definition include the axilla. *Id.* at 1381:16-22.

Cutter (2001) further presents clinical data demonstrating that administration of testosterone to the axilla as an application site did not result in elevated DHT levels. Potts 1381:23-1383:7. In Table 2 of Cutter (2001), reproduced below, Dr. Cutter provided measurements of the DHT levels of ten patients, which included seven patients administering testosterone gel to the scrotum and three patients administering testosterone gel to the axilla. PTX-302 at 4. Each of the three subjects who had the drug administered to the axilla demonstrated DHT levels within the normal physiological range of 30-100 ng/dL, whereas each of the seven subjects who had the drug administered to the scrotum demonstrated DHT levels above 100 ng/dL. *Id.*

**Table 2. Testosterone Gel Effects on Major Sex Steroid Hormones.**

Patient No, Gel Amount, Strength, and Site of Application	Total Testosterone (normal 300-1,200 ng/dL)		Free Testosterone (normal 34-194 pg/mL)		Dihydrotestosterone (normal 30-100 ng/dL)		Estradiol (normal 25-50 pg/mL)	
	Pre	Post	Pre	Post	Pre	Post	Pre	Post
1. 2 mL, 1.5%, 30 mg, scrotum	3	463	15	118	13	160	10	19
2. 3 mL, 3.0%, 90 mg, scrotum	23	644	5	198	8	298	16	37
3. 2 mL, 3.0%, 60 mg, scrotum	19	301	2	39	2	440	10	27
4. 1 mL, 10%, 100 mg, scrotum	63	245	28	120	10	114	137	103
5. 1 mL, 1.5%, 15 mg, axilla	197	338	30	68	48	85	28	36
6. 2 mL, 3.0%, 60 mg, axilla	160	285	48	95	-	98	38	33
7. 2 mL, 3.0%, 60 mg, axilla	188	320	31	97	31	49	37	36
8. 2 mL, 6.0%, 120 mg, scrotum	268	922	60	250	33	395	23	32
9. 2 mL, 3.0%, 60 mg, scrotum	239	411	74	133	-	228	10	53
10. 2 mL, 6.0%, 120 mg, scrotum	203	320	49	85	19	125	32	24
Average	136.3	442.9	34.2	120.3	20.5	199.2	34.1	40.0
P value	<.001		<.001		.006		.191	

PTX-302 at 4. A POSA would understand that Dr. Cutter's description of the "axilla" as the site of application in Table 2 to refer to part of the axilla. Potts 1381:23-1383:7; *see* Chambliss 1614:4-24. Cutter (2001) therefore teaches that it would be appropriate to apply a testosterone gel to the axilla and that elevated DHT levels would not be expected. Potts 1382:4-1383:7.

### ***Internal Acrux Correspondence Related to DHT and the Axilla***

In internal documents from 2004, Acrux noted certain concerns regarding application of testosterone to the axilla. For example, in a March 2004 email, Acrux recognized: "[T]here is still concern re DHT levels, even after application, because DHT is a 5-fold more potent androgen than [testosterone]. Need to make sure this is measured in any [pharmacokinetic] studies that Acrux completes." PTX-1033, March 9, 2004, E-mail from Charman, at 1. Acrux meeting minutes from December 2004 also reflect discussion of potential concerns regarding applying testosterone to the axilla, including increased hair growth, increased sweating or smell, increased 5-alpha reductase and DHT:T ratio, and interaction from shaving and cosmetics. PTX-657, Acrux Dec. 15, 2004, Meeting Minutes, at 1.

However, in an April 26, 2006 email from Ms. Paulina Hall (Acrux's FDA consultant) to Acrux recounting a conversation she had had with Mr. John Kim (the FDA's representative) occurring earlier that day, Ms. Hall clearly states that the FDA was "not concern[ed] with using the axilla as the application site for the proposed IND study." PTX-1035 at 1. In his direct testimony, Dr. Goldstein offered an opinion as to why the

FDA would have had no concern with selecting the axilla as an application site, (Goldstein 670:8-23), stating that the FDA was at first concerned about DHT levels, but that the FDA was subsequently convinced that there were no concerns, because “data shown to [the FDA of any earlier Acrux clinical study] did not show elevations in DHT when a testosterone formulation was applied to a region with high 5-alpha reductase activity, the axilla.” *Id.* However, the email correspondence from Ms. Hall does not state that the FDA ever had had any concerns with elevated DHT levels from application of testosterone to the axilla. PTX-1035 at 1. Nor does Ms. Hall explain the reason the FDA had had no concerns. *Id.*

Further, the premise of Dr. Goldstein’s opinion on the FDA correspondence is that the FDA had reviewed the data from Acrux clinical study MTE04 in evaluating whether there was any concern with applying testosterone to the axilla. Goldstein 670:8-23. But it is not clear whether the FDA had actually reviewed the data at the point it expressed no concern regarding application of testosterone to the axilla. In the April 11, 2006 correspondence, Ms. Hall inquired of the FDA as to whether it had “any concerns about the use of the axilla as the proposed application site, potentially the levels of DHT.” *Id.* at 664:17-23, 668:5-22; PTX-1034 at 1. Ms. Hall attached to her letter a protocol for clinical study MTE04 (PTX-1034 at 1), noting that “the results from this study will be available at the end of April/06” and asking whether the FDA would “recommend Acrux to submit the results from study MTE04 for review prior to submitting the IND.” PTX-1034 at 1. In the later April 26, 2006 email, when Ms. Hill reported that the FDA had no concern, she did not state that the FDA had reviewed any patient data from MTE04.

PTX-1035 at 1. Rather, in response to Acrux's earlier question as to when the FDA recommended that Acrux submit the results from the study, Ms. Hall reported that the "[r]esults from study MTE04 will be included in the initial IND for review." *Id.* In fact, the clinical study dates for MTE04 extended to May 5, 2006 (subsequent to the April 26, 2006 email from Ms. Hall) and the final report was dated April 20, 2007. PTX-100, MTE04 Clinical Study Report at 5. Thus, it is not clear whether, at the time of the April 26, 2006 email from Ms. Hall, the FDA had received the clinical study MTE04 data or if that data impacted the FDA's opinion regarding whether the axilla was expected to raise DHT levels.

***Impact of the Axilla's Characteristics on Its Suitability as an Application Site for Transdermal Drug Delivery***

Plaintiffs maintain that a POSA in June 2005 would have been discouraged from administering a transdermal drug to the axilla because of concerns regarding hair, creases and folds in the skin, sweat, bacteria, and interference with deodorants and antiperspirants that are regularly applied to the area. However, the prior art does not support either this contention or these concerns and does not teach away from the axilla as an application site for non-occlusive testosterone formulations based on any of these concerns.

***Prior Art Related to the Presence of Hair and Creases and Folds of the Skin***

**A. Berti (1995)**

Dr. Hadgraft relied on a set of guidelines for transdermally delivered drugs described in Berti (1995) to support his opinion that the prior art taught away from topical administration to a hairy area of the skin. Hadgraft 189:8-190:10; PTX-264 at 5. Berti (1995) states that “[t]he device should be applied to a region that has the least amount of hair possible; otherwise, hair may be clipped rather than shaved.” Hadgraft 457:18-22; PTX-264 at 5. As Dr. Hadgraft conceded on cross-examination, however, a POSA would have understood that the guidelines referencing a “device” is specific to transdermal patch products, where the presence of hair may limit the ability of the patch device to adhere to the skin and maintain contact for drug delivery. Hadgraft 458:10-459:5; *see also* Snyder 915:16-916:6. By contrast, the claimed transdermal testosterone formulations are limited to formulations that are applied to the skin “without occlusion by a patch device.” PTX-4 at Claim 13, 20; Potts 1402:18-21.

#### **B. Tomlinson ‘250 Patent**

These known disadvantages of transdermal patch products are consistent with the teachings of the Tomlinson ’250 patent. Potts 1401:1-1402:17. The Tomlinson ’250 patent is a second reference upon which Dr. Hadgraft relied for his opinion that the prior art teaches away from transdermal drug delivery to areas of the skin with hair and significant creasing and folding. Hadgraft 276:10-20; PTX-592. However, the Tomlinson ’250 patent teaches that these factors are the limitations of the prior art relating to adhesive patches which may be applied to only “a non-hairy area of the skin that is substantially free of wrinkles, creases, and folds.” PTX-592 at col. 2, ll. 7-16;

Potts Tr. 1401:1-22. The Tomlinson '250 patent further teaches that for non-occlusive compositions, “the presence of hair does not create as significant a problem as is the case with adhesive patches” and “the presence of wrinkles, creases and folds in the skin are not an impediment to the application of the composition of the invention to a particular area of the body.” PTX-592 at col. 2, ll. 25-32, col. 2, l. 63 – col. 3, l. 5; Potts 1401:23-1402:11. A POSA would understand from the Tomlinson '250 patent that, since the claimed testosterone formulations are applied without occlusion by a patch device, the presence of hair or creases and folds in the skin would not present a significant problem. Potts Tr. 1402:12-17.)

The Tomlinson '250 patent was considered by the PTO prior to allowance of the '944 patent. PTX-4, '944 patent, at 2; PDX-3049, Tomlinson '250 Patent (2001): PTX-592; Hadgraft 276:19-20.

### **C. AndroGel® and Testim®**

The two prior art non-occlusive testosterone gels, AndroGel® and Testim®, are also applied to skin sites where men often grow hair such as the shoulders, upper arms, and abdomen. Potts 1400:1-15. Unlike with patches, the presence of hair does not present an obstacle for testosterone gels or solutions, which can flow past the hair and be absorbed through the axilla skin. Snyder 931:7-14.

### ***Prior Art Related to Sweat and Bacteria in Axilla***

Dr. Hadgraft further opined that a POSA would have been discouraged from application of testosterone to the axilla due to the presence of sweat. Hadgraft 176:17-

177:8, 178:10-14, 179:22-180:10, 279:13-280:13. But Dr. Hadgraft testified on direct examination that the impact of sweat on transdermal drug delivery is “unpredictable.” *Id.* at 279:13-280:13. Further, he does not identify any prior art reference that discusses any adverse effect of sweat on transdermal delivery of testosterone. *See id.* at 176:17-177:8, 178:10-14, 179:22-180:10, 279:13-280:13.

Dr. Hadgraft also opined that “if you have bacteria in the armpit, then you have the potential for breaking down any active . . . [and] then it will never get through to the skin in the systemic blood supply. Hadgraft 122:2-13; *see also id.* at 177:23-178:1, 180:22-181:3. However, he failed to identify any specific bacteria that had been shown to have this effect or any prior art reference discussing the effect of skin bacteria on the transdermal delivery of testosterone. *Id.*

Even if this were a real concern regarding sweat or bacteria in the axilla, the prior art testosterone gels, AndroGel® and Testim®, recommended application of the testosterone product to “intact, clean, dry skin.” PTX-1059 at 1; PTX-641 at 1. These instructions to wash and dry the skin prior to application of a testosterone product would likely avoid any issues with the presence of excessive sweat or bacteria on the skin. Potts 1404:11-22. Axiron® includes a similar instruction to apply the testosterone composition when the axilla is clean, dry, and intact. PTX-633 at 1; PTX-1061 at 1.

#### ***Prior Art Related to Presence of Deodorants and Antiperspirants***

Dr. Hadgraft further opined that a POSA would have been discouraged from application of testosterone to the axilla which is repeatedly treated with both deodorants

and antiperspirants. Hadgraft 176:8-177:8, 188:24-189:7, 279:9-280:13. Likewise, Dr. Goldstein opined that a physician would expect that the presence of antiperspirants and deodorants would affect testosterone blood levels. Goldstein 675:11-676:13. But Drs. Hadgraft and Goldstein did not identify any specific deodorant or antiperspirant agent that has been shown to interact or counteract with testosterone or otherwise impede transdermal drug delivery. *Id.* Nor did Dr. Hadgraft rely on any prior art reference warning that deodorants and antiperspirants were expected to affect transdermal delivery of testosterone. *Id.* To the contrary, the prior art contemplates adding deodorants and antiperspirants to transdermal testosterone formulations, as shown below.

**A. Aschkenasy '268 Publication**

The Aschkenasy '268 publication, for example, anticipates that deodorants and antiperspirants may be added to its transdermal testosterone composition. PTX-243 at [0139]. Specifically, the Aschkenasy '268 publication, like the axilla patent, teaches that the testosterone composition may comprise additives, including deodorants and antiperspirants. Hadgraft 437:22-439:4; PTX-243 at [0139], PTX-4 at col. 18, ll. 14-23. The Aschkenasy '268 publication provides an extensive list of deodorant agents and antiperspirants—agents that are commonly applied to the axilla—for addition to the topical testosterone formulation. PTX-243 at [0141], [0142]; Hadgraft 433:10-434:18.

**B. AndroGel® and Testim®**

As discussed above, the prior art testosterone gels, AndroGel® and Testim® recommended application of the testosterone product to “intact, clean, dry skin.” PTX-



1059 at 1; PTX-641 at 1. These instructions to wash and dry the skin prior to application of a testosterone product avoid the issues that might present with a deodorant agent or antiperspirant on the skin. Potts 1404:11-22. Axiron® includes a similar instruction to apply the testosterone composition when the axilla is clean, dry, and intact. PTX-633 at 1; PTX-1061 at 1.

***Acrux's Clinical Studies Applying Its Transdermal Testosterone Formulation to the Axilla***

In 2004, Acrux began clinical trials to assess the safety, efficacy, and feasibility of transdermal testosterone application to the axilla. The initial pilot study was conducted in women, and the follow-up study was conducted in healthy men with compressed testosterone. PTX-4 at 16, col. 20, l. 32-col. 23, l. 9; PTX-96; PTX-117. The results of the studies showed that applying testosterone to the axilla was effective at increasing testosterone blood levels and did not lead to abnormally high DHT levels or increase sweat or odor despite the increased perspiration usually associated with the use of testosterone. Hadgraft 296:10-300:15; Goldstein 612:17-613:8, 671:3-674:25, 682:17-683:17; PTX-4 at col. 22, l. 65-col. 23, l. 8.

One of Acrux's initial studies, Clinical Trial No. DDS16, showed efficacy without elevated DHT levels following application to the axilla. PTX-14; PTX-96; PTX-133; PDX-7032; PDX-7033; Goldstein 669:15-20, 676:23-677:9. In fact, the reported DHT levels were lower than those seen in the forearm. Goldstein 669:13-20; PTX-133 at 46 ("Whilst the inner arm treatment showed no significant change in T:DHT ratio over the

72 hour time course, the average ratio of 5:1 was significantly higher than the average ratio for the axilla treatment (3.7”).) Later studies by Acrux confirmed this finding, including, for example, Clinical Trial No. MTE04 (mean DHT:T ratio within the normal physiological range). PTX-14; PTX-100 at 76; PDX-7032; PDX-7033; Goldstein 677:10-14.

***Alleged Unexpected and Surprising Results of the Method Claimed in the ‘944 Patent***

***No Increased Sweating***

Dr. Goldstein opined that a POSA would expect that testosterone increases the activity of the apocrine glands and should result in increased sweating and odor in the axilla. It therefore was surprising that application of testosterone to the axilla in Plaintiffs’ clinical studies did not increase sweat or odor.<sup>12</sup> Goldstein 675:11-676:13.

However, because a hypogonadal man has decreased testosterone blood levels, a physician would expect that his sweating would also be less than normal. Snyder 930:1-

23. If testosterone replacement therapy returns a hypogonadal man to normal physiologic

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<sup>12</sup> Dr. Goldstein relies on a study reported in Example 4 of the axilla patent to support his opinion that administration of testosterone surprisingly resulted in “no increased sweating.” Goldstein 680:4-18; PTX-4 at Example 4. However, this study did not directly measure the amount of sweating following application of testosterone, so there is no evidence that the men who received it did not sweat or that they sweated less than usual in Example 4. PTX-4 at Example 4. Instead, the study participants were instructed that they could “apply deodorant if they were distressed with symptoms of sweating,” and that they should report any such application. *Id.* None of the 16 subjects reported the need to apply deodorant or antiperspirant. *Id.* Thus, the only conclusion that can be reasonably drawn from this study is that none of the study participants felt particularly distressed enough to need the use of a deodorant or antiperspirant. Snyder 930:24-931:6.

ranges, a physician would then expect the amount of sweating to increase to normal levels. *Id.* A physician would further understand that perspiration is a systemic effect of testosterone. *Id.* Increased testosterone blood levels increases sweating in all areas where men normally perspire. *Id.* Sweating does not increase just at the local site of application of testosterone. *Id.* Regardless of the site of application, a physician would expect that returning testosterone blood levels to normal physiologic ranges would result in normal amounts of sweating. *Id.*

### ***Seven-Fold Increase in Permeability Across the Axilla***

Dr. Hadgraft opined that it was unexpected that drug delivery across the axilla provided a seven-fold greater absorption of testosterone per unit surface area of the skin than that of the forearm. Hadgraft 514:5-515:4. Dr. Hadgraft's opinion relied upon the results from plaintiff Acrux's Clinical Study DDS16 comparing drug delivery of testosterone across the skin of the axilla and the inner forearm, which results were later adjusted by inventor Dr. Adam Watkinson to account for the surface areas of the respective application sites. Based on his calculations, Dr. Watkinson asserted that the drug delivery across the axilla was seven-fold greater per unit surface area than that across the forearm. *Id.*

Clinical Study DDS16 is entitled: "A pharmacokinetic phase I study to assess the effect of different application sites on the pharmacokinetics of testosterone from a Testosterone Metered Dose (MD) Lotion™." PTX-96 at 1. In this study, a transdermal testosterone composition was applied to the skin of the axilla and the inner forearm. *Id.*

at 7; Potts Tr. 1406:6-21. The study investigators did not measure the surface area of the application site on the axilla or the forearm or otherwise control for the size of the surface area of the application site. *Id.* The study found that “mean baseline-corrected total testosterone AUC<sub>0-72</sub> for the axilla was 5617 ng.hr/mL, a result almost double that achieved for the inner arm (2979 ng.hr/mL).” PTX-96 at 45; Potts Tr. 1406:22-1407:5. The study investigators found that “the different extents of absorption observed for the two application sites in this study are *consistent with* a previous investigation of variations in skin penetration where the extent of hydrocortisone absorption from the axilla was 3.6 times greater than from the ventral forearm,” as reported in Feldmann (1967). PTX-96 at 45, 77 (emphasis added); Potts Tr. 1406:22-1407:7. Dr. Hadgraft does not dispute that the two-fold enhanced permeation of the axilla relative to the forearm as measured in Clinical Study DDS16 would have been expected. Hadgraft Tr. 459:10-25; *see also* Watkinson Dep. Tr. 114:22-116:14. His opinion on unexpected results based on enhanced permeation is limited to the seven-fold size adjustment made by Dr. Watkinson. *Id.*

In his 2010 declaration, Dr. Watkinson relied on a measurement of the median size of the female axilla obtained from the measurements of 60 women who had their axillae measured for a deodorant/antiperspirant study reported in Cowan-Ellsberry (2008) (PTX-299) and a measurement of the median size of the inner forearm of 15 women from Acrucx’s offices who had their forearms measured by Dr. Watkinson in order to calculate the “flux” per unit surface area of testosterone across the skin in the axilla and inner

forearm of the subjects in DDS16. PTX-14 at 5-6, ¶¶ 13-15. Flux is a term used to describe the rate of transfer of a drug across the skin. Hadgraft 303:23-304:3. When Dr. Watkinson performed this calculation correcting for the surface area of the two administration sites in DDS16, he determined that there was a seven-fold increase in flux for the axilla as compared to the inner arm. PTX-14 at 8, ¶ 21; Hadgraft 299:18-304:6. In making this comparison, Dr. Watkinson relied upon the assumption that the areas of the axillae and forearms measured represented the areas of application in the original Clinical Study DDS16. Potts 1411:12-20, 1411:24-1412:7. In his 2010 declaration to the PTO regarding unexpected results, Dr. Watkinson explained that the seven-fold greater absorption of testosterone in the axilla was unpredictable in view of the variability in the prior art, depending on the compound and site of application. PTX-14 at 9, ¶ 22.

Clinical Study DDS16 did not include any discussion of the axilla providing a seven-fold greater permeation than the forearm. Potts 1407:8-11. None of the publications of the Clinical Study DDS16 results, other than Dr. Watkinson's declaration to the PTO, included any discussion of the axilla providing a seven-fold greater permeation than the forearm. *Id.* at 1407:12-1410:3. Specifically, the results of Clinical Study DDS16 are reported in Example 1 of the axilla patent, but the inventors did not make any claim in the specification that the axilla resulted in a seven-fold greater permeation than the forearm. *Id.* at 1407:19-1408:4; PTX-4 at Example 1. The study investigators later published the results of Clinical Study DDS16 in a 2014 peer-reviewed article by lead author Dr. Susan Davis. Potts 1408:5-1409:5; PTX-303. The authors

report that administration of testosterone to the axilla resulted in two-fold greater absorption than across the forearm. Potts 1409:9-17; PTX-303 at 1, 6. The authors did not make any claim that absorption across the axilla was seven-fold greater than across the forearm. *Id.*

## **VI. The Applicator Patent**

The '861 applicator patent, entitled "Spreading Implement," claims an implement for topical delivery of a therapeutic liquid or lotion – here, the claimed transdermal testosterone lotion – to the "axilla area of the user." PTX-5 at Abstract.

### ***Definition of a Person of Ordinary Skill in the Art for the '861 Patent***

A person of ordinary skill in the art ("POSA") for the '861 applicator patent would have been someone with a bachelor of science degree in mechanical engineering or the packaging fields and one to three years of experience, or equivalent education and/or experience, in the design of medical products and/or design and manufacture of products and packaging for pharmaceutical applications. Slocum 565:11-567:17; DDX-418 (Singh definition of POSA for '861 patent).

### ***The Invention and the '861 Patent***

For safety and efficacy, Acrux needed to show that its patented testosterone solution could be applied accurately and consistently. PTX-75 at 30-32 (listing requests from FDA regarding the applicator). Since there were no similar products on the market at the time (*i.e.*, a low-viscosity transdermal testosterone formulation applied to the

axilla), Acrux did not believe an applicator was then in existence that was suitable for its purpose. PTX-1093 at 7 (providing market research on known applicators for other products to the axilla).

To assist in developing a no-touch applicator implement to apply its testosterone formulation to the axilla, Acrux engaged the Bayly Group. PTX-1066 at 3; PTX-1093; PTX-1153; Slocum 541:12-24. The inventors considered numerous possible designs for the applicator. PTX-1093 at 6-7, 10; PTX-1148 at 4; Slocum 545:3-16, 548:11-549:25. Their first design attempts embodied applicators with convex heads, similar to roll-on and ball-shaped applicators for the axilla known at the time. PTX-1148 at 4, 6; Slocum 548:4-549:25. Because the axilla is primarily a concave surface, the general wisdom at the time was to use an applicator with a complementary shape: a convex applicator to fit the concave surface. PTX-1093 at 7; Slocum 546:15-22.

The first design pursued by the inventors was a dome-shaped applicator referred to as the “mushroom” applicator. *E.g.*, PTX-1093 at 6-7; Slocum 545:3-546:2, 549:19-25. As previously noted, the mushroom applicator had a convex head and was designed to apply the solution in a manner similar to the known roll-on deodorant applicators. PTX-1066 at 6, 8. The mushroom applicator concept was eventually abandoned, however, for several reasons. PTX-1066 at 7. Importantly, the metered-dose testosterone lotion was not effectively retained on the surface of the head; the solution would run down the bottle and did not reliably deliver the required dose. PTX-1066 at 6, 7; PTX-1144 at 2; Slocum 552:3-15, 559:18-23.

The inventors began to pursue a design of a “simple axilla applicator.” (PTX-1066 at 6, 7, 10. The “simple axilla applicator” was so named because it was made with fewer parts than the mushroom applicator. PTX-1066 at 7, 10. Ultimately, the inventors struck upon the idea of an applicator with a concave receptacle. PTX-1066 at 17; PTX-1157 at 3-5; PTX-1158 at 2, 4-6; Slocum 554:4-555:3. The simple axilla applicator: (1) retains the solution dispensed from the pump and allows for the applicator to be tilted to angles up to 45 degrees without spilling the dose; (2) includes a soft, collapsible head to aid in the smooth and effective dosing to the axilla; (3) delivers a full dose; and (4) is easy to clean. PTX-1066 at 6, 10, 17. Those applicator concepts were the foundation of the patent application that issued as the ’861 patent. Slocum 554:4-555:3.

An overview of the preferred applicator embodiment is shown in Figure 1 (PTX-5 at col. 3, ll. 6-17 and Fig. 1.); a cross-sectional view of the applicator with additional detail is shown in Figure 2 (*Id.* at col. 3, ll. 18-33 and Fig. 2). The applicator is used as follows: therapeutic liquid is dispensed into the applicator reservoir (4) (Figure 1), after which the user places the applicator in contact with the skin surface to deposit and spread the liquid onto the skin. *See id.* at col. 3, ll. 6-17. The ’861 patent claims describe the applicator and its components, various therapeutic compositions, and the application method. PTX-5.



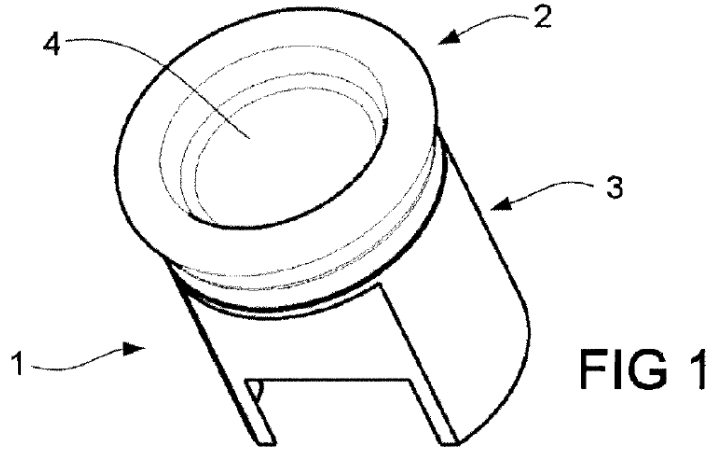


Figure 1. The preferred embodiment of the '861 patent is an applicator (1) having a receptacle (2), support means (3), and reservoir space (4).

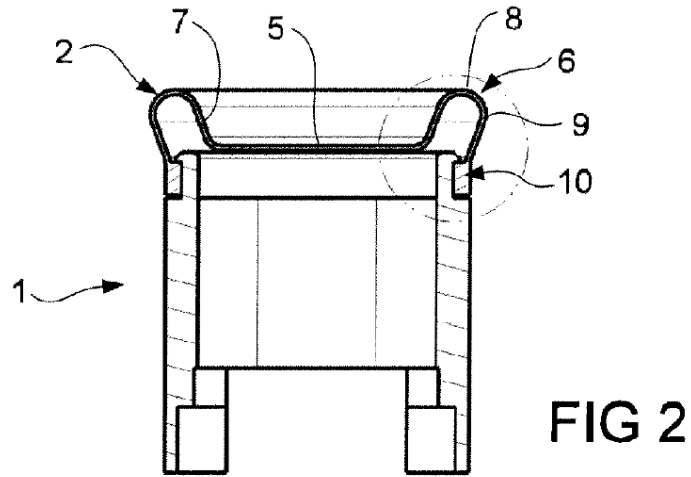


Figure 2. The cross-section of the applicator (1) shows that the receptacle (2) contains a base (5) and wall (6). The wall (6) has an inner portion (7) and an upper portion (8). The outer side of the wall contains a skirt portion (9) and a lower edge (10). The lower edge (10) is attached to the support means (3) (see Fig. 1 and Fig. 3).

PTX-5 at col. 3, ll. 6-17 and Fig. 1; *id.* at col. 3, ll. 18-33 and Fig. 2.

***Claims 9 and 10 of the '861 Patent***

As discussed above, in this litigation, Plaintiffs have asserted against Defendants dependent claims 9 and 10 of the '861 patent. These claims (and those from which they depend) recite as follows:

**1.** A system for transdermal administration of a physiologically active agent from a liquid composition, the system including a container containing the liquid composition including the physiologically active agent, a dispensing device for delivering liquid composition from the container; and an applicator for applying the liquid to an area of skin for transdermal administration said applicator including a support detachably contactable to the dispensing device or container being adapted to detach to permit said dispensing device to deliver said liquid composition, a receptacle mounted on the support defining a reservoir space which receives a volume of the liquid composition from the container, the receptacle having a base and a resiliently deformable wall, the wall being substantially transverse to the base and having a working surface that is used to spread the liquid composition over the area of the skin surface, the base having a surface such that the liquid composition cannot pass through the base.

**9.** A method of transdermal administration of a physiologically active agent to a subject including providing a system according to claim **1**; applying the liquid composition including the physiologically active agent to the reservoir space; and deforming the wall of the receptacle containing the liquid composition against the skin of the subject and spreading the liquid composition over the area of the skin surface in at least one axilla.

**10.** A system according to claim **1** wherein the receptacle defining the reservoir space has an open top being configured to receive the liquid composition from the dispensing device through the open top.

PTX-5 at claims 1, 9, 10.

***Claim Construction of the '861 Patent***

The parties have agreed that the claimed “wall” is defined as “[p]art of the receptacle having an inner portion and an outer skirt portion which form a double-wall structure.” Dkt. 105 at 2. The “double-wall structure” is “[a] structure having two walls, i.e., not the two surfaces of a single wall.” *Id.* In the context of the ’861 applicator patent, the claimed wall must comprise an inner portion (“[o]ne of the two walls of the double-wall structure that is closest to the reservoir space”) and an outer skirt portion (“[o]ne of the two walls of the double-wall structure that is furthest from the reservoir space”) that together form a double-wall structure. *Id.* at 1-2; PTX-5 at claim 1. The parties agree that the asserted claims of the ’861 patent require a wall that is “substantially transverse to the base.”

The parties have also agreed that the terms “has a continuous surface such that liquid cannot pass through the base” and “having a surface such that the liquid composition cannot pass through the base,” mean “[the] surface does not contain openings or pores that would permit liquid to pass through the base.”

#### **A. The Actavis and Perrigo Applicators<sup>13</sup>**

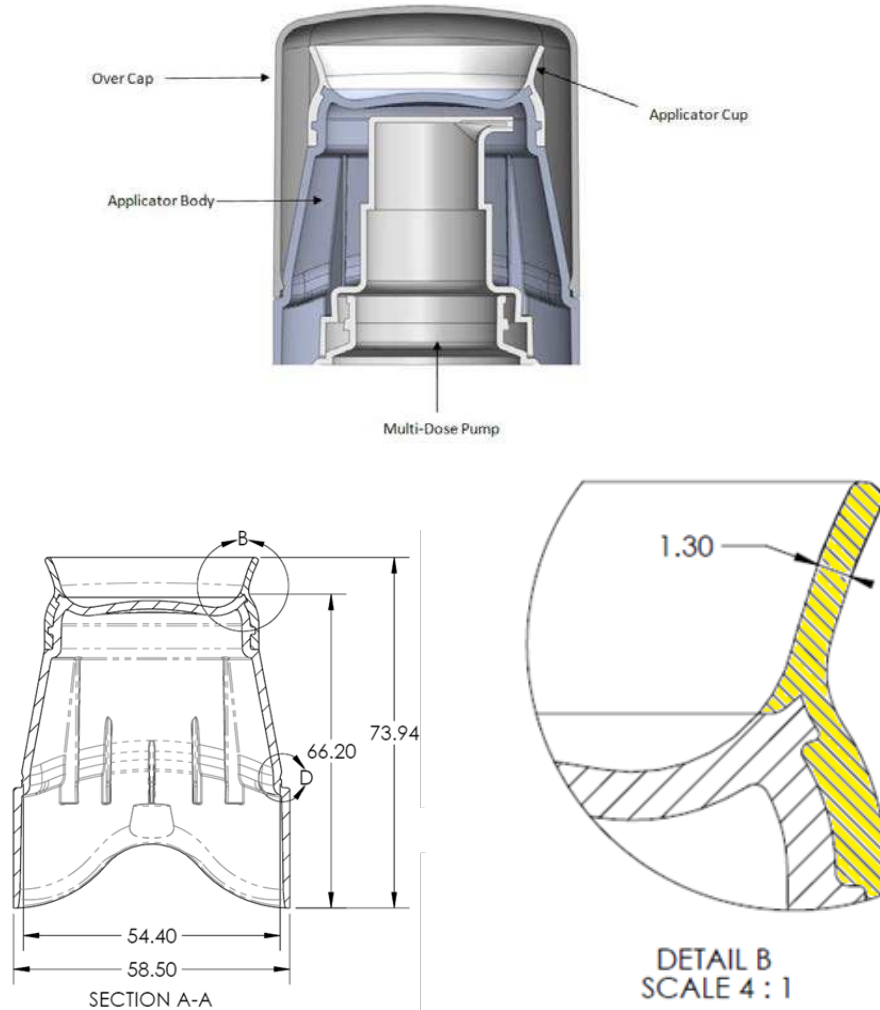
##### ***The Actavis Applicator***

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<sup>13</sup> Plaintiffs’ expert Dr. Slocum testified that his infringement opinions and analyses regarding the claimed “wall” were substantively the same with respect to the Actavis applicator and the Perrigo applicator, and that there are no differences between the Actavis applicator and the Perrigo applicator that are material to his opinions regarding the “wall” limitation. *See, e.g.*, Slocum 817:4-11, 818:1-14, 819:13-820:1, 829:8-11, 979:8-981:4. Plaintiffs have stipulated that Dr. Singh’s testimony, including, among other things, his testimony regarding the Actavis applicator, applies equally to Perrigo and the Perrigo applicator, and that Perrigo may rely on that testimony (and the exhibits Dr. Singh relied on during his testimony) for any purpose related to this case. Dkt. 410 ¶ 1.

Actavis's ANDA applicator is depicted in the schematics below:

### Schematics of Actavis's Applicator

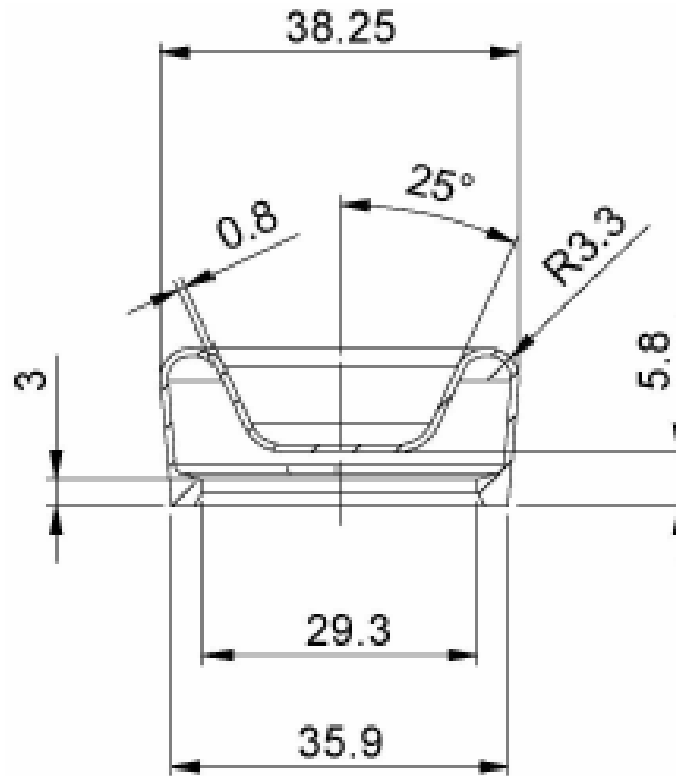


PTX-218 at 1658-59; see PTX-1174; DTX-1277. Detail B depicts the single wall of Actavis's applicator that Plaintiffs allege folds over to form a double-wall structure when used in accordance with Actavis's labeling instructions.

### *The Perrigo Applicator*

Perrigo Israel submitted ANDA No. 204255 to FDA on April 3, 2012. Dkt. 134

¶ 58; DTX-13 at 1-4. As originally submitted, Perrigo Israel's ANDA included information regarding an original proposed applicator device, including:

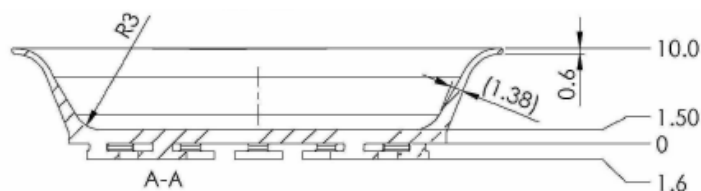
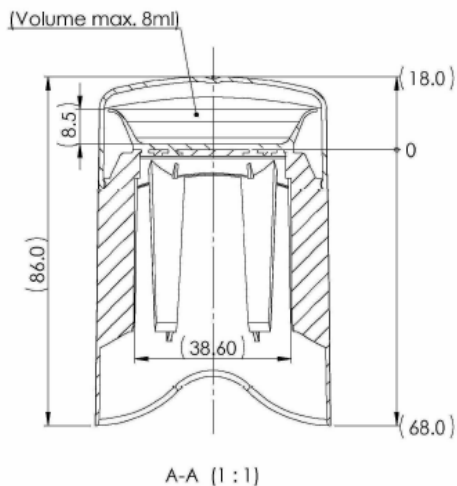


DTX-13 at 756; *see also* DTX-13 at 753-55.

In 2014, Perrigo Israel's ANDA was amended to include information regarding the current proposed applicator device, which is the applicator that Perrigo intends to include as part of the its ANDA Product. *See* PTX-206 at 992-95.

The Perrigo ANDA applicator is depicted in the schematics below:

### **Schematics of the Perrigo Applicator**



DTX-32 at 1-3; PTX-206 at 992, 994-95; DTX-30 at 1-3; *see* PTX-1175.

***The “Wall” Limitation***<sup>14</sup>

As discussed above, the “wall” limitation in the asserted claims has been construed to require a double-walled structure. Plaintiffs concede that both the Actavis and Perrigo applicators have only a single wall at rest, and therefore neither applicator meets the limitations of claims 9 and 10 of the ‘861 patent at rest. *See, e.g.,* Slocum

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<sup>14</sup> Because, for the reasons detailed *infra* in Section IV.A.1, we hold that Plaintiffs have failed to establish by a preponderance of the evidence that the Actavis and Perrigo applicators meet the wall limitation, and therefore cannot show that the accused devices meet every limitation of the asserted claims as required to prove infringement, we need not and do not address the disclaimer and disclosure issues or any other disputed claim limitations raised by Actavis and Perrigo.

774:14-17, 978:18-20; Slocum 817:16-20, 856:8-22. Plaintiffs contend, however, that the wall of both the Actavis and Perrigo applicators folds over when used in accordance with the devices' respective labeling instructions to form the infringing double-walled structure.

### ***The Basis of Dr. Slocum's Testimony Regarding the Wall Limitation***

Plaintiffs rely in support of this contention solely on Dr. Slocum's testimony that the Actavis and Perrigo applicators form a claimed double-wall structure in use. Dr. Slocum based his opinion that the Actavis and Perrigo applicators form a claimed double-wall structure in use on:

- portions of the Actavis and Perrigo labeling (Slocum 778:20-779:15; PDX 4088; Slocum 819:13-820:1; PDX 4067; PDX 4068);
- his theoretical understanding of the materials used in the wall (Slocum 781:14-23);
- his manipulation of the applicators in the offices of the Finnegan lawyers ("Finnegan testing") (Slocum 783:5-25); and
- his March 2016 at-home testing in his shower ("wet testing") (*id.*)

*See id.* at 817:9-11, 818:1-14. In reaching his conclusions, Dr. Slocum never saw a patient or any other person actually use the Actavis or Perrigo applicator. *Id.* at 895:2-4; 979:8-981:4.

### ***The Structure and Materials Used in the Walls of the Actavis and Perrigo Applicators***

The wall of Actavis's applicator is made of a thermoplastic elastomer; Perrigo's applicator has a wall made of silicone. Both thermoplastic elastomer and silicone are flexible plastics. Dr. Slocum testified, and Dr. Singh did not dispute, that the walls of both the Actavis and Perrigo applicators can be deformed when force is applied to them and will then return to their original shape when the force is removed. Slocum 793:23-794:6, 827:6-16; Singh 1015:24-1016:4, 1116:18-1118:14.

Dr. Slocum further testified that, when Actavis's and Perrigo's applicators are used as directed in the labeling instructions, the flexible walls are pressed against the axilla. He also opined that the instructions included with the Actavis and Perrigo applicators teach the patient to use the applicators in a manner that would avoid leakage of the testosterone formulation. According to Dr. Slocum, the force created when the devices are pressed against the surface of the axilla with enough pressure to prevent leakage causes the walls of the respective applicators to double over on themselves, forming a double-walled structure as disclosed in claims 9 and 10 of the '861 patent. To support this testimony, Dr. Slocum relies on Actavis's and Perrigo's labeling instructions as well as his personal observations during his hands-on testing of the accused applicators.

### ***Dr. Slocum's Finnegan Testing***

Prior to submitting his January 2016 infringement reports, in which he opined that the Actavis and Perrigo applicators would form a claimed double wall in use, Dr. Slocum met at the law offices of Plaintiffs' counsel which provided him an opportunity to handle



the accused applicators; this visit was referenced at trial as the “Finnegan testing.” Slocum 783:5-25, 862:14-863:8, 870:5-11, 872:25-873:3; 979:8-981:4. Dr. Slocum’s Finnegan testing consisted of him manipulating by hand in a fashion he described as “playing with” the Actavis and Perrigo applicators there in Plaintiffs’ counsel’s office. *Id.* at 783:5-17, 862:14-863:8, 863:18-864:10, 864:19-865:11, 865:19-866:21, 979:8-981:4. Dr. Slocum was uncertain as to whether he used liquid in the applicators during the testing, but he testified that, if he had, it would have been “just a little bit of water.” *Id.* at 863:18-23, 864:1-10, 1172:8-16. Dr. Slocum’s Finnegan testing process did not include placement of the Actavis or Perrigo applicators against the axilla, nor did it include utilizing the applicators according the Actavis or Perrigo labeling. *Id.* at 864:1-10, 864:19-865:11, 865:19-24. Dr. Slocum admitted that his Finnegan testing was not performed in a way that a typical user would use the applicators, and that a typical user would not have Dr. Slocum’s level of knowledge regarding sealing structures. *Id.* at 865:25-866:14.

Dr. Slocum took no photographs, video, or contemporaneous notes to document or otherwise record his Finnegan testing on the Actavis and Perrigo applicators. Slocum 866:15-21, 867:7-25. Generally, in his testing conducted outside a litigation context, Dr. Slocum keeps notes, photographs, video, computer records, or other documentation of his testing procedures, data, and results. *Id.* 856:23-857:5, 860:21-861:11.

***Dr. Slocum’s Wet Testing***

After reading defendants' expert reports rebutting his January 2016 infringement report opinions, Dr. Slocum performed his "wet testing" experiment in March 2016 for purposes of preparing his reply report. Slocum 783:5-25, 862:14-863:17, 870:5-11, 872:25-873:8, 979:8-981:4. Dr. Slocum's wet testing consisted of his using the Actavis and Perrigo applicators to apply a homemade contrived liquid formulated by him from ingredients he found at his personal residence (consisting of a combination of cranberry juice and household rubbing alcohol in unknown amounts) to his own axilla, while standing in his bathroom shower. *See, e.g., id.* at 783:5-784:9, 863:14-17, 874:17-19, 875:24-876:6, 877:13-21, 878:13-18; 979:8-981:4. He testified that he "pretend[ed]" to be "a typical user" during his wet testing and that he did not intend for the wet testing to be a scientifically reliable experiment, rather he simply wanted to do a "quick play" with the accused applicators. *Id.* at 783:5-25, 786:17-21, 863:14-17, 891:9-892:2.

At trial, Dr. Slocum could not recall various details about his wet testing. For example, he was unable to remember the date on which he performed his wet testing. Slocum 873:4-12. He also testified that he could not remember the length of time it took him to perform the wet testing on each applicator because "he did not record the time," but he believed that it took "less than an hour and more than a minute." *Id.* at 875:14-23. He could not recall precisely how many times he tested the Actavis or Perrigo applicators during the wet testing, (*see, e.g.,* Slocum 884:4-16), stating that it was "a bunch of times," and "probably around ten" times, but was "more than one time and less than 20" times. *Id.* Additionally, although Dr. Slocum reportedly tested all four applicators on the

same day, one after the other, he did not recall the order in which he tested defendants' accused applicators. *See* Slocum 874:17-875:9. Dr. Slocum testified that he was "pretty sure [he] did Lupin last, but [he doesn't] recall," nor does he recall whether he tested Actavis's, Perrigo's, or Amneal's applicator first.<sup>15</sup> *Id.*

When conducting his wet testing, Dr. Slocum did not use either Actavis's or Perrigo's ANDA formulation that will be sold with the applicators, or even an accurate substitute for those formulations. *See, e.g.,* Slocum 783:5-784:9, 875:24-876:15, 877:13-21, 878:13-18, 878:21-879:2; *see also id.* at 979:8-981:4. Dr. Slocum conceded that he could have asked for and used an Axiron placebo formulation, but he did not. *Id.* at 876:3-17. He also admitted that he had access to Perrigo's ANDA and the formulation described therein, but he did not use that information to make a placebo formulation because he is "not a chemist" and "wouldn't know what to do with [that information] anyway." *Id.* at 876:18-877:3; *see also id.* at 877:8-12. Instead, Dr. Slocum used a homemade mixture of his own devising – cranberry juice and "household rubbing alcohol that [he] found at [his] house" – as a substitute for Actavis's and Perrigo's ANDA formulations. *See, e.g., id.* at 875:24-876:15, 877:13-21. Dr. Slocum did not know how the rubbing alcohol he used in his cranberry juice/alcohol mixture compared to the isopropyl alcohol in the ANDA formulations. *See id.* at 877:4-7.

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<sup>15</sup> During his testimony at trial, Dr. Slocum also exhibited confusion regarding the various accused applicators. *See, e.g.,* Slocum 871:4-11, 895:2-10, 978:18-24.

Despite knowing that Actavis's and Perrigo's ANDA formulations contain a thickening agent, Dr. Slocum did not include any thickener in his cranberry juice/rubbing alcohol mixture. Slocum 877:18-878:7; *see also id.* at 979:8-981:4. He admitted that a formulation containing a thickener would have a higher viscosity than his cranberry juice/alcohol mixture, and that his cranberry juice/alcohol mixture is "more sensitive to detecting leakage from the applicator." *Id.* at 878:8-18. Dr. Slocum did not measure the viscosity of the cranberry juice/alcohol mixture used in his wet testing of the Actavis and Perrigo applicators, but he estimated that it would be "about one centipoise" and "very close to water." *Id.* at 879:4-9. Plaintiffs' expert, Dr. Hadgraft, testified that, based on the ingredients in the Axiron formulation, the viscosity of the Axiron formulation is "between 14 and 35 centipoise," which is "roughly the viscosity of something like vegetable oil." Hadgraft 171:3-18. Actavis's ANDA formulation and Perrigo's ANDA formulation have the same ingredients in roughly the same amounts as the Axiron formulation. *Cf.* PTX-218 at 239 (Actavis ANDA formulation) and DTX-14 at 20 (Perrigo ANDA formulation) *with* PTX-75 at 211 (Axiron formulation); *see* Hadgraft 168:14-169:22.

Thus, according to the testimony of plaintiffs' experts, the viscosity of Dr. Slocum's cranberry juice/alcohol mixture differed significantly from the viscosity of the Actavis and Perrigo ANDA formulations, and Dr. Slocum's wet testing exaggerated the leakage that one would expect from use of Actavis's and Perrigo's applicators by patients

according to the Actavis or Perrigo labeling to apply the Actavis or Perrigo ANDA formulations. *See* Hadgraft 171:3-18; Slocum 877:18-878:18, 879:4-9, 979:8-981:4.

Dr. Slocum also failed to use the amount of liquid directed in Actavis's and Perrigo's labeling instructions when he performed his wet testing. Both Actavis's and Perrigo's labeling specifies that only 1.5 ml of liquid (one pump) at a time is to be transferred into the Actavis and Perrigo applicators for application to the axilla. *See, e.g.*, PTX-218 at 2614-15, 2623; PTX-216 at 16-17. Dr. Slocum admitted that the Actavis and Perrigo labeling tells the patient "exactly" how much liquid to use. Slocum 881:17-19.

Dr. Slocum, however, did not precisely measure the amount of liquid he used in Actavis's and Perrigo's applicators during his wet testing. He testified that he did not use any type of medical syringe or accurate measuring device to measure the amount of liquid he transferred to the Actavis and Perrigo applicators during his wet testing. Slocum 881:6-8. Rather, he used a common kitchen teaspoon that "[they] eat with," which holds approximately "4 to 5 mL total."<sup>16</sup> *Id.* at 880:9-881:5, 785:7-21, 882:16-883:5.

At his deposition, Dr. Slocum first testified that he used 3 ccs per application for his wet testing, which is 3 ml and double the amount of liquid called for in Actavis's and Perrigo's labeling. Slocum 881:20-22, 979:8-981:4. Later in his deposition, he testified

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<sup>16</sup> At trial, Dr. Slocum admitted that, at his deposition, he "couldn't remember" whether he had used a teaspoon or a tablespoon (which is about 15 ml) to measure the liquid for his wet testing, and that he "had some confusion in [his] mind" that apparently cleared up between his May 2016 deposition testimony and his July 2016 trial testimony. Slocum at 785:7-21, 879:10-880:19.

that he used 1.5 ccs per application for his wet testing. *Id.* at 881:23-882:3. At trial, Dr. Slocum could not recall the exact amount of liquid he used in Actavis's and Perrigo's applicators during the wet testing. He testified variously that he used "what looked like a reasonable amount" of liquid for his wet testing, (*id.* at 785:7-21, 882:13-15); "a fraction of a teaspoon," (*id.* at 785:7-14), "about a third of a teaspoon," (*id.* at 879:10-880:6), "a reasonable guesstimate," (*id.* at 882:13-21), "a few milliliters lower than the rim" of the teaspoon, (*id.*), "less than [4 to 5 mL], on the order of the one and a half, (*id.* at 882:16-883:2), and "a third to a half, probably." *Id.* at 883:3-5.

As with his Finnegan testing, Dr. Slocum took no photographs, video, or contemporaneous notes to document his wet testing on the Actavis and Perrigo applicators. Slocum 873:13-16, 875:10-23, 880:24-881:5, 888:1-6, 894:20-21, 895:11-19. Because he elected to perform his wet testing in the bathroom of his home, without anyone witnessing his use or otherwise documenting the testing with photographs or video, Dr. Slocum was able to determine whether a double-wall formed only by looking at himself directly while using the applicators, and, for parts he could not observe in that way, by looking at himself in his bathroom mirror while standing in his shower about five or six feet away from the mirror. *See, e.g.*, Slocum 885:15-886:16.

Based on his wet testing, Dr. Slocum testified that users will "learn" to form a double wall when using the Actavis and Perrigo applicators because they are instructed to prevent all leakage during application. *See, e.g.*, Slocum 783:5-785:6, 883:12-884:3, 890:5-891:4. He testified that the applicators would not be "working right" if there were

any amount of leakage more than “a drip now and then.” *Id.* at 892:19-893:21. Thus, Dr. Slocum testified that patients will press the Actavis and Perrigo applicators with sufficient force to form a double wall simply because he did so to avoid excessive leakage, which he defines as anything more than “a drip now and then.” Dr. Slocum did not test the Axiron® applicator as a control, in order to compare the leakage experienced with the Actavis and Perrigo applicators with leakage associated with the Axiron® applicator. With regard to his belief as to the acceptable amount of leakage, Dr. Slocum testified that “if it was drippy, runny, ineffective ... I don’t think the FDA would have approved it as a product.” Slocum Tr. 869:5-870:4, 902:3-903:2.

Dr. Slocum testified that he cannot say precisely the amount of force he applied in order for the single wall of Perrigo’s applicator to fold over in use. Slocum 884:17-885:14, 890:11-891:8, 979:8-981:4. Although Dr. Slocum testified that the amount of force with which the applicator is pressed against the axilla can affect whether a double wall is formed, he utilized no special instrument to control (or measure) the amount of force that he used when wet testing Actavis’s and Perrigo’s applicators. *Id.* at 884:17-885:14, 890:11-891:8. Dr. Slocum testified that he himself pressed Actavis’s and Perrigo’s applicators to his axilla with enough force to create a so-called “rolling diaphragm” seal in order to avoid what he deemed to be excessive leakage, but he conceded that typical users do not have his level of knowledge regarding sealing structures. *See id.* at 777:18-778:8, 783:5-785:6, 866:12-14.

Dr. Slocum also testified that he followed the instructions on Actavis's and Perrigo's labeling "as closely as possible." Dkt. 318 at 11. He concedes that neither Actavis's nor Perrigo's labeling contains express instructions to apply sufficient force to avoid all leakage or to create a seal. *See* Dkt. 318 at 10. The instructions direct patients only to "keep[] the applicator upright" and to "place [the applicator] up into the axilla and wipe steadily down and up into the axilla." *E.g.*, DTX-258. Actavis's and Perrigo's labeling both warn patients about the risk of secondary exposure to testosterone and instruct the user to apply the testosterone lotion only to the axilla and not to touch the solution with their hands. With regard to possible leakage, the instructions direct that "[i]f the solution drips or runs, it can be wiped back up with the applicator cup." *Id.*

***Dr. Slocum's Animation of the Accused Applicators***

During cross examination, Dr. Slocum admitted that an animation he used in connection with his infringement testimony (PDX 4084), which demonstrated the wall of Actavis' applicator folding over to form a double wall in use, depicted the axilla as a "simple," "upside-down bowl" that lacked any "other stuff that's in the axilla," such as hair. Slocum 1214:25-1215:23, 1216:7-15; *see also id.* at 817:6-11, 818:1-819:7; PDX 4063. However, Dr. Slocum had previously testified that the axilla is a "very complex" surface, is "not just a smooth bowl," and has "all kinds of stuff going on in there." Slocum 1214:12-24; *see id.* at 794:22-795:6. Dr. Slocum admitted that his animation does not show the applicator being wiped up and down according to the labeling or moving laterally across the skin surface. *Id.* at 1217:1-4, 11-13. Dr. Slocum provided no



pictures or video of the Actavis or Perrigo applicators actually being used in a human axilla, nor did he demonstrate use of the applicators on a human axilla. Slocum 1216:16-25.

***Dr. Singh's Testimony Regarding the Wall Limitation***

At trial, Dr. Singh opined that the Actavis and Perrigo applicators, when used in accordance with the Actavis and Perrigo labeling, do not form a double wall and therefore do not infringe claims 9 and 10 of the '861 patent. His opinions were based on, among other things, his review of the '861 applicator patent and its prosecution history, the Actavis (and Perrigo) ANDA labeling, Lilly's demonstrative videos of the Axiron applicator, information regarding the Actavis (and Perrigo) applicator including schematics, and a sample of the Actavis (and Perrigo) applicator. Singh 1013:2-17, 1015:6-8; *see* Dkt. 410 at ¶ 1.

Dr. Singh testified that the Actavis and Perrigo labeling does not include any requirements or directions that, in using the Actavis or Perrigo applicators, the patient should or must use them in such a way to form a double wall, apply a certain amount of force against the axilla, or form a seal against the axilla. Singh 1018:4-1019:2; PTX-218; *see also* Dkt. 410 ¶ 1; PTX-206; PTX-216. He further testified that, contrary to Dr. Slocum's opinion, the labeling does not instruct the patient to push the applicators with enough pressure against the axilla to cause the single wall to fold over onto itself. Singh Tr. 1019:13-19. According to Dr. Singh, a patient using the Actavis or Perrigo

applicators consistent with the labeling will not form a seal or double wall against the axilla. Singh 1019:3-12, 1023:14-16, 1024:4-16.

In support of this opinion, Dr. Singh testified that, contrary to Dr. Slocum's description, the surface of the armpit is relatively flat (rather than concave) when the applicators first make contact with the skin. Singh 1019:20-1020:5. Dr. Singh pointed to Figure 3 of the Actavis labeling as showing the relatively flat surface to which the applicator is initially applied:

- To apply the testosterone topical solution, keep the applicator upright, place it up into the armpit application site and wipe steadily down and up (see Figure 3).



Figure 3

PTX-218 at 2633; *see* Singh 1019:20-1020:5. Figure 3 of the Perrigo labeling also shows the relatively flat surface to which the Perrigo applicator is initially applied:



Figure 3

- Remove the cap and the applicator cup from the pump. Then, position the nozzle over the applicator cup and depress the pump gently (*see* Figure 2).
- To apply the Testosterone Topical Solution, keep the applicator upright, place it up into the armpit application site and wipe steadily down and up (*see* Figure 3).
- If Testosterone Topical Solution drips or runs, wipe it back up with the applicator cup. Do not rub in the solution with your fingers or hand once it has been applied.

PTX-216 at 19; *see* Singh 1019:20-1020:5; Dkt. 410 at ¶ 1.

Dr. Singh also referenced Lilly’s Axiron® video (DTX-1283), entitled “Application Video,” which purports to provide patients with “step by step instructions on how to properly apply Axiron,” according to the Axiron® labeling. DTX-1283 at 00:00 to 00:06, *available at* <http://axiron.com/how-to-apply-axiron-for-testosterone-treatment.aspx>. As Dr. Slocum admitted, the Axiron labeling and the Actavis and Perrigo labeling are substantively the same. Slocum Tr. 904:22-905:6; *see also id.* at 979:8-25. Thus, Lilly’s Axiron video also illustrates the proper application of the Actavis and Perrigo applicators according to the Actavis and Perrigo labeling. Indeed, Dr. Singh testified that Lilly’s Axiron video is representative of applications using Actavis’ and Perrigo’s applicators according to the Actavis and Perrigo labeling. *See id.* at 1022:20-1023:16, 1025:23-1026:5; *see also* Dkt. 410 ¶ 1.

During Lilly’s Axiron video, patients are instructed to “start swiping a little above and ending a little below your underarms to help avoid spilling and to speed drying.” DTX-1283 at 01:19 to 01:25. Excerpted photographs from video show the following:



DDX 405; *see* DTX-1283.



DDX 408; *see* DTX-1283.

Using Lilly’s Axiron video (DTX-1283), specifically at the 1:24 mark to the 1:39 mark, Dr. Singh explained that the applicator is first placed up against a relatively flat surface of the axilla (as opposed to a relatively concave or convex surface), then is

swiped down and steadily up. Singh 1020:24-1022:7; DTX-1283. He also testified that, as the applicator is swiped down and up, the leading portion of the wall is folded inwards into the receptacle while the trailing wall portion is not deformed at all. *Id.* at 1021:14-1022:19; DDX 405, 408; DTX-1283.

Dr. Singh opined that the Actavis and Perrigo applicators would behave similarly during application according to the Actavis and Perrigo labeling. Singh 1022:20-1023:16; DDX 407; *see also* Dkt. 410 ¶ 1. Specifically, Dr. Singh testified that, during application, the leading edge of the Actavis and Perrigo applicators would fold inward (therefore not forming a double wall even according to Dr. Slocum's theory) and the trailing edge would not deform against the axilla (therefore not forming a double wall even according to Dr. Slocum's theory). Singh 1022:25-1023:16; DDX 407; *see also* Dkt. 410 ¶ 1. Dr. Singh specifically stated that the Actavis and Perrigo applicators do not form a double wall during application. Singh 1023:14-16; *see also* Dkt. 410 ¶ 1. He also testified that the video shows that the applicators do not form a seal during application (including a "rolling diaphragm seal"), primarily because the applicators are held relatively upright and a portion of the wall is not touching the axilla skin in any way. Singh 1023:17-1024:20, 1025:23-1026:5; DDX 408.

Dr. Singh's interpretations of Lilly's Axiron video, including the position of the leading and trailing edges of the applicators during application, was not rebutted by Dr. Slocum or any other witness.

Dr. Singh pointed out that Dr. Slocum had not demonstrated that the Actavis or Perrigo applicators form a “rolling diaphragm effect” or a “rolling diaphragm seal.” Singh Tr. 1025:12-22; *see also* Dkt. 410 ¶ 1. In his view, “[a] diaphragm seal is usually used to retain fluids or liquid under high pressure,” and that he is not aware of any instances of a diaphragm seal being used to apply a liquid to the skin, such as in the cosmetics or pharmaceutical fields. Singh 1025:16-1026:11. He testified that the Actavis and Perrigo applicators do not, in fact, form a rolling diaphragm seal during application. Singh 1025:23-1026:5.

### **B. The Amneal Applicator**

Plaintiffs have brought claims for direct and indirect infringement against Amneal, alleging that Amneal’s proposed applicator literally infringes claims 9 and 10 of the ‘861 patent. Amneal maintains that its applicator does not infringe the asserted claims because it does not meet the “wall” limitation of the ‘861 patent.

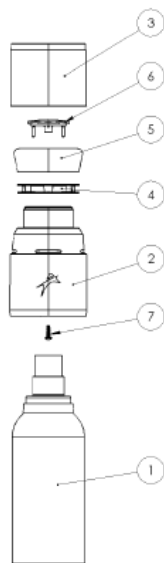
#### ***Components of the Amneal Applicator***

Amneal’s non-infringement expert, Hermann Plank, testified that Amneal’s proposed applicator includes a handle (2), a cap (3), a moveable skirt (4), diaphragm (5), a diaphragm insert (6), and a set-screw (7), as shown in the figure below and described in detail in Amneal’s ANDA.<sup>17</sup> DTX-2082 at 16-17; PTX-1091 at 128; *see also* PTX-186

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<sup>17</sup> By stipulation, in lieu of live testimony from Mr. Plank at trial, the parties admitted the Expert Report of Hermann Plank MSc., dated February 19, 2016 (“Plank Report”), including Exhibits 1 and 2 of the Plank Report as his direct testimony. *See* Dkt. 411. Mr. Plank’s report was admitted as DTX-2082.

at 1646. The handle (blue), the cap (white), the skirt (blue), and the diaphragm insert (white) are all made of the same material, polypropylene, with differences only in colors. DTX-2082 at 16-17; PTX-1091 at 128; *see also* PTX-186 at 1646.



Mr. Plank testified that the diaphragm (5) is a single piece of membrane made of clear silicone. DTX-2082 at 16-17; PTX-1091 at 128; *see also* PTX-186 at 1646. The first end of the diaphragm (5) is mounted onto the rigid handle (2) through the diaphragm insert (6) through the set-screw (7). DTX-2082 at 16-17; PTX-1091 at 128; *see also* PTX-186 at 1646. The other end (*i.e.* the second end) of the diaphragm (5) is folded over and coupled with the moveable skirt (4). DTX-2082 at 16-17; PTX-1091 at 128; *see also* PTX-186 at 1646. The second end of the diaphragm (5) and the moveable skirt (4) are not affixed to the handle (2) or the diaphragm insert (6), and can move freely relative to the handle (2) in a longitudinally axial direction. DTX-2082 at 16-17; DDX 148; *see also* DTX-2082 at 9, 17.

The diaphragm (5) of the Amneal applicator is the “wall” of the receptacle and the element of the device that Plaintiffs contend meets the double-wall structure limitation of the ‘861 patent. *Id.* at 2072-73; PDX-4014 and 4017; Slocum 843:3-13. Dr. Slocum testified that the silicone rubber diaphragm of Amneal’s applicator comprises an inner portion and an outer skirt portion that forms a double-wall structure. PTX-186 at 2072-73; PDX-4014 and 4017; Slocum 843:3-13. Mr. Plank agreed that there is a portion of the silicone wall of the Amneal applicator that is closed to the reservoir space and one that is furthest from the reservoir space. DTX-2083, Plank Dep. Tr. 39:19-40:1.

### ***Relevant Claim Construction***

As explained above, the agreed construction of “wall” in terms of the device claimed in the ‘861 patent is a “part of the receptacle having an inner portion and an outer skirt portion which form a double-wall structure” Dkt. No. 105; DTX-2021. A “double-wall structure” has been construed to mean “a structure having two walls, *i.e.*, not the two surfaces of a single wall.” *Id.* The two walls are the inner portion (“one of the two walls of the double-wall structure that is closest to the reservoir space”) and the outer skirt portion (“one of the two walls of the double-wall structure that is furthest from the reservoir space”). *Id.* The parties’ agreed constructions for the “double-wall structure” and the “outer skirt portion”/“skirt portion” do not require the outer skirt to be attached to the support to be a double-wall structure. *See* Dkt. 105 at 2.

### ***The “Double-Wall Structure” Claim Amendment***



During prosecution of the related application for U.S. Patent No. 8,177,449 (“the ’449 patent”), the feature of “wherein the inner portion and skirt portion form a double-wall structure” was added in an attempt to distinguish prior art such as U.S. Patent No. 3,462,230 (“Beard”). *See* PTX-10 at 335, 343-45; DTX-2082 at 13-15.

Applicants argued in the Amendment that Beard does not teach or disclose an implement with a double-wall structure because Beard only discloses a single-walled device made of a flexible molded plastic material. *See* PTX-10 at 344; DTX-2082 at 13-15. Further, the applicants represented that Beard is distinguishable from the claimed invention, because “Beard does not teach or suggest an implement having a wall that includes an inner portion which extends from the base to an upper end and an outer skirt portion, wherein the inner portion and skirt portion form a double wall structure, as recited in the instant claims.” *See* PTX-10 at 344; DTX-2082 at 13-15. The applicants made no specific statements during the claim amendment process regarding attachment of the wall to the support.

The term “double-wall structure” is not expressly defined in either the ’861 or ’449 patents. DTX-2082 at 13-15. In amending the pending claims, the patent applicants represented that “support for the added clause regarding the wall is found at page 5, paragraph 26, and in figures, and in original claims 10 and 36, which are canceled without prejudice or disclaimer.” *See* PTX-10 at 341; DTX-2082 at 14-15. Dr. Slocum admitted on cross examination that all three sources of support for the claim amendment illustrate that the outer skirt portion of the double-wall structure is attached to the

support. Slocum 1226:24-1227:2, 1231:5-9, 1234:13-1235:14. For example, Paragraph 26 of the specification reads as follows:

Referring now to Figure 2 which shows the implement 1 in cross section 10 and it can be noted that the receptacle 2 includes a base 5 and a wall 6. The wall includes an inner portion 7 which extends continuously from the base 5 towards an upper end 8 of the wall 6. *A skirt portion 9 of the wall extends continuously from the upper end 8 of the wall to a lower edge 10 which is attached to the support means 3.* Figure 3 shows more clearly the lower edge of 15 the skirt being formed with a thickened rib 10 which locates in a recess 12 formed on the support means 3. Other means for connecting the receptacle to the support means are clearly possible however this arrangement allows the receptacle 2 to be detached from the support means 3 for purposes such as cleaning of the receptacle 2.

PTX-10 at 10 (emphasis added).

Paragraph 26 of the specification references Figures 2 and 3 and describes how the inner portion and the skirt portion together create a double-wall structure. *Id.* at 10 and 38. As shown in FIGS. 2-3 (copied below), the receptacle 2 of the implement 1 includes a base 5 and a wall 6. Wall 6 includes an inner portion 7 and an outer skirt portion 9 which is attached to the support means 3. Specifically, the lower edge of the skirt is formed with a thickened rib 10 which locates in a recess 12 formed on the support means 3. PTX-5 at col. 3, ll. 18-34. Although paragraph 26 suggests that other means for connecting the receptacle to the support means (besides the disclosed “thickened rib”) may be “possible,” no such other means are disclosed in the specification. Dr. Slocum agreed on cross examination that each of the embodiments featured in the Figures shows

a double-wall structure with the outer skirt attached to the support. PTX-10 at 10, 38-40; PTX-5 at 4-6; DDX 120-126; Slocum 1227:3-5, 1227:20-25, 1228:24-1229:11, 1229:21-1230:1, 1230:10-19, 1231:5-9, 1236:10-13.

Dr. Slocum also confirmed on cross examination that both original claims 10 and 36 depend from original claim 8, which requires “the wall includes a skirt portion a lower edge of which is attached to the support means.” PTX-10 at 2, 5; *see also* Slocum 1234:13-25. Because a dependent claim incorporates every limitation of the claim from which it depends, these original claims incorporate the limitation that the outer skirt be attached to the support.

As a result of the claim amendment process, claim 1 of the '449 patent was amended during prosecution to add the clause “wherein the wall includes an inner portion which extends from the base to an upper end and an outer skirt portion, wherein the inner portion and skirt portion form a double-wall structure.” PTX-10 at 335. Paragraph 26 contains almost verbatim support for the clause added to claim 1. In particular, paragraph 26 states: “[t]he wall includes an inner portion 7 which extends continuously from the base 5 towards an upper end 8 of the wall 6. A skirt portion 9 of the wall extends continuously from the upper end 8 of the wall to a lower edge 10 which is attached to the support means 3.” *Compare* PTX-10 at 10, *with* PTX-10 at 335 (emphasis added to show the overlap between paragraph 26 and the clause added to claim 1). Even though paragraph 26 contains language that would have allowed the applicants to amend claim 1

to recite that the skirt portion is attached to the support, the patentees did *not* amend claim 1 to recite this requirement. PTX-10 at 335; Slocum 850:1-5.

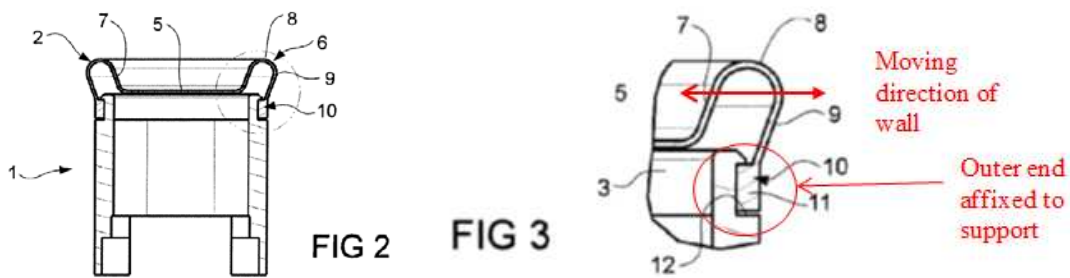
### ***The Claims of the '861 Patent Regarding Attachment of the Wall to the Support***

Independent claim 1 of the '861 patent is the broadest claim, and it does not expressly require the outer skirt portion to be attached to the support. PTX-5, '861 patent, at claim 1; *see also* PDX-4138 (depicting an embodiment consistent with claims 1, 9, and 10 with the outer skirt portion unattached); Slocum 849:25-850:9. Dependent claim 12, however, does include this requirement, explicitly stating that the “lower edge of the skirt portion is attached to the support.” PTX-5, '861 patent, at claim 12; *see also* PDX-4137 (depicting an embodiment consistent with claim 12 with the skirt portion attached to the support); Slocum 849:5-24.

This understanding of the claims is consistent with the '861 patent specification, which indicates that the outer skirt portion is *optionally* attached to the support. Slocum 848:10-25. That is, although the skirt of the wall may have “a lower edge of which is attached to the support means,” this is only an example of a “preferred embodiment,” and does not require that the skirt be attached to the support means. PTX-5 at col. 2, ll. 15-17; Slocum 848:10-25.

### ***Differences in Structure and Function Between the Amneal and Claimed Applicators***

Mr. Plank testified that Amneal’s proposed applicator has a different structure and functions differently from the applicator in the asserted claims of the ’861 applicator patent. DTX-2082 at 17-19. For example, in the applicator of claim 1 of the ’861 applicator patent, the double-wall structure acts as “a blade-like member when spreading the liquid across the treatment surface.” PTX-5 at col. 3, ll. 34-57. The structure and the moving direction of the wall are shown in annotated FIG. 3, which illustrate that the “blade-like” action occurs when the applicator is moved back and forth parallel to the base. PTX-5 at 3:34-57; *see also* DTX-2082 at 15-16; DDX 145, 146.



Mr. Plank testified that, unlike the claimed device, when the user applies the membrane in Amneal’s proposed applicator to a treatment surface, and pressure is applied to the upper folded end, the second end moves distally down, resulting in little to no lateral deformation of the upper folded end against the surface. DTX-2082 at 17-19. Rather, the upper folded end deforms relatively uniformly around its perimeter along an axis traverse to the diaphragm insert, resulting in a rolling action. *Id.* As a result, Amneal’s proposed applicator uniformly deforms in the axial direction to create a

controlled, free sliding movement of the single wall against the user's skin using a rolling action without lateral deformation. *Id.*

However, the asserted claims do not require the wall to move or deform in any particular way. Claim 1 merely recites that the wall is "resiliently deformable," and claim 9 recites "deforming the wall of the receptacle containing the liquid composition against the skin of the subject and spreading the liquid composition over the area of the skin surface in at least one axilla." There is no directionality in these elements, and nothing in the asserted claims or specification suggest to a POSA that the wall must move in a certain direction (i.e., axially but not laterally).

Despite the differences testified to by Mr. Plank, Amneal has informed the FDA that "it is confirmed that the Amneal applicators are [the] same as that of the RLD [Reference Listed Drug (Axiron<sup>®</sup>)] in their performance and functionality." PTX-186 at 885. Amneal has represented to the FDA that "the Amneal applicator was designed, fabricated and manufactured to function in the similar fashion as the RLD applicator," and that "[i]t is evident from the pictures that the physical shape and applicability of Amneal drug product packaging components are very similar to that of the RLD." *Id.* at 476. Furthermore, Amneal told the FDA that "Amneal has chosen these packaging components, based on their design, reproducibility and performance characteristics for the drug product and their sameness with respect to the principal operation to the applicator of the Reference Listed drug (RLD)." *Id.* at 489.

### ***Amneal's Labeling Instructions***

Amneal intends for its applicator to be used to apply its testosterone solution, supplying its applicator with its generic testosterone solution and providing instructions on how to apply the solution using its applicator. PTX-186 at 27 (“For topical use only with enclosed applicator”), 54-56 (“When it is time to throw away the bottle, safely throw away all parts of the testosterone topical solution dispenser including bottle applicator cup and cap.”).

Amneal instructs users to “[r]emove the cap and the applicator cup from the pump. Then, position the nozzle over the applicator cup and depress the pump gently,” thus applying the liquid composition including the physiologically active agent to the reservoir space. *Id.* at 54-55. Similar instructions are found throughout Amneal’s labeling. *Id.* at 37-38.

Amneal further directs users “[t]o apply the testosterone topical solution, keep the applicator upright, place it up into the armpit application site and wipe steadily down and up.” *Id.* at 55. Amneal also instructs users that “[i]f testosterone topical solution drips or runs, wipe it back up with the applicator cup. Do not rub in the solution with your fingers or hand once it has been applied.” *Id.* When Amneal’s applicator is used according to Amneal’s instructions, the wall of the receptacle containing the liquid composition is deformed against the skin of the subject and the liquid composition is spread over the skin of the user’s axilla. *Id.* at 54-55; Slocum 844:15-845:1.

***Amneal’s U.S. Patent No. 9,227,044***

The U.S. Patent and Trademark Office issued Amneal U.S. Patent No. 9,227,044 on January 5, 2016 for its applicator with knowledge of the '449 patent. *See* DTX-2028 at 5:15-39.

***Prior Art to the '861 Patent***

The relevant scope and content of the prior art is determined as of January 11, 2007, the priority date of U.S. Provisional Application No. 60/884,482, to which the '861 patent is entitled priority under 35 U.S.C. § 119. PTX-5; Slocum 568:3-9.

Amneal contends that U.S. Patent No. 6,773,187 (PTX-373, “the Gueret '187 patent) anticipates the claims of the '861 patent, and further, that if not anticipatory, the Gueret '187 patent, when combined with the teachings of U.S. Patent Application No. 2007/0206986 (PTX-374, “the Gueret '986 publication”), renders the claims of the '861 patent obvious. Both the Gueret '986 Publication and the Gueret '187 Patent were considered by the USPTO prior to allowance of the '861 patent. PTX-5 at 3. The Gueret '187 Patent was examined by the same examiner, David Walczak, who reviewed and granted the '861 patent. PTX-5 at 2; PTX-373 at 1; Slocum 576:16-23, 583:3-7.

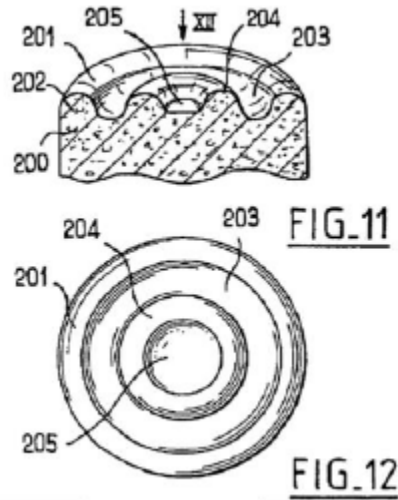
**1. Gueret '187 Patent**

The Gueret '187 patent discloses “a device for packaging and applying a substance, for example, a cosmetic or a care product.” PTX-373 at 13, col. 1, ll. 4-6. The assignee of the Gueret '187 patent is L'Oréal SA. PTX-373 at 1; Slocum 576:11-15. The



applicators of the Gueret '187 Patent are generally directed to cosmetics applicators. Slocum 576:24-577:2.

Amneal cites Figures 11 and 12, reproduced below, as disclosing the claimed applicator. Slocum 577:3-8.



PTX-373 at 7.

Figures 11 and 12 are different perspectives of the same applicator device. Slocum 577:10-14. Figures 11 and 12 depict a device made of an open cell foam. Slocum 579:1-13. As shown in Figures 11 and 12, the applicator element (200) of the Gueret '187 patent may also include a “central depression 205 and the groove 203” that “may be suitable for becoming filled with substance P for application purposes.” PTX-373 at col. 11, ll. 1-4. The annular rib (204) illustrated in Figures 11 and 12 may be excluded. *Id.* at col. 10, l. 61- col. 11, l. 4.

Neither the peripheral portion (202) nor the annular rib (204) provides a double-wall structure. Slocum 275:17-25. The ridges that form the peripheral portion (202) and annular rib (204) are textural ridges that do not have the geometry capable of forming a double-wall structure. Slocum 578:17-25. A POSA would understand that to form a double-wall structure, the wall should be at least five times taller than it is thick (i.e., the thickness of the wall should be at most 1/5 of its height) to achieve a flexible wall that will fold over on itself. Slocum 571:13-572:3. Nothing in the Gueret '187 Patent teaches or suggests such a wall. That is, each ridge may show some flexibility, but not enough to fold over on itself to form a double-wall structure given its geometry. Slocum 578:17-25.

Dr. Singh admitted that “there’s no disclosure of a double wall in the original language [of the Gueret '187 patent],” but asserts that “in anticipation there is a double wall.” Singh 1070:11-15. According to Dr. Singh, a POSA would modify the device of Figures 11 and 12 by (1) replacing the open cell foam with an elastomeric material, (2) removing annular rib (204), and (3) molding the elastomeric material to “form the outer shape of [the] applicator,” but to be hollow on the inside. DDX-454; Singh 1070:11-15.

Dr. Singh testified that the first two modifications (replacing the open cell foam with an elastomeric material and removing annular rib (204)) are disclosed in the Gueret '187 patent. DDX-454; Singh 1071:14-1073:17. Dr. Singh did not testify that there is any disclosure of this third modification, to wit, to use a thin sheet of elastomeric material, molding it so that the applicator would be hollow inside. DDX-454 (failing to cite any support in the Gueret '187 Patent for the third modification); Singh 1072:21-

1073:17, 1136:4-6 (agreeing that his modified figure 11 is “nowhere directly shown in the patent”), 1136:14-19.

Dr. Singh testified on cross examination that if the applicator in Figures 11 and 12 of the Gueret '187 patent were modified as he suggests, it would no longer work for its intended purpose. PTX-373; Singh 1137:22-1138:3. The proposed modification to replace the open cell foam of the applicator in Figures 11 and 12 of the Gueret '187 patent with an impermeable sheet of elastomeric material would mean that it would no longer be able to absorb cosmetics as it was intended to do. PTX-373; Singh 1137:22-1138:6.

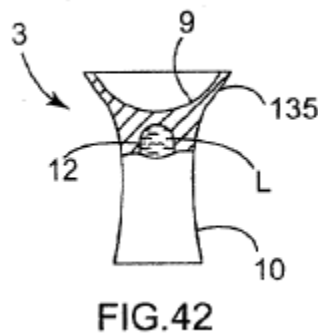
## **2. Gueret '986 Publication**

The Gueret '986 Publication discloses systems for “the cosmetic or dermatological treatment of the skin.” PTX-374 at 13, ¶ [0002]. The assignee is L'Oréal, a company that is in the business of manufacturing and selling cosmetics. Slocum 568:22-25. Cosmetics are typically applied to convex surfaces such as the cheek and nose. Slocum 569:1-4.

The Gueret '986 Publication is directed to devices for use in applying substances that are heated. PTX-374 at 1; Singh 1124:20-1126:15. The abstract of the Gueret '986 publication states that “[t]he applicator further includes at least one material with thermal properties such that, when the at least one material is heated to a temperature above 30° C . . . application surface maintains . . . a temperature above or equal to 30° C.” PTX-374 at Abstract. As described in the Gueret '986 Publication, its heated applicators can

beneficially dilate the pores, stimulate circulation, and “impart a relaxing effect” on the user. *Id.* at 13, ¶ [0012]. Further explanation of how to make, and the benefits of, the heated applicators is disclosed throughout the Gueret ’986 publication. *Id.* at ¶¶ [0007], [0012], [0014], [0015], [0021]-[0026], [0031]-[0039], [0063], [0065], [0097], [0098], etc.

Figure 42 of the Gueret ’986 patent (reproduced below) is the primary focus of Amneal’s invalidity challenge.



PTX-374 at 10.

Compound L of Figure 42 is intended to store heat, for example, a wax, an oil, or water. *Id.* at 17, ¶ [0097]; Singh 1124:15-1127:7. The device depicted in Fig. 42 “can include a flexible lip, for example arranged in the manner of a suction cup.” PTX-374 at 15, ¶ [0053]. The reference teaches that the applicator (3) “can be at least partially resiliently deformable.” PTX-374 at [0151]; *see also* Singh Tr. 1054:3-12. The Gueret ’986 publication discloses that the applicator wall may take different shapes. Specifically, it discloses that the “applicator can be made with a shape adapted to the area of the body to be treated,” and made with a wide variety of external shapes, for example,

an elongated shaped with a widened head.” PTX-374 at [0104], [0132].) The reference goes on to explain that the wall “can include [] flexible” material. *Id.* at [0023].

Figure 42 does not disclose the claimed wall. There is no disclosure anywhere in the Gueret '986 publication of the wall of the device depicted in Figure 42 folding over to form a double-wall structure, and Defendants offered no evidence that the wall of the Gueret '986 publication would form a double-wall structure. Singh 1127:21-1128:4. Dr. Singh testified only that a POSA would know that single walls could fold over to form double-wall structures. Singh 1090:16-1091:7.

### *Secondary Considerations of Nonobviousness*

The devices disclosed in both the Gueret '986 publication and the Gueret '187 patent are generally directed to cosmetics applicators. Dr. Slocum testified that, even if a POSA were to review these references in searching for a solution to the issues faced by the inventors of the '861 patent, he or she would recognize that the cosmetics applicators in the Gueret '986 publication and Gueret '187 patent do not have the degree of sealing and spreading ability required to apply a volume of liquid onto a largely concave surface, like the axilla. Slocum 573:2-11; 582:5-10.

Some of the modifications proposed by Amneal would render the disclosed devices unsuitable for their intended purposes. For example, as discussed above, the proposed modification to replace the open cell foam of the applicator in Figures 11 and 12 of the Gueret '187 patent with an impermeable sheet of elastomeric material would

render it inoperable since it would no longer be able to absorb cosmetics as it was intended to do. PTX-373; Singh 1137:22-1138:6.

In internal documents, the inventors of the '861 patent reported that the applicator claimed therein was unexpectedly capable of accurately applying a liquid composition when the applicator is tilted. PTX-1066, Applicator Development Presentation, at 6, 10. The inventors reviewed the state of the art at the time and could find no applicator that was known to be suitable to the application of a liquid composition to the surface of the axilla. PTX-1093 at 7; Slocum 546:15-22. The inventors tried the conventional wisdom of the day, starting with a "mushroom applicator" design. PTX-1148 at 4, 6; Slocum 548:4-549:25. It was only after failed attempts to develop the traditional roll-on style applicators that the inventors struck upon an entirely different type of applicator, the claimed applicator having a resiliently deformable double-wall structure with a working surface to spread the composition. PTX-1093, Acrux Design Report, at 6-7; PTX-1066, Applicator Development Presentation, at 17; PTX-1157, Sept. Design Concepts Presentation - Simple Axilla Phase 1, at 3-5; PTX-1158, Oct. Design Concepts Presentation - Simple Axilla Phase 2, at 2, 4-6; Slocum 545:3-546:2, 549:19-25, 554:4-555:3. It was reported internally that the applicator claimed in the '861 patent was unexpectedly able to apply and spread a liquid composition without scraping up the composition upon application. PTX-1066, Applicator Development Presentation, at 6, 10. And it had the added benefit of having no moving parts so that it was easy for a user to operate. PTX-1066, Applicator Development Presentation, at 6, 10.

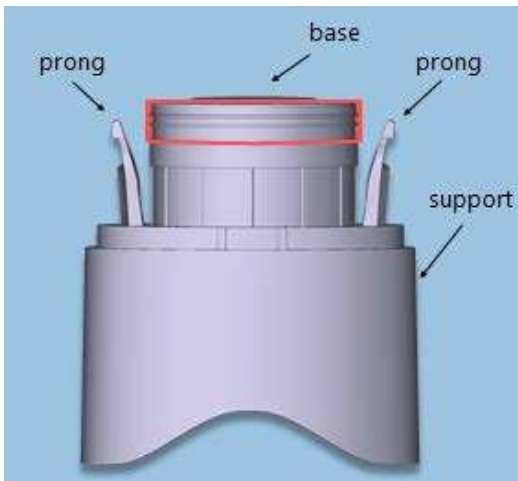
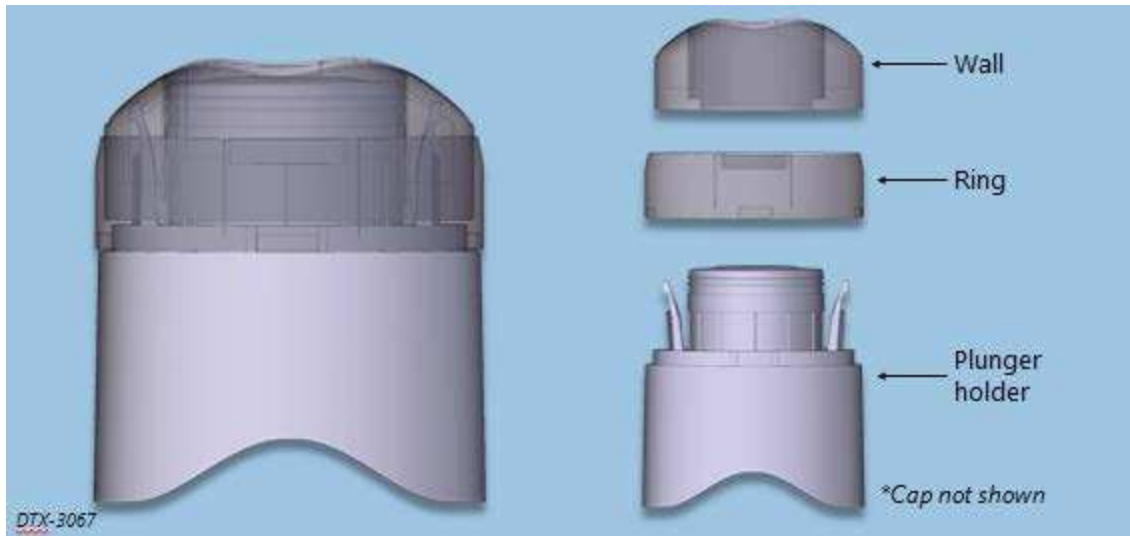
### **C. The Lupin Applicator**

Plaintiffs offered no evidence to show that Lupin's applicator literally infringes asserted claims 9 and 10 of the '861 applicator patent. Slocum 1258:24-1259:5; MacLean 1675:12-19; DDX 528. Instead, Plaintiffs' infringement claim against Lupin rests entirely on a doctrine of equivalents theory. Slocum 1258:24-1259:5, 1259:21-23; MacLean 1675:12-19; DDX 528.

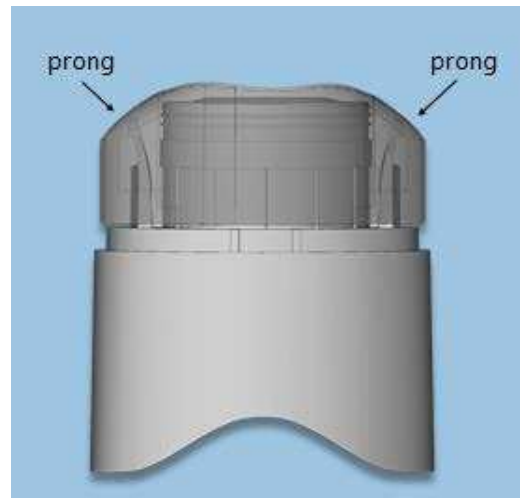
#### ***Components of the Lupin Applicator***

Lupin's applicator as described in ANDA No. 208061 (depicted below) consists of a plunger holder, wall, ring, and cap. MacLean 1678:8-16; DTX-3067; DDX 533. The plunger holder is a two-shot injection molded component. MacLean at 1678:17-24; DDX 534. The first shot is made of polypropylene and consists of a support, a base and prong features as shown in Lupin Figure (a), below. MacLean 1679:4-7, 1680:23-1681:25; DTX-3067; DDX 534. The second shot (outlined in grey in Lupin Figure (a)), which is selectively over-molded on top of the base feature of the first shot, is made of Santoprene thermoplastic vulcanizate (TPE) and forms the base of the applicator receptacle. MacLean 1679:4-10, 1679:14-1680:1, 1680:23-1682:8; DTX-3067; DDX 534. The plunger holder has prongs that fit between the inner and outer portions of the wall (Lupin Figure (b)). MacLean 1680:4-14; DDX 35. The wall, as shown in Lupin Figure (c), is made of polypropylene. MacLean 1680:4-14; DDX 535. The base and upper portion of the wall form a reservoir for the therapeutic liquid. MacLean 1683:11-13.

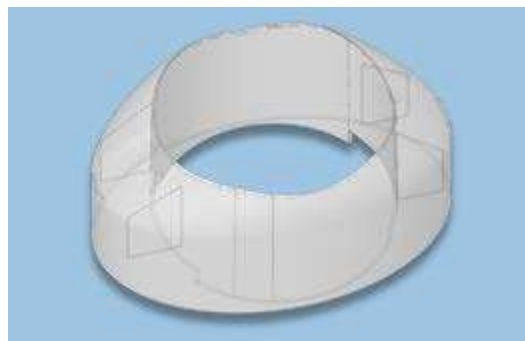
Lupin's ANDA applicator is depicted in the figures below:



(a)



(b)



(c)

Lupin Figures.

The plunger holder of Lupin's applicator has a support with prongs and the receptacle base (a). When assembled with the plunger holder, the wall (c) fits



around the base and rests on the prongs (b).

DDX 533-535.

### ***Operation of the Lupin Applicator***

The user applies the treatment solution using the Lupin applicator by repeatedly pressing it up against the axilla in a stamping motion. MacLean 1684:5-14, 1684:25-1686:1; DTX-3010\_004 (“place [the applicator] up into the axilla and squeeze it steadily down and up into the axilla”); DDX 536. During use, the Lupin applicator and its wall move in an up and down, uni-axial motion, to accomplish depositing of the liquid into the axilla, rather than side-to-side spreading. MacLean 1691:16-1692:1; DDX 537.

According to the instructions in Lupin’s product label, “[i]f the solution drips or runs, it can be wiped up with the applicator.” DTX-3010\_004; DDX 543. This wiping instruction is a conditional event needed only if some amount of the therapeutic liquid has escaped the treatment surface or dripped. MacLean 1692:2-14. The wiping motion is used merely to collect excess liquid that escapes the treatment area back into the reservoir and then to subsequently stamp back into the axilla, not to spread the liquid within the axilla. MacLean 1691:21-1692:18.

During use, the wall of Lupin’s applicator experiences downward displacement. MacLean 1686:10-23, 1687:6-25, 1688:18-20, 1688:23-1689:7; DDX 537-539. The prongs are bent inwards as the user pushes the applicator up against the treatment surface. MacLean 1687:14-18; DDX 537-539. The wall moves down relative to the base, allowing the therapeutic liquid to contact and be deposited onto the treatment surface.

MacLean 1687:19-25. The prongs act as springs to push the wall up to its resting position when the downward force is removed. MacLean 1686:10-1687:25, 1689:1-7; DDX 537-539. Only the prongs, which are part of the plunger holder, deform to any meaningful degree during use. MacLean 1686:10-23. The wall, on the other hand, simply translates up and down relative to the base during use. *Id.* at 1687:6-13; DDX 537-539.

### ***Lupin's Prescribing Information***

Lupin's prescribing information instructs users as follows:

Keeping the applicator upright, patients should place it up into the axilla and squeeze it steadily down and up into the axilla. If the solution drips or runs, it can be wiped back up with the applicator. The solution should not be rubbed into the skin with fingers or hand.

DTX-3010\_004. Lupin's prescribing information does not instruct or encourage users to spread the liquid within the axilla. *See, e.g.,* DTX-3010, PTX-188.

### ***Operation of the Applicator Claimed in the '861 Patent***

The '861 patent discloses the applicator shown in Figure 1 and Figure 2 for topical delivery of a therapeutic liquid or lotion (e.g., testosterone gel). *See* PTX-5 at col. 3, ll. 6-33 and Figs. 1 and 2. The user dispenses therapeutic liquid into the applicator reservoir (4) (Figure 1) and then places the applicator in contact with the skin surface to deposit and spread the liquid onto the skin. *See id.* at col. 3, ll. 6-16. The claims of the '861 patent describe the applicator and its components,

various therapeutic compositions, and the application method. *See id.* at col. 14, l. 56 – col. 16, l. 39. During use, the “resiliently deformable” wall “maintains contact with the treatment surface when spreading the liquid.” *Id.* at col. 2, ll. 1-3.

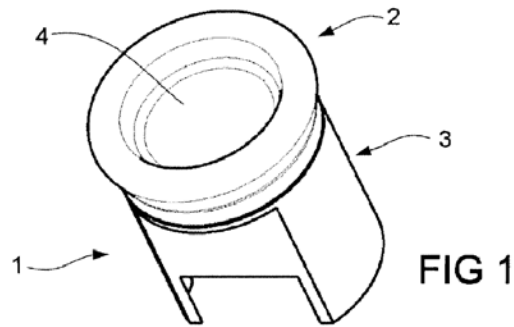


Figure 1. The preferred embodiment of the '861 patent is an applicator (1) having a receptacle (2), support means (3), and reservoir space (4).

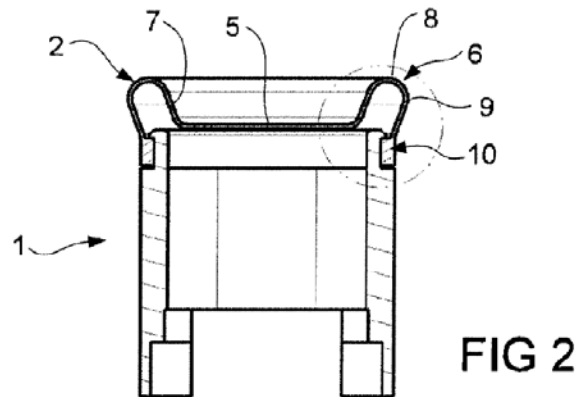


Figure 2. The cross-section of the applicator (1) shows that the receptacle (2) contains a base (5) and wall (6). The wall (6) has an inner portion (7) and an upper portion (8). The outer side of the wall contains a skirt portion (9) and a lower edge (10). The lower edge (10) is attached to the support means (3) (*see* Fig. 1 and Fig. 3).

PTX-5 at col. 3, ll. 6-17 and Fig. 1; *id.* at col. 3, ll. 18-33 and Fig. 2; DDX 530.

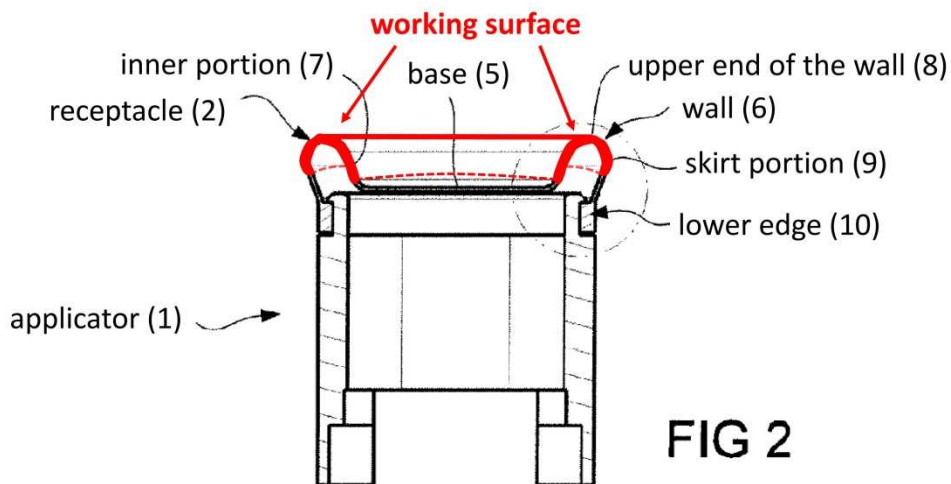
According to the '861 patent, during use, the “working surface” of the wall “is used to spread the liquid over the treatment surface.” *Id.* at col. 1, l. 64 – col. 2, l. 3. The wall resiliently deforms during use so that the “working surface maintains contact with the treatment surface when spreading the liquid.” *Id.* The “working surface” intended to maintain contact with the skin during use preferably “extends along the wall between the inner portion and the skirt” and may also include the “inner portion of the wall” as well as “over the skirt of the wall.” *Id.* at col. 2, ll. 33-37. The working surface described in the specification is shown in Annotated Figure 2, below. DDX 541. A POSA would understand that the working surface of the wall, not the base or any other component, applies the therapeutic liquid during use. MacLean 1677:9-19, 1690:6-1691:13; PTX-5 at col. 3, ll. 37-39, col. 3, ll. 43-48, col. 14, ll. 4-6; DDX 531, DDX 541, DDX 546.

The receptacle and wall are further described as follows:

... the receptacle **2** is formed from a relatively flexible membrane which allows at least the wall **6** to flex acting as a blade-like member when spreading the liquid across the treatment surface. The relative flexibility of the membrane allows the wall **6** to roll across the treatment surface spreading the liquid rather than wiping the liquid off the treatment surface.

PTX-5 at col. 3, ll. 42-48. The receptacle wall of the '861 patent applicator is designed to spread the liquid with a blade-like motion. Given that the working surface is disclosed to consist of both inner and outer portions of the wall (Annotated Figure 2), a POSA would understand that the blade-like motion is achieved by a side-to-side bending motion of the wall. MacLean Tr. 1677:9-19. During use, the applicator of the '861 applicator and its walls move in a multi-axial manner to accomplish spreading of the liquid across the

axilla. MacLean Tr. at 1677:9-1678:2; DDX 531. The '861 patent teaches that the applicator wall spreads the liquid onto the treatment surface and expressly teaches away from an applicator wall that wipes the liquid off the treatment surface. MacLean Tr. at 1693:4-19; PTX-5 at col. 3, ll. 45-48; DDX 543.



Annotated Figure 2. Annotated version of Fig. 2 of the '861 patent with “working surface” that extends from inner portion (7) to skirt portion (9) as indicated by the grey outline.

(DDX 541.)

### Conclusions of Law

#### **I. Controlling Principles of Law**

As noted above, Plaintiffs have asserted infringement claims against each defendant as to each patent in suit – the '075 formula patent only against Actavis, the '944 axilla patent against all defendants and the '861 patent against all defendants. Actavis has conceded infringement of the '075 patent, but challenges its validity on grounds of lack of written description and enablement. All Defendants concede

infringement of the '944 patent, but challenge its validity on grounds of anticipation and obviousness. With regard to the '861 patent, all Defendants contend that their respective applicators do not infringe, and that, even if their products do infringe, the '861 patent is invalid on the grounds that it is anticipated, obvious, and contains indefinite terms.

To prove infringement of the '861 patent, Plaintiffs must demonstrate by a preponderance of the evidence that Defendants' applicators infringe the asserted claims of that patent. *Tech. Licensing Corp. v. Videotek, Inc.*, 545 F.3d 1316, 1327 (Fed. Cir. 2008). In order to satisfy this burden, Plaintiffs "must supply sufficient evidence to prove that the accused product ... meets every element or limitation of a claim." *Rohm and Haas Co. v. Brotech Corp.*, 127 F.3d 1089, 1092 (Fed. Cir. 1997).

Because issued patents are statutorily presumed valid under 35 U.S.C. § 282, with regard to their invalidity defenses and counterclaims, Defendants have "the ultimate burden of persuasion to prove invalidity by clear and convincing evidence, as well as the initial burden of going forward with evidence to support [their] invalidity allegation[s]." *Titan Tire Corp. v. Case New Holland, Inc.*, 566 F.3d 1372, 1377 (Fed. Cir. 2009) (citation omitted). Clear and convincing evidence "has been described as evidence which produces in the mind of the trier of fact 'an abiding conviction that the truth of [the] factual contentions are 'highly probable.'" *Buildex Inc. v. Kason Indus. Inc.*, 849 F.2d 1461, 1463 (Fed. Cir. 1988) (quoting *Colorado v. New Mexico*, 467 U.S. 310, 316 (1984)).

## **II. The '075 Patent**

### **A. Scope of Claim 13**

Actavis contends that claim 13 of the '075 patent is invalid for lack of written description and enablement. Claim 13 recites a method of treating a hypogonadal man by applying a therapeutically effective amount of testosterone. PTX-1 at claim 13. As a dependent claim, claim 13 must “incorporate ... all the limitations of the claim[s] to which it refers.” *See* 35 U.S.C. § 112(d). Accordingly, claim 13 comprises a formulation with: (a) a therapeutically effective amount of testosterone to treat a testosterone deficient hypogonadal man; (b) the penetration enhancer octyl salicylate in an amount from 10-10,000% by weight of testosterone; and (c) ethanol and/or isopropanol in an amount sufficient to act as a vehicle. PTX-1 at claims 1, 5, 9-11, 13.

Actavis contends that claim 13 is invalid because the specification of the '075 patent does not provide adequate written description to suggest to a POSA that the inventors possessed a testosterone formulation with 10,000% octyl salicylate by weight of testosterone and also would not have enabled a POSA to use such a formulation for transdermal drug delivery without undue experimentation. Although Plaintiffs asserted throughout the preliminary stages of this litigation, including up to and through opening statements at trial, that the 10-10,000% range from claim 1 was incorporated into asserted claim 13, (*see* PDX-2019; Tr. 11:4-9), they now argue that there is no explicit requirement that the method of claim 13 make use of testosterone formulations that contain amounts of penetration enhancer throughout the entire range recited in claim 1 as

long as the amount of penetration enhancer used in the formulation falls somewhere within the 10-10,000% by weight of testosterone range.

In support of this contention, Plaintiffs argue that, unlike claim 1, which is directed to “therapeutically effective” treatments for any number of conditions, including treatment for testosterone deficient women, claim 5, from which claim 13 depends, narrows claim 1 to include only those treatments that would be effective for treating hypogonadal men. Claim 11, from which claim 13 also depends, further narrows claim 1, Plaintiffs assert, by naming octyl salicylate as the penetration enhancer to be used. The ‘075 patent specification states that the performance of the penetration enhancer to deliver testosterone varies with differences in the nature of the penetration enhancer and further teaches in examples 6, 10, 12, 13, and 15 that the particular combination of testosterone and octyl salicylate does not require operating at the high end of the penetration enhancer range. On this basis, Plaintiffs argue, a POSA would understand claim 13 to be narrowed to an amount of octyl salicylate less than the 10-10,000% by weight of testosterone found in independent claim 1.

By failing to raise this theory until trial was well underway, Plaintiffs waived this interpretation. Even if not waived, however, we do not find it to have merit. As noted above, dependent claims, like claim 13, incorporate all of the limitations of the claims from which they depend, unless further limitation is specified in the dependent claim. *See* 35 U.S.C. § 112(d). Here, while it is true that claim 13 depends from claims 5 and 11 and is therefore limited to formulations that use octyl salicylate as the penetration



enhancer and are therapeutically effective for the treatment of hypogonadal men, neither claim 13 nor any of the claims on which it depends contains a further limitation on the range of penetration enhancer recited in claim 1. We cannot read such a limitation into the claim when it is not otherwise there. This conclusion is in line with the testimony of Defendants' expert, Dr. Potts, who explained that claim 13 allows for use of up to 100 times more octyl salicylate than testosterone. Potts 1308:2-8. Plaintiffs' expert, Dr. Hadgraft, never contradicted Dr. Potts's testimony on this point, nor did he offer the opinion that a POSA would interpret claim 13 to cite a narrower range of the amount of octyl salicylate than that recited in claim 1 or what a POSA would understand the bounds of such a narrower range to be. Accordingly, we hold that claim 13 encompasses a formulation having up to 10,000% by weight of testosterone, or 100 times more octyl salicylate than testosterone.

### **B. Validity of Claim 13**

Having determined the scope of the claimed method of treatment recited in claim 13 of the '075 patent, we now turn to address whether the specification provides adequate written description and enablement of the full scope of the invention. A valid patent must have adequate written description and enablement support in the patent specification. 35 U.S.C. § 112. The statutory basis for these requirements is laid out in 35 U.S.C. § 112, which provides that the specification must contain: "a written description of the invention and of the manner and process of making and using it, in such full, clear, concise and exact terms as to enable any person skilled in the art to which it pertains, or with which it

is most nearly connected, to make and use the same.” *Id.* § 112(a). We address each of these requirements in turn below.

## 1. Written Description

“The test for the sufficiency of the written description ‘is whether the disclosure of the application relied upon reasonably conveys to those skilled in the art that the inventor had possession of the claimed subject matter as of the filing date.’” *Vasudevan Software, Inc. v. MicroStrategy, Inc.*, 782 F.3d 671, 682 (Fed. Cir. 2015) (quoting *Ariad Pharms., Inc. v. Eli Lilly & Co.*, 598 F.3d 1336, 1351 (Fed. Cir. 2010)). In other words, the written description requirement is met when a POSA would find it “reasonably clear what the invention is and that the patent specification conveys that meaning.” *All Dental Prodx, LLC v. Advantage Dental Prods., Inc.*, 309 F.3d 774, 779 (Fed. Cir. 2002). The specification “must describe an invention understandable to [a POSA] and show that the inventor actually invented the invention claimed.” *Ariad Pharms.*, 598 F.3d at 1351. “Whether a patent claim is supported by an adequate written description is a question of fact.” *AbbVie Deutschland GmbH & Co., KG v. Janssen Biotech, Inc.*, 759 F.3d 1285, 1297 (Fed. Cir. 2014) (citation omitted).

Here, it is undisputed that the ‘075 patent contains no examples of a transdermal drug formulation containing a therapeutically effective amount of testosterone with the penetration enhancer octyl salicylate present in an amount of 100 times (or 10,000%) the amount of testosterone for the treatment of hypogonadal men. Hadgraft 324:16-325:4; Potts 1321:11-1322:6. Rather, the only examples of testosterone samples set forth in the

specification include 12% w/v testosterone and 8% v/v of penetration enhancer, which computes to approximately 0.67 times (or 67%) of the penetration enhancer by weight of testosterone, which is clearly far below the upper most end of the claimed range of penetration enhancer. PTX-1 at Examples 6, 10, 12, 13, and 15; Potts 1320:8-17, 1321:11-1322:6; Hadgraft 348:5-8.

It is true that “a claim will not be invalidated on section 112 grounds simply because the embodiments of the specification do not contain examples explicitly covering the full scope of the claimed language.” *LizardTech, Inc. v. Earth Res. Mapping, Inc.*, 424 F.3d 1336, 1346 (Fed. Cir. 2005). However, the purpose of the written description requirement is “to ensure that the scope of the right to exclude, as set forth in the claims, does not overreach the scope of the inventor’s contribution to the field of art as described in the patent specification.” *Ariad Pharms.*, 598 F.3d at 1353 (quotation marks and citation omitted). Accordingly, the specification must in some way “reasonably convey to a person skilled in the art that [the inventor] had possession of the claimed subject matter at the time of filing. *LizardTech*, 424 F.3d at 1346. We are not persuaded that the ‘075 patent specification reasonably conveys to a POSA that the inventors had possession of the full scope of the claimed invention, namely, using a formulation consisting of 100 times more octyl salicylate than testosterone.

Although the specification states that the amount of penetration enhancer “may be in the range of 10-10,000 weight percent” (PTX-1 at col. 12, ll. 35-45) and that for some active ingredients, it “may well be that the upper range of 10,000% [of penetration

enhancer] will be required,” (*id.*) the specification does not identify testosterone as an active ingredient for which the inventors believed that 100 times more penetration enhancer might be required nor does the specification support such a conclusion. Potts 1319:13-22; Hadgraft 339:20-340:6, 341:23-342:20. Rather, as described above, the examples set forth in the specification teach a POSA that testosterone is effectively delivered using *less* penetration enhancer than testosterone. *See* PTX-1 at Examples 6, 10, 12, 13, 15. The specification also discusses the fact that dermal penetration enhancers are irritating and emphasizes the importance of minimizing skin irritation by using as little penetration enhancer as possible. PTX-1 at col. 2, ll. 51-53, col. 4, ll. 13-15, col. 12, ll. 41-42. Another objective of the invention listed in the specification is to minimize drying time following application of the testosterone product. PTX-1 at col. 4, ll. 1-6, col. 10, ll. 50-56. Defendants’ expert, Dr. Potts, testified that the wide range of penetration enhancer incorporated in claim 13 of the ‘075 patent, particularly at the upper end of the range, “would be at odds” with the goals of reducing skin irritation and minimizing drying time discussed in the specification.<sup>18</sup> Potts 1324:15-18.

For these reasons, we conclude that, while there is adequate written description support for some narrower part of the range of penetration enhancer claimed, given the absence of information regarding formulations using testosterone and penetration enhancer in an amount anywhere near the upper end of the disclosed range, coupled with

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<sup>18</sup> Dr. Potts’s testimony on the written description requirement was not contested by Plaintiffs’ experts. Dr. Hadgraft’s opinions were limited to the issue of enablement, a distinct requirement, and he did not opine as to whether a POSA would understand that the inventors possessed the invention.

the explicit direction in the specification to limit as much as possible the amount of penetration enhancer used, there is insufficient written description support for the entire range disclosed. In reading the specification, a POSA would not have understood the inventors to have possessed a formulation with 100 times more octyl salicylate than testosterone. To satisfy the written description requirement, the specification must do more than merely invite other researchers to discover the upper amount of penetration enhancer that could conceivably work. *See Boston Sci. Corp. v. Johnson & Johnson*, 647 F.3d 1353, 1367 (Fed. Cir. 2011) (“The patent laws do not reward an inventor’s invitation to other researchers to discover which of the thousands of macrocyclic lactone analogs of rapamycin could conceivably work in a drug-eluting stent.”). Accordingly, we find that Actavis has presented clear and convincing evidence that the ‘075 patent specification does not reasonably convey to a POSA that the inventors had possession of the full scope of their claimed invention. Claim 13 of the ‘075 patent is therefore invalid for lack of written description.

## **2. Enablement**

“To meet the enablement requirement, ‘the specification of a patent must teach those skilled in the art how to make and use the full scope of the claimed invention without undue experimentation.’” *Martek Biosciences Corp. v. Nutrinova, Inc.*, 579 F.3d 1363, 1378 (Fed. Cir. 2009). “A claim is sufficiently enabled even if ‘a considerable amount of experimentation’ is necessary, so long as the experimentation ‘is merely routine, or if the specification in question provides a reasonable amount of guidance with

respect to the direction in which the experimentation should proceed.” *Vasudevan Software*, 782 F.3d at 684 (quoting *In re Wands*, 858 F.2d 731, 737 (Fed. Cir. 1988)). In determining whether a disclosure requires undue experimentation, courts consider the following factors: “(1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims.” *Cephalon, Inc. v. Watson Pharm., Inc.*, 707 F.3d 1330, 1336 (Fed. Cir. 2013) (quoting *Wands*, 858 F.2d at 737).

Enablement does not require the specification to “necessarily describe how to make and use every possible variant of the claimed invention, for the artisan’s knowledge of the prior art and routine experimentation can often fill gaps, interpolate between embodiments, and perhaps even extrapolate beyond the disclosed embodiments, depending upon the predictability of the art.” *AK Steel Corp. v. Sollac and Ugine*, 344 F.3d 1234, 1244 (Fed. Cir. 2003). However, it does require that, “when a range is claimed, there must be reasonable enablement of the scope of the range.” *Id.*

At trial, Defendants’ expert, Dr. Potts, conceded that, with routine experimentation, a POSA would be able to make a transdermal formulation with up to 100 times more octyl salicylate than testosterone because “[m]aking is simply a recipe.” Potts 1327:6-7. The parties’ dispute regarding enablement, therefore, is limited to whether the patent contains sufficient enabling support for a POSA to *use* a transdermal

formulation containing 100 times more octyl salicylate than testosterone to effectively deliver testosterone for the treatment of hypogonadism without undue experimentation. We find that Actavis has established by clear and convincing evidence that the '075 patent would not enable a POSA to use such a formula without undue experimentation, and thus the full scope of claim 13 is not enabled.

As discussed above, the specification does not disclose any transdermal drug formulation containing a therapeutically effective amount of testosterone with a penetration enhancer present in an amount of 100 times the amount of testosterone for the treatment of hypogonadal men. Both Dr. Potts and Dr. Hadgraft testified that they are unaware of any person who has ever made or tested a transdermal formulation containing 100 times more penetration enhancer than testosterone. Hadgraft 325:9-12; Potts 1334:10-13. Although the specification notes that “for some actives, it may well be that the upper range of 10,000% by weight will be required,” (PTX-1 at col. 12, ll. 35-45), there is no indication that testosterone is one of those active ingredients and the examples contained in the specification teach otherwise, as each testosterone formulation includes approximately 0.67 times of the penetration enhancer by weight of testosterone, much less than the upper limit of 100 times the weight of testosterone that is claimed. PTX-1 at Examples 6, 10, 12, 13, and 15; Potts 1320:8-17, 1321:11-1322:6; Hadgraft 348:5-8. Nowhere in the specification are the particular actives that could require the upper range of penetration enhancer listed, nor does it conclusively state that such a high ratio of enhancer would necessarily be required, only that such an amount “may well be

required.” The specification’s disclosure that certain active ingredients might require using 100 times more enhancer than active ingredient is insufficient to enable using 100 times more of octyl salicylate to deliver testosterone. *See Genentech, Inc. v. Novo Nordisk*, 108 F.3d 1361, 1366 (Fed. Cir. 1997) (“Patent protection is granted in return for an enabling disclosure of an invention, not for vague intimations of general ideas that may or may not be workable.”).

The ‘075 patent specification in fact teaches away from using the large amounts of penetration enhancer at the upper end of the claimed range. For example, Dr. Potts testified that in order to make a formulation with 100 times more octyl salicylate than testosterone according to the asserted claim, a POSA would need to use 12.5 milligrams of testosterone, 1,250 milligrams of octyl salicylate, and 5,050 milligrams of volatile liquid, for a total of approximately 6,300 milligrams of material. According to Dr. Potts, this amount of material would need to be spread over several thousand square centimeters of skin. Potts 1330:14-1331:3. It is not clear how such a substantial formulation could be put to practical use for transdermal drug delivery, particularly considering that it would defeat the objective listed in the ‘075 patent of ensuring a convenient application and drying time by applying the formulation to a small area of the skin. Potts 1324:1-5. Additionally, using such a large amount of octyl salicylate at a higher concentration than is generally recognized as safe contradicts the specification’s teaching to use the least amount of penetration enhancer as necessary to avoid skin irritation. The Federal Circuit has held that in cases in which “the specification teaches against a purported aspect of an



invention, such a teaching ‘is itself evidence that at least a significant amount of experimentation would have been necessary to practice the claimed invention.’ *Liebel-Flarsheim Co. v. Medrad, Inc.*, 481 F.3d 1371 (Fed. Cir. 2007) (quoting *AK Steel*, 344 F.3d at 1244).

Moreover, even if a POSA prepared a formulation with 100 times more octyl salicylate than testosterone, undue experimentation would be needed to test whether a formulation with such an extreme ratio of low active ingredient to high penetration enhancer could be used to treat hypogonadism. Plaintiffs’ own expert, Dr. Hadgraft, testified regarding the significant experimentation on the formulation that would be required, including skin penetration studies to ensure that it delivered a therapeutically effective amount of testosterone into the bloodstream, stability studies to determine it remained physically stable, and skin irritancy studies to make sure that it would not be excessively irritating when applied to the skin, particularly considering that such a formulation would require using a higher concentration of octyl salicylate than is generally recognized as safe.<sup>19</sup> Hadgraft 320:4-23. Dr. Hadgraft further testified on cross-examination that transitioning from these *in vitro* experiments to *in vivo* experiments can itself be an unpredictable process. Hadgraft 323:14-21. According to Dr. Hadgraft, even if a POSA knew how much testosterone he wanted to deliver into a

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<sup>19</sup> Octyl salicylate is generally recognized as safe in concentrations up to 5%, but in Dr. Pott’s hypothetical formulation, the octyl salicylate is present in an amount of about 19.8%. Potts. 1330:2-1331:5, 1439:2-15.

patient's bloodstream, such a person would still not be able to formulate a transdermal product with any degree of certainty without further testing.<sup>20</sup> Hadgraft 324:11-15.

Given that the patent provides no working examples or other guidance for a POSA to use a formulation with such an extreme ratio between penetration enhancer and active ingredient to treat hypogonadism, the level of experimentation that would be required to enable a POSA to do so is far from routine and clearly undue. There is no indication that a POSA's knowledge of the prior art combined with routine experimentation could "fill in the gaps" left by the specification to enable him to use the invention on the upper end of the range of penetration enhancer disclosed, particularly given that there is no indication that anyone had ever tried to make such a formula and the specification points away from such an embodiment. *AK Steel*, 344 F.3d at 1244. For these reasons, we find that claim 13 of the '075 patent is invalid for lack of enablement.

### **III. The '944 Patent**

#### **A. Anticipation**

Defendants contend that claim 20 of the '944 patent is invalid as anticipated in light of the Morgan '725 publication/'983 patent. "Invalidity on the ground of 'anticipation' requires lack of novelty of the invention as claimed. The invention must

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<sup>20</sup> In his direct examination, Dr. Hadgraft opined that the '075 patent specification enabled a POSA to make and use the commercial Axiron® product, which contains 2.5 times more octyl salicylate than testosterone. This opinion, however, does not address the relevant question before us, to wit, whether the specification enables the *full scope* of the claimed invention, which recites a formulation having up to 100 times more octyl salicylate than testosterone.

have been known to the art in the detail of the claim; that is, all of the elements and limitations of the claim must be shown in a single prior reference, arranged as in the claim.” *Karsten Mfg. Corp. v. Cleveland Golf Co.*, 242 F.3d 1376, 1383 (Fed. Cir. 2001). Even if a reference does not explicitly disclose a feature of the claimed invention, a prior art reference may still be deemed to anticipate “if that missing characteristic is necessarily present, or inherent, in the single anticipating reference.” *SmithKline Beecham Corp. v. Apotex Corp.*, 403 F.3d 1331, 1343 (Fed. Cir. 2005) (citing *Continental Can Co. v. Monsanto Co.*, 948 F.2d 1264, 1268 (Fed.Cir.1991)).

Claim 20 recites a method of treating a testosterone-deficient man by applying a therapeutically effective amount of testosterone. PTX-1 at claim 13. As a dependent claim, claim 20 must “incorporate ... all the limitations of the claim[s] to which it refers.” *See* 35 U.S.C. § 112(d). Accordingly, incorporating all of the limitations of the claims to which it refers, claim 20 comprises a method of increasing the testosterone blood level of an adult male subject in need thereof by applying to at least one axilla of the subject, without occlusion by a patch device, a non-occlusive transdermal drug delivery composition consisting of: (a) a pharmaceutically effective amount of testosterone; (b) one or more lower alkyl alcohols selected from a group consisting of ethanol, isopropanol, and mixtures thereof, wherein the combined volume of the lower alkyl alcohol(s) is more than 80% (v/v) of the composition;<sup>21</sup> (c) the penetration enhancer

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<sup>21</sup> Claims 13 and 17, from which claim 20 depends, require the combined volume of the alkyl alcohol(s) to be greater than 60% and 70%, respectively. However, because claim 18 requires the combined volume to be greater than 80%, we have incorporated only that limitation into claim

octisalate in an amount of from 0.01% to 15% (w/v); (d) the viscosity modulating agent polyvinyl pyrrolidone present in an amount from 1% to 3% (w/v) of the composition, in an amount effective to increase the viscosity of the composition to within the range of from greater than the viscosity of water to less than 300 centipoise; and (e) optionally, water, wherein the composition is applied in an amount effective to achieve a testosterone blood level in the subject of at least 200 ng/dL. PTX-4 at claims 13, 14, 15, 16, 17, 18, 19, 20.

In his testimony at trial, Dr. Chambliss broke these limitations into three groups – (1) the “blood level” limitations, which include the method of increasing the testosterone blood level of an adult male subject in need to at least 200 ng/dL; (2) the “formula” limitations, which include the non-occlusive testosterone composition limitation as well as limitations (a) through (e) listed above; and (3) the “axilla” limitation, which requires the composition be applied to at least one axilla of the subject. For the reasons detailed below, while we find that Defendants have established by clear and convincing evidence that the formula and blood level limitations are disclosed by the ‘725 publication, they have failed to show that the axilla limitation is disclosed therein and therefore have failed to establish that claim 20 of the ‘944 patent is anticipated by the ‘725 publication.

### **1. Blood Level Limitations**

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20 because, if satisfied, the lower thresholds required in claims 13 and 17 are also necessarily met.

We find that Defendants have shown by clear and convincing evidence that the ‘725 publication discloses the “blood level limitations” of claim 20, which require, “a method of increasing the testosterone blood level of an adult male subject in need thereof” and “wherein the composition is applied in an amount effective to achieve a testosterone blood level in the subject of at least 200 ng/dL.” The abstract of the ‘725 publication states in relevant part that the invention “provides a method for administering at least one acting hormone to an animal which comprises applying an effective amount of the hormone in the form of the drug delivery system of the present invention.” PTX-483 at 1. Paragraph 57 of the ‘725 publication teaches that the formulations disclosed in the publication, including the formulation in 13A, are methods of the invention which include “male hormone therapy in testosterone deficient hypogonadal men.” PTX-483 at [0057].

Dr. Chambliss testified that although the ‘725 publication does not explicitly disclose the testosterone blood level of at least 200 ng/dL, that limitation is inherently disclosed because the ‘725 publication discusses providing a therapeutically effective amount of the hormone to treat a testosterone deficient hypogonadal man and it was known in the art at that time that effectively treating a testosterone deficient hypogonadal man would raise his testosterone blood level to at least 200 ng/dL. Chambliss 1560:1-13. In other words, following the method disclosed in the ‘725 publication would necessarily result in a testosterone blood level in the subject of at least 200 ng/dL. Chambliss 1560:

14-17. Plaintiffs presented no evidence that contradicted Dr. Chambliss's testimony regarding the blood level limitations.

## **2. The Formula Limitations**

Example 13A of the '725 publication explicitly discloses a number of the formula limitations set forth in claim 20 of the '944 patent. Specifically, Example 13A discloses a topical lotion composition with testosterone in an amount of 1% w/v; octyl salicylate in an amount of 2.5% w/v; hydroxyl propyl cellulose in an amount of 1.5% w/v; and aqueous ethanol (90% v/v) in an amount to 100 mL. PTX-483 at Example 13A.

Dr. Chambliss testified that the composition disclosed in Example 13A is a nonocclusive lotion formulation that is not a patch, so it meets the limitation of claim 20 that requires a nonocclusive, non-patch transdermal drug delivery composition.

Chambliss 1548:19-23. Example 13A also discloses testosterone 1%, which Dr.

Chambliss testified was known to be a pharmaceutically effective amount of testosterone, thereby meeting limitation (a) of claim 20. Chambliss 1546:12-14. The last ingredient

listed in Example 13A is aqueous ethanol 90%, which Dr. Chambliss testified equates to 85% ethanol, thereby meeting limitation (b) of claim 20 which discloses one or more

lower alkyl alcohols selected from a group consisting of ethanol, isopropanol, and

mixtures thereof, wherein the combined volume of the lower alkyl alcohol(s) is more than 80% (v/v) of the composition. Chambliss 1552:6-18. Because aqueous ethanol is a

mixture of ethanol and water, this ingredient also meets limitation (e) of claim 20, which is optionally water. Chambliss 1547:11-13. The third ingredient listed in Example 13A

is octyl salicylate, 2.5%, which is simply another name for octisalate (the penetration enhancer disclosed in limitation (c) of claim 20) and falls within the 0.01% to 15% (w/v) range disclosed in claim 20 for the penetration enhancer. Chambliss 1546:15-18. Plaintiffs' expert, Dr. Hadgraft, offered no testimony that rebuts Dr. Chambliss's testimony on these limitations.

Dr. Chambliss also opined that the '725 publication discloses limitation (d) of claim 20, to wit, the viscosity modulating agent polyvinyl pyrrolidone – often referred to as povidone – present in an amount from 1% to 3% (w/v) of the composition, in an amount effective to increase the viscosity of the composition to within the range of from greater than the viscosity of water to less than 300 centipoise. Chambliss 1557:7-12. Paragraph 24 of the '725 publication discloses the optional use of a thickening agent in the formulations and specifically lists povidone as a potential option. PTX-483 at [0024]. Paragraph 27 of the '725 publication then teaches that a preferred formulation would include 1-3% of the hormone, a penetration enhancer, ethanol or isopropanol, water, and, optionally, 0.5 to 5% of a thickening agent. PTX-483 at [0027]. Dr. Chambliss testified that these paragraphs teach a POSA to use the thickening agents listed in paragraph 24 (which include povidone) in a range of 0.5 to 5% in formulations that contain the other elements listed in paragraph 27. Both Examples 13A and 13B disclose variations of such a preferred formula, and each contains different thickening agents from the list in paragraph 24 (hydroxyl propyl cellulose in Example 13A and ethyl cellulose in Example 13B) at 1.5%. According to Dr. Chambliss, the teachings in paragraphs 24 and 27,

combined with the disclosure in Examples 13A and 13B showing that the thickening agents listed in paragraph 24 are interchangeable, would teach and disclose to a POSA that he could replace the thickening agents contained in Examples 13A and 13B with povidone in the same amount (which is within the range specified in claim 20) and that the formulation would have the same type of composition.<sup>22</sup> Chambliss 1555:10-25; 1556:1-15. In Dr. Chambliss's expert opinion, using such thickening agents in this manner would necessarily result in a viscosity between that of water and 300 centipoise as required in claim 20. Plaintiffs' expert, Dr. Hadgraft, again offered no testimony that rebuts Dr. Chambliss's testimony on the thickening agent limitation.

We do not find persuasive Plaintiffs' argument that one or more of the non-axilla limitations are not disclosed in the '725 publication because they are not all disclosed in a single example or because impermissible "picking and choosing" from the disclosures in the '725 publication is required in order to arrive upon the formulation disclosed in claim 20. *See Application of Arkley*, 59 CCPA 804, 455 F.2d 586, 587 (1972) (stating that anticipating reference "must clearly and unequivocally disclose the claimed compound to direct those skilled in the art to the compound without *any* need for picking, choosing, and combining various disclosures not directly related to each other by the teachings of

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<sup>22</sup> Plaintiffs argue that arriving at the thickening agent limitation set forth in claim 20 (*i.e.*, using povidone in a range of 1-3%) would require impermissible picking and choosing among the disclosures of the '725 patent. Because the disclosures in paragraphs 24 and 27 providing the list of thickening agents and the preferred range of those agents are directly related to the disclosure in Example 13A, however, it does not require an impermissible combining of distinct disclosures to arrive at the thickening agent limitation in claim 20. *See Purdue v. Pharma L.P. v. Epic Pharma, LLC*, 811 F.3d 1345, 1359 (Fed. Cir. 2016) ("The disclosures pointed to by the district court are all 'directly related' and thus there is no impermissible picking and choosing.").



the cited reference”). As Dr. Chambliss’s testimony established, the majority of the formulation limitations are expressly disclosed in Example 13A. Those disclosures that are not found explicitly in Example 13A are directly related to the disclosures in Example 13A and to the same embodiment, namely, a transdermal testosterone formulation to treat male hypogonadism. Therefore, arriving at the formulation disclosed in claim 20 does not require impermissibly combining of unrelated and distinct disclosures in the ‘725 publication. *See Purdue Pharma L.P. v. Epic Pharma, LLC*, 811 F.3d 1345 (Fed. Cir. 2016) (rejecting argument that court erred by “using distinct sections of [the anticipatory reference] and reassembling them into an embodiment to find that all of the limitations were present). For these reasons, we hold that Defendants have shown by clear and convincing evidence that each of the formulation limitations in claim 20 is disclosed in the ‘725 publication as arranged in the claim.

### **3. Axilla Limitation**

Finally, claim 20 requires that the claimed testosterone formulation be applied to at least one axilla of the subject. It is undisputed that there is no express reference of transdermal testosterone application to the axilla in the Morgan ‘725 publication. Rather, Defendants assert that the ‘725 publication discloses this limitation because it teaches applying the formulations to human skin (which would include the axilla) and also discloses a preferred surface area over which to apply the formulations (within which the surface area of the axilla would fall). The relevant disclosure in the ‘725 publication provides as follows: “Preferably, the drug delivery system is applied to the skin of the

animal covering a delivery surface area between about 10 and 800 cm<sup>2</sup>, more preferably between about 10 and 400 cm<sup>2</sup>, and most preferably between about 10 and 200 cm<sup>2</sup>.” PTX-483 at [0058].

Defendants have failed to establish by clear and convincing evidence that a POSA would have understood the ‘725 publication to disclose application of the testosterone formulation to the axilla based on this generic disclosure, which describes only how much surface area is preferred to deliver a therapeutic dose, but not where to apply the formulation. The amount of surface area to be covered for purposes of delivering an effective dose of a hormone is simply not the same as a description of a site of application. The ‘725 publication therefore does not suggest that the transdermal formulation disclosed be applied to any location in particular, much less express any preference for a specific location of administration.

The surface area of the skin of a normal adult is about 20,000 cm<sup>2</sup>. PTX-611 at 6; Hadgraft 185:2-6. Accordingly, there are many skin surfaces that a POSA would have understood to fall within the preferred surface area ranges disclosed in the ‘725 publication, particularly considering that each anatomical region on the body could be further divided into smaller application sites that would meet the preferred ranges disclosed, resulting in countless options. Hadgraft 291:11-15, 292:11-293:10; Chambliss 1603:10-14, 1607:19-25. Defendants argue that based on the disclosure of the preferred surface area, a POSA would think in terms of a limited genus of application sites then known in the art to be suitable for transdermal drug delivery, including the axilla. It is

true that in situations in which the genus is so limited that a POSA can “at once envisage each member of this limited class,” a reference “describing the genus anticipates every species within the genus.” *In re Gleave*, 560 F.3d 1331, 1337-38 (Fed. Cir. 2009). But the ‘725 publication does not disclose the genus of known transdermal application sites. Rather, the disclosure in the ‘725 publication is limited to preferred *surface areas* for application of the transdermal drug formulations disclosed. It was well known in the art at the time that the efficacy of transdermal drug delivery could be affected by at least three variables, including the surface area of application, the permeability of the skin at the application site, and the type of compound being delivered. Defendants have failed to establish by clear and convincing evidence that a POSA would understand the ‘725 publication’s disclosure which is focused solely on the first of these variables, to wit, surface area, to necessarily disclose the limited genus of known transdermal application sites that would include the axilla. This is particularly true given that the ‘725 publication is silent regarding the distinct issue of location of application.

Because we are not persuaded that a POSA would understand the generic disclosure of application to the skin of preferred surface area ranges in the ‘725 publication to be a specific disclosure of application to the axilla, Defendants have failed to establish by clear and convincing evidence that the Morgan ‘725 publication anticipates every limitation of claim 20 of the ‘944 patent.

## **B. Obviousness**

Although Defendants have failed to establish that the Morgan ‘725 publication anticipates claim 20 of the ‘944 patent, they have shown by clear and convincing evidence that a POSA would have been motivated to combine the teachings of the ‘725 publication with the teachings of other prior art to develop the claimed invention and would have had a reasonable expectation of success in doing so. Accordingly, for the reasons detailed below, we rule that claim 20 of the ‘944 patent is invalid as obvious.<sup>23</sup>

A patent claim is invalid on the grounds of obviousness “if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains.” 35 U.S.C. § 103(a) (2006).<sup>24</sup> When assessing obviousness, courts consider “whether a [POSA] would have been motivated to combine the prior art to achieve the claimed invention and whether there would have been a reasonable expectation of success in doing so.” *DyStar Textilfarben GmbH & Co. Deutschland KG v. C.H. Patrick Co.*, 464 F.3d 1356, 1360 (Fed. Cir. 2006) (citation omitted).

“Obviousness under 35 U.S.C. § 103(a) is ultimately a legal question, based on underlying factual determinations.” *Eisai Co. v. Dr. Reddy’s Labs., Ltd.*, 533 F.3d 1353,

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<sup>23</sup> The prior art references we have relied on in rendering our obviousness determination were considered by the PTO before allowance of the ‘944 patent. Therefore, while the standard of proof remains clear and convincing evidence, in proving obviousness, Defendants “shoulder an enhanced burden.” *Tokai Corp. v. Easton Enterprises, Inc.*, 632 F.3d 1358, 1367 (Fed. Cir. 2011). Defendants have met that burden here.

<sup>24</sup> Because the application for the ‘944 patent was filed before March 16, 2013, the pre-AIA amended version of 35 U.S.C. § 103(a) is applicable here. *See* § 3(n)(1) of the AIA.

1356 (Fed. Cir. 2008). The factual determinations underlying the obviousness analysis include consideration of the scope and content of the prior art; the differences between the prior art and the claimed subject matter as a whole; the level of skill in the art; and any relevant secondary factors, also known as objective evidence of non-obviousness. *Allergan, Inc. v. Sandoz Inc.*, 726 F.3d 1286, 1290-91 (Fed. Cir. 2013). Secondary considerations include surprising or unexpected results, prior art teaching away from the claimed invention, and unpredictability in the art. *See, e.g., id.*; *Gator Tail, LLC v. Mud Buddy LLC*, 618 F. App'x 992, 998-99 (Fed. Cir. 2015).

As discussed above, the Morgan '725 publication teaches a POSA to use a non-occlusive transdermal testosterone formulation to increase testosterone blood levels of testosterone deficient hypogonadal men as disclosed in claim 20 of the '944 patent. Example 13A of the '725 publication also expressly discloses the composition of the claimed non-occlusive transdermal testosterone formulation, save for its use of hydroxyl propyl cellulose as the thickening agent, rather than the polyvinyl pyrrolidone (also known as povidone) disclosed in claim 20. However, the '725 publication teaches that the thickening agent used in Example 13A is interchangeable with a number of other thickening agents listed in paragraph 24 of the '725 publication, including povidone, and, in paragraph 27, the publication also teaches using a range of 0.5 to 5% of the chosen thickening agent. Based on these disclosures, it would have been obvious to a POSA to follow the teachings of the '725 publication to replace the thickening agent used in Example 13A with povidone in the claimed range of 1 to 3%. Given the '725

publication's disclosure, coupled with the FDA's prior approval of two transdermal testosterone gels, a POSA would have understood that testosterone could be effectively delivered transdermally to raise the testosterone blood level of a testosterone deficient hypogonadal man to within a normal range.

The dispositive issue, before us, therefore, is whether it would have been obvious to a POSA to apply the testosterone formula to the axilla. Based on the evidence adduced at trial, we find, as explained in detail below, that Defendants have established by clear and convincing evidence that application of the formulation to the axilla would have been obvious in light of the teachings of the prior art.

### **1. *Prima Facie* Evidence of Obviousness**

First, the axilla was expressly disclosed as a potential site for transdermal testosterone application in the relevant literature. The Aschkenasy '268 publication, for example, discloses pharmaceutical compositions for transdermal drug delivery, including testosterone, and also discloses a list of seven potential application sites including "the abdomen, an armpit, an inside arm, the back, a thigh, a shoulder, or the scrotum." PTX-243 at [0065], [0066]. It is undisputed that a POSA would understand the armpit to be a reference to the axilla. As Dr. Hadgraft conceded, each of these application sites other than the axilla were areas of the skin where prior FDA-approved transdermal testosterone products had been applied. Hadgraft 447:5-452:16. Accordingly, a POSA would have understood these seven application sites to be a curated and finite list of sites appropriate for transdermal drug delivery, and, among those application sites, the industry would

have viewed application of testosterone to the armpit as an opportunity for differentiation from prior commercial products. Potts 1365:2-1366:6, 1473:5-14; Chambliss 1611:10-1612:10.

The fact that the Aschkenasy '268 publication also discloses an extensive list of deodorants and antiperspirants that could be added to the topical testosterone formulations disclosed therein buttresses the conclusion that a POSA would have viewed Aschkenasy as contemplating application of testosterone to the axilla, given that these are common products applied to the axilla. *See* PTX-243 at [0141], [0142]. While it is true that the Aschkenasy '268 publication does not include any exemplary data from a clinical study, that fact does not lessen the teaching of the publication, particularly when considered in combination with other prior art at the time.

For example, by June 2005, it was known that the skin of the axilla was more permeable to transdermal drug delivery than other skin sites, including the forearm, trunk, back, and abdomen. PTX-340 at 2; PTX-449 at 4; PTX-607 at 1; Potts 1357:21-1358:4, 1361:1-22. Based on the findings disclosed in prior art references like Feldmann and Maibach, it would have been reasonable for a POSA to believe that administering a topical testosterone formulation to the axilla could yield higher testosterone blood levels than administering to other identified skin sites, given the axilla's greater than average skin permeability.

Cutter 2000 and Cutter 2001 provide further motivation for a POSA to apply a transdermal testosterone formulation to the axilla to increase testosterone blood levels.

Cutter (2000) recommends transdermal application of testosterone to “the trunk or *axillary area*” and reports that such administration in adult men results in a balance of testosterone, DHT, and estradiol blood levels that is “very much in the normal physiologic range. PTX-301 at 3 (emphasis added). Cutter (2001) discusses data from a clinical study of ten patients instructed to apply testosterone gel to “either the upper inner arm or chest near the axilla or the inner thigh and scrotum.” PTX-302 at 3. The study results demonstrated that selecting the “axilla” as the site of application for transdermal delivery of testosterone effectively increases testosterone blood levels while maintaining normal physiologic levels of DHT. *Id.* at 4. Dr. Cutter further reported that in his clinical practice he found that the “most useful starting dose [of testosterone] for most men is 6% gel, 2.5 mL, applied to the nonhairy area of the axilla.” *Id.* at 9.

A POSA would have understood Cutter (2000) and Cutter (2001) as teaching the application of testosterone to a part of the axilla. The Cutter references specifically report application to the axilla’s “nonhairy area,” and, as Dr. Hadgraft testified, the axilla is comprised of both hairy and nonhairy parts. Hadgraft 362:14-17. Despite this clear reference to a portion of the axilla, as well as Dr. Cutter’s references to the application of testosterone to “the axilla,” “the axillary area,” and “the upper inner arm or the chest near the axilla,” Dr. Hadgraft nevertheless unconvincingly reads the Cutter references as “not applying the testosterone to the axilla.” Hadgraft 255:8-18. Dr. Hadgraft opined that Dr. Cutter was either using a “shorthand” when he referenced the axilla or may have been “misleading” in describing his work. Hadgraft 416:19-417:12, 420:18-421:12. Given



that the Cutter references stress that “[t]he choice of application site is quite important,” we do not find it credible to infer that when Dr. Cutter subsequently recommended application of testosterone to the “axillary area” in order to maintain normal testosterone and DHT levels, and identified the “nonhairy area of the axilla” as an effective application site used in his clinical practice, that he must have been using those terms as some sort of shorthand to refer instead to an area that *excludes* the axilla.<sup>25</sup> This interpretation simply makes no sense. Accordingly, upon reading the Cutter references, a POSA would have reasonably expected that administering a testosterone composition to the axilla would succeed in effectively increasing the testosterone blood levels of a hypogonadal man as the clinical study reported in Cutter (2000) and Cutter (2001) demonstrated that administration to the axilla would in fact work.

Cutter (2000) and Cutter (2001) also disclose additional motivation for a POSA to have applied the transdermal testosterone composition to the axilla in order to reduce the risk of inadvertent transfer of testosterone to others. It was widely known by June 2005 that transference of testosterone to women and children was linked with serious adverse side effects. *See, e.g.*, PTX-1059 at 12; PTX-641 at 10. Recognizing this risk, Cutter (2001) recommends that “by using the gel in the axillary area, at bedtime, transmission [of testosterone] can be avoided.” PTX-302 at 10. A POSA would understand from this disclosure that one significant benefit of choosing the axilla as an application site would

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<sup>25</sup> A POSA would have understood other prior art references at the time, including the Chein ‘790 patent, Ben-Galim (1980), and Papa (1967), to have also identified the axilla as a potential site for administration of testosterone.

be to avoid inadvertent transference of testosterone as the armpit is an area that does not frequently come into contact with others.

For at least these reasons, a POSA would have been motivated to combine the teachings of the prior art to apply, with a reasonable expectation of success, the testosterone composition taught in the Morgan '725 publication to the skin of the axilla to develop the claimed method of treatment recited in claim 20 of the '944 patent. As explained above, the Morgan '725 publication explicitly disclosed the elements of the claimed testosterone formulation. When combined with the Aschkenasy '268 publication's disclosure of a finite list of application sites appropriate for transdermal drug delivery that included the axilla, it would have been sheer common sense to select the axilla as an application site. *See C.W. Zumbiel Co. v. Kappos*, 702 F.3d 1371, 1387 (Fed. Cir. 2012) (finding obviousness where the invention involved "no more than the exercise of common sense in selecting one out of a finite – indeed very small – number of options"). A POSA would have been particularly motivated to select the axilla as an application site, considering that application to the axilla not only addressed the known issue of inadvertent transference of testosterone but also represented a way to differentiate from other transdermal testosterone products on the market. Moreover, a POSA would have had a reasonable expectation of success in doing so, given the axilla's known above-average permeability and the teaching of the Cutter references that application of testosterone to the axillary area effectively increases testosterone blood levels while maintaining normal DHT levels.

## 2. Secondary Considerations

It is well-established that “[s]econdary considerations of non-obviousness must be considered when present.” *Geo M. Martin Co. v. Alliance Machine Sys. Int’l, LLC*, 618 F.3d 1294, 1304 (Fed. Cir. 2010). Here, Plaintiffs argue that the secondary considerations of teaching away and unexpected results preclude a conclusion that claim 20 of the ‘944 patent is obvious.

Plaintiffs’ first argument is the prior art teaches away from the application of testosterone to the axilla. A reference teaches away “when a person of ordinary skill, upon reading the reference, would be discouraged from following the path set out in the reference, or would be led in a direction divergent from the path that was taken by the applicant.” *Galderma Labs., L.P. v. Tolmar, Inc.*, 737 F.3d 731, 738 (Fed. Cir. 2013) (quoting *DePuy Spine, Inc. v. Medtronic Sofamor Danek, Inc.*, 567 F.3d 1314, 1327 (Fed. Cir. 2009)). According to Plaintiffs, the prior art teaches away from the axilla as a suitable site for transdermal testosterone application due to concerns of elevated DHT levels as well as the presence of hair, creases and folds in the skin, sweat, bacteria, and cosmetics in the axilla. Upon careful review of the prior art, however, we are not persuaded that a POSA would understand the applicable references to teach away from administering testosterone to the axilla for any of these reasons.

Plaintiffs maintain that the prior art teaches away from applying testosterone to the axilla due to concerns of elevated levels of DHT. Specifically, Plaintiffs contend that a POSA would have been discouraged from applying testosterone to the axilla because of

concerns that high 5-alpha reductase activity in the axillary skin, similar to the level of activity found in scrotal skin, would result in elevated DHT levels associated with negative side effects, including BPH and prostate cancer. However, in reaching his conclusion on this issue, Plaintiffs' expert, Dr. Goldstein, did not rely on any prior art references which compare the 5-alpha reductase activity in axillary skin to that observed in scrotal skin nor did he cite to any prior art reference teaching that administration of testosterone to the axilla results in elevated DHT levels. To the contrary, the only prior art reference that reported DHT levels following application of testosterone to any part of the axilla is Cutter (2001), which reported normal DHT levels following application to the axillary area.

In support of his opinion that a POSA would, in fact, be concerned about elevated DHT levels associated with application of testosterone to the axilla, Dr. Goldstein relies solely upon a single study reported in Takayasu (1980), which measured the 5-alpha reductase activity of various skin tissues, including the "sweat (probably apocrine) glands" obtained from microscopic samples of axillary skin of two patients. PTX-583 at 188. Takayasu (1980) reported that the sweat glands of the axillary skin demonstrated high 5-alpha reductase activity, while the activity of the sebaceous glands and dermis in the axilla fell in the middle of the reported results. PTX-583 at 4. However, the study measured the 5-alpha reductase activity only in isolated components of the skin, such as the sweat glands, rather than such activity of the entire, intact axillary skin and did not report the amount of sweat gland in the skin sample relative to other components.

Accordingly, a POSA would not have understood Takayasu (1980)'s measure of the 5-alpha reductase in axillary sweat glands to be representative of the entire axillary skin, nor would a POSA have relied upon Takayasu (1980) to compare the 5-alphas reductase activity in differing whole skin samples. Additionally, the study was not designed to consider the amount of testosterone that would actually be delivered to the components tested. In other words, the study was not designed to assess the diffusion of testosterone from the surface of the skin into the sweat pores and through the sweat ducts to reach the sweat glands.<sup>26</sup>

Importantly, neither Takayasu (1980) nor any other prior art reference disclosed a direct comparison between the 5-alpha reductase activity found in scrotal skin with that found in the axillary skin; thus, it was not clear in the art how the activity compared. Assuming, however, that a POSA would have understood the skin of the axilla and the scrotum to have comparable 5-alpha reductase activity and would have expected that both would increase DHT levels in the same manner, the clinical significance of elevated DHT levels was uncertain in June 2005 and thus would not have dissuaded a POSA from pursuing the axilla as a site of administration for transdermal testosterone therapy.

To explain further: although it was well-known in the art that transdermal administration of testosterone to the scrotum increased DHT levels, the FDA nevertheless approved the Testoderm® scrotal patch in 1993, and, by 2000, studies on long-term use

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<sup>26</sup> Dr. Potts testified that a POSA would understand that drug delivery through the sweat ducts into the sweat glands comprises a minor fraction – roughly 0.03-0.05% -- and is not a major route for drug delivery through the skin. Potts 1393:21-1394:17.

of the Testoderm® patch had been performed, revealing that “the incidence of prostate problems in those who wore scrotal patches was no greater than in subjects given placebo.” PTX-301 at 7. In the 1990s, the prior art acknowledged that the clinical significance of elevated DHT levels was “unknown,” (PTX-290 at 3), and that, after much research, it was recognized that “less credence is given to the simple concept that elevated DHT levels may be a factor in BPH.” PTX-468 at 4. Moreover, despite it being known that scrotal administration of testosterone resulted in elevated DHT levels, the prior art continued to recommend the scrotum as a site of application for transdermal testosterone leading up to June 2005. *See, e.g.*, PTX-302 at 4; PTX-431 at col. 4, ll. 36-50. On this basis, we conclude that, if the known connection between transdermal application of testosterone to the scrotum and elevated DHT levels did not discourage those in the art from considering the scrotum as an appropriate application site, a POSA likewise would not have been dissuaded from pursuing the axilla as an application site based on a potentially comparable level of 5-alpha reductase activity. For these reasons, we hold that a POSA would not have found that concerns of elevated DHT levels taught away from using the axilla as an application site.

Plaintiffs also contend that a POSA would have been discouraged from administering testosterone to the axilla because of the presence of hair in the area as well as creases and folds in the skin. Although Dr. Hadgraft testified that a number of prior references taught away from transdermal administration of testosterone in areas of the skin with hair and/or significant creases and folds, on cross-examination he conceded that

such concerns were primarily associated with transdermal patch devices which rely on secure adhesion to be effective. Hadgraft 189:8-190:10, 457:18-458:15. The prior art, in fact, recognizes that the presence of hair and creases and folds of the skin do not present a significant problem for non-occlusive transdermal formulations such as the testosterone lotions at issue in this litigation. PTX-592 at col. 2, ll. 25-32, col. 2, l. 63 – col. 3, l. 5; Potts 1401:23-1402:11. Moreover, both AndroGel® and Testim®, the two prior art non-occlusive testosterone gels, are applied to areas in which men often grow hair, including the shoulders, upper arms, and abdomen. Potts 1400:1-15. Accordingly, a POSA would not understand the prior art to point away from transdermal testosterone application to the axilla on the basis of hair or creases and folds of the skin and would not expect these characteristics of the axilla to impede transdermal drug delivery.

Nor does the prior art point away from the axilla as an application site because of the presence of sweat, bacteria, antiperspirants or deodorants on the surface of the axillary skin. There is no prior art reference that discusses any adverse effects on transdermal drug delivery due to the presence of any of these characteristics. Indeed, the Aschkenasy '268 publication anticipates that deodorants and antiperspirants may be added to its transdermal testosterone formulations. PTX-243 at 12. Even assuming a POSA would be concerned regarding the possible impact that sweat, bacteria, antiperspirants, or deodorants might have on transdermal drug delivery, the prior art testosterone gels, AndroGel® and Testim®, address the issue by instructing users to apply the gels to “intact, clean, dry skin.” PTX-1059 at 1; PTX-641 at 1. The instruction

to wash and dry the skin prior to application of the testosterone formulation would avoid concerns related to sweat, bacteria, or cosmetics in the axillary area. Potts 1404:11-22. For these reasons, teach away from transdermally applying testosterone to the axilla on this basis.

Plaintiffs also point to what they contend were unexpected results of the invention of the '944 patent as evidence of nonobviousness. "To be particularly probative, evidence of unexpected results must establish that there is a difference between the results obtained and those of the closest prior art, and that the difference would not have been expected by one of ordinary skill in the art at the time of the invention." *Bristol-Myers Squibb Co. v. Teva Pharms. USA, Inc.*, 752 F.3d 967, 977 (Fed. Cir. 2014). Here, Plaintiffs cite four examples of unexpected results: (1) seven-fold greater absorption of testosterone per unit area in the axilla than the forearm; (2) no excessive sweating or odor following transdermal application of testosterone to the axilla; (3) normal DHT levels following application of testosterone to the axilla; and (4) effectiveness of transdermal delivery of testosterone to axilla despite presence of hair, bacteria, creases and folds in the skin, and deodorants and antiperspirants. We address these contentions in turn below.

In support of their argument that application of the testosterone formulation of the '944 patent to the axilla resulted in unexpectedly better absorption compared to the forearm, Plaintiffs rely on Acrux Clinical Study DDS16 ("DDS16") and inventor Dr. Watkinson's adjustment of that data to account for the surface area of the respective application sites. DDS16 reported that the axilla provided two-fold greater delivery of



testosterone than the forearm, which Dr. Hadgraft conceded was not unexpected. Such a result was not surprising (or unexpected) as a POSA would have reasonably anticipated, based on the known permeabilities of the axilla and the forearm, that administering a dosage of testosterone to the axilla would result in higher blood serum concentration levels than administering the same dosage to the forearm. DDS16 likewise reported that the approximately two-fold greater absorption in the axilla was “consistent with” the prior art’s disclosure of variations in skin permeation.

Plaintiffs’ unexpected results argument is based, therefore, not on the data from the DDS16 study alone, but rather on Dr. Watkinson’s attempt to use that data to retroactively calculate the amount of testosterone delivered per unit area of the respective skin surfaces. Dr. Watkinson’s finding that, after an adjustment of the clinical data for the supposed size of the respective application sites, the axilla provided seven-fold greater absorption per unit area than the forearm, was calculated using measurements from three unrelated sources – the testosterone absorption data from the ten women who were administered testosterone in the DDS16 study; the axilla measurements of the sixty women who had their axillae measured for an antiperspirant/deodorant study reported in Cowan-Ellsberry (2008); and the forearm measurements from fifteen women from Acrux’s offices who had their forearms measured by Dr. Watkinson. Potts 1412:11-1413:6. In reaching his conclusion, Dr. Watkinson necessarily relied upon the assumption that the areas of the axillae and forearms measured in women who were not participants in the DDS16 study accurately represented the areas of application in the

original clinical study. Because Dr. Watkinson used data from three distinct groups of women and also relied upon the unsubstantiated assumption that the application sites in the DDS16 study corresponded with the measurements of completely different women, we are not persuaded that Dr. Watkinson's retroactive size adjustment represents a reliable measurement of the difference in absorption per unit area between the axilla and the forearm.<sup>27</sup>

Moreover, even if the axilla did demonstrate a seven-fold increase in testosterone permeation per unit area as compared to the forearm, a POSA would not find that result altogether unexpected. The prior art, for example, reported that the physiological agent, parathion, permeated the skin of the axilla in an amount 7.4-fold greater than that of the forearm. PTX-340. Given that the axilla was known in the art to be more permeable than the forearm for various compounds, any enhanced permeation of testosterone would be, at most, only a "difference in degree" of a known and expected property, rather than a difference in "kind." *Bristol-Myers*, 752 F.3d at 977. It is well-established under Federal Circuit precedent that differences in degree "are not as persuasive in rebutting obviousness as differences in 'kind' – i.e., a new property dissimilar to the known property." *Id.*; see *Galderma*, 737 F.3d at 739 ("Unexpected results that are probative of nonobviousness are those that are different in kind and not merely in degree from the results of the prior art.") (citation and quotation marks omitted).

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<sup>27</sup> We note that Dr. Watkinson's size adjustment calculation is not included in the clinical study report, the '944 patent specification, or the peer-reviewed publication of the results from clinical study DDS16.

Plaintiffs next invoke their clinical study results showing that application of a testosterone formulation to the axilla did not cause excessive sweating or odor as unexpected, given that testosterone increases the activity of the apocrine glands and would be expected to result in increased sweat and odor in the axilla. Goldstein 675:11-676:13. However, Plaintiffs presented no prior art reference(s) suggesting that a POSA would have expected that administering testosterone to the axilla of a hypogonadal man would result in excessive sweating. Failure to present “any evidence of what the skilled artisan would have expected” defeats a claim of unexpected results. *See Pfizer, Inc. v. Apotex, Inc.*, 480 F.3d 1348, 1371 (Fed. Cir. 2007) (emphasis removed). To the contrary, because a hypogonadal man has below normal levels of testosterone and sweats less than the average adult male, a POSA would not expect that applying testosterone to the axilla of a hypogonadal man would lead to excessive sweating and odor. Rather, one skilled in the art would expect that, if testosterone therapy returns a hypogonadal man to normal physiologic ranges, that the amount of sweating and odor would increase to normal levels as well, and would not be excessive.

Finally, Plaintiffs contend that the invention of the ‘944 patent of applying testosterone to the axilla was surprisingly effective at increasing testosterone blood levels without increasing DHT levels and despite the presence of hair, sweat, and/or antiperspirants or deodorants. However, as discussed above, a POSA would not have expected anything other than normal DHT levels when applying testosterone to the axilla, given the disclosure in the Cutter references that application of testosterone to the axillary

area resulted in normal DHT levels, coupled with the absence in the prior art of any disclosure showing elevated DHT levels following testosterone application to the axilla. The fact that Acrux and Lilly's clinical studies showed normal DHT levels when a testosterone formulation was applied to the axilla therefore cannot be evidence of unexpected or surprising results. Similarly, Plaintiffs have failed to establish that its studies showing that application of Axiron® to the axilla was effective despite the presence of hair, bacteria, creases and folds in the skin, and deodorants and antiperspirants were, in fact, surprising. The prior art did not teach away from applying testosterone to the axilla based on any of these factors, nor has it been shown that a POSA would have expected that these factors would materially affect transdermal drug delivery.

For these reasons, we hold that Plaintiffs' asserted secondary considerations of non-obviousness do not overcome the strong *prima facie* evidence of obviousness rendering claim 20 of the '944 patent invalid as obvious.

#### **IV. The '861 Patent**

##### **A. Infringement**

Plaintiffs allege that each of Defendants' respective applicators infringes the '861 patent, either directly or indirectly. Plaintiffs bear the burden of "proving infringement by a preponderance of the evidence," and the "failure to meet a single limitation is sufficient to negate infringement of [a] claim." *Laitram Corp. v. Rexnord, Inc.*, 939 F.2d 1533, 1535 (Fed. Cir. 1991). A determination of direct patent infringement requires a

two-step analysis. The court first must construe the claims to determine their scope and meaning and then compare the properly construed claims to the allegedly infringing device. *Dynacore Holdings, Corp. v. U.S. Phillips Corp.*, 363 F.3d 1263, 1273 (Fed. Cir. 2004). “To prove infringement, the patentee must show that the accused device meets each claim limitation, either literally or under the doctrine of equivalents.” *Id.*

Liability for indirect infringement, whether inducement to infringe or contributory infringement “is dependent upon the existence of direct infringement.” *Joy Techs., Inc. v. Flakt, Inc.*, 6 F.3d 770, 774 (Fed. Cir. 1993). It is well-established that “[t]here can be no inducement or contributory infringement without an underlying act of direct infringement.” *Linear Tech. Corp. v. Impala Linear Corp.*, 379 F.3d 1311, 1326 (Fed. Cir. 2004). For a party to be liable for contributory infringement under 35 U.S.C. § 271(c), the plaintiff must establish: (1) “there is direct infringement,” (2) “the accused infringer had knowledge of the patent,” (3) “the component has no substantial noninfringing uses,” and (4) “the component is a material part of the invention.” *Fujitsu Ltd. v. Netgear, Inc.*, 620 F.3d 1321, 1326 (Fed. Cir. 2010). “To prove inducement of infringement, the patent must show that the accused inducer took an affirmative act to encourage infringement with the knowledge that the induced acts constitute patent infringement.” *Info-Hold, Inc. v. Muzak LLC*, 783 F.3d 1365, 1372 (Fed. Cir. 2015) (internal quotation marks and citation omitted).

We address Plaintiffs’ infringement claims against each Defendant in turn below.

### **1. The Actavis and Perrigo Applicators**

Plaintiffs have stipulated that Actavis and Perrigo do not directly infringe claims 9 and 10 of the '861 patent because their respective applicators are both single wall devices and therefore do not meet the "wall" limitation of the asserted claims, which has been construed to require "an inner portion and an outer skirt portion which form a *double-wall structure*." Dkt. 105 at 2 (emphasis added). Instead, Plaintiffs claim that Actavis and Perrigo are liable for indirect infringement of claims 9 and 10.

As noted above, there can be no indirect infringement without proof of direct infringement, "though the direct infringer is typically someone other than the defendant accused of direct infringement." *Dynacore*, 363 F.3d at 1272. Such is the case here, where Plaintiffs' indirect infringement claims against Actavis and Perrigo are premised on the assertion that users of the respective applicators, when using the accused products in the manner set forth in Actavis's and Perrigo's labeling instructions, will directly infringe the '861 patent. Specifically, Plaintiffs claim that, although both Actavis's and Perrigo's accused products are single-wall applicators at rest, when used in accordance with the included directions for use, the single wall folds over to form a double wall that meets the limitations set forth in claims 9 and 10.

Upon careful consideration of the evidence adduced at trial, we find that Plaintiffs have failed to establish by a preponderance of the evidence that Actavis's and Perrigo's applicators directly infringe claims 9 and 10. Plaintiffs rely exclusively on the testimony of their expert, Dr. Slocum, to support their claim that the single wall in the Actavis and Perrigo applicators folds over in use to form an infringing double wall. Dr. Slocum, in

turn, based his opinion that Actavis's and Perrigo's applicators form a double wall in use on his professional knowledge and experience, Defendants' proposed drug labeling, and his own testing of the accused applicators.

Before trial, Defendants sought to have Dr. Slocum's testimony regarding the testing he performed on the Actavis and Perrigo applicators as well as his opinions based on that testing excluded under Federal Rule of Evidence 702 and the principles set forth in *Daubert v. Merrell Dow Pharmaceuticals, Inc.*, 509 U.S. 579 (1993). At the final pretrial conference, the Court withheld a ruling on the *Daubert* issue, recognizing that because Dr. Slocum's testimony would be offered at a bench trial, not before a jury, it was unnecessary to address the admissibility issues in advance of trial. At trial, Defendants' *Daubert* objection was renewed and the Court, recognizing the continuing objection, permitted Dr. Slocum to testify, explaining that the *Daubert* issues would be considered "in the context of the testimony and taking into account the cross-examination and so forth." Tr. 523:9-11.

"Where a trial judge conducts a bench trial, the judge need not conduct a *Daubert* (or Rule 702) analysis before presentation of the evidence, even though [s]he must determine admissibility at some point." *Kansas City So. Railway Co. v. Sny Island Levee Drainage District*, \_\_\_ F.3d \_\_\_, 2016 WL 4123857, at \*6 (7th Cir. Aug. 3, 2016). Having now heard the testimony and cross-examination of Dr. Slocum, we begin by addressing Defendants' *Daubert* challenge.

The admissibility of expert testimony is governed by Rule 702 and the *Daubert* principles. To be admissible, expert testimony must be both relevant and reliable. *United States v. Allen*, 390 F.3d 944, 949 (7th Cir. 2004). The case law recognizes that this test “is a flexible one, and no single factor is either required in the analysis or dispositive as to its outcome.” *Smith v. Ford Motor Co.*, 215 F.3d 713, 719 (7th Cir. 2000). Moreover, the Federal Circuit has observed that, while expert testimony must still meet the *Daubert* standards of relevance and reliability where the case is tried to the court, *Daubert* concerns are “of lesser import in a bench trial.” *Seaboard Lumber Co. v. United States*, 308 F.3d 1283, 1302 (Fed. Cir. 2002). Accordingly, as explained by Judge Posner, “a judge in a bench trial should have discretion to admit questionable technical evidence, though of course [s]he must not give it more weight than it deserves.” *SmithKline Beecham Corp. v. Apotex Corp.*, 247 Fed. Supp. 2d 1011, 1042 (N.D. Ill. 2003) (Posner, J., sitting by designation), *aff’d on other grounds*, 403 F.3d 1331 (Fed. Cir. 2005).

Here, it is undisputed that Dr. Slocum is an expert by “knowledge, skill, experience, training, [and] education” qualified to render an opinion concerning infringement. *See* Fed. R. Evid. 702. The thrust of Defendants’ *Daubert* challenge is that Dr. Slocum’s opinions based on the at-home testing methods he performed on the Perrigo and Actavis applicators are inadmissible because that testimony is not the product of reliable principles and methods. However, the case law recognizes that expert testimony based on personal observation is not inherently unreliable and that “hands on testing” as



Dr. Slocum performed here “may suffice as a reasonable methodology upon which to base an opinion.” *Clark v. Takata Corp.*, 192 F.3d 750, 758 (7th Cir. 1999). Dr. Slocum’s testimony that, based on his informal tests in which he acted as a regular “user” of the Actavis and Perrigo devices, the accused applicators meet the limitations of the asserted claims, is relevant to the ultimate infringement issue. While Defendants question whether the testing performed by Dr. Slocum supports his infringement opinions, the “[s]oundness of the factual underpinnings of the expert’s analysis and the correctness of the expert’s conclusions based on that analysis are factual matters to be determined by the trier of fact.” *Smith*, 215 F.3d at 718. Given that *Daubert* concerns are not implicated to the same degree when the case is tried to the court and because we find that Defendants’ objections to Dr. Slocum’s testimony and opinions go more to their weight, rather than their admissibility, we deny the *Daubert* objections and decline to exclude Dr. Slocum’s testimony on those grounds.

At trial, Dr. Slocum opined that both the Actavis and Perrigo applicators form a double-wall structure when the devices are used as instructed by Actavis’s and Perrigo’s respective labeling and package inserts. Specifically, Dr. Slocum testified that the materials used in the Actavis and Perrigo wall structures – and silicone, respectively – are flexible, and thus, when the devices are pressed against the surface of the axilla with sufficient force, the pressure combined with the motion cause the wall of each accused device to double over on itself, when in use, such that the wall meets the limitations of the asserted claims. To support his opinions regarding the “wall” limitation, Dr. Slocum

relies heavily on the results of the hands-on testing he performed on the Actavis and Perrigo applicators. Our review of Dr. Slocum's testimony including Defendants' cross-examination explicating the testing he performed, for the reasons detailed below, we find that, while admissible, Dr. Slocum's opinions fail to establish the threshold requirement of direct infringement.

Dr. Slocum testified that he first tested the accused applicators in the Finnegan law firm office ("Finnegan testing"), where he manipulated the applicators with his hands by "play[ing] with" them and placing them in "different body regions," while observing the manner in which they behaved and responded. Slocum 862:18-25. However, Dr. Slocum did not document any of these manipulations he performed on the applicators, either by taking notes or with photographs or video, and in fact he testified that he did not "exactly recall the exact things I did." Slocum 862:23-24. Dr. Slocum testified that during the Finnegan law office testing, he may have put water in the applicators and used the applicators on his forearm and in the crook of his arm, but he did not attempt to use the applicators in his axilla or to use any liquid in the applicators other than water. Slocum 863:22-25, 864:5-10, 864:22-25, 865:1-2.

Following the Finnegan law office procedures, Dr. Slocum prepared his January 2016 expert report, setting forth his opinion that both the Actavis and Perrigo applicators form double-walled structures while in use. This testing is wholly insufficient to show the manner in which the respective walls of Actavis's and Perrigo's applicators behave in use. As Dr. Slocum himself conceded, his testing did not simulate the manner in which

patients would actually use the applicators, since he did not follow the labeling instructions for either applicator when manipulating the devices, nor did he use either applicator to apply liquid to the axilla. Slocum 863:18-23, 864:1-10, 864:19-865:11, 865:19-866:14, 1172:8-16. For these reasons, Dr. Slocum's opinion based on his incomplete and undocumented manipulations of the applicators during the Finnegan law firm office testing that, when used as directed, the Actavis and Perrigo applicators form a claimed double-wall structure has only limited, if any, relevance, including for the reason that his opinion was not based on any use or testing of the applicators according to Actavis's or Perrigo's labeling.

Shortly after reviewing Defendants' experts' rebuttal reports, Dr. Slocum performed a second set of tests on the accused applicators for purposes of preparing his reply report. These follow-up tests were referred to at trial as the "wet testing." Dr. Slocum's wet testing involved using the Actavis and Perrigo applicators to apply to his own axilla a homemade liquid of his own devising that he created by combining cranberry juice and rubbing alcohol. Dr. Slocum testified that he performed the wet testing at home, alone, in his bathroom shower, and, as with the Finnegan testing, Dr. Slocum took no contemporaneous notes or otherwise documented the wet testing protocol or his findings with photographs or video. As a result, at trial, Dr. Slocum could not remember the specific date on which he performed the wet testing, (Slocum 873:4-12), the order in which he tested the accused applicators, (*id.* 874:17-875:9), the precise number of times he tested each applicator, (*id.* 884:4-16), or, with any specificity, the

length of time it required to complete the testing. *Id.* 875:14-23 (recalling only that his wet testing took “less than an hour and more than a minute”). Based on his personal observations of the accused applicators during the wet testing, Dr. Slocum opined that in order to avoid excessive leakage of the testosterone formulation, patients would “learn” to push the Actavis and Perrigo applicators against the axilla with sufficient force to create a seal, which in turn would cause the wall of the device to fold over and thereby create the infringing double wall. Dr. Slocum’s wet testing protocol and procedures are riddled with inadequacies. It thus cannot be received as support for his opinion that the Actavis and Perrigo applicators meet the “wall” limitation of the ‘944 patent.

Dr. Slocum explained that the purpose of his wet testing was to allow him to “pretend[]” to be a “typical user” in order to observe how the applicators would perform under such conditions. Slocum 783:5-25, 863:14-17. However, rather than use a placebo formulation of Actavis’s or Perrigo’s testosterone product to simulate the experience of an actual user, the liquid Dr. Slocum applied to his axilla during the wet testing was a homemade mixture of unknown amounts of cranberry juice and rubbing alcohol that he created from ingredients he found at his home. Slocum 875:24-876:15, 877:13-21. Dr. Slocum conceded at trial that this mixture had a lower viscosity than a placebo formulation and was therefore “more sensitive to detecting leakage from the applicator.” Slocum 878:8-18. This distinction is particularly important here as Dr. Slocum’s opinion that the Actavis and Perrigo applicators will form the double wall structure in use is based on his belief that, in order to avoid “excessive leakage,” which he defined as “more

than a drip now and then,” users will be required to use an amount of force that will necessarily cause the single wall of the accused applicators to fold over and create the infringing double wall. Slocum 892:19-893:21. Dr. Slocum’s failure to use placebo formulations of the ANDA formulations that will be sold with the Actavis and Perrigo applicators, or, at the very least, a formulation that included a thickening agent to approximate the same viscosity as those testosterone formulations, renders his opinion that the force a user of the Actavis and Perrigo applicators would be required to apply to avoid excessive leakage would necessarily cause the single wall of the respective applicators to fold over to create a double wall, pure conjecture.

In addition to using a liquid mixture of a completely different type and composition than that of Actavis’s and Perrigo’s ANDA formulations, Dr. Slocum also failed to precisely measure the amount of liquid he used in Actavis’s and Perrigo’s applicators during his wet testing. The labeling accompanying both the Actavis and the Perrigo applicators instructs patients to use exactly 1.5 mL of liquid (one pump) for application to the axilla. *See, e.g.*, PTX-218 at 2614-15, 2623; PTX-216 at 16-17; Slocum 881:17-19. Rather than use a syringe or other precise measuring tool, Dr. Slocum instead used a common kitchen teaspoon he had stored in his bathroom (which he testified holds a total of 4 to 5 mL) to measure the liquid he transferred to the accused applicators during his wet testing. At trial, Dr. Slocum could not testify definitively as to the amount of liquid he used in the Actavis and Perrigo applicators, alternatively testifying that he used “a fraction of a teaspoon,” (Slocum 785:7-14), “what looked like a

reasonable amount,” (*id.* 785:15-21, 882:13-15), “about a third of a teaspoon,” (*id.* 879:10-880:6), “a reasonable guesstimate,” (*id.* 882:13-21), “a few milliliters lower than the rim” of the teaspoon, (*id.*), “less than [4 to 5 mL], on the order of the one and a half,” (*id.* 882:16-883:2), and “[a] third to a half, probably.”<sup>28</sup> *Id.* 883:3-5.

Dr. Slocum’s inability to testify definitively regarding the amount of liquid he used for each application during the wet testing no doubt stemmed in part from his failure to utilize an accurate measuring device to ensure that he was, in fact, delivering the correct amount of liquid into the applicator each time. As with the viscosity variable, the amount of liquid used in the applicator can clearly affect the amount of leakage that is to be expected. Without knowing the exact amount of liquid used by Dr. Slocum, in his wet test, it is impossible to know the effect of such imprecision on his observations and findings. Accordingly, Dr. Slocum’s failure to ensure that he was applying the amount of liquid indicated in Actavis’s and Perrigo’s labeling completely undermines the reliability of his opinion that the Actavis and Perrigo applicators infringe the ‘944 patent’s “wall” limitation when used in accordance with those labeling instructions. Having clearly failed to follow those instructions himself when performing the wet testing that is the basis for his opinion, his opinion is not credible.

Dr. Slocum also performed the wet testing in the bathroom (at his home) without any witnesses, photographs, or video. His conclusion that both the Actavis and Perrigo

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<sup>28</sup> At his deposition, Dr. Slocum first testified that he used 3 ccs (or 3 mL) per application for his wet testing. He later testified at his deposition that he used 1.5 ccs (or 1.5 mL) per application. Slocum 881:20-22; 881:23-882:3; 979:8-981:4.

applicators formed the double wall during the wet testing is thus based only on his personal, undocumented observations of himself made while he was in the process of using the devices. For the parts of the test when he could not observe himself, by looking at himself in his bathroom mirror as he stood in his shower, approximately five or six feet away, his testimony is further impeached. Thus, the results of the wet testing by Dr. Slocum consist solely of his undocumented and unrecorded observations, some of which were made as he observed his reflection in a mirror some five feet away. Dr. Slocum's memory of the order in which he tested Defendants' accused applicators was also lacking. Plaintiffs have failed to establish that Dr. Slocum's observations were accurate and reliable and complete with regard to the way in which the wall of the respective applicators behaved during use. Further, his reported results for a particular defendant's applicator were unconvincing, given that they were based on his unorthodox testing procedures and resultant observations of each defendant's applicator.

In sum, Dr. Slocum's wet testing does not support his infringement opinion that a patient using either the Actavis or Perrigo applicator in accordance with the labeling instructions will press the applicator against his axilla with sufficient force to cause the single wall to fold over in use because, absent such force, the patient would experience excessive leakage of the testosterone formula. This opinion emanates from Dr. Slocum's use of the accused applicators in accordance with the products' labeling. However, Dr. Slocum clearly did not do so, having used a liquid composition without a thickening agent that he conceded was less viscous than Actavis's and Perrigo's ANDA

formulations and having failed to ensure that only 1.5 mL of liquid was used for each application as described in the labeling instructions. Both of these steps as part of the wet testing would make the applicators more susceptible to leakage, thereby impacting the amount of force that would have been required to prevent leakage under Dr. Slocum's theory. Given that Dr. Slocum testified that the amount of force with which the applicator is pressed against the axilla can affect whether a double wall is formed (which is confirmed by the fact that Dr. Slocum conceded that in some of his trials the accused products did not form the claimed double-walled structure), his failure to control for these variables erodes the credibility of his opinion that the respective walls of the Actavis and Perrigo applicators would fold over when used in accordance with the labeling instructions and it is therefore entitled to very little weight.<sup>29</sup>

The fact that Dr. Slocum testified that he did not intend his wet testing to be a scientifically reliable test, but rather intended only to do a "quick play" with the Actavis

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<sup>29</sup> While these factors alone render his wet testing results unreliable, Dr. Slocum's infringement opinion is also based on the premise that the labeling instructions in some way direct patients to use sufficient force with the applicators to create a seal with the device in order to avoid leakage. But, Dr. Slocum acknowledged that neither Actavis's nor Perrigo's labeling instructions direct patients in this manner. Rather, the labeling instructions direct patients only to "keep[] the applicator upright" and to "place [the applicator] up into the axilla and wipe steadily down and up into the axilla." *E.g.*, DTX-258. Further, the instructions specifically contemplate at least some leakage, directing that "[i]f the solution drips or runs, it can be wiped back up with the applicator cup." *Id.* Because Dr. Slocum failed to document his wet testing protocol, there is no way to determine whether the leakage he contends would occur if insufficient force was used on the applicators to create the double wall would nonetheless have been within the bounds contemplated in the labeling instructions. Nor did Dr. Slocum conduct a control with Plaintiffs' applicator to determine how much leakage a user experiences with Axiron®. Accordingly, even if Dr. Slocum had documented the amount of leakage experienced with the Actavis and Perrigo applicators, we would have no way of knowing whether such leakage was excessive in comparison.



and Perrigo applicators (Slocum 783:5-25, 786:17-21, 891:9-892:2), does not excuse or explain away the many procedural inadequacies described above. Dr. Slocum's failure to accurately recall many seemingly basic as well as critical details about his testing and alleged results puts the credibility of his opinions in serious doubt. For these reasons, Dr. Slocum's testimony, which comprised the only evidence on which Plaintiffs rely for their assertion that the Actavis and Perrigo applicators meet the "wall" limitation of the '944 patent, is insufficient as proof of that assertion, to wit, that, when in use, the Actavis and Perrigo applicators have the claimed double wall required by claims 9 and 10.

Contrary to Dr. Slocum's opinion, Dr. Singh testified that Actavis's and Perrigo's applicators will not form a double wall when used according to their labeling. Dr. Singh based his non-infringement opinion first on the Actavis and Perrigo labeling, which does not include any requirement or direction that, in using the respective applicators, a patient should apply a certain amount of force against the axilla or form a seal against the axilla. Singh 1018:4-1019:2, 1019:13-19; PTX-218. In support of his conclusion that a patient using the Actavis or Perrigo applicators in accordance with their labeling will not form a seal or double wall against the axilla, Dr. Singh relied on video evidence of actual application of a testosterone solution to a human axilla. Specifically, Dr. Singh analyzed Lilly's Axiron® application video (it is undisputed that the instructions for using the Axiron® applicator are substantively the same as those for the Actavis and Perrigo applicators), opining that the patient is shown applying the applicator up against a relatively flat surface of the axilla to start and then wipes up and down, but does not form

a seal or double wall. In fact, as Dr. Singh testified, the Axiron® video shows that, as the applicator is swiped down and up, the leading portion of the wall folds inward toward the receptacle while the trailing wall is not deformed at all. Singh 1020:24-1022:7; DTX-1283 at 1:24 to 1:39. Dr. Singh opined that the Actavis and Perrigo applicators would perform in substantially the same way, to wit, the leading edge of the single wall of the accused applicators would likewise deform inward and the trailing edge would remain undeformed, therefore not forming the double wall structure even according to Dr. Slocum's theory. Singh 1022:25-1023:16; DDX-407. We found Dr. Singh's testimony in this regard, based on the labeling instructions as well as the actual application of a testosterone formulation to the axilla, to be both credible and supported by a preponderance of the evidence adduced at trial.

For these reasons, we hold that Plaintiffs have failed to establish that Actavis and Perrigo's applicators will meet the "wall" limitation of the '861 patent. Because Plaintiffs have failed to establish by a preponderance of the evidence that the Actavis and Perrigo applicators meet every limitation of claims 9 and 10 of the '944 patent, their effort to prove direct infringement falls short.<sup>30</sup> See *Dynacore*, 363 F.3d at 1273 ("To

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<sup>30</sup> At trial, Actavis and Perrigo raised several other arguments in response to Plaintiffs' infringement claim, including their contention that Plaintiffs previously disclaimed single-wall devices as a matter of law and that claims 9 and 10 of the '861 patent do not encompass single-wall devices that fold over to form a double wall. Actavis and Perrigo also argued that their respective applicators failed to meet other limitations of claims 9 and 10, including, *inter alia*, the "resiliently deformable" and "substantially transverse" limitations. We need not reach these disclaimer and disclosure issues related to the wall limitation or Actavis and Perrigo's arguments regarding other claim limitations, however, because Plaintiffs have failed to satisfy their burden to prove by a preponderance of the evidence that Actavis's and Perrigo's applicators will fold over in use to form a double-wall structure when used according to the labeling.

prove infringement, the patentee must show that the accused device meets each claim limitation, either literally or under the doctrine of equivalents.”). Plaintiffs’ failure to prove direct infringement necessarily dooms their indirect infringement claims as well against Actavis and Perrigo because “[a]bsent direct infringement of the patent claims, there can be neither contributory infringement nor inducement of infringement.” *Met-Coil Sys. Corp. v. Korners Unlimited, Inc.*, 803 F.2d 684, 687 (Fed. Cir. 1986) (internal citations omitted).

## **2. Amneal’s Applicator**

Plaintiffs allege that Amneal’s applicator and its use will literally infringe the ‘861 patent. Amneal stipulates that, under the Court’s current claim construction, its applicator and/or the use thereof meets all elements of claim 10 of the ‘861 patent except for the “wall” limitation, and meets all elements of claim 9 of the ‘861 patent, except for the “wall” limitation and the step of claim 9 reciting “deforming the wall.” For the reasons detailed below, Plaintiffs have established by a preponderance of the evidence that Amneal’s applicator has the required “double-wall structure” of the asserted claims and also meets the “deforming the wall” limitation of claim 9 and therefore directly infringes claims 9 and 10 of the ‘861 patent. *See Southwall Techs., Inc. v. Cardinal IG Co.*, 54 F.3d 1570, 1575 (Fed. Cir. 1995) (“To establish literal infringement, every limitation set forth in a claim must be found in an accused product, exactly.”). Plaintiffs have further shown by a preponderance of the evidence that Amneal’s applicator and its use will indirectly infringe the asserted claims.

The key dispute for purposes of Plaintiffs' infringement claims is whether the double-wall structure of the applicator claimed in the '861 patent requires that the outer skirt be attached to the support. The wall of Amneal's applicator consists of a membrane, folded over, with the first end mounted onto the handle and the second end folded over and coupled with the moveable skirt. PTX 1091 at 128; PTX 186 at 1646; DTX 2082 at 16-18. The second end and the moveable skirt are not affixed to the handle and can uniformly deform to move freely relative to the handle in a longitudinally axial direction without lateral deformation (basically, functioning like a plunger). DDX-148; DTX-2082 at 9, 17. Plaintiffs do not dispute that the second end of the membrane in Amneal's applicator is not affixed to the support. Accordingly, if claims 9 and 10 require attachment, Amneal's applicator does not meet such a limitation.

As discussed above, the parties have agreed to construe the term "wall" as "part of the receptacle having an inner portion and outer skirt portion which form a double-wall structure" and the phrase "double-wall structure" as "a structure having two walls, i.e., not the two surfaces of a single wall." Dkt. 105 at 2. The parties' agreed definition of "outer skirt portion" is "one of the two walls of the double-wall structure that is furthest from the reservoir space." *Id.* None of these joint constructions include the requirement that the outer skirt portion of the double-wall structure be connected to the support.

The parties' agreed constructions are consistent with the specification of the '861 patent, which provides that, while the wall may have a "lower edge of which is attached to the support means," that is an example only of a "preferred embodiment." PTX-5 at

col. 2, ll. 15-17. The Federal Circuit has “repeatedly warned” that “although the specification often describes very specific embodiments of the invention,” courts should not “confin[e] the claims to those embodiments.” *Phillips v. AWH Corp.*, 415 F.3d 1303, 1323 (Fed. Cir. 2005).

Amneal nonetheless argues that the prosecution history of the ‘449 patent, which the grandparent of the ‘861 patent, establishes that the outer skirt of the wall must be attached to the support to satisfy the double-wall structure limitation. “Double-wall structure” is not expressly defined in either the ‘449 patent or the ‘861 patent. Accordingly, Amneal contends that the limitation must be understood in the context of the claim amendment. In pursuing the “double-wall structure” amendment, the patentees argued that Beard discloses only a single-walled device made of a flexible molded material and does not teach a double-wall structure. The applicants further argued that Beard “does not teach or suggest an implement having a wall that includes an inner portion which extends from the base to an upper end and an outer skirt portion, wherein the inner portion and skirt portion form a double wall structure, as recited in the instant claims.” PTX-10 at 344.

In support of its conclusion that the patentees’ representations during the claim amendment process establish that there must be attachment of the outer skirt to the support to be a double-wall structure, Amneal relies on the fact that each of the sources cited by the patentees’ in support of the amendment, namely, paragraph 26, the figures, and original claims 10 and 36, reference or show the outer skirt of the double-wall

structure being attached to the support of the device. Paragraph 26, for example, states: “The wall includes an inner portion 7 which extends continuously from the base 5 towards an upper end 8 of the wall 6. A skirt portion 9 of the wall extends continuously from the upper end 8 of the wall to a lower edge 10 which is attached to the support means.” PTX-10 at 10. Similarly, Figures 2 and 3, both of which are referenced in Paragraph 26, as well as the other embodiments pictured in the application, show the outer skirt attached to the support. PTX 10 at 10, 38-40. Finally, original claims 10 and 36 both depend from original claim 8 and therefore incorporate all the limitations set forth in claim 8, which requires “the wall includes a skirt portion a lower edge of which is attached to the support means.” PTX-10 at 2, 5; Slocum 1234:13-25.

However, the patentees never specifically argued during the claim amendment process that, in order to distinguish Beard, the outer skirt portion of the double-wall structure had to be attached to the support. Moreover, claim 1 of the ‘449 patent was not amended to recite that the skirt portion was attached to the support, but rather only to add the clause “wherein the wall includes an inner portion which extends from the base to an upper end and an outer skirt portion, wherein the inner portion and skirt portion form a double-wall structure.” PTX-10 at 335. Therefore, while it is true that the patentees cited sources during the claim amendment process that would have allowed them to amend claim 1 to recite that the skirt portion is attached to the support, they did not do so.

This understanding is consistent with the claims of the ‘861 patent. Independent claim 1 is the broadest claim and does not require the outer skirt portion to be attached to

the support. PTX-5 at claim 1. Dependent claim 12, however, does include this requirement, explicitly requiring that the “lower edge of the skirt portion is attached to the support.” PTX-5 at claim 12. Thus, a person of ordinary skill in the art would not understand the requirement of claim 12—that the lower edge of the skirt portion be attached to the support—to be present in broader claim 1 of the ’861 patent (or claims 9 and 10, which both depend from claim 1). *See, e.g., Forest Labs., Inc. v. Abbott Labs.*, 239 F.3d 1305, 1310 (Fed. Cir. 2001) (“Where claims use different terms, those differences are presumed to reflect a difference in the scope of the claims.”); *Karlin Tech., Inc. v. Surgical Dynamics, Inc.*, 177 F.3d 968, 971-72 (Fed. Cir. 1999) (doctrine of claim differentiation normally means that limitations stated in dependent claims are not to be read into the independent claim from which they depend).

For these reasons, a POSA would understand in light of the prosecution history and the specification of the ’861 patent that there is no additional requirement that the outer skirt portion of the double-wall structure be connected to the support. Having determined that the “double-wall structure” disclosed in the ’861 patent does not require attachment, we find that Plaintiffs have established by a preponderance of the evidence that Amneal’s applicator meets this limitation. While Amneal’s expert, Hermann Plank, testified that Amneal’s applicator has a “single wall design” because it is made of a “single piece of membrane,” (DTX-2082 at 9), he agreed that there is a portion of the silicone wall of the Amneal applicator that is closest to the reservoir space and one that is furthest from the reservoir space. DTX-2083 at 39:19-40:1. This understanding is

consistent with Dr. Slocum's testimony that the silicone rubber "diaphragm" of Amneal's applicator comprises an inner portion and an outer skirt portion, which satisfies the parties' agreed definition of a double-wall structure. PTX-186 at 2072-73; Slocum 843:3-13. Accordingly, we find that the diaphragm of Amneal's applicator meets the "wall" limitation of the asserted claims. Because Amneal stipulates that its applicator meets all other elements of claim 10, Plaintiffs have established by a preponderance of the evidence that Amneal's applicator will directly infringe claim 10 of the '861 patent.

With regard to the method claim 9 of the '861 patent, Amneal stipulates that its applicator meets all elements of claim 9, except the "wall" limitation, which we have already addressed, and the step of claim 9 that requires "deforming the wall of the receptacle containing the liquid composition against the skin of the subject and spreading the liquid composition over the area of the skin surface of at least one axilla." PTX-5 at claim 9. Plaintiffs have established that use of Amneal's applicator will meet this limitation. Amneal's ANDA instructs that the "[t]estosterone topical solution is applied to the axilla," and that patients should place the applicator "up into the armpit application site and wipe steadily down and up." PTX-186 at 37-38, 55. The evidence adduced at trial also establishes that the wall of Amneal's applicator will deform when pressed against the axilla and then return to its original shape when the force is removed, given that the wall is made of a flexible silicone rubber material. Slocum 844:15-22. Although Amneal argues that its wall functions in a different manner than the claimed applicator and therefore deforms in a different manner (i.e., deformation in the axial direction rather



than the lateral deformation of the claimed applicator), the claim does not require deformation of the wall to occur in any particular way and therefore any difference in the manner of deformation is not dispositive.<sup>31</sup> Accordingly, Plaintiffs have established direct infringement by a preponderance of the evidence.

Plaintiffs have further established that Amneal is liable for induced infringement and contributory infringement of claims 9 and 10 of the '861 patent. "To prove inducement of infringement, the patent must show that the accused inducer took an affirmative act to encourage infringement with the knowledge that the induced acts constitute patent infringement." *Info-Hold*, 783 F.3d at 1372 (Fed. Cir. 2015) (internal quotation marks and citation omitted). Here, Amneal's applicator is known by Amneal to be made or adapted for use in a manner that infringes the asserted claims of the '861 patent. The labeling information directly encourages and promotes infringement because it instructs users to use Amneal's applicator in a way that will infringe the asserted claims. For example, Amneal intends for users to apply the prescribed dose of its generic testosterone solution, which is a physiologically active agent, and for its applicator to be

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<sup>31</sup> We also note that Amneal represented to the FDA that "it is confirmed that the Amneal applicators are [the] same as that of the RLD [Reference Listed Drug (Axiron<sup>®</sup>)] in their performance and functionality." PTX-186 at 885. Amneal has represented to the FDA that "the Amneal applicator was designed, fabricated and manufactured to function in the similar fashion as the RLD applicator," and that "[i]t is evident from the pictures that the physical shape and applicability of Amneal drug product packaging components are very similar to that of the RLD." *Id.* at 476. Amneal told the FDA that "Amneal has chosen these packaging components, based on their design, reproducibility and performance characteristics for the drug product and their sameness with respect to the principal operation to the applicator of the Reference Listed drug (RLD)." *Id.* at 489.

used to apply that formula, supplying its applicator with the testosterone solution and providing instructions on how to apply it using its applicator. PTX-186 at 27, 54-56.

Amneal instructs users to “[r]emove the cap and the applicator cup from the pump. Then position the nozzle over the applicator cup and depress the pump gently,” thereby instructing users to apply the liquid composition, including the physiologically active agent, to the reservoir space as required by the asserted claims. *Id.* at 54-55. Amneal’s labeling instructions further direct users to “[t]o apply the testosterone topical solution, keep the applicator upright, place it up into the armpit application site and wipe steadily down and up.” *Id.* at 55. Amneal instructs users that “[i]f testosterone topical solution drips or runs, wipe it back up with the applicator cup. Do not rub in the solution with your fingers or hand once it has been applied.” *Id.* When Amneal’s applicator is used according to Amneal’s instructions, the wall of the receptacle containing the liquid composition is deformed against the skin of the subject and the liquid composition is spread over the skin of the user’s axilla. *Id.* at 54-55; Slocum 844:15-845:1.

Accordingly, the distribution of Amneal’s label will encourage and cause patients to use the system claimed in claim 10 of the ‘861 patent and cause the method claimed in claim 9 of the ‘861 patent to be practiced by patients in the United States. For these reasons, Amneal is liable for induced infringement of claims 9 and 10 of the ‘861 patent.

“A party is liable for contributory infringement if that party sells, or offers to sell, a material or apparatus for use in practicing a patented process.” *i4i Ltd. Partnership v. Microsoft Corp.*, 598 F.3d 831 (Fed. Cir. 2010). The “material or apparatus” must be “a

material part of the invention, have no substantial noninfringing uses, and be known (by the party) ‘to be especially made or especially adapted for use in an infringement of such patent.’ *Id.* (quoting 35 U.S.C. § 271(c)). Here, Amneal intends to market its applicator, with its associated container and pump dispenser, which, as shown above, infringes the asserted system claim 10 and which Amneal intends to be used to infringe method claim 9 of the ‘861 patent.

The applicator is clearly a material part of the asserted claims as claim 1, from which both asserted claims 9 and 10 depend, recites a system comprising three parts: a container, a dispensing device, and an applicator. PTX-5 at claim 1.

We find that Amneal’s applicator has no substantial noninfringing uses, because: (1) there is no evidence that Amneal’s applicator will be sold or used for any other purpose than with Amneal’s generic testosterone product; and (2) there is no evidence that Amneal’s applicator can be used in a noninfringing manner when applying Amneal’s generic testosterone product. *Id.* at 25, 54-56.

Finally, Amneal’s labeling instructs its users that its transdermal testosterone formula is “[f]or topical use only with enclosed applicator.” PTX-186 at 27. Amneal’s applicator is especially made to apply its generic testosterone product according to the instructions provided by Amneal, which for the reasons detailed above, will infringe claims 9 and 10 of the ‘861 patent. *Id.* at 27, 54-56. Accordingly, Amneal’s applicator is especially made or adapted for use in infringement of the ‘861 patent.

For these reasons, Plaintiffs have successfully established that Amneal is liable for contributory infringement of claims 9 and 10 of the '861 patent.

### **3. Lupin's Applicator**

Plaintiffs also contend that Lupin's applicator will infringe the asserted claims of the '861 patent under the doctrine of equivalents.<sup>32</sup> Infringement under the doctrine of equivalents requires proof that "a component in the accused subject matter performs substantially the same function as the claimed limitation in substantially the same way to achieve substantially the same result." *Ethicon Endo-Surgery, Inc. v. United States Surgical Corp.*, 149 F.3d 1309, 1315-1316 (Fed. Cir. 1998) (citing *Warner-Jenkinson Co. v. Hilton Davis Chem. Co.*, 520 U.S. 17, 39 (1997)). For the reasons detailed below, we hold that Lupin's applicator will not infringe claims 9 and 10 of the '861 patent under the doctrine of equivalents, given that Plaintiffs have failed to establish by a preponderance of the evidence that Lupin's applicator contains an element equivalent to the "resiliently deformable wall" recited in claim 10 or that the use of Lupin's device will include a step equivalent to the "deforming the wall of the receptacle" step of the method recited in claim 9 of the '861 patent.

Asserted claims 9 and 10 of the '861 patent both depend from claim 1, which requires the applicator to have a "resiliently deformable wall." PTX-5 at claim 1. Here, Plaintiffs' proof is insufficient in establishing by a preponderance of the evidence that a

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<sup>32</sup> Plaintiffs' infringement case against Lupin rests solely on a doctrine of equivalents theory as they presented no evidence of literal infringement at trial.

component of Lupin's applicator performs the function of the resiliently deformable wall, to wit, allowing the wall to maintain a seal with the treatment surface in substantially the same manner as the claimed device in the '861 patent.

It is undisputed that the wall of Lupin's applicator is made of polypropylene, which is a hard, rigid plastic. Slocum 833:14-17. Therefore, the wall of Lupin's applicator does not itself deform in any way when the applicator is used; rather, the wall displaces or translates downward relative to the base of the applicator. MacLean 1687:6-13. This displacement allows the base to stand "proud" of the rigid wall and deposit the liquid composition into the axilla. *Id.* at 1686:10-1687:25; DDX-537.

The downward displacement of the wall of Lupin's applicator is effected by a spring-driven mechanism where the prongs of the device act as springs, bending inward as the patient pushes the applicator against the axillary skin. MacLean 1686:10-23, 1687:6-25, 1688:23-1689:23; DDX-537; DDX-539; DDX-540. When the downward force is removed, the wall returns to its resting position. *See* MacLean 1686:10-1687:25, 1689:1-7. It is clear, therefore, that the wall of Lupin's applicator experiences only up and down displacement, not deformation during use. Dr. Slocum agreed that the wall of Lupin's applicator functions by displacing up and down. Slocum 831:21-832:3. Such movement is not substantially similar to deformation. Dr. MacLean testified that displacement is the act of a solid component undergoing movement from one spatial location to another, while deformation is defined by the change in shape of a solid object when subjected to forces. MacLean 1688:8-20. It is clear, therefore, that the displacing

behavior of the wall of the Lupin applicator is not equivalent to the deforming behavior of the wall in the asserted claims.

At trial, Dr. Slocum opined that the deformation of the prongs against the wall of Lupin's applicator is equivalent to the "resiliently deformable wall" of the '861 patent. However, Dr. Slocum's testimony on this issue, to wit, that the deformable prongs would be equivalent to the resiliently deformable wall "in terms of the function of what happens, the way it does it using deformations and the result that I can maintain a seal and then I can wipe stuff up when it leaks, if it leaks," is too general and conclusory to be helpful for our analysis. Slocum 833:23-834:4. We find the opinion of Dr. MacLean to be more credible and supported by the evidence adduced at trial, to wit, that the spring-driven mechanism of the Lupin applicator, whereby the user applies force to the rigid wall downward toward the base, causing the prongs to bend to facilitate the uni-axial displacement of the wall does not function in substantially the same manner as the flexible wall claimed in the '861 patent, which stretches and changes shape during use in order to maintain a seal with the skin by moving multi-axially (*i.e.*, both up-and-down and side-to-side movement). *See* MacLean 1677:9-1678:2, 1686:10-1687:25, 1688:10-20; DDX-531; DDX-537; DDX-538. Accordingly, we conclude that the prongs of the Lupin applicator are not an equivalent to a "resiliently deformable" wall, as claimed.

Plaintiffs have also failed to show that Lupin's applicator meets the "deforming the wall" limitation of claim 9 of the '861 patent. Claim 9 discloses the method of applying a therapeutic liquid with the applicator of claim 1 and requires that the use of

the applicator involve “deforming the wall of the receptacle containing the liquid composition against the skin of the subject and spreading the liquid composition over the area of the skin surface.” PTX-5 at col. 16, ll. 4-7. For the same reasons explicated above, the displacing action of the wall of Lupin’s applicator is not equivalent to the deforming behavior of the wall required in claim 9. Moreover, the substantial difference in delivery method of the two applicators is evidenced by the fact that, while it is the skin that deforms the wall of the device claimed in the ‘861 patent, the opposite is true of the Lupin applicator, where it is the rigid wall of the device that deforms the skin in use. MacLean 1686:24-1687:5, 1694:13-1695:21; DDX-537. Accordingly, Plaintiffs have failed to show that Lupin’s applicator infringes the “deforming the wall” limitation of claim 9 of the ‘861 patent under the doctrine of equivalents.

Given that “there can be no infringement under the doctrine of equivalents if even one limitation of a claim or its equivalent is not present in the accused device,” (*Lockheed Martin Corp. v. Space Sys./Loral Inc.*, 324 F.3d 1308, 1321 (Fed. Cir. 2003), Plaintiffs’ have failed to prove that Lupin’s applicator infringes under the doctrine of equivalents. Plaintiff’s indirect infringement claims against Lupin also necessarily fail because “[a]bsent direct infringement of the patent claims, there can be neither contributory infringement nor inducement of infringement.” *MetCoil*, 803 F.2d at 687.

## **B. Invalidity**

All Defendants have filed counterclaims seeking declaratory judgments that the asserted claims of the ‘861 patent are invalid on various grounds, including anticipation,

obviousness, and indefiniteness. It is well-established that “[a] district court judge faced with an invalidity counterclaim challenging a patent that it concludes was not infringed may either hear the claim or dismiss it without prejudice, subject to review only for abuse of discretion.” *Liquid Dynamics Corp. v. Vaughan Co., Inc.*, 355 F.3d 1361, 1370-71 (Fed. Cir. 2004). Because of the complexity of the invalidity arguments and the necessity of issuing a timely ruling given exigencies associated with this case, we hold that it would not be an efficient use of judicial resources to address the invalidity issues raised by Actavis, Perrigo, and Lupin in light of our holding of non-infringement as to those Defendants. Accordingly, Actavis’s, Perrigo’s, and Lupin’s counterclaims alleging that the asserted claims of the ‘861 patent are invalid are hereby dismissed without prejudice.

We therefore address only those invalidity counterclaims raised by Amneal. Amneal asserts that the ‘861 patent is invalid as anticipated and obvious. We resolve these claims in turn below.

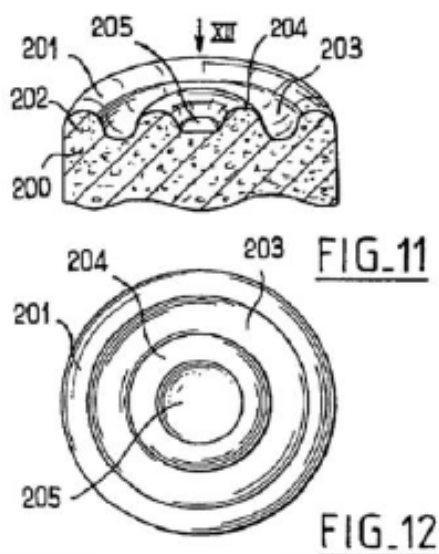
### **1. Anticipation**

Amneal contends that the asserted claims of the ‘861 patent are invalid as anticipated by the Gueret ‘187 patent. As discussed above, “[a] prior art reference anticipates a patent claim if the reference discloses, either expressly or inherently, all of the limitations of the claim.” *Marrin v. Griffin*, 599 F.3d 1290, 1295 (Fed. Cir. 2010). Because, for the reasons detailed below, Amneal has failed to establish by clear and



convincing evidence that the Gueret '187 patent<sup>33</sup> discloses the claimed wall of the '861 patent, we hold that the reference does not anticipate the asserted claims.

The Gueret '187 patent discloses “a device for packaging and applying a substance, for example, a cosmetic or a care product.” PTX-373 at col. 1, ll. 4-6. Amneal focuses on Figures 11 and 12 of the Gueret '187 patent as disclosing the claimed applicator. Figures 11 and 12 are different perspectives of the same applicator device and both depict a device made of an open cell foam. The applicator element (200) of the Gueret '187 patent may also include a “central depression 205 and the groove 203” that “may be suitable for becoming filled with substance P for application purposes.” PTX-373 at col. 11, ll. 1-4. The annular rib (204) illustrated in Figures 11 and 12 may be excluded and the open cell foam may be replaced with an elastomeric material. *Id.* at col. 10, l. 61-col. 11, l. 4.



<sup>33</sup> The PTO considered the Gueret '187 patent prior to allowance of the '861 patent. The Gueret '187 patent and the '861 patent both had the same examiner.

PTX-373 at 7.

The parties' have agreed that the term "wall," as used in the asserted claims of the '861 patent, means "part of the receptacle having an inner portion and an outer skirt portion which form a double-wall structure." Dkt. 105 at 2. The parties further agree that "double-wall structure" means "a structure having two walls, i.e., no the two surfaces of a single wall." *Id.* On direct examination, Dr. Singh conceded that "there's no disclosure of a double wall in the original language [of the Gueret '187 patent]." Singh 1070:11-15. Dr. Singh testified that the Gueret '187 patent nevertheless anticipates the wall limitation of the '861 patent because a POSA would know to modify the device depicted in Figures 11 and 12 in order to create the double-wall structure by, first, replacing the open cell foam with an elastomeric material; second, removing the annular rib (204); and finally, molding the elastomeric material to retain the same outside shape of the applicator, but to be hollow on the inside. Singh 1070:19-1073:20; DDX-454.

Even assuming that the Gueret '187 patent specification discloses that the applicator can be made with an elastomeric material instead of open cell foam and that the annular rib is optional and therefore removable as Dr. Singh testified, there is no disclosure of Dr. Singh's third suggested modification, to wit, the use of a thin sheet of elastomeric material to form only the outer shape of the applicator and molded to be hollow. On cross-examination, Dr. Singh conceded that his modified versions of Figure 11 are "nowhere directly shown in the patent," (Singh 1136:4-9), and Dr. Singh failed to

cite any other part of the Gueret '187 patent specification that would evidence support for his third modification, much less an express or inherent disclosure of such.

Moreover, Dr. Singh further admitted on cross-examination that, if the applicator in Figures 11 and 12 of the Gueret '187 patent were modified in the manner he suggests, then the resulting device would no longer work for its intended purpose. Specifically, Dr. Singh agreed that his proposed modification of replacing open cell foam with an impermeable sheet of elastomeric material would mean that the device could no longer absorb cosmetics as designed. Singh 1137:22-1138:6; PTX-373. The fact that Dr. Singh's proposed modification would render the device inoperable for its intended purpose is further evidence that the proposed modification is not disclosed in the Gueret '187 patent.

For these reasons, a POSA would not understand the Gueret '187 patent to disclose a double-wall structure as required under the parties' agreed definition of the claimed wall in the asserted claims. Accordingly, Amneal has failed to establish by clear and convincing evidence that the reference discloses, either expressly or inherently, all limitations of the asserted claims of the '861 patent, and therefore the Gueret '187 patent is not anticipatory.

## **2. Obviousness**

Amneal also claims that the asserted claims of the '861 patent are invalid for obviousness. According to Amneal, a POSA would be motivated to combine the teachings of the Gueret '986 publication and the Gueret '187 patent to create the claimed

double-wall structure. Upon careful review of the relevant prior art references, we find that Amneal has failed to prove by clear and convincing evidence that it would have been obvious to a POSA to combine the teachings of the prior art to create the claimed double-wall structure of the '861 patent, particularly considering that Amneal relies solely on prior art that was before the patent examiner during prosecution of the '861 patent and thus bears an “especially difficult” burden. *Al-Site Corp. v. VSI Int'l, Inc.*, 174 F.3d 1308, 1323 (Fed. Cir. 1999).

Dr. Singh testified that a POSA would have been motivated to create the double-wall structure claimed in the '861 patent because the '861 patent “requires a pharmaceutical type composition to be applied to the axilla,” which is a “sensitive area of the skin, and therefore ... a double-wall structure provides a more soothing application as opposed to a single-wall sharpened-edge kind of applicator.” Singh 1082:1-1083:1. Dr. Singh further opined that “creating the double-wall design would be obvious because of the requirement of an increased comfort. This applicator is to be used in the axilla, which is a sensitive area.” *Id.* 1093:4-9. However, Dr. Singh failed to identify any teaching or suggestion within the cited references (which disclose only applying “liquids on the skin”) that disclosed concerns about comfort or sensitivity such that it would have served to motivate a POSA to create the double-walled structure.

Moreover, while Dr. Singh testified that the combination of the Gueret '986 publication and the Gueret '187 patent render the asserted claims obvious, he did not opine as to how the combination of the Gueret '986 publication and the Gueret '187

patent would lead to the creation of the claimed double-wall structure. Rather, Dr. Singh testified as to each reference separately, providing testimony regarding how a POSA could modify the figures in each reference to form a double-wall structure without reference to each other.

With respect to the Gueret '986 publication, Dr. Singh testified only that a POSA would understand that a flexible single wall could fold over to form double-wall structures, so it would be obvious to modify a single-wall structure to include a double wall structure. However, he provided no testimony or explanation as to the manner in which a POSA would modify Figure 42 in order to do so, or why one would make such a modification to the device disclosed in Figure 42, considering that it functions as an applicator for its intended purpose, to wit, to store heat to raise the temperature of a wax, an oil, or water. The only modification of Figure 42 that Dr. Singh discussed was making the lip of Figure 42 more transverse to the base: “*if you would need a surface that requires a larger amount of liquid, you would make the walls more transverse.*” Singh 1084:2-10 (emphasis added). Most importantly, the only motivation Dr. Singh identified was based on the language of the '861 patent, *not* on any teaching or suggestion within the Gueret references.

Dr. Singh also opined that a POSA would modify the applicator shown in Figures 11 and 12 of the Gueret '187 patent by removing the annular rib (2014), replacing the open cell foam with an elastomeric material, and molding a sheet of elastomeric material to retain the same outer shape of the applicator, but leave the applicator hollow on the

inside. Singh 1091:9-1092:19. But Dr. Singh identified no credible reason why a POSA would have been motivated to do so. Moreover, as discussed above, making such modifications would render the device inoperable for the purpose disclosed in the Gueret '187 patent, and thus, there would have been no suggestion to modify the device in such a manner. *See In re Gordon*, 733 F.2d 900, 902 (Fed. Cir. 1984) (finding no suggestion to modify a prior art device where the modification would render the device inoperable for its intended purpose).

In short, it is simply a bridge too far to conclude that a POSA would have been motivated to combine the teachings in the Gueret '986 publication and Gueret '187 patent to create the claimed double-wall structure, particularly considering that some of those modifications would render the disclosed devices inoperable for their intended purposes. Moreover, the source of motivation cited by Dr. Singh, to wit, to create a more comfortable applicator for a sensitive area like the axilla was not based on anything disclosed in either of the Gueret references. Dr. Singh's testimony failed to establish any reason a POSA would have been motivated to combine the teachings of the two references to arrive at the claimed double-wall structure.<sup>34</sup> Neither the Gueret '986 reference nor the Gueret '187 patent suggests, much less teaches, the claimed wall

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<sup>34</sup> As Dr. Slocum testified, the applicators disclosed in the Gueret references are generally directed to cosmetics applicators. Therefore, even if a POSA were to review these references in searching for a solution to the issues faced by the inventors of the applicator claims, he or she would recognize that the cosmetics applicators in these prior art references do not have the degree of sealing and spreading ability required to apply a volume of liquid onto the axilla, which is a largely concave surface. Instead, a POSA would focus on modifying the known mechanisms for applying substances to the axilla, such as those found in, for example, the deodorant arts. Slocum 582:14-583:1.

disclosed in the asserted claims of the '861 patent. The nonobviousness of the inventions of the '861 patent is further reinforced by the fact that the disclosures of both the Gueret '986 publication and the Gueret '187 patent were considered by the PTO during examination of the '861 patent. *See Sciele Pharma, Inc. v. Lupin Ltd.*, 684 F.3d 1253, 1260 (Fed. Cir. 2012) (recognizing that there is “a high burden of proof created by the necessary deference to the PTO”). For these reasons, we hold that Amneal has failed to establish that the asserted claims of the '861 patent are invalid as obvious.

## **V. Conclusion**

For all of the reasons explicated above, the Court hereby declares that:

- (1) Actavis has proved by clear and convincing evidence that claim 13 of the '075 patent is invalid for lack of written description and enablement under 35 U.S.C. § 112 and is therefore invalid.
- (2) Defendants have proved by clear and convincing evidence that claim 20 of the '944 patent is invalid for obviousness under 35 U.S.C. § 103 and is therefore invalid.
- (3) Plaintiffs have failed to prove by a preponderance of the evidence that Actavis's, Perrigo's or Lupin's applicators will directly or indirectly infringe claims 9 and 10 of the '861 patent, either literally (Actavis's and Perrigo's applicators) or under the doctrine of equivalents (Lupin's applicator).

(4) Amneal has failed to prove by clear and convincing evidence that claims 9 and 10 of the '861 patent are invalid for anticipation or obviousness. The asserted claims of the '861 patent are therefore valid and enforceable as to it.

(5) Plaintiffs have proved by a preponderance of the evidence that Amneal's applicator and/or its use will directly and indirectly infringe claims 9 and 10 of the '861 patent.

Accordingly, it is hereby ordered that:

(1) Actavis is found not to have infringed any valid and enforceable patent-in-suit, and therefore is entitled to proceed to assert its rights based on its ANDA No. 205328 (including its statutory exclusivity rights) and is not otherwise enjoined.

(2) Perrigo is found not to have infringed any valid and enforceable patent-in-suit, and therefore is entitled to proceed to assert its rights based on its ANDA No. 204255 as soon as statutorily permitted and is not otherwise enjoined.

(3) Lupin is found not to have infringed any valid and enforceable patent-in-suit, and therefore is entitled to proceed to assert its rights based on its ANDA No. 208061 as soon as statutorily permitted and is not otherwise enjoined.

As to Amneal:

(1) U.S. Patent No. 8,435,944 is invalid and therefore unenforceable against Amneal;

(2) Pursuant to 35 U.S.C. § 271(e)(4)(A), the effective date of any approval of the testosterone applicator product that is the subject of ANDA No. 206998 SHALL



NOT BE a date earlier than the latest date of expiration of Plaintiffs' U.S. Patent No. 8,807,861; and

(3) Pursuant to 35 U.S.C. § 238 and 35 U.S.C. § 271(e)(4)(B), Defendant Amneal Pharmaceuticals, LLC, and its officers, agents, servants, employees, privies, and others acting for, on behalf of, or in concert with it are PERMANENTLY ENJOINED from the commercial manufacture, use, offer to sell, or sale within the United States, or importation into the United States, of the testosterone applicator product that is the subject of ANDA No. 206998 or any testosterone applicator product not colorably different therefrom prior to the latest date of expiration of Plaintiffs' United States Patent No. 8,807,861. This permanent injunction order is effective immediately upon the entry of this ruling on this Court's docket.

By stipulation, the parties proceeded to trial only on certain claims of the patents-in-suit, agreeing that disposition of the representative claims controls the disposition of the remaining asserted claims. However, with regard to other non-asserted claims of the patents-in-suit that were not pursued at trial, Plaintiffs have failed to adduce any evidence in support of patent infringement. Because Plaintiffs presented no evidence at trial on the following claims, final judgment of noninfringement shall enter in favor of Defendants on the following claims

(1) Perrigo: claims 11 and 12 of the '944 patent; claims 2-8, 12-18 and 20 of the '861 patent; claim 5 of the '307 patent; claims 2-9, 11-16, 21-22, 24, and 26-35 of the '449 patent.

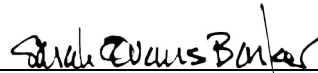
(2) Actavis and Amneal: claims 11 and 12 of the '944 patent; and claims 2-8 and 12-20 of the '861 patent.

(3) Lupin: claims 11 and 12 of the '944 patent; and claims 2-8 and 11-20 of the '861 patent.

By stipulation, final judgment of noninfringement in favor of Actavis, Amneal, and Lupin shall issue as to claims 1-23 of the '307 patent and claims 1-35 of the '449 patent. Dkt. 219; Dkt. 272; Dkt. 284.

IT IS SO ORDERED.

Date: 8/22/2016



SARAH EVANS BARKER, JUDGE  
United States District Court  
Southern District of Indiana

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