**UNITED STATES DISTRICT COURT**
**FOR THE DISTRICT OF NEW JERSEY**

The Honorable Freda L. Wolfson, U.S.D.J.

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| ROCHE PALO ALTO LLC,<br><br>Plaintiff,<br><br>vs.<br><br>RANBAXY LABORATORIES LIMITED, et al.,<br><br>Defendants. | : | Civil Action No. 06-2003<br><br>**OPINION** |

APPEARANCES:

Attorneys for Plaintiff Roche Palo Alto LLC

David E. De Lorenzi, Esq.
Sheila F. McShane, Esq.
GIBBONS P.C.
One Gateway Center
Newark, NJ 07102-5310

Bartholomew Verdirame, Esq.
Michael P. Dougherty, Esq.
Tony V. Pezzano, Esq.
Kent Stevens, Esq.
Jeffrey Z. Y. Liao, Esq.
Vinny Lee, Esq.
Christopher Dove, Esq.
CADWALADER, WICKERSHAM & TAFT LLP
1 World Financial Center
New York, NY 10281

Attorneys for Defendant Ranbaxy Laboratories Limited, et al.

Karen A. Confoy, Esq.
Erica S. Helms, Esq.
STERNS & WEINROTH
A Professional Corporation
50 West State Street, Suite 1400
Trenton, NJ 08607-1298

William R. Zimmerman, Esq.
Darrell L. Olson, Esq.
Joseph F. Jennings, Esq.
Joseph M. Reisman, Esq.
Thomas P. Krzeminski, Esq.
Christy G. Lea, Esq.
Erik T. Anderson, Esq.
KNOBBE, MARTENS, OLSON & BEAR LLP
550 West C Street, Suite 1200
San Diego, CA 92101

Glossary of Abbreviations

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| ANDA | Abbreviated New Drug Application |
| API | Active Pharmaceutical Ingredient |
| CMV | Cytomegalovirus |
| DMF | Drug Master File |
| DTX-# | Defendant's Trial Exhibit |
| DX-#, col. #, ll. # | Patents Exhibit Number, Column Number and Line Numbers |
| FDA | Food and Drug Administration ("FDA") |
| FDCA | Food, Drug and Cosmetic Act |
| GI | Gastrointestinal |
| HCl | Hydrochloride |
| ICDD | International Center for Diffraction Data |
| IV | Intravenous |
| NDA | New Drug Application |
| PCT | Patent Cooperation Treaty |
| PTO | Patent and Trademark Office |
| PTX-# | Plaintiff's Trial Exhibit |
| RaCL # | Ranbaxy Proposed Conclusions of Law |
| RaFF # | Ranbaxy Proposed Findings of Fact |
| RaR # | Ranbaxy Response to Roche's Findings of Fact & Conclusions of Law |
| RoCL # | Roche Proposed Conclusions of Law |

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| RoFF # | Roche Proposed Findings of Fact |
| RoRFF # | Roche Response to Ranbaxy's Findings of Fact |
| RoRCL # | Roche Response to Ranbaxy's Conclusions of Law |
| SF-# | Stipulated facts from the Pretrial Order |
| SGF | Simulated Gastric Fluid |
| STP | Standard Test Procedure |
| USP | United States Pharmacopeia |
| Vx-y:l | Trial Transcript Volume "x" at page "y" and line "l" |
| XRD | X-ray Diffraction |

**WOLFSON, United States District Judge:**

This matter comes before the Court upon a Complaint brought by Plaintiff Roche Palo Alto LLC ("Roche") against Defendants Ranbaxy Laboratories Limited and Ranbaxy Inc. (collectively, "Ranbaxy") for patent infringement in violation of the Patent and the Food and Drug Laws of the United States, Titles 35 and 21 of the United States Code. In response, Ranbaxy filed a Counterclaim against Roche for declaratory judgment that the patent in suit is invalid and that Ranbaxy did not infringe the patent at issue.

This suit is based on the purported infringement on Roche's United States Patent No. 6,083,953 (the "'953 patent"). The '953 patent includes claims to the compound valganciclovir hydrochloride ("HCl") "in crystalline form," pharmaceutical compositions containing that compound "in crystalline form," and methods of using that compound "in crystalline form" to treat herpes simplex virus and cytomegalovirus ("CMV") infections. The instant action, brought under 35 U.S.C. § 271(e)(2), focuses on the meaning of "in crystalline form" and how one determines whether valganciclovir HCl is "in crystalline form." The current action arises from Ranbaxy's filing of an Abbreviated New Drug Application ("ANDA") for approval to market a generic version of Roche's antiviral drug Valcyte®, the tradename for Roche's valganciclovir HCl tablets, prior to the expiration of Roche's '953 patent.

The Court conducted a nine-day bench trial with numerous experts and witnesses testifying as to claim construction, direct infringement, induced infringement, the prior art, the testing of valganciclovir HCl in crystalline form, and the active pharmaceutical ingredient ("API") in Ranbaxy's generic product, valganciclovir HCl in amorphous form. Roche's three theories of infringement are: (1) that Ranbaxy induces infringement because it knowingly uses

a process to manufacture its tablets that permits the presence of crystalline seeds, which promotes the conversion of its valganciclovir HCl to crystalline form when exposed to moisture; (2) that Ranbaxy directly infringes because the valganciclovir HCl in its tablets will convert to the crystalline form upon ingestion; and (3) that Ranbaxy directly infringes because consumers will store Ranbaxy's tablets in pill trays, wherein the valganciclovir HCl will convert to the crystalline form. Roche relies on data from three tests presented by Dr. Jan-Olaf Henck ("Dr. Henck"): the spiking study or crystalline seed study ("seed study"), the simulated gastric fluid ("SGF") study, and the pill tray study, respectively.

Ranbaxy argues that the '953 patent is invalid based on three grounds: anticipation, failure of written description, and obviousness. First, Ranbaxy asserts that the claims of the patent in suit are anticipated. Ranbaxy, however, did not assert its anticipation claim in the Final Pretrial Order and its own experts state that the claims are not anticipated. Second, Ranbaxy asserts that the claimed invention is invalid for lack of written description support because the '953 patent does not discuss how to determine if the compound is "in crystalline form." Such argument, however, is not persuasive. A person of ordinary skill in the art understands that XRD is a reliable means to test for valganciclovir HCl in crystalline form. Further, the Court rejects Ranbaxy's argument that the '953 patent does not cover valganciclovir HCl presenting as a mixture of amorphous and crystalline material. Finally, Ranbaxy contends that the claims of the patent in suit were obvious in light of the prior art because Dr. Lilia Beauchamp's ("Dr. Beauchamp") prior patent, United States Patent No. 5,043,339 (the "'339 patent"), and papers teach valganciclovir, the oral biovailability of the compound, and crystallinity. The Court disagrees because Ranbaxy does not meet its heavy

burden of proving by clear and convincing evidence that the crystalline form of the compound was taught by prior art or is obvious. Thus, the Court finds that the '953 patent is valid.

In light of the evidence presented at trial, the Court does not find that Ranbaxy infringed on Roche's '953 patent. Roche relies solely on the existence of a single XRD peak at 3.5° 2θ to demonstrate the presence of valganciclovir HCl in crystalline form. This premise, as Ranbaxy argues and the Court agrees, is flawed because Roche has not shown by the preponderance of the evidence that only valganciclovir HCl "in crystalline form" exhibits this peak. Therefore, the Court finds that the mere presence of a peak at 3.5° 2θ, without more, cannot be used as a determinative factor to find that Ranbaxy's tablets infringe on the '953 patent. Thus, the Court finds that Roche fails to prove its infringement case.

## I. Overview

### A. Parties

Roche is the assignee of the '953 patent issued on July 4, 2000.[1] SF-3. The patent in suit includes "claims to the compound valganciclovir [HCl] in crystalline form, pharmaceutical compositions containing the compound, and methods of using the compound to treat herpes simplex virus and [CMV] infections." SF-21; DTX-1. On September 28, 2000, Roche filed a New Drug Application ("NDA"), which was approved on March 29, 2001, for valganciclovir HCl tablets for use in treating CMV retinitis in AIDS patients. SF-23. Roche filed a supplemental NDA, on November 11, 2002, to use its tablets in the prevention of CMV disease in certain solid organ transplant patients, which the Food and Drug Administration ("FDA")

[1]In the late 1990s, Roche purchased Syntex (U.S.A.), Inc., which prosecuted, and was the original assignee of, the '953 patent. DTX-1; V1-64:7-9.

also approved. SF-25. Roche sells its valganciclovir HCl tablets under the tradename Valcyte® ("Valcyte"). SF-24.

Defendant/Counterclaimant Ranbaxy Inc. ("RI"), based in Princeton, New Jersey, markets and sells generic drug products throughout the United States that Defendant/Counterclaimant Ranbaxy Laboratories Limited ("RLL") manufactures in India. SF-2. On December 22, 2005, RLL filed ANDA No. 78-078, seeking FDA approval to market generic 450 mg valganciclovir HCl tablets containing the same amount of drug substance and imparting the same medical benefit as Valcyte. SF-4, 8. The FDA has tentatively approved this ANDA. V5-158:11-16. On March 17, 2006, Ranbaxy sent a notice to Roche, pursuant to 21 U.S.C. § 355(j)(2)(B)(iv), certifying that, under the Food, Drug and Cosmetic Act ("FDCA") Section 505(j)(2)(A)(vii), paragraph IV, the manufacture, use, sale, or offer for sale of tablets under Ranbaxy's ANDA would not infringe the '953 patent. PTX-287; SF-5.[2]

**B. Procedural History**

Roche filed a Complaint against Ranbaxy alleging infringement of the '953 patent under 35 U.S.C. § 271(e)(2), on April 28, 2006. On August 15, 2006, Roche filed an Amended Complaint, which added a claim for inducing infringement under 35 U.S.C. § 271(b) and further requested a judgment and decree that the '953 patent is valid and enforceable. SF-12. On September 25, 2006, Ranbaxy filed its Answer and Counterclaims, denying infringement, counterclaiming for noninfringement and invalidity of the '953 patent, and requesting an award

[2]Ranbaxy's only asserted defense was that its product would not infringe the '953 patent because the patent requires the valganciclovir HCl to be "in crystalline form" and Ranbaxy's valganciclovir HCl is in amorphous form. RoFF 5; PTX-287 at 2. Ranbaxy did not assert that the '953 patent is invalid or unenforceable on any ground. RoFF 5.

of attorney's fees and costs, pursuant to the "exceptional case" provision of 35 U.S.C. § 285. SF-13; Answer & Counterclaims ¶¶ A-G. Motions for summary judgment were denied by the Court, after which, a nine-day bench trial was conducted in December of 2008. Subsequently, the parties submitted proposed Findings of Fact and Conclusions of Law, which were supplemented by Reply briefs.

## II. Findings of Fact

### A. CMV, Valcyte, and the '953 Patent

CMV is present in a large percentage of the adult population and generally produces no symptoms. Stipulation Regarding Expert Test. of David M. Snydman, M.D. ("Snydman Stip.") ¶ 5. CMV, however, can cause serious problems in persons with depressed immune systems, such as AIDS patients and organ transplant recipients who are taking immunosuppressive medication to prevent the rejection of a transplanted organ. Id.; V1-84:21-85:23. In AIDS patients, a common manifestation is CMV retinitis, which can result in blindness. V1-85:24-86:2. In organ transplant recipients, CMV can cause rejection of the transplanted organ and increase the cost of medical care by 40 to 80% in the first year after the transplant. Snydman Stip. ¶¶ 6-7.

Valcyte is an orally administered antiviral medication, which the FDA approved for the treatment of CMV retinitis in AIDS patients and for the prevention of CMV disease in organ transplant recipients. V1-56:3-22; PTX-653 at 8. Valcyte is "considered the 'gold standard,' the 'drug of choice,' the 'treatment of choice,' and the 'standard of care' for the prevention and treatment of CMV disease." RoFF 3 (citing V8-159:5-11; V1-86:3-6; Snydman Stip. ¶¶ 8, 22). The active ingredient in Valcyte is the subject matter of claim 1 of the '953 patent,

valganciclovir HCl in crystalline form. Snydman Stip. ¶ 23; V1-55:1-12; PTX-653, ll. 11, 19.

The '953 patent contains six claims. Claim 1, the only independent claim, of the '953 patent reads: "The compound 2-(2-amino-1,6-dihydro-6-oxo-purin-9-yl) methoxy-3-hydroxy-1-propanyl-L-valinate hydrochloride in crystalline form." DTX-1, col. 30, ll. 42-44. The parties agree for purposes of this case that the chemical name refers to valganciclovir HCl, so claim 1 means valganciclovir HCl "in crystalline form." V9-85:11-13. The parties disagree as to the meaning of only one claim term: the requirement that the compound be "in crystalline form." RoFF 10; RaFF 1. Claim 1 is a compound claim and not a manufacturing claim, and covers valganciclovir HCl in crystalline form regardless of how it is produced. V2-108:11-21; see Part III.A., infra. Claims 2-6 relate to a pharmaceutical composition comprising the compound and involve methods of treating viral infections by administering the compound; these claims are not in dispute. See n. 42, infra.

**B. Background of Crystalline and Noncrystalline Materials**

A crystalline material is a material composed of crystals, which are solids that have molecules organized into a repeating pattern in three dimensions, containing a three-dimensional long range order. V2-80:2-8; V6-25:12-17. By contrast, an amorphous material is noncrystalline material that has molecules distributed randomly in a solid material, lacking long range order. V6-25:12-23, 27:19-28:8; V2-80:2-13; V10-175:10-177:1, 180:21-181:2; PTX-772 at 1 ("[T]he crystalline state [of solids] differs from the amorphous state in the regular arrangement of the constituent molecules, atoms or ions into some fixed and rigid pattern known as a lattice."). Amorphous material has greater free energy than crystalline material due to the random distribution of its molecules and is thermodynamically inclined to

convert to crystalline form. RoFF 7; V2-80:2-23. Increases in temperature and exposure to water or humidity can promote this conversion. RoFF 7; V2-80:24-82:2.

Ranbaxy argues that crystalline and amorphous solids are endpoints on a continuum, and there may be numerous noncrystalline, semi-amorphous solids between these endpoints. RaFF 9 (citing V6-26:8-27:12, 29:21-30:23; DTX-803.1). According to Ranbaxy, crystalline and amorphous solids can transition among each other based on the conditions to which the material is exposed, and these transitions can take varying amounts of time. Id. (citing V6-28:9-29:20). Roche maintains, and Ranbaxy does not dispute, that crystalline and amorphous solids may co-exist in the same compound as a mixture. A physical mixture of amorphous and crystalline solids is not the same as a semi-amorphous or a partially ordered solid.[3] V6-37:3-38:10. Roche has not demonstrated that semi-amorphous or partially ordered solids do not exist. At trial, Dr. Henck initially denied the existence of partially ordered solids, and instead asserted that a material can be either crystalline or amorphous with no intermediate state in between these two forms. V2-98:22-24; V10-175:10-16, 180:21-181:2, PTX-572. He admitted, however, that "there are materials that are noncrystalline but [also] not amorphous." V3-60:24-61:7.[4] Further, prior to this litigation, Dr. Henck co-authored an article, entitled Designing a Molecular Delivery System Within a Preclinical Timeframe, in Drug Discovery Today ("Molecular Delivery System") in which he wrote:

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[3]A partially ordered solid is a solid that has some ordering and is considered an intermediate state between crystalline and amorphous material. V6-37:3-18; V10-180:21-181:16.

[4]In fact, Roche initially characterized valganciclovir HCl Forms A and B as semi-amorphous. See Part II.D.1., infra.

> Solids can also produce diffuse scattering. For amorphous and disordered solids, only diffuse scattering is produced. For systems with intermediate order between crystals and amorphous, a mixture of diffuse scattering and Bragg peaks is observed.

DTX-821 at 3 (emphasis added); see V10-181:3-19; V10-179:20-23.11. Thus, Court finds that semi-amorphous or partially ordered solids do exist, as well as mixtures of amorphous and crystalline solids.

### C. X-ray Diffraction Testing

The parties' experts agree that the "the primary method of choice" among persons of skill in the art and the "best technique" for determining whether a material is in crystalline form is powder X-ray diffraction, or "XRD." V2-83:1-6; V6-162:22-164:4; V7-42:6-44:2. Indeed, Ranbaxy relied on XRD as the sole basis for the contention that its valganciclovir HCl is not "in crystalline form" in its Paragraph IV notice sent to Roche. V2-105:4-106:8; PTX-287 at 3.

When a crystalline material is subjected to XRD, the X-rays are diffracted at specific angles ("degrees 2θ" or "°2θ"), resulting in a pattern similar to a fingerprint, which exhibits one or more sharp, well-defined "peaks." V2-83:13-84:14; V6-33:21-34:11. An amorphous material subjected to XRD does not produce peaks, but exhibits broad humps, referred to as a "halo" pattern. V2-93:15-94:9; V6-33:6-20; DTX-183 at 7. According to Ranbaxy, the XRD pattern of a semi-amorphous or a partially ordered solid depends on the amount of order present in the material and can exhibit both an amorphous hump and broad, ill-defined peaks. V6-34:12-20. Conversely, a physical mixture containing both crystalline and amorphous solids exhibits the broad hump characteristic of the amorphous material superimposed on the sharp, well-defined XRD peaks of the crystalline material. V6-34:21-36:11, 155:15-156:20. Thus, the peak positions of a crystalline solid will not change if mixed with an amorphous solid nor

will it exhibit the broad, ill-defined peaks characteristic of a partially ordered solid. V6-36:12-37:2.

At trial, Dr. Henck testified that noncrystalline solids with intermediate order, which exhibit one low angle peak, do not exist. V10-178:13-17. The Court finds this position unpersuasive in light of Dr. Rogers' testimony and the different XRD patterns presented at trial. Indeed, Dr. Henck admits that solids in different states produce different XRD patterns. DTX-821 at 3; see Part II.B., supra. Thus, the evidence shows that noncrystalline solids with intermediate order do exist and can exhibit a single low angle peak. See Part II.D.2., infra.

### D. Valganciclovir HCl Forms and XRD Testing

#### 1. Valganciclovir HCl Forms

Valganciclovir HCl exists in at least two forms: crystalline and amorphous.[5] V6-156:21-159:2. In its March 1996 "RS-79070-194 Preformulation Book" ("Preformulation Book"), Roche stated that "[t]here are two crystalline forms (X and Y) and two metastable forms (A and B) of the racemic mixture of the diastereomers of [valganciclovir HCl]." DTX-589 at 9; V6-38:13-39:20; V3-65:18-66:2. Roche contrasted the two crystalline forms of valganciclovir HCl, Forms X and Y, with the two noncrystalline, metastable forms of valganciclovir HCl, Forms A and B. V6-38:25-39:7, 46:1-9; V3-66:22-25. Roche described valganciclovir HCl Form A as a "semi-amorphous, flake-like material" that is "not stable under ambient conditions," which "converted to Form X" under accelerated conditions of 98% relative humidity for three days. DTX-104 at 16; V6-168:9-21. Roche described Form B as a

[5]Roche, however, argues that the only two forms are crystalline and amorphous. V10-175:10-16.

"gelatinous amorphous material" that is "not stable under ambient conditions" and "converted to a crystalline form." DTX-104 at 16; V4-168:22-25; V2-142:8-143:1. Thus, Roche determined that Forms A and B are neither crystalline nor stable, and converted to crystalline under certain conditions. DTX-589 at 15, 26.

In July 1998, Dr. Henck's employer, SSCI, conducted various tests on the compound valganciclovir HCl for Roche. DTX-216; V6-46:10-19. SSCI repeated the statement found in Roche's Preformulation Book that "[t]here are two crystalline forms (X and Y) and two metastable forms (A and B) of the racemic mixture of the diastereomers of [valganciclovir HCl]." DTX-216 at 4. SSCI also determined that there was little difference between the various forms (crystalline and metastable) and found that the XRD patterns of "X and A are difficult to distinguish." DTX-216 at 4-5.[6] SSCI speculated that while the XRD patterns of Forms X and Y are similar, the XRD pattern of Form A "could be interpreted as arising from poorly crystalline Form X." Id. at 4. Therefore, Roche characterized Forms A and B as less stable than the "very crystalline" Forms X and Y. Id. at 9.

Roche submitted its NDA for Valcyte to the FDA, on August 15, 2000, six weeks after the '953 patent issued with claims limited to valganciclovir HCl "in crystalline form;" Roche's prior attempts to obtain a patent for valganciclovir HCl had been unavailing and it was only after adding the claim limitation of "in crystalline form" that it was successful. DTX-659; DTX-1. In its NDA, Roche wrote: "There are two crystalline forms of valganciclovir HCl (termed X and Y) and an amorphous form." DTX-659 at 1; V3-67:1-15; DTX-803.3;

[6]SSCI did not identify a peak at 3.5° 2θ as distinguishing between the crystalline and metastable forms. RaFF 16.

V6-48:22-49:4, 49:16-22. Roche stated that "[n]o crystalline forms other than form X and Y have been observed." DTX-659 at 1; V3-67:16-68:11. Roche summarized its studies on valganciclovir HCl explaining:

> Early in the development process, two metastable forms (originally called A and B) were thought to be present; however, these appear to be merely amorphous material containing low amounts of crystalline material.

DTX-659 at 1; see also DTX-803.8; V6-55:16-56:19, 165:1-167:8; V3-141:15-142:8. Thus, contrary to its prior characterizations, in its NDA, Roche changed its own definition of these metastable forms by claiming that they do not exist; rather, Roche re-defined these "metastable forms" as merely mixtures of amorphous and crystalline material, and therefore, classified them as containing Forms X and Y, making them "in crystalline form."[7]

Although Ranbaxy does not dispute that amorphous and crystalline valganciclovir HCl can co-exist as a mixture, it contends that additional forms of valganciclovir HCl also exist. Specifically, Ranbaxy submits that there are other semi-amorphous forms between pure amorphous and pure crystalline; for example, Ranbaxy cites to Roche's own initial descriptions of Forms A and B, of valganciclovir HCl. For support, Ranbaxy relies on the opinion of Dr. Robin D. Rogers ("Dr. Rogers"), who is an expert in solid state chemistry, XRD, and various aspects of crystallinity. V6-21:1-25:10; DTX-656. Dr. Rogers explained that Form A is a partially ordered solid between crystalline and amorphous on the continuum. DTX-803.09;

[7]While Roche asserts that there is "no inconsistency between Roche's description of Forms A and B" in its Preformulation Book and its NDA, RoRFF 4, the Court disagrees. Indeed, this re-characterization is essential to the disagreement between the parties – whether semi-amorphous or partially ordered solids exist.

V6-59:7-60:20.[8] Consistent with Roche's initial characterizations and Ranbaxy's submissions, the Court finds that there are other possible, semi-amorphous forms of valganciclovir HCl, and these other forms are not "in crystalline form." V6-58:11-21, 67:15-20; see Part III.A., infra. In contrast, Roche claims that Forms A and B do not exist because they are merely mixtures of crystalline and amorphous forms, as opposed to semi-amorphous material. The Court finds, however, that Roche has failed to prove that position.

### 2. Whether a Sole Peak at 3.5° 2θ Indicates Valganciclovir HCl in Crystalline Form

As a preliminary matter, the parties' experts agree that every XRD pattern of crystalline valganciclovir HCl, namely, Forms X and Y, contain a peak at 3.5° 2θ, which is used as a "reference peak to determine crystalline valganciclovir [HCl]." V2-131:15-22. "In Dr. Henck's expert opinion, a peak at 3.5° 2θ is the 'distinguishing fingerprint' or 'signature peak' for identifying valganciclovir [HCl] in crystalline form." RoFF 41 (citing V2-131:23-132:2, 10-19). Ranbaxy's expert, Dr. Rogers, agrees that crystalline valganciclovir HCl always has an XRD peak at 3.5° 2θ, V6-169:25-170:5, and admits that he has never seen an XRD pattern of crystalline valganciclovir HCl that did not have an XRD peak at 3.5° 2θ. V6-170:6-9. Further, Ranbaxy's expert Dr. Jeremy Karl Cockcroft ("Dr. Cockcroft"), an expert in solid state structural characterization, agreed that he has never seen an XRD pattern of crystalline valganciclovir HCl that did not have a peak at 3.5° 2θ, and upon inquiry by the Court, that in this case "distinctive" peak and "strongest" peak have the same meaning. V7-44:22-45:10.

The parties, however, disagree whether a single peak is determinative of whether a

[8] "The details of Form B were not similarly discussed by either party at trial." RaFF 20.

sample of valganciclovir HCl is in crystalline form; specifically, whether a sole XRD peak at 3.5° 2θ establishes the presence of valganciclovir HCl "in crystalline form." Dr. Henck testified that a person of skill in the art understands that the presence of a compound "in crystalline form" is detected by an XRD pattern that records "at least one peak." V2-103:16-104:2, 17-22. Citing to Dr. Henck, Roche asserts that it is accepted practice among crystallographers that when looking at a sample that consists of a mixture of different compounds, and there is one unique peak that can identify a specific crystalline material and no other component of the mixture exhibits a peak at that position, a single peak in an XRD is enough to identify that specific compound. V2-84:15-25, 132:3-9, 133:14-17. Roche argues, and Dr. Rogers agrees, that when the ingredients of a sample are known, a single peak can be determinative of whether a specific compound in the sample has crystalline material. RoFF 39; RaFF 22-23.[9] On the other hand, a single peak cannot be used to identify the presence of a specific material in an unknown sample when that single peak is not unique to the material being assessed. V6-60:21-63:7.

In this case, the excipients, coating, and active ingredient in Ranbaxy's tablets are all known.[10] V6-171:4-18; V2-132:10-19. The parties' experts agree, however, that Forms X and

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[9]"Peer-reviewed scientific literature confirms that the presence of a single distinctive XRD peak is sufficient to identify the presence of a given compound in crystalline form within a mixture of other known materials." RoFF 39, n. 1.

[10]Another ingredient, magnesium stearate, in Ranbaxy's tablets also peaks around 3.552º 2θ. See Part II.F.1.a., infra. According to Roche, this peak is typically weaker than that of valganciclovir HCl, and thus, it should not interfere with the defining peak of crystalline valganciclovir HCl. V2-132:20-25, 133:1-13. The Court need not even reach the issue of whether the peak from magnesium stearate is problematic to Roche's premise that 3.5º 2θ is sufficient to show crystalline form because Roche cannot show that 3.5º 2θ alone establishes valganciclovir HCl in crystalline form.

Y of valganciclovir HCl, as well as what Roche originally categorized as Forms A and B, demonstrate a strong distinctive peak at 3.5º 2θ. V3-68:12-22; V6-57:7-59:3. Thus, the inquiry is whether the mere presence of a peak at 3.5º 2θ sufficiently distinguishes valganciclovir HCl in crystalline form – whether it is pure crystalline or in a mixture of crystalline material and other forms – from other possible semi-amorphous forms of valganciclovir HCl. The Court finds that it does not.

Dr. Henck contends that an XRD peak at 3.5° 2θ alone is sufficient to establish the presence of crystalline valganciclovir HCl, V3-61:13-24; he asserts that this peak appears in what Ranbaxy might refer to as noncrystalline forms because these forms are in actuality merely mixtures of amorphous and crystalline valganciclovir HCl, and not distinctive, separate forms of semi-amorphous material. V3-142:9-143:4. Underlying Dr. Henck's conclusion is his assumption that there are no semi-amorphous forms of valganciclovir HCl, and that Roche's early categorizations that Forms A and B are semi-amorphous were inaccurate. Dr. Henck, however, fails to offer support for this conclusion.[11] Rather, he admits that a peak at 3.5° 2θ does not distinguish among the XRD patterns for Forms X, Y, and the contested Forms A and B; in fact, he made no effort to determine the peaks necessary to distinguish among these forms. V3-68:12-22; see V6-44:13-45:25, 58:22-9, 59:3. Further, in Roche's Preformulation Book, the XRD patterns for pure crystalline Forms X and Y, as well as "metastable" Forms A and B each contained a prominent XRD peak at 3.5° 2θ. DTX-104 at 19, 23-24. Because of its own unproven assumption that semi-amorphous forms of valganciclovir HCl do not exist,

[11]Instead, Dr. Henck asserts that because these forms demonstrate the same peak as Forms X and Y, this indicates that they contain crystalline.

Roche concludes that a peak at 3.5° does uniquely identify valganciclovir HCl in crystalline form. However, the Court finds this assumption erroneous, and thus, Roche's own testing does not establish that a peak at 3.5° is unique to the crystalline forms. V6-44:1-45:25; DTX-803.02.

Dr. Rogers explains, and the Court agrees, that in this case, a peak at 3.5° 2θ alone does not establish the presence of valganciclovir HCl "in crystalline form" because other possible semi-amorphous forms may also exhibit a peak at this position. V6-63:8-22. While the height of the peak or limit of detection may vary based on whether the API is contaminated with valganciclovir HCl "in crystalline form," see Part II.E.1., infra, and thus a single peak at 3.5° 2θ alone with more definitive characteristics could be sufficient for detection, there is insufficient evidence in the record as to what the height of the peak or the area under the curve should be for the various forms of valganciclovir HCl, and specifically for Forms X and Y. Furthermore, Roche does not explain nor demonstrate by a preponderance of the evidence that the peak cannot be formed by other possible semi-amorphous forms. See Part III.B.1., infra (discussing how this peak could be the result of semi-amorphous material or some other excipient mixed with valganciclovir HCl). Thus, based on the record, because the mere presence of a peak at 3.5° 2θ does not distinguish between valganciclovir HCl "in crystalline form," Forms X and Y, and other possible semi-amorphous forms, that particular peak cannot alone establish the presence of valganciclovir HCl in crystalline form in Ranbaxy's tablets.

**3. Multi-Peak "Fingerprint" Indicates Crystalline Valganciclovir HCl**

In its NDA, Roche provided XRD patterns for Forms X and Y, DTX-659 at 3, the only two known and recognized forms of crystalline valganciclovir HCl. V2-131:8-14. The XRD

patterns for crystalline Forms X and Y show, inter alia, the strongest peak at 3.5° 2θ, with additional strong peaks and 9.5° and 11.8° 2θ, which is consistent with Roche's Preformulation Book. DTX-104 at 19; DTX-803.02; V2-134:7-135:15; V3-93:8-17; V6-40:10-41:11; V7-18:15-24. Roche's NDA submission also contained an XRD pattern for amorphous valganciclovir HCl, showing the hump characteristic of amorphous material and no peaks. DTX-659 at 2, 5; DTX-803.06-07; V6-54:3-55:8. The XRD patterns for the contested Forms A and B show a strong peak at 3.5° 2θ, but do not show the peaks at 9.5° and 11.8° 2θ, characteristic of crystalline Forms X and Y. V6-42:25-43:7, 43:13-25, 56:20-57:20; DTX-104 at 23-24. Thus, according to Ranbaxy, semi-amorphous Forms A and B of valganciclovir HCl may be distinguished from the crystalline Forms X and Y based on the lack of the presence of peaks at 9.5° and 11.8° 2θ. V6-58:22-59:6.

Roche asserts that every XRD pattern of crystalline valganciclovir HCl contains a peak at 3.5° 2θ, but the presence, as well as the height, width, and position of a peak, or absence of peaks at other angles, such as 9.5° and 11.8° 2θ, can vary based on numerous factors, including but not limited to, preparation of the sample, how the sample was obtained, and other components in the sample.[12] RoFF 53; V2-91:24-93:14. For example, samples of both Forms X and Y of crystalline valganciclovir HCl prepared with isopropanol solvent display a peak at 3.5° 2θ as well as at 9.5°, 11.8°, 14.7°, 15.6°, and 17.1° 2θ. V2-134:7-135:21; DTX-104 at 16. A sample of crystalline valganciclovir HCl prepared with a different solvent, ethanol, still

[12]Roche has not offered evidence demonstrating that the height of the peak or area under the curve differs based on whether the valganciclovir HCl is in crystalline or **semi-amorphous** form. Only Ranbaxy offers a rejection test if the limit of detection is above the testing sample, as determined by a computer scan of the XRD patterns. See Part II.E.1., infra. Ranbaxy's test, however, does not distinguish among the causes for this peak. See Id.

contains a peak at 3.5° 2θ, but only has weak peaks at 9.5° and 14.7° 2θ and no peaks at 11.8°, 15.6°, and 17.1° 2θ. V2-135:22-137:10; PTX-281A. In another sample of crystalline valganciclovir HCl obtained from an ethanol solvent and then exposed to ambient conditions for two hours, the XRD pattern has a peak at 3.5° 2θ and weak peaks at 9.5° and 11.8° 2θ and no peaks at 14.7°, 15.6°, and 17.1° 2θ. V2-137:11-138:14; PTX-282A. In the Form X and Y samples of crystalline valganciclovir HCl prepared with isopropanol and the two samples of valganciclovir HCl prepared with ethanol, PTX-281A and PTX-282A,[13] the common peak found in all the samples is at 3.5° 2θ. V2-139:4-8; PTX-33. Ranbaxy's experts, Drs. Rogers and Cockcroft, also agreed that XRD patterns PTX-281A and PTX-282A, which Dr. Rogers contends are XRD patterns of noncrystalline Form B, V6-196:25-197:14, of valganciclovir HCl prepared with ethanol do not include peaks at 9.5 and 11.8° 2θ. V7-60:15-62:5.

While the parties disagree what the multi-peak fingerprint of valganciclovir HCl in crystalline form should look like, if one even exists, the Court need not decide the exact fingerprint here. Roche could have presented evidence that a peak occurring at least at one other angle in addition to 3.5° 2θ distinguishes valganciclovir HCl in crystalline from noncrystalline form, but it has not. Instead, Roche failed to present any evidence that Ranbaxy's tablets peak at any location besides 3.5° or 3.552° 2θ, which is the peak for the

[13]Roche argues that PTX-281A and PTX-282A are unnamed crystalline forms of valganciclovir. RoFF 54-55. Roche essentially asserts that the XRD patterns of "Forms A and B" are in fact XRD patterns of mixtures of crystalline and amorphous material that are prepared in different solvents. The Court finds, however, that merely because such a mixture may exhibit a similar XRD pattern to that of the contested Form A or B, it does not prove that Form A or B cannot possibly exist as well. Furthermore, preparing a mixture in different solvents might in fact create semi-amorphous material. Indeed, Roche's Preformulation Book states that treating the compound with ethanol, the solvent used in PTX-281A and PTX-282A, produced Form B. DTX-589 at 14; PTX-281A; PTX-282A.

excipient magnesium stearate.[14] V2-132:20-25. As discussed herein, a peak at 3.5° 2θ alone is insufficient to establish the presence of valganciclovir HCl in crystalline form. See Part II.D.2., supra.

Accordingly, the Court finds that although the presence of valganciclovir HCl "in crystalline form" detectable by XRD is sufficient to infringe the '953 patent, none of Dr. Henck's XRD patterns for Ranbaxy's tablets identify any additional peaks, such as at 9.5° or 11.8° 2θ, or other features, such as the height of the peak or area under the curve, that might uniquely identify the presence of valganciclovir HCl in crystalline form. V6-149:16-20; see Parts III.A. & III.B.1., infra.

**E. Ranbaxy's Tablet Composition & Testing**

Ranbaxy was aware that the '953 patent was directed to valganciclovir HCl "in crystalline form," which is why it purportedly developed an amorphous valganciclovir HCl product to avoid the patent in suit. V4-12:17-13:3. According to Ranbaxy, it spent two years and invested approximately $3.7 million in developing a stable amorphous valganciclovir HCl product. V4-11:17-12:4, 89:2-7. Ranbaxy's ANDA and Drug Master File ("DMF") specify that the valganciclovir HCl API must be amorphous, DTX-625 at 4; DTX-626 at 2, and the DMF describes the carefully controlled manufacturing, handling, and storage processing to ensure that Ranbaxy's API is amorphous. DTX-49; DTX-624. Ranbaxy's process for making the amorphous API and Ranbaxy's tablet formulation are different from Valcyte. V4-27:2-8, 106:20-107:25; Sharma Dep., dated Apr. 18, 2007, at 157:2-21.

[14]Dr. Henck testified that this weak peak from magnesium stearate does not "interfere" with the ability to identify crystalline valganciclovir HCl in Ranbaxy's tablets. V2-133:1-13.

Associate Directors of Chemical Research at Ranbaxy, Dr. Chandra Khanduri ("Dr. Khanduri") and Mukesh Sharma ("Sharma"), testified that Ranbaxy's API manufacturing process produces a solid crystalline intermediate for ease of handling and operating prior to subjecting the API to a spray-drying process.[15] V4-18:25-19:21, 26:4-9, 77:2-18, 85:11-17; V2-7:2-11 (Video Dep. Tr. 176:21-177:7, 179:6-180:7). Next, the crystalline intermediate is mixed in a vessel with deionized water in which it completely dissolves into a liquid solution and it is then spray-dried into an amorphous powder. V4-31:23-36:12; DTX-49. Dr. Khanduri's and Sharma's testimony demonstrate that Ranbaxy knew that Roche's '953 patent claims valganciclovir HCl in crystalline form and that Ranbaxy's valganciclovir HCl tablets could not be in crystalline form because of the '953 patent. V2-4:15-5:9, 6:15-16; V4-73:13-74:16; PTX-380.

Roche contends, however, that Ranbaxy manufactures its API in crystalline form, then subjects it to a spray-drying process to purportedly convert it to amorphous form, V2-125:14-25, 126:16-127:13; PTX-329, but that this process does not ensure its valganciclovir HCl is 100 percent amorphous.[16] Rather, according to Dr. Henck, crystalline seeds, which promote crystallization, remain. V2-127:14-18. However, Roche's testing fails to show that Ranbaxy tablets contain any valganciclovir HCl in crystalline form. See Part II.F., infra.

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[15]Spray-drying is a common process for producing amorphous material. V4-17:25-18:2. According to Roche, however, Ranbaxy took full advantage of the teachings of the '953 patent regarding manufacturing its valganciclovir HCl in crystalline form for the purpose of ease of manufacturing and handling, which Ranbaxy's Patent Cooperation Treaty ("PCT") application for its valganciclovir HCl cited to "three times." V2-124:11-14, 125:4-13; V4-55:18-56:11; PTX-303 at RVHRX0025671.

[16]Roche does not contend, however, that XRD testing of Ranbaxy's tablets shows anything other than amorphous valganciclovir HCl at release or on stability testing.

### 1. Ranbaxy's Testing

Ranbaxy performs two types of XRD tests: (1) an identification test on the API to confirm that it is amorphous and (2) a detection test on both the API and tablets to ensure there is no detectable crystalline contamination. V5-64:8-19. Ranbaxy's identification test is described in its ANDA and DMF, as submitted to the FDA. V4-43:5-44:3; DTX-625-26. "The detection test is internal to Ranbaxy, but such release specifications can only be changed in response to an FDA query." RaFF 71 (citing DTX-84; DTX-382; V5-51:5-21, 120:24-121:1).

Ranbaxy's XRD limit of detection test indicates the minimum level of crystalline valganciclovir HCl that can be detected, V5-89:11-14; see also V5-86:17-21, 89:3-9; V6-77:7-11, such a limit is determined mathematically by repeatedly testing known amounts of a particular material. V6-78:19-79:20; V5-92:13-93:3. A response or "peak" cannot be distinguished from "noise"[17] in concentrations below this limit of detection. V5-89:15-19; V6-79:21-80:4. Thus, even though there may visually appear to be a "peak" in an XRD pattern of a tested sample, if such a "peak" is below the limit of detection, then it cannot accurately be attributed to crystalline contamination rather than noise. RaFF 73; V5-104:1-105:12. "The limit of detection for crystalline valganciclovir HCl in Ranbaxy's API is 0.5%, which correlates to a limit of detection for the tablets of 0.8%." RaFF 74; V5-94:3-5, 100:2-14. Dr. Henck did not know and did not assess the limit of detection in Ranbaxy's Standard Test Procedure ("STP"). V3-118:5-13. In its XRD detection test, Ranbaxy compared the test sample "to a standard that is spiked at the limit of detection: 0.5% crystalline material." RaFF 75;

[17]As Dr. T.G. Chandrashekhar states, "noise" is defined as disturbances in the baseline "caused because of the instrument or electronic disturbances." V5-89:22-25. It is not due to the presence of a particular material at issue during the test.

V5-123:3-128:21.[18] To prepare the standard, Ranbaxy prepared a placebo that contains all of the excipients in the same proportions as in Ranbaxy's tablets, but lacked the drug and coating, and was spiked with 0.5% crystalline valganciclovir HCl. DTX-382; DTX-367 at 101; V4-137:17-139:6; V5-97:20-98:10, 99:16-100:1; V6-88:12-23. Ranbaxy then used a computer to calculate and compare the XRD scans, particularly the area under the curve at 3.5° 2θ, of the standard and sample to determine if the sample showed a peak above the limit of detection. V5-97:20-98:10; DTX-382.

Dr. T.G. Chandrashekar ("Dr. Chandrashekar"), Ranbaxy's Vice President of Global Quality and Analytical Research, has read and interpreted thousands of XRD patterns, including those generated by his department. Dr. Chandrashekar testified that Ranbaxy has chosen to detect the "presence of crystalline valganciclovir hydrochloride" based "solely by an [XRD] peak at 3.5° 2θ," which it has done since 2005. V5-61:9-10, 62:3-64:19, 140:9-17. Shalender Gupta ("Mr. Gupta"), an Analyst at Ranbaxy, similarly testified that "an XRD peak at 3.5° 2θ" indicates the "presence of crystalline valganciclovir HCl." V2-5:10-17. Drs. Rogers and Cockcroft acknowledged that Ranbaxy relies "solely" on a peak at 3.5° 2θ to detect the presence of valganciclovir HCl in crystalline form. V6-171:25-173:1; V7-49:3-24. Therefore, Roche argues Ranbaxy's STP demonstrates that a single peak at 3.5º 2θ is sufficient to demonstrate the presence of crystalline valganciclovir HCl. See RoFF 44-46.[19]

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[18]Roche asserts that after the spray-drying process, Ranbaxy only rejects samples above the limit of detection, and therefore, Ranbaxy permits an API containing up to 0.5% crystalline valganciclovir HCl to pass muster. RoFF 22.

[19]For support, Roche directs the Court to Ranbaxy's STP, PTX-338 and PTX-339; for analyzing batches of its API, Ranbaxy relies on the presence of a peak at 3.5° 2θ as the sole criterion for identifying crystalline valganciclovir HCl, and for determining "low levels of

Ranbaxy, however, asserts that when it developed its STP, Ranbaxy was only aware of two forms of valganciclovir HCl: crystalline and amorphous.[20] V5-103:5-14. As a result, it simply chose the peak at 3.5° 2θ, as a rejection test, because crystalline valganciclovir HCl exhibits its most intense peak at this location, thereby providing the lowest possible limit of detection of crystalline contamination. RaFF 76-78. If the area under the curve at 3.5° 2θ in the XRD pattern of an API sample is less than the area under the curve of the reference standard having 0.5% crystalline valganciclovir HCl, then Ranbaxy permits the sample to pass through for tablet manufacturing. V5-121:11-122:10; V2-128:4-129:3; DTX-802.09-10; PTX-338 at RVHRX0030933.[21] "Conversely, if the area of a peak at 3.5° 2θ is larger than the area of the peak at 3.5° 2θ of the standard, the sample fails." RaFF 76. Therefore, the Court can conclude that, at best, Ranbaxy is aware that its tablets can "theoretically . . . include up to

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contamination, if any, of crystalline valganciclovir hydrochloride" because the "peak at 3.5 [°2θ] is distinct and has the maximum intensity compared to all the other distinctive peaks observed in the pattern." RoFF 45-46. In addition, Roche cites to PTX-290, in which a Ranbaxy employee wrote "[q]ualitatively crystalline content clearly detected" next to two XRD analyses and refers to a peak at 3.5° 2θ. RoFF 46. Further, Roche asserts that Ranbaxy uses the words "crystalline form" to describe the crystalline portion of a mixture of crystalline and amorphous valganciclovir HCl, as detected by XRD, in its PCT application. RoFF 47.

[20]Ranbaxy contends that it was not even aware of any semi-amorphous forms of valganciclovir HCl that can also peak at 3.5° 2θ. RaFF 78. Roche never published its internal testing showing multiple forms, i.e., crystalline forms X and Y and its initially characterized semi-amorphous forms A and B. V6-57:21-58:10; V7-13:22-14:3.

[21]Roche offers an internal Ranbaxy email, dated August 18, 2005, which "identifies several batches of API tested by Ranbaxy's [STP], including batch number 1546609, as containing crystalline material below 0.5%: "Complies with WS. Crystalline valganciclovir HCl peak is det[e]cted in all the above mentioned batches but it is below [limit of detection]. [Limit of detection] is 0.5%." V2-129:4-130:6; V5-141:8-142:1; PTX-334A. API batch 1546609 was used to make Exhibit Batch #1557337 of tablets that is the subject of Ranbaxy's ANDA 78-078. V5-142:7-143:4; V2-130:7-20; PTX-387; DTX-611; PTX-286 at RVHRX0001457." RoFF 23.

0.5% crystalline valganciclovir hydrochloride." RoFF 22; V5-121:24-125:18, 128:8-21.

Ranbaxy argues that its STP cannot, and is not designed to, detect the presence of crystalline material below the limit of detection nor distinguish whether any peak at 3.5° is attributable to crystalline Forms X or Y, or other possible semi-amorphous forms. Ranbaxy is not concerned about the precise nature of the contamination in a rejected sample and performs no further testing to identify the contamination. V5-101:6-25. Rather, Ranbaxy uses its STP to provide a simple pass/fail test that can be performed easily in a manufacturing setting, V5-87:19-24, to ensure that Ranbaxy does not pass samples that contain detectable crystalline contamination.[22] RaFF 76; V5-101:2-5. The Court finds Ranbaxy's internal testing uses a peak at 3.5° 2θ as only a means to reject a sample, without determining what actually caused the peak. It does not sufficiently distinguish whether this is the result of the crystalline or semi-amporphous forms of valganciclovir HCl or merely noise, and thus, Ranbaxy's testing is not helpful in that regard.

**2. Ranbaxy's Argument that its API is Amorphous Valganciclovir HCl**

Ranbaxy asserts that its own testing and its expert's XRD testing show that Ranbaxy's API and tablets are amorphous and have no crystalline contamination at release or during accelerated or long term stability testing. RaFF 80-81. Ranbaxy performed its XRD identification and detection tests in accordance with its STP on each API batch used to make its tablets, on the tablets after manufacture ("at release"), and performed accelerated and long term stability testing at various time intervals and conditions after manufacture of its API and

[22]Thus, Ranbaxy's and Dr. Henck's uses of a peak at 3.5° are quite different because while Dr. Henck attempts to use the presence of a peak at 3.5° as affirmative proof of crystalline valganciclovir HCl, Ranbaxy uses this peak as a rejection criterion. V6-209:9-23.

tablets. V5-76:4-10, 76:17-77:1, 110:19-111:16. Dr. Rogers analyzed Ranbaxy's XRD results and found that XRD patterns from Ranbaxy's API, as made and as tested for stability, did not contain "peaks characteristic of the crystalline or the metastable forms of valganciclovir HCl." RaFF 82-83. Dr. Cockcroft also tested Ranbaxy's tablets and concluded, based on the absence of the peaks at 3.5°, 9.5° and 11.8° 2θ, that they contained amorphous and not crystalline valganciclovir HCl. V7-18:15-24, 26:13-27:3, 35:14-36:1. Ranbaxy asserts that "[b]y relying on the three strongest XRD peaks, [Dr.] Cockcroft followed the guidelines issued by the International Center for Diffraction Data ("ICDD"), which instruct that characterization by XRD should be based on the three most prominent peaks, as listed in the Hanawalt Index. V7-8:11-15:7." RaFF 84. Dr. Rogers agreed with these findings. Id.; V6-99:6-16.

Dr. Rogers' analysis of Ranbaxy's and Dr. Cockcroft's data, however, were of tablets that were stored in the bottle and/or subjected to a nitrogen environment, which Dr. Cockcroft admitted were unlike the indoor conditions to which the tablets would be exposed during ordinary use by solid organ transplant and AIDS patients. RoFF 75; V7-56:6-24, 57:1-7, 57:14-17. Dr. Rogers did not personally conduct XRD testing on Ranbaxy's or Roche's valganciclovir HCl tablets, nor make any findings with regard to Ranbaxy's valganciclovir HCl tablets that were taken out of the bottle and exposed to ambient conditions. RoFF 75; V6-188:2-6, 188:20-189:23. Similarly, Dr. Cockcroft did not analyze Ranbaxy's valganciclovir HCl API or tablets that were exposed to such conditions. V7-51:11-22, 52:16-21, 55:21-56:5. Therefore, the Court finds that Ranbaxy's testing was conducted in conditions very different from the actual conditions to which patients subject the tablets, and thus, do not show that Ranbaxy tablets' API is amorphous valganciclovir HCl when used and stored under normal

patient conditions.

### 3. Ranbaxy's Efforts to Prevent its Valganciclovir HCl From Crystalizing

Ranbaxy's tablets are comprised of the drug valganciclovir HCl and three excipients: crospovidone (disintegrant), microcelac 100 (filler), and magnesium stearate (lubricant), and an Opadry coating.[23] DTX-43 at 34 (Table 20); V4-98:19-99:1; V5-41:3-44:20, 46:21-47:5. Dr. Henck observed that the API "acts like a sponge" and absorbs water very quickly and easily. V2-115:9-22. Ranbaxy's API is hygroscopic, which means that it has a tendency to absorb moisture when exposed to the atmosphere, and once the tablets are taken out of its packaging and exposed to normal humidity conditions, which contain moisture, it will convert to some "crystalline" form.[24] See RoFF 31; V5-137:22-140:8; V2-4:15-5:9, 117:9-17; V4-72:22-73:1. Ranbaxy's own data shows that its API converts to crystalline after being exposed for 3 days to conditions of 40°C and 75% relative humidity, and converted to crystalline after being exposed for 7 days to room temperature and 45% relative humidity, which are normal ambient conditions. V5-29:14-33:24, 77:6-8; PTX-367 at RVHRX0033329; PTX-361 at

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[23]Roche complains that none of these excipients protects Ranbaxy's API in the core of the tablet from moisture. RoFF35; V2-7:21-8:8; V2-7:21-8:8; V5-41:3-7, 44:17-45:1, 45:17-46:13; V2-109:21-110:11, 116:13-117:3; PTX-286 at RVHRX0000934. The ingredients Ranbaxy uses in the coating for its valganciclovir tablets are Opadry pink, polyethylene glycol-400, methylene chloride, and acetone, which do not prevent moisture absorption. RoFF 35; V5-46:21-48:25; V2-115:23-117:3. According to Roche, Ranbaxy uses this coating for "aesthetics" – to make them look like Valcyte – and it has taken no precautions to formulate its tablets in a way to prevent its valganciclovir HCl API from absorbing moisture. RoFF 35-36; V5-46:21-48:25; V2-117:4-8. Ranbaxy has not demonstrated that it intends to change its formulation now that it has learned of Roche's contention of infringement. RoFF 36.

[24]Roche, however, fails to show by a preponderance of the evidence that Ranbaxy's API even contains valganciclovir HCl "in crystalline form." See Part III.B.1., infra.

RVHRX0032400-01. Ranbaxy's XRD data also shows that its valganciclovir HCl converts to crystalline when stored in open bottles at standard ambient temperature and relative humidity conditions. V5-136:4-137:9; PTX-322 at RVHRX0027852.

Roche asserts that Ranbaxy is aware that its valganciclovir HCl API is hygroscopic and crystallizes when exposed to the atmosphere, and as a result, Ranbaxy packages its API in three layers of vacuum-sealed polymer bags under nitrogen conditions, uses molecular sieves to absorb moisture, and then places the triple-bagged API in a sealed drum. RoFF 33. Further, Ranbaxy admitted in its Patent Cooperation Treaty ("PCT") application that its valganciclovir HCl must be stored "under nitrogen in the strict absence of atmosphere or other water" in order to prevent such crystallization. V2-119:13-120:11; PTX-303 at 8.[25]

**F. Roche's Testing**

To prove infringement, Roche uses three types of testing: the spiking study, which is also referred to as the crystalline seed study ("seed study"); the simulated gastric fluid ("SGF") study; and the pill tray study. In all three studies, Dr. Henck used XRD testing to look for a single peak in the low angle region, specifically a peak at 3.5° 2θ. V10-177:9-13, 180:15-17. However, as discussed herein, because the experts agree that Forms A, B, X and Y all show a peak at 3.5° 2θ, the presence of this single peak without more does not distinguish between the existence of valganciclovir HCl in crystalline and other possible semi-amorphous forms. See Part II.D.2., supra; Part III.B.1., infra. Dr. Henck asserts that an XRD peak at 3.5° 2θ alone is sufficient to establish the presence of crystalline valganciclovir HCl because the peak is due to

[25]Roche, however, bears the burden of demonstrating that Ranbaxy's tablets infringe the '953 patent before the Court may address the specific intent required in the infringement by inducement analysis. See Part III.C., infra.

the crystalline material located in the Forms A and B, which he opines are merely mixtures of amorphous and crystalline valganciclovir HCl. V3-61:13-24, 142:9-143:4. He admits, however, that he made no effort to distinguish the XRD patterns among the crystalline and other possible semi-amorphous, noncrystalline forms because in his opinion noncrystalline forms simply do not exist. V3-68:12-22; see V6-44:13-45:25, 58:22-9, 59:3. Further, in Roche's Preformulation Book, the XRD patterns for stable crystalline Forms X and Y as well as noncrystalline, unstable, semi-amorphous Forms A and B each contained a prominent XRD peak at 3.5° 2θ. DTX-104 at 19, 23-24; V6-42:5-24, 43:8-25, 169:16-20; V3-64:5-10, 64:22-25, 65:5-8, 65:13-17; V2-134:7-135:10, 140:10-142:7. Therefore, Roche's own testing establishes that a peak at 3.5° is not unique to the crystalline forms; rather it also appears for other possible semi-amorphous forms. V6-44:1-45:25; DTX-803.2. Accordingly, the Court finds that, based on this lone peak, Roche's studies are insufficient to prove the existence of valganciclovir HCl in crystalline form in Ranbaxy's tablets. See Part III.B.1., supra. The concerns with regard to the methodology of each particular study and results are discussed in detail below.[26]

### 1. The Spiking Study or Crystalline Seed Study

Roche asserts that the purpose of its seed study is not to demonstrate direct infringement, but is additional evidence that Ranbaxy had the requisite intent for inducing infringement, i.e., Ranbaxy has chosen a manufacturing process which permits crystalline seeds to be present and that promote the conversion of its valganciclovir HCl to crystalline form

[26]The Court notes that while Ranbaxy also complains that the tablets tested in the study had expired, V3-139:13-140:19, there is no evidence that the expiration affected the results, nor did Ranbaxy furnish additional, non-expired tablets for testing.

when the tablets are exposed to moisture. RoRCL 4.[27]

**a. Methodology**

During the seed study, a total of six samples were prepared and tested, including: (1) a placebo containing the excipients used by Ranbaxy, specifically crospovidone, microcelac 100, and magnesium stearate; (2) a mixture containing 0.1% crystalline valganciclovir HCl; (3) a mixture containing 0.3% crystalline valganciclovir HCl; (4) a mixture containing 0.5% crystalline valganciclovir HCl; and (5) and (6) two of Ranbaxy's valganciclovir HCl tablets. V2-155:5-15; 157:1-7, 158:7-159:1; PTX-577 at R0319832-36.

Dr. Henck did not perform the seed study, was not present when it was conducted, did not supervise or design it, and was unaware of its results until after it was completed. RaFF 36; V3-96:14-97:11, 104:10-12. Dr. Henck testified that he had knowledge of how the SSCI laboratory prepared the sample tablets and conducted the experiments for the crystalline seed study because he discussed it with his technicians and reviewed the notebook pages on which they recorded all the steps for the study. V2-143:17-145:17, 150:3-154:22; PTX-577. According to Roche, SSCI used the same XRD instrument and experiment parameters set forth in Ranbaxy's STP, PTX-339, including the same XRD angle measurement range, lowered from the usual 2 to 40° 2θ to the analytically relevant range of 3 to 6° 2θ, to focus on the 3.5° 2θ peak. V2-145:18-148:12, 150:3-151:3; PTX-339. Dr. Henck, however, conceded that there were several unexplainable differences between SSCI's study and Ranbaxy's STP. V3-97:12-103:15. Further, Dr. Henck admitted that he could not identify those who were

[27]Roche asserts that it relies on the pill tray and SGF studies to demonstrate direct infringement. RoRCL 4.

responsible for the testing nor did he control their actions. V3-103:16-24, 104:3-9. Thus, Dr. Henck was unable to lay a foundation for the seed study data and Roche did not present testimony from anyone who actually performed the study. Therefore, the Court finds that the seed study data and Dr. Henck's testimony regarding this study lack foundation, and thus, they are inadmissible.

Notwithstanding the foregoing, the Court finds additional problems with the seed study worth noting. Roche did not control the length of time the tablets were ground, protect the ground tablets from exposure to the atmosphere, nor use homogeneous samples for testing. V6-102:21-104:6; V3-106:2-15. Further, Roche did not run the experiments in duplicate, the only analysis was made through visual inspection,[28] the XRD for the placebo was run months after the samples, and the excipients used in the placebo did not match those in Ranbaxy's tablets; these flaws all contribute to the unreliability of the study. RaFF 41, 43-44; V6-100:22-102:14, 104:7-105:2; PTX-578. Thus, the methodology of Roche's seed study is scientifically unsound and the data cannot demonstrate that Ranbaxy's tablets contain, or that Ranbaxy knew that its tablets contain, valganciclovir HCl "in crystalline form." V6-99:19-100:13, 120:12-20; DTX-803.20.

In addition, both parties' experts agree that it is important to plot actual counts of data on the Y-axis of an XRD pattern to draw accurate qualitative conclusions from a study. V3-115:15-18; V6-53:19-54:2. Dr. Henck prepared XRD plots for the seed study by plotting the 2θ values from the underlying data on the X-axis and the intensity values on the Y-axis.

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[28]Roche acknowledged that Ranbaxy's STP required the use of computer XRD scans to determine the area under the curve and did not use visual scans. RoFF 21. This demonstrates, for example, how Roche's techniques differed from Ranbaxy's.

V3-108:2-17, 111:24-113:17; V10-160:14-161:15; PTX-578; PTX-699; DTX-603 at 52-69. First, Dr. Henck said that he did not remember whether the plots accurately reflected the underlying data or were altered; specifically, he did not mention that he "normalized" the data. V3-113:18-114:5. Later, he admitted that he "normalized" the data. V10-146:23-25, 159:5-16, 182:7-23. When XRD patterns are normalized, the intensity of the highest peak is set at 100 percent and the intensities of all of the other peaks in the pattern are scaled relative to that peak. RoFF 87. Thus, normalization alters each plot to a different degree and visual comparisons among different plots are not meaningful and may even be deceptive. For example, if two XRD patterns show their most intense peak at 3.5° 2θ and each is separately normalized, the peak height at 3.5° 2θ will appear to be the same in each pattern, even if the peak heights at 3.5° 2θ are different. RaR at 7.

Dr. Henck's seed study XRD plots did not show actual counts on the Y-axis; instead, without indication, the plots utilized multiple arbitrary Y-scales. V6-109:22-25; PTX-578. Roche contends that normalizing data is common and using an arbitrary Y-axis is a well accepted technique when comparing XRD patterns. RoRFF 6. For support, Roche cites to Ranbaxy's normalization of a single XRD plot, RoFF 88, which Ranbaxy does not dispute. Ranbaxy, however, takes issue with the way Dr. Henck normalized data for Roche's purposes here. Dr. Rogers explained that it is not possible to draw valid conclusions from Dr. Henck's XRD plots because there is no appropriate baseline to compare the data where the data is not scaled in the same way in the Y-direction and the plot of the placebo data was scaled differently than the plots for the other samples. V6-116:14-117:7, 120:3-6. Because Dr. Henck's plots are scaled independently, they do not accurately reflect the relationship between

the various samples tested and cannot be assessed by visual comparison. V6-117:8-22.

Dr. Rogers analyzed the underlying raw data for the seed study and prepared accurate plots which used actual counts on the Y-axis. V6-108:5-109:21,110:1-111:11; DTX-803.22-23. Dr. Henck conceded that Dr. Rogers' plots of the seed study data were accurate. V10-181:20-25, 188:4-7. Dr. Henck also admitted that his "normalization" changed the relationship among the plots from the actual relationship in the data; for example, his "normalization" makes the peak at 3.5° 2θ for the 0.3% spiked sample appear larger than the same peak for the 0.1% spiked sample, when in fact the reverse is true. RaFF 33; V10-189:4-190:6. As Dr. Rogers' plots indicate, the peak at 3.5° 2θ for the 0.1% spiked sample is larger than the peak at 3.5° 2θ for the 0.3% spiked sample. RaFF 48; DTX-803.22-23. Dr. Henck's incorrect conclusions were based solely on visual inspection of his "normalized" data. V10-189:22-25, 190:7-9; V3-102:18-25; cf. Part II.E.1., supra (Ranbaxy used computer scans). In analyzing XRD data, it is important to differentiate between a meaningful signal and noise by comparing the area under a peak to the area of the background over the same range of the XRD plot. See Part II.E.1., supra; V6-75:13-78:18. When analyzing a sample for a particular material, it is also critical to know the limit of detection in order to draw any meaningful conclusions. V6-80:5-11. Dr. Henck did not determine a limit of detection, the signal to noise ratio, conduct any statistical analysis of the data, or prepare a calibration curve. See V6-102:15-20; V3-104:13-105:24. Dr. Henck attempted to justify his use of visual inspection by citing an FDA Guidance for Industry ("FDA Guidance") document, which permits visual inspection where the detection limit has been determined "by establishing the minimum level at which the analyte can reliably be detected." PTX-763 at 7. Dr. Henck,

however, did not determine the detection limit for crystalline valganciclovir HCl in the seed study nor did he repeat the study to determine its reliability. V10-203:1-204:4. Thus, the FDA Guidance document does not support Dr. Henck's use of visual inspection in analyzing the seed study data here. The Court agrees that scaling the data arbitrarily in the Y-direction, as Dr. Henck did, without using computer comparisons changes the appearance of the XRD plots as well as the relationship between the various plots. V6-117:23-120:2; DTX-803.24.

There are additional problems with the methodology of this study, as evident from the testing of the placebo. Ranbaxy's tablets and the placebo both contain magnesium stearate, which exhibits XRD peaks at approximately 3.552° and 5.338° 2θ.[29] V2-132:20-25; V3-107:3-108:1; DTX-549 at 4. The ratio of the peak height at 5.338° 2θ to that at 3.552° 2θ is approximately 2 to 1, DTX-549 at 4; V6-86:13-87:7, but the XRD pattern for Roche's placebo containing only excipients, including magnesium stearate, does not show a peak at 3.552° 2θ. V2-161:8-18; PTX-578 (bottom pattern); PTX-699 at 1. Thus, Dr. Henck's XRD plot of the placebo, which was not subjected to XRD until three and a half months after it was made, fails to show the expected peaks. V10-198:25-199:14.

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[29]When the parties discuss the first magnesium stearate peak, they characterize the peak differently. Specifically, Ranbaxy rounds the peak to 3.5°, while Roche rounds the peak to 3.6°. The evidence, however, indicates that while a peak many not appear in the exact same place every time, see V2-139:22-140:5 (discussing how even the scientists look for a peak in a certain range), the peak for magnesium stearate typically shows between 3.5° and 3.6° and the difference between the characterization is immaterial. V3-107:3-108:1. In Ranbaxy's exhibit for the magnesium stearate XRD peak, the peak is at 3.552°, and thus, the Court finds and refers to the peak for magnesium stearate at 3.552°. DTX-549 at 4. Similarly, the parties characterize the second peak for magnesium stearate differently, but they interchange this peak at 5.3° and 5.4°. Dr. Henck testified that this second peak ranges between 5.1° through 5.5°. V3-111:8-12. As Ranbaxy's exhibit for the second magnesium stearate XRD peak is at 5.338°, the Court will refer to this peak as at 5.338° herein. DTX-549 at 4.

Further, the placebo did not contain the same brand and grade of magnesium stearate used in Ranbaxy's tablets. RaFF 44; V10-191:3-7; V6-205:16-22; see also V10-174:18-175:10; DTX-716 at 4 (SSCI used Fischer brand); DTX-45 at 4 (Ranbaxy used Mallinckrodt brand). Even though Dr. Henck recognized that different types and brands of magnesium stearate have different peak heights, he did not offer any data comparing the magnesium stearate used in the seed study to that used in Ranbaxy's tablets. V10-191:8-192:25. While Dr. Henck postulated that "[t]he Ranbaxy tablets will not show peaks for magnesium stearate at 3.6 or 5.4 degrees two theta because of the nominal concentration of magnesium stearate . . . . ," PTX-767.06; V10-193:1-18, he admitted that the XRD plots for Ranbaxy's tablets did show a peak at 5.338° 2θ, which could only be caused by magnesium stearate. V10-195:8-196:22; PTX-699. He further conceded that because the concentration of magnesium stearate is greatest in the placebo, its XRD plot should show a more intense peak at 5.338° 2θ than Ranbaxy's tablets, but it did not. V10-170:3-11, 197:15-198:24; V3-110:2-111:7. Dr. Henck could not explain why the placebo's XRD did not show the expected peaks at 5.338° 2θ or 3.552° 2θ for magnesium stearate. V10-197:9-198:12; V3-109:18-23. Dr. Henck conceded that if the plot for the placebo was incorrect, he did not know if it could be used to draw qualitative conclusions. V3-115:23-116:8. Because the placebo does not exhibit the peaks that the experts agree it should, the Court finds that this is an additional reason why the seed study is unreliable, and thus, no qualitative conclusions may be drawn. For the sake of completeness, the Court will nonetheless discuss the conclusions Dr. Henck reached from his seed study.

**b. Results**

Dr. Henck testified that the XRD patterns for the samples containing 0.1%, 0.3%, and

0.5% crystalline valganciclovir HCl each had a peak at 3.5° 2θ. V2-162:8-15; PTX-578; PTX-699 at 2-4. He also determined that both of Ranbaxy's valganciclovir HCl tablets contained a peak at 3.5° 2θ and, based on a qualitative visual comparison of the 3.5° 2θ peak for both tablets with the peak at 3.5° 2θ of the tablet samples containing 0.1%, 0.3% and 0.5% crystalline valganciclovir HCl, Ranbaxy's tablets each contained crystalline valganciclovir HCl greater than approximately 0.1% by weight. V2-162:16-165:9; PTX-578; PTX-745; PTX-746.

Dr. Rogers clearly explained some of the inconsistencies with the seed study's findings. RaFF 48. Dr. Rogers determined that the XRD pattern for the placebo, which contained magnesium stearate, failed to show peaks at 3.552° and 5.338° 2θ while the spiked samples and Ranbaxy's tablets showed peaks at these locations from magnesium stearate. Id. Dr. Rogers also found that the 0.1% spiked sample had a larger peak at 3.552° 2θ than the 0.3% spiked sample. V6-112:23-113:6; DTX-803.22-23. Moreover, Dr. Henck's own explanations reveal the study's flaws.

Because the placebo, which contained only magnesium stearate and other excipients used by Ranbaxy, does not show a peak at 3.5° 2θ, Dr. Henck determined that the peaks at 3.5° 2θ in the two Ranbaxy tablets were not the result of magnesium stearate.[30] This conclusion, however, is at odds with his own testimony regarding the XRD plot for the placebo at 5.338° 2θ. There, Dr. Henck admitted that because the concentration of magnesium stearate is greatest in the placebo, the placebo should show a more intense peak at 5.338° 2θ than Ranbaxy's tablets. V10-170:4-11, 197:15-198:24; V3-110:2-111:7. Yet, while the XRD for Roche's

[30]Dr. Henck explained that the peak from magnesium stearate is distinguishable from that of valganciclovir HCl because it is weaker. V2-132:20-133:13.

placebo did not show a peak at 5.338° 2θ, the XRD plots for Ranbaxy's tablets did show such a peak, which admittedly could only be from the magnesium stearate. V10-195:8-196:22; PTX-699. Dr. Henck could not explain why the XRD for the placebo lacked a peak at 5.338° 2θ. V10-197:9-14, 197:25-198:12. It follows that even though the XRD pattern for Roche's placebo did not show a peak at 3.552° 2θ, the peak at about 3.5° 2θ for Ranbaxy's tablets could have been caused by magnesium stearate rather than crystalline valganciclovir HCl. While Dr. Henck testified that magnesium stearate is only approximately 1% by weight in a Ranbaxy tablet while the concentration of valganciclovir HCl API in Ranbaxy's tablets is approximately 62% by weight, V2-166:6-167:7, 171:2-13; V6-177:21-178:4; PTX-286 at RVHRX000963, even he could not rule out the possibility that the peak he purported to observe at about 3.5° 2θ for Ranbaxy's tablets was caused by magnesium stearate or Form A or Form B of valganciclovir HCl. V3-116:21-118:4. Therefore, Roche has provided insufficient evidence demonstrating the cause of the peak or ruling out other possible causes of such a peak in the seed study. Moreover, even if Roche established that the peak at 3.5° 2θ in the seed study was the result of valganciclovir HCl, Roche does not show that such a peak is the result of valganciclovir HCl "in crystalline form" within the meaning of the '953 patent. See Part III.A., infra.

Finally, Roche contends that this study demonstrates that Ranbaxy's tablets as manufactured and packaged contain seeds of crystalline valganciclovir HCl. Specifically, Roche asserts the study further shows Ranbaxy's knowledge that its tablets contained crystalline seed contamination, which causes its API to convert to crystalline form. RoFF 30; RoRFF 7; V2-167:8-168:22; V5-33:25-35:22; PTX-361 at RVHRX0032400-01. Roche argues

that even if Ranbaxy did not manufacture its tablets with seeds of crystalline material, Ranbaxy knew that its amorphous tablets with high free energy would crystallize when exposed to moisture, which facilitates conversion to a crystalline lower free energy state. RoFF 30; V2-169:17-171:1. As Roche's seed study fails to demonstrate by a preponderance of the evidence that Ranbaxy's tablets even contain crystalline contamination, the Court finds that it cannot serve as additional evidence of the requisite intent for inducing infringement. RoRFF 7.

**2. Simulated Gastric Fluid Study**

The ANDA package inserts for Ranbaxy's tablets state that the tablets are for oral administration. RoFF 66; PTX-286 at RVHRX0000127. To test for infringement during the digestion process, Roche used the simulated gastric fluid ("SGF") study to simulate what would be expected to occur in the human stomach after a Ranbaxy tablet is swallowed. V2-22:25-23:19.

**a. Methodology**

The SGF study involved placing 7 Ranbaxy tablets, one at a time, in a basket, United States Pharmacopeia ("USP") Apparatus 1, and then lowering the basket for a specific time interval into SGF rotated by a paddle, USP Apparatus 2. RoFF 67. After exposure to SGF for a specified time period, the tablet was subjected to XRD testing. Id.; V3-4:5-7, 4:15-7:5, 7:23-9:4, 9:7-10:5; PTX-466, PTX-696, PTX-697. Roche's gastroenterology expert, Dr. Mark Feldman ("Dr. Feldman") determined that the SGF in Dr. Henck's study: (i) followed the "Gastric Fluid, Simulated, TS" entry in the USP, which is recommended to simulate human gastric fluid, V2-28:25-29:13; V3-10:6-23; PTX-575 at 82; PTX-467; (ii) used concentrations of hydrochloric acid, pepsin, and sodium within the physiological range in human gastric fluid,

V2-30:9-16; PTX-467; (ii) used the physiological pH of 1.2, V2-23:17-24:18, 29:6-15, 30:17-32:6; V3-10:6-23; PTX-575; PTX-467; DTX-164; PTX-469; and (iv) was maintained at 37°C body temperature, V2-32:7-25; PTX-575 at 82. RoFF 69.

Dr. Feldman determined that combining the basket of USP Apparatus I and paddle of USP Apparatus II and using a paddle rotation of 50 RPM, within the recommended range of 50 to 75 RPMs, was appropriate. V2-27:2-28:24; PTX-575 at 82; PTX-466 at 278. Dr. Feldman concluded that: (i) the SGF study simulated the conditions in the human stomach; (ii) the concentrations of components in the study are the same as in human gastric fluid; (iii) a Ranbaxy tablet ingested by a patient would undergo the same conditions simulated by Dr. Henck's study; and (iv) there was no reason to believe that any of the inactive ingredients in a Ranbaxy tablet would react with any chemical in the SGF. RoFF 70; V2-33:20-34:10, 35:9-36:2, 36:16-22.

Dr. Henck's opinions hinge on Dr. Feldman's testimony that the SGF study accurately represents the conditions in a patient's stomach. V3-128:24-129:9. Dr. Feldman, however, admitted that his opinions regarding the purported accuracy of the SGF study end once Ranbaxy's tablets are removed from the SGF, V2-53:24-54:3; specifically, when the tablets are exposed to the atmosphere, subjected to a lower temperature, and then ground. V2-51:8-16, 52:10-25. Dr. Henck agreed with Dr. Feldman that these latter conditions do not replicate the exact conditions of Ranbaxy's tablets during the human digestive process. V3-129:14-130:14. Dr. Henck admitted that his attempted justifications of the differences were "just speculation." RaFF 54; V3-130:15-131:16. Ranbaxy did not offer a medical expert to rebut Dr. Feldman's testimony.

The methodology of Roche's SGF study is flawed because Ranbaxy's tablets were drip dried after removal from the SGF for an unknown period of time and then ground into a powder, some of which was moist.[31] RaFF 56; V3-118:25-121:19; DTX-712 at 43. The times between removal from the SGF and the XRD testing were 10, 11, 12, and 22 minutes for the samples that were exposed to SGF for 0.5, 1, 2, and 4 minutes, respectively. RaFF 56; V10-200:8-19. But the time between removal from the SGF and the XRD testing was not recorded for the 8 and 15-minute samples, which Dr. Henck could not explain. V10-200:20-25, 202:17-19. Thus, the study failed to account for changes that may have been caused by processing between the time the tablet was removed from the SGF and the time it was actually tested, including grinding the tablet, which may have induced moisture from the outside of the tablet into the powder, and the exposure to the atmosphere. V6-123:5-125:3. These processing steps after removal from the SGF, which do not appear to be adequately controlled or documented, could induce ordering and thus influence the results of the study. V6-125:4-7.

Ranbaxy again challenges Dr. Henck's data plots. Dr. Henck only tested one Ranbaxy tablet to obtain each XRD plot, and he did not determine if the SGF chemically reacted with Ranbaxy's tablets. RaFF 52; V3-122:22-123:4. Dr. Henck prepared the XRD plots for the SGF study by plotting the 2θ values from the underlying data on the X-axis and the intensity values on the Y-axis for the SGF study from the underlying data. V3-108:8-17, 124:10-125:18; PTX-576; DTX-603 at 70-175. In plotting the data from the SGF study with actual counts on

[31]Dr. Henck was unable to identify which powders were moist and which were dry, and made no effort to measure the moisture content of these powders. V3-121:20-122:18.

the Y-axis, Dr. Rogers noted that Dr. Henck's XRD patterns again used an arbitrary Y-scale, and the plot of the data for the 8-minute tablet showed a different noise level than the other plots, which indicates arbitrary scaling. RaFF 31; V6-127:9-131:22; DTX-603 at 70-175; DTX-803.26-.27; PTX-576.[32] Dr. Rogers' accurate plots of the SGF study data confirmed that Dr. Henck had independently scaled at least the plot for the 8-minute tablet, making it impossible to draw any meaningful conclusions from Dr. Henck's visual inspection. RaFF 31; V6-127:25-128:2, 135:10-136:1. Thus, the Court finds that Dr. Henck's XRD plots do not accurately represent the underlying experimental data. Rather, Dr. Henck again manipulated the presentation of the data in an attempt to support his conclusions.

Ranbaxy, however, not only challenges the methodology of Roche's SGF study as flawed, but also asserts that the data does not show any evidence of crystalline valganciclovir HCl in Ranbaxy's tablets. V6-100:14-21; DTX-803.20.

**b. Results**

The data at time zero, when Ranbaxy's tablet is first removed from the bottle, and between time zero and 15 minutes display a hump characteristic of amorphous material and show no peak at 3.5° 2θ. RaFF 55; V6-125:8-126:13, 139:9-140:5; V3-126:17-20; PTX-576; PTX-700; DTX-803.25. The Ranbaxy tablets placed in SGF for 0.5, 1, 2, 4, and 8 minutes all show a peak at 3.5° 2θ. RoFF 71; RaFF 56. The Ranbaxy tablet placed in the SGF for 15 minutes disintegrated. Id.; V3-17:11-18:18, 19:14-20:2; PTX-576; PTX-700 at 3-7.

Dr. Henck testified that in his expert opinion, after Ranbaxy's tablets are swallowed by

[32]Although Dr. Henck did not recall altering or normalizing the data in his plots, see Part II.F.1.a., supra, on cross-examination during his rebuttal testimony, he conceded that Dr. Rogers' plots of the seed and SGF study data were accurate. V10-188:4-7; see also V10-181:20-25.

a patient and exposed to gastric fluid in a patient's stomach, the vast majority of the valganciclovir HCl API converts rapidly to crystalline form within 30 seconds to 8 minutes after being swallowed by patients. RoFF 72; V3-20:3-22:1, 23:6-21, 146:7-147:4; PTX-700. Since both Dr. Henck's and Dr. Rogers' analyses of the XRD data from Dr. Henck's SGF study confirm a peak at 3.5° 2θ, Roche asserts that this demonstrates that at least "some crystals" of valganciclovir HCl formed in the Ranbaxy tablets subjected to the SGF study. RoFF 73. The conclusion rests on the premise that a peak at 3.5° 2θ is dispositive of valganciclovir HCl in crystalline form rather than in the noncrystalline form. Although Dr. Henck did not analyze the XRD plots from the SFG study to determine if they correspond to other possible semi-amorphous forms of valganciclovir HCl because he disputes the existence of such forms,[33] V3-128:19-23, Dr. Rogers did compare his plots to the XRD patterns for Forms X, Y and A. RaFF 57. Dr. Rogers found that the data from the SGF study did not show the peaks at 9.5° and 11.8°, which Ranbaxy asserts is characteristic of crystalline Forms X and Y, but did show features that aligned with the pattern of the semi-amorphous Form A as defined in Roche's own Preformulation Book. RaFF 57 (citing V6-136:2-139:4; DTX-803.28-30; PTX-576).

In addition, based on Dr. Rogers' plots of the underlying data, the height of the peak at 3.5° for the 30-second, 1-minute, 2-minute, and 4-minute samples could correspond to the time it took to prepare the samples for XRD after removal from SGF, rather than the time the samples were exposed to SGF. RaFF 56; V6-130:6-9, 132:1-134:1; V10-201:1-202:4,

[33]Specifically, Dr. Henck contends that Form A is merely a mixture of amorphous and crystalline Forms X and Y.

202:20-23.[34] Therefore, it is not possible to draw any scientifically valid qualitative conclusions from the SGF study because it is unknown whether the peaks would similarly be present if Ranbaxy's tablet was tested during a consumer's digestion. Moreover, even if the peaks existed, Roche does not establish that they resulted from valganciclovir HCl in crystalline form rather than other possible semi-amorphous forms.

It is also unclear whether Ranbaxy's tablet will convert to crystalline form in the stomach of a patient before it dissolves. Dr. Henck made such a conclusion, which he admitted was "complete speculation," by using comparative dissolution data between Ranbaxy's tablets and Valcyte from Ranbaxy's ANDA. RaFF 58; V3-131:17-133:16. Roche argues that Dr. Henck's testimony that he "observed the material crystallizes before it dissolves," V10-152:17-154:13, and "[t]he crystallization [rate] caused by exposure to ambient conditions is significantly lower, by an order of magnitudes, than compared to the exposure of the warm and moist conditions that we have in the stomach," RoRFF 11 (quoting V10-155:1-18), rebuts Ranbaxy's assertion that Ranbaxy's tablets dissolve before they convert to crystalline form. However, the Court is not convinced.

The evidence from the SGF study demonstrates that by the 15-minute point, Ranbaxy's tablet had completely dissolved. V6-134:15-21; V3-18:10-18, 127:11-13, 128:9-11. Further, Ranbaxy's formulation group leader, Dr. Romi Singh ("Dr. Singh"), testified that, based on various testing done at Ranbaxy, Ranbaxy's amorphous tablet will dissolve in the stomach before any potential conversion to a crystalline form could take place. V4-103:19-105:9. Dr.

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[34]Indeed, Dr. Rogers concluded that the peaks at 3.5° were caused by processing the tablets after removal from SGF. V6-134:2-14.

Singh also explained that:

> [W]hen the amorphous API containing tablet is there in the stomach, it is surrounded by the gastrointestinal fluid. Now, we have an amorphous state where the molecules are in a state of disorder compared to a crystalline state where the molecules are in a state of order. Now, when the drug goes into solution, the disorder increases. The solvent molecules increases [sic] the disorder of the solute molecules. The solute in this case is valganciclovir hydrochloride API. So from an amorphous state of disorder, the driving force would be the solubility, the high solubility of this drug substance to go into a further state of disorder, that is the solution state. It will not come back from this disorder state to a state of order, that is, the crystalline state, and then go back to a state of further disorder. That is against thermodynamics . . . .

V4-104:14-105:5; see also V5-10:6-11:22. Dr. Rogers agreed that Ranbaxy's tablets will not crystallize in the SGF, but will instead dissolve. V6-141:10-24.[35] Accordingly, the Court does not find that the Roche has proven that the API in Ranbaxy's tablets converts to crystalline form in a patient's stomach before the tablets dissolve.

**3. Pill Tray Study**

AIDS and solid organ transplant patients typically store their Valcyte tablets and other tablet medications in medical pill tray organizers, which they load from individual medicine bottles once per week. Snydman Stip. ¶ 3; V1-88:7-11, 89:6-13; see, e.g., PTX-573; PTX-715. If a generic version of valganciclovir HCl were approved and sold in the United States, it could be substituted for and used and handled in the same way as Valcyte. RoFF 58. Thus, Roche designed the pill tray study to test Ranbaxy's tablets after they have been exposed to the air in

[35]The Court notes that although Roche asserts that Ranbaxy, in its attempt to discredit Dr. Henck's study, failed to conduct SGF tests of its own or to show that Ranbaxy's tablets dissolve before they convert to crystalline form, RoRFF 11, the burden is not on Ranbaxy to prove that it did not infringe. See Part III.B.1., infra.

pill trays, where they would commonly be stored by patients.[36]

**a. Methodology**

Dr. Henck supervised a medical pill tray organizer study that involved storing Ranbaxy's valganciclovir HCl tablets in a pill tray organizer, which held pills for a seven-day week. RoFF 59; V3-29:1-16; PTX-573. Based on the dosage instructions on Ranbaxy's packaging insert, Roche placed two 250 milligram tablets in a pill tray compartment for each day of the week. RoFF 66. Roche then resealed the pill bottle with the drying agent left inside and placed it in a stability chamber in the laboratory set to 25°C and 60% humidity – the conditions recommended by the International Conference for Harmonization to represent indoor conditions in the United States. Id.; V3-29:17-31:7, 32:7-17; PTX-718 at R0319837-76; PTX-573; PTX-694. Throughout the study, Roche kept the pill tray in a laboratory at ambient conditions between 20-25°C and 50-75% relative humidity. RoFF 60.

Roche conducted an XRD analysis on a tablet straight from the bottle each week and on a tablet that was taken from the medical pill tray organizer on each day of the week. RoFF 61. Roche repeated the experiment for five weeks. Id.; V3-29:17-31:7, 32:7-17; PTX-718 at R0319837-76; PTX-573; PTX-694. When it conducted the XRD testing, immediately after each tablet was removed from the pill tray, Roche purportedly rendered, not ground, each tablet into a powder in ambient conditions in the laboratory by lightly crushing it in a mortar and

[36]Dr. Singh's testimony that she never saw a medical pill tray organizer until July 2007 at a Walmart, after the present case had been filed, and that Ranbaxy did not intend for patients to use pill trays is simply not credible. V4-125:20-126:16. Ranbaxy contends that they do nothing to induce or encourage such usage. RaFF 85-88. Instead, Ranbaxy asserts that its packing and label instructions to"[d]ispense in tight containers as defined in the USP/NF" will somehow deter patients from the convenience of using pill trays. Id. The Court is not persuaded.

pestle, which does not change the chemical composition of the tablet. RoFF 61; V3-32:18-33:17; V10-139:11-141:6, 142:25-144:3; PTX-718 at R0319838; PTX-765.01; PTX-765.03.

Ranbaxy argues that the methodology of Dr. Henck's pill tray study is flawed for several reasons; specifically, Ranbaxy complains that the samples were ground, which increases the surface area of the sample, which is then exposed to the atmosphere, and thus to moisture; that Roche did not control the grinding time of the tablets nor the length of exposure to the atmosphere; Dr. Henck did not run duplicate samples or ensure that the powders tested were homogeneous; and Dr. Henck did not perform any statistical analysis of the pill tray data and did not determine the limit of detection for these experiments. RaFF 61.[37] The Court finds that because the API is purportedly unstable and converts to crystalline under certain conditions, Roche should have carefully controlled and recorded the process by which it tested Ranbaxy's tablets. Instead, it is unknown whether Roche's manner in conducting the study induced ordering or conversion to crystalline.[38]

**b. Results**

For the sake of completeness, the Court will explain the results of the medical pill tray organizer study. In Week 1, a peak at 3.5° 2θ appeared in the Day 2 tablets, indicating a peak within 48 hours of exposure to ambient conditions. RoFF 62. The tablets for every subsequent

[37]As Roche quickly points out, Ranbaxy does not challenge Dr. Henck's manipulation of the XRD data plots for the pill tray study, as it does in the seed and SGF studies. RoRFF 6.

[38]Moreover, the Court notes that the fatal flaw with this study is, as Ranbaxy argues, the use of a single peak at 3.5° 2θ as proof of the presence of valganciclovir HCl in crystalline form. See Part II.D.2., supra; Part III.B.1., infra.

day also showed a peak at 3.5° 2θ. Id.; V3-37:14-40:2, 42:2-8, PTX-581; PTX-698 at 1-8. In Week 2, a peak at 3.5° 2θ appeared in the Day 1 tablets, indicating a peak within 24 hours of exposure to ambient conditions. RoFF 63. The tablets for every subsequent day also showed a peak at 3.5° 2θ. Id.; V3-42:9-43:14; PTX-582; PTX-698 at 9-16. Tablets from Weeks 3, 4, and 5 also show a peak at 3.5° 2θ within 24 to 48 hours of exposure to ambient conditions. RoFF 64.

Based on these results, Dr. Henck concluded that within 24 to 48 hours after Ranbaxy's tablets are exposed to ambient conditions, the vast majority of the valganciclovir HCl in those tablets converts to crystalline form. RoFF 65; V3-144:4-145:18; PTX-698. During the study, Dr. Henck observed that after 24 to 48 hours the surface color of Ranbaxy's tablets started to become opaque and the coating began to crack, which he attributed to crystallization. RoFF 65; V3-43:22-45:16; DTX-708A. Further, Dr. Rogers agreed that "some crystals" of valganciclovir HCl may have formed in Ranbaxy's tablets during the medical pill tray organizer study. V6-199:21-200:2. Thus, Roche argues that the sale of Ranbaxy's generic valganciclovir HCl tablets will induce infringement of the '953 patent by patients because the API in Ranbaxy's product converts to crystalline form under normal conditions used by patients, such as storing the drug in a medical pill tray; this makes the patients direct infringers.[39]

The Court, however, finds that Roche has not shown that the material to which

[39]The Court notes that Roche's argument in its proposed rebuttal findings that it uses the pill tray study to demonstrate direct infringement contradicts its original argument that this study demonstrates that Ranbaxy's tablets will induce infringement. Compare RoRCL 4, with RoFF at 18.

Ranbaxy's tablets convert is valganciclovir HCl "in crystalline form." Instead, Roche baldly asserts that the peak at 3.5° within the XRD analysis of Ranbaxy's tablets in the pill tray study demonstrates that Ranbaxy's tablets contain valganciclovir HCl in crystalline form. Again Dr. Henck did not compare his XRD plots from the pill tray study to those of Forms X and Y or any other possible semi-amorphous forms of valganciclovir HCl. V3-91:22-92:12. He continued to assert his unproven position that there are no other forms of valganciclovir HCl other than pure amorphous and pure crystalline. Id. Indeed, Dr. Henck did not even have an opinion as to which form of valganciclovir HCl caused the peak at 3.5°, and had no reason to believe that the peaks he observed were not caused by other possible semi-amorphous forms. V3-94:10-15. Dr. Henck admitted that none of the XRD plots show the peaks at 9.5° or 11.8°, which Ranbaxy asserts are characteristic of crystalline Forms X and Y. V3-93:18-94:9. On the other hand, Dr. Rogers did compare Dr. Henck's XRD plots to those of Forms X, Y and A and determined that the data did not align with or contain the features of Forms X and Y, but contained many of the features characteristic of semi-amorphous Form A, as defined by Roche's own Preformulation Book. RaFF 64; V6-145:4-148:3; PTX-581-85; DTX-803.31-.33. Because a single peak at 3.5° does not differentiate between the crystalline and other possible semi-amorphous forms of valganciclovir HCl, see Part III.A., infra, this study too fails to show that Ranbaxy's tablets converted to the crystalline forms of valganciclovir HCl, Forms X and Y.

### G. Patent Invalidity Contentions

Ranbaxy asserts that it has by clear and convincing evidence proven that the '953 patent is invalid for obviousness under 35 U.S.C. § 103. As discussed herein, the ultimate decision

regarding whether a new or a useful product or process is patentable based on nonobvious is a question of law based on the totality of the evidence. See Part III.D., infra.

The parties agree that a person of ordinary skill in the art to which the '953 patent is directed would have a doctorate degree in chemistry, pharmaceutics, pharmacy, or pharmaceutical science and some industry or postgraduate experience, or would have a lesser academic degree and a longer period of experience. V9-59:16-24; V7-104:17-105:9; see also V9-59:16-60:1.

**1. Oral Prodrug Administration Versus Intravenous Administration**

When chemical compounds can be delivered to the body safely and effectively, they can be effective as drugs. RoFF 113. One method to deliver drugs is to inject them intravenously, which introduces the drug immediately into the bloodstream. Id. In such intravenous ("IV") administration, 100% of the drug is assumed to be delivered into systemic circulation and the drug is said to be 100% "bioavailable." Id. (citing V10-13:8-14:24). IV infusion, however, is very inconvenient and can require the involvement of skilled healthcare personnel. RoFF 113; V1-94:23-96:21; Snydman Stip. ¶ 16. Further, because this route of administration requires the skin to be punctured, there is always the risk of infection, particularly in patients that are immune-compromised. RoFF 113 (citing Snydman Stip. ¶ 15). Therefore, researchers seek ways to deliver drugs orally. RoFF 113; V9-58:14-59:1.

A significant problem with attempting to administer drugs through oral delivery is that oftentimes they are plagued by poor absorption rates. V10-16:3-17:6; 17:24-18:21; PTX-683. Chemists try to solve this problem by combining the parent drug with another molecule to form a new prodrug. RoFF 114. A prodrug is a new molecular entity which overcomes the barriers

through which the parent drug could not pass. Id. Once the prodrug has overcome the barriers, the prodrug breaks down, i.e. converts back to the parent drug, so the parent drug can exhibit its desired action in the body. V10-18:13-21; V9-50:20-51:10, 124:20-125:1. However, the discovery of a prodrug is extremely difficult. RoFF 119. A prodrug not only has to survive the assault of the human digestive system, it must also be capable of passing through cell membranes of the gastrointestinal ("GI") tract and into the bloodstream. RoFF 115-18. Once there, it has to successfully break down into the parent drug and the prodrug molecule, allowing the parent drug to take its effect, but the leftover prodrug molecule cannot be toxic to the body and must be capable of being excreted safely. RoFF 118.

To discover a prodrug that satisfies all of the foregoing requirements is a difficult task that takes a high degree of creativity. RoFF 119; V10-17:24-18:21, 25:10-26:4. There is no way to predict from a chemical structure whether any molecule will be a successful prodrug and nontoxic. V10-21:11-17; 23:11-19; 25:4-26:4. One unusual feature of valganciclovir is that it is a mixture of "diastereomers." RoFF 122. Normally, when a mixture of diastereomers is produced, only one of the diastereomers is useful and non-toxic, and the others must be separated and discarded. Valganciclovir, however, does not exhibit this toxicity. RoFF 125-26. Furthermore, this mixture crystallizes easily together. Id. As such, valganciclovir satisfies all the requirements of a prodrug, and according to Dr. Valentino J. Stella ("Dr. Stella"), an expert in drug delivery and prodrugs, it is "a great drug." V10-34:20-35:2. "Valganciclovir readily dissolves in the contents of the GI tract, survives the assault from enzymes in the GI tract, passes through the enterocyte cell membranes, and undergoes cleavage to release ganciclovir in the bloodstream, providing superb oral bioavailability for ganciclovir."

RoFF 126; V10-19:25-26:4; PTX-754 at 9, 12.

### 2. Allegations That the Claimed Invention Is Obviousness

#### a. Prior Art & Prosecution History

Ranbaxy presents the Court with four prior art references that it argues make the '953 patent obvious: the Beauchamp '339 patent, the 1992 Beauchamp paper, the 1993 Beauchamp paper, and the Martin Paper. The '339 patent, which issued on August 27, 1991, describes a way to increase the bioavailability of a genus of compounds by combining them with a list of amino acids to form esters. RaFF 100-02. One of the compounds mentioned by the '339 patent is ganciclovir. Id. The '339 patent also mentions the amino acid valine, which is used to produce valganciclovir, an ester of ganciclovir. Id. at 104. Ranbaxy posits that because ganciclovir is mentioned by the '339 patent and valganciclovir was formed by using one of the amino acids listed in the '339 patent, this makes the '953 patent obvious. But Ranbaxy fails to provide any support to buttress this conclusion, i.e., a bridge between the '339 patent's reference to ganciclovir and crystallinity. Indeed, the '339 patent makes no mention of the crystallinity of any of the esters taught by the patent, which Ranbaxy concedes. RaFF 106. Because the '339 patent did not discuss crystallinity, the Court finds that the '339 patent alone does not lead one skilled in the art to the crystalline form of valganciclovir HCl.

The 1992 Beauchamp paper titled "Amino Acid Ester Prodrugs of Acyclovir" and the 1993 Beauchamp paper titled "Acyclovir Prodrugs: The Road to Valacyclovir" describe the discovery of a prodrug, valacyclovir, for oral delivery of acyclovir, a compound with a very similar chemical structure to ganciclovir. DTX-170; DTX-171. The 1992 and 1993 Beauchamp papers also describe how to prepare valacyclovir in crystalline form as a HCl salt.

DTX-170; DTX-171. Ranbaxy submits that these papers would lead one skilled in the art to the discovery of valganciclovir and, thereafter, to the discovery of the crystalline form of valganciclovir. Whether or not the discovery of valacyclovir would lead to the discovery of valganciclovir, however, is not before this Court because the '953 patent is not over the compound; rather, it is limited to the compound "in crystalline form." DTX-8 at 168-74, 177-88, 215. Furthermore, merely because one compound may be produced in crystalline form does not suggest that another compound may be similarly produced in crystalline form, even if they have similar chemical structures.[40] Thus, the Court finds that neither the 1992 Beauchamp paper nor the 1993 Beauchamp paper make the crystalline form of the valganciclovir compound obvious.

The Martin Paper, written by John C. Martin, et al., titled "Synthesis and Antiviral Activity of Various Esters of 9-[(1,3-Dihydroxy-2-propoxy)methyl]guanine," discussed the synthesis and effectiveness of the mono-form of certain prodrugs. DTX-154 at 3. The paper discusses how production of the mono-form of a prodrug, one of which includes valganciclovir, results in a reduction in activity. Id. The Martin Paper thus discourages the creation of a prodrug, such as valganciclovir. The Court fails to conceptualize how this would make the '953 patent obvious.

During the prosecution history of the '953 patent, which includes three applications

[40]Acyclovir and ganciclovir differ in structure only by the existence of one additional hydroxymethyl group present in ganciclovir. RoFF 133. Roche described how one additional hydroxymethyl group can drastically change the properties of a chemical. RoFF 134. For example, ethylene glycol is an antifreeze, but glycerine, which is ethylene glycol with one additional hydroxymethyl group, is a food additive. Id. The Court agrees that if one discovered a method to crystalize ethylene glycol, it is not necessarily obvious that the same method would produce glycerine in crystalline form.

leading up to the '953 patent's issuance, DTX-5, DTX-8, DTX-10, and three follow-on applications in which Roche continued to pursue claims to the compound, DTX-3; DTX-6; DTX-2, the PTO made similar findings. The PTO rejected Roche's attempts to obtain a patent broadly claiming the compounds valganciclovir or valganciclovir HCl on a variety of grounds, including obviousness and anticipation in view of: (1) the prior art '339 patent, which disclosed amino acid esters of ganciclovir to improve its oral bioavailability; and (2) the 1992 Beauchamp paper, regarding valacyclovir and the reasonable expectation of one skilled in the art that the same technique would improve the oral bioavailability of ganciclovir. See RaFF 111; DTX-10 at 1029-48. Specifically, the PTO rejected Roche's argument that the oral bioavailability of valganciclovir was unexpected. DTX-10 at 1032-33.

Thereafter, Roche submitted an amended application on June 7, 1999, limiting the invention to valganciclovir HCl in crystalline form. DTX-8 at 175. The declarants indicated that they made numerous efforts to produce crystalline compounds, including efforts with HCl salts not even attempted in the '339 patent examples. V8-48:17-49:2, 113:1-14; V9-87:25-89:9 (describing attempts by co-inventor Dvorak); DTX-8 at 192; V10-113:25-114:5, 114:24-115:8 (describing attempts by co-inventor Maag); DTX-180 at 6-7; V8-42:19-43:12 (describing attempts by technician Han). The PTO issued the '953 patent after finding that producing valganciclovir HCl in crystalline form was neither obvious nor expected. DTX-10 at 1032-33.

After examining the evidence in the record, the Court finds that the prior art references do not make the '953 patent obvious at the time of issuance. None of the four references, either individually or cumulatively, make valganciclovir HCl in crystalline form obvious. Moreover, three of the four prior art references were considered by the PTO during patent prosecution, and

the patent examiner determined that they do not render the '953 patent obvious. See RaFF 111-15. The 1993 Beauchamp paper is the only prior art Ranbaxy offers here that was not before the PTO. The 1993 Beauchamp paper, however, is a review, inter alia, of the work reported in the 1992 Beauchamp paper and thus cumulative of the record that was before the PTO. V8-77:6-12, V7-124:9-24. Because the 1993 Beauchamp paper is merely a summary of earlier work that the PTO considered during the patent prosecution and does not contain any new references, it does not support Ranbaxy's argument that the invention in the '953 patent was obvious. See Part III.D.3., infra.

Even Dr. George Gokel ("Dr. Gokel"), Ranbaxy's expert in design and synthesis of biologically active molecules, conceded that one could not know how many attempts would be required to crystallize a compound, V8-119:1-6, and his criticisms of Dvorak, Maag, and Han's Declarations were not based on any experiments that he had done or that were done on his behalf attempting to make ganciclovir bis-valinate acetate or HCl or to repeat the prior art or the work done in the declarations. V8-109:18-111:7. Therefore, in light of the PTO's expert findings, and the Court's independent assessment that confirms those findings, the Court finds that the unexpectedness of the stable, crystalline form led to issuance of the '953 patent.

**b. Post-Inventor Discovery**

Roche, as the assignee of U.S. Patent No. 4,355,032 that described and claimed ganciclovir, had the exclusive rights to ganciclovir, DTX-168; V8-35:10-19, which did not expire until June of 2003. V1-69:15-19. Ranbaxy claims Roche had been conducting research to identify and develop an oral prodrug of ganciclovir, as reflected in a 1995 memorandum, DTX-459 at 3, which purportedly shows that the discovery of valacyclovir would lead one of

skill in the art to valganciclovir just as it did for Roche.[41] RaFF 108-09. Roche, however, applied for a patent over the valganciclovir HCl compound on July 28, 1994. See DTX-5 at 47. It is evident that this compound was already discovered by Roche prior to the 1995 memorandum. Ranbaxy cannot claim that the memorandum led to the discovery of a compound that was already discovered. The Court finds that obviousness cannot be shown by introduction of the inventor's 1995 memorandum where the invention had been made in 1994 at the latest. See Part III.D.3., infra; RoRFF 24.

**c. Secondary Considerations**

Drugs used to treat or prevent CMV disease prior to Valcyte had serious disadvantages. See V1-90:4-104:22; Snydman Stip. ¶¶ 10-17. Valcyte, however, satisfied a long felt but unsatisfied need for a drug to treat or prevent this disease. It offers the efficacy of IV ganciclovir due to its excellent bioavailability as well as provides the safety and convenience of oral dosing. See RoFF 149 (citing V1-60:9-62:23, 102:16-103:14, 106:18-107:18, 110:9-111:12; Snydman Stip. ¶ 19; PTX-114; PTX-458; PTX-639 at 21; PTX-647 at 611-12). Specifically, Valycte allows patients to receive the benefits of ganciclovir without dealing with

[41] According to Ranbaxy, the memorandum states "that the research program 'was rejuvenated in 1992 following the detailed publications (of Beauchamp's work) on a successful prodrug for Acyclovir, Valacyclovir.' DTX-459 at 3. The memorandum also admits that '(b)ased on the structural analogy between (valganciclovir HCl) and Valaciclovir (sic), coupled with the significant enhancement of the oral bioavailability versus the parent drug in both cases, allows for the argument that (the two compounds) are substrates for the same active transport system.' Id. at 8. The memorandum then notes that "(i)t is therefore not unreasonable to predict that (valganciclovir HCl) will have a similar oral bioavailability in humans as Valaciclovir (sic)." Id. The memorandum refers to nothing beyond the teachings of the prior art as providing the motivation for valganciclovir HCl and the expectation that it would provide improved oral bioavailability. V8-14:5-15:17." RaFF 109. The investigators were investigating numerous prodrugs of ganciclovir, not just valganciclovir HCl. See DTX-458 at 3-5, 13-21.

the risk of infection, pain and inconvenience, and costly involvement of skilled healthcare personnel, associated with IV administration.

The Court finds that Valcyte has been a tremendous commercial success. See V9-155:15-165:19; V1-53:14-15; PTX-548; PTX-549; PTX-551; PTX-552. Valcye grossed $290 million in sales in 2008 alone, and it is Roche's fifth or sixth leading product in the United States. V1-53:14-15. The commercial success of Valcyte is attributable to the medical benefits of its active ingredient, including its method of administration, bioavailability, cost, and the lack of available of alternatives offering similar benefits, rather than marketing or other factors. RoFF 151; V1-112:15-23; Snydman Stip. ¶ 24; V9-160:8-171:19; PTX-258.

Ranbaxy, however, argues that Valcyte's sales are not driven by the fact that its valganciclovir HCl is in crystalline form, but because of the oral bioavailability of the valganciclovir HCl compound, regardless of its physical form. V1-112:4-13, 116:20-117:23; V8-145:17-147:21; V9-15:23-19:4. While it may be that valganciclovir HCl in a different physical form, namely, amorphous form, could be just as successful as valganciclovir HCl is in crystalline form, RaFF 144-47, Ranbaxy has not demonstrated that this is the case. Rather, because the compound is not available in any other form at this time, the Court cannot separate the commercial success of Valcyte due to its oral bioavailability from the physical form of its active ingredient. Thus, the Court finds that, based on the record, Valcyte's commercial success is probative, although not dispositive, of the nonobviousness of the '953 patent. See Part III.D.3., infra.

**3. Allegations That The '953 Patent Are Anticipated By Reference**

Ranbaxy did not assert in the Final Pretrial Order that the prior art anticipates claims

1-6 of the ’953 patent and its experts admit that it does not. See RoFF143. The prior art did not disclose: (1) the valganciclovir molecule, i.e. the monovalinate ester of ganciclovir; (2) in the form of a HCl salt; and (3) in crystalline form. V9-49:5-8, 80:13-23. Ranbaxy’s expert Dr. Gokel conceded that none of the prior art he was aware of anticipates any claim of the ‘953 patent. V8-76:12-24. Ranbaxy’s expert Dr. Sloan also admitted that no one isolated the valganciclovir HCl molecule prior to the time of the invention of the ’953 patent. V9-27:1-4. Thus, claims 1-6 are not anticipated by any prior art reference upon which Ranbaxy relies. See Part III.D.1., infra.

#### 4. Allegations That the Claimed Invention Is Invalid for Lack of Written Description Support

Ranbaxy asserts that the ‘953 patent claims are invalid under 35 U.S.C. § 112(1) for failing to satisfy the written description requirement. A person skilled in the art would understand the words “in crystalline form” in claim 1 of the ’953 patent to mean that crystallinity in the context of the patent can be determined by employing a standard and reliable analytical test. V2-104:23-105:3. The prosecution history of the ‘953 patent confirms that the presence of valganciclovir HCl in crystalline form should be detected by XRD, a standard and reliable analytical test. In declarations submitted to the PTO during prosecution, inventors Dvorak and Maag, and technician Han, each referred to testing valganciclovir HCl and other materials for crystallinity by XRD. V8-119:19-22, DTX-178 at 7; DTX-180 at 5; DTX-183 at 3; V2-107:6-15.

The patent specification as filed in 1994, including its description of the structure of valganciclovir HCl and the methods for synthesizing it and preparing it in crystalline form, would have clearly conveyed to a person skilled in the art that the inventors were “in

possession" of valganciclovir HCl in crystalline form, which was readily confirmable by XRD, a standard technique for detecting crystallinity at that time. V2-83:1-6; V6-162:22-164:4; V7-42:6-44:2. In 1994, as now, the typical medicinal chemist or drug formulator would not have had the equipment and expertise to conduct XRD analyses for him or herself. RoFF 155; RoRFF at 2. Rather, the standard practice in 1994 was for the medicinal chemist or drug formulator to send a sample of the material in question to a co-worker with the requisite expertise and equipment for conducting an XRD analysis. RoFF 155; RoRFF at 2. Such individuals were commonly present in the analytical chemistry departments of research-based pharmaceutical companies. V2-102:7-103:2; V9-60:2-16.

This is exactly what the '953 patent inventors did. RoFF 154-56; V2-103:1-13. The inventors requested and received the results of XRD tests to detect valganciclovir HCl in crystalline form before the filing date of the '953 patent application. RoFF 157. Dvorak, an inventor of the '953 patent, sent samples to members of Roche's pharmaceutical analytical department to be analyzed by XRD. RoFF 156. Since "Dvorak was not a crystallographer and did not have experience interpreting XRD analyses, he relied on his colleagues in that department to perform the XRD analyses, interpret them and provide him with the results." Id. Co-inventor Paul Fatheree's notebook 18951 describes the first preparation of valganciclovir HCl on June 2, 1994, and the XRD analysis of that material on June 10, 1994. RoFF 157. "The '953 patent, Example 3, discloses a similar experiment on a larger scale." Id.

This is also exactly what Ranbaxy's scientists do when they send samples of valganciclovir HCl to Ranbaxy's analytical department to determine whether the samples contain crystalline material. V4-16:8-24, 30:15-25. Accordingly, as discussed herein, the

Court rejects Ranbaxy's argument that the '953 patent claims are invalid under 35 U.S.C. § 112(1) for failing to satisfy the written description requirement. See Part III.D.2., infra.

## III. Conclusions of Law

### A. Claim Construction

To determine whether there has been patent infringement, courts construe the patent's claims and then apply that construction to the accused product. Chimie v. PPG Industries, Inc., 402 F.3d 1371, 1376 (Fed. Cir. 2005). Claim construction, a determination of the correct claim meaning and scope, is a determination exclusively for the court as a matter of law. Markman v. Westview Instruments, Inc., 52 F.3d 967, 978-79 (Fed. Cir. 1995) (en banc), aff'd, 517 U.S. 370 (1996). "[C]laims of a patent define the invention to which the patentee is entitled the right to exclude." Phillips v. AWH Corp., 415 F.3d 1303, 1312 (Fed. Cir. 2005) (internal quotations and citations omitted). The court can only interpret claims, and "can neither broaden nor narrow claims to give the patentee something different than what it has set forth" in the specification. E.I. Du Pont de Nemours v. Phillips Petroleum Co., 849 F.2d 1430, 1433 (Fed. Cir. 1988).

This interpretive analysis begins with the language of the claims, which is to be read and understood as it would be by a person of ordinary skill in the field of the invention at the time of the invention, i.e., as of the effective filing date of the patent application. Dow Chem. Co. v. Sumitomo Chem. Co., 257 F.3d 1364, 1372 (Fed. Cir. 2001); Markman, 52 F.3d at 986 ("The focus [in construing disputed terms in claim language] is on the objective test of what one of ordinary skill in the art at the time of invention would have understood the terms to mean"); Phillips, 415 F.3d at 1312-13. In construing the claims, the court may examine both

intrinsic evidence (e.g., the patent, its claims, the specification and prosecution history) and extrinsic evidence (e.g., expert reports, testimony and anything else). Pitney Bowes, Inc. v. Hewlett-Packard Co., 182 F.3d 1298, 1309 (Fed. Cir. 1999). However, claims may not be construed with reference to the accused device, which means that the court may not construe a claim to fit the dimensions of the accused device, thus to prejudice the claim construction by "excluding or including specific features of the accused device." Wilson Sporting Goods Co. v. Hillerich & Bradsby Co., 442 F.3d 1322, 1330 (Fed. Cir. 2006). However, the knowledge of the accused device before or during claim construction is not only permissible, but also necessary to claim construction because it "supplies the parameters and scope of the infringement analysis." Id. at 1330-31; Lava Trading Inc. v. Sonic Trading Mgmt., 445 F.3d 1348, 1350 (Fed. Cir. 2006).

In interpreting the disputed terms, it is well-settled that the court should look first to the intrinsic evidence. Vitronics Corp. v. Conceptronic, Inc., 90 F.3d 1356, 1362 (Fed. Cir. 1996). The determination of how a person of ordinary skill in the art understands a claim term provides an objective starting point from which to begin claim interpretation based on the understanding that inventors are typically persons skilled in the field of the invention and that patents are addressed to and intended to be read by others of skill in the pertinent art. See Phillips, 415 F.3d at 1313 (citing cases).

Moreover, courts are instructed to look to the specification, which is a written description of the invention. See Phillips, 415 F.3d at 1313. "[C]laims 'must be read in view of the specification, of which they are a part.'" Id. at 1315 (quoting Markman, 52 F.3d at 979). Indeed, specification is perhaps "the single best guide to the meaning of a claim term" due to

its statutory requirements of being in "full, clear, concise, and exact terms." Id. at 1316; see 35 U.S.C. § 112. "The specification acts as a dictionary when it expressly" or implicitly defines terms used in the claims. Markman, 52 F.3d at 979. In Multiform Desiccants, Inc. v. Medzam, Ltd., 133 F.3d 1473, 1477 (Fed. Cir. 1998), the Federal Court explained this principle:

> It is the person of ordinary skill in the field of the invention through whose eyes the claims are construed. Such person is deemed to read the words used in the patent documents with an understanding of their meaning in the field, and to have knowledge of any special meaning and usage in the field. The inventor's words that are used to describe the invention-the inventor's lexicography-must be understood and interpreted by the court as they would be understood and interpreted by a person in that field of technology. Thus the court starts the decisionmaking process by reviewing the same resources as would that person, viz., the patent specification and the prosecution history.

Thus, the specification effectively limits the scope of the claim. On demand Mach. Corp. v. Ingram Industries, Inc., 442 F.3d.1331, 1340 (Fed. Cir. 2006). Due to its nature, "the specification 'is always highly relevant to the claim construction analysis. Usually it is dispositive. . . .'" Id. (quoting Vitronics Corp. v. Conceptronic, Inc., 90 F.3d 1576, 1582 (Fed. Cir. 1996)).

Extrinsic evidence includes all evidence external to the patent and prosecution history, i.e., expert and inventor testimonies, dictionaries, and learned treatises. Markman, 52 F.3d at 980. It is considered only where the intrinsic evidence does not provide a sufficient description to resolve ambiguities in the scope of the claim. See Vitronics, 90 F.3d at 1583; Johnson Worldwide Associations v. Zebco Corp., 175 F.3d 985, 989 (Fed. Cir. 1999). However, the Federal Circuit cautioned, in Phillips, that dictionary definitions should not be used to interpret patent claim terms in a manner that is divorced from the context and description of the invention in the specification. 415 F.3d at 1321. The Phillips Court reasoned that because of

the nature of the patent claims, the dictionary definitions, as extrinsic evidence, are usually less reliable than the patent documents themselves in establishing the ordinary meaning of a claim term. Id. at 1314; Toro Co. v. White Consol. Indus., 199 F.3d 1295, 1299 (Fed. Cir. 1999). Ultimately, extrinsic evidence cannot be used to vary or contradict claim terms when their meanings are discernible from intrinsic evidence. C.R. Bird, Inc. v. U.S. Surgical Corp., 388 F.3d 858, 862 (Fed. Cir. 2004).

Here, to determine the scope and meaning of the '953 patent, the Court first analyzes the intrinsic evidence in the record. The parties agree that the person of ordinary skill in the field to which the '953 patent is directed would have a doctorate degree in chemistry, pharmaceutics, pharmacy, or pharmaceutical science and some industry or postgraduate experience, or would have a lesser academic degree and a longer period of experience. V2-100:10-14; V9-59:16-24; V7-104:17-105:9; see also V9-59:16-60:1. Claim 1 of the '953 patent recites: "The compound 2-(2-amino-1,6-dihydro-6-oxo-purin-9-yl)methoxy-3-hydroxy -1-propanyl-L-valinate hydrochloride in crystalline form." DTX-1, col. 30, ll. 42-44. The parties further agree for purposes of this case that the chemical name refers to valganciclovir HCl, and the Court agrees that claim 1 unambiguously means the compound valganciclovir HCl.[42] SF-21. As discussed herein, the parties disagree as to the meaning of only one claim

[42]Dependent claim 2 of the '953 patent reads: "An antiviral pharmaceutical composition comprising the compound of claim 1 and a pharmaceutically acceptable excipient." When claim 2 recites "the compound of claim 1," it is referring to valganciclovir HCl in crystalline form, as defined in claim 1. There is no dispute that an "excipient" is a "substance[] other than the active ingredient that. . . [can be] added to the formulation in manufacturing the drug." Warner-Lambert Co. v. Teva Pharms. USA, 418 F.3d 1326, 1330 n. 1 (Fed. Cir. 2005). "'Pharmaceutically acceptable' means generally safe and non-toxic and . . . acceptable for . . . human pharmaceutical use." PTX-1, col. 10, ll. 1-4. The word "comprising" is a term of art which means that the claim does not exclude additional, unrecited elements. Accordingly, claim

term: the requirement that the compound be "in crystalline form."

Claim 1 of the '953 patent is a "product" or "composition of matter" claim. RoCL 2. Such claims define the claimed subject matter solely in terms of its structure or other physical characteristics. Id. Claim 1 is directed to a chemical compound per se and not a method of manufacturing such a compound. SF-21; V2-108:11-21; V7-182:7-184:18; PTX-1; DTX-8 at 171. The language "in crystalline form" means that the valganciclovir HCl molecules are arranged in a regularly repeating three dimensional pattern. RoCL 3; V2-80:2-8; V6-25:12-17. According to Roche, claim 1 means "nothing more nothing less" than this construction. RoCL 3. This definition, however, does not indicate whether in crystalline form means the presence of a single crystal or something more.

The Court must determine what "in crystalline form" in claim 1 of the patent-in-suit encompasses. In SmithKline Beecham Corp. v. Apotex Corp., 403 F.3d 1331, 1339-41 (Fed. Cir. 2005), the Federal Circuit determined that the claim, which contained the four words

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2 requires the presence of valganciclovir HCl in crystalline form and a pharmaceutically acceptable excipient, but does not exclude the presence of other materials, such as amorphous valganciclovir HCl.

Dependent claims 3, 4, 5, and 6 of the '953 patent are directed to methods of treating an "animal" infected with a virus by administering a therapeutically effective amount of "the compound of Claim 1," i.e., valganciclovir HCl in crystalline form. The term "animal" in claim 3 includes humans. PTX-1, col. 10, ll. 63-65. The other terms in claims 3-6 do not require separate analysis. In claim 4, the reference to "the method of claim 2" is an obvious typographical error. In Hoffer v. Microsoft Corp., 405 F.3d 1326, 1331 (Fed Cir. 2005), the court found that a district court can correct a harmless obvious error in a patent when it is not subject to reasonable debate, as it may for other legal documents. In this case, claim 4 is referring back to a method claim. Claim 2, however, is not a method claim, and claim 3 is the only method claim that appears prior to claim 4. Therefore, it is obvious that claim 4 was intended to recite "the method of claim 3." V3-51:14-16, 52:8-54:14. Accordingly, the Court corrects this typographical error to reflect "the method of claim 3" in claim 4. None of these claims, however, are in dispute nor do they help the Court in determining the validity or scope of claim 1 of the '953 patent.

"crystalline paroxetine hydrochloride hemihydrate," unambiguously described a specific product – the structural compound of the single crystal of hemihydrate. Id. at 1339. This differs from the instant claim because that compound could not be produced without the presence of at least one single crystal. Id. at 1346. In this case, there is no dispute that amorphous valganciclovir HCl exists,[43] and that it can be produced without the presence of a single crystal.

While the compound within claim 1 of the'953 patent unambiguously refers to valganciclovir HCl, the requirement that the compound be "in crystalline form" is ambiguous. Specifically, the Court cannot discern from the plain language of claim 1 whether it encompasses pure crystalline valganciclovir HCl or other semi-amorphous forms containing partially ordered solids. While the claims themselves do not provide any insight into the meaning of "in crystalline form," the written description does provide some guidance. The '953 patent states that:

> The compound of the invention can be, and has been, produced in crystalline form. This is a decisive advantage over the compounds disclosed in the prior art which have been described as non-crystalline materials. The advantage resides in the fact that pharmaceutical formulations can be more easily produced with a crystalline material. A crystalline material can be processed efficiently and is susceptible of being more reproducibly characterized than a non-crystalline material, and the quality of the crystalline materials of the invention can be much more readily ascertained than that of non-crystalline materials.

DTX-1, col. 21, ll. 21-31. Therefore, in its patent, Roche describes that the HCl and acetate salts of valganciclovir "can be prepared as crystalline materials and therefore can be easily manufactured into stable oral formulations." DTX-1, col. 15, ll. 7-9. On the other hand, the

[43]Roche concedes that the amorphous form does not infringe. See RoCL 6.

patent explains that prior art compounds were "non-crystalline materials which are difficult to process for the manufacture of oral pharmaceutical dosage forms." Id., col. 3, ll. 32-34; V6-70:6-25. The patent itself equates in crystalline form with crystalline material, and distinguishes crystalline from noncrystalline material based upon the relative ease with which crystalline material permits a formulation chemist to make a stable oral dosage form. While the manufacturing or storage advantages of crystalline material should not be read into the patent's claims, the stability of the compound in crystalline form helps to inform the Court of the properties of what Roche meant and the PTO understood claim 1 of the proposed patent to encompass.

The prosecution history provides further insight into the meaning of the terms. Roche's March 1996 Preformulation Book stated that "[t]here are two crystalline forms (X and Y) and two metastable forms (A and B) of the racemic mixture of the diastereomers of [valganciclovir HCl]." DTX-589 at 9; V6-38:13-39:20; V3-65:18-66:2.[44] Roche contrasted the two crystalline forms of valganciclovir HCl, Forms X and Y, with the two metastable forms of valganciclovir HCl, Forms A and B. V6-38:25-39:7, 46:1-9; V3-66:22-25. Roche determined that the metastable forms, A and B, were unstable, semi-amorphous materials that converted to crystalline, Form X, under certain conditions. DTX-589 at 15, 26; DTX-104 at 16. In its 2000 NDA submission to the FDA for Valcyte, Roche stated that "[t]here are two crystalline forms of valganciclovir HCl (termed X and Y) and an amorphous form" and that "[n]o crystalline forms other than form X and Y have been observed." DTX-659 at 1. After it obtained the '953

[44]Ranbaxy asserts, and Roche does not dispute, that Roche submitted its Preformulation Book to the PTO during the '953 patent prosecution. RaFF 13.

patent, Roche essentially re-characterized Forms A and B as merely amorphous material containing low amounts of crystalline material. Id. at 1-2. However, at the time it applied for the '953 patent, Roche believed that Forms A and B were neither crystalline nor stable, but amorphous and converted to crystalline under certain conditions. DTX-589 at 15, 26.

Prior to the issuance of the '953 patent, Roche had tried to obtain a patent over the valganciclovir HCl compound. Roche did not distinguish between the crystalline and noncrystalline forms in that attempt. The patent examiner rejected Roche's proposed patent based, inter alia, on the fact that it was anticipated by the '339 patent and obvious in light of this prior art. DTX-8 at 170-71. In the '339 patent, Beauchamp taught a genus of compounds, which would make the existence of valganciclovir HCl obvious to one of ordinary skill in the art. Id. Thus, the claim of valganciclovir HCl without any limitations is overly broad because it covers "both crystalline and non-crystalline" forms of the compound, which would result in double-patenting. Id. at 174. However, after Roche limited its application to valganciclovir HCl in crystalline form, the PTO allowed the patent based on the fact that the prior art did not specify the "crystalline form" of valganciclovir HCl, and such a distinction should not be read into the patent. The PTO issued the '953 patent based on the inventors' representations that the crystalline form was not naturally occurring nor easily produced "without undue effort, if at all." Id. at 181-83, 215. Thus, the PTO determined that crystallinity was not obvious or anticipated by the '339 patent or the prior art.

The importance of these determinations is that (i) Roche and the PTO were aware of at least two different forms of valganciclovir HCl, amorphous and crystalline, when Roche sought the '953 patent, (ii) Roche knew that the stability of valganciclovir HCl varied based on which

form the compound was in, and argued that the stable crystalline forms were not obvious and required undue experimentation, and thus, (iii) the '953 patent only covered valganciclovir HCl in crystalline form, the known crystalline Forms X and Y. In fact, Roche does not assert that the amorphous form of the compound spontaneously converts to the crystalline form nor does Roche contend that the only natural state of the compound is the crystalline form. Indeed, Roche cannot make these arguments because such positions would contradict the inventors' assertions that producing this form was difficult, and thus, that the crystalline form was not obvious nor expected. Further, such an argument or claim construction would provide a patent over the entire valgancyclovir HCl compound, which the PTO already rejected. Therefore, the Court construes claim 1 to include only the stable, crystalline forms of the compound valganciclovir HCl. See E.I. Du Pont de Nemours, 849 F.2d at 1433 (finding that a court can only interpret claims).

Roche argues that the patent also covers the crystalline material found in a mixture with amorphous or semi-amorphous forms of the valganciclovir HCl compound. The Court agrees. While the '953 patent does not refer to trace amounts of crystalline material in an otherwise noncrystalline material, V3-74:21-75:1; V6-71:4-7, a person of ordinary skill in the field may understand valganciclovir HCl "in crystalline form" to mean even a single crystal. But this does not mean that other possible semi-amorphous forms are necessarily covered by the patent. In its submission to the PTO, Roche admitted that there were other noncrystalline forms of valganciclovir HCl, which the '953 patent excludes. See RoCL 6. Roche even defined Form A as semi-amorphous and unstable, and excluded it from the known crystalline forms mentioned in the patent prosecution history and its Preformulation Book. DTX-104 at 16; see also

DTX-659 at 1-2. It is clear that the nonobviousness of the crystallinity of valganciclovir HCl was the basis for the '953 patent's issuance. DTX-8 at 178-88, 214-15. The language in the '953 patent indicates that the claimed compound is more stable than its noncrystalline counterpart. DTX-1, col. 21, ll. 21-31. The patent specifically excluded those unstable forms that were noncrystalline; based upon Roche's own representation at the time, this would necessarily exclude Forms A and B. DTX-8 at 168-74, 214-15. Therefore, while the Court agrees with Roche that a mixture containing any amount of detectable crystalline material (namely Forms X and Y) is covered by the '953 patent, the Court also finds that other possible semi-amorphous forms of valganciclovir HCl may exist, but are noncrystalline and not covered by the patent. See E.I. Du Pont de Nemours, 849 F.2d at 1433 (finding that the court cannot broaden nor narrow claims to give the patentee something different than what it has set forth). Thus, the Court finds that the patent language and prosecution history lead to a claim construction that "in crystalline form" covers only the stable, crystalline forms of valganciclovir HCl, Forms X and Y, whether as a pure crystalline solid or in a mixture with other amorphous forms, but any other forms of valganciclovir HCl, specifically amorphous and other possible semi-amorphous forms of valganciclovir HCl, are not covered by the patent.

The parties further dispute how to determine whether a product is "in crystalline form:" whether the valganciclovir HCl is in crystalline form X or Y or in other possible semi-amorphous forms. In this case, Roche offers XRD testing to prove crystallinity. The parties do not dispute that the '953 patent never refers to XRD, never identifies XRD as the sole technique for determining whether a material is crystalline, nor does it provide an XRD pattern or "fingerprint" to assist in determining which XRD feature, if any, might indicate the presence

of valganciclovir HCl in crystalline form. DTX-1; V3-72:21-78:9; V6-71:1-3. Accordingly, the patent never suggests that XRD would be necessary to detect valganciclovir HCl in crystalline form

Ranbaxy argues that the patent points to crystalline material's handling properties, not its XRD pattern, and the prosecution history reveals that those properties would have been apparent to a medicinal or formulation chemist without resort to a more sensitive XRD analysis. The Court disagrees. While the stability of the compound is a characteristic of the defined form, even Drs. Rogers and Cockcroft admitted that XRD is a standard technique for detecting material in crystalline form. Further, the evidence establishes that the person of ordinary skill at the time the patent was issued would know that the best way to identify whether a sample is "in crystalline form" is to subject it to XRD, and that such a person would send the sample to an analytical lab for such testing, which in fact is what the '953 inventors did. See Part II.G.4., supra. Indeed, Ranbaxy's scientists do the same. See Id. Thus, the Court finds that XRD testing is an appropriate way to determine whether a given sample is valganciclovir HCl "in crystalline form."[45]

**B. Direct Infringement**

**1. Literal Infringement**

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[45]Relying on the distinctions between crystalline and noncrystalline materials, as emphasized in the '953 patent and its prosecution history, Ranbaxy contends that "in crystalline form" means exhibiting the properties of a crystalline material, specifically defined by the multi-peaked fingerprint and the stability of the compound. V6-67:1-70:25. Roche contends that "in crystalline form" means crystalline as determined by the presence of at least a single peak in an XRD pattern. V2-103:21-104:2, 104:13-22. Because, however, the patent is silent with regard to the XRD pattern for valganciclovir HCl "in crystalline form," it is not part of the claim construction. Rather, the XRD pattern is more appropriately analyzed under the infringement analysis. See Part III.B.1., infra.

Title 35, Section 271 of the U.S. Code covers direct infringement of a patent, which occurs when a person "without authority makes, uses or sells any patented invention, within the United States during the term of the patent . . . ." Novartis Pharms. Corp. v. EON Labs Mfg., 234 F. Supp. 2d 464, 467 (D. Del. 2002) (citing 35 U.S.C. § 271(a)). To succeed on a claim of infringement, the patent owner has to satisfy the burden of proof by a preponderance of the evidence. Id. (citing SmithKline Diagnostics, Inc. v. Helena Lab. Corp., 859 F.2d 878, 889 (Fed. Cir. 1988)). After a court "construe[s] the disputed terms of the patent at issue," it then "compare[s] the accused products with the properly construed claims of the patent." Id. at 467 ("Infringement is a two step inquiry."). One theory of infringement is "literal infringement," which "occurs where each element of at least one claim of the patent is found in the alleged infringer's product." Id. (citing Panduit Corp. v. Dennison Mfg. Co., 836 F.2d 1329, 1330 n. 1 (Fed. Cir. 1987) and Robert L. Harmon, Patents and the Federal Circuit 195 & n. 31 (3d ed. 1994)).

Ranbaxy argues that the patent is invalid, see Part III.D., infra, but even if the Court finds that it is not, its tablets do not infringe. "Neither [Roche's] burden to prove infringement nor [Ranbaxy's] burden to prove invalidity, both ultimate burdens of persuasion, ever shifts to the other party-the risk of decisional uncertainty stays on the proponent of the proposition." Technology Licensing Corp. v. Videotek, Inc., 545 F.3d 1316, 1327 (Fed. Cir. 2008) (citing Hybritech Inc. v. Monoclonal Antibodies, Inc., 802 F.2d 1367, 1375 (Fed. Cir. 1986); Ralston Purina Co. v. Far-Mar-Co, Inc., 772 F.2d 1570, 1574 (Fed. Cir. 1985); American Hoist & Derrick Co. v. Sowa & Sons, Inc., 725 F.2d 1350, 1360 (Fed. Cir. 1984)).

In this case, claim 1, the only claim in dispute, involves the compound valganciclovir

HCl in crystalline form. In order to prevail on a claim of literal infringement, Roche must prove by the preponderance of the evidence that Ranbaxy's accused generic product contains valganciclovir HCl in crystalline form. As discussed herein, Roche offers three studies by Dr. Henck to prove that Ranbaxy infringed on the patent-in-suit because Ranbaxy's API converts to valganciclovir HCl in crystalline form, which Ranbaxy allegedly induced. See Part II.F., supra. All three studies, however, rest on the flawed premise that a lone peak at 3.5° 2θ is indicative of valganciclovir HCl in crystalline form, as claimed in the '953 patent.

As a preliminary matter, although Roche asserts that Ranbaxy, in its attempt to discredit Dr. Henck's studies, fails to conduct SGF tests of its own, see, e.g., RoRFF 11, the burden is not on Ranbaxy to prove that it did not infringe. Plaintiff/patentee Roche, alleging infringement by Ranbaxy, has the burden of persuasion that Ranbaxy infringes, under the usual civil law standard of preponderance of the evidence; this burden never shifts to Ranbaxy. See Tech. Licensing Corp. v. Videotek, Inc., 545 F.3d 1316, 1327 (Fed. Cir. 2008). Therefore, Ranbaxy need not discredit Roche's studies by proving the opposite; rather, demonstrating that the methodology and results are inaccurate is sufficient. Accordingly, the Court does not credit Roche's numerous assertions that Ranbaxy failed to conduct its own studies to rebut Roche's purported findings.

To prove direct infringement, Roche points to its SGF and pill tray studies.[46] These studies, however, do not demonstrate that Ranbaxy's tablets contain any crystalline

[46]Roche does not rely on the seed study to prove direct infringement. Rather, Roche contends that, along with Ranbaxy's own testing, the seed study demonstrates that Ranbaxy had the requisite specific intent to infringe, warranting a finding of infringement by inducement. Thus, the Court discusses the flaws with the seed study in the inducement section. See Part III.C., infra.

valganciclovir HCl at release. The parties agree that when a crystalline material is subjected to XRD, the X-rays are diffracted at specific angles, and the material exhibits one or more sharp, well-defined peaks, whereas amorphous material subjected to XRD does not produce peaks, but exhibits broad humps, referred to as a halo pattern. See Part II.C., supra. Roche's studies demonstrate that Ranbaxy's tablets do not contain valganciclovir HCl in crystalline form upon release. In the SGF study, Roche subjected Ranbaxy's tablets to XRD and found that the data at time zero, and between time zero and 15 minutes display a hump characteristic of amorphous material and show no peak at 3.5° 2θ. See Part II.F.2., supra. Thus, Roche's own study demonstrates that there is no peak in Ranbaxy's tablets at time zero. Similarly, the results of Roche's pill tray study show that Ranbaxy's tablets do not have a peak at 3.5° 2θ until 24 to 48 hours of exposure to ambient conditions. See Part II.F.3., supra. Indeed, Roche's own studies show that the XRD patterns for Ranbaxy's tablets at time zero are indicative of valganciclovir HCl in amorphous form and do not contain any peak at 3.5° 2θ. See Part II.F., supra.

Because XRD analysis of Ranbaxy's tablets do not show anything other than amorphous valganciclovir HCl at release and Roche cannot demonstrate that Ranbaxy's tablets contain valganciclovir HCl in crystalline form at that time, Roche relies solely on a theory of conversion to show infringement. Roche asserts that the presence of a peak at 3.5° 2θ in the XRD pattern of Ranbaxy's tablets after exposure to ambient conditions or after being ingested indicates valganciclovir HCl in crystalline form and thus infringement. The Court disagrees with this premise.

Roche argues that a single peak is commonly used by a person of ordinary skill in the art to identify a compound within a mixture of known materials. The parties' experts agree that

it is accepted practice among crystallographers that when looking at a sample that consists of a mixture of different known compounds, and there is one unique peak that can identify a specific crystalline material and no other component of the mixture exhibits a peak at that position, a single peak in an XRD is sufficient to identify that specific compound. V2-84:15-25, 132:3-9, 133:14-17. On the other hand, a single peak cannot be used to identify the presence of a specific material in an unknown sample because there is insufficient information to uniquely identify that single peak. V6-60:21-62:4. In this case, Roche has failed to prove that even though all of the materials in the sample are known, that no other component of the mixture exhibits a peak at that position. Indeed, magnesium stearate peaks in the same range at 3.552° 2θ. See n. 8, Part II.F.1.a., supra. Moreover, and more importantly, the record demonstrates that the crystalline and other possible semi-amorphous, noncrystalline forms of valganciclovir HCl both show a peak at 3.5° 2θ.

The experts agree that Forms X and Y of valganciclovir HCl, as well as what Roche originally categorized as Forms A and B, all show a peak 3.5° 2θ when subjected to XRD analysis. See Part II.D.2., supra. Because the mere existence of a peak at 3.5° 2θ, without more, does not distinguish between valganciclovir HCl "in crystalline form," Forms X and Y, and other possible semi-amorphous forms like Forms A and B, such a peak alone does not establish the presence of valganciclovir HCl in crystalline form in Ranbaxy's tablets. Id. Despite acknowledging that all four forms show a peak at 3.5° 2θ, Dr. Henck admitted that he did not attempt to determine the characteristics of the XRD patterns necessary to distinguish among these forms, because he assumed that Forms A and B, and indeed all semi-amorphous forms, do not exist. Id.; V3-68:12-22.

Roche asserts that Forms A and B are not distinct forms at all, but merely mixtures of amorphous and crystalline forms of valganciclovir HCl because there is a single peak at 3.5° 2θ. Roche fails to offer any support for the contention that crystalline material in the amorphous material causes the peak at 3.5° 2θ beyond citing to its NDA for Valcyte to the FDA, on August 15, 2000, in which it categorized Forms A and B as amorphous but containing low amounts of crystalline material. DTX-659 at 1-2. Yet, when Roche applied for the '953 patent, which was issued just six weeks prior, Roche had characterized Forms A and B as semi-amorphous material, which it knew converted to Form X under certain conditions. See DTX-216 at 4; DTX-104 at 16. It did not characterize Forms A and B as crystalline forms. Roche has not proven which of these categorizations of Forms A and B is accurate, and the Court finds that the distinction is material. Indeed, a disagreement between the parties centers around whether there are other forms of valganciclovir HCl beyond amorphous and crystalline. Roche has not shown by a preponderance of the evidence that Forms A and B are mixtures containing crystalline material, and that it is the crystalline material inside these mixtures that causes the peak at 3.5° 2θ. Therefore, Roche's tests fail to show that Ranbaxy's tablets have a peak at 3.5° 2θ due to the presence of valganciclovir HCl in crystalline form (Form X or Y), rather than the composition of valganciclovir HCl in other possible semi-amorphous forms or because of some other excipient within Ranbaxy's tablet, i.e., magnesium stearate.

While it is possible that the height of the peak at 3.5° 2θ or limit of detection varies based on whether the API is contaminated with valganciclovir HCl in crystalline form, Roche has not presented sufficient evidence with regard to what the area under the curve should be for the various forms of valganciclovir HCl. See Part II.D.2., supra. Further, Roche has not

presented evidence that additional peaks, at, for, example, 9.5° and 11.8° 2θ, are defining of the crystalline forms of valganciclovir HCl and present in Ranbaxy's tablets. See Part II.D.3., supra. Accordingly, the Court finds that the mere presence of a peak at 3.5° 2θ alone, as offered here, cannot sustain a finding of infringement because such a peak may be caused by either the crystalline forms X and Y or other possible semi-amorphous forms of valganciclovir HCl like Forms A and B. See Part II.D.2., supra. Since all of Roche's studies and its entire case is grounded on the presence of a single peak at 3.5° 2θ, the Court finds Roche's evidence lacking. While this flawed premise is enough to find that Roche fails to show by a preponderance of the evidence that Ranbaxy's tablets convert to valganciclovir HCl in crystalline form, and thus, infringe on the '953 patent, see Zenith, 19 F.3d at 1424 (explaining that the trial court must compare the claim with the purported infringing product after conversion to establish infringing use of the claimed compound), the Court nonetheless notes some of the additional flaws with each study.

The SGF study's methodology contains additional flaws because it fails to account for changes that may have been caused by processing between the time the tablet was removed from the SGF, ground, and the time it was actually tested, none of which appear to be adequately controlled or documented and all of which could induce ordering and thus influence the results of the study. See Part II.F.2., supra. Further, in the SGF study, as well as the seed study, Dr. Henck's normalized data plots manipulated the studies' findings, failed to demonstrate a baseline or comparison for the purported results, and prevented visual comparison of the results. See Parts II.F.1. & II.F.2., supra. Therefore, this study does not show that Ranbaxy's tablets ever contain the crystalline Forms X and Y of valganciclovir HCl.

Similarly, the pill tray study also fails to establish infringement. Roche did not carefully control nor record the process by which it tested Ranbaxy's tablets, and thus, it is unknown whether Roche's manner in conducting the study induced ordering or conversion to crystalline material. See Part II.F.3., supra. Moreover, Roche fails to show by a preponderance of the evidence that Ranbaxy's tablets contain valganciclovir HCl in crystalline form, within the meaning of the '953 patent. Admittedly, Dr. Henck had no opinion on the form of valganciclovir HCl shown, did not compare his XRD plots from the pill tray study to those of Forms X, Y, or other possible semi-amorphous forms, and had no reason to believe that the peaks he observed were not caused by the semi-amorphous forms. See Part II.F.3.b., supra. Roche's responds that "[t]he assertion that Dr. Henck's data show conversion to Form A, not to Form X or Y, is not material." RoRFF 13. The Court disagrees. Based on Roche's conversion theory, a showing that Ranbaxy's tablet contained Forms X or Y would serve to demonstrate that Ranbaxy infringed here; conversely, a finding that it converted to Form A, in accordance with this Court's findings – that it is unclear whether Form A is a mixture containing crystalline material or semi-amorphous in nature – does not establish infringement. Thus, Roche's studies do not establish by a preponderance of the evidence that Ranbaxy's tablets contain or convert to valganciclovir HCl in crystalline form. Accordingly, the Court finds that Roche's studies have not proven that Ranbaxy has literally infringed on the claimed invention in the '953 patent.

**2. Doctrine of Equivalents**

A second theory of infringement is based on the doctrine of equivalents. "For there to be infringement under the doctrine of equivalents, the accused product or process must embody

every element of a claim, either literally or by an equivalent." Novartis Pharms. Corp. v. EON Labs Mfg., 234 F. Supp. 2d 464, 467 (D. Del. 2002) (citing Warner-Jenkinson, 520 U.S. 17, 41 (1997)). In this case, Roche has not claimed that Ranbaxy has infringed on the '953 patent under the doctrine of the equivalents. Given that it is Plaintiff's burden to raise such a theory of recovery, Ranbaxy's arguments on why it is inappropriate and foreclosed here need not be addressed further. See Festo Corp. v. Shoketsu Kinzoku Kogyo Kabushiki Co., 535 U.S. 722, 740 (2002).

**C. Inducement of Infringement 35 U.S.C. § 271(b)**

Title 35, Section 271(b) of the U.S. Code governs inducement of infringement of a patent: "(b) Whoever actively induces infringement of a patent shall be liable as an infringer." 35 U.S.C. § 271(b). Inducement occurs by "'actively and knowingly aiding and abetting another's direct infringement.'" Upjohn Co. v. Syntro Corp., 1990 U.S. Dist. LEXIS 11512, at *16 (D. Del. Mar. 9, 1990) (quoting Water Technologies Corp. v. Calco, Ltd., 850 F.2d 660, 668 (Fed. Cir.), cert. denied, 109 S.Ct. 498 (1988)). To establish infringement on an inducement claim, "the patentee must establish first that there has been direct infringement, and second that the alleged infringer knowingly induced infringement and possessed specific intent to encourage another's infringement." ACCO Brands, Inc. v. ABA Locks Mfg. Co., 501 F.3d 1307, 1312 (Fed. Cir. 2007). Specific intent is described as a "showing that the alleged infringer's actions induced infringing acts and that he knew or should have known his actions would induce actual infringements." Id. (citing DSU Med. Corp. v. JMS Co., Ltd., 471 F.3d 1293, 1304 (Fed. Cir. 2006) (en banc in relevant part) (quoting Manville Sales Corp. v. Paramount Sys., Inc., 917 F.2d 544, 554 (Fed. Cir. 1990)).

While § 271(b) does not explicitly require knowledge, most courts find liability only for knowing and intentional inducement of infringement. Aventis Pharms., Inc. v. Barr Labs., Inc., 411 F. Supp. 2d 490, 515 (D.N.J. 2006) (citing Sims v. Western Steel Co., 551 F.2d 811, 817 (10th Cir. 1977); Knapp-Monarch Co. v. Casco Products Corp., 342 F.2d 622, 626-27 (7th Cir. 1965); Electronized Chem. Corp. v. Rad-Mat, Incorp., 288 F. Supp. 781, 784 (D. Md. 1968) (dictum); Nordberg Mfg. Co. v. Jackson Vibrators, Inc., 153 U.S.P.Q. 777, 784 (N.D. Ill. 1967); 4 Chisum on Patents § 17.04[1] at 17.46; Miller, Some Views on the Law of Patent Infringement by Inducement, 53 J.Pat.Off.Soc. 86, 119 (1971); contra Hauni Werke Koerber & Co., KG. v. Molins Ltd., 183 U.S.P.Q. 168, 171 (E.D. Va. 1974) (dictum)). Liability under § 271(b) requires a state of mind at least as culpable as is required for liability under section 271(c), which is "directed to encouraging another's infringement, not merely that the inducer had knowledge of the direct infringer's activities." Broadcom Corp. v. Qualcomm Inc., 543 F.3d 683, 697-8 (Fed. Cir. 2008) (citing DSU Med. Corp. v. JMS Co., Ltd., 471 F.3d 1293, 1304 (Fed. Cir. 2006) (en banc in relevant part)); Nordberg, 153 U.S.P.Q. at 784; Electronized Chem., 288 F. Supp. at 784; 4 Chisum on Patents § 17.04 at 17-47; see also Sims, 551 F.2d at 817 (inducer must be in the nature of an accessory before the fact to the infringement). Because inducement can be "established through circumstantial evidence," the court considers the totality of the circumstances when it determines liability for inducement of infringement. Abraxis Bioscience, Inc. v. Navinta, LLC, --- F. Supp. 2d ----, 2009 WL 2382251, at *14 (D.N.J. Aug. 3, 2009) (quoting Broadcom Corp., 543 F.3d at 699).

In this case, Roche offers Ranbaxy's own testing and Dr. Henck's seed study to prove inducement. Although Roche points to Ranbaxy's testing to show evidence of infringement, or

knowledge of the same, Ranbaxy's testing is merely a rejection test. See Part II.E.1., supra. The testing is not designed to determine what caused the spike or show that the peaks result from the crystalline rather than the noncrystalline forms of valganciclovir HCl. See Id. Ranbaxy did not conduct further analysis to determine the cause of any peak at 3.5°. See Id. Rather, it merely used it as a simple pass/fail test. See Id. Therefore, because Ranbaxy's testing does not demonstrate that its tablets contain Forms X or Y, this testing cannot be used as evidence of infringement or inducement.

Roche argues that the seed study additionally demonstrates that Ranbaxy knowingly used a manufacturing process for its tablets that permits crystalline seeds, which promotes the conversion of its API to crystalline form when exposed to moisture. As discussed herein, there are numerous flaws with the seed study. See Part II.F.1., supra. Dr. Henck did not perform the seed study, was not present when it was conducted, did not supervise or design it, and was unaware of its results until after it was completed. See Id. Dr. Henck conceded that there were numerous differences between SSCI's study and Ranbaxy's STP, which he could not explain, V3-97:12-103:15, and Dr. Henck could not identify those who were responsible for the testing. V3-103:16-24, 104:3-9. Roche did not present testimony from anyone who actually performed the study. Further, the XRD testing on the placebo lacked peaks at around 3.552° and 5.338° 2θ for magensium stearate, which demonstrates additional problems with the seed study. See Part II.F.1.b., supra. Even Dr. Henck conceded that if the plot for the placebo was incorrect, he did not know if it could be used to draw qualitative conclusions. V3-115:23-116:8. Indeed, because the placebo does not exhibit the peaks that the experts agree it should, the study is unsound and no qualitative conclusions may be drawn. Therefore, the Court finds that the seed

study data and Dr. Henck's testimony regarding this study lack foundation, are unreliable, and thus, they are inadmissible. Because Roche fails to establish by a preponderance of the evidence that Ranbaxy's tablets contained valganciclovir HCl in crystalline form, the seed study cannot serve as additional evidence that Ranbaxy had knowledge that its tablets infringed on the '953 patent, as Roche contends.

While there is evidence in the record that Ranbaxy was aware that its tablets would change in form upon exposure to air and moisture and thus it took precautions when packaging its product, evidence of knowledge without demonstrating direct infringement fails to satisfy the first element of a claim of infringement by inducement. Roche fails to demonstrate that Ranbaxy's tablets contain valganciclovir HCl in crystalline form because all of its testing relies on the flawed assumption that a peak at 3.5° 2θ is indicative of crystalline valganciclovir HCl. Indeed, this assumption does not distinguish between the patented forms of valganciclovir HCl, Forms X and Y, and other possible semi-amorphous forms of valganciclovir HCl, which are beyond the scope of the patent. See Part III.B.1., supra. Roche fails to show by a preponderance of the evidence the form of valganciclovir HCl to which Ranbaxy's tablets convert. Dr. Henck did not compare his XRD plots from the different studies to those of Forms X, Y, or other possible semi-amorphous forms, he had no opinion on the form of valganciclovir HCl shown, and he had no reason to believe that the peaks he observed were not caused by, for example Form A, which Roche has failed to prove is not semi-amorphous. V3-91:22-92:12; see Part II.F.3.b., supra. Thus, because Roche has not established that Ranbaxy's tablets infringe on the '953 patent, the Court cannot find that Ranbaxy infringed by inducement. See Zenith, 19 F.3d at 1424 (reversing a finding that the accused infringer induced infringement

where the patentee did not first establish infringing use of the claimed compound).

Roche also argues that the sale of Ranbaxy's generic valganciclovir HCl tablets will induce infringement of the '953 patent by patients because the API in Ranbaxy's product converts to crystalline form under normal conditions used by patients, such as storing the drug in a medical pill tray; this makes the patients direct infringers. Because, however, Roche fails to show by a preponderance of the evidence that Ranbaxy's tablets do convert to valganciclovir HCl in crystalline form, Forms X or Y, and thus that there has been direct infringement, the Court need not reach the second element of specific intent. See ACCO Brands, Inc, 501 F.3d at 1312. Accordingly, the Court finds that Roche cannot establish that Ranbaxy has induced infringement.

**D. Patent Validity**

In response to the argument by Roche that Ranbaxy infringes claim 1 of the '953 patent, Ranbaxy also raises the affirmative defense that the patent is invalid based on anticipation, failure of written description, and obviousness. The Court will address each of Ranabxy's assertions in turn.

"Issued patents have a strong presumption of validity in infringement proceedings." Al-Site Corp. v. VSI Int'l, Inc., 174 F.3d 1308, 1323 (Fed. Cir. 1999) (citing 35 U.S.C. § 282). To overcome the presumption of validity, the party challenging any claim of a patent has the heavy burden of proving facts supporting a determination of invalidity by clear and convincing evidence. Pfizer, Inc. v. Apotex, Inc., 480 F.3d 1348, 1359 (Fed. Cir. 2007). It is well-established that when an alleged infringer attacks the validity of an issued patent, the burden of persuasion rests with the attacker and never shifts to the patentee. Tech. Licensing

Corp., 545 F.3d at 1327. "[T]he challenger's burden is especially difficult when the prior art . . . was before the PTO examiner during prosecution of the application." Al-Site Corp., 174 F.3d at 1323; see also Metabolite Labs. Inc. v. Lab. Corp. of Am. Holdings, 370 F.3d 1354, 1368 (Fed. Cir. 2004) ("where the PTO previously considered the prior art reference, [there is] an even heavier burden to prove invalidity"). This extra-heavy burden applies also where one of the references being relied upon to show invalidity was not cited during prosecution, but is cumulative to other references that were of record. Id. "Although a patentee has the burden of going forward with rebuttal evidence should a challenger present a prima facie case of invalidity, the trial court has the responsibility to determine whether the challenger has met its burden of proof . . . considering the totality of the evidence, 'including any rebuttal evidence presented by the patentee.'" Purdue Pharma Products L.P. v. Par Pharmaceutical, Inc., --- F. Supp. 2d ----, 2009 WL 2486807, at *34 (D. Del. Aug. 14, 2009) (quoting Pfizer, Inc. v. Apotex, Inc., 480 F.3d at 1360)).

**1. Allegations That the Claimed Invention Was Anticipated**

Roche argues that Ranbaxy has waived any assertion that the '953 patent claims are invalid under 35 U.S.C. § 102 because Ranbaxy failed to set forth in the Final Pretrial Order any defense that the subject matter claimed by the '953 patent is unpatentable for anticipation. In Phoenix Canada Oil Co. v. Texaco, Inc., 842 F.2d 1466, 1476 (3d Cir. 1988), the Third Circuit determined that the district court acted in its discretion when it rejected a claim for consequential damages as untimely asserted because it was after trial but not in the pretrial order. Similarly, Ranbaxy failed to assert invalidity based on any of the subsections of 35 U.S.C. § 102 in the Final Pretrial Order here. Further, Ranbaxy fails to pursue this argument in

its Response to Roche's Proposed Findings of Fact and Conclusions of Law, or dispute that its claim under § 102 was raised in an untimely manner in the instant case. Accordingly, the Court dismisses Ranbaxy's § 102 claim because it was untimely asserted.[47]

### 2. Allegations That the '953 Patent Would Be Invalid For Lack Of Written Description Support

Ranbaxy asserts that this Court should find that the '953 patent should be invalid for lack of written description support. A patent must include a "written description" that describes the claimed invention in sufficient detail so that a person of ordinary skill in the art would reasonably conclude that the inventor had possession of the claimed invention at the time of filing. 35 U.S.C. § 112(1); Moba v. Diamond Automation, Inc., 325 F.3d 1306, 1319 (Fed. Cir. 2003). Possession is shown through words, structures, figures, diagrams, or formulas that fully set forth the claimed invention. Lockwood v. American Airlines, Inc., 107 F.3d 1565, 1572 (Fed. Cir. 1997). The written description requirement "guards against the inventor's overreaching by insisting that he recount his invention in such detail that his future claims can be determined to be encompassed within his original creation." Vas-Cath, Inc. v. Mahurkar, 935 F.2d 1555, 1561 (Fed. Cir. 1991). "In order to satisfy the written description requirement, the disclosure as originally filed does not have to provide in haec verba support

[47]Nonetheless, the Court notes that this argument is unavailing because there is no contention that the pure amorphous form of valganciclovir HCl cannot be made without infringement of the '953 patent nor that the amorphous form spontaneously converts to the crystalline form. See Part III.A., supra; cf. SmithKline, 403 F.3d at 1345 ("[The patentee] did not offer any evidence that [the compound] can be produced in facilities that are not seeded."). If the amorphous form of valganciclovir HCl could not be produced without crystalline seeds, the Court would necessarily invalidate the patent because the prior art could not be practiced without infringing on the '953 patent, see SmithKline, 403 F.3d at 1345; however, this is not the case before the Court.

for the claimed subject matter at issue." Yingbin-Nature (Guangdong) Wood Industry Co., Ltd. v. International Trade Com'n, 535 F.3d 1322, 1334 (Fed. Cir. 2008) (quoting Purdue Pharma L.P. v. Faulding Inc., 230 F.3d 1320, 1323 (Fed. Cir. 2000)). "Nonetheless, the disclosure of the prior application must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, (the inventor) was in possession of the invention." Id. at 1334-35 (internal quotations and omitted). That inquiry of determining precisely how close the original description must come to comply with the description requirement of § 112 is a factual one and must be assessed on a case-by-case basis. See Purdue Pharma, 230 F.3d at 1323; Vas-Cath, 935 F.2d at 1561.

Ranbaxy contends that because the '953 patent never refers to XRD, does not teach that XRD should be used to assess crystallinity, nor does it point to trace crystals in an otherwise noncrystalline material, DTX-1; V3-72:21-75:1; V6-71:4-7, the patent does not reasonably convey that the inventors considered trace crystalline material, only detectable by XRD, to be a material "in crystalline form." This argument is not persuasive because a person of ordinary skill in the field would know that XRD is a reliable means to test for valganciclovir HCl in crystalline form. See Part III.A., supra. Indeed, the co-inventors of the '953 patent used XRD analysis, and Ranbaxy's own STP employs XRD as a rejection test for crystallinity. Id. While the '953 patent does not provide a description to demonstrate that the inventors considered an otherwise noncrystalline material, containing trace amounts of crystalline valganciclovir HCl, to be "in crystalline form," the Court has already determined that the '953 patent does cover amorphous valganciclovir HCl containing crystalline material detectable by XRD. Id. It does not, however, cover any possible forms of semi-amorphous material. As

such, Ranbaxy's argument in this regard is unavailing. Accordingly, the Court finds that the '953 patent is not invalid for lack of written description support.

### 3. Allegations That the Claimed Invention Was Obvious in Light of Prior Art

Ranbaxy asserts that it proves by clear and convincing evidence that the '953 patent is invalid for obviousness under 35 U.S.C. § 103. Obviousness under § 103 is a legal issue based on four underlying factual inquiries: (1) the scope and content of the prior art; (2) the differences between the prior art and the claimed invention; (3) the level of ordinary skill in the art; and (4) objective evidence of nonobviousness, including "secondary considerations as commercial success, long felt but unsolved needs, failure of others, etc." KSR Int'l Co. v. Teleflex Inc., 550 U.S. 398, 406 (2007), (citing Graham v. John Deere Co., 383 U.S. 1, 17 (1966)). The patent challenger must establish a prima facie of obviousness before a finding of invalidity. Merck Sharp & Dohme Pharms., SRL v. Teva Pharms USA., Inc., et al., No. 07-1596, (D.N.J. Aug. 19, 2009) (citing Yamanouchi Pharm. Co. v. Danbury Pharmacal, Inc., 231 F.3d 1339, 1345 (Fed. Cir. 2000); Kaufman Co. v. Lantech, Inc., 807 F.2d 970, 974-75 (Fed. Cir. 1986)). For a chemical compound, a prima face case of obviousness requires: (1) structural similarity between the claimed compound and the prior art; (2) motivation to modify the prior art compound(s) to arrive at the claimed molecule; and (3) a reasonable expectation that the new compound will be effective for its intended purpose. See Eli Lily and Co. v. Zenith Goldline Pharms., 471 F.3d 1369, 1377 (Fed. Cir. 2006). The Court should also consider the unique properties of the claimed compound. Id. at 1378. Section 103 requires analysis of a claimed invention as a whole, and it is error to consider the obviousness of individual claim limitations in isolation. See Ruiz v. A.B. Chance Co., 357 F.3d 1270, 1275

(Fed. Cir. 2004).

In KSR, the Supreme Court relaxed the standard for evaluating obviousness in cases where the prior art provided "a finite number of identified, predictable solutions"[48] to the problem the inventor was trying to solve. 550 U.S. at 421. The Federal Circuit has distinguished KSR, from the facts presented in cases involving pharmaceutical compounds, noting that the design of a new drug involves a large number of steps and choices, the results of which are unpredictable. See, e.g., Abbott Labs. v. Sandoz, Inc., 2008 U.S. App. LEXIS 21880, at *30 (Fed. Cir. Oct. 21, 2008) (distinguishing KSR and holding drug nonobvious where there was no "identified, predictable solution"). In Sandoz, the Federal Circuit explained that a claimed invention may be invalid for obviousness if it was "obvious to try" a combination of elements, after considering "characteristics of the science or technology, its state of advance, the nature of the known choices, the specificity or generality of the prior art, and the predictability of results in the area of interest." Id. at *29.

As discussed herein, there are numerous differences between each prior art reference and the claimed invention. See Part II.G.2.a., supra. Even if the references are combined, they do not disclose all of the features of the '953 invention. The '953 patent covers valganciclovir HCl in crystalline form, but the prior art either did not discuss the crystallinity of any compound, or when it did, it was about the crystallinity of a completely different compound. Furthermore, Ranbaxy offered very little evidence to rebut Roche's assertion that valganciclovir HCl in crystalline form is non-obvious and difficult to produce when compared

[48]KSR involved the obviousness of a patented gas pedal for automobiles that combined the features of a prior art adjustable acceleration pedal with a prior art sensor for detecting an acceleration pedal's position. Id. at 406.

to other forms of valganciclovir HCl. Ranbaxy's experts, Drs. Gokel and Sloan, did not address the issue of diastereomers and the ability of the diastereomers to form a crystalline material. V10-12:3-25. In fact, Dr. Gokel did not mention diastereomers at all in his direct testimony. V8-83:14-21. Ranbaxy's argument that the prior art makes valganciclovir HCl, the compound, obvious is a finding the PTO made when it rejected the patent, and is not before this Court.

Ranbaxy also argues that the prosecution history suggests that Roche presented incomplete data with regard to the difficulty in producing the crystalline form of the compound. Specifically, Ranbaxy argues that Roche did not exhaust all commonly known methods of preparing a compound in crystalline form. Even if this were to raise some doubt as to whether valganciclovir HCl in crystalline form is difficult to produce, Ranbaxy has offered no evidence that there is any other commonly available method that the PTO did not consider that would make valganciclovir HCl in crystalline form easy to produce, nor that such a method was available at the time the PTO considered the '953 patent application. Thus, Ranbaxy has not established a prima facie case of obviousness. While this ends the inquiry on invalidity, for the sake of completeness, the Court will complete the analysis.

Although this Court is not bound by the PTO's decision to issue a patent,[49] the Federal Circuit has stated that a challenger's burden of showing invalidity by clear and convincing evidence may be more easily carried when relying on prior art that was not considered by the

[49]"The courts are the final arbiter of patent validity and, although courts may take cognizance of, and benefit from, the proceedings before the patent examiner, the question is ultimately for the courts to decide, without deference to the ruling of the patent examiner." Quad Environ. Techs. Corp. v. Union Sanitary Dist., 946 F.2d 870, 876 (Fed. Cir. 1991).

examiner during patent prosecution. See, e.g., Uniroyal, Inc. v. Rudkin-Wiley Corp., 837 F.2d 1044, 1050 (Fed. Cir. 1988). Similarly, the challenger's burden may be more difficult to carry when relying on prior art that was considered by the examiner. See, e.g., Hewlett-Packard Co. v. Bausch & Lomb Inc., 909 F.2d 1464, 1467 (Fed. Cir. 1990) (reiterating that meeting the clear and convincing evidence standard is especially difficult when relying on art the PTO previously considered). The only prior art that Ranbaxy presents here that was not before the PTO is the 1993 Beauchamp paper. This paper, however, reviews, inter alia, the work reported in the 1992 Beauchamp paper and is cumulative to the papers of record during prosecution of the '953 patent, V8-77:6-12, V7-124:9-24, and thus does not assist Ranbaxy in satisfying its burden. Al-Site Corp., 174 F.3d at 1323 ("[T]he challenger's burden is especially difficult when the prior art. . . was before the PTO examiner during prosecution of the application" and where one of the references being relied upon to show invalidity was not cited during prosecution, but is cumulative to other references that were of record.); see also Metabolite Labs. Inc., 370 F.3d at 1368 ("where the PTO previously considered the prior art reference, [there is] an even heavier burden to prove invalidity").

Ranbaxy also points to the Roche 1995 memorandum to show obviousness. Ranbaxy argues that the 1995 memorandum shows that the discovery of valacyclovir and its excellent oral bioavailability, described by the 1992 Beauchamp paper, led Roche to the discovery of valganciclovir. It is well-settled, however, that obviousness cannot be shown through a memorandum prepared by an inventor after the invention has been made. See Std. Oil Co. v. Am. Cyanamid Co., 774 F.2d 448, 454 (Fed. Cir. 1985) ("[O]ne should not go about determining obviousness under §103 by inquiring into what patentees (i.e., inventors) would

have known or would likely have done, faced with the revelations of references."); see also KSR, 550 U.S. at 420-21 (same). While the Court finds that the 1995 memorandum demonstrates that Roche was interested in researching the commercial viability of valganciclovir, this memorandum was written after Roche submitted its patent application in 1994 for the valganciclovir compound. Thus, because at the time the memorandum was written, Roche had already "invented" the compound, the memorandum, at best, indicates Roche's desire to discover possible commercial uses of its own invention. Therefore, the Court finds Ranbaxy's use of the 1995 memorandum unavailing to support its argument that the '953 patent was obvious.

With regard to the objective evidence or secondary considerations, such as commercial success, long-felt but unmet need, and industry acclaim, the Court finds that these considerations do not demonstrate obviousness; instead, they support Roche's contention that the '953 patent was not obvious at the time of its issuance. "Evidence of commercial success, or other secondary considerations, is only significant if there is a nexus between the claimed invention and the commercial success." Ormco Corp. v. Align Tech., Inc., 463 F.3d 1299, 1311-12 (Fed. Cir. 2006). The patentee has the burden to show this connection or nexus between the objective evidence and the merits of the claimed invention to warrant consideration of the objective evidence in the determination of nonobviousness. Demaco Corp. v. F. Von Langsdorff Licensing Ltd., 851 F.2d 1387, 1392 (Fed. Cir. 1988).

Valycte has undeniably seen commercial success and has satisfied a long-felt but unmet need based on its API, valganciclovir HCl in crystalline form, as disclosed and claimed in the patent. See Part II.G.2.c., supra. The sales of Valcyte over other drugs used to treat or prevent

CMV disease establish that doctors prescribe Valcyte because of its higher oral bioavailability and ease of administration. See Id. Thus, Roche has presented a prima facie case of the required nexus between the claimed invention, which shared the efficacy of IV ganciclovir with the safety and convenience of oral dosing, and the commercial success. Ranbaxy, however, argues that Valcyte's sales are not driven by the fact that its valganciclovir HCl is in crystalline form, but because of the oral bioavailability of valganciclovir HCl. V1-112:4-13, 116:20-117:23; V8-145:17-147:21; V9-15:23-19:4. While it is possible that Ranbaxy's contention that valganciclovir HCl in a different physical form, namely, amorphous form, can or will be just as successful as valganciclovir HCl is in crystalline form, the record does not support such a conclusion here. See Part II.G.2.c., supra. Valcyte's commercial success, while not dispositive, weighs in favor of Roche, and further supports the Court's prior determination that valganciclovir HCl in crystalline form was not obvious in light of prior art at the time the patent was issued. See Merck & Co., Inc. v. Teva Pharm. USA, Inc., 395 F.3d 1364, 73 U.S.P.Q.2d 1641 (Fed. Cir. 2005) (finding that commercial success is not significantly probative of non-obviousness where others are barred from acting on the prior art). Accordingly, the Court finds that Ranbaxy has failed to meet its heavy burden in demonstrating by clear and convincing evidence that the '953 is invalid for nonobviousness.

**E. Exceptional Case Does Not Exist Here**

Ranbaxy seeks a finding that the instant action is exceptional, warranting an award of attorney's fees and costs, because Dr. Henck manipulated his plots of the XRD data. The requirements for awarding attorney's fees under Section 285 are: "(1) the case must be exceptional, (2) the fees must be reasonable, and (3) the fees may be awarded only to the

prevailing party." Gentry Gallery Inc. v. Berkline Corp., 134 F.3d 1473, 1480 (Fed. Cir. 1998) (quoting Machinery Corp. of Am. v. Gullfiber AB, 774 F.2d 467, 470 (Fed. Cir. 1985)). An alleged infringer who has not infringed is the prevailing party and that "other defenses, such as invalidity of the patent, were unsuccessful or withdrawn, does not change [that] outcome." Brooks Furniture Manufacturing v. Dutailier Int'l Incorp., 393 F.3d 1378, 1381 (Fed. Cir. 2005).

Section 285 provides an award of attorney's fees in limited circumstances and it is not intended to be an "ordinary thing in patent suits." Forest Laboratories, Inc. v. Abbott Laboratories, 339 F.3d 1324, 1329 (2d Cir. 2003) (quoting Rohm & Haas Co. v. Crystal Chem. Co., 736 F.2d 688, 690-91 (Fed. Cir.1984) (quoting S.Rep. No. 79-1503 (1946))). A party may seek an "award [of] attorney's fees under section 285" if it successfully argues that the instant case is "exceptional." 35 U.S.C. §§ 271(e)(4), 285. The party must establish that the case is exceptional by clear and convincing evidence. Wedgetail Ltd. v. Huddleston Deluxe, Inc., 576 F.3d 1302, 1304 (Fed. Cir. 2009) (internal citations and quotations omitted). In Serio-US Industries, Inc. v. Plastic Recovery Technologies Corp., 459 F.3d 1311, 1321-22 (Fed. Cir. 2006), the Federal Circuit explained that "exceptional cases usually feature some material, inappropriate conduct related to the matter in litigation, such as willful infringement, fraud or inequitable conduct in procuring the patent, misconduct during litigation, vexatious or unjustified litigation, conduct that violates Federal Rule of Civil Procedure 11, or like infractions." "Absent misconduct in the litigation or in securing the patent, a trial court may only sanction the patentee if both the litigation is brought in subjective bad faith and the litigation is objectively baseless." E-Pass Technologies, Inc. v. 3Com Corp., 559 F.3d 1374,

1379 (Fed. Cir. 2009) (quoting Serio-US Industries, 459 F.3d at 1322 (citations omitted)) (emphasis in original omitted). A lawsuit is objectively baseless when no reasonable litigant could realistically expect success on the merits. Professional Real Estate Investors v. Columbia Pictures Indus., 508 U.S. 49, 60 (1993).

In this case, Ranbaxy, the prevailing accused infringer, does not contend that Roche engaged in misconduct in securing the patent. See Brooks Furniture Mfg., 393 F.3d at 1381. Instead, Ranbaxy argues that this case is exceptional because Roche knew or should have known that Dr. Henck "manipulated the data" on which Roche bases its claims for direct and induced infringement. Specifically, Ranbaxy asserts that Dr. Henck knowingly manipulated and misrepresented scientific data by altering the appearance of the data points and drawing conclusions based upon his visual inspections of these graphical representations. RaFF 26-34; see Parts II.F.1. & II.F.2., supra. According to Ranbaxy, because Roche was aware of these misrepresentations, it should have withdrawn its claims. RaCL 70. Thus, Ranbaxy's argument for an award of fees is based on the quality of evidence Roche presented at trial. The Court finds that Dr. Henck and Roche merely offered flawed scientific reporting and analysis at trial, but did not engage in inappropriate litigation misconduct contemplated by § 285. See Wedgetail Ltd., 576 F.3d at 1304-05 (discussing how § 285 provides attorney's fees and costs only in very limited circumstances, which must be shown by clear and convincing evidence).

As Ranbaxy has failed to establish by clear and convincing evidence that Roche engaged in misconduct in the litigation or in securing the patent, the Court may award attorney's fees and costs only if Roche brought this lawsuit in subjective bad faith and the litigation is objectively baseless. The Federal Circuit has repeatedly stated that:

> A patentee that has a good faith belief that its patents are being infringed violates no protected right when it so notifies infringers. Accordingly, a patentee must be allowed to make its rights known to a potential infringer so that the latter can determine whether to cease its allegedly infringing activities, negotiate a license if one is offered, or decide to run the risk of liability and/or the imposition of an injunction.

Serio-US Industries, Inc., 459 F.3d at 1321. As evident from the case history, there were genuine issues of material fact that needed to be resolved at trial. In addition, the claim construction of the patent in suit is neither clear on its face nor easy to interpret. See Part III.A., supra. Because Roche could conclude that this lawsuit is reasonably calculated to elicit a favorable outcome, the Court finds that the challenged litigation is not objectively baseless. See Professional Real Estate Investors, 508 U.S. at 60. Therefore, Roche did not bring this lawsuit in bad faith nor was the litigation objectively baseless. Indeed, Roche sought to protect the infringement of its patent when filing this lawsuit. Accordingly, because Ranbaxy has failed to show that the instant case rises to the level of an exceptional case, as required under § 285, the Court declines Ranbaxy's application for fees and costs here.

Similarly, while Roche has preserved its right to submit a formal motion, based on the record, an exceptional case award is not appropriate here. Not only there has there been no litigation misconduct, such as vexatious or unjustified litigation or frivolous filings nor willful infringement, warranting a finding that this case is exceptional, Roche is not a prevailing party on its infringement claim and cannot recoup attorney's fees or costs under § 285. See Brooks Furniture Mfg., 393 F.3d at 1381; Glaxo Group Ltd. v. Apotex, Inc., 376 F.3d 1339, 1349 (Fed. Cir. 2004). Accordingly, each side shall bear its own costs.

## IV. Conclusion

For the foregoing reasons, the Court finds that the '953 patent is not invalid. Further, Roche has not shown that Ranbaxy has infringed on the '953 patent.

/s/ Freda L. Wolfson
The Honorable Freda L. Wolfson
United States District Judge

Date: September 30, 2009