

IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE

EXELIXIS, INC.,
Plaintiff,
v.
MSN LABORATORIES PRIVATE
LIMITED, et al.,
Defendants.

J. Caleb Boggs Courthouse
844 North King Street
Wilmington, Delaware

Tuesday, October 24, 2023
8:29 a.m.
Bench Trial

BEFORE: THE HONORABLE RICHARD G. ANDREWS, U.S.D.C.J.

APPEARANCES:

MORRIS NICHOLS ARSHT & TUNNELL LLP
BY: ANTHONY D. RAUCCI, ESQUIRE
BY: JACK B. BLUMENFELD, ESQUIRE

-and-

WILMERHALE
BY: KEVIN S. PRUSSIA, ESQUIRE
BY: LISA J. PIROZZOLO, ESQUIRE
BY: AMY KREIGER WIGMORE, ESQUIRE
BY: JONATHAN A. COX, ESQUIRE
BY: KEVIN M. YURKERWICH, Ph.D.

For the Plaintiff

1 APPEARANCES CONTINUED:

2 HEYMAN ENERIO GATTUSO & HIRZEL LLP

3 BY: DOMINICK GATTUSO, ESQUIRE

4 -and-

5 WINSTON & STRAWN LLP

6 BY: GEORGE LOMBARDI, ESQUIRE

7 BY: BRYCE COOPER, ESQUIRE

8 BY: KURT A. MATHAS, ESQUIRE

9 BY: ELIZABETH GRDEN, ESQUIRE

10 BY: KEVIN BOYLE, ESQUIRE

11 BY: BRIAN O'GARA, ESQUIRE

12 For the Defendants

13 Also Present:

14 Dr. Kondal Reddy Bairy

15 *** PROCEEDINGS ***

08:08:45 16 DEPUTY CLERK: All rise. Court is now in

08:08:45 17 session. The Honorable Richard G. Andrews presiding.

08:13:15 18 THE COURT: All right. Good morning. Please be

08:29:39 19 seated.

08:29:40 20 Are we ready to begin or what?

08:29:44 21 MR. PRUSSIA: We are, Your Honor. We could

08:29:50 22 either address the issue we discussed last night now or

08:29:52 23 after Lepore's cross is over.

08:29:56 24 THE COURT: Well, if it's ready to be discussed

08:29:57 25 now, you might as well discuss it now and we'll give whoever

Shah - Direct

02:32:52 1 tablet manufacturing process and gets the tablets to
02:32:57 2 produce, you know, consistent product.

02:33:00 3 And in particular, I would say there was
02:33:03 4 obviously lots of -- lots of areas that had to be optimized
02:33:08 5 for the API and the product, particularly for the API, there
02:33:11 6 was an impurity, the 6,7-dimethoxy-quinoline-4-ol, and that
02:33:17 7 was particular challenge, certainly from the API standpoint.

02:33:21 8 Q. What challenges were presented -- presented in
02:33:24 9 controlling the impurity profile of the API?

02:33:29 10 A. Right. So in particular with this 1-1 impurity,
02:33:33 11 because it was a starting material in the API synthetic
02:33:37 12 process and an impurity but also a degradant, it was
02:33:41 13 particularly challenging because the degradant would form
02:33:44 14 during the subsequent manufacturing steps of the API,
02:33:48 15 therefore particularly challenging to control.

02:33:51 16 Q. Now, can we refer to the 6,7-dimethoxy-quinoline-4-ol
02:33:55 17 impurity as the 1-1?

02:33:56 18 A. Yes.

02:33:57 19 Q. Okay. What is the significance that 1-1 appears as
02:34:01 20 both starting material and as a degradant?

02:34:04 21 A. Well, particularly challenging because, you know, if
02:34:07 22 it was just a starting material, you would expect that with
02:34:10 23 subsequent chemistry steps. You would be able to purge that
02:34:13 24 material and essentially eliminate it prior to the
02:34:16 25 completion of the manufacturing process, but in this

Shah - Direct

02:34:18 1 particular case, because the 1-1 was a degradant, it was
02:34:23 2 basically decomposing from the subsequent chemistry steps.
02:34:26 3 And as it was decomposing, it was showing itself up in the
02:34:30 4 finished API and, therefore, quite challenging to control.

02:34:35 5 Q. How did Exelixis discover the 1-1 impurity?

02:34:37 6 A. Right. So Exelixis, initially there was a in silico
02:34:43 7 screen that was conducted where all the different potential
02:34:46 8 impurities and actual impurities of the API were examined
02:34:50 9 through the in silico process which is a computational
02:34:54 10 process that provides structural alerts for impurities, and
02:34:58 11 the 1-1 impurity was found to be positive in that particular
02:35:03 12 evaluation. And then the unequivocal confirmation that the
02:35:07 13 1-1 impurity was indeed positive for genotoxicity was
02:35:13 14 through what's called an Ames assay or a bacterial assay,
02:35:17 15 which essentially confirmed that the 1-1 was indeed a
02:35:20 16 genotoxic impurity.

02:35:22 17 Q. What is a genotoxic impurity?

02:35:23 18 A. So at a high level, a genotoxic impurity is
02:35:28 19 essentially a compound that could damage DNA and potentially
02:35:33 20 cause cancer in humans.

02:35:37 21 Q. Please mark PTX-35 on the screen.

02:35:40 22 It's Tab 6 of your binder. What is this
02:35:43 23 document?

02:35:43 24 A. This is the manufacturing process development section
02:35:48 25 of the NDA that was submitted to the FDA.

MacMillan - Direct

03:59:48 1 Q. Have you heard testimony in the course of this case
03:59:51 2 about genotoxic impurities?

03:59:52 3 A. Yes, I have.

03:59:54 4 Q. What, if anything, does Brown disclose about whether
03:59:56 5 the 1-1 compound is genotoxic?

03:59:59 6 A. The Brown document does not disclose that the 1-1
04:00:03 7 impurity is genotoxic.

04:00:05 8 Q. Are you familiar with a term "hydrolysis"?

04:00:07 9 A. I am.

04:00:08 10 Q. What is hydrolysis?

04:00:10 11 A. Hydrolysis, as the name suggests, is basically taking
04:00:14 12 the atoms, the elements of water and adding it to any other
04:00:19 13 compound to either create a new compound that incorporates
04:00:22 14 water or multiple compounds that incorporates the constant
04:00:25 15 the elements of water.

04:00:26 16 Q. You testified about degradation. Can hydrolysis play
04:00:31 17 a role in degradation?

04:00:32 18 A. Yes, it can.

04:00:35 19 Q. Is that a desirable or undesirable result?

04:00:38 20 A. Most of the time, it's undesirable. There are a few
04:00:41 21 occasions where hydrolysis is desired, but it's when
04:00:43 22 degradation happens, but for the most part, it's
04:00:47 23 undesirable.

04:00:47 24 MS. WIGMORE: If we could please have PDX-5.

04:00:47 25 BY MS. WIGMORE:

MacMillan - Direct

04:00:51 1 Q. Dr. MacMillan, in February of 2011, would a POSA,
04:00:55 2 looking at the synthetic scheme, Scheme 1 in Brown, have
04:00:58 3 expected the 1-1 impurity to form through hydrolysis?

04:01:02 4 A. No, they would not.

04:01:03 5 Q. And using PDX-5, can you please explain why not?

04:01:07 6 A. Yes. Would it be okay if I use a laser pointer?

04:01:10 7 THE COURT: Sure.

04:01:11 8 THE WITNESS: Okay. Thank you.

04:01:12 9 So, just to explain this the way I think an
04:01:16 10 organic chemist or a POSA would look at this, if you look at
04:01:19 11 this molecule, you can see there's these two hexagons, which
04:01:23 12 are aromatic rings. And you can see in red these are two
04:01:27 13 chemical rings and the O for oxygen. That's the ether.
04:01:29 14 That's the biaryl ether.

04:01:32 15 To organic chemists, this is a very, very, very
04:01:35 16 stable compound. It's a stable functional group to the
04:01:38 17 point that they would not expect that that would undergo
04:01:41 18 hydrolysis.

04:01:41 19 BY MS. WIGMORE:

04:01:43 20 Q. Dr. MacMillan, the compound shown on this slide is
04:01:45 21 what compound?

04:01:46 22 A. Oh, I apologize. This compound shown on the slide is
04:01:49 23 cabozantinib, and it's referring to the two red bonds in the
04:01:53 24 red oxygen on the slide.

04:01:55 25 Q. Now, would the formation of the malate salt make

MacMillan - Direct

04:01:58 1 hydrolysis more likely?

04:02:00 2 A. No.

04:02:02 3 Q. What are the reasons for that?

04:02:03 4 A. Well, so the formation of a malate salt means if --
04:02:07 5 what would happen is this nitrogen which is shown here will
04:02:10 6 undergo, which is the bottom of the hexagon of cabozantinib,
04:02:13 7 would undergo the proton -- the protonation of the acid
04:02:16 8 would go right there. That would make it more electron
04:02:19 9 deficient. However, you can see on the left-hand side of
04:02:22 10 these two oxygens shown in blue, and these are donating
04:02:27 11 electron density into these ring systems.

04:02:29 12 What that's doing is effectively deactivating or
04:02:33 13 negating the impact of this proton being on the nitrogen.
04:02:37 14 So, again, the stability of this is such the person of
04:02:40 15 ordinary skill would not expect it to undergo hydrolysis.

04:02:42 16 Q. Would a POSA have expected that malic acid could
04:02:47 17 catalyze the formation of the 1-1 impurity?

04:02:49 18 A. No, they would not.

04:02:51 19 Q. What are the reasons for that?

04:02:52 20 A. Malic acid is a relatively weak acid in the grand
04:02:57 21 scheme of acids because the proton being here would not
04:03:02 22 sufficiently activate this because of this electron density
04:03:05 23 being added in. As such the person of ordinary skill in the
04:03:08 24 art would not expect that the malic acid to activate this to
04:03:12 25 towards hydrolysis.

MacMillan - Direct

04:03:13 1 Q. And just for the record, the proton you're referring
04:03:16 2 to is the nitrogen at the bottom of the hexagon in the
04:03:20 3 cabozantinib diagram?

04:03:21 4 A. Yeah, there's three nitrogens in this compound. It's
04:03:23 5 the one lowest on the slide at the bottom of the hexagon.
04:03:27 6 That's the one that would undergo what's called protonation
04:03:30 7 where the hydrogen would associate with it.

04:03:31 8 Q. So, what did you conclude about whether a POSA would
04:03:34 9 have expected the 1-1 impurity to form by degradation in the
04:03:39 10 Brown process?

04:03:39 11 A. They would not expect that to happen.

04:03:42 12 Q. Was the structure that we know today as cabozantinib
04:03:46 13 in clinical development as of the priority date for the
04:03:49 14 '349 patent?

04:03:50 15 A. Yes, it was.

04:03:52 16 Q. What was the compound known today as cabozantinib
04:03:55 17 referred to in the published literature before 2010?

04:03:59 18 A. In the -- excuse me. In the public literature it had
04:04:03 19 that anonymous name. It was known as XL184. That was the
04:04:07 20 name that was given to it for those -- while it was in
04:04:09 21 clinical development.

04:04:10 22 Q. Was there any definitive connection in the literature
04:04:14 23 between XL184 and cabozantinib at the time of the
04:04:18 24 '349 patent invention?

04:04:21 25 A. As I said, it was -- XL184 was an anonymous name,

MacMillan - Direct

04:08:07 1 A. That is correct.

04:08:08 2 Q. And is that all part of the first step of Brown
04:08:11 3 Scheme 1?

04:08:11 4 A. That is just the first step, yes.

04:08:13 5 Q. What would a person of skill in the art have expected
04:08:16 6 regarding the amount of the 1-1 impurity if any, that would
04:08:20 7 remain after Step 1.1?

04:08:22 8 A. They would expect it to be a very small amount of any
04:08:26 9 starting material left at that stage.

04:08:29 10 Q. Is Step 1.1 the only step disclosed in Example 1?

04:08:33 11 A. No, it's not.

04:08:34 12 MS. WIGMORE: If we could please have PDX-6.

04:08:34 13 BY MS. WIGMORE:

04:08:37 14 Q. What is shown here?

04:08:38 15 A. This is all of the steps involved in Scheme 1, and
04:08:43 16 the critical part here is you can see there's multiple
04:08:45 17 chemical steps beyond just this first step.

04:08:48 18 MS. WIGMORE: Let's have PDX-7.

04:08:48 19 BY MS. WIGMORE:

04:08:51 20 Q. What is shown on PDX-7?

04:08:53 21 A. What I'm showing here is you can see there's Step 1.
04:08:56 22 That's the one we just stalked about, but you can see
04:08:58 23 there's Step 2. And then there's the purification process
04:09:02 24 associated with this. Step 3, same again. Step 4,
04:09:06 25 purification process. Step 5, purification process all the

MacMillan - Direct

04:09:10 1 way before you get to the (L)-malate salt of cabozantinib.

04:09:14 2 Q. Now, I noticed you haven't marked the bottom

04:09:17 3 left-hand corner with any step. Why is that?

04:09:19 4 A. So the bottom left-hand corner, these are a branching

04:09:23 5 point. You can see this is a synthetic sequence where you

04:09:26 6 have one sequence. They're called the longest linear

04:09:29 7 sequence. That makes sense because you can see it's the

04:09:32 8 longest number of steps.

04:09:33 9 You can also see there's this branching point

04:09:35 10 that comes in at this point here which is a shorter number

04:09:37 11 of steps. So I've only focused on the steps which begin

04:09:41 12 from the 1-1 impurity starting material.

04:09:45 13 Q. So if we're looking at Scheme 1, it's basically the

04:09:47 14 first two rows; is that right?

04:09:49 15 A. That's correct.

04:09:51 16 Q. Now, looking at Scheme 1 as a whole, would a person

04:09:55 17 of skill in the art have been motivated to control for the

04:09:57 18 starting material after all those steps were completed?

04:10:01 19 A. No, they would not.

04:10:02 20 Q. And what are the reasons they would not?

04:10:04 21 A. Because as we've already mentioned, there's basically

04:10:08 22 very little of this starting material after Step 1. Now,

04:10:11 23 keep in mind you have all of these other steps and each one

04:10:15 24 of these has a purification component to it. But beyond

04:10:18 25 that, you're also adding reagents which could also react

MacMillan - Direct

04:10:22 1 with it to also remove or purge as we've heard earlier
04:10:26 2 today.

04:10:27 3 Because of all these purification steps, these
04:10:29 4 purging steps, a person of ordinary skill would not believe
04:10:32 5 there would be any of this material way over here ending up
04:10:34 6 way down here.

04:10:35 7 Q. And by "way over here," you're referring to Step 1?

04:10:40 8 A. At the beginning of Step 1, ending up at the end of
04:10:43 9 Step 5.

04:10:43 10 Q. And so what does that mean as to whether they would
04:10:45 11 be motivated to control for it?

04:10:47 12 A. Well, if they don't believe that it would be there,
04:10:50 13 they would have no expectation it would be there. There
04:10:53 14 would not be a motivation to control for it.

04:10:55 15 Q. Now, moving to your next opinion. You were here for
04:11:01 16 Dr. Shah' testimony; is that right?

04:11:02 17 A. Yes.

04:11:03 18 Q. And what did he explain about what Exelixis learned
04:11:08 19 about the 1-1 impurity and their development program?

04:11:11 20 A. They learned --

04:11:12 21 MR. MATHAS: I object. Dr. Shah just testified,
04:11:14 22 and asking this witness to repeat it is cumulative and
04:11:18 23 irrelevant.

04:11:19 24 THE COURT: Well, I assume he's going to have
04:11:21 25 some opinion about it or say it somehow -- can you rephrase?

Myerson - Direct

04:44:00 1 MS. PIROZZOLO: Okay. Could you turn to Page 8
04:44:02 2 of Plaintiff's Exhibit 35.

04:44:05 3 THE WITNESS: Yes.

04:44:05 4 BY MS. PIROZZOLO:

04:44:05 5 Q. Did Exelixis encounter problems other than the
04:44:09 6 formation of the 1-1 impurity with the A-2 process?

04:44:11 7 A. Yes. Well, the A-2 process, they first still were
04:44:18 8 having trouble with the 1-2 to 1-3 conversion, and they were
04:44:23 9 still seeing 1-1 there. But they also found that the use of
04:44:29 10 ethanol in the final salt forming step was producing ethanol
04:44:35 11 esters of malic acid in the product stream which were
04:44:37 12 difficult to detect and remove.

04:44:41 13 Q. Did Exelixis modify the A-2 process in an attempt to
04:44:46 14 minimize the 1-1 impurity?

04:44:47 15 A. They did.

04:44:50 16 Q. What did Exelixis do?

04:44:51 17 A. Well, they -- they -- as we heard from Dr. MacMillan,
04:44:56 18 they actually changed the chemistry. So, what they did was
04:45:00 19 they eliminated the step from 1-2 to 1-3 and they changed
04:45:06 20 the chemistry to go directly from 1-2 to 1-4, thus
04:45:11 21 eliminating the 1-3 that was decomposing to form 1-1.

04:45:17 22 Q. Did these changes control formation of the 1-1
04:45:20 23 impurity?

04:45:21 24 A. They did.

04:45:23 25 Q. Did Exelixis further -- did Exelixis modify the B-1

Myerson - Direct

04:45:28 1 process?

04:45:29 2 A. They did. They modified the conditions used in the
04:45:34 3 final salt formation step by adding a vacuum distillation to
04:45:39 4 reduce the heat and water required such that they would do
04:45:43 5 things at a -- at a lower temperature with less water.
04:45:46 6 Again, that helped minimize 1-1.

04:45:49 7 Q. Okay. Were these modifications enough to control for
04:45:53 8 the formation of 1-1?

04:45:54 9 A. Yes. The B-2 process was very effective in
04:45:59 10 controlling for 1-1.

04:46:01 11 Q. Okay. Now, looking at Plaintiff's Exhibit 35, are
04:46:06 12 the process modifications that we just discussed described
04:46:10 13 in Exhibit 35?

04:46:11 14 A. Yes.

04:46:13 15 MS. PIROZZOLO: Could you turn to Table 2 on
04:46:15 16 Page 16 of Exhibit 35?

04:46:20 17 THE WITNESS: Yes.

04:46:20 18 BY MS. PIROZZOLO:

04:46:21 19 Q. What does Table 2 show?

04:46:23 20 A. Table 2 is a table that shows, first, lists on the
04:46:28 21 left the four processes A-1, A-2, B-1 and B-2. And it looks
04:46:35 22 at the contents of the 1-1 impurity made in each of these
04:46:41 23 processes and we see in the A-2 process, it ranges from 35
04:46:46 24 to 411 PPM. In the B-1 process, 84 PPM. And in the B-2
04:46:54 25 process, less than 2 to 12 PPM. In addition, the yields in