

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

INTAS PHARMACEUTICALS LTD.,

Petitioner

v.

ATOSSA THERAPEUTICS, INC.,

Patent Owner

Case PGR2023-00043

Patent No. 11,572,334

**JOINT IDENTIFICATION OF OBJECTIONS TO ORAL ARGUMENT
DEMONSTRATIVES**


Objections to Demonstratives

Pursuant to the Order Setting Oral Argument (Paper 25) at 3 the parties jointly provide their objections to the opposing parties' demonstratives as set out below.

Patent Owner's Objections to Petitioner's Demonstratives

Slide 36:

Patent Owner did not antedate Milroy



ARTICLE INFO

Article history:
Received 6 February 2018
Revised 25 February 2018
Accepted 2 March 2018
Available online 13 March 2018

Ex. 1019

United States Patent
Owey et al.

Patent No. US 11,572,334 B2
Date of Patent: Feb. 7, 2023

Related U.S. Application Data

(63) Continuation of application No. 16/641,985, filed as application No. PCT/US2018/050272 on Sep. 10, 2018, now Pat. No. 11,261,151.

(60) Provisional application No. 62/693,885, filed on Jul. 3, 2018, provisional application No. 62/624,787, filed on Jan. 31, 2018, provisional application No. 62/556,884, filed on Sep. 11, 2017, provisional application No. 62/556,799, filed on Sep. 11, 2017.

Ex. 1001 at cover

DEMONSTRATIVE EXHIBIT – NOT EVIDENCE 36

Patent Owner objects to Petitioner's Slide 36 as constituting new argument because Petitioner has relied on the '334 patent's priority date (i.e., September 11, 2017) since filing the Petition, *see* Petition at 5, has never asserted Milroy as a prior art reference and has even conceded that Milroy "need not qualify as statutory prior art" when responding to Patent Owner's argument that Petitioner failed to demonstrate that Milroy was publicly available as of the '334 Patent's priority date (September 11, 2017), *see* Paper 10 at 8 n.4, and has never disputed the '334 Patent's priority date.

Slide 47:

PO's New Unsupported Sur-Reply Argument: Heat is problem

Sur-Reply

Moreover, Dr. McConville testified that an enteric coating is applied to the outside of a capsule *after* it has been filled with the active ingredient. (EX2028 at 52:8-56:11.) Heat is applied to the filled capsule to dry the coating. A POSA would know that “[t]he high temperatures (>40°C) associated with functional coating application and drying can degrade ... sensitive active [ingredients].” (EX1010 at 2; Pet. at 48.)

Petitioner’s argument that one could swap paracetamol for (Z)-endoxifen (Rep. at 13-15) ignores that (Z)-endoxifen is sensitive to heat. (POR at 63-64.) Dr. **Sur-Reply at 19**

DEMONSTRATIVE EXHIBIT – NOT EVIDENCE 47

Patent Owner objects to Petitioner’s Slide 47 as including an incorrect heading because Patent Owner and its expert, Dr. Stephen Davies, have consistently argued that under a number of conditions, (Z)-endoxifen’s instability causes rapid isomerization to a mixture of (Z)-endoxifen and (E)-endoxifen, including when exposed to elevated temperatures (i.e., heat). *See, e.g.*, Paper 7 at 34 (citing EX2001 at ¶ 51 (“[A] POSA would understand that exposure to elevated temperatures would accelerate the isomeric conversion of (Z)-endoxifen or (E)-endoxifen to an equilibrated mixture of (Z)-endoxifen and (E)-endoxifen.”)); Paper 14 at 60 (citing EX2020 at ¶ 56 (“[E]levated temperatures would accelerate the isomeric conversion of (Z)- endoxifen . . .”).

Slide 90:

PO's Unsupported Sur-Reply Argument

PO Sur-Reply

in the '334 patent. It is undisputed that the synthetic pathways of Ahmad and the '334 patent are dissimilar, and the resulting products would have different impurity profiles—assuming a POSA could even make 90% (Z)-endoxifen by following Ahmad. (EX2029 ¶27.) These different impurities could impact the resulting pharmacokinetics. (EX2029 ¶28-29.) Dr. McConville did not address this.

Sur-Reply at 24

DEMONSTRATIVE EXHIBIT – NOT EVIDENCE 90

Patent Owner objects to Petitioner's Slide 90 as including an incorrect heading because Patent Owner and its expert, Dr. Stephen Davies, have consistently argued that impurities can affect the pharmacokinetics of a formulation. *See, e.g.*, Paper 7 at 46-47 ("EX1004 is silent on whether residual solvents or other impurities might be present, which would make the resulting endoxifen product unsuitable for a pharmaceutical formulation." (citing EX2001 at ¶ 69 (demonstrating improved pharmacokinetics based on impurity-free formulations), ¶ 114 ("Liu's synthetic pathway is distinct from what is taught in the '334 patent and could result in a different stability profile and different impurity profiles, both of which are important to characterize for further use of a composition for an oral formulation."))); EX2020 at ¶ 111 (demonstrating improved pharmacokinetics based on impurity-free formulations).

Petitioner's Objections to Patent Owner's Demonstratives

Slide 30

Petitioner objects to the red text on slide 30 stating “and used endoxifen starting material with a different Z:E ratio than Liu” highlighted below:

Dr. Bihovsky's Experimental Work Differed From Liu

Liu Example 5: Recrystallization of ~50:50 E:Z Endoxifen Mixture



Dr. Bihovsky performed his experiments on a scale over 1000 times smaller than Liu and used endoxifen starting material with a different Z:E ratio than Liu. (EX2027 at 38:22-39:7; EX2029 at ¶¶ 16, 17, 21; EX1030 at ¶¶ 40-41)

- Impact of Dr. Bihovsky's changes:
 - **Scale:**
 - “A POSA would know that reactions on a small scale are not useful models to predict the same reactions on a large scale.” (EX2029 at ¶ 8)
 - **Starting material with a different Z:E ratio:**
 - “And when you're crystalizing stuff on a large scale, that's very different to on a small scale ... a large scale acting very differently with impurity profiles, isomer ratios than you would have on a small scale.” (EX1033 at 74:20-75:2).

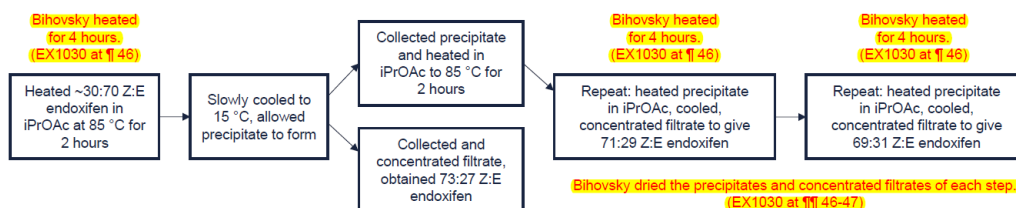
Petitioner believes the yellow highlighted portion is a new argument.

Slide 31

Petitioner also objects to all of the red text on slide 31, stating “Bihovsky heated for 4 hours” and “Bihovsky dried the precipitates and concentrated filtrates of each step” as well as the black text stating “Heating time: and “Drying the precipitates and concentrated filtrates of each step” as highlighted below:

Dr. Bihovsky's Experimental Work Differed From Liu

Liu Example 6: Isomerization of E-Enriched Endoxifen to Z-Enriched Endoxifen



- Impact of Dr. Bihovsky's changes (EX2029 at ¶ 20):
 - Heating time:**
 - "[Dr. Bihovsky carries out Liu's example 6] [o]n a smaller scale, which is not representative of the large-scale reaction and for different time." (EX1033 at 68:4-6)
 - Drying the precipitates and concentrated filtrates of each step:**
 - "[E]ven slight changes in methodology can lead to different results [...] different synthetic pathways can result in different stability and impurity profiles." (EX2029 at ¶ 27; EX2027 at 83:16-84:7)

Petitioner believes the yellow highlighted portions are new arguments.

Objections to Demonstratives

Respectfully submitted on behalf of both parties,

McANDREWS, HELD & MALLOY, LTD.

Dated: October 29, 2024

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CERTIFICATE OF SERVICE

Under 37 C.F.R. §§ 42.6(e)(4) and 42.105, the undersigned certifies on this date, a true and correct copy of these Joint Objections were sent to counsel for Patent Owner at the following email addresses:

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