

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

SYNAFFIX B.V.

Petitioner

v.

HANGZHOU DAC BIOTECH CO., LTD.,

Patent Owner

Patent No. 10,131,682

Ex Parte Reexamination Certificate Issued: January 4, 2021

Title: HYDROPHILIC LINKERS AND THEIR USES FOR CONJUGATION OF
DRUGS TO A CELL BINDING MOLECULES

Inter Partes Review No. IPR2022-01531

**PETITIONER'S OBJECTIONS TO EVIDENCE SUBMITTED
WITH PATENT OWNER'S PRELIMINARY RESPONSE**

Petitioner SynAffix B.V. (“Petitioner”) hereby objects to certain evidence submitted by Hangzhou DAC Biotech Co., Ltd. (“Patent Owner”) with the Patent Owner Preliminary Response (“POPR,” Paper 9) in the above-captioned proceeding. In accordance with 37 C.F.R. § 42.64(b)(1), these objections are being timely filed and served within ten (10) business days of the institution of trial (Paper 25).

Petitioner’s objections are based on the Federal Rules of Evidence (“FRE”), relevant case law, federal statute, and the Patent Trial and Appeal Board (“PTAB”) Rules. Petitioner’s objections are set forth with particularity below.

I. Exhibit 2001

Exhibit 2001 is described as the Declaration of Lawrence Nathan Tumey, Ph.D. Petitioner objects to Exhibit 2001, including specifically to the extent it includes subject matter that is not permitted pursuant to FRE 602 or 702-703, including without limitation, to the extent that the declaration presents as “facts” information that is outside the personal knowledge of the declarant and/or to the extent that the testimony is not based on sufficient facts or data or the product of reliable principles and methods reliably applied in this case. *See, e.g.*, Exhibit 2001, ¶¶54, 58-63. Petitioner further objects to the portions of Exhibit 2001 that cite an exhibit objected to herein for the reasons stated herein.

II. Exhibit 2003

Exhibit 2003 is described on Patent Owner's Exhibit List as Maeda, H., et al., *Polymeric drugs for efficient tumor-targeted drug delivery based on EPR-effect*, European Journal of Pharmaceutics and Biopharmaceutics (2009) 71:3, 409-419. Petitioner objects to Exhibit 2003 as lacking authentication under FRE 901 and as containing hearsay under FRE 801 and FRE 802 to the extent that Patent Owner attempts to rely on it to prove the truth of any matter asserted therein (*see, e.g.*, EX2001 at ¶29; POPR at 10 (citing, *inter alia*, EX2001 at ¶29)), but the exhibit fails to meet the requirements of any hearsay exception or exemption under FRE 803-807. For example, Patent Owner fails to offer sufficient evidence that Exhibit 2003 was publicly accessible in its presented form as of the alleged publication date or that Exhibit 2003 is what Patent Owner claims it to be.

III. Exhibit 2004

Exhibit 2004 is described on Patent Owner's Exhibit List as Adair, J.R., et al., *Antibody-Drug Conjugates – A Perfect Synergy*, Expert Opinion on Biological Therapy (2012) 12:9, 1191-1206. Petitioner objects to Exhibit 2004 as lacking authentication under FRE 901 and as containing hearsay under FRE 801 and FRE 802 to the extent that Patent Owner attempts to rely on it to prove the truth of any matter asserted therein (*see, e.g.*, EX2001 at ¶¶30, 34, 48; POPR at 9-11 (citing, *inter alia*, EX2001 at ¶¶30, 34, 48)), but the exhibit fails to meet the requirements of any

hearsay exception or exemption under FRE 803-807. For example, Patent Owner fails to offer sufficient evidence that Exhibit 2004 was publicly accessible in its presented form as of the alleged publication date or that Exhibit 2004 is what Patent Owner claims it to be.

IV. Exhibit 2005

Exhibit 2005 is described on Patent Owner's Exhibit List as Kovtun, Y.V., et al., *Antibody-Maytansinoid Conjugates Designed to Bypass Multidrug Resistance*, Cancer Research (2010) 70 (6): 2528–2537. Petitioner objects to Exhibit 2005 as lacking authentication under FRE 901 and as containing hearsay under FRE 801 and FRE 802 to the extent that Patent Owner attempts to rely on it to prove the truth of any matter asserted therein (*see, e.g.*, EX2001 at ¶¶30-32; POPR at 10-11 (citing, *inter alia*, EX2001 at ¶¶30-32)), but the exhibit fails to meet the requirements of any hearsay exception or exemption under FRE 803-807. For example, Patent Owner fails to offer sufficient evidence that Exhibit 2005 was publicly accessible in its presented form as of the alleged publication date or that Exhibit 2005 is what Patent Owner claims it to be. Petitioner further objects to Exhibit 2005 under FRE 106, 403, and 1006 because is it incomplete. For example, Exhibit 2005 does not include the supplementary data noted and cited throughout the document (*e.g.*, EX2005 at 2528 (“Note: Supplementary data for this article are available at Cancer Research Online....”), 2531-33 (repeatedly citing “Supplementary” figures and tables without

reproducing the referenced figures and tables)). Any probative value is substantially outweighed by the unfair prejudice to Petitioner of not having the complete document.

V. Exhibit 2006

Exhibit 2006 is described on Patent Owner's Exhibit List as Goldmacher, V., et al., *Antibody–Drug Conjugates: Using Monoclonal Antibodies For Delivery Of Cytotoxic Payloads To Cancer Cells*, Therapeutic Delivery (2011) 2:3, 397-416. Petitioner objects to Exhibit 2006 as lacking authentication under FRE 901 and as containing hearsay under FRE 801 and FRE 802 to the extent that Patent Owner attempts to rely on it to prove the truth of any matter asserted therein (*see, e.g.*, EX2001 at ¶¶30, 35; POPR at 10-11 (citing, *inter alia*, EX2001 at ¶¶30, 35)), but the exhibit fails to meet the requirements of any hearsay exception or exemption under FRE 803-807. For example, Patent Owner fails to offer sufficient evidence that Exhibit 2006 was publicly accessible in its presented form as of the alleged publication date or that Exhibit 2006 is what Patent Owner claims it to be.

VI. Exhibit 2007

Exhibit 2007 is described on Patent Owner's Exhibit List as Ducry, L., et al., *Antibody-Drug Conjugates: Linking Cytotoxic Payloads to Monoclonal Antibodies*, Bioconjugate Chemistry (2010) 21:1, 5–13. Petitioner objects to Exhibit 2007 as lacking authentication under FRE 901 and as containing hearsay under FRE 801 and

FRE 802 to the extent that Patent Owner attempts to rely on it to prove the truth of any matter asserted therein (*see, e.g.*, EX2001 at ¶¶31-33, 45-46, 48; POPR at 9-12 (citing, *inter alia*, EX2001 at ¶¶31-33, 45-46, 48)), but the exhibit fails to meet the requirements of any hearsay exception or exemption under FRE 803-807. For example, Patent Owner fails to offer sufficient evidence that Exhibit 2007 was publicly accessible in its presented form as of the alleged publication date or that Exhibit 2007 is what Patent Owner claims it to be.

VII. Exhibit 2008

Exhibit 2008 is described on Patent Owner's Exhibit List as Carter P.J., Senter P.D., *Antibody-Drug Conjugates for Cancer Therapy*, Cancer Journal (2008) 14:3, 154-169. Petitioner objects to Exhibit 2008 as lacking authentication under FRE 901 and as containing hearsay under FRE 801 and FRE 802 to the extent that Patent Owner attempts to rely on it to prove the truth of any matter asserted therein (*see, e.g.*, EX2001 at ¶¶32-33, 36; POPR at 2 (citing, *inter alia*, EX2001 at ¶36), 9-11 (citing, *inter alia*, EX2001 at ¶¶32-33, 36)), but the exhibit fails to meet the requirements of any hearsay exception or exemption under FRE 803-807. For example, Patent Owner fails to offer sufficient evidence that Exhibit 2008 was publicly accessible in its presented form as of the alleged publication date or that Exhibit 2008 is what Patent Owner claims it to be.

VIII. Exhibit 2009

Exhibit 2009 is described on Patent Owner's Exhibit List as Daugherty, A.L., et al., *Formulation and Delivery Issues for Monoclonal Antibody Therapeutics*, *Advanced Drug Delivery Reviews* (2006) 58:5-6, 686-706. Petitioner objects to Exhibit 2009 as lacking authentication under FRE 901 and as containing hearsay under FRE 801 and FRE 802 to the extent that Patent Owner attempts to rely on it to prove the truth of any matter asserted therein (*see, e.g.*, EX2001 at ¶¶34, 48; POPR at 9-11 (citing, *inter alia*, EX2001 at ¶¶34, 48)), but the exhibit fails to meet the requirements of any hearsay exception or exemption under FRE 803-807. For example, Patent Owner fails to offer sufficient evidence that Exhibit 2009 was publicly accessible in its presented form as of the alleged publication date or that Exhibit 2009 is what Patent Owner claims it to be.

IX. Exhibit 2010

Exhibit 2010 is described on Patent Owner's Exhibit List as Pappanaicken, R.K., et al., *Evaluation of Ketone-Oxime Method for Delivering Therapeutic On-Demand Cleavable Immunoconjugates*, *Bioconjugate Chemistry* (2016) 19:6, 1313-1318. Petitioner objects to Exhibit 2010 as lacking authentication under FRE 901 and as containing hearsay under FRE 801 and FRE 802 to the extent that Patent Owner attempts to rely on it to prove the truth of any matter asserted therein (*see, e.g.*, EX2001 at ¶37; POPR at 2 (citing, *inter alia*, EX2001 at ¶37), 9 (citing, *inter*

alia, EX2001 at ¶37), 11 (citing, *inter alia*, EX2001 at ¶37)), but the exhibit fails to meet the requirements of any hearsay exception or exemption under FRE 803-807. For example, Patent Owner fails to offer sufficient evidence that Exhibit 2010 was publicly accessible in its presented form as of the alleged publication date or that Exhibit 2010 is what Patent Owner claims it to be.

X. Exhibit 2011

Exhibit 2011 is described on Patent Owner's Exhibit List as Jeffrey, S.C., et al., *Expanded Utility of the β -Glucuronide Linker: ADCs That Deliver Phenolic Cytotoxic Agents*, ACS Medicinal Chemistry Letters (2010) 1, 277-80. Petitioner objects to Exhibit 2011 as lacking authentication under FRE 901 and as containing hearsay under FRE 801 and FRE 802 to the extent that Patent Owner attempts to rely on it to prove the truth of any matter asserted therein (*see, e.g.*, EX2001 at ¶38; POPR at 9 (citing, *inter alia*, EX2001 at ¶38), 12 (citing, *inter alia*, EX2011 at 277 & EX2001 at ¶38)), but the exhibit fails to meet the requirements of any hearsay exception or exemption under FRE 803-807. For example, Patent Owner fails to offer sufficient evidence that Exhibit 2011 was publicly accessible in its presented form as of the alleged publication date or that Exhibit 2011 is what Patent Owner claims it to be.

XI. Exhibit 2012

Exhibit 2012 is described on Patent Owner's Exhibit List as Mather, B., et al., *Michael Addition Reactions in Macromolecular Design for Emerging Technologies*, Progress in Polymer Science (2006), 31:5, 487-531. Petitioner objects to Exhibit 2012 as lacking authentication under FRE 901 and as containing hearsay under FRE 801 and FRE 802 to the extent that Patent Owner attempts to rely on it to prove the truth of any matter asserted therein (*see, e.g.*, EX2001 at ¶¶40, 44, 50-51, 53; POPR at 2 (citing, *inter alia*, EX2001 at ¶40), 8-9 (citing, *inter alia*, EX2001 at ¶¶40, 44), 11-13 (citing, *inter alia*, EX2012 at 488-89, 491, 523 & EX2001 at ¶¶40, 44, 50-51, 53)), but the exhibit fails to meet the requirements of any hearsay exception or exemption under FRE 803-807. For example, Patent Owner fails to offer sufficient evidence that Exhibit 2012 was publicly accessible in its presented form as of the alleged publication date or that Exhibit 2012 is what Patent Owner claims it to be.

XII. Exhibit 2013

Exhibit 2013 is described on Patent Owner's Exhibit List as Lopez-Jaramillo, F., et al., *Vinyl Sulfone: A Multi-Purpose Function in Proteomics*, Integrative Proteomics InTech (2012) 16:301-326. Petitioner objects to Exhibit 2013 as lacking authentication under FRE 901 and as containing hearsay under FRE 801 and FRE 802 to the extent that Patent Owner attempts to rely on it to prove the truth of any matter asserted therein (*see, e.g.*, EX2001 at ¶¶41, 51; POPR at 2 (citing, *inter alia*,

EX2001 at ¶41), 8-9 (citing, *inter alia*, EX2001 at ¶41), 11-13 (citing, *inter alia*, EX2013 at 303-307 & EX2001 at ¶¶41, 51)), but the exhibit fails to meet the requirements of any hearsay exception or exemption under FRE 803-807. For example, Patent Owner fails to offer sufficient evidence that Exhibit 2013 was publicly accessible in its presented form as of the alleged publication date or that Exhibit 2013 is what Patent Owner claims it to be.

XIII. Exhibit 2014

Exhibit 2014 is described on Patent Owner's Exhibit List as Acchione, M., et al., *Impact of Linker and Conjugation Chemistry on Antigen Binding, Fc Receptor Binding and Thermal Stability of Model Antibody-Drug Conjugates*, mAbs (2012) 4:3, 362-372. Petitioner objects to Exhibit 2014 as lacking authentication under FRE 901 and as containing hearsay under FRE 801 and FRE 802 to the extent that Patent Owner attempts to rely on it to prove the truth of any matter asserted therein (*see, e.g.*, EX2001 at ¶¶41-42, 48; POPR at 2 (citing, *inter alia*, EX2001 at ¶¶41-42), 8-9 (citing, *inter alia*, EX2001 at ¶¶41-42), 11-12 (citing, *inter alia*, EX2001 at ¶¶41-42)), but the exhibit fails to meet the requirements of any hearsay exception or exemption under FRE 803-807. For example, Patent Owner fails to offer sufficient evidence that Exhibit 2014 was publicly accessible in its presented form as of the alleged publication date or that Exhibit 2014 is what Patent Owner claims it to be.

XIV. Exhibit 2015

Exhibit 2015 is described on Patent Owner's Exhibit List as Hamblett, K., et al., *Effects of Drug Loading on the Antitumor Activity of a Monoclonal Antibody Drug Conjugate*, Clinical Cancer Research (2004) 10:20, 7063-7070. Petitioner objects to Exhibit 2015 as lacking authentication under FRE 901 and as containing hearsay under FRE 801 and FRE 802 to the extent that Patent Owner attempts to rely on it to prove the truth of any matter asserted therein (*see, e.g.*, EX2001 at ¶¶41-42, 48; POPR at 2 (citing, *inter alia*, EX2001 at ¶¶41-42), 8-9 (citing, *inter alia*, EX2001 at ¶¶41-42), 11-12 (citing, *inter alia*, EX2001 at ¶¶41-42)), but the exhibit fails to meet the requirements of any hearsay exception or exemption under FRE 803-807. For example, Patent Owner fails to offer sufficient evidence that Exhibit 2015 was publicly accessible in its presented form as of the alleged publication date or that Exhibit 2015 is what Patent Owner claims it to be.

XV. Exhibit 2016

Exhibit 2016 is described on Patent Owner's Exhibit List as Junutula, J., et al., *Site-specific Conjugation of a Cytotoxic Drug to an Antibody Improves the Therapeutic Index*, Nature Biotechnology (2008) 26, 925–932. Petitioner objects to Exhibit 2016 as lacking authentication under FRE 901 and as containing hearsay under FRE 801 and FRE 802 to the extent that Patent Owner attempts to rely on it to prove the truth of any matter asserted therein (*see, e.g.*, EX2001 at ¶43; POPR at

2 (citing, *inter alia*, EX2001 at ¶43), 8-9 (citing, *inter alia*, EX2001 at ¶43), 11 (citing, *inter alia*, EX2001 at ¶43)), but the exhibit fails to meet the requirements of any hearsay exception or exemption under FRE 803-807. For example, Patent Owner fails to offer sufficient evidence that Exhibit 2016 was publicly accessible in its presented form as of the alleged publication date or that Exhibit 2016 is what Patent Owner claims it to be. Petitioner further objects to Exhibit 2016 under FRE 106, 403, and 1006 because it is incomplete. For example, Exhibit 2016 does not include the supplementary information noted and cited throughout the document (e.g., EX2016 at 926-932 (repeatedly citing “Supplementary” figures and tables available only “online” and further noting that “[s]upplementary information is available on the Nature Biotechnology website”)). Any probative value is substantially outweighed by the unfair prejudice to Petitioner of not having the complete document.

XVI. Exhibit 2017

Exhibit 2017 is described on Patent Owner’s Exhibit List as Casi, G., *Antibody-Drug Conjugates: Basic Concepts, Examples, and Future Perspectives*, *Journal of Controlled Release* (2012) 161:2, 422-428. Petitioner objects to Exhibit 2017 as lacking authentication under FRE 901 and as containing hearsay under FRE 801 and FRE 802 to the extent that Patent Owner attempts to rely on it to prove the truth of any matter asserted therein (*see, e.g.*, EX2001 at ¶47; POPR at 9 (citing,

inter alia, EX2001 at ¶47), 12 (citing, *inter alia*, EX2001 at ¶47)), but the exhibit fails to meet the requirements of any hearsay exception or exemption under FRE 803-807. For example, Patent Owner fails to offer sufficient evidence that Exhibit 2017 was publicly accessible in its presented form as of the alleged publication date or that Exhibit 2017 is what Patent Owner claims it to be.

XVII. Exhibit 2018

Exhibit 2018 is described on Patent Owner's Exhibit List as Li, L., et al., *Vinyl Sulfone Bifunctional Derivatives of DOTA Allow Sulfhydryl- or Amino-Directed Coupling to Antibodies. Conjugates Retain Immunoreactivity and Have Similar Biodistributions*, *Bioconjugate Chemistry* (2002) 13:1, 110–115. Petitioner objects to Exhibit 2018 as lacking authentication under FRE 901 and as containing hearsay under FRE 801 and FRE 802 to the extent that Patent Owner attempts to rely on it to prove the truth of any matter asserted therein (*see, e.g.*, EX2001 at ¶49; POPR at 12 (citing, *inter alia*, EX2001 at ¶49), 57 (citing, *inter alia*, EX2001 at ¶49)), but the exhibit fails to meet the requirements of any hearsay exception or exemption under FRE 803-807. For example, Patent Owner fails to offer sufficient evidence that Exhibit 2018 was publicly accessible in its presented form as of the alleged publication date or that Exhibit 2018 is what Patent Owner claims it to be.

XVIII. Exhibit 2019

Exhibit 2019 is described on Patent Owner's Exhibit List as Ballini, R., et al., *Conjugate Additions of Nitroalkanes to Electron-Poor Alkenes: Recent Results*, Chemical Reviews (2005) 105:3, 933–972. Petitioner objects to Exhibit 2019 as lacking authentication under FRE 901 and as containing hearsay under FRE 801 and FRE 802 to the extent that Patent Owner attempts to rely on it to prove the truth of any matter asserted therein (*see, e.g.*, EX2001 at ¶53; POPR at 13 (citing, *inter alia*, EX2019 at 933 & EX2001 at ¶53)), but the exhibit fails to meet the requirements of any hearsay exception or exemption under FRE 803-807. For example, Patent Owner fails to offer sufficient evidence that Exhibit 2019 was publicly accessible in its presented form as of the alleged publication date or that Exhibit 2019 is what Patent Owner claims it to be.

XIX. Exhibit 2020

Exhibit 2020 is described on Patent Owner's Exhibit List as Gallagher, S., et al., *Immunoblotting and Immunodetection*, Current Protocols in Cell Biology (2011) 52:6.2.1-6.2.28. Petitioner objects to Exhibit 2020 as lacking authentication under FRE 901 and as containing hearsay under FRE 801 and FRE 802 to the extent that Patent Owner attempts to rely on it to prove the truth of any matter asserted therein (*see, e.g.*, EX2001 at ¶¶58-59; POPR at 16-19 (citing, *inter alia*, EX2001 at ¶¶58-59), 46 (citing, *inter alia*, EX2001 at ¶58)), but the exhibit fails to meet the

requirements of any hearsay exception or exemption under FRE 803-807. For example, Patent Owner fails to offer sufficient evidence that Exhibit 2020 was publicly accessible in its presented form as of the alleged publication date or that Exhibit 2020 is what Patent Owner claims it to be.

XX. Exhibit 2021

Exhibit 2021 is described on Patent Owner's Exhibit List as Springer Nature, Citation Details, Retrieved May 24, 2023, from <https://citations.springernature.com/item?doi=10.1007/BF00493477>. Petitioner objects to Exhibit 2021 as lacking authentication under FRE 901 and as containing hearsay under FRE 801 and FRE 802 to the extent that Patent Owner attempts to rely on it to prove the truth of any matter asserted therein (*see, e.g.*, EX2001 at ¶59; POPR at 17-19 (citing, *inter alia*, EX2001 at ¶59)), but the exhibit fails to meet the requirements of any hearsay exception or exemption under FRE 803-807. For example, Patent Owner fails to offer sufficient evidence that Exhibit 2021 was publicly accessible in its presented form as of the alleged publication date or that Exhibit 2021 is what Patent Owner claims it to be.

XXI. Exhibit 2026

Exhibit 2026 is described on Patent Owner's Exhibit List as WO1997/41897 (Lees). Petitioner objects to Exhibit 2026 under FRE 801 and FRE 802 as containing hearsay to the extent that Patent Owner attempts to rely on it to prove the truth of

any matter asserted therein (*see, e.g.*, EX2001 at ¶¶104-107; POPR at 23 (citing, *inter alia*, EX2001 at ¶¶104-107), 25-26 (citing, *inter alia*, EX2026 at 20:10-19, 23:9-15 & EX2001 at ¶¶104-107)), but the exhibit fails to meet the requirements of any hearsay exception or exemption under FRE 803-807.

XXII. Exhibit 2030

Exhibit 2030 is described on Patent Owner's Exhibit List as Widdison, W.C., et al., *Semisynthetic Maytansine Analogues for the Targeted Treatment of Cancer*, Journal of Medicinal Chemistry (2006) 49:14, 4392-4408. Petitioner objects to Exhibit 2030 as lacking authentication under FRE 901. Petitioner further objects to Exhibit 2030 under FRE 106, 403, and 1006 because is it incomplete. For example, Exhibit 2030 does not include the supporting information noted in the document (*e.g.*, EX2030 at 4408 ("Supporting Information Available: Analytical data (elemental analysis and HRMS and HPLC purity data) for target compounds. This material is available free of charge via the Internet at <http://pubs.acs.org>.")). Any probative value is substantially outweighed by the unfair prejudice to Petitioner of not having the complete document.

XXIII. Exhibit 2034

Exhibit 2034 is described on Patent Owner's Exhibit List as WO2009/134976 (Singh '976). Petitioner objects to Exhibit 2034 under FRE 801 and FRE 802 as containing hearsay to the extent that Patent Owner attempts to rely on it to prove the

truth of any matter asserted therein (*see, e.g.*, EX2001 at ¶108; POPR at 23 (citing, *inter alia*, EX2001 at ¶108), 26-27 (citing, *inter alia*, EX2034 & EX2001 at ¶108)), but the exhibit fails to meet the requirements of any hearsay exception or exemption under FRE 803-807.

Respectfully submitted,

Dated: September 16, 2024

By: /Michael R. Houston/

Michael R. Houston
Reg. No. 58,486
Counsel for Petitioner

CERTIFICATE OF SERVICE

The undersigned hereby certifies that a copy of the foregoing
**PETITIONER’S OBJECTIONS TO EVIDENCE SUBMITTED WITH
PATENT OWNER’S RESPONSE** was caused to be served electronically via e-mail on September 16, 2024 in its entirety on the following:

F. Dominic Cerrito
nickcerrito@quinnemanuel.com

Frank Calvosa
frankcalvosa@quinnemanuel.com

Catherine T. Mattes
catherinemattes@quinnemanuel.com

Tara Srinivasan
tarasrinivasan@quinnemanuel.com

qe-hangzhoudac2@quinnemanuel.com

By: /Michael R. Houston/

Michael R. Houston
Reg. No. 58,486
Counsel for Petitioner