**IN THE UNITED STATES PATENT AND TRADEMARK OFFICE**

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| In re Patent of: | Diaz et al. | | |
| U.S. Patent No.: | 11,934,356 | Attorney Docket No.: | 52261-0006IP1 |
| Issue Date: | March 2, 2021 | | |
| Appl. Serial No.: | 16/144,549 | | |
| Filing Date: | September 27, 2018 | | |
| Title: | CHECKPOINT BLOCKADE AND MICROSATELLITE INSTABILITY | | |

# DECLARATION OF MS. JENNIFER NEWBERGER

I currently hold the opinions expressed in this declaration. However, my analysis may continue, and I may acquire additional information and/or attain supplemental insights that may result in added observations.

I hereby declare that all statements made of my own knowledge are true and that all statements made on information and belief are believed to be true. I further declare that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code.

Dated: 1/7/2025 By: Jennifer Newberger
Jennifer Newberger

JHU 2137
Merck Sharp v. Johns Hopkins
IPR2024-00622



MERCK EX1281
Merck Sharp & Dohme LLC v. The Johns Hopkins University
IPR2024-00625

## I. QUALIFICATIONS

1. I have 17 years of experience as a lawyer focused on U.S. Food and Drug Administration regulatory matters.

2. I hold a J.D. from the University of Miami School of Law and an M.P.H. from Emory University Rollins School of Public Health. I also hold a B.A. in Anthropology from Washington University in St. Louis.

3. I am a Director at Hyman, Phelps & McNamara, P.C., where I provide counsel to clients on a range of matters, including clinical trial study design and applicable requirements, including registration on ClinicalTrials.gov.

4. I have been an attorney in private practice for approximately nine of my 17 years of experience. I spent just under one year as a Policy Advisor at the U.S. Food and Drug Administration, four years working as in-house counsel at Apple Inc., one year as regulatory counsel at Abbott Laboratories, and one year as Vice President, followed by a year as Senior Vice President, of Regulatory and Compliance at Cognito Therapeutics.

5. My roles at Apple and Cognito involved close work with teams responsible for executing clinical studies for approval of FDA-regulated products. I reviewed and advised on clinical trial protocols, statistical analyses plans, and was an approver of ClinicalTrials.gov submissions.

6. I have authored or co-authored articles, blog posts, and textbook chapters on a variety of issues pertaining to FDA law. I have given speeches and presentations on FDA matters, and am a past member of the Food and Drug Law Journal's Editorial Advisory Board.

7. A more extensive discussion of my background and qualifications can be found in my curriculum vitae, included as Appendix A.

## II. MATERIALS CONSIDERED AND COMPENSATION

8. In preparing this declaration, I have considered the materials cited in this declaration. In forming the opinions laid out in this declaration, I have also consulted my many years of experience, including in advising on ClinicalTrials.gov requirements and approving materials to be submitted to that registry.

9. I am being compensated at a rate of $1,000 per hour for my time on this matter. My compensation does not depend on the substance of my opinions or the outcome of the matter.

## III. ASSIGNMENT

10. I have been asked to provide my opinions on the legal requirements with respect to clinical trial submissions to ClinicalTrials.gov and the consequences of failure to meet those requirements. I have also been asked to

assess JHU's compliance with those requirements with respect to its June 10, 2013 submission for NCT01876511.[1]

## IV. OPINIONS

### A. The Need for Clinical Trials Registries

11. Discussions about the need for a clinical trials registry have taken place since at least the 1980s. At the eighth annual meeting of the Society for Clinical Trials, in 1987, there was a plenary session titled, "The Case for Registers of Clinical Trials."[2] The session discussed a variety of reasons for having clinical trial registers, including collaboration among researchers, providing a basis for methodologic research, and providing a means for the meta-analysis of resulting data independent of published literature, which may be subject to selection or other biases.

12. A paper in 1993 noted that investigators are more likely to publish trials with positive outcomes, resulting in "publication bias."[3] Moher further notes that this publication bias can lead to "systematic errors in the in the evaluation of treatments."[4] He also states: "Ethically, it is inappropriate to allow patients to

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[1] ClinicalTrials.gov, NCT01876511, "Study of MK-3475 in Patients With Microsatellite Unstable (MSI) Tumors (Cohorts A, B and C)," (June 10, 2013). EX1005.
[2] Controlled Clinical Trials, 01 Mar 1988, 9(1):76-81. EX2138.
[3] Moher, D., *Clinical trial registration: a call for its implementation in Canada*, Can Med Assoc J 1993; 149(11), 1657. EX2139.
[4] *Id*.

undergo experimental therapy, with its sometimes life-threatening side effects, and not report the results. Failure to make such data available for public scrutiny has been considered scientific misconduct."[5]

13. The ethical obligation to report clinical trial results is also emphasized by the World Health Organization (WHO), which maintains that the registration of all interventional trials "is a scientific, ethical and moral responsibility."[6]

14. Trial registration is important to ensure that healthcare providers have all available evidence when making decisions about treatment for patients.

15. Informed decision-making is dependent on the availability of complete and transparent information to avoid publication bias and selective reporting.

16. Transparency of clinical trial information is also necessary to facilitate recruitment by making potential participants aware of studies for which they may be eligible. Registration also allows researchers to be aware of studies in which they may have an interest in participating, for which they may have potentially eligible patients.

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[5] *Id* (internal citations omitted).
[6] https://www.who.int/clinical-trials-registry-platform. EX2140.

17. Thus, clinical trials registries are needed to ensure transparency of information to facilitate clinical trial registration and enable appropriate healthcare decision-making.

### B. Requirements for Registration on ClinicalTrials.gov and Consequences of Failing to Comply.

18. Registration on ClinicalTrials.gov is required by the U.S. Food and Drug Administration, the National Institutes of Health, the International Committee of Medical Journal Editors, and the Declaration of Helsinki.

19. ClinicalTrials.gov was created pursuant to the Food and Drug Administration Modernization Act of 1997 (FDAMA). FDAMA amended the U.S. Public Health Service Act, requiring the U.S. National Institutes of Health (NIH) to create a data bank of information on clinical trials for drugs for serious or life-threatening diseases and conditions.[7]

20. FDAMA required NIH to "collect, catalog, store, and disseminate the information" required under the law. It further stated that this dissemination was to occur "through information systems, which shall include toll-free telephone communications, available to individuals with serious or life-threatening diseases

[7] Public Law 105-115, Food and Drug Administration Modernization Act of 1997 (Nov. 21, 1997), Section 113. EX2141.

and conditions, to other members of the public, to health care providers, and to researchers."[8]

21. FDAMA required the data bank to include a registry of clinical trials, whether federally or privately funded, of experimental treatments for serious or life-threatening diseases and conditions, which provides a description of the purpose of each experimental drug. The required information included eligibility criteria for participation in the clinical trials, a description of the location of trial sites, and point of contact for those wanting to enroll in the trial. The information had to be provided "in a form that can be readily understood by members of the public."[9]

22. Sponsors had to provide the required information to the data bank not later than 21 days after the approval of the study protocol by the U.S. Food and Drug Administration (FDA).

23. Sponsors are not compensated by FDA or NIH for submitting information regarding their trials to ClinicalTrials.gov.

24. In response to the FDAMA mandate, ClinicalTrials.gov launched in 2000, through collaboration between NIH and FDA.

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[8] *Id.* at (a)(2).
[9] *Id.*

25. In 2005, the International Committee of Medical Journal Editors (ICMJE) launched a policy stating that it would only consider for publication trials beginning after July 1, 2005, if registration for those trials on ClinicalTrials.gov occurred before the first patient was enrolled. This caused a significant increase in registration on the site. Before the ICMJE policy, ClinicalTrials.gov contained 13,153 trials. One month after the policy went into effect, the number increased to 22,714 trials. By April 2007, two years after implementation of the policy, the registry contained over 40,000 trials.[10]

26. In 2007, Congress passed the Food and Drug Administration Amendments Act (FDAAA). Section 801 of FDAAA, Expanded Clinical Trial Registry Data Bank, expanded the requirements for registration on ClinicalTrials.gov and provided additional information about which studies were required to be registered, and the information to be included.[11]

27. In 2008, the updated ClinicalTrials.gov results database was launched for the public.[12] This update specifically required inclusion of a description of the

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[10] Laine, C., et al., Update on Trials Registration: Clinical Trial Registration: Looking Back and Moving Ahead (June 2007). EX2142.
[11] Food and Drug Administration Amendments Act of 2007, Pub. L. 110–85, Sept. 27, 2007, 121 Stat. 823. EX2143.
[12] About ClinicalTrials.gov, Nat'l Library of Medicine, ClinicalTrials.gov, https://clinicaltrials.gov/about-site/about-ctg. EX2145.

group of participants who joined and completed the study, and findings from the study, including safety information.

28. Also in 2008, the World Medical Association launched a revised version of the Declaration of Helsinki, an ethical guideline first launched in 1964 to set the standard for ethical human subjects research.[13] The 2008 revision included the following requirement: "Every research study involving human subjects must be registered in a publicly accessible database before recruitment of the first subject." While the Declaration of Helsinki does not have the power of law, it is commonly accepted that clinical trials follow the principles set forth in that document, and many medical journals will not publish results of studies that do not comply with the guidelines set forth therein.

29. In 2017, the Department of Health and Human Services (HHS) implemented a final rule providing additional detail about what needs to be submitted to ClinicalTrials.gov.[14] **Image 1**,[15] below, sets forth the key timelines related to establishment of ClinicalTrials.gov and global policies regarding clinical trial registration requirements.

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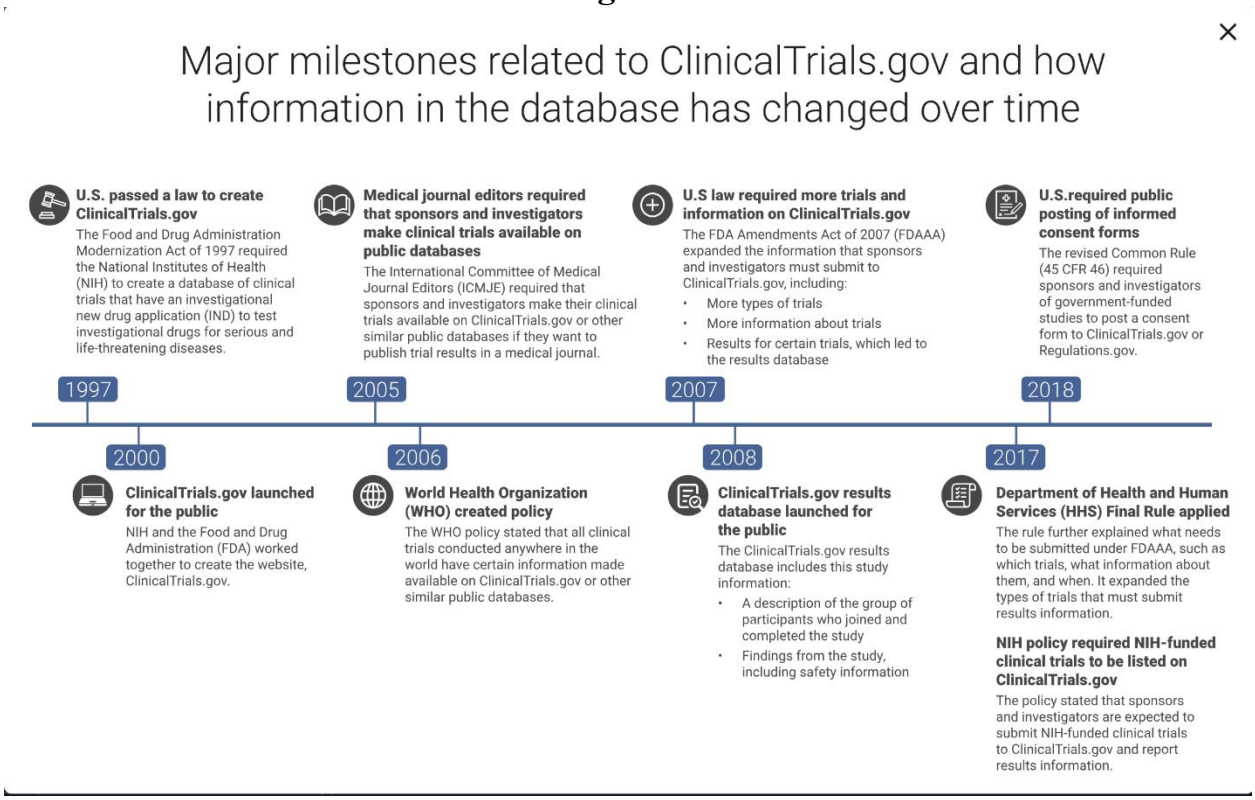
[13] Karmela Krleža-Jerić et al., *7th Revision of the Declaration of Helsinki: Good News for the Transparency of Clinical Trials*, Croat Med J. 2009; 50: 105-10, doi: 10.3325/cmj.2009.50.105. EX2146.
[14] 42 C.F.R. Pt. 11 (2024). EX2147.
[15] *See* https://clinicaltrials.gov/about-site/about-ctg. EX2145.

**Image 1**




### C. The Statutory Requirements of FDAAA and NIH Guidance

30. The requirements of FDAAA were codified in the Public Health Service Act, 42 U.S.C. 282(j) were in effect as of September 27, 2007, and mandated that all sponsors of interventional clinical trials register with ClinicalTrials.gov.[16] FDAAA specifically mandated NIH to expand the clinical trials registry and ensure that the registry is made publicly available through the

[16] 42 U.S.C. § 282(j). EX2148.

Internet in order to enhance patient enrollment and provide a mechanism to track subsequent progress of clinical trials.

31. The responsibility for complying with the requirements under 42 U.S.C. 282(j) lies with the responsible party, defined as the sponsor of the clinical trial or the principal investigator, if so designated by the sponsor.

32. Trials subject to the reporting requirements are those that meet the definition of an "applicable drug clinical trial," defined as "a controlled clinical investigation, other than a phase I clinical investigation, of a drug subject to section 505 of the Federal Food, Drug, and Cosmetic Act or to section 351 of [the Public Health Service] Act."[17] "Clinical investigation" was given the same meaning as in 21 CFR 312.3: "any experiment in which a drug is administered or dispensed to, or used involving, one or more human subjects."

33. The information required to be submitted to ClinicalTrials.gov is set forth in 42 U.S.C. 282(j)(2), and includes the following: (1) a brief title and brief summary, intended for the lay public; (2) the primary study purpose; (3) the study design; (4) the study phase; (5) study type; (6) the primary disease or condition being studied, or the focus of the study; (7) the intervention name and intervention type; (8) the study start date; (9) the expected completion date; (10) the target number of subjects; and (11) outcomes, including primary and secondary outcome

[17] 42 U.S.C. § 282(j)(1)(A)(iii). EX2148.

measures. NIH provided additional guidance on its website detailing the information to be provided.[18]

34. Recruitment information is also required, including (1) eligibility criteria; (2) gender; (3) age limits; (4) whether the trial accepts healthy volunteers; (5) overall recruitment status; (6) individual site status; and (7) whether there is expanded access to the drug for those who do not qualify for enrollment in the clinical trial and how to obtain information about such access.

35. Additional required information includes (1) location and contact information, including name of the sponsor, responsible party, and facility name and contact information; (2) administrative data, including the unique protocol identification number or other protocol identification numbers and the FDA Investigational New Drug protocol number and record verification date.

36. Timelines for submission are set forth in 42 U.S.C. 282(j)(2)(C). The responsible party for an applicable clinical trial initiated after the date of enactment of FDAAA (September 27, 2007) must submit the required information no later than the later of (1) 90 days after enactment of FDAAA; (2) 21 days after the first patient is enrolled in the clinical trial; or (3) in the case of a clinical trial that is not for a serious or life-threatening disease or condition and that is ongoing on the date of enactment, one year after the date of enactment. Although 42. U.S.C.

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[18] https://clinicaltrials.gov/policy/protocol-definitions. EX2149.

282(j)(2)(C) specifies a timeline of within 21 days after first patient enrollment, as described in Paragraph 25, if a sponsor intends to publish the study results with an ICJME journal, the study would need to be registered before enrollment of the first patient.

37. The responsible party must submit updates to the clinical trial information for inclusion in the database to reflect changes to information previously submitted. These updates must be provided not less than once every 12 months, unless there were no changes, and must include the dates such changes occurred. If recruitment status of the trial changes, the responsible party must include an update regarding recruitment status not later than 30 days after the status of the trial changes. The responsible party also must update the registration within 30 days of trial completion.

38. When a sponsor submits its clinical trial results to FDA for initial drug approval, such submission must be accompanied by a certification that the sponsor has complied with all applicable requirements pertaining to ClinicalTrials.gov.

### D. Failure to Comply with ClinicalTrials.gov Requirements Can Result in Civil Money Penalties, Public Notices of Such Failure, and Inability to Publish Study Results in Leading Medical Journals.

39. If a responsible party fails to submit the required information to ClinicalTrials.gov after an initial registration, NIH will include in the entry for that clinical trial that the responsible party is not in compliance with applicable

requirements by failing to submit required clinical trial information.[19] The notice will also include information about any applicable penalties for the violation.

40. FDCA Section 301(jj) (21 U.S.C. 331(jj)) states that the failure to submit the required information to ClinicalTrials.gov constitutes a prohibited act.[20]

41. FDCA Section 303(f)(3)(A) (21 U.S.C. 333(f)(3)(A)) provides that any person who fails to submit the required information to ClinicalTrials.gov shall be subject to a civil monetary penalty of not more than $10,000 for all violations adjudicated in a single proceeding. If the violation is not corrected within the 30-day period following notification, the person shall, in addition to the prior stated penalty, be subject to a civil monetary penalty of not more than $10,000 for each day of the violation after such period until the violation is corrected.[21]

42. Per ICJME policy, the failure to register on ClinicalTrials.gov prior to enrollment of the first study participant will result in the inability to publish in any ICJME journal.[22]

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[19] 42 U.S.C. 282(j)(5)(E)(i). EX2148.
[20] 21 U.S.C. § 331. EX2150.
[21] 21 U.S.C. § 333. EX2151.
[22] Editorial, Clinical Trial Registration: A Statement from the International Committee of Medical Journal Editors (Sept. 2004), https://www.icmje.org/news-and-editorials/clin_trial_sep2004.pdf. EX2152.

### E. Johns Hopkins University Properly Registered with ClinicalTrials.gov on June 10, 2013, and Included Only the Information Required by Law.

43. Johns Hopkins University (JHU) first submitted information to ClinicalTrials.gov about the Study of MK-3475 in Patients with Microsatellite Unstable (MSI) Tumors (Cohorts A, B and C) (NCT01876511) on June 10, 2013.[23] On the date of that submission the ClinicalTrials.gov requirements had already been in place for nearly six years.

44. The requirements apply to an "applicable clinical trial." An "applicable drug clinical trial" is defined as "a controlled clinical investigation, other than a phase I clinical investigation, of a drug subject to section 505 of the Federal Food, Drug, and Cosmetic Act." 42 USC 282(j)(1)(A)(iii)(II) states that "clinical investigation" has the same meaning as provided in 21 CFR 312.3: "any experiment in which a drug is administered or dispensed to, or used involving, one or more human subjects. For the purposes of this part, an experiment is any use of a drug except for the use of a marketed drug in the course of medical practice."[24]

45. JHU's study (Unique protocol ID J1365) met this definition. It was a Phase 2 study of an investigational drug for patients with certain tumor types. It was not a marketed drug and was not being used in the course of medical practice.

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[23] EX1005.
[24] 42 USC 282(j). EX2148.

Therefore, the requirements related to ClinicalTrials.gov registration were applicable to JHU at the time of posting.

46. Responsible parties of applicable clinical trials initiated after the date of enactment of FDAAA were required to submit the information required under 42 U.S.C. 282(j)(2)(A)(ii) no later than 21 days after the first patient is enrolled in such clinical trial. However, in order to publish in an ICJME journal, a trial sponsor would need to register on ClinicalTrials.gov before the first patient was enrolled. That JHU posted in advance of study start was therefore consistent with the ICJME policy.

47. The first submission of June 10, 2013, included the elements required by 42 U.S.C. 282(j)(2)(A), as provided in **Table 1** below, and complied with the descriptions of required information provided by NIH on its website.

**Table 1**

| Posted Element | Information Posted | Legal Requirement | NIH Description |
|---|---|---|---|
| **Study Identification** | | | |
| Unique protocol ID | J1365 | 42 USC 282(j)(2)(A)(ii)(IV)(aa) | Any unique identifier assigned to the protocol by the sponsor. |
| Brief title of the study | Phase 2 Study of MK-3475 in Patients With Microsatellite Unstable (MSI) Tumors | 42 USC 282(j)(2)(A)(ii)(I)(aa) | A short title of the clinical study written in language intended for the lay public. The title should include, where possible, information on the participants, condition being evaluated, and |

| Posted Element | Information Posted | Legal Requirement | NIH Description |
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| | | | intervention(s) studied. |
| Secondary IDs | MK-3475-016, NA_00085756 | 42 USC 282(j)(2)(A)(ii)(IV)(bb) | An identifier(s) (ID), if any, other than the organization's Unique Protocol Identification Number or the NCT number that is assigned to the clinical study. This includes any unique clinical study identifiers assigned by other publicly available clinical trial registries. If the clinical study is funded in whole or in part by a U.S. Federal Government agency, the complete grant or contract number must be submitted as a Secondary ID. |
| Study Type | Interventional | 42 USC 282(j)(2)(A)(ii)(I)(ff) | The nature of the investigation or investigational use for which clinical study information is being submitted. |
| **Study Status** | | | |
| Recruitment status | Not yet recruiting | 42 USC 282(j)(2)(A)(ii)(II)(ee) | The recruitment status for the clinical study as a whole, based upon the status of the individual sites. If at least one facility in a multi-site clinical study has an Individual Site Status of “Recruiting,” then the Overall Recruitment Status for the study must be “Recruiting.” |
| Study start date | 2013-07 | 42 USC 282(j)(2)(A)(ii)(I)(ii) | The estimated date on which the clinical study will be open for recruitment of participants, or the actual date on which the first participant was enrolled. |

| Posted Element | Information Posted | Legal Requirement | NIH Description |
|---|---|---|---|
| Estimated completion date | 2017-06 [Estimated] | 42 USC 282(j)(2)(A)(ii)(I)(jj) | The date that the final participant was examined or received an intervention for the purposes of final collection of data for the primary outcome, whether the clinical study concluded according to the pre-specified protocol or was terminated. In the case of clinical studies with more than one primary outcome measure with different completion dates, this term refers to the date on which data collection is completed for all of the primary outcomes. |
| **Sponsor/Collaborators** | | | |
| Responsible Party | Sponsor | 42 USC 282(j)(2)(A)(ii)(III)(bb) | An indication of whether the responsible party is the sponsor, the sponsor-investigator, or a principal investigator designated by the sponsor to be the responsible party. |
| Sponsor | Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins | 42 USC 282(j)(2)(A)(ii)(III)(aa) | The name of the entity or the individual who is the sponsor of the clinical study. |
| Collaborator | Merck Sharp & Dohme LLC | 42 USC 282(j)(2)(A)(ii)(I)(dd) | Other organizations (if any) providing support. Support may include funding, design, implementation, data analysis or reporting. The responsible party is responsible for confirming all collaborators before listing them. |
| **Oversight** | | | |
| Data Monitoring | Yes | 42 USC 282(j)(2)(A)(ii)(I)(dd) | Indicate whether a data monitoring committee has been appointed for this study. |

| Posted Element | Information Posted | Legal Requirement | NIH Description |
|---|---|---|---|
| | | | The data monitoring committee (board) is a group of independent scientists who are appointed to monitor the safety and scientific integrity of a human research intervention, and to make recommendations to the sponsor regarding the stopping of the trial for efficacy, for harms or for futility. The composition of the committee is dependent upon the scientific skills and knowledge required for monitoring the particular study. |
| **Study Description** | | | |
| Brief summary of the study | This study will be looking at whether MK-3475 (an antibody that blocks negative signals to T cells) is effective (anti-tumor activity) and safe in three different patient populations. These include: 1. patients with MSI positive colon cancer, 2. patients with MSI negative colon cancer, and 3. patients with other MSI positive cancers. | 42 USC 282(j)(2)(A)(iii)(I)(bb) | A short description of the clinical study, including a brief statement of the clinical study's hypothesis, written in language intended for the lay public. |
| **Conditions and Keywords** | | | |
| Conditions to be treated | MSI Positive Colorectal Cancer<br>MSI Negative Colorectal Cancer<br>MSI Positive Non-Colorectal Cancers | 42 USC 282(j)(2)(A)(iii)(I)(gg) | The name(s) of the disease(s) or condition(s) studied in the clinical study, or the focus of the clinical study. Use, if available, appropriate descriptors from NLM's Medical Subject Headings (MeSH)-controlled |

| Posted Element | Information Posted | Legal Requirement | NIH Description |
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| | | | vocabulary thesaurus or terms from another vocabulary, such as the Systematized Nomenclature of Medicine—Clinical Terms (SNOMED CT), that has been mapped to MeSH within the Unified Medical Language System (UMLS) Metathesaurus. |
| **Study Design** | | | |
| Study design | Interventional | 42 USC 282(j)(2)(A)(ii)(I)(ff) | The main objective of the intervention(s) being evaluated by the clinical trial. |
| Primary purpose | Treatment | 42 USC 282(j)(2)(A)(ii)(I)(cc) | The main objective of the intervention(s) being evaluated by the clinical trial. |
| Study phase | Phase 2 | 42 USC 282(j)(2)(A)(ii)(I)(ee) | For a clinical trial of a drug product (including a biological product), the numerical phase of such clinical trial, consistent with terminology in 21 CFR 312.21 and in 21 CFR 312.85 for phase 4 studies. |
| Interventional Study Model | Parallel Assignment | 42 USC 282(j)(2)(A)(ii)(I)(hh) | The strategy for assigning interventions to participants. |
| Number of arms | 3 | 42 USC 282(j)(2)(A)(ii)(I)(ff) | The number of arms in the clinical trial. For a trial with multiple periods or phases that have different numbers of arms, the maximum number of arms during all periods or phases. |
| Masking | None (Open Label) | 42 USC 282(j)(2)(A)(ii)(I)(ff) | The party or parties involved in the clinical trial who are prevented from having knowledge of the |

| Posted Element | Information Posted | Legal Requirement | NIH Description |
|---|---|---|---|
| | | | interventions assigned to individual participants. |
| Allocation | Non-Randomized | 42 USC 282(j)(2)(A)(ii)(I)(ff) | The method by which participants are assigned to arms in a clinical trial. |
| Enrollment | 71 [Estimated] | 42 USC 282(j)(2)(A)(ii)(I)(kk) | The estimated total number of participants to be enrolled (target number) or the actual total number of participants that are enrolled in the clinical study. |
| **Arms, Groups, and Interventions** | | | |
| Arm Information | Experimental: MSI Positive Colorectal Cancer<br>Experimental: MSI Negative Colorectal Cancer<br>Experimental: MSI Positive Non-Colorectal Cancer | 42 USC 282(j)(2)(A)(ii)(I)(hh) | A description of each arm of the clinical trial that indicates its role in the clinical trial; provides an informative title; and, if necessary, additional descriptive information (including which interventions are administered in each arm) to differentiate each arm from other arms in the clinical trial. |
| Interventions | Drug: MK-3475<br>MK-3475 10 mg/kg every 14 days | 42 USC 282(j)(2)(A)(ii)(I)(hh) | Specify the intervention(s) associated with each arm or group; at least one intervention must be specified for interventional studies. For observational studies, specify the intervention(s) / exposure(s) of interest, if any. If the same intervention is associated with more than one arm or group, provide the information once and use the Arm or Group/Intervention Cross-Reference to associate it with more than one arm or group. |

| Posted Element | Information Posted | Legal Requirement | NIH Description |
|---|---|---|---|
| **Outcome Measure** | | | |
| Primary Outcome Measure Information | 1. Immune-related progression free survival (irPFS) rate at 20 weeks in patients with MSI positive and negative colorectal adenocarcinoma using immune related response criteria (irRC)<br><br>[Time Frame: 4 years]<br><br>2. Objective response rate (irORR) at 20 weeks in patients with MSI positive and negative colorectal adenocarcinoma using immune related response criteria (irRC)<br><br>[Time Frame: 4 years]<br><br>3. Immune-related progression free survival (irPFS) rate in patients with MSI positive non-colorectal adenocarcinoma using immune related response criteria (irRC) at 20 weeks<br><br>[Time Frame: 4 years] | 42 USC 282(j)(2)(A)(ii)(I)(ll) | A description of each primary outcome measure (or for observational studies, specific key measurement[s] or observation[s] used to describe patterns of diseases or traits or associations with exposures, risk factors or treatment). |
| Secondary Outcome Measures | 1. Overall survival<br><br>[Time Frame: 4 years]<br><br>2. irPFS and PFS in patients with MSI positive and negative | 42 USC 282(j)(2)(A)(ii)(I)(ll) | A description of each secondary outcome measure (or for observational studies, specific secondary measurement[s] or observation[s] used to describe patterns of diseases |

| Posted Element | Information Posted | Legal Requirement | NIH Description |
|---|---|---|---|
| | tumors at 28 weeks using irRC and RECIST 1.1<br><br>[Time Frame: 4 years]<br><br>3. Best overall response rate and disease control rate in patients with MSI positive and negative tumors<br><br>[Time Frame: 4 years]<br><br>4. Number of participants experiencing immune-related toxicities (IRAEs)<br><br>[Time Frame: Continuous]<br><br>5. Does MSI as a marker predict treatment response<br><br>[Time Frame: 4 years] | | or traits or associations with exposures, risk factors or treatment). |
| **Eligibility** | | | |
| Sex/Gender | All | 42 USC 282(j)(2)(A)(ii)(II)(bb) | The sex and, if applicable, gender of the participants eligible to participate in the clinical study. |
| Minimum Age | 18 years | 42 USC 282(j)(2)(A)(ii)(II)(cc) | The minimum and maximum age of potential participants eligible for the clinical study, provided in relevant units of time. |
| Eligibility criteria | Inclusion Criteria: | 42 USC 282(j)(2)(A)(ii)(II)(aa) | A limited list of criteria for selection of participants in the clinical study, provided in |

| Posted Element | Information Posted | Legal Requirement | NIH Description |
|---|---|---|---|
| | 1. Arm 1 only: Patients with MSI positive colorectal cancer<br>2. Arm 2 only: Patients with MSI negative colorectal cancer<br>3. Arm 3 only: Patients with MSI positive non-colorectal cancer<br>4. Have measurable disease<br>5. ECOG Performance Status of 0 to 1<br>6. Adequate organ function as defined by study-specified laboratory tests<br>7. Must use acceptable form of birth control through the study and for 28 days after final dose of study drug<br>8. Signed informed consent form<br>9. Willing and able to comply with study procedures<br>10. Agree to have a biopsy of their cancer<br><br>Exclusion Criteria:<br><br>1. Currently have or have history of certain study-specified heart, liver, kidney, lung, neurological, immune or other medical conditions<br>2. Systemically active steroid use<br>3. Patients on home oxygen | | terms of inclusion and exclusion criteria and suitable for assisting potential participants in identifying clinical studies of interest. Use a bulleted list for each criterion below the headers "Inclusion Criteria" and "Exclusion Criteria." |

| Posted Element | Information Posted | Legal Requirement | NIH Description |
|---|---|---|---|
| | 4. Patients who have had prior treatment with anti-PD-1, anti-PD-L1, anti-PD-L2, anti-CD137, anti-OX-40, anti-CD40, or anti-CTLA-4 antibodies<br>5. Another investigational product within 28 days prior to receiving study drug<br>6. Pregnant or lactating<br>7. Conditions, including alcohol or drug dependence, or intercurrent illness that would affect the patient's ability to comply with study visits and procedures | | |
| **Contacts, Locations, and Investigator Information** | | | |
| Facility Information, including address and facility contact | Dung Le, MD, Principal Investigator<br><br>Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins<br><br>Contact<br>Holly Kemberling, RN<br>443-287-5013<br>hkember1@jhmi.edu | 42 USC 282(j)(2)(A)(ii)(III)(cc) | For each facility participating in a clinical study, including the name or title, telephone number, and email address of a person to whom questions concerning the study and enrollment at that site can be addressed. |

48. Throughout the duration of the trial, the above information was updated as needed to comply with 42 U.S.C. 282(j)(4)(C). These updates included, among other things, changes to inclusion/exclusion criteria, investigation sites,

investigator contact information, and study status. A list of updates through July 2015 are included in Appendix B.

**F. Conclusion**

49. In conclusion, JHU was legally required to submit the registration to ClincalTrials.gov regarding study J1365 at the time of its first registration in June 2013. It provided the information legally required by statute, and consistent with NIH Guidance on types of information to include. It included no more information than was required for compliance.

50. At the time JHU submitted its registration for Study J1365 to ClinicalTrials.gov, the requirements of 42 U.S.C. 282(j)(2) were in effect and applicable to JHU.

51. JHU's registration followed the applicable legal requirements as well as with the requirements of ICJME. JHU did not submit any more information than was required and necessary to fulfill its legal obligations.

52. Had JHU failed to include the information provided, it would have been committing a prohibited act under the FDCA, subjecting itself to potential civil monetary penalties. It would also have been precluded from publishing the results of its clinical study in any member journal of ICJME, which includes major medical journals such as the New England Journal of Medicine, Nature Medicine, British Medical Journal, The Lancet, and Annals of Internal Medicine.

# APPENDIX A

# Jennifer Newberger

## FDA Legal Expert

### Contact

(202) 821-6381

### Education

University of Miami School of Law
*J.D., Magna Cum Laude*
*2004-2007*

Emory University Rollins School of Public Health
*Master of Public Health, 1999-2001*

Washington University in St. Louis
*B.A., Anthropology, 1995-1999*

### Memberships

Bar of the District of Columbia

Food and Drug Law Journal Editorial Advisory Board (2009-2013)

### Teaching Engagements

Johns Hopkins University, October 2014 (single course), Medical Device Law for Graduate Engineering Students

University of Maryland, Fall Semester 2014, Medical Device Law for Graduate Engineering Students

### Selected Publications

*Wound Products, Antimicrobial Resistance, and Commercial Speech: FDA's Solution in Search of a Problem,* Washington Legal Foundation, https://www.wlf.org/2024/07/15/publishing/wound-products-antimicrobial-resistance-and-commercial-speech-fdas-solution-in-search-of-a-problem/.

*Practicing Law Institute, FDA Deskbook: A Compliance and Enforcement Guide*, Chapter 10 (Recalls), Chapter 11 (Medical Device Reports) (James P. Ellison and Anne K. Walsh eds., 2016) (co-authored with Jeffrey Shapiro)

*The European Lawyer Reference, Commercialisation of Health Care, United States*, 291-313 (Jeffrey N. Gibbs and Jeffrey S. Graham eds., 2013) (co-authored with Jeffrey N. Gibbs and Alexander Varond)

### Profile

With nearly 20 years working in the regulated health area, I have had the good fortune to be able to be both passionate about my work and contribute to the public's health. During the course of my career I have worked with regulators to reconsider traditional approaches to new and novel technologies, and I never shy away from a challenge. I am an experienced, creative contributor who thrives on thinking outside the box. I am a proven leader who is able to work well cross-functionally, lead teams, and engage successfully with regulatory agencies.

### Experience

Hyman, Phelps & McNamara, P.C.
*Director, May 2024-Present*

- Advise medical device clients on the full product life cycle.
- Provide assistance on pre-market activities, including pre-submissions and meetings with FDA.
- Draft requests for Breakthrough Device Designation.
- Provide guidance on mergers and acquisitions involving medical device companies, including conducting regulatory due diligence and advising on asset purchase, stock purchase, and merger agreements.
- Respond to FDA enforcement actions, including Warning Letters and 483 inspectional observations.
- Provide guidance on clinical study design, protocol development, statistical plans, and ClinicalTrials.gov registration requirements.
- Review and advise on promotional materials to ensure compliance with FDA's requirements.
- Assist clients in strategic thinking about approach to FDA oversight, product regulatory status, and claims.

Cognito Therapeutics, Inc.
*Senior Vice President, Regulatory and Compliance, April 2023-May 2024*
*Vice President, Regulatory and Compliance, December 2021-April 2023*

- Serve as member of leadership team advising CEO and Board of Directors on key strategic decisions related to regulatory, quality, compliance, and overall business direction.
- Work closely with cross-functional teams to develop informed consent, protocol, statistical analysis plan, and other study documents to enable launch of pivotal study.
- Review and approve documents to be provided to ClinicalTrials.gov. Advise on timing and necessary updates of such submissions.

*FDA defines medical device accessory, proposes new means forclassification*, Westlaw Journal Medical Devices (Feb. 2015), at 3

*Draft Guidance on Medical Device Recalls: Improvements are Needed,* The Food and Drug Law Institute – Update, Issue 4, July/August 2013, pgs. 11-14 (co-authored with JeffreyShapiro and Jeffrey Gibbs)

*Keeping up with events: the US FDAand its draft guidance on medical device appeals*, SCRIP Regulatory Affairs (April 2013), at 15 (co-authored with Jeffrey Shapiro)

*FDASIA: New Opportunities, New Complexities for Pharma and Medtech*, SCRIP Regulatory Affairs,September 2012, at 6-9 (co- authored with Jeffrey Gibbs and Nisha Shah)

Blog posts regarding medical devices at www.fdalawblog.net

- Provide expertise on applicable provisions of the Federal Food, Drug, and Cosmetic Act as they pertain to clinical studies and regulation of medical devices.
- Collaborate with external advisors to develop creative approaches to regulatory approval.
- Implement system to formalize review of promotional labeling and scientific materials.
- Update Board of Directors on key regulatory, quality, and compliance metrics, including hiring plans, risks and benefits to different regulatory approaches, and potential trade-offs regarding options.
- Serve as key advisor to colleagues on a variety of issues, including program and project management, risk analyses, clinical trial design, statistical analysis, FDA regulation of hardware and software medical devices, and differences between drug and device pathways.
- Participate in potential investor meetings to advise on FDA discussions, regulatory pathways, and clinical study requirements.

### Abbott Laboratories, Alameda, CA

*Senior Regulatory Counsel, February 2021-December 2021*

- Support diagnostics and diabetes care teams to advise on regulatory strategy, marketing materials, and permissible communications related to sales, distribution, and marketing of products.
- Serve on the Digital Health Task Force and other digital health teams working to better understand global digital health regulatory policy and approach and assess ways to best advocate for Abbott in that space.
- Collaborate with the diagnostics team on matters related to the sales, marketing, and distribution of COVID tests authorized by FDA for emergency use during the COVID pandemic.
- Work closely with regulatory teams to review and interpret the proposed VALID Act, which will significantly alter the way in which in vitro diagnostics products are regulated.
- Drive cross-functional collaboration to revise and update policies and procedures related to regulatory strategy.

### Apple Inc., Cupertino, CA

*Principal Counsel and Sr. Manager, October 2020-February 2021*
*Principal Counsel, October 2018-October 2020*
*Senior Counsel, April 2017-October 2018*

- Lead executive-level meetings, including with the Apple COO, regarding regulatory and legal challenges associated with shipping regulated health features.
- Serve as expert advisor on key aspects of the Federal Food, Drug, and Cosmetic Act and its implementing regulations, along with related oversight of the Federal Trade Commission and Office of the Inspector General compliance guidelines.
- Manage the cross-functional team responsible for obtaining Apple's first de novo authorizations for the ECG app and irregular rhythm notification.
- Worked closely with Government Affairs globally to

organize meetings with FDA and other regulators to discuss an appropriate risk-based approach to regulating software applications.
- Work with regulators on a global scale to adapt historical, hardware-only laws and regulations to unique aspects of software regulation, distribution, and marketing.
- Partner closely with engineering, regulatory, operations, marketing, and clinical teams to advise on potential regulatory status and pathway of proposed health products.
- Primary health lead for products law group, advising teams on study protocols and informed consent forms, ClinicalTrials.gov registration, compliance with 21 CFR Part 11 and good clinical practices, adverse event reporting, and other study-related requirements.
- Negotiate agreements with universities and other entities, including contract research organizations (CROs), to facilitate research, data collection, and complex clinical studies.
- Work closely with the regulatory and quality teams on global product submissions, including drafting quality agreements with third party vendors and intra-company agreements between Apple Inc. and its global subsidiaries.
- Advise on advertising and promotion of both regulated and unregulated health features.
- Coordinate with global legal teams on issues related to import, distribution, licensing, and advertising of regulated health features.

Hyman, Phelps & McNamara, P.C., Washington, D.C.
*Director, January 2016-April 2017*
*Associate, January 2011-December 2015*

- Advise medical device companies on pre-market strategies, including selection of appropriate regulatory pathway.
- Assist medical device companies to appeal decisions by FDA's Center for Devices and Radiological Health (CDRH) regarding regulatory strategy, additional information requests, and not substantially equivalent decisions.
- Draft medical device pre-market submissions and lead meetings with FDA regarding those submissions.
- Firm expert in FDA's approach to regulation of digital health products.
- Assist multi-national, multi-billion dollar technology company in developing its FDA regulatory strategy.
- Serve on promotional review committees for clients to approve marketing materials prior to product launch.
- Draft and negotiate clinical trial and research agreements between device companies and universities, clinician investigators, and contract research organizations.
- Draft regulatory provisions in stock purchase agreements, asset purchase agreements, distributor agreements, and other contractual arrangements requiring regulatory representations and warranties.
- Review and edit government regulation and risk factors sections for medical device company 10-Ks and 10-Qs.

- Conduct regulatory review of S-1 for device company IPOs.
- Assist in negotiating a consent decree for a medical device client.
- Lead regulatory due diligence for multinational corporations and private equity firms looking to acquire medical device companies.
- Advise on anti-kickback and Sunshine Act compliance, as well as state licensing laws regarding medical device sale and distribution.
- Review and edit clinical study protocols and informed consent documents.
- Assist in defense of large medical device companies in criminal and civil enforcement actions brought by the Department of Justice.

### U.S. Food and Drug Administration, Center for Devices and Radiological Health (CDRH), Silver Spring, MD

*Policy Advisor, April 2010-December 2010*

- Coordinate review of 510(k) premarket review process, including responding to public comments.
- Draft responses to Citizen Petitions.
- Advise ombudsman in responding to complaints received from concerned citizens and medical device companies.
- Coordinate appeals of review decisions to the Director of CDRH.
- Review and edit proposed guidance documents and regulations prior to publication and advise on related policy and legal issues.
- Represent CDRH on working groups addressing good manufacturing practices for combination products and First Amendment challenges to FDA regulation.

### Arnold & Porter, LLP, Washington, D.C.

*Associate, September 2007-April 2010*
*Summer Associate, May-August 2006*

- Advise pharmaceutical, biotechnology, and medical device companies on regulatory compliance, legislative issues, fraud and abuse, and litigation strategies related to issues arising under the Federal Food, Drug, and Cosmetic Act, its implementing regulations, and related statutes and regulations administered by other agencies.
- Conduct internal investigation of multi-product line medical device firm to assure compliance with fraud and abuse statutes, regulations, and guidance, and FDA law, including FDA's prohibition against off-label promotion and marketing, company sponsorship of Continuing Medical Education sessions, and permissible relationships with consultants and other physicians.
- Analyze biotechnology company patient assistance programs to assess compliance with fraud and abuse and FDA law, including compliance with FDA's prohibition against off-label promotion and marketing.
- Participate in document productions to the Energy and Commerce Committee of the U.S. House of Representatives in response to a congressional

investigation of a manufacturer of an active pharmaceutical ingredient, and to the Committee on Finance of the U.S. Senate in response to a congressional investigation of a major pharmaceutical manufacturer.

# APPENDIX B

## APPENDIX B

**UPDATES MADE BY JHU BEFORE JULY 10, 2015**

1. On June 12, 2013, JHU submitted an update with respect to the secondary outcome measure, Number of participants experiencing immune-related toxicities. This time frame was updated from "Continuous" to "4 years."

2. On September 20, 2013, JHU updated their registration to change the status from "Not yet recruiting" to "Recruiting," and to update the study start from July 2013 to September 2013.

3. On May 21, 2014, the registration was updated to include "Keywords" in the "Conditions" section.

4. On June 25, 2014, the secondary outcomes measures were updated to include alternative markers of MSI status, with a time frame of four years. Three additional sites were also added—Stanford University, Ohio State University, and Providence Portland Medical Center.

5. On September 15, 2014, the status of the Portland site was updated from "Not yet recruiting" to "Recruiting."

6. On December 26, 2014, the Stanford and Ohio State University sites were updated from "Not yet recruiting" to "Recruiting."

7. On January 29, 2015, the Investigator Thoracic and Gastrointestinal Oncology Branch, Center for Cancer Research, NIH, was added as a site.

8. On February 26, 2015, University of Pittsburgh Cancer Institute was added as a site.

9. On April 15, 2015, exclusion criteria were updated and the status of the Center for Cancer Research, NIH was updated from "Not yet recruiting" to "Recruiting."

10. On June 9, 2015, the estimated study completion date was added as October 2020. The registration was also amended to update estimated enrollment from 71 to 171 and to further modify the exclusion criteria.