**No. 23-2254**

# In the United States Court of Appeals for the Federal Circuit

MERCK SHARP & DOHME B.V., MERCK SHARP & DOHME, LLC,
*Plaintiffs-Appellees*,

*v.*

AUROBINDO PHARMA USA, INC., AUROBINDO PHARMA LTD., USV PRIVATE LIMITED, GLAND PHARMA LIMITED, MANKIND PHARMA LTD., LIFESTAR PHARMA LLC, FRESENIUS KABI USA, LLC, DR. REDDY'S LABORATORIES, INC., DR. REDDY'S LABORATORIES, LTD., SUN PHARMACEUTICAL INDUSTRIES, INC., SUN PHARMACEUTICAL INDUSTRIES LIMITED, SANDOZ INC., LEK PHARMACEUTICALS, D.D., MYLAN API US LLC, MYLAN PHARMACEUTICALS INC., MYLAN INC., EUGIA PHARMA SPECIALTIES LIMITED,
*Defendants-Appellants,*

LUPIN LTD., LUPIN PHARMACEUTICALS, INC., LUPIN INC.,
TEVA PHARMACEUTICALS USA, INC.,
*Defendants.*

Appeal from the U.S. District Court for the District of New Jersey, No. 2:20-cv-02576 (Consolidated), Hon. Claire Cecchi

## CORRECTED NON-CONFIDENTIAL OPENING BRIEF FOR THE APPELLANTS

Eric T. Werlinger
Timothy H. Gray
KATTEN MUCHIN ROSENMAN LLP
1919 Pennsylvania Ave. NW
Suite 800
Washington, DC 20006
(202) 625-3500

Deepro R. Mukerjee
Lance A. Soderstrom
KATTEN MUCHIN ROSENMAN LLP
50 Rockefeller Plaza
New York, NY 10020
(212) 940-6330
deepro.mukerjee@katten.com

*Counsel for Mylan Inc., Mylan Pharms. Inc., and Mylan API US LLC*
(*Additional counsel on the signature block*)

November 9, 2023

## PATENT CLAIMS AT ISSUE

### U.S. Patent No. RE44,733 E: Claims 4, 12, and 21 (Appx00069-00070)

4. A 6-mercapto-cyclodextrin derivative according to claim 1 selected from the group consisting of:

6-per-deoxy-6-per-(2-carboxyethyl)thio-γ-cyclodextrin;

6-per-deoxy-6-per-(3-carboxypropyl)thio-γ-cyclodextrin;

6-per-deoxy-6-per-(4-carboxyphenyl)thio-γ-cyclodextrin;

6-per-deoxy-6-per-(4-carboxyphenylmethyl)thio-γ-cyclodextrin;

6-per-deoxy-6-per-(2-carboxypropyl)thio-γ-cyclodextrin; and

6-per-deoxy-6-per-(2-sulfoethyl)thio-γ-cyclodextrin;

or a pharmaceutically acceptable salt thereof.

12. 6-Per-deoxy-6-per-(2-carboxyethyl)thio-γ-cyclodextrin, sodium salt.

21. A method for reversal of drug-induced neuromuscular block in a subject, which comprises parenterally administering to said subject an effective amount of 6-per-deoxy-6-per-(2-carboxyethyl)thio-γ-cyclodextrin, sodium salt.

# UNITED STATES COURT OF APPEALS
# FOR THE FEDERAL CIRCUIT

## CERTIFICATE OF INTEREST

**Case Number** 2023-2254

**Short Case Caption** MERCK SHARP & DOHME B.V. et al. v. AUROBINDO PHARMA USA, INC. et al.

**Filing Party/Entity** DEFENDANT-APPELLANT GLAND PHARMA LIMITED

**Instructions:** Complete each section of the form. In answering items 2 and 3, be specific as to which represented entities the answers apply; lack of specificity may result in non-compliance. **Please enter only one item per box; attach additional pages as needed and check the relevant box**. Counsel must immediately file an amended Certificate of Interest if information changes. Fed. Cir. R. 47.4(b).

I certify the following information and any attached sheets are accurate and complete to the best of my knowledge.

Date: 10/24/2023

Signature: 

Name: Matthew T. Wilkerson

| **1. Represented Entities.** Fed. Cir. R. 47.4(a)(1). | **2. Real Party in Interest.** Fed. Cir. R. 47.4(a)(2). | **3. Parent Corporations and Stockholders.** Fed. Cir. R. 47.4(a)(3). |
|---|---|---|
| Provide the full names of all entities represented by undersigned counsel in this case. | Provide the full names of all real parties in interest for the entities. Do not list the real parties if they are the same as the entities.<br><br>☐ None/Not Applicable | Provide the full names of all parent corporations for the entities and all publicly held companies that own 10% or more stock in the entities.<br><br>☐ None/Not Applicable |
| Gland Pharma Limited | Gland's Business Partner | Parent: Fosun Pharma Industrial Pte. Ltd. |
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☐ Additional pages attached

**4. Legal Representatives.** List all law firms, partners, and associates that (a) appeared for the entities in the originating court or agency or (b) are expected to appear in this court for the entities. Do not include those who have already entered an appearance in this court. Fed. Cir. R. 47.4(a)(4).

☐ None/Not Applicable ☐ Additional pages attached

| | | |
|---|---|---|
| Arun J. Mohan | Former employee of ArentFox Schiff LLP | not expected to appear in this court for the entity |
| James S. Richter | Parnter, Midlige Richter LLC | not expected to appear in this court for the entity |
| | | |

**5. Related Cases.** Provide the case titles and numbers of any case known to be pending in this court or any other court or agency that will directly affect or be directly affected by this court's decision in the pending appeal. Do not include the originating case number(s) for this case. Fed. Cir. R. 47.4(a)(5). See also Fed. Cir. R. 47.5(b).

☑ None/Not Applicable ☐ Additional pages attached

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**6. Organizational Victims and Bankruptcy Cases**. Provide any information required under Fed. R. App. P. 26.1(b) (organizational victims in criminal cases) and 26.1(c) (bankruptcy case debtors and trustees). Fed. Cir. R. 47.4(a)(6).

☑ None/Not Applicable ☐ Additional pages attached

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# UNITED STATES COURT OF APPEALS
# FOR THE FEDERAL CIRCUIT

## CERTIFICATE OF INTEREST

**Case Number** 2023-2254

**Short Case Caption** Merck Sharp & Dohme B.V. v. Aurobindo Pharma USA, In

**Filing Party/Entity** USV Private Limited

**Instructions:**

1. Complete each section of the form and select none or N/A if appropriate.
2. Please enter only one item per box; attach additional pages as needed, and check the box to indicate such pages are attached.
3. In answering Sections 2 and 3, be specific as to which represented entities the answers apply; lack of specificity may result in non-compliance.
4. Please do not duplicate entries within Section 5.
5. Counsel must file an amended Certificate of Interest within seven days after any information on this form changes. Fed. Cir. R. 47.4(c).

I certify the following information and any attached sheets are accurate and complete to the best of my knowledge.

Date: 10/24/2023

Signature: /s/ Robert L. Florence

Name: Robert L. Florence

| **1. Represented Entities.** Fed. Cir. R. 47.4(a)(1). | **2. Real Party in Interest.** Fed. Cir. R. 47.4(a)(2). | **3. Parent Corporations and Stockholders.** Fed. Cir. R. 47.4(a)(3). |
|---|---|---|
| Provide the full names of all entities represented by undersigned counsel in this case. | Provide the full names of all real parties in interest for the entities. Do not list the real parties if they are the same as the entities.<br><br>☑ None/Not Applicable | Provide the full names of all parent corporations for the entities and all publicly held companies that own 10% or more stock in the entities.<br><br>☑ None/Not Applicable |
| USV Private Limited | | |
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☐ Additional pages attached

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☐ None/Not Applicable ☐ Additional pages attached

| | | |
|---|---|---|
| Edward J. Dauber<br>Greenberg Dauber Epstein & Tucker | Robert J. Fettweis<br>Fleming Ruvoldt PLLC | Karen L. Carroll, formerly of<br>Parker Poe Adams & Bernstein LLP |
| Micheal L. Binns, formerly of<br>Parker Poe Adams & Bernstein | | |
| | | |

**5. Related Cases.** Other than the originating case(s) for this case, are there related or prior cases that meet the criteria under Fed. Cir. R. 47.5(a)?

☑ Yes (file separate notice; see below) ☐ No ☐ N/A (amicus/movant)

If yes, concurrently file a separate Notice of Related Case Information that complies with Fed. Cir. R. 47.5(b). **Please do not duplicate information.** This separate Notice must only be filed with the first Certificate of Interest or, subsequently, if information changes during the pendency of the appeal. Fed. Cir. R. 47.5(b).

**6. Organizational Victims and Bankruptcy Cases**. Provide any information required under Fed. R. App. P. 26.1(b) (organizational victims in criminal cases) and 26.1(c) (bankruptcy case debtors and trustees). Fed. Cir. R. 47.4(a)(6).

☑ None/Not Applicable ☐ Additional pages attached

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# UNITED STATES COURT OF APPEALS
# FOR THE FEDERAL CIRCUIT

## CERTIFICATE OF INTEREST

**Case Number** 2023-2254

**Short Case Caption** Merck Sharpe & Dohme B.V. v. Aurobindo Pharma USA, L

**Filing Party/Entity** Sun Pharmaceuticals Industries, Inc. and Sun Pharmaceuticals Industries Limited

**Instructions:**

1. Complete each section of the form and select none or N/A if appropriate.
2. Please enter only one item per box; attach additional pages as needed, and check the box to indicate such pages are attached.
3. In answering Sections 2 and 3, be specific as to which represented entities the answers apply; lack of specificity may result in non-compliance.
4. Please do not duplicate entries within Section 5.
5. Counsel must file an amended Certificate of Interest within seven days after any information on this form changes. Fed. Cir. R. 47.4(c).

I certify the following information and any attached sheets are accurate and complete to the best of my knowledge.

Date: 10/24/2023 Signature: /s/ Charles B. Klein

Name: Charles B. Klein

| **1. Represented Entities.** Fed. Cir. R. 47.4(a)(1). | **2. Real Party in Interest.** Fed. Cir. R. 47.4(a)(2). | **3. Parent Corporations and Stockholders.** Fed. Cir. R. 47.4(a)(3). |
|---|---|---|
| Provide the full names of all entities represented by undersigned counsel in this case. | Provide the full names of all real parties in interest for the entities. Do not list the real parties if they are the same as the entities.<br><br>☑ None/Not Applicable | Provide the full names of all parent corporations for the entities and all publicly held companies that own 10% or more stock in the entities.<br><br>☑ None/Not Applicable |
| Sun Pharmaceuticals Industries, Inc. | | |
| Sun Pharmaceuticals Industries Limited | | |
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☐ Additional pages attached

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☐ None/Not Applicable ☐ Additional pages attached

| | | |
|---|---|---|
| Charles B. Klein | Winston & Strawn LLP | |
| Jovial Wong | Winston & Strawn LLP | |
| | | |

**5. Related Cases.** Other than the originating case(s) for this case, are there related or prior cases that meet the criteria under Fed. Cir. R. 47.5(a)?

☐ Yes (file separate notice; see below) ☑ No ☐ N/A (amicus/movant)

If yes, concurrently file a separate Notice of Related Case Information that complies with Fed. Cir. R. 47.5(b). **Please do not duplicate information.** This separate Notice must only be filed with the first Certificate of Interest or, subsequently, if information changes during the pendency of the appeal. Fed. Cir. R. 47.5(b).

**6. Organizational Victims and Bankruptcy Cases**. Provide any information required under Fed. R. App. P. 26.1(b) (organizational victims in criminal cases) and 26.1(c) (bankruptcy case debtors and trustees). Fed. Cir. R. 47.4(a)(6).

☑ None/Not Applicable ☐ Additional pages attached

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# UNITED STATES COURT OF APPEALS FOR THE FEDERAL CIRCUIT

## CERTIFICATE OF INTEREST

**Case Number** 2023-2254

**Short Case Caption** Merck Sharp & Dohme B.V. v. Aurobindo Pharma USA, Inc.

**Filing Party/Entity** Aurobindo Pharma USA, Inc., Aurobindo Pharma, Ltd. and Eugia Pharma Specialties Ltd.

**Instructions:**

1. Complete each section of the form and select none or N/A if appropriate.
2. Please enter only one item per box; attach additional pages as needed, and check the box to indicate such pages are attached.
3. In answering Sections 2 and 3, be specific as to which represented entities the answers apply; lack of specificity may result in non-compliance.
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I certify the following information and any attached sheets are accurate and complete to the best of my knowledge.

Date: 10/24/2023

Signature: /s/ R Touhey Myer

Name: R Touhey Myer

| **1. Represented Entities.** Fed. Cir. R. 47.4(a)(1). | **2. Real Party in Interest.** Fed. Cir. R. 47.4(a)(2). | **3. Parent Corporations and Stockholders.** Fed. Cir. R. 47.4(a)(3). |
|---|---|---|
| Provide the full names of all entities represented by undersigned counsel in this case. | Provide the full names of all real parties in interest for the entities. Do not list the real parties if they are the same as the entities.<br><br>☑ None/Not Applicable | Provide the full names of all parent corporations for the entities and all publicly held companies that own 10% or more stock in the entities.<br><br>☐ None/Not Applicable |
| Aurobindo Pharma USA, Inc. | | Aurobindo Pharma Ltd. |
| Aurobindo Pharma Ltd. | | |
| Eugia Pharma Specialties, Ltd. | | Aurobindo Pharma Ltd. and<br>Mviyes Pharma Ventures Private Limited |
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☐ Additional pages attached

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☑ None/Not Applicable ☐ Additional pages attached

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☑ None/Not Applicable ☐ Additional pages attached

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# UNITED STATES COURT OF APPEALS
# FOR THE FEDERAL CIRCUIT

## CERTIFICATE OF INTEREST

**Case Number** 23-2254

**Short Case Caption** Merck Sharp & Dohme B.V. v. Aurobindo Pharma USA, In

**Filing Party/Entity** Mylan API US LLC, Mylan Pharmaceuticals Inc., and Mylan Inc.

**Instructions:**

1. Complete each section of the form and select none or N/A if appropriate.
2. Please enter only one item per box; attach additional pages as needed, and check the box to indicate such pages are attached.
3. In answering Sections 2 and 3, be specific as to which represented entities the answers apply; lack of specificity may result in non-compliance.
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I certify the following information and any attached sheets are accurate and complete to the best of my knowledge.

Date: 10/24/2023

Signature: /s/ Deepro R. Mukerjee

Name: Deepro R. Mukerjee

| **1. Represented Entities.** Fed. Cir. R. 47.4(a)(1). | **2. Real Party in Interest.** Fed. Cir. R. 47.4(a)(2). | **3. Parent Corporations and Stockholders.** Fed. Cir. R. 47.4(a)(3). |
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| Provide the full names of all entities represented by undersigned counsel in this case. | Provide the full names of all real parties in interest for the entities. Do not list the real parties if they are the same as the entities.<br><br>☑ None/Not Applicable | Provide the full names of all parent corporations for the entities and all publicly held companies that own 10% or more stock in the entities.<br><br>☐ None/Not Applicable |
| Mylan API US LLC (n/k/a Apicore US LLC) | | 4C Pharma Holdings LLC |
| Mylan Pharmaceuticals Inc. | | Mylan Inc. |
| Mylan Inc. | | Viatris Inc.* |
| | | *Viatris is a publicly held company, and no other publicly held company owns 10% or more of Viatris's stock |
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☐ Additional pages attached

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☐ None/Not Applicable ☐ Additional pages attached

| | | |
|---|---|---|
| Arnold B. Calmann (Saiber LLC) | Shannon M. Bloodworth (Perkins Coie LLP) | Christopher J. Marth (Perkins Coie LLP) |
| Jakob B. Halpern (Saiber LLC) | Brandon M. White (Perkins Coie LLP) | Emily J. Greb (Perkins Coie LLP) |
| Catherine Soliman (Saiber LLC) | Bryan D. Beel (Perkins Coie LLP) | |

**5. Related Cases.** Other than the originating case(s) for this case, are there related or prior cases that meet the criteria under Fed. Cir. R. 47.5(a)?

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☑ None/Not Applicable ☐ Additional pages attached

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# UNITED STATES COURT OF APPEALS
# FOR THE FEDERAL CIRCUIT

## CERTIFICATE OF INTEREST

**Case Number** 2023-2254

**Short Case Caption** Merck Sharp & Dohme B.V. v. Aurobindo Pharma USA, Inc.

**Filing Party/Entity** Dr. Reddy's Laboratories, Inc.; Dr. Reddy's Laboratories, Ltd.

**Instructions:**

1. Complete each section of the form and select none or N/A if appropriate.
2. Please enter only one item per box; attach additional pages as needed, and check the box to indicate such pages are attached.
3. In answering Sections 2 and 3, be specific as to which represented entities the answers apply; lack of specificity may result in non-compliance.
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I certify the following information and any attached sheets are accurate and complete to the best of my knowledge.

Date: 10/24/2023 Signature: /s/ Brian Burgess

Name: Brian Burgess

| **1. Represented Entities.** Fed. Cir. R. 47.4(a)(1). | **2. Real Party in Interest.** Fed. Cir. R. 47.4(a)(2). | **3. Parent Corporations and Stockholders.** Fed. Cir. R. 47.4(a)(3). |
|---|---|---|
| Provide the full names of all entities represented by undersigned counsel in this case. | Provide the full names of all real parties in interest for the entities. Do not list the real parties if they are the same as the entities.<br><br>☑ None/Not Applicable | Provide the full names of all parent corporations for the entities and all publicly held companies that own 10% or more stock in the entities.<br><br>☐ None/Not Applicable |
| Dr. Reddy's Laboratories, Inc. | | Dr. Reddy's Laboratories, Ltd. |
| Dr. Reddy's Laboratories, Ltd. | | Dr. Reddy's Laboratories, S.A. |
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☐ Additional pages attached

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☐ None/Not Applicable ☑ Additional pages attached

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**6. Organizational Victims and Bankruptcy Cases**. Provide any information required under Fed. R. App. P. 26.1(b) (organizational victims in criminal cases) and 26.1(c) (bankruptcy case debtors and trustees). Fed. Cir. R. 47.4(a)(6).

☑ None/Not Applicable ☐ Additional pages attached

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**UNITED STATES COURT OF APPEALS**
**FOR THE FEDERAL CIRCUIT**

**Merck Sharp & Dohme B.V. v. Aurobindo Pharma USA, Inc., No. 2023-2254**

Certificate of Interest

**4. Legal Representatives** (continued from page 3):

- Goodwin Procter LLP:
    - Elaine Herrmann Blais
    - Molly R. Grammel
    - Kathleen McGuinness
    - Thomas V. McTigue IV
    - Lauren E. Jackson
    - Alexandra D. Valenti
    - James Breen
    - Madeline R. DiLascia
- Hill Wallack LLP:
    - Eric I. Abraham
    - Nakul Y. Shah*

* *Denotes that attorney is no longer with listed firm*

# UNITED STATES COURT OF APPEALS FOR THE FEDERAL CIRCUIT

## CERTIFICATE OF INTEREST

**Case Number** 2023-2254

**Short Case Caption** Merck Sharp & Dohme B.V. v. Aurobindo Pharma USA, Inc.

**Filing Party/Entity** Fresenius Kabi USA, LLC

**Instructions:**

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I certify the following information and any attached sheets are accurate and complete to the best of my knowledge.

Date: 10/24/2023 Signature: /s/ Brian Burgess

Name: Brian Burgess

| **1. Represented Entities.** Fed. Cir. R. 47.4(a)(1). | **2. Real Party in Interest.** Fed. Cir. R. 47.4(a)(2). | **3. Parent Corporations and Stockholders.** Fed. Cir. R. 47.4(a)(3). |
|---|---|---|
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| Fresenius Kabi USA, LLC | | Parent: Fresenius SE & Co. |
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☐ Additional pages attached

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**UNITED STATES COURT OF APPEALS**
**FOR THE FEDERAL CIRCUIT**

**Merck Sharp & Dohme B.V. v. Aurobindo Pharma USA, Inc., No. 2023-2254**

Certificate of Interest

**4. Legal Representatives** (continued from page 3):

- Goodwin Procter LLP:
    - Molly R. Grammel
    - Kathleen McGuinness
    - Thomas V. McTigue IV
    - James Breen
    - John T. Bennett*
- Hill Wallack LLP:
    - Eric I. Abraham
    - Nakul Y. Shah*

* *Denotes that attorney is no longer with listed firm*

# UNITED STATES COURT OF APPEALS
# FOR THE FEDERAL CIRCUIT

## CERTIFICATE OF INTEREST

**Case Number** 2023-2254

**Short Case Caption** Merck Sharp & Dohme B.V. v. Aurobindo Pharma USA, Inc.

**Filing Party/Entity** Sandoz Inc.; Lek Pharmaceuticals, d.d.

**Instructions:**

1. Complete each section of the form and select none or N/A if appropriate.
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3. In answering Sections 2 and 3, be specific as to which represented entities the answers apply; lack of specificity may result in non-compliance.
4. Please do not duplicate entries within Section 5.
5. Counsel must file an amended Certificate of Interest within seven days after any information on this form changes. Fed. Cir. R. 47.4(c).

I certify the following information and any attached sheets are accurate and complete to the best of my knowledge.

Date: 10/24/2023

Signature: /s/ Brian Burgess

Name: Brian Burgess

| **1. Represented Entities.** Fed. Cir. R. 47.4(a)(1). | **2. Real Party in Interest.** Fed. Cir. R. 47.4(a)(2). | **3. Parent Corporations and Stockholders.** Fed. Cir. R. 47.4(a)(3). |
|---|---|---|
| Provide the full names of all entities represented by undersigned counsel in this case. | Provide the full names of all real parties in interest for the entities. Do not list the real parties if they are the same as the entities.<br><br>☑ None/Not Applicable | Provide the full names of all parent corporations for the entities and all publicly held companies that own 10% or more stock in the entities.<br><br>☐ None/Not Applicable |
| Sandoz Inc. | | Sandoz AG, Sandoz Group AG |
| Lek Pharmaceuticals d.d. | | Sandoz AG, Sandoz Group AG |
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☐ Additional pages attached

**4. Legal Representatives.** List all law firms, partners, and associates that (a) appeared for the entities in the originating court or agency or (b) are expected to appear in this court for the entities. Do not include those who have already entered an appearance in this court. Fed. Cir. R. 47.4(a)(4).

☐ None/Not Applicable ☑ Additional pages attached

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**5. Related Cases.** Other than the originating case(s) for this case, are there related or prior cases that meet the criteria under Fed. Cir. R. 47.5(a)?

☐ Yes (file separate notice; see below) ☑ No ☐ N/A (amicus/movant)

If yes, concurrently file a separate Notice of Related Case Information that complies with Fed. Cir. R. 47.5(b). **Please do not duplicate information.** This separate Notice must only be filed with the first Certificate of Interest or, subsequently, if information changes during the pendency of the appeal. Fed. Cir. R. 47.5(b).

**6. Organizational Victims and Bankruptcy Cases**. Provide any information required under Fed. R. App. P. 26.1(b) (organizational victims in criminal cases) and 26.1(c) (bankruptcy case debtors and trustees). Fed. Cir. R. 47.4(a)(6).

☑ None/Not Applicable ☐ Additional pages attached

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**UNITED STATES COURT OF APPEALS**
**FOR THE FEDERAL CIRCUIT**

**Merck Sharp & Dohme B.V. v. Aurobindo Pharma USA, Inc., No. 2023-2254**

Certificate of Interest

**4. Legal Representatives** (continued from page 3):

- Goodwin Procter LLP:
    - Molly R. Grammel
    - Kathleen McGuinness
    - Thomas V. McTigue IV
    - Lauren E. Jackson
    - Alexandra D. Valenti
    - James Breen
    - Madeline R. DiLascia
- Hill Wallack LLP:
    - Eric I. Abraham
    - William Murtha
    - Nakul Y. Shah*

* *Denotes that attorney is no longer with listed firm*

# UNITED STATES COURT OF APPEALS
# FOR THE FEDERAL CIRCUIT

## CERTIFICATE OF INTEREST

**Case Number** 2023-2254

**Short Case Caption** Merck Sharp & Dohme B.V. v. Aurobindo Pharma USA, In

**Filing Party/Entity** Mankind Pharma Limited, Lifestar Pharma LLC

**Instructions:**

1. Complete each section of the form and select none or N/A if appropriate.
2. Please enter only one item per box; attach additional pages as needed, and check the box to indicate such pages are attached.
3. In answering Sections 2 and 3, be specific as to which represented entities the answers apply; lack of specificity may result in non-compliance.
4. Please do not duplicate entries within Section 5.
5. Counsel must file an amended Certificate of Interest within seven days after any information on this form changes. Fed. Cir. R. 47.4(c).

I certify the following information and any attached sheets are accurate and complete to the best of my knowledge.

Date: 10/24/2023

Signature: /s/ Dmitry Shelhoff

Name: Dmitry V. Shelhoff

| **1. Represented Entities.** Fed. Cir. R. 47.4(a)(1). | **2. Real Party in Interest.** Fed. Cir. R. 47.4(a)(2). | **3. Parent Corporations and Stockholders.** Fed. Cir. R. 47.4(a)(3). |
|---|---|---|
| Provide the full names of all entities represented by undersigned counsel in this case. | Provide the full names of all real parties in interest for the entities. Do not list the real parties if they are the same as the entities.<br><br>☑ None/Not Applicable | Provide the full names of all parent corporations for the entities and all publicly held companies that own 10% or more stock in the entities.<br><br>☐ None/Not Applicable |
| Mankind Pharma Limited | | None. |
| Lifestar Pharma LLC | | Mankind Pharma Limited |
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☐ Additional pages attached

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☑ None/Not Applicable ☐ Additional pages attached

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☑ None/Not Applicable ☐ Additional pages attached

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## TABLE OF CONTENTS

## CONFIDENTIAL INFORMATION STATEMENT

The identify of Defendant-Appellant Gland Pharma Limited's business partner was placed under seal by order of the district court. This Court also allowed Gland to file a confidential copy of its certificate of interest to protect this non-public information. On the following pages, such information has been highlighted in Defendants' Confidential Opening Brief and redacted in Defendants' Non-Confidential Opening Brief: **iii**.

# TABLE OF AUTHORITIES

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## Cases

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**Regulations**



**Agency Authorities**

**Other Authorities**

## STATEMENT OF RELATED CASES

No other appeal in or from this action was previously before this or any other appellate court.

## INTRODUCTION

This appeal presents a straightforward question of statutory construction: When is a reissue patent "issued"? This answer matters because the Patent Act refers to "the date the patent is *issued*" to determine a patent term extension (PTE) under 35 U.S.C. § 156(c). (Emphasis added.) Here, determining the issue date of RE44,733 (the '733 patent) is dispositive of whether the patent is expired, and whether Merck may continue to block generic sugammadex products from entering the market.[1]

The answer is simple. The Patent Act states all patents "issue" following a notice of allowance by the PTO and the payment of an "issue fee" by the applicant. 35 U.S.C. § 151. Once that happens, a signed and sealed version of the patent "shall be issued" and recorded by the PTO. *Id.* § 153. The date reflected in the PTO's records corresponds to the "issue date" displayed in bold print on the cover of every certified copy of a patent. Nothing in § 156 disturbs this common-sense understanding. And nowhere

[1] Plaintiffs-Appellees are collectively referred to as "Merck." Unless otherwise noted, reference to "Merck" includes Merck's predecessor(s)-in-interest. Defendants-Appellants are collectively referred to as "Defendants," with the exception of Teva Pharmaceuticals USA, Inc., which does not join this brief.

in the Patent Act has Congress provided a special definition of "issue" for reissue patents like the '733 patent. To the contrary, the reissue-specific provisions of the Act confirm that reissue patents "issue" just like an original patent. *Id.* §§ 251(b), 252. This comports with over 100 years of precedent confirming that reissue patents are distinct legal instruments and the surrendered patents that precede them are "void *ab initio*"—subject only to limited, statutory exceptions that do not apply here. *Fresenius USA, Inc. v. Baxter Int'l, Inc.*, 721 F.3d 1330, 1346 (Fed. Cir. 2013) (collecting cases).

Here, the '733 patent "issued" on January 28, 2014. Appx00056. Using that issue date, it is undisputed that the '733 patent expired no later than December 14, 2022. Appx03071.

But the district court took a different approach. Siding with Merck, it said a reissue patent is not "issued" on the day the PTO issued it. Rather, the district court read into the statute a fiction that appears nowhere in the language of the Patent Act: that a reissue patent "inherits" the issue date of the surrendered patent from which it derived. It accordingly deemed the '733 patent "issued" on December 30, 2003—the issue date of the surrendered patent preceding the '733 patent—and thus declared the '733 patent does not expire until January 27, 2026. In doing so, the district court

achieved what it believed to be the "remedial" purpose of § 156: affording Merck the maximum possible patent term.

This is wrong. If Congress wanted a reissue patent to inherit a surrendered patent's issue date, it would have said so explicitly. But it didn't. The law presumes Congress has always been aware of the long-held understanding that reissue patents are distinct instruments and that surrendered patents are "dead" upon the reissue. Yet, despite awareness of this fact for well over a century, Congress has chosen to craft only narrow exceptions that target known ramifications of the rule. For example, Congress explicitly allowed for the continuation of certain infringement actions that would otherwise die along with the original patent. 35 U.S.C. § 252. Significantly, however, Congress did not provide for special treatment of reissue patents in the § 156 extension process ushered in via the Hatch-Waxman Act in 1984—despite awareness of how existing precedent would impact the framework it created.

Under settled rules of construction, the district court should have treated Congress's silence as a deliberate decision to treat all patents as "issued" on their actual issue date. Instead, the district court derived a purpose-driven rule principally from 35 U.S.C. §§ 251 and 252. But neither

provision purports to redefine "issued" as applied to reissue patents. Instead, they provide express and narrow exceptions to the general rule that a surrendered patent is "dead" upon reissue. This Court said as much in *Fresenius*. The district court's attempt to infer a much broader rule from these provisions cannot be squared with the statutory text or key interpretative canons. It also leads to an incoherent reading of the Patent Act that produces inconsistent applications of § 156.

Deference under *Skidmore v. Swift & Co.*, 323 U.S. 134 (1944), cannot save the district court's judgment. Deference should not apply at all because the statutory text is clear. Moreover, the PTO has not articulated *any* interpretation of § 156 to which a court could defer—and certainly not the type of thorough, consistent, and persuasive interpretation sufficient to merit *Skidmore* deference. Rather, the PTO has adopted only a set of conflicting, inconsistent, and ever-changing conclusions on how to treat reissue patents in the patent-term-extension process. Even if one were to glean an interpretation of § 156 from these actions, it's not one worthy of deference.

Simply put, no one would reasonably understand the '733 patent to have been issued on December 30, 2003—almost a decade before Merck even

filed for the patent. To hold otherwise, as the district court did, requires jettisoning basic precepts of English and long-standing canons of statutory construction, and replacing them with purposivism. But that's not how Courts construe statutes. Properly understood, the '733 patent—the only barrier to low-cost generic sugammadex products entering the market—is expired. The district court's decision to the contrary is untenable and should be reversed.

## JURISDICTIONAL STATEMENT

This Court has jurisdiction pursuant to 28 U.S.C. § 1295(a)(1). The district court entered final judgment against the Defendants on June 29, 2023. Appx00001-00008. Defendants timely filed their notice of appeal on July 24, 2023. Appx03704-03715.

## STATEMENT OF THE ISSUES

When is a reissue patent "issued" for purposes of calculating a patent term extension under 35 U.S.C. § 156?

## STATEMENT OF THE CASE

### A. Bridion®, the '340 Patent, and the '733 Patent.

The material facts of this case are undisputed. Appx00011.

Sugammadex is the active ingredient in Bridion®, which is used to reverse a neuromuscular blockade induced by rocuronium and vecuronium in general anesthesia. Appx03068. Merck first obtained claims covering sugammadex through U.S. Patent No. 6,670,340 (the '340 patent). Entitled "6-Mercapto-Cyclodextrin Derivatives: Reversal Agents For Drug-Induced Neuromuscular Block," the '340 patent issued from U.S. Patent Application No. 10/148,307 (filed November 23, 2000) (the '307 application) and claimed priority to European Patent Application No. 99309558 (filed November 29, 1999). Appx03064.

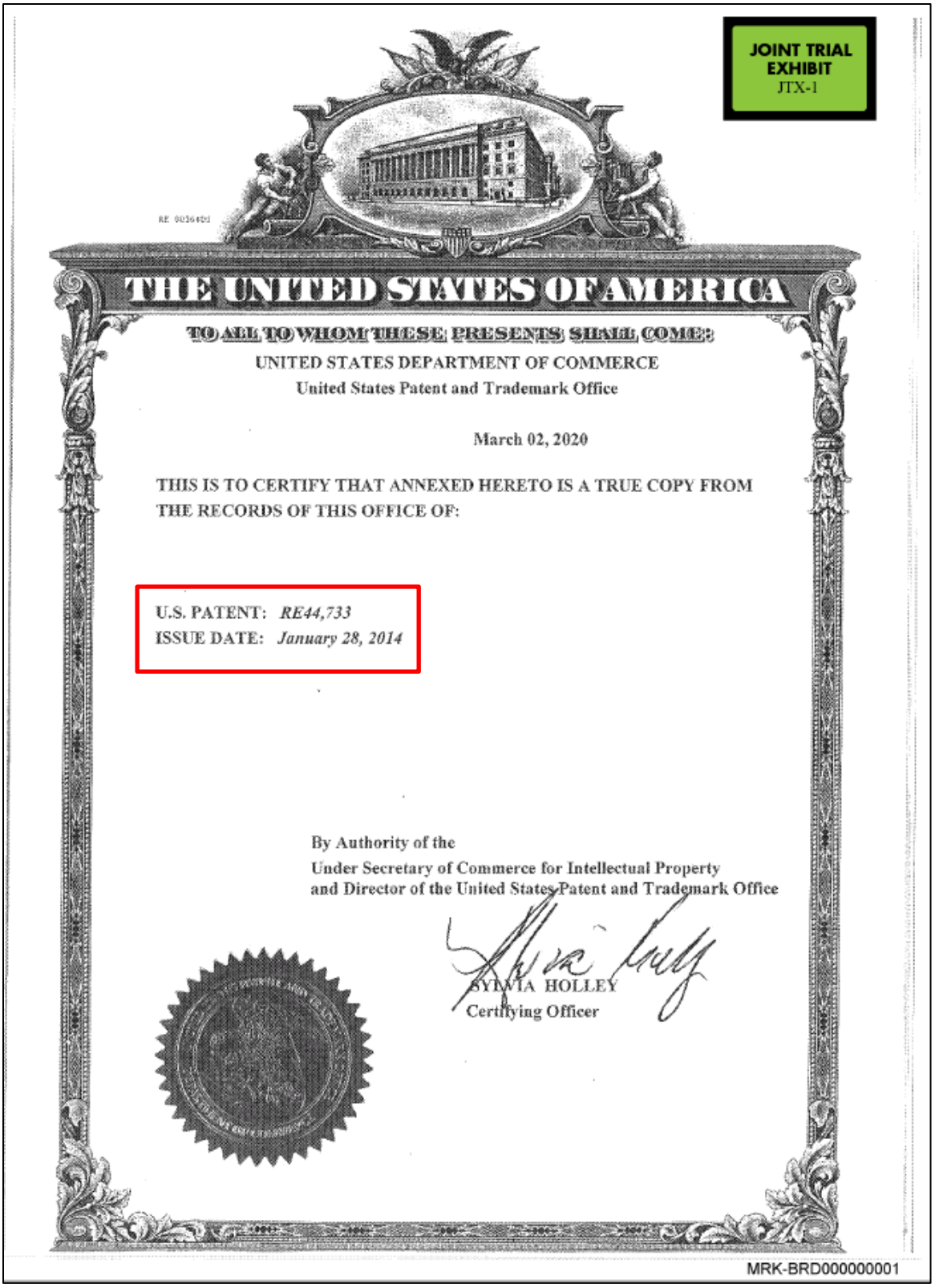
The PTO issued the '340 patent on December 30, 2003, and it was originally set to expire on January 27, 2021. Appx03065. The '340 patent had nine claims covering a group of compounds that included sugammadex and methods for using compounds including sugammadex. Appx06871-06872. Claim 4 recited a genus consisting of sugammadex and five other compounds, as well as their pharmaceutically acceptable salts.[2] Appx06872.

A few months after the '340 patent issued, on April 13, 2004, Merck filed an investigational new drug (IND) application for sugammadex

[2] The patent referred to sugammadex by its chemical name: 6-per-deoxy-6-per-(2-carboxyethyl)thio-γ-cyclodextrin.

sodium. Appx03066. After several years, Merck filed a new drug application (NDA) for Bridion on October 31, 2007. Appx03066-03067. The FDA approved the application on December 15, 2015. Appx03067. Bridion launched in the United States in January 2016. *Id.*

In March 2012—eight years after it filed its IND and nearly five years after it filed its NDA—Merck applied for a reissue patent to correct "errors" made by Merck in the '340 patent. U.S. Patent Application No. 13/432,742 (Mar. 28, 2012) (the '742 application). This application resulted in the issuance of the '733 patent and the cancellation of the '340 patent. Appx03064. The '742 application claimed priority to the same US and European applications as the '307 application. But it had a distinct prosecution history, which involved several rejections. Appx05098-05103; Appx05723-05727. At the end of the prosecution, the PTO issued a new notice of allowance on the '742 application, Appx06268, and Merck paid a new issue fee. Appx06277-06280. The '733 patent issued thereafter, bearing an "Issue Date" of January 28, 2014, on its front cover. The cover from a certified copy of the '733 patent is displayed in full on the next page.




Appx00056 (red box added).

The ’733 patent issued with all nine claims that appeared in the ’340 patent. It also added 12 new claims directed to narrower species of the genus to which sugammadex belongs. Of those, claims 12 and 21 are relevant here. Claim 12 claims a sodium salt of sugammadex, while claim 21 claims a method for reversing neuromuscular blocks using an effective amount of the same sodium salt of sugammadex.

**B. Merck Files for a Patent Term Extension.**

About two months after regulatory approval, in February 2016, Merck applied for a patent term extension under 35 U.S.C. § 156. Appx03067-03068. Section 156(c) requires that a term extension be limited to the "regulatory review period for the approved product" that "occurs after the date the patent is issued." The "regulatory review period" is calculated from the testing and approval phases for the drug product. 35 U.S.C. § 156(g)(1). Only half of the days in the testing phase are counted, but all the days in the approval phase are counted. *Id.* § 156(c)(2); *see also* 37 C.F.R. § 1.775. The applicant must subtract from this calculation any days in the testing or approval phase preceding issuance of the patent. 35 U.S.C. § 156(c); *see also* 37 C.F.R. § 1.775(d)(1)(i). Finally, a patent term extension is capped at a maximum of five years, and is further limited such that the remaining term

of the patent plus the extension cannot exceed 14 years after FDA approval of the patented product. 35 U.S.C. § 156(g)(6)(A); *id.* § 156(c)(3).

In its application, Merck identified the ′733 patent as the patent for which it sought PTE. Appx06284. It confirmed the ′733 patent was a reissue of the ′340 patent. Appx06284-06285. Merck also identified the "issue" date of both patents:

**U.S. PATENT NO.: RE44,733**

**INVENTORS: Mingqiang Zhang, Ronald Palin, and David Jonathan Bennett**

**ISSUE DATE:**

**FOR REISSUE PATENT (U.S. Patent No. RE44,733): January 28, 2014**

**FOR ORIGINAL PATENT (U.S. Patent No. 6,670,340): December 30, 2003**

**EXPIRATION DATE: January 27, 2021**

Appx06290.

Despite admitting that the "issue date" for the ′733 patent was January 28, 2014, Merck requested the maximum available five-year patent term extension based on the issue date of the surrendered ′340 patent, which would result in a modified expiration date of January 27, 2026. Appx06302. In calculating the length of extension claimed, Merck subtracted "0 days" from the regulatory review period for Bridion because that "is the number

of days in the testing and approval phases on or before the issuance of the original U.S. Patent No. 6,670,340 on December 30, 2003, which was reissued as U.S. Patent No. RE44,733 patent on January 28, 2014." Appx06303. Merck's application identified both original claims (including claim 4) and new claims (including claims 12 and 21) as covering sugammadex. Appx06293-06297. Merck also relied upon "Claim 4 of the reissued '733 patent (and claim 4 of the original '340 patent)" to demonstrate the manner in which at least one patent claim read on Bridion. Appx06293-06294.

Based upon Merck's representations, the FDA determined the total length of the regulatory review period for Bridion to be 4,265 days, with 1,297 days accruing in the testing phase and 2,968 days in the approval phase. Using those values, the PTO calculated a potential period of extension of 3,617 days. Appx06815-06816. The PTO then calculated the extension like Merck, using the issue date of the '340 patent, not the '733 patent. *Id.* However, the PTO did not explain why it used the '340 patent's issue date. *Id*; *see also* Appx03380 (65:22-24); Appx03383 (68:6-7) (Merck conceding the PTO did not provide an explanation).

These calculations are all undisputed, though the key presumption upon which they are based (the correct issue date) is contested. The parties

agree that, if the '340 patent's issue date is applied, the '733 patent would expire on January 27, 2026. Appx03071. Similarly, the parties agree, had the PTO used January 28, 2014, as the issue date for the '733 patent, Merck would have been entitled to only 686 days of patent term extension. *Id.* This would mean the '733 patent expired on December 14, 2022. *Id.*

### C. Procedural History.

#### 1. Pretrial Proceedings.

Defendants filed abbreviated new drug applications seeking FDA approval for generic sugammadex products. Merck sued, ultimately asserting claims 4, 12, and 21 of the '733 patent. The various actions against Defendants were eventually consolidated. Appx00083-00084. Initially, Defendants asserted additional theories of noninfringement and invalidity. But as the case moved closer to trial, they all stipulated to infringement and focused their case on a single invalidity theory: the '733 patent is expired because PTE was improperly calculated. *See* 35 U.S.C. § 282(c).

The parties' dispute distilled to a question of statutory construction: When was the '733 patent "issued" for purposes of calculating a patent term extension under 35 U.S.C. § 156? *See* Appx00025-00027. Both sides either stipulated to or did not dispute the key factual predicates of this question—

including (importantly) the appropriate patent term extension and corresponding expiration date under each parties' proposed construction. Appx00013.

Defendants urged a plain-meaning construction of "issued," under which the '733 patent "issued" on January 28, 2014—the date reflected on the front cover of the patent and in the PTO's public records. Defendants argued that this understanding comported with the text of § 156, other relevant provisions of the Patent Act, and precedent from the Supreme Court and this Court.

Conversely, Merck argued that "issued" could not be defined as applied to a reissue patent by looking at the '733 patent or § 156. Instead, Merck emphasized § 252, which states that a reissue patent "shall have the same effect and operation in law, on the trial of actions for causes thereafter arising, as if the same had been originally granted in such amended form." As Merck saw things, the interpretative question here arose at "trial" of a cause of action under the '733 patent. So, to give the patent that same effect and operation as if it had been originally granted in amended form, the court must deem the '733 patent "issued" on the date of the original (and surrendered) '340 patent—December 30, 2003. To support this legal fiction,

Merck pointed to § 251, which says the PTO "shall . . . reissue *the* patent"—*i.e.*, the surrendered '340 patent. It further pointed to various purported policies of the PTO to support this construction, asserting that its preferred outcome was compelled by *Skidmore* deference.

**2. The District Court's Opinion.**

Though the material facts were not disputed, the district court held a one-day bench trial to take testimony on the PTO's practices and policies related to patent term extensions on reissue patents. Following post-trial briefing, the district court issued a decision siding with Merck. It agreed with Merck's construction of the word "issued" as applied to reissue patents. And it further concluded that the PTO had a practice of deeming reissue patents as issued on the date of the original patent for purposes of calculating patent term extensions, and that this practice merited *Skidmore* deference.

Starting with statutory construction, the district court observed that § 156 "does not . . . expressly address the treatment of patents that are *reissued*." Appx00026. So it spent relatively little time analyzing the text of this operative provision and, instead, focused almost exclusively on the texts of §§ 251 and 252. The district court held that, under § 251, the PTO does "not issue a new patent" upon reissue, but rather "'reissue[s] the [original]

patent.'" Appx00030 (quoting § 251); *see also* Appx00034 ("[T]he question presented is simply how to treat the reissued patent in this cause of action arising after reissue."). Observing further that reissue patents inherit "'the unexpired part of the term of the original patent,'" the district court construed § 251 as "treat[ing] the reissued patent not as an entirely new patent with a new term, but as an amended version of the original that takes on the original's term." Appx00031 (quoting § 251). It criticized Defendants' position, stating it "would overlook the dependency of the reissue's term on the original's term, and the relationship between the two." Appx00031.

Turning to § 252, the district court zeroed in on the requirement that "'every reissued patent shall have the same effect and operation in law, on the trial of actions for causes thereafter arising, as if the same had been originally granted in such amended form.'" Appx00032 (quoting § 252). By its lights, this case was "a trial of a cause arising after reissue," so the district court needed to "give the ['733 patent] 'the same effect and operation in law . . . as if [it] had been originally granted in such amended form.'" Appx00032 (quoting § 252). This meant giving the '733 patent the benefit of the '340 patent's issue date. Appx00032-00033.

Defendants argued that the quoted sentence from § 252 provided for the effect of continuity on certain causes of action and did not impact the outside-of-litigation calculation of a patent term extension. Criticizing this position, the district court separately highlighted that § 252 "also provides that 'the reissued patent, to the extent that its claims are substantially identical with the original patent, shall constitute a continuation thereof and have effect continuously from the date of the original patent.'" Appx00037 (quoting § 252). It held that, because claim 4 of the '340 patent appeared unamended in the '733 patent, "imposing [the '733 patent's] issue date on Claim 4 for purposes of patent term extension would be inconsistent with § 252's command to give substantially identical claims continuous effect 'from the date of the original patent.'" Appx0037 (quoting § 252).

The district court pointed to perceived "absurd results" and policy concerns to support its construction of § 156. It noted that difference in timing of when a patentee seeks (and the PTO approves) a reissue patent could have drastic consequences on how much of an extension a patentee might receive—a result that the district court believed Congress did not intend. Appx00039-00040. The district court also noted that its construction comported with the so-called "remedial" purpose of the Hatch-Waxman Act

(and § 156 in particular): "to achieve restoration for time lost to extensive FDA review." Appx00041-00045.

Lastly, the district court noted that, were § 156 deemed ambiguous, the PTO had articulated an interpretation of the statute as applied to reissue patents that warranted *Skidmore* deference. Looking principally to the PTO's Manual of Patent Examining Procedure, Appx00046-00047, the district court gleaned a policy of "treat[ing] the claims in a reissue application 'as if they had the same effective filing date as the original patent' because 'a reissue patent replaces the original patent, and thus is merely continuing the patent privilege of the original patent as opposed to being an independent (regular) patent with its own privilege (and its own term).'" Appx00047 (quoting MPEP § 1440). The district court candidly noted that "the MPEP did not have a specific provision applying this overarching policy to reissued patents seeking term extension at the time Merck sought PTE." Appx00048.

Nevertheless, it concluded that the PTO understood § 156 to allow granting extensions on reissue patents based upon the surrendered patent's issue date. Appx00048-00049. The district court pointed to prior instances in which the PTO granted extensions on reissue patents using the surrendered patent's issue date, as well as the PTO's later enactment of MPEP § 2766.

Originally promulgated in 2020 (years after Merck obtained its extension), the first incarnation of § 2766 recognized that, when a reissue patent is issued, "the original patent, by operation of law, no longer exists." MPEP § 2766 (2020).[3] It therefore called for the transfer of documents regarding PTE from the original patent file to the reissue patent file once a reissue patent has issued. *Id.* There was no substantive statement about how to determine PTE for a reissue patent. *Id.* Only in 2022 did the PTO add an instruction regarding calculating PTE: "[S]o long as the original patent claimed the approved product and the reissued patent claims the approved product," the original grant date would be utilized. MPEP § 2766 (2022). Notwithstanding the lack of a clear policy at the time of Merck's extension application and the subsequent evolution of the PTO's policy, the district court concluded *Skidmore* deference was warranted. Appx00050-00055.

Defendants filed a timely appeal to this Court. Appx03704-03715.

## SUMMARY OF THE ARGUMENT

**I.A.** This case begins and ends with the meaning of the word "issued." The word is not explicitly defined by the Patent Act, so it must

[3] Available at https://www.uspto.gov/web/offices/pac/mpep/old/e9r10-2019/mpep-2700.pdf.

carry its dictionary meaning: "To put forth officially." Usage throughout the Patent Act confirms this plain-text reading. Congress consistently used the word "issue" to refer to the PTO's promulgation of a patent following prosecution and allowance. This aligns with observable reality: the first page of a certified copy of a patent bears an "issue date," which matches the PTO's public record of when the patent issued.

Significantly, Congress nowhere provided a special meaning for the word "issued" as applied to reissue patents. It certainly could have if that's what it intended. Congress has passed several express edicts applicable to reissue patents to address consequences flowing from the long-standing rule that the original patent is "void *ab initio*" upon the issuance of a reissue patent. *Fresenius*, 721 F.3d at 134. Despite crafting specific rules addressing patent terms and continuity of litigation, Congress never re-defined "issue." The silence was purposeful. It intended the plain meaning of "issue" to control. And under that plain meaning, the '733 patent "issued" on January 28, 2014.

**I.B.** The district court's results-driven statutory analysis fails as a matter of law. Rather than focusing on the meaning of the word "issued" as used in § 156, the district court lost itself in §§ 251 and 252. True, § 156 should

be construed in light of these provisions. But the district court's analysis fails to achieve that end. It took out-of-context snippets of text, misconstrued them in a way to support its conclusion, and failed to harmonize this conclusion with the broader statutory language and this Court's precedent.

For example, § 252 states that reissue patents "have the same effect and operation in law, on the trial of actions for causes thereafter arising, as if the same had been originally granted in such amended form." The district court interpreted this to mean that, in a litigation forum, a reissue patent steps into the shoes of the original patents for *all* purposes—including inheriting the issue date of the original patent. This reads far too much into a very limited provision. Nowhere does § 252 purport to redefine the term "issue." To the contrary, the statute uses the word "issue" to refer to the official act of putting forth the reissue patent—the same plain-text meaning employed throughout the Patent Act. The district court's interpretation cannot be squared with this usage. Further, this Court has expressly rejected the district court's *nunc pro tunc* interpretation.

Section 252 concerns issues of liability and damages in litigation: prospective, for all reissued claims in "causes thereafter arising," and retrospective, for "substantially identical" claims in causes of action accruing

prior to reissuance. Section 252 has *specific language* concerning substantially identical claims and their legal effect. But the district court's sweeping reading of "effect and operation in law" would make that language surplusage. The district court's understanding of § 252's proviso on "continuations" similarly misreads the statute. Substantially identical claims continuously "have effect" from the date of the original patent—but that, too, addresses liability and damages. Those concepts—which have nothing to do with issuance in the first place—do not mean that the entire reissue patent *actually* "issued" on the grant of the original patent. Holding otherwise violates clear limits on the right of continuation.

The district court's interpretation of § 251 likewise fails. The fact that a reissue patent inherits "the unexpired part of the term of the original patent" does not suggest that the reissue patent inherits the issue date of the original patent. Again, if that's what Congress intended, it could have and would have said so explicitly.

**I.C.** Policy concerns do not trump the meaning of the statutory text. And, in any event, the district court's policy analysis is defective. Deeming § 156 a "remedial" statute, the district court invoked the canon of liberal construction to justify skewing the operation of the statute in favor of what

the district court perceived to be its underlying policy: providing a maximum possible term extension. This analysis is flawed because the Supreme Court has repeatedly criticized substituting the liberal-construction canon for sound statutory construction. Moreover, the district court's analysis of the supposed policies underlying § 156 specifically, and the Hatch-Waxman Act generally, is defective. The Hatch-Waxman Act represents a careful balance of competing interests struck by Congress and reflected in text, not a single "remedial" interest in favor of the patentee.

**II.** *Skidmore* deference does not apply here. Deference has no place at all when, as here, there is no ambiguity in the relevant statutory text. Moreover, the PTO has never articulated *any* interpretation of § 156 or the word "issued"—much less a reasonable interpretation worthy of deference. It has announced only a conclusion of how it will treat certain reissue patents during the PTE process. That conclusion didn't exist at the time of Merck's extension application—and, even after it came into being, has changed in contradictory ways over time. Finally, in light of the PTO's shallow and inconsistent treatment, any interpretation that might be gleaned from the PTO's behavior does not warrant *Skidmore* deference.

## ARGUMENT

***Standard of Review.*** The only issue on appeal is the appropriate construction of § 156(c). "Statutory construction is a matter of law that [this Court] review[s] *de novo*." *Hawkins v. United States*, 469 F.3d 993, 1000 (Fed. Cir. 2006). To the extent the district court deferred to the PTO's purported interpretation of the statute, the application of deference is likewise reviewed *de novo*. *Chudik v. Hirshfeld*, 987 F.3d 1033, 1039 (Fed. Cir. 2021).

### I. BY THE PLAIN TEXT OF THE PATENT ACT, THE '733 PATENT IS EXPIRED BECAUSE MERCK SHOULD HAVE RECEIVED ONLY 686 DAYS OF PTE.

#### A. The '733 Patent "Issued" on the Day It Was Issued by the PTO.

Statutory construction always starts "with the language of the statute itself." *United States v. Ron Pair Enters., Inc.*, 489 U.S. 235, 241 (1989). Here, the operative text says: "The term of a patent eligible for extension . . . shall be extended by the time equal to the regulatory review period for the approved product which period occurs *after the date* ***the patent is issued***." 35 U.S.C. § 156(c) (emphasis added). It is undisputed that the "patent eligible for extension" is the '733 patent. Appx03250. The key question is: When was the '733 patent "issued"?

The Patent Act does not define "issue," so it must be "construe[d] . . . in accordance with its ordinary or natural meaning."

*ClearCorrect Operating, LLC v. ITC*, 810 F.3d 1283, 1290-91 (Fed. Cir. 2015) (quoting *FDIC v. Meyer*, 510 U.S. 471, 476 (1994)). Ordinary meaning, in turn, is informed by dictionary definitions. *See, e.g.*, *Nicely v. United States*, 23 F.4th 1364, 1369 (Fed. Cir. 2022). And "issue" has a readily ascertainable definition: "To be put forth officially." *Issue*, BLACK'S LAW DICTIONARY (11th ed. 2019); *see also Issue*, BLACK'S LAW DICTIONARY (5th ed. 1979) ("to promulgate," "to send out officially," "to go forth as authoritative or binding").

Statutory context leaves no doubt that this is Congress's intended meaning. *See Robinson v. Shell Oil Co.*, 519 U.S. 337 (1997) (statutes are construed "by reference to the language itself, the specific context in which that language is used, and the broader context of the statute as a whole"). The Act says that, "[i]f it appears that an applicant is entitled to a patent under the law, a written notice of allowance of the application shall be given or mailed," and that the notice shall specify an "*issue* fee." 35 U.S.C. § 151(a) (emphasis added). "Upon payment of this sum[,] the patent may *issue*." *Id.* § 151(b) (emphasis added). The Act further states, "Patents shall be *issued* in the name of the United States of America, under the seal of the Patent and Trademark Office, and shall be signed by the Director or have his signature

placed thereon and shall be recorded in the Patent and Trademark Office." *Id.* § 153 (emphasis added). These provisions confirm that a patent is "issued" on the date rendered by the PTO and recorded in the PTO's public records—*i.e.*, "put forth officially."

Section 156 confirms this general meaning. "[T]he normal rule of statutory interpretation [is] that identical words used in different parts of the same statute are generally presumed to have the same meaning." *IBP, Inc. v. Alvarez*, 546 U.S. 21, 34 (2005). The context of § 156 confirms that Congress intended "issued" to carry its plain and ordinary meaning. The provision defines the word "patent" as "a patent issued by the United States Patent and Trademark Office"—again, tying issuance to the official act of rendering the instrument by the PTO. *Id.* § 156(f)(6).

Applying this definition, there's no question that the '733 patent "issued" on January 28, 2014—the date in bold print on the front cover of the patent. This date corresponds with the issue date recorded in the PTO's public records. *E.g.*, Appx09437. It follows the completion of prosecution of Merck's reissue application, the PTO's notice of allowance on that application, and Merck's payment of the issue fee. Appx06277-06280; *see also* 35 U.S.C. § 41(a)(4)(D) (setting forth the "issue fee" for "issuing each reissue

patent"). Indeed, Merck identified January 28, 2014, as the "issue date" for the '733 patent in its application for a patent term extension. Appx06290. It similarly conceded in its complaint that "[t]he '733 patent was duly and legally issued on January 28, 2014." Appx01008. Even the district court recognized that the '733 patent "issued" in January 2014—not in December 2003. *E.g.*, Appx00016.

The fact that the '733 patent is a reissue of the '340 patent does not disturb this common-sense conclusion. Merck surrendered the '340 patent upon the issuance of the '733 patent. Upon issuance of the reissue 733 patent, the surrendered '340 patent was "dead." *Seattle Box Co. v. Indus. Crating & Packing*, 731 F.2d 818, 827 (Fed. Cir. 1984). As the Supreme Court has long held, "if a reissue is granted, the patentee has no rights except such as grow out of the reissued patent. He has none under the original." *Peck v. Collins*, 103 U.S. 660, 664 (1880).[4] This Court too has recognized that a reissue patent is legally distinct from the original patent, as the "rights [a patentee] had in

[4] This rule traces back to the Patent Act of 1836, which stated that reissue patents "shall have the same effect and operation in law, on the trial of all actions hereafter commenced for causes subsequently accruing, as though the same had been originally filed in such corrected form, before the issuing out of the original patent." Act of July 4, 1836, ch. 357, § 13, 5 Stat. 122.

and under the original patent are forfeited *ab initio* upon the grant of the reissue." *Fresenius*, 721 F.3d at 1337 (alteration in original) (citation omitted).

In other words, *the* reissue patent is distinct from *the* original patent; the latter ceases to exist on the date the former is issued. The Fourth Circuit confronted this question in *Mylan Pharmaceuticals, Inc. v. U.S. Food & Drug Administration*, 594 F. App'x 791 (4th Cir. 2014). Construing a parallel statute that referred—just like § 156(c) does—to "the" patent, the *Mylan* court specifically *rejected* the argument that a reference to "the" patent collapses original and reissue patents into one. *Id.* at 797. Referring to "the" patent where reissue patents are concerned unambiguously meant the *reissued* one: it "is a separate grant of rights, even if elements of the reissued patent overlap with those of the original patent." *Id.*

The settled conclusion that original and reissue patents are related but distinct patents accords with reality. The '340 patent had a different issue date (December 30, 2003) on its first page. Appx06860. It arose from a separate application and a separate prosecution. Appx03064-03065. The PTO issued a separate notice of allowance and Merck had to pay a separate issue fee for each patent. Appx06277-06280; Appx07439; *see also* Appx03248 (alleging the '340 patent "issued on December 30, 2003").

The rule that original patents are "dead" upon the grant of a reissue patent may have seemingly harsh consequences in some cases. *E.g.*, *Moffitt v. Garr*, 66 U.S. 273, 283 (1861) (holding that a pending lawsuit predicated upon a surrendered patent must "fail" after a reissue patent is granted); *Abercrombie & Fitch Co. v. Baldwin*, 245 U.S. 198, 209-10 (1917) (upon reissuance, a "patentee los[t] all in the way of an accounting under the original patent"). ***But Congress knew this.*** It responded by crafting an express and limited "exception to the rule" reflected in 35 U.S.C. § 252. *Fresenius*, 721 F.3d at 1337.

This provision has a clear and specific purpose: addressing the vitality of litigation liability and damages upon the issuance of a reissue patent. The statute starts by reciting the general rule enshrined in cases like *Moffitt*, *Peck*, and *Abercrombie*: "The surrender of the original patent shall take effect upon the issue of the reissued patent, and every reissued patent shall have the same effect and operation in law, on the trial of actions for causes thereafter arising, as if the same had been originally granted in such amended form." 35 U.S.C. § 252 (emphasis added). In plain English, a reissue patent is a distinct legal instrument that takes the place of the surrendered patent for the limited purpose of litigation claims accruing after the issuance of the

reissue patent. This rule is subject to so-called "intervening rights," as described in the second paragraph of § 252. Significantly, this language confirms that reissue patents are "issued" separate and apart from the surrendered patent: "The surrender of the original patent shall take effect upon the ***issue*** *of the reissued patent*." *Id.* (emphasis added). Nowhere does the statute say that this "issue" is backdated to the issuance of the surrendered patent.

For "pending" or "existing" litigation claims, Congress carved out an express and limited exception to this rule:

> *but in so far as the claims of the original and reissued patents are substantially identical*, such surrender shall not affect *any action then pending nor abate any cause of action then existing*, and the reissued patent, to the extent that its claims are substantially identical with the original patent, shall constitute a continuation thereof and have effect continuously from the date of the original patent.

*Id.* (emphasis added). As this Court has previously explained, this exception is limited in scope to its express terms. Surrender of the original patent is "a legal cancellation of it." *Moffitt*, 66 U.S. at 283. And, "[w]hen it amended the pertinent statutory language in 1928, Congress acknowledged that cancelled claims were void *ab initio*. ***It did not overrule the application of that principle*** to cancelled claims, but rather modified the rule to allow

continuation of pending suits under circumstances inapplicable here." *Fresenius*, 721 F.3d at 1346 (emphasis added).

Certainly, § 252 nowhere says that a reissue patent "inherits" the issue date of the original patent, as the district court held. Appx00031. Far from it, Congress explicitly referenced the "*issue* of the reissued patent" and gave legal significance to that date by recognizing limits on actions that accrued before then. Congress did all this without uttering a word that would link the "issue of the reissued patent" back to the issue of the original patent. Accordingly, the reader is left with the firm conviction that the basic rule holds: a reissue patent's issue date is what is displayed on the cover page of the certified copy in bold print.

Section 251 reinforces this conclusion. It explicitly refers to the "issue" of reissue patents, without providing any unique definition of the term as applied to reissue patents: "The Director may ***issue*** several reissued patents for distinct and separate parts of the thing patented, upon demand of the applicant, and upon payment of the required fee for a reissue for each of such reissued patents." 35 U.S.C. § 251(b) (emphasis added). Absent a provision-specific definition, the same plain-meaning definition used throughout the Patent Act controls. *IBP, Inc.*, 546 U.S. at 34.

Contrast this with § 251(a), which explicitly provides a special rule for determining the *expiration* of the reissue patent: "the Director shall, on the surrender of such patent and the payment of the fee required by law, reissue the patent for the invention disclosed in the original patent, and in accordance with a new and amended application, ***for the unexpired part of the term of the original patent***." (Emphasis added.) Two notable conclusions follow from this. *First*, § 251(a) demonstrates that Congress clearly knew how to use express statutory language to craft special rules for reissue patents. *See also* 35 U.S.C. § 100(i)(2) (crafting special definition of effective filing date for reissue patents). The fact that it did so regarding the expiration of these patents, while saying nothing at all about the issue date, strongly suggests that the omission of the latter was intentional. *E.g.*, *Whitfield v. United States*, 543 U.S. 209, 216 (2005) ("Congress has included an express overt-act requirement in at least 22 other current conspiracy statutes, clearly demonstrating that it knows how to impose such a requirement when it wishes to do so.").

*Second*, this statutory caveat clearly indicates that reissue patents are separate instruments arising from separate applications, with separate filing and issue dates. Were that not the case—and "a reissue patent replace[d] the

original patent *nunc pro tunc*," as the district court effectively held—then there would be no reason to limit expressly the term of the reissue patent to "the unexpired part of the term of the original patent." *Intel Corp. v. Negotiated Data Sols., Inc.*, 703 F.3d 1360, 1364 (Fed. Cir. 2012) (rejecting this "simplistic proposition").[5] It would inherit the surrendered patent's expiration date as a matter of course.

### B. Reissue Patents Do Not Inherit the Issue Date of a Surrendered Patent.

The affirmative argument above demonstrates what is wrong with the district court's analysis and Merck's position below. Neither § 251 nor § 252 offers a contrary view to what § 156 says. Critically, neither purports to redefine the word "issued" as it is applied to a reissue patent. Nevertheless, the district court got lost among several out-of-context quotations from these

[5] Merck may claim that *Intel*'s holding is limited to instances in which third parties have intervening rights under § 252. *See* Appx00036. Wrong. Intel argued (much like Merck) that § 252 categorically "provides that the reissue patent takes the place of the original patent *nunc pro tunc*." 703 F.3d at 1364. It analogized reissue patents to certificates of correction. This Court rejected Intel's argument, pointing first to § 252's protection of intervening rights: "In this important aspect alone, it is clear that a reissue patent does not simply replace an original patent *nunc pro tunc*." 703 F.3d at 1364. But it didn't stop there. It went on to thoroughly reject Intel's analogy to certificates of correction—and the underlying proposition that "a reissue patent replaces the original patent *nunc pro tunc*." *Id.*

provisions and arrived at the erroneous conclusion that the ′733 patent "inherited" the issue date of the surrendered ′340 patent. Applying that flawed understanding to § 156, the district court incorrectly deemed the ′733 patent "issued" on December 30, 2003.

The district court stressed up front that § 156 must be "read in conjunction" with §§ 251 and 252. Appx00028. No doubt, statutory language must be construed "in the context of the entire statute." *Caraco Pharm. Lab'ys, Ltd. v. Novo Nordisk A/S*, 566 U.S. 399, 412 (2012). But that truism is not a license to redefine the plain text of the statute being construed. *Fourco Glass Co. v. Transmirra Prod. Corp.*, 353 U.S. 222, 224, 229 (1957) (rejecting the proposition that the general venue statute and the specific patent venue statue may be "read together" to alter the meaning of the patent venue statue). That's particularly true when reading statutory language that *specifically* addresses the question at hand (patent term extension and the meaning of "issued") in the context of more general statutory language (reissue patents). *Gozlon-Peretz v. United States*, 498 U.S. 395, 407 (1991) ("A specific provision controls over one of more general application."); *see also Fourco Glass Co.*, 353 U.S. at 228-29 ("Specific terms prevail over the general in the same or another statute which otherwise might be controlling.").

Here, the two provisions central to the district court's opinion—35 U.S.C. §§ 251 and 252—simply do not stand for the proposition that a reissue patent inherits the issue date of the surrendered patent that precedes it.

**1. The district court misconstrued § 252.**

Consider the district court's treatment of § 252. Appx00032-00034. It homed in on the language: "every reissued patent shall have the same effect and operation in law, on the trial of actions for causes thereafter arising, as if the same had been originally granted in such amended form." Appx00032. The district court held that, "[a]s this is a trial of a cause arising after reissue," it must "do as the statute requires: give the RE'733 Patent 'the same effect and operation in law . . . as if [it] had been originally granted in such amended form.'" *Id.* In essence, the district court read this first provision of § 252 to mean that a reissue patent "steps into the shoes" of the surrendered patent for *all* purposes—litigation-related or otherwise—simply because the parties are currently in a litigation forum. Appx00033-00034. Respectfully, that's a facile application of § 252 that ignores both the provision's plain text, the context in which it was created, and this Court's precedent.

First and foremost, § 252 nowhere purports to redefine the term "issue." To the contrary, the statute uses the word "issue" to refer to the

official act of putting forth the reissue patent: "The surrender of the original patent shall take effect upon the ***issue*** *of the reissued patent*." *Id.* (emphasis added). As explained above, this comports with the plain-text meaning of the word used throughout the Patent Act. To otherwise construe § 252 to mean that a reissue patent is "issued" on the same date as the surrendered patent for purposes of § 156 would violate this plain text and give the same word two completely different meanings without any textual basis for doing so. *Contra, e.g.*, *Agro Dutch Indus. Ltd. v. United States*, 508 F.3d 1024, 1032 (Fed. Cir. 2007) (recognizing "normal rule of statutory construction that identical words used in different parts of the same act are intended to have the same meaning"). If Congress wanted to deem a reissue patent as "issued" on the same date as the surrendered patent that preceded it, then Congress would have and easily could have said so. But it did not.

Even if one ignores this fatal problem, the district court's reasoning fails on its own terms because it does not make sense within the full context of § 252. As explained above, Congress passed the current version of § 252 to address very specific problems related to the termination of litigation claims and resulting damages. And that's exactly what the text says: reissue patents have "the same effect and operation in law" as the original patent

for the limited purpose of trying "actions for causes thereafter arising," *i.e.*, after "the issue of the reissued patent." *Id.* This phrase (like the whole of § 252) is specifically pegged to litigation liability and damages. It has nothing to do with determining when a patent is "issued" or how to calculate a patent term extension—neither of which is a "cause[]" arising "[]after" the "issue of the reissued patent."

If the district court were right, the meaning of § 252—and various other provisions in the Patent Act, including § 156—would change radically based upon the forum. Consider patent term extensions. Though these issues have arisen in the context of patent litigation here, that need not be the case. The PTO's patent term extension determinations are made in an administrative process entirely outside of litigation. That administrative decision-making may be challenged directly under the Administrative Procedure Act. *E.g.*, *Angiotech Pharms. Inc. v. Lee*, 191 F. Supp. 3d 509, 512 (E.D. Va. 2016). Because the plaintiff is challenging agency decision-making, rather than suing on the patent, § 252 would not apply. So, under the district court's reasoning, the word "issued" may mean one thing in an administrative proceeding and something completely different in the context of patent litigation. That can't possibly be right—it makes no sense

for the plain and ordinary meaning of "issued" to apply in one context but not in another.

The district court's flawed analysis also proves too much. The way it reads § 252, a reissue patent steps into the shoes of the original patent for *all* purposes within the forum of litigation. If that were true, then there would be no need for the second half of the first paragraph of § 252—the "but" clause addressing pre-existing claims. This, of course, would contravene the fundamental interpretive precept that a statute should be read to give effect to every word and avoid surplusage. *Wolfe v. McDonough*, 28 F.4th 1348, 1354 (Fed. Cir. 2022). If that weren't enough (and it is), this Court has rejected outright the district court's result: "[A] reissue patent does not simply replace an original patent *nunc pro tunc." Intel Corp.*, 703 F.3d at 1364; *see id.* (describing prevailing party's position that "35 U.S.C. § 252 as a whole defines a nuanced arrangement where only substantially identical claims reach back to the date of the original patent").

The district court's reliance on the second half of § 252's first paragraph fares no better. Appx00037-00038. As previously noted, this provision addresses a very specific and limited issue: "Congress amended the reissue statute to authorize actions for infringement of the original claims to

continue after reissue," but only "'to the extent that [the reissued patent's] claims are substantially identical with the original patent.'" *Fresenius*, 721 F.3d at 1337-38 (quoting S. Rep. No. 70-567, at 1 (1928)). Here, the district court got hung up on the following language: "[T]he reissued patent, to the extent that its claims are substantially identical with the original patent, shall constitute a continuation thereof and have effect continuously from the date of the original patent." 35 U.S.C. § 252. The district court held that, because claim 4 appears in "substantially identical" form in both the '340 patent and the '733 patent, *the entirety* of the '733 patent must be understood to "inherit" the '340 patent's issue date. Appx00037.

This is doubly wrong. For one thing, it reads far too much into very modest language applicable only to limited circumstances that are not present here. By providing continuity of "substantially identical" claims for purposes of litigation claims accruing prior to reissue, Congress eliminated harsh outcomes in which an infringer's liability—and therefore damages—accruing prior to reissue would fall away. *E.g.*, *Kaufman Co. v. Lantech, Inc.*, 807 F.2d 970, 977 (Fed. Cir. 1986) (claims meeting identicality standard of Section 252 allow damages for infringement prior to reissue date). This gives substance to the preceding proviso that actions and causes of action are not

automatically terminated by the surrender of the original patent. It hardly compels the conclusion that old claims reappearing in the reissue patents—let alone *all* claims in the reissue patent—somehow inherit the issue date of the original patent, particularly for purposes of the unambiguous text of an entirely separate statute (Section 156(c)).

This dovetails into the second (and more troubling) problem: the district court's interpretation violates the plain language of the *same* statute. Section 252 explicitly limits the right of continuation to "claims [that] are substantially identical with the original patent"—meaning new claims are excluded. Applying the district court's logic (continuity includes a patent's issue date), deeming the *entire* patent issued as of the date of the original patent would grant continuity to *all* claims, in direct violation of the statutory text.

More problems occur when the district court's reasoning is applied to construe § 156—which is the ultimate goal of this exercise. By its plain text, patent term extensions are not calculated on a claim-by-claim basis. The PTO extends "[t]he term of a ***patent*** eligible for extension," which is calculated with reference to "[t]he date the ***patent*** is issued." 35 U.S.C. § 156(c) (emphasis added). That means all claims in the "patent," new and old. The

'733 patent only has one issue date. Appx00056. Using a claim-by-claim provision to read a non-existent rule into a provision that operates patent-by-patent makes no sense.

**2. The district court misconstrued § 251**.

The district court's consideration of § 251 is equally flawed. It focused on the isolated phrases "reissue the patent" and "the unexpired part of the term of the original patent." Looking only at these snippets, the district court concluded that: "This provision thus treats the reissued patent not as an entirely new patent with a new term, but as an amended version of the original that takes on the original's term." Appx00030-00031.

This misconstrues the statute and the law. Citing *In re Yamazaki*, 702 F.3d 1327 (Fed. Cir. 2012), the district court suggested that, as a matter of statutory construction, reading the word "term" consistently across § 156(c) and § 251 *requires* that the "term" of the original and reissue patents be *the same* "term." Under the district court's interpretation, they cannot be "distinct." Appx00031. But *In re Yamazaki* itself demonstrates that they *are* distinct—though, to be sure, not unrelated. The term of the original patent is a "benchmark used to fix the maximum term for reissued patents." *In re Yamazaki*, 702 F.3d at 1332. Reissue patents, however, receive their own new

term: "the *term of a reissued patent* may not extend beyond *that of the original*." *Id.* at 1331 (emphasis added). Further confirming that reissue patents have their own terms is that nothing in § 251 suggests the term of a reissue cannot be *shorter*—*e.g.*, as the result of a terminal disclaimer.

Erroneously positing a single "term"—that of the original patent—the district court took an undisputed proposition (a reissue patent inherits the expiration of the surrendered patent) and made an unsupported leap to a wrong conclusion (a reissue patent is just "an amended version of the original"). Appx00031. As this Court has explained, that "simplistic proposition" is wrong because "it is clear that a reissue patent does not simply replace an original patent *nunc pro tunc*" in all respects. *Intel Corp.*, 703 F.3d at 1364.[6] Indeed, the district court ignored the full context in which the quoted language appears. The patentee must "surrender" the "original" patent before the PTO will issue the "reissue" patent. Once the "original" patent is "surrender[ed]" to the PTO, it is extinguished. Treating the reissue patent as merely "an amended version of the original" can't be squared with

[6] *See also Mylan Pharms., Inc.*, 594 F. App'x at 796-97); *Horizon Meds. LLC v. Apotex Inc.*, 2022 WL 16739909, at *6-8 (D. Del. Nov. 7, 2022); *Eizo Corp. v. Barco N.V.*, IPR2014-00358, 2015 WL 4381586, at *4 (PTAB July 14, 2015) (Paper No. 21).

this text. It would reduce the word "surrender" to meaningless language, and would eliminate the distinction between the words "original" and "reissue." Further, it fails to appreciate the entirety of § 251, which confirms that reissue patents are "issue[d]." 35 U.S.C. § 251(b). Read properly, § 251 confirms that reissue patents have their own issue dates, distinct from the issue date of the original, surrendered patent and refutes Merck's contention that reissue patents are "issued" on the same date as the original patent under § 156.

**3. The district court's statutory analysis is unsupported by the case it relied upon and disregards statutory history.**

The district court's heavy reliance on a single line of text from *Cooper Techs. Co. v. Dudas*, 536 F.3d 1330 (Fed. Cir. 2008), is also misplaced. There, the Court determined that the PTO was entitled to *Chevron* deference on its interpretation of the phrase "original application" as used to determine the availability of *inter partes* reexamination. *Id.* at 1331-32. The plaintiff argued that the PTO's interpretation of "original application" was wrong because it would exclude reissue patents; they "issue directly from a 'reissue application,' not an 'original application.'" *Id.* at 1341. Rejecting this point, the Court observed: "Such reissues are deemed by operation of law to

replace the surrendered originals and, thus, are entitled to treatment as original patents." *Id.* This simple proposition does not address (let alone redefine) the meaning of the word "issued." Nor does it stand for the proposition that a reissue patent replaces the surrendered patent *nunc pro tunc*. The Court simply said that reissue patents are not some entirely different species of patent than those arising from an "original" patent application. Subject only to Congress's express exceptions, the same rights and rules apply, which is exactly what the first phrase of § 252 says.

A final but important point about the statutory chronology: Congress passed § 156 (the provision that's ultimately being construed) as part of the Hatch-Waxman Act in 1984. *See, e.g.*, *Unimed, Inc. v. Quigg*, 888 F.2d 826, 827, 829 (Fed. Cir. 1989). It did so against the backdrop of the general rule that surrendered patents are legally "dead" (dating back to the 19th Century) and existing legislative exceptions to this rule (dating back to 1928). Courts "assume that Congress is aware of existing law when it passes legislation." *Hall v. United States*, 566 U.S. 506, 516 (2012) (quoting *Miles v. Apex Marine Corp.*, 498 U.S. 19, 32 (1990)). Despite awareness of the blunt application of the law to reissue patents and the limited scope of prior statutory edicts to soften this application, Congress crafted no special rule for reissue patents

when it wrote § 156. Instead, it used a broad definition of the term "patent" that includes reissue patents. 35 U.S.C. § 156(f).

All told, the district court's statutory analysis does not withstand scrutiny. Rather than focusing on the principal question of this case—determining when the '733 patent "issued" for purposes of § 156(c)—it embarked on a results-oriented analysis of two different statutory provisions that provide little insight into the meaning of "issued." Its conclusions contradict the plain text of these provisions, violate multiple canons of construction, can't be harmonized with the history of the Patent Act, and ultimately make little sense when applied to § 156. This Court should reject the district court's deeply flawed analysis.

### C. The District Court's Appeal to Policy Does Not Save Its Flawed Statutory Construction.

#### 1. The canon of liberal construction does not apply.

The district court also held that the "underlying purpose of the Hatch-Waxman Act further confirms the appropriateness of" its statutory interpretation. Appx00041-00045. Specifically, it relied upon the purported "remedial" nature of §§ 251, 252, and 156. Appx00042 ("[T]he relevant provisions here are all remedial."). From there, the district court invoked the

canon of liberal construction of remedial statutes. Per the district court, "Under traditional rules of statutory construction, a statute that "'is remedial in nature . . . should be read broadly.'" *Id.* (citing *Wells Fargo & Co. v. United States*, 827 F.3d 1026, 1036 (Fed. Cir. 2016)).

The district court's reasoning is profoundly flawed. A relic of a bygone era, contemporary Supreme Court precedent rightly criticizes the liberal-construction canon as the "last redoubt of losing causes." *Dir., Off. of Workers' Comp. Programs, Dep't of Labor v. Newport News Shipbuilding & Dry Dock Co.*, 514 U.S. 122, 135 (1995). It is at odds to the cardinal rule of construction that "Congressional intent is discerned primarily from the statutory text." *CTS Corp. v. Waldburger*, 573 U.S. 1, 12 (2014). Further, it just proves too much: "[A]lmost every statute might be described as remedial in the sense that all statutes are designed to remedy some problem." *Id.* At most, the liberal-construction canon applies only to "some subset of statutes [that are] especially remedial" in aim and purpose—particularly those that pit individuals against the government. *Id.*; *see Wells Fargo & Co.*, 827 F.3d at 1036 (applying the canon in a tax-refund case); *Henderson ex rel. Henderson v. Shinseki*, 562 U.S. 428, 441 (2011) (referencing the canon in a veteran-benefits case). And even then, the canon is one of last resort. *See Procopio v. Wilkie*, 913

F.3d 1371, 1380 (Fed. Cir. 2019) (finding no need to apply the liberal-construction canon because "the intent of Congress is clear from the text").

The district court invoked the liberal-construction canon in this case based upon a passing line of dicta from *Merck & Co. v. Kessler*: "The statute contemplates a patentee receiving time lost in its patent term by reason of FDA delay, and the statute should be liberally interpreted to achieve this end." 80 F.3d 1543, 1552 (Fed. Cir. 1996).[7] One line at the end of an opinion hardly amounts to an invocation of the canon, let alone justifies invoking it in this case. The district court's subsequent analysis demonstrates why the liberal-construction canon is inapposite here. It's an appeal to policy—a review of the district court's understanding of the congressional "purpose" of the Hatch-Waxman Act. Appx00043-00045.

Critically, however, there is no single "remedial purpose" of the Hatch-Waxman Act. *Cf., e.g.*, *Boone v. Lightner*, 319 U.S. 561, 575 (1943) ("The

[7] The Court in *Merck* referenced liberal construction as a way of dispensing with "special problems [that] may"—or may not—"arise in a few instances" in future cases based upon its efforts to harmonize patent term extensions under § 156 with the then-recently-enacted provisions of the Uruguay Round Agreements Act (35 U.S.C. § 154). *Id.* at 1551-52. Even if that were a holding (as opposed to dicta), it would be invoking the canon as a last resort to solve an issue not otherwise resolved through the text or other canons of construction. That is not the case here.

Soldiers' and Sailors' Civil Relief Act is always to be liberally construed to protect those who have been obliged to drop their own affairs to take up the burdens of the nation."). Rather, as this Court has recognized, the Hatch-Waxman Act is "a complex statutory framework that tries to balance generic and brand interests within the pharmaceutical industry." *Celgene Corp. v. Mylan Pharms. Inc.*, 17 F.4th 1111, 1117 (Fed. Cir. 2021). One recognized "aim of Hatch-Waxman was to 'speed the introduction of low-cost generic drugs to the market.'" *Id.* (quoting *Caraco Pharm. Labs., Ltd.*, 566 U.S. at 405). Putting a thumb on the interpretive scale in favor of maximizing patent term extensions, Appx00044-00045, plainly harms that objective. *See GD Searle LLC v. Lupin Pharm., Inc.* 790 F.3d 1349, 1354-55 (Fed. Cir. 2015) (applying a strict test to the application of 35 U.S.C. § 121 "[g]iven the potential windfall [a] patent term extension could provide to a patentee").

This type of zero-sum policy debate is precisely why courts typically stick to the text when construing a statute: The "judicial role is to follow the plain meaning of the particular provision at issue, even if there are policy concerns that could be addressed by declining to adhere to the strict literal terms of the statutory language Congress has employed." *Allergan, Inc. v. Alcon Lab'ys, Inc.*, 324 F.3d 1322, 1345 (Fed. Cir. 2003). As explained above,

Congress has already weighed the policy pros and cons, and it has enshrined the balance it wanted in the text of the statute. *Glaxo Operations UK Ltd. v. Quigg*, 894 F.2d 392, 399-400 (Fed. Cir. 1990) ("Striking balances in legislative language is Congress' job[.]") (construing § 156(f)(2)). The liberal-construction canon should not be used to upset that balance. *See* ANTONIN SCALIA & BRYAN A. GARNER, READING LAW 365 (2012) (criticizing the canon because "identifying what a 'liberal construction' consists of is impossible" and amounts to "an open invitation to engage in 'purposive' rather than textual interpretation").

**2. There is nothing absurd about applying the plain meaning of the statutory text.**

Similarly, there is nothing absurd or unjust about holding Merck to the plain-text application of § 156. As a threshold matter, Merck itself is responsible for any harsh treatment flowing from a literal application of the statutory text. Merck's predecessor allegedly made an error when it filed for the original patent—*i.e.*, not claiming the specific sodium salt of sugammadex that was ultimately used in Bridion. Appx05042. This supposed error should have been apparent long before Merck filed its reissue application in 2012. But Merck chose to wait.

The scenario presented here—a reissue patent adversely impacting a patent term extension—thus arises only when a patentee like Merck: (1) makes "an error," (2) makes the tactical decision to seek different patent protection through the reissue process, and (3) obtains PTE after obtaining the reissue patent. By correcting this "error," Merck obtained the benefit of twelve additional claims. Under its interpretation (and the district court's), it would obtain five years of patent term extension for those claims even though they didn't even exist for that entire time period. Holding Merck to the consequences of its patent prosecution decisions is not a basis to stray from the plain meaning of § 156. *See Amgen Inc. v. F. Hoffmann-La Roche Ltd.*, 580 F.3d 1340, 1352-54 (Fed. Cir. 2009) (refusing to apply the safe harbor of § 121 to continuation applications that otherwise qualified as divisionals because the patentee made the choice and "[t]he statute on its face applies only to divisional applications").

Further, the maximum potential impact of using the plain meaning of "issue"—as opposed to Merck's and the district court's results-oriented construction—is the difference between the issue dates of the original and the reissue patents. The gap is wide here because Merck sat on its hands for years before filing its reissue application despite knowing that it was

focusing on sugammadex at least by the filing date of its NDA (October 31, 2007)—and likely much earlier than that (*e.g.*, as of its April 13, 2004 IND). Merck could have avoided (or at least mitigated) the "harm" that animates its public policy argument through the exercise of basic diligence.[8] And even under the plain meaning of "issue," Merck still obtained 686 days of PTE.

Applying the plain meaning of "issue," moreover, avoids incongruous outcomes. Consider the case of a patent that is broadened through reissue. The original, narrower patent might not have covered a certain drug, but the broader reissue patent might. Appx03507 (192:22-24); *see* 35 U.S.C. § 251(d). Under the district court's interpretation of § 156(c)—reading into "date the patent is issued" the fiction that a reissue patent "inherits" the issue date of the original—the patentee would receive PTE credit for a period when it didn't even have a patent that *covered* the product at issue. The district

[8] The district court stated that it was "[n]otabl[e]" Merck sought reissue after the Federal Circuit "had just clarified" that the addition of narrower claims was a proper basis for seeking reissue. Appx00012 (citing *In re Tanaka*, 640 F.3d 1246 (Fed. Cir. 2011)). But Merck never argued that it relied upon *Tanaka* in deciding when to file a reissue application. In any event, *Tanaka* did not make new law. The Court said its conclusions followed from the plain text of § 251, "longstanding precedent" dating back to 1963, and "principles of stare decisis." 640 F.3d at 1247, 1249-51.

court's results-oriented interpretation doesn't just favor patentees without statutory warrant. It grants patentees potential windfalls.[9]

Nor, finally, does faithfully following the plain text of § 156(c) lead to "absurd" results. *Contra* Appx00039-00040. Yes, there are hypothetical timelines where a difference in days could result in substantial differences in patent term. But it is not uncommon in the law for minor differences to have a dramatic impact. File a notice of appeal on one day, and this Court has jurisdiction; file it the next, and this Court lacks jurisdiction. 28 U.S.C. § 2107(a). File a patent one day it is valid; file it the next and it is invalid for a statutory bar. 35 U.S.C. § 102(b). File a patent application checking the box as a divisional, it is valid; file the same application on the same day checking the box as a continuation, it may be invalid for obviousness-type double patenting. *Amgen*, 580 F.3d at 1349-54. Dealing with issues and consequences like this is one of the most basic reasons why lawyers exist. Merck and its

[9] The district court was "not convinced that the statute would operate this way." Appx00040. Except for the (irrelevant) temporal restriction of § 251(d), however, the district court was unable to provide a *statutory* explanation for why, under its rubric, this windfall would not result. Instead, it invoked a 2022 amendment to § 2766 of the Manual of Patent Examining Procedure. But, as detailed *infra*, MPEP § 2766 directly refutes the district court's principal basis for its decision—namely, § 252's statement that every reissue patent has the same effect as if originally granted in such amended form.

lawyers made decisions, and it is not unjust to hold them to the consequences. *See, e.g.*, *In re Cellect, LLC*, 81 F.4th 1216, 1228-29 (Fed. Cir. 2023) (invalidating patent claims based on applicant's failure to file a terminal disclaimer before expiration of the patent at issue).

* * * * *

Determining "the date the ['733] patent is *issued*" is case-dispositive. 35 U.S.C. § 156(c) (emphasis added). As a matter of basic English, the PTO "issued" the '733 patent on January 28, 2014. Nobody—not the district court, Merck, or Defendants—takes the position that the patent in fact "issued" in December 2003, nearly 10 years before Merck even filed for it. It would be preposterous to argue otherwise. That should be the end of the matter. The district court's attempt to replace reality with legal fiction fails because it cannot be reconciled with the text, applicable interpretive canons, and Supreme Court and Federal Circuit precedent. Because the '733 patent "issued" on January 28, 2014, it is now expired. Appx03071. The district court's decision to the contrary should be reversed.

## II. THE DISTRICT COURT IMPROPERLY DEFERRED TO THE PTO'S DECISION ON PTE FOR THE '733 PATENT.

The text of the Patent Act unambiguously forecloses the argument that reissue patents are "issued" on the issue date of the surrendered patent that they precede. That should be the end of the inquiry. There is no basis for deference "to agency interpretations at odds with the plain language of the statute itself." *Wyeth v. Kappos*, 591 F.3d 1364, 1372 (Fed. Cir. 2010) (quotation marks omitted) (citation omitted). Deference only comes into play when the statutory text is "genuinely ambiguous" after the court has "exhaust[ed] all the 'traditional tools of construction.'" *Kisor v. Wilkie*, 139 S. Ct. 2400, 2415 (2019) (citation omitted). Nevertheless, the district court alternatively held that the PTO had articulated such a position and that it was owed *Skidmore* deference. Appx00054-00055. For two overarching reasons, that is wrong.

### A. The PTO Does Not Have a Coherent Interpretation of the Word "Issued."

First, courts may defer to an agency's "explanation" and analysis of the statute, not its bare "conclusion" as to what it means. *Wyeth v. Levine*, 555 U.S. 555, 576 (2009). This rule applies with greater force in the context of *Skidmore* deference, which applies only to the extent that an agency has articulated "thorough" and "persuasive" interpretation of the statute. *United*

*States v. Mead Corp.*, 533 U.S. 218, 234-35 (2001). Here, the PTO's treatment of the '733 patent's PTE is a mere "conclusion." It contains no reasoning at all. When the relevant agency order "do[es] not interpret the statutory text, cite any case law . . . , or provide any legal reasoning," it cannot persuade. *Maglioli v. All. HC Holdings LLC*, 16 F.4th 393, 404 (3d Cir. 2021). Simply put, there is nothing in the PTO's grant of the patent term extension to persuade anyone of anything—just *ipse dixit*.[10] The fact that the PTO's unreasoned conclusion follows an alleged pattern of prior action, *see* Appx00049, does not alter this conclusion, especially where even the district court acknowledged that the PTO has not universally followed any particular approach. Appx00023-00024; Appx00049; *see also Eizo Corp.*, 2015 WL 4381586, at *4 (articulating an irreconcilable interpretation of §§ 251, 252). There is hardly a "thorough" or "persuasive" *policy*. *Mead Corp.*, 533 U.S. at 234-35.

[10] The district court tried to side-step this rule by pointing to *Hagans v. Comm'r of Soc. Sec.*, 694 F.3d 287, 305 (3d Cir. 2012). Appx00054. *Hagans* is far off point. In *Hagans*, the SSA had issued a ruling that expressly addressed the precise question presented, and the agency had then "consistently applied the policy" for 20 years. *Id*.

Indeed, the PTO has not articulated a reasoned interpretation of "the date the patent is issued" in § 156 as it relates to reissue patents, much less one that is consistent with the plain language of the statute. This Court typically looks to the PTO's Manual of Patent Examining Procedure as the Office's "official interpretation of statutes or regulations with which it is not in conflict." *Litton Sys., Inc. v. Whirlpool Corp.*, 728 F.2d 1423, 1439 (Fed. Cir. 1984). That said, the MPEP "does not have the force of law" and "does not bind [this Court]." *Natural Alternatives Int'l, Inc. v. Iancu*, 904 F.3d 1375, 1382 (Fed. Cir. 2018) (cleaned up).

There is no MPEP section that sets forth a reasoned interpretation of the meaning of the "date the patent is issued" in relation to reissue patents. The closest the PTO has come to touching the operative language from § 156 is MPEP § 2766. But even that enshrines little more than a bare conclusion—not a persuasive interpretation of the text. The fraught history of § 2766 demonstrates this fact.

MPEP § 2766 did not even exist until 2020—four years *after* Merck filed for a patent term extension on the '733 patent. And even then, the 2020 version of MPEP § 2766 didn't state the purported policy the district court deferred to. Rather, it expressed the PTO's policy on the transfer of

paperwork "[w]hen the filing of a reissue occurs during processing of a patent term extension application" on the original patent. MPEP § 2766 (2020). It wasn't until ***2022***—while this case was pending—that the PTO amended § 2766 to express a conclusion that would arguably apply here: "[S]o long as the original patent claimed the approved product and the reissued patent claims the approved product, the original patent grant date would be used to calculate the extension to which the reissued patent would be entitled." MPEP § 2766 (2022).

Even more troubling, the position staked out in the various versions of MPEP § 2766 clashes with the decision-making of the PTAB, the policy of the FDA, and, ironically, a primary rationale set forth by the district court. First, the PTAB considered the relationship between reissue and original patents in *Eizo Corp. v. Barco N.V.*, 2015 WL 4381586 (PTAB July 14, 2015). It reasoned that a reissue patent is a "distinct property right that does not simply replace an original patent *nunc pro tunc*." *Id.* at *4 (quotation marks omitted). The reissuance of the original patent as a reissue patent "did not *continue*" the original patent, "but rather resulted in the *surrender* of the [original] patent and the *issuance* of a new patent," the reissue patent. *Id.* It therefore held that § 315(b)'s reference to "the patent" was a reference specifically to the reissue

patent as distinguished from the original. *See id.*; *see also* Notice Regarding Options for Amendments by Patent Owner Through Reissue or Reexamination During a Pending AIA Trial Proceeding (April 2019), 84 Fed. Reg. 16654, 16656 (Apr. 22, 2019) (PTO Notice relying on *Eizo Corp.* to establish this distinction). Applying that same base logic here, the '733 patent is not just an amended version of the original, as the district court found. Rather, the '733 patent is a unique patent that issued as a new patent at its own, later issuance date.

Similarly, for purposes of interpreting other provisions of the Hatch-Waxman Act applicable to reissue patents, the FDA has recognized that reissue patents are not just amended versions of the original. Rather, they are separate and distinct instruments. Following the Fourth Circuit's decision in *Mylan*, it set forth a new policy recognizing the same. *See* Abbreviated New Drug Applications and 505(b)(2) Applications, 81 Fed. Reg. 69580, 69601 (Oct. 6, 2016) ("[T]he agency now considers reissued patents as separate and distinct from the original patent for purposes of administering the patent certification requirements of the FD&C Act and any 30-month stay of approval or 180-day exclusivity.").

The district court reasoned that § 252 mandates that *every* reissue patent must have the same effect and operation in law as if it had been originally granted in such amended form. Appx00032-00033. Under that reasoning, the PTO would use the issue date of the original patent for calculating patent term extensions on *every* reissue patent. But that is not what the 2022 version of § 2766 says. After citing §§ 251 and 252, MPEP § 2766 states only certain reissue patents use the original issue date: those in which the original covered the approved product. The necessary implication is that, for reissue patents where the original did not cover the approved product, the PTO would *not* use the original patent's issue date. This flatly contradicts the district court's interpretation of § 252. It also refutes the district court's impression that the PTO never considers the issue date of a reissue for any purpose. Appx00047; Appx00053.

These ever-changing statements establish that the PTO has not adopted a consistent policy—let alone a persuasive interpretation of 35 U.S.C. § 156(c) that would merit deference. Even under the most deferential of standards, courts do not defer "to a merely convenient litigating position or a post hoc rationalization." *Kisor* 139 S. Ct. at 2417 (cleaned up) (addressing *Auer* deference); *Gose v. U.S. Postal Serv.*, 451 F.3d 831, 838 (Fed.

Cir. 2006) (same, as applied under the *Skidmore* standard). To be worthy of deference, "the interpretation must truly be one that had been applied by the agency, either prior to or, at the latest, during the exercise of its administrative powers in the present matter." *Gose*, 451 F.3d at 838. That is demonstrably not the case here.

None of the other provisions from the MPEP relied upon by the district court salvages the court's analysis. The district court relied heavily on MPEP § 1460, Appx00053-00054, which states, a "reissued patent will be viewed as if the original patent had been originally granted in the amended form provided by the reissue." From this, the district court understood it to be the PTO's policy that at reissue patent "steps into the shoes of the original patent and is as though anything that came out of that reissue was issued on the date that the original patent is issued" Appx00047 (quoting Appx03518 (203:8-21)). But that's not what MPEP § 1460 says. This provision merely addresses § 252's carve-out for continuity of certain infringement actions, which does not affect patent term extensions for the reasons discussed above. As for the suggestion that a reissue patent "steps into the shoes of the original patent," the PTAB rejected that proposition in *Eizo Corp.*, and so too has this Court. *Intel Corp.*, 703 F.3d at 1364.

The district court also referenced MPEP § 1440, which instructs examiners to treat reissue applications "as if they had the same effective filing date as the original patent" because "a reissue patent replaces the original patent, and thus is merely continuing the patent privilege of the original patent as opposed to being an independent (regular) patent with its own privilege (and its own term)." By its plain terms, this provision addresses the *effective filing date* for a reissue patent, not the reissue patent's *issue date*. This merely acknowledges what Congress said in the text of 35 U.S.C. § 100(i)(2). The "effective filing date" is used to determine the scope of prior art—not for calculating a patent term extension. 35 U.S.C. § 102. If anything, this all proves Defendants' point on the text of § 156. Whenever Congress wanted a reissue patent to assume some characteristic of the original patent that it replaced, Congress explicitly said so.

In passing, the district court also cited MPEP §§ 1405, 1490, and 1415.01. None of these is on point. MPEP § 1405 says that a reissue patent's "term may be subsequently shortened" from the original term, "e.g., through the filing of a terminal disclaimer." That unremarkable proposition follows from 35 U.S.C. § 251(a), which explicitly says a reissue patent inherits the unexpired term of the original patent that it replaces. As noted above,

this cuts against the district court's holding. The fact that "a terminal disclaimer shortens the term of the original patent rather than creates a new term" is not relevant. Appx00048 (citing MPEP § 1490). And MPEP § 1415.01 merely provides that a reissue patent has the same schedule for payment of maintenance fees as the original patent, with the result that a patentee does not get lower fees through reissuance. *See* 37 C.F.R. § 1.20(e)–(f) (maintenance fees increase as time from issuance increases).

### B. To the Extent the PTO Had an On-Point Policy, It Did Not Merit Deference.

Even if one looks past the categorical reasons not to apply deference at all, the district court's *Skidmore* analysis does not withstand scrutiny. Under *Skidmore*, courts may defer to an agency's practice based on "the thoroughness evident in [the agency's] consideration, the validity of its reasoning, [and] its consistency with earlier and later pronouncements." *Mead Corp.*, 533 U.S. at 228 (quoting *Skidmore*, 323 U.S. at 140). Or as this Court puts it, *Skidmore* deference applies: "[1] if the agency has conducted a careful analysis of the statutory issue, [2] if the agency's position has been consistent and reflects agency-wide policy, and [3] if the agency's position constitutes a reasonable conclusion as to the proper construction of the

statute." *Cathedral Candle Co. v. U.S. Int'l Trade Comm'n*, 400 F.3d 1352, 1366 (Fed. Cir. 2005). All these considerations cut strongly against the application of *Skidmore* deference here for the reasons noted above.

***Thoroughness***. As explained above, the PTO has not articulated *any* "analysis of the statutory issue," let alone a "careful" one. *Cathedral Candle Co.*, 400 F.3d at 1366. The letter granting Merck's extension application is a single-page document devoid of any analysis. Appx06858-06859. Bare conclusions by lower-level employees do not reflect "a careful analysis of the statutory issue" by the agency. *Cathedral Candle Co.*, 400 F.3d at 1366-67 (deferring to a letter from the chairman of the ITC because it "it made clear the statutory basis for the Commission's position," "explained its reason for adopting the policy," and was "not an interpretation that was made at a low level within the agency").

At the time of Merck's extension application, the MPEP was completely silent on the issue of patent term extensions on reissue patents. And even today, the MPEP lacks any analysis of the statute—just conclusory statements that would not even apply to the circumstances of the '733 patent. The closest the PTO has ever come to an on-point statutory analysis is the

PTAB's decision in *Eizo Corp.*, which is diametrically opposite to what the district court found to be the PTO's deference-worthy policy.

Simply put, there is no "careful analysis of the statutory issue" in this case that merits deference.

***Consistency***. Insofar as the PTO's disparate decisions and musings can be said to constitute a "policy" on the issue date of reissue patents (which they are not), the PTO is owed no deference due to its demonstrated inconsistency on the matter. Such inconsistency strongly militates against deference. Indeed, the circumstances here are similar to those seen in *PhotoCure ASA v. Dudas*, in which the PTO articulated one position in the MPEP but took the complete opposite approach in formal adjudications on patent term extensions. 622 F. Supp. 2d 338, 349 (E.D. Va. 2009), *aff'd sub nom. PhotoCure ASA v. Kappos*, 603 F.3d 1372 (Fed. Cir. 2010). Unsurprisingly, both the *PhotoCure* district court and this Court concluded that *Skidmore* deference was not warranted in light of this inconsistency. *PhotoCure*, 603 F.3d at 1376.

***Validity***. Nor is the PTO's reasoning (or lack thereof) resulting in a reissue patent "inheriting" the original's issue date valid. It is inconsistent with the plain text of the statute for the reasons discussed in Part I *supra*. "Even if some level of deference were owed to the PTO's interpretation,"

*Skidmore* does not "permit[] a court to defer to an incorrect agency interpretation." *PhotoCure ASA*, 603 F.3d at 1376; *see also Facebook, Inc. v. Windy City Innovations, LLC*, 973 F.3d 1321, 1354 (Fed. Cir. 2020).

* * * * *

No manner of deference is warranted here. The statute is unambiguous, the PTO has never articulated any coherent construction of § 156(c) as applied to reissue patents, and, in all events, analysis of the relevant factors demonstrates that *Skidmore* deference is inappropriate. To the extent the district court purported to defer to a PTO policy in this case, it erred as a matter of law and should be reversed.

## CONCLUSION

The district court's judgment should be reversed.

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Respectfully submitted,

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# ADDENDUM

# TABLE OF AUTHORITIES

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

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|---|---|
| IN RE SUGAMMADEX | Civil Action No. 20-2576 (CCC) (LDW)<br>(CONSOLIDATED)<br><br>*Document Electronically Filed* |

**FINAL JUDGMENT**

NOW THEREFORE, IT IS HEREBY ORDERED, ADJUDGED, AND DECREED THAT:

1. This Court has jurisdiction over Plaintiffs Merck Sharp & Dohme B.V. and Merck Sharp & Dohme LLC (collectively, "Merck"), Defendants[1], and subject matter of this action.

2. In accordance with the Court's June 13, 2023 Opinion and Order (ECF Nos. 418 and 419), pursuant to Federal Rule of Civil Procedure 58, Final Judgment is entered in favor of Merck and against Defendants with respect to RE44,733 ("the '733 patent"). Defendants' ANDA Products that are the subject of ANDA Nos. 214307 (Aurobindo), 213915 (Mylan), 214276 (USV), 214236 (DRL), 214364 (Gland), 214230 (Mankind), 214311 (Sandoz), 214319 (Sun), 213868 (Fresenius), and 214126 (Teva) (collectively, "Defendants' ANDAs") infringe claims 4, 12, and 21 of the '733 patent.

3. There is no finding of invalidity as to the '733 patent.

[1] Aurobindo Pharma USA, Inc., Aurobindo Pharma Ltd., and Eugia Pharma Specialties Ltd. (collectively, "Aurobindo"); Mylan API US LLC, Mylan Pharmaceuticals Inc., and Mylan Inc. (collectively, "Mylan"); USV Private Ltd. ("USV"); Dr. Reddy's Laboratories, Inc. and Dr. Reddy's Laboratories, Ltd. (collectively, "DRL"); Gland Pharma Ltd. ("Gland"); Sandoz Inc. and Lek Pharmaceuticals d.d. (collectively, "Sandoz"); Mankind Pharma Ltd. and Lifestar Pharma LLC (collectively, "Mankind"); Sun Pharmaceutical Industries, Inc. and Sun Pharmaceutical Industries Ltd (collectively, "Sun"); Fresenius Kabi USA, LLC ("Fresenius"); and Teva Pharmaceuticals USA, Inc. ("Teva") (Aurobindo, Mylan, USV, DRL, Gland, Sandoz, Mankind, Sun, Fresenius, and Teva are collectively referred to herein as "Defendants").

4. The portion of the patent term extension for the '733 patent after December 14, 2022 is not invalid.

5. The '733 patent does not expire until January 27, 2026.

6. Pursuant to 35 U.S.C. § 271(e)(4)(A), the effective date of any approval by FDA of Defendants' ANDAs shall be no earlier than the expiration date of the '733 patent, except to the extent subsequently (a) agreed between any Defendant(s) and Merck or (b) ordered by this Court.

7. Pursuant to 35 U.S.C. § 271(e)(4)(B), Defendants and their officers, agents, servants, employees, and attorneys, and other persons in active concert or participation with any of them, are hereby enjoined from commercially manufacturing, using, offering to sell, or selling within the United States, or importing into the United States, the products that are the subject of Defendants' ANDAs until January 27, 2026, except to the extent subsequently (a) agreed between any Defendant(s) and Merck or (b) ordered by this Court.

8. All pending motions and other outstanding requests for relief not specifically addressed herein are DENIED.

SO ORDERED this 29 day of June 2023.

s/ Claire C. Cecchi
Hon. Claire C. Cecchi, U.S.D.J

AGREED TO BY:

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

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|---|---|
| **IN RE SUGAMMADEX** | Civil Action No.: 20-2576 (CCC) (LDW)<br>(CONSOLIDATED)<br><br>**OPINION** |

**CECCHI, District Judge.**

Plaintiffs Merck Sharp & Dohme B.V. and Merck Sharp & Dohme LLC (collectively, "Plaintiffs" or "Merck") bring this consolidated action under the Hatch-Waxman Act against defendants Aurobindo Pharma USA, Inc., Aurobindo Pharma Ltd., and Eugia Pharma Specialties Ltd. (collectively, "Aurobindo"); Dr. Reddy's Laboratories, Inc. and Dr. Reddy's Laboratories, Ltd. (collectively, "DRL"); Gland Pharma Ltd. ("Gland"); Mankind Pharma Ltd. and Lifestar Pharma LLC (collectively, "Mankind"); Mylan API US LLC, Mylan Pharmaceuticals Inc., and Mylan Inc. (collectively, "Mylan"); Sandoz Inc., and Lek Pharmaceuticals d.d. (collectively, "Sandoz"); Sun Pharmaceutical Industries, Inc. and Sun Pharmaceutical Industries Ltd. (collectively, "Sun"); and USV Private Ltd. ("USV") (Aurobindo, DRL, Gland, Mankind, Mylan, Sandoz, Sun and USV are collectively referred to herein as "Defendants").

Merck holds the patent covering sugammadex sodium ("sugammadex"), the active ingredient in a drug called Bridion®, which assists patients' recovery of muscle function after a form of paralysis is induced during surgery. That patent, U.S. Patent No. 6,670,340 (the "'340 Patent"), was subsequently reissued as U.S. Patent No. RE44,733 (the "RE'733 Patent"). The Patent and Trademark Office (the "PTO") granted the RE'733 Patent a five-year extension from its original expiration date of January 27, 2021 to January 27, 2026, due to the nearly 12-year regulatory review of Bridion® by the Food and Drug Administration ("FDA"). Defendants contest

the validity of Claims 4, 12, and 21 of the RE'733 Patent by way of a challenge to the portion of the patent term extension ("PTE") granted by the PTO to the RE'733 Patent after December 14, 2022.[1] ECF No. 389 ("Final Pretrial Order") at 2. Specifically, Defendants contend that calculation of a patent term extension for a reissued patent must be based on the date the *reissued* patent issued, pursuant to § 156(c) of the Patent Act. *See* 35 U.S.C. § 156(c). Defendants argue that reading § 156(c) in this way entitles Merck to only 686 days of a patent term restoration, rather than the five years granted by the PTO. Defendants' validity challenge, if meritorious, would render the portion of the patent after December 14, 2022 invalid under 35 U.S.C. § 282(c).

By contrast, Merck argues that § 156(c)'s reference to "the date the patent is issued," when read in its proper statutory context including 35 U.S.C. §§ 251 and 252, refers to the date the *original* patent is issued. Merck also contends that Defendants' interpretation is contrary to well-established PTO policy and practice. Under Merck's interpretation, the PTO was correct to award a five-year patent term extension, and the PTO's determination should be left undisturbed. Defendants do not contest infringement of the RE'733 Patent. Therefore, the only the issue for this Court to decide is whether the portion of the extension of the RE'733 Patent's term after December 14, 2022 is invalid under 35 U.S.C. § 282(c).

The Court held a one-day bench trial in this matter on December 19, 2022. ECF No. 390. The parties briefed the patent term extension issue before trial (ECF Nos. 335, 336, 341, 342), then submitted post-trial briefing and proposed findings of fact and conclusions of law. ECF Nos. 401 ("DFOF"), 401-1 ("Def. Br."), 402 ("Pl. Br."), 403 ("PFOF"). Thereafter, the parties submitted responsive briefs. ECF Nos. 404 (*corrected at* 407 ("Def. Reply Br.")), 405 ("Pl. Reply Br.").

[1] Prior to trial, Defendants withdrew all previously asserted invalidity defenses, with the exception of the PTE defense.

Closing arguments were held on February 3, 2023. ECF No. 409 ("Closing Tr.").

This Opinion constitutes the Court's findings of fact and conclusions of law pursuant to Federal Rule of Civil Procedure 52(a). The findings of fact are based on the Court's observations and credibility determinations of the witnesses who testified at trial, and a thorough review of all the evidence admitted at trial. While the Court has reviewed the entirety of the record, the Court includes references only to the evidence most pertinent to its analysis. For the reasons set forth below, the Court finds that the extension of the RE'733 Patent's term after December 14, 2022 is not invalid under 35 U.S.C. § 282(c).

## I. BACKGROUND

The facts of this case are almost entirely undisputed. The original patent covering sugammadex, the '340 Patent, issued on December 30, 2003. Although the patent issued in December 2003, sugammadex could not be marketed until December 15, 2015—nearly 12 years later—when the FDA completed its regulatory review of Bridion®. The December 15, 2015 FDA approval of Bridion® left Merck with approximately five years of market exclusivity (based on an original expiration date of January 27, 2021), even though 35 U.S.C. § 154(a)(2) provides for a term "ending 20 years from the date on which the application for the patent was filed." Congress, however, passed the Hatch-Waxman Act in 1984 in part to allow for restoration of a patent term lost to lengthy FDA regulatory review. On February 10, 2016, pursuant to the Hatch-Waxman Act and specifically 35 U.S.C. § 156, Merck sought a patent term extension for the maximum allowable five-year period to compensate for the almost 12 years of marketability lost during the FDA's regulatory review. The PTO reviewed Merck's application and granted that request on February 4, 2020, restoring five years of the lost patent term.

None of this would be cause for dispute between the parties if not for the sequencing of the *reissue* of the patent. In March 2012, while the FDA was in the midst of what would eventually be its nearly-12-year review process, Merck's predecessor-in-interest sought reissue of the '340 Patent because it had omitted narrower claims directed more specifically to sugammadex. Notably, the Federal Circuit had just clarified in 2011 that the addition of narrower claims was a proper basis for seeking reissue. *See In re Tanaka*, 640 F.3d 1246 (Fed. Cir. 2011). On January 28, 2014, the '340 Patent was reissued as the RE'733 Patent, containing the nine original claims in identical form and an additional 12 narrower species claims directed specifically to sugammadex. At that point, the RE'733 Patent inherited the "unexpired part of the term of the original patent," and thus was set to expire on the original expiration date of January 27, 2021. 35 U.S.C. § 251. Even when reissue was approved by the PTO on January 28, 2014, Merck still had to wait nearly another two years to market Bridion® because FDA approval would not be completed until December 15, 2015.

Accordingly, when Merck applied for a patent term extension in 2016, the original '340 Patent had been surrendered and the RE'733 Patent put in effect in its place. Understanding "the date the patent is issued" in § 156(c) to refer to the term of the original patent which the reissue patent had inherited, Merck calculated that it was entitled to the maximum allowable five-year patent term extension. The PTO agreed with Merck's understanding and calculation, and granted the five-year patent-term extension Merck sought, extending the RE'733 Patent through January 27, 2026.

Defendants presented an invalidity defense at trial that challenged the patent term extension calculation by Merck and the PTO. As noted above, instead of relying on the date of issue of the original patent (as Merck and the PTO did), Defendants assert that the date on which the *reissue*

patent (RE'733) issued must form the basis of that calculation under 35 U.S.C. § 156. Consequently, Defendants maintain that Merck is only entitled to 686 days of restoration—compared to the five years the PTO actually granted. This corresponds to an expiration date of December 14, 2022 under Defendants' theory, versus the expiration date of January 27, 2026 which the PTO assigned upon the patent term extension. With the facts almost entirely stipulated, *see* Final Pretrial Order, Section 3, Defendants contend, purely as a matter of statutory interpretation, that the PTO's use of the original patent's issue date was incorrect and thus represents a material failure to comply with § 156(c). This trial ensued to determine if Defendants' PTE defense established the invalidity of the RE'733 Patent—at least insofar as Defendants allege the term was erroneously extended beyond December 14, 2022, the date on which the RE'733 Patent would expire under Defendants' determination of the patent term extension.

**A. Jurisdiction and Parties**

Because this action arises under the patent laws of the United States, *see* 35 U.S.C. § 271 *et seq.*, this Court has original jurisdiction over the subject matter of this action pursuant to 28 U.S.C. §§ 1331 and 1338(a). No party contests jurisdiction or venue. *See* Final Pretrial Order, Section 1.

Plaintiff Merck Sharp & Dohme B.V., the owner by assignment of the '733 Patent, is a corporation organized and existing under the laws of the Netherlands, and has its principal place of business at Waarderweg 39, Haarlem, Netherlands 2031 BN. Merck Sharp & Dohme B.V. is an indirect, wholly owned subsidiary of Merck & Co., Inc., a New Jersey corporation, which has its principal place of business at 126 East Lincoln Ave, P.O. Box 2000, Rahway, NJ 07065 USA. Final Pretrial Order, Section 3.A ¶ 7; PFOF ¶ 2. Plaintiff Merck Sharp & Dohme LLC, which holds approved New Drug Application No. 022225 for Bridion®, is a limited liability company

formed and existing under the laws of New Jersey, having its corporate offices and principal place of business at 126 East Lincoln Ave, P.O. Box 2000, Rahway, NJ 07065 USA. Merck Sharp & Dohme LLC is a direct, wholly owned subsidiary of Merck & Co., Inc. Section 3.A ¶ 8; PFOF ¶ 3.

Defendant Aurobindo Pharma USA, Inc. is a corporation organized and existing under the laws of the State of Delaware, with a principal place of business at 279 Princeton Hightstown Road, East Windsor, New Jersey 08520. Final Pretrial Order, Section 3.B. Defendant Aurobindo Pharma Ltd., which filed Abbreviated New Drug Application ("ANDA") No. 214307, is a corporation organized and existing under the laws of India, with a place of business at Maitri Vihar, Plot #2, Ameerpet, Hyderabad, Telangana, 500038 India. *Id.* Defendant Eugia Pharma Specialties Ltd. is a corporation organized and existing under the laws of India, with a principal place of business at Galaxy, Floor: 22-24, Plot No.1, Sy No.83/1 Hyderabad Knowledge City, Raidurg Panmaktha, Hyderabad, Telangana – 500032, India. *Id.*

Defendant Dr. Reddy's Laboratories, Inc. is a corporation organized and existing under the laws of the State of New Jersey, having a principal place of business at 107 College Road East, Princeton, New Jersey 08540. *Id.* Section 3.C. Defendant Dr. Reddy's Laboratories, Ltd. is a corporation organized and existing under the laws of India, having a place of business at 8-2-337 Road No. 3, Banjara Hills, Hyderabad, 500034, India. *Id.*

Defendant Gland is a corporation organized and existing under the laws of India, with a place of business at Survey No. 143-148, 150 & 151 Near Gandimaisamma 'X' Roads D.P. Pally, Dundigal Gandimaisamma Mandal Medchal-Malkjgiri District, Hyderabad, Telangana, 500043 India. *Id.* Section 3.D.

Defendant Mankind Pharma Ltd. is a corporation organized and existing under the laws of

India, with a place of business at 208 Okhla Industrial Estate Phase III, New Delhi, 110020 India. *Id.* Section 3.E. Defendant Lifestar Pharma LLC is a corporation organized and existing under the laws of the State of Delaware, with a principal place of business at 1200 MacArthur Blvd., Mahwah, New Jersey 07430. *Id.* Lifestar Pharma LLC is a subsidiary of Mankind Pharma Ltd. *Id.*

Defendant Mylan Pharmaceuticals Inc. is a corporation organized and existing under the laws of the State of West Virginia, having a principal place of business at 3711 Collins Ferry Road, Morgantown, West Virginia 26505. *Id.* Section 3.F. At the time of the filing of the Complaint, Defendant Mylan API US LLC was a corporation organized and existing under the laws of the State of Delaware, having a principal place of business at 45 Napoleon Court, Somerset, New Jersey 08873. *Id.* Defendant Mylan Inc. is a corporation organized and existing under the laws of the State of Pennsylvania, having a principal place of business at 1000 Mylan Boulevard, Robert J. Coury Center, Canonsburg, Pennsylvania 15317. *Id.*

Defendant Sandoz Inc. is a corporation organized and existing under the laws of the State of Delaware, having a principal place of business at 100 College Road West, Princeton, New Jersey 08540. *Id.* Section 3.G. Defendant Lek Pharmaceuticals d.d. is a corporation organized and existing under the laws of Slovenia, having a place of business at Verovškova 57, 1526 Ljubljana, Slovenia. *Id.*

Defendant Sun Pharmaceutical Industries, Inc. is a corporation organized and existing under the laws of the State of Delaware, having a principal place of business at 1 Commerce Drive, Cranbury, New Jersey 08512. *Id.* Section 3.H. Defendant Sun Pharmaceutical Industries Limited is a corporation organized and existing under the laws of India, having a place of business at Sun House, CTS No. 201 B/1, Western Express Highway, Goregaon (East), Mumbai, Maharashtra, 400063 India. *Id*.

Defendant USV is a corporation organized and existing under the laws of India, having a place of business at Arvind Vithal Gandhi Chowk, B.S.D. Marg, Station Road, Govandi East, Mumbai, Maharashtra, 400 088 India. *Id.* Section 3.I.

**B. Patent-in-Suit and Relevant Prosecution History**

The RE'733 Patent, issued on January 28, 2014 and entitled "6-Mercapto-Cyclodextrin Derivatives: Reversal Agents For Drug-Induced Neuromuscular Block," is a reissue of the '340 Patent. PFOF ¶ 17; DFOF ¶¶ 23-28. Approximately ten years before the reissue, on December 30, 2003, the '340 Patent issued with nine claims covering a group of compounds including sugammadex, and methods of using sugammadex. PFOF ¶ 18. On March 28, 2012, "Merck's predecessor-in-interest filed a reissue application to add erroneously omitted claims narrowly directed to sugammadex," including the narrower species claims 10-21. PFOF ¶ 21; *see also id.* ¶ 22; DFOF ¶ 25; Trial Transcript ("Trial Tr.") 194:4–25 (Mojica). The RE'733 Patent subsequently issued on January 28, 2014 with 21 claims: original claims 1 through 9 (unchanged from the '340 Patent); and the 12 newly-added narrower species claims (10-21). PFOF ¶ 22; JTX-1.14–15. When the RE'733 Patent issued, its original expiration date was January 27, 2021. DFOF ¶ 27.

**C. Regulatory Review Process for Bridion®**

On April 13, 2004, four months after the issuance of the '340 patent, Merck's predecessor-in-interest filed Investigational New Drug ("IND") application No. 68,029 for the sugammadex compound. PFOF ¶ 24. On October 31, 2007, Merck's predecessor-in-interest filed New Drug Application ("NDA") No. 022225, seeking commercial approval for Bridion®. PFOF ¶ 25; DFOF ¶ 32. Bridion® was ultimately approved by the FDA on December 15, 2015. PFOF ¶ 26; DFOF ¶ 33.

The FDA determined that the period from the filing of the IND to approval of the NDA for

Bridion® (the "Regulatory Review Period") lasted 4,265 days. PFOF ¶ 36; DFOF ¶ 39. Pursuant to 35 U.S.C. § 156(g)(1), the Regulatory Review Period included the Testing Phase—determined by the FDA to be April 13, 2004 to October 31, 2007 (1,297 days)—and the Approval Phase—determined by the FDA to be October 31, 2007 to December 15, 2015 (2,968 days). PFOF ¶ 36; DFOF ¶¶ 34-37. As discussed, when the FDA ultimately granted approval to market sugammadex on December 15, 2015, nearly 12 years had elapsed since the start of the application process.

**D. The Patent and Trademark Office's Determination of Patent Term Extension**

1. General Calculation of Patent Term Extension

Section 156(c) requires calculation of PTE based on the "regulatory review period for the approved product" which "occurs after the date the patent is issued." The "regulatory review period" is the sum of the testing and approval phases for the drug product. *See* 35 U.S.C. § 156(g)(1). However, in calculating PTE, only half of the days in the Testing Phase are counted, but all the days in the Approval Phase are counted. *See id.* § 156(c)(2); *see also* 37 C.F.R. § 1.775. The applicant must subtract from this calculation any days in the Testing or Approval Phase preceding issuance of the patent. Finally, PTE is capped at a maximum of five years, and is further limited such that the remaining term of the patent plus PTE cannot exceed 14 years after FDA approval of the patented product. *See id.* § 156(g)(6)(A); *id.* § 156(c)(3). The parties do not dispute the math behind the calculation of PTE; they disagree on how to interpret "the date the patent is issued" as a matter of statutory construction.

2. Merck's Patent Term Extension Application

On February 10, 2016, within 60 days of FDA approval as required by 35 U.S.C. § 156(d)(1), Merck submitted an Application for Extension of Patent Term Under 35 U.S.C. § 156 ("PTE Application") for the RE'733 Patent based upon the FDA regulatory review of Bridion®.

PFOF ¶ 29; DFOF ¶ 40; JTX-3.1267–80. In its PTE Application, Merck explained that the RE'733 Patent was a reissue of the '340 Patent and identified both the original issue date (December 30, 2003) and the date of reissue (January 28, 2014). *See* JTX-3.1267–68. Specifically, Merck identified "the patent for which an extension is being sought by the name of the inventor, the patent number, the date of issue, and the date of expiration" as follows:

> **U.S. PATENT NO.: RE44,733**
>
> **INVENTORS: Mingqiang Zhang, Ronald Palin, and David Jonathan Bennett**
>
> **ISSUE DATE:**
>
> **FOR REISSUE PATENT (U.S. Patent No. RE44,733): January 28, 2014**
>
> **FOR ORIGINAL PATENT (U.S. Patent No. 6,670,340): December 30, 2003**
>
> **EXPIRATION DATE: January 27, 2021**

JTX-3.1273; *see also* PFOF ¶ 31; DFOF ¶ 45.

Based on a calculation using December 30, 2003 as "the date the patent is issued" under 35 U.S.C. § 156(c), Merck requested the maximum available five-year patent term extension, which would result in a modified expiration date of January 27, 2026. PFOF ¶¶ 32-33; DFOF ¶ 48; JTX-3.1284–87. In calculating the length of extension claimed, Merck subtracted "0 days" from the Regulatory Review Period for Bridion® (sugammadex) because that "is the number of days in the [T]esting and [A]pproval [P]hases on or before the issuance of the original U.S. Patent No. 6,670,340 on December 30, 2003, which was reissued as U.S. Patent No. RE44,733 patent on January 28, 2014." JTX-3.1286. Merck's PTE Application identified both original claims (including Claim 4) and new claims (including Claims 12 and 21) as covering sugammadex. JTX-3.1276–80. Merck also used "Claim 4 of the reissued '733 patent (and claim 4 of the original '340 patent)" to demonstrate the manner in which at least one patent claim read on the Approved Product. JTX-3.1276–80.

The FDA determined the total length of the Regulatory Review Period for Bridion® to be 4,265 days, with 1,297 days accruing in the Testing Phase and 2,968 days in the Approval Phase. These periods of time were derived from the following:

> (i) The date an exemption under section 505(i) of the Federal Food, Drug, and Cosmetic Act (FD&C Act) (21 U.S.C. 355(i)) became effective: April 13, 2004. FDA verified the applicant's claim that the date the investigational new drug application became effective was on April 13, 2004.
>
> (ii) The date the application was initially submitted with respect to the human drug product under section 505 of the FD&C Act: October 31, 2007. FDA verified the applicant's claim that the new drug application (NDA) for BRIDION (NDA 022225) was initially submitted on October 31, 2007.
>
> (iii) The date the application was approved: December 15, 2015. FDA verified the applicant's claim that NDA 022225 was approved on December 15, 2015.

Final Pretrial Order, Section 3.A ¶ 43; PFOF ¶ 36.

3. The Patent and Trademark Office's Notice of Final Determination

The PTO issued a Notice of Final Determination on February 4, 2020, determining the RE'733 Patent was eligible for a patent term extension under 35 U.S.C. § 156, with a period of extension of five years. PFOF ¶ 38; DFOF ¶ 52. The PTO's calculation of PTE for the RE'733 Patent was performed by attorneys at the Office of Patent Legal Administration. PFOF ¶ 37 (citing Trial Tr. 117:6–16 (Burke), 166:11–25 (Burke)). In the Notice of Final Determination, the PTO explained that the RE'733 Patent was a reissue of the '340 Patent and determined PTE based on the original issue date of December 30, 2003, stating:

> U.S. Patent No. RE44,733 is a reissue of U.S. Patent No. 6,670,340 ("the '340 patent"). The '340 patent issued on December 30, 2003. Since the [R]egulatory [R]eview [P]eriod for BRIDION® began on April 13, 2004, which is after the December 30, 2003 date of issuance for the '340 patent, the entire [R]egulatory [R]eview [P]eriod has been considered in the above determination of the length of the extension period under 35 U.S.C. § 156(c).

JTX-3.1798; *see also* PFOF ¶ 39; DFOF ¶ 53. Accordingly, the PTO used December 30, 2003 as "the date the patent is issued" under 35 U.S.C. § 156(c), and recognized the entire Regulatory Review Period for Bridion® to have occurred after December 30, 2003. PFOF ¶¶ 40-41; DFOF ¶ 54. With these inputs, it is uncontested that the length of the extension is five years under 35 U.S.C. § 156(c). Final Pretrial Order, Section 3.A ¶ 77.

On June 24, 2020, the PTO issued a certificate under 35 U.S.C. § 156 extending the patent term of the RE'733 Patent for a period of five years from its original expiration date (as defined in 35 U.S.C. § 156(a)) of January 27, 2021 to January 27, 2026. DFOF ¶ 56. No determination of a lack of due diligence under 35 U.S.C. 156(c)(1) was made with respect to the PTO's PTE determination for the RE'733 patent. PFOF ¶ 44; DFOF ¶ 55.

**E. The Patent and Trademark Office's Treatment of Reissued Patents**

1. General Treatment of Reissued Patents

At trial, the parties offered expert witnesses to opine on the PTO's policy and practice as to the treatment of reissued patents. *See* Final Pretrial Order at 3 (providing for live testimony of Lissi Mojica ("Mojica" or "Ms. Mojica") for Merck[2] and Dr. Julie Burke, Ph.D ("Burke" or "Dr.

[2] Ms. Mojica received her B.S. in Aeronautical Engineering from Embry Riddle Aeronautical University in 1988 and received her MBA in Legal Administration from Marymount University in 2000. After receiving her B.S. degree, Ms. Mojica worked in various roles and departments in the PTO, including as a Patent Examiner (1989-98), in the Office of Petitions (1998), as a Patent Cooperation Treaty Legal Advisor (1999-2000), as a Supervisory Programs Review Examiner (2000-03), and as the first Director of the Central Reexamination Unit (2003-08). Her responsibilities in her various positions included training Patent Examiners on reissue, reviewing reissue application declarations for compliance with PTO practice, addressing all issues regarding merged reissue and reexamination proceedings, working closely with the Office of Patent Legal Administration, and establishing policies to streamline and improve the patent examination process. *See* Final Pretrial Order, Section 10.A.

Burke") for Defendants[3]). Both witnesses explained that PTO office policy is outlined in the Manual of Patent Examining Procedure ("MPEP"), which is "a large volume of guidance for patent applicants and instructions for the examining corps that covers the more bread-and-butter type of situations that commonly crop up during the … course of patent examination." Trial Tr. 122:7–11 (Burke). The MPEP is "what all the patent office looks to for policy and procedure." *Id.* 190:15–16 (Mojica). Examiners "are authorized or required to follow" the policies set forth in the MPEP. *Id.* 154:24–155:14 (Burke).

Before reaching the issue concerning PTE of reissue patents, the experts opined on whether the PTO has an overarching policy concerning the effect of reissue patents generally. Ms. Mojica testified that, on the whole, the PTO treats the reissued patent as "step[ping] into the shoes of the original patent." Trial Tr. 203:8-21; *see also id.* 185:2-7 (same). In support, she referred to MPEP § 1460, which provides: "With respect to the Office treatment of the reissued patent, the reissued patent will be viewed as if the original patent had been originally granted in the amended form provided by the reissue." MPEP § 1460; *see* Trial Tr. 195:23-196:2. Ms. Mojica also explained that, pursuant to office policy, a reissue patent is not deemed to "have its own privileges" because it is not "an independent regular patent." *Id.* 197:15-22 (referring to MPEP § 1440). Instead, the reissue patent operates "merely [as] a continuation of the original patent's privilege." *Id.* Dr. Burke

[3] Dr. Burke holds a B.A. in Molecular and Cellular Biology from the Johns Hopkins University, a Ph.D. in Biochemistry from the Imperial College of Science, Technology and Medicine at the University of London, and completed a Post-Doctoral Research Fellowship at the Johns Hopkins University School of Medicine's Department of Biochemistry. Dr. Burke worked for the PTO for twenty years (1995–2015). After first working as a Patent Examiner, she was placed on detail to the Deputy Commissioner for Patent Examination Policy and assisted editors in revising the MPEP. She also worked as a Special Program Examiner and then a Quality Assurance Specialist at Technology Center 1600. In these roles, Dr. Burke developed quality initiatives and recommendations for Technology Center 1600, responded to applicant, examiner, and supervisor questions about patent examination, and trained supervisors and examiners on various aspects of examination practice. *See* Final Pretrial Order, Section 10.C.

did not expressly dispute this general policy and instead directed her testimony on PTO policy towards the PTO's choice concerning which issue date to use for PTE calculation of a reissued patent. *See id.* 114:17-21.

As to specific applications of the general PTO policy, Ms. Mojica also pointed to various areas of PTO practice in which the reissue patent is treated in line with MPEP § 1460's directive, including: assessing prior art relevant to a reissue, calculation of maintenance fees for reissued patents, terminal disclaimers, and transferring PTE applications filed on an original patent to a reissued patent where the reissue application was pending at the time the patentee files for PTE. *See* Trial Tr. 197:6–199:2 (prior art); *id.* 200:4-24 (terminal disclaimers); *id.* 202:19–21 (maintenance fees); *id.* 208:17–209:11 (transfer of PTE applications when reissue was pending).

2. The Patent and Trademark Office's Treatment of Reissued Patents for Purposes of Determining Patent Term Extension

The parties' experts also opined on whether the PTO had a specific policy regarding the determination of a patent term extension for reissued patents, and whether the PTO's treatment of such situations was consistent. Dr. Burke expressed her view that "[t]he patent office has no policy upon this topic." Trial Tr. 114:24. In contrast, Ms. Mojica opined that, pursuant to the PTO's broader policy concerning reissued patents, the date the patent is reissued never affects the patent's term, even in cases of term extension. *Id.* 199:10-25. In other words, the general policy concerning reissue patents also applies in the specific circumstances of patent term extension. *Id.* She raised various examples in which the PTO uses the original issue date or original application date for purposes of a reissue patent. *Id.* 197:6–199:2; 202:19–21. Ms. Mojica added that she believed the date of reissue is used solely for "administrative" purposes to track when the reissue occurred. *Id.* 204:4-14. Dr. Burke could not identify any PTO policy guidance using the reissue date for any

purpose and could not recall any experience she had in her time at the PTO when the reissue date was used for any reason. *Id.* 178:9-179:13.

When addressing the consistency of the PTO's practice, the experts analyzed a data set of relevant instances in which the PTO dealt with a reissued patent applying for patent term extension. Together, the experts identified a total of 40 examples spanning over the last four decades. PFOF ¶ 56; DFOF ¶ 60. Of those 40 PTE determinations, Ms. Mojica identified 36 in which the PTO used the original issue date to calculate PTE. Tr. 214:5–215:20. In all 36 of these instances, the PTO issued its notice of final determination after the patent reissued, consistent with its practice with the RE'733 Patent here. *Id*. 214:15–215:20 (Mojica). Ms. Mojica thus concluded that the PTO consistently used the original issue date when determining PTE for reissue patents. *Id.* 215:5-7; 217:1-22. Additionally, beyond the practice of the PTO, testimony at trial showed that some patentees expect the PTO to calculate PTE based on the original issue date because it is "self-evident" from the concept of reissue. *See* Dep. Tr. of Keith D. MacMillan ("MacMillan") 158:9–159:1, 159:12–25, 160:3–10.[4]

Dr. Burke identified four PTE determinations in which the PTO used the reissue date to calculate PTE. Trial Tr. at 139:7-12; *see also* DTX-4, DTX-8, DTX-9, DTX-10. In two of these, the choice of date had no effect on the PTE allowed—the extension would have been the same regardless of which issue date was used. Tr. 217:3–217:22 (Mojica discussing RE'30,811 and RE'34,712). And in the remaining two, the PTO never awarded the extension based on the date

[4] Mr. MacMillan is a former Merck in-house counsel, who was involved in the prosecution of Merck's patents related to sugammadex, including the RE'733 Patent and its patent term extension. Final Pretrial Order, Section 8.A(i). The parties agreed to submit up to 20 minutes of designations from Mr. MacMillan's deposition. *Id.* To the extent that the parties objected to the deposition testimony discussed in this Opinion, those objections are overruled. *See* Final Pretrial Order Section 11.A-B (listing deposition designations and objections).

of reissue (even though it used that date for calculation purposes), because the patentee ultimately chose to elect PTE on other patents, leading to withdrawal of the original PTE applications. *Id.* (Mojica discussing RE'42,072 and RE'43,691). The patentee in the latter two examples also chose to seek a shorter extension by seeking PTE based on the date of reissue. *See* DTX-9.621, 628 (PTE application for RE'42,072); DTX-10.101, 110 (PTE application for RE'43,691). Further, in the four instances in which the reissue date was used, the PTO did not expressly note that the subject patent was a reissued patent, as it did with its determination for RE'733. *Compare* DTX-4, DTX-8, DTX-9, DTX-10 *with* JTX-3.1798 ("U.S. Patent No. RE44733 is a reissue of U.S. Patent No. 6,670,340…."). When asked, Dr. Burke was unable to identify an instance where the PTO later re-calculated a patent term extension for any of Ms. Mojica's 36 examples. Trial Tr. 172:20-173:4. Dr. Burke concluded that, based on her examination of these 40 instances, "the PTO's practice has been mixed." Trial Tr. 115:17.[5] As noted above, Ms. Mojica rejected Dr. Burke's conclusion, opining that the existence of the four examples referenced by Dr. Burke did not undermine the PTO's overall consistency, given the examples' particularized circumstances. *Id.* 217:7-24.

Lastly, the Court notes that MPEP § 2766 (Processing of Patent Term Extension Applications When Reissue Has Been Filed) [R-07.2022] was recently amended to address situations where a patent term extension is sought on a reissue patent, as before the Court presently. Section 2766 now states the original patent grant date is used to calculate PTE, explaining:

> With respect to calculating the amount of extension to which the reissued patent is entitled to receive, so long as the original patent claimed the approved product and the reissued patent claims the approved product, the original patent grant date would be used to

[5] Dr. Burke also testified that nine (9) of the 36 instances identified by Ms. Mojica involved situations in which an application for PTE was filed on the original patent before the patent was surrendered and the PTO issued a reissue patent. Trial Tr. at 139:1-6.

> calculate the extension to which the reissued patent would be entitled.

Although neither expert opined on the updated provision at trial, the Court may "take notice of public reports and filings, such as those prepared by an administrative agency or pursuant to government regulation, to extent they have indicia of authenticity." *In re Plum Baby Food Litig.*, No. 21-2417, 2022 WL 16552786, at *3 (D.N.J. Oct. 31, 2022) (citing *Sturgeon v. Pharmerica Corp.*, 438 F. Supp. 3d 246, 259 (E.D. Pa. 2020)).

## II. ISSUE TO BE DECIDED

As stated above, prior to the commencement of trial, Defendants advised that they did not contest infringement. Final Pretrial Order at 2; *see also* ECF Nos. 249, 250, 252, 253, 254, 255, 276, 277, 357, 380, 381. Accordingly, the sole issue before this Court concerns Defendants' PTE defense: whether the portion of the patent term extension for the RE'733 Patent after December 14, 2022 is invalid under 35 U.S.C. §282(c). Final Pretrial Order at 2.

## III. LEGAL STANDARD

Issued patents are presumed valid. *See* 35 U.S.C. § 282(a). To rebut this presumption, a defendant bears the burden of proving invalidity by clear and convincing evidence. *Titan Tire Corp. v. Case New Holland, Inc.*, 566 F.3d 1372, 1376 (Fed. Cir. 2009). Questions of statutory interpretation, however, are legal questions for the court to decide. *See Wyeth v. Kappos*, 591 F.3d 1364, 1369 (Fed. Cir. 2010); *see also Microsoft Corp. v. i4i Ltd. P'ship*, 564 U.S. 91, 114 (2011) (Breyer, J., concurring) (clarifying that on an "invalidity question," the presumption of validity is an "evidentiary standard of proof [that] applies to questions of fact and not to questions of law").

## IV. DISCUSSION

This Hatch-Waxman Act litigation requires the Court to determine how to treat a reissued patent for purposes of calculating a patent term extension under 35 U.S.C. § 156(c). Section 156

generally "provides the holders of patents on approved patented products with an extended term of protection under the patent to compensate for the delay in obtaining FDA approval." *Merck & Co., Inc. v. Kessler*, 80 F.3d 1543, 1547 (Fed. Cir. 1996) [hereinafter *Kessler*]. Broadly speaking, when a patentee loses part of its exclusivity to market a covered drug because the patentee is awaiting FDA approval, the patentee may seek to extend the patent up to five years, subject to certain other statutory exceptions that are not implicated here. 35 U.S.C. § 156(c). Section 156(c) specifically speaks to calculation of that extension, restoring to the term of the patent "the time equal to the regulatory review period for the approved product which period occurs after the date the patent is issued." 35 U.S.C. § 156(c). It does not, however, expressly address the treatment of patents that are *reissued* pursuant to 35 U.S.C. § 251 ("Reissue of Defective Patents"). *See also id.* § 252 ("Effect of Reissue"). Accordingly, the crux of the legal dispute concerns whether the Patent Act requires a patent term extension of a reissued patent to be calculated based on the issue date of the original patent—the term of which is inherited by the reissue patent—or, conversely, based on the issue date of the reissued patent.

Defendants assert that the plain meaning of the language of § 156(c), read in isolation and using basic rules of grammar, requires using the issue date of the *reissued* patent. They contend there is no ambiguity, and thus there is no need to look past this provision's language. By contrast, Merck argues that § 156, understood in the statutory context of the provisions governing reissue (§ 251 and § 252) as it must be, unambiguously directs PTE to be calculated based on the issue date of the original patent which sets the term for the reissue. Although Merck maintains that the Court need not look further than the plain meaning established by the statutory scheme, Merck argues that to the extent there is ambiguity, it should be resolved by the Hatch-Waxman Act's remedial purpose of restoring portions of the patent's term lost to FDA delay and by deferring to

the PTO's consistent use of the original issue date.

For the reasons set forth below, the Court finds that § 156(c), when read in its proper context alongside the provisions of the Patent Act addressing reissue, unambiguously supports Merck's interpretation that the issue date of the original patent must be used for calculating PTE. Defendants' isolated interpretation of § 156 requires an untenable reading of the statutory scheme on the whole, creating conflict with various provisions of the Patent Act as well as unintended results. Moreover, Defendants' interpretation would undermine the purpose of the Hatch-Waxman Act, in contrast to Merck's interpretation, which aligns with it. Using the original issue date also comports with the PTO's policy and longstanding practice of treating reissued patents as if they were originally granted in amended form for purposes relevant to the PTO's administration of the Patent Act. And even if the underlying statutory language were ambiguous, the PTO's policy and consistent practice over the last four decades would be entitled to some deference pursuant to *Skidmore v. Swift & Co.*, 323 U.S. 134 (1944).

**A. Statutory Language**

1. Overview of the Parties' Positions

Both parties contend that this issue can be decided by the unambiguous meaning of the relevant provisions of the Patent Act. Of course, they present different views of what that unambiguous meaning is. The Court turns first to Defendants, who argue that § 156(c), read on its own, requires a patent term extension to be determined based on the issue date of the reissue patent, namely the RE'733 Patent here. Defendants point to what they view as the operative provision of § 156(c): "*[t]he term of a patent eligible for extension* … shall be extended by the time equal to the regulatory review period for the approved product which period occurs after *the date the patent is issued*." 35 U.S.C. § 156(c) (emphasis added). They assert that this provision "refers to only one patent, such that the same patent for which PTE is sought must be the same

patent whose issue date is used for calculating PTE." Def. Br. at 8-9. In other words, because "the definite article 'the' is 'a function word indicating that a following noun or noun equivalent is definite or has been previously specified by context,'" it follows that "the patent" in the second clause must refer to the same patent that is "eligible for extension" in the first. *Id.* at 9 (quoting *Nielsen v. Preap*, 139 S. Ct. 954, 965 (2019)). And, Defendants continue, there is no dispute that the "patent eligible for extension" here is the RE'733 Patent—the only patent in existence since the '340 Patent was surrendered years before applying for PTE, and the patent which was identified as eligible for extension in Merck's application. *Id.* Therefore, Defendants assert § 156(c)'s reference to "the date the patent is issued" must refer to January 28, 2014, the date the RE'733 Patent "issued." Under Defendants' theory, then, only 686 days of the Regulatory Review period should be restored to the patent's term—the time between the reissue date (January 28, 2014) and the FDA's approval of Bridion® (December 15, 2015).

Merck, for its part, argues that § 156, which does not reference reissue patents specifically, must be read in conjunction with § 251 and § 252, the provisions addressing reissue. Pl. Br. at 5. Once they are read together (as they must be under principles of statutory construction), Merck contends that it is unambiguous that the issue date of the original patent should be used for calculation of PTE. *Id.* at 5-6 (citing *Syngenta Crop Prot., LLC v. Willowood, LLC*, 944 F.3d 1344, 1359 (Fed. Cir. 2019)). Turning to § 252, Merck points out that this provision, entitled "Effect of Reissue," mandates that "every reissued patent shall have the same effect and operation in law, on the trial of actions for causes thereafter arising, as if the patent had been originally granted in amended form." *Id.* at 6 (citing 35 U.S.C. § 252). Merck explains that because there is no dispute that this is the trial of an action for a cause arising after reissue, § 252 requires the RE'733 Patent to be given "the same effect and operation in law . . . as if [the RE'733 Patent] had been originally

granted in amended form." *Id.* at 7 (citing *Cooper Techs. Co. v. Dudas*, 536 F.3d 1330, 1341 (Fed. Cir. 2008)). And to give the RE'733 Patent that same effect and operation as if it had been originally granted in amended form, the original issue date must be used. *Id.* Merck therefore contends that § 252 "resolves the parties' dispute regarding what effect to give the reissued RE'733 patent for purposes of this case." Pl. Br. at 6.

Moreover, Merck asserts that § 251 further supports its interpretation. *Id.* at 9-10. Section 251 speaks to the relationship between the original patent and the reissue: when "any patent" contains a correctable error, the PTO "shall … reissue *the* patent." *Id.* at 9 (citing § 251) (emphasis added in brief). Mirroring Defendants' reasoning, Merck suggests "the use of 'the' in § 251 demonstrates that a reissued patent is 'the' original patent in amended form and should be treated accordingly." *Id.* Further, because § 251 provides that the reissued patent takes on "the unexpired part of the term of the original patent," the "term" of a reissued patent is dictated entirely by the original patent. *Id.* Merck argues that not only do § 251 and § 252 affirmatively support its interpretation but Defendants' interpretation would create an unnecessary conflict between the reissue provisions and the patent term extension provision. *Id.* at 14-15. Merck thus concludes that a holistic view of the statutory scheme which gives effect to all relevant provisions requires using the original patent's issue date when calculating PTE under § 156(c).

2. Analysis

*a) Principles of Statutory Construction*

"It is a fundamental canon of statutory construction that the words of a statute must be read in their context and with a view to their place in the overall statutory scheme." *W. Virginia v. Envtl. Protec. Agency,* 142 S. Ct. 2587, 2607 (2022) (internal quotation omitted); *see also Syngenta Crop Prot., LLC v. Willowood, LLC*, 944 F.3d 1344, 1359 (Fed. Cir. 2019) ("The meaning of statutory language is determined by reference to the language itself, the specific context in which that

language is used, and the broader context of the statute as a whole.") (internal quotation omitted). Defendants' suggestion to begin and end with the language of § 156(c)—and disregard other provisions relevant to reissue—thus runs counter to standard principles of statutory interpretation. *See Turkiye Halk Bankasi A.S. v. United States*, 143 S. Ct. 940, 948 (2023) ("But this Court has a duty to construe statutes, not isolated provisions.") (internal quotation omitted); *Tyler v. Cain*, 533 U.S. 656, 662 (2001) ("We do not, however, construe the meaning of statutory terms in a vacuum."); *Vectra Fitness, Inc. v. TNWK Corp.*, 162 F.3d 1379, 1383 (Fed. Cir. 1998) ("[S]tatutory interpretation is a holistic endeavor that requires consideration of a statutory scheme in its entirety.") (internal quotation omitted). Indeed, the Federal Circuit has already determined that this fundamental canon of construction applies specifically to § 156 when it relied on "the combined effects of [other Patent Act amendments] and the Hatch-Waxman Act" to construe the phrase "'original expiration date' in § 156(a)." *Merck & Co., Inc. v. Kessler*, 80 F.3d 1543, 1550 (Fed. Cir. 1996) (reaching conclusion after finding "[u]nder this interpretation, all provisions … can reasonably be given effect"). It is therefore incumbent upon this Court to interpret the Patent Act in a way that gives meaning to all provisions and avoids conflict. *See Baude v. United States*, 955 F.3d 1290, 1305 (Fed. Cir. 2020) (relying on "one of the most basic interpretive canons: that a statute … should be construed so that effect is given to all its provisions") (internal quotation omitted). Defendants' isolated interpretation of § 156(c), however, violates these principles of statutory construction by creating unnecessary conflict with § 251 and § 252, the provisions concerning reissued patents. The Court now turns to these provisions of the Patent Act.

*b) Section 251*

Defendants' interpretation, if accepted, would conflict with § 251, the initial provision governing the process for reissue and its term. Section 251 expressly states that the PTO must "*reissue* the patent" which contains an error—not issue a new patent. 35 U.S.C. § 251 (emphasis

added). Section 251 further directs that the reissued patent inherits "the unexpired part of the term of the original patent." *Id*. This provision thus treats the reissued patent not as an entirely new patent with a new term, but as an amended version of the original that takes on the original's term. In other words, § 251 provides that the term of a reissue patent lacks an independent basis; its existence and length depend entirely on the term of the original. *Id.* And § 251's focus on the identity of a patent term between the original and the reissue links back to § 156(c), which discusses extension specifically in the context of "[t]he *term* of a patent." *Id.* § 156(c) (emphasis added). Against this backdrop, Defendants' interpretation would overlook the dependency of the reissue's term on the original's term, and the relationship between the two. Instead, it would create two unrelated and distinct terms: the original term, which retains its statutory guarantee of up to five years' restoration based on FDA delay; and the reissue term, which would be dictated not necessarily by the requirements of § 251 but by the happenstance of the date the PTO approves reissue and/or the date the FDA finishes its regulatory review—both of which are out of the control of the patentee. *See* Def. Br. at 11-12. Moreover, the Federal Circuit has already observed the requirement of reading § 156 and § 251 harmoniously, holding that a patent's "term" in the Act must be read consistently across the two provisions. *See In re Yamazaki*, 702 F.3d 1327 (Fed. Cir. 2012). There, after noting that § 156 and § 251 are among a series of statutes that "use[] the word 'term,'" the Federal Circuit explained that "[t]o hold that § 251 uses 'term' in a sense . . . distinct from §§ 155, 155A, 156, and 253 would be to endorse an untenable reading of the statutory scheme…." *Yamazaki*, 702 F.3d at 1332. Defendants' isolated interpretation does precisely that—

endorses an untenable reading of the statutory scheme established by § 251 and reaffirmed by the Federal Circuit in *Yamazaki*.[6]

*c) Section 252*

Similarly, Defendants' interpretation conflicts with § 252. Section 252 requires that "every reissued patent shall have the same effect and operation in law, on the trial of actions for causes thereafter arising, as if the same had been originally granted in such amended form." 35 U.S.C. § 252. As this is a trial of a cause arising after reissue, *see* Final Pretrial Order 3.B-I (Defendants filed their ANDAs in 2019, nearly six years after reissue), the Court must do as the statute requires: give the RE'733 Patent "the same effect and operation in law … as if [it] had been originally granted in such amended form." Pl. Br. at 6 (quoting 35 U.S.C. § 252). Moreover, as with any statute, the Court must strive to give meaning to every word in § 252. *See Sullivan v. McDonald*, 815 F.3d 786, 791 (Fed. Cir. 2016) ("[W]e attempt to give full effect to *all words* contained within that statute ….") (emphasis added) (quoting *Glover v. West*, 185 F.3d 1328, 1332 (Fed. Cir. 1999)). To give the RE'733 Patent the "same effect and operation in law" as if it had been "originally granted in amended form," then, the Court must also give meaning to "originally." 35 U.S.C. § 252. This, in turn, provides another reason to treat RE'733's issue date as if it were the *original* issue date. And the Federal Circuit observed as much in *Cooper Techs. Co. v. Dudas*,

[6] Merck also explains that § 251(a), by providing that the remainder of the original term carries over to the patent as reissued, "necessarily requires the expiration date of the reissued patent to be calculated based on the filing date of the original application, . . . not the reissue application filing date." ECF No. 335 at 9 (citing 35 U.S.C. § 154(a)(2) (term extends from issue date to 20 years after application filing)). Further underscoring the importance of the original patent's issue date to the term of the reissue patent, the Court notes that prior to 1995, the expiration date of a reissued patent was based not on the filing date of the original application but on the *issue date* of the original patent. *See Kessler*, 80 F.3d at 1547 ("Prior to June 8, 1995, U.S. patents had an expiration date under 35 U.S.C. § 154 measured as 17 years from the date the patent issued ….").

when it explained that "reissues are deemed by operation of law to replace the surrendered originals and, thus, are entitled to treatment as original patents." 536 F.3d 1330, 1341 (Fed. Cir. 2008) (rejecting argument that the statute establishing *inter partes* reexamination of "original applications" filed after a certain date would insulate reissue patents from such reexamination altogether because they issued from "reissue applications" instead of "original applications"). Therefore, in addition to being inconsistent with § 251, Defendants' interpretation would further disrupt the statutory scheme by creating conflict with § 252.

Defendants respond that this interpretation would misconstrue § 252 and its subject matter. *See* Def. Br. at 16-17. They assert that § 252, in contrast to Merck's understanding, is "really focused on … what is the effect of reissue in later litigation." Closing Tr. 18:17-18. Although that qualification might be taken to support Merck's interpretation (as this litigation commenced after reissue and involves its effects), Defendants maintain that § 252 must be understood in its context: namely, settling "complicated questions that arise sometimes with reissued patents" including infringement that occurs before reissue, and distinguishing claims that are carried over from the original patent from claims that are newly added by the reissue. *Id.* 20:16-17. Putting aside that Defendants ask the Court to view § 252 in statutory context they are unwilling to afford § 156, their argument is belied by *Cooper Techs.* There, the Federal Circuit used § 252 to ground its understanding of reissue patents even though it was reviewing an Administrative Procedure Act challenge to a PTO decision, and not infringement litigation. *Cooper Techs.*, 536 F.3d at 1341. Moreover, the language of § 252 itself is broadly stated; its text is not limited to specific questions arising in subsequent litigation such as damages or intervening rights, as Defendants have suggested. *See* Closing Tr. 18:12-16 (Defendants' counsel arguing § 252's import to "damages," and "intervening rights and equitable intervening rights"). Accordingly, § 252 provides an

explanation of reissue patents (and their relation to their predecessor patents) that is not as limited as Defendants propose.

Defendants also refute that their interpretation conflicts with § 252 because, they contend, reissue patents and original patents are "legally distinct." Def. Br. at 11. To justify that position, they offer three principal supporting arguments. First, Defendants note that in prior versions of the Patent Act, "the 'rights [a patentee] had in and under the original patent are forfeited *ab initio* upon the grant of the reissue.'" Def. Br. at 11 (quoting *Fresenius v. Baxter*, 721 F.3d 1330, 1337 (Fed. Cir. 2013)). Second, they assert that the Federal Circuit, in *Intel Corp. v. Negotiated Data Sols., Inc.*, 703 F.3d 1360 (Fed. Cir. 2012), already rejected the proposition that a reissue patent replaces an original. *Id.* at 12. And third, they point to other tribunals' decisions—namely the Fourth Circuit and the Patent Trial and Appeals Board ("PTAB")—which they believe support the proposition that original patents and reissues are always distinct. *Id.*

The Court is not persuaded. As an initial matter, whether the original patent and reissue patent are "legally distinct" mischaracterizes the question before the Court as well as the guidance provided by § 252. The question here is not whether the two patents are the same, for all conceivable purposes or in some abstract, theoretical sense. *Compare* Closing Tr. 18:2-9 *with id.* 44:18-45:2 (debating whether, and to what effect, Merck's theory is a "legal fiction"). Rather, the question presented is simply how to treat the reissued patent in this cause of action arising after reissue. Indeed, § 252 (as well as Merck, the PTO, and this Court) recognizes that the reissue does not *literally* issue on the date the original did. *See, e.g.*, Closing Tr. 54:7-9 ("Merck's position is not that reissues always go back in time and replace an original and we all pretend that the original never existed."). But § 252 nevertheless directs the Court, on actions arising after reissue, to give the reissue "the same effect and operation in law . . . *as if*" it issued on the date the original did. 35

U.S.C. § 252 (emphasis added). That is, for the purpose to which § 252 speaks—the effect of reissue on causes of action thereafter arising—the Court is directed to set aside the timeline and instead treat the reissue patent "as if" it were "originally granted in amended form." *Id.* Defendants' argument that the two patents are distinct may have some truth in certain other unrelated contexts, *see, e.g.*, *Aspex Eyewear, Inc. v. Marchon Eyewaer, Inc.*, 672 F.3d 1335 (Fed. Cir. 2012),[7] but fails to speak to the central issue here.

In any event, Defendants' supporting arguments are unavailing. As to Defendants' first argument, *Fresenius,* in its detailed history of § 252, noted that Congress found the idea that patentees forfeited all rights *ab initio* on reissue "an almost unbelievable and inequitable situation" and thus amended the Patent Act nearly a century ago to do away with this rule. *Fresenius*, 721 F.3d at 1337 (quoting S.Rep. No. 70-567, at 1 (1928)). And to the extent Defendants turn to prior eras of patent law, there is longstanding precedent that original and reissue patents are inextricably linked rather than distinct. *See, e.g.*, *Grant v. Raymond*, 31 U.S. 218, 244 (1832) (questioning whether "the second patent could be considered as independent of the first" but concluding that "it is in no respect so considered").

With respect to Defendants' second argument, *Intel* is distinguishable from the instant action, and the language Defendants cite therein is not as broad as they contend. 703 F.3d 1360 (Fed. Cir. 2012). *Intel* concerned a contract dispute over whether a license granted to original patents extended to reissue of those patents. *Id.* at 1362-63. Intel, the licensee, argued that (i) § 252 required the reissued patents to be given the same effect in the contract as if they were the

[7] Defendants point to *Aspex Eyewear*, in which the Federal Circuit "made clear that claim preclusion d[id] not apply" to a circumstance involving a reissue patent. Def. Br. at 12 (quoting *Aspex Eyewear,* 672 F.3d at 1341-42). As the Court finds with respect to the other cases Defendants cite for this proposition, *see infra*, the discussion of claim preclusion in *Aspex Eyewear* is inapposite to the issues presented here.

original patents, and (ii) the contract itself was intended to cover both original and reissued patents. *Id*. The court ruled in Intel's favor on the contract argument, but rejected Intel's "simplistic proposition that a reissue patent replaces the original *nunc pro tunc*." *Id.* at 1364. Defendants seize upon this language to argue that the Federal Circuit's statement in this licensing case applies with similar force here. *See* Def. Br. at 2. However, the Federal Circuit carefully explained that a reissue patent did not replace an original patent *nunc pro tunc* because that would "ignore[] the specific language of the statute that grants intervening rights to those who may infringe only new claims added by reissue." *Intel*, 703 F.3d at 1364. In other words, the court observed that treating a reissued patent as the original patent *for all purposes* would disregard § 252's provision of intervening rights to certain third parties. *See id.* (qualifying its assertion about reissue patents as applying "*[i]n this important aspect alone*") (emphasis added). Yet Merck makes no such broad, unqualified assertion. Indeed, Merck's interpretation here does not conflict with the treatment of intervening rights in § 252; it clearly allows for them. *See* Closing Tr. 54:10-11 ("If you [treat the original patent as having never existed for all purposes], you vitiate intervening rights."); *id.* 79:12-13 ("Intervening rights is the exception to treating a reissued patent as if originally granted in amended form."). Moreover, the *Intel* court ultimately found the licensing agreement had to be understood to cover reissue patents arising from those original patents as well, even if not explicitly set forth in the agreement. *See Intel*, 703 F.3d at 1367. Therefore, putting aside the distinguishable facts and narrow language, the *Intel* result is ultimately consistent with the treatment Merck seeks here.

Defendants' third argument, which relies on *Mylan Pharms., Inc. v. U.S. Food & Drug Admin.*, 594 F. App'x 791 (4th Cir. 2014), and *Eizo v. Barco N.V.*, IPR 2014-358, 2015 WL 43815867 (PTAB July 14, 2015) is similarly unavailing. *See* Def. Br. at 12-14. While each

decision suggests some degree of distinction between the original and reissue patent in certain other contexts, neither addressed the issue of patent term extension. *See Mylan*, 594 F. App'x at 797 (interpreting a different, since-amended statute to permit a new 180-day exclusivity period for generics upon a court decision concerning the infringement or validity of a reissued patent); *Eizo*, 2015 WL 4381586, at *5 (PTAB decision limiting its applicability to "the purposes of Section 315(b)," i.e., the *inter partes review* time-bar provision). Further, relying solely on Black's Law Dictionary's definition of "patent" may have been sufficient to resolve the 180-day exclusivity issue in *Mylan*, but its lack of engagement with § 251 and § 252 renders that case less persuasive here. And even if these cases had relevant facts or legal questions that applied to this context, neither *Mylan,* as an unpublished decision from outside the Federal Circuit, nor *Eizo*, a decision by the PTAB, has binding effect here. Accordingly, Defendants' supporting arguments cannot undo their interpretation's fundamental conflict with § 252's mandate to treat reissue patents in subsequent litigation as if they were originally granted in amended form.

Even if Defendants offered an argument that somehow sidestepped this conflict, Defendants' interpretation would still independently conflict with a separate clause of § 252. Section 252 also provides that "the reissued patent, to the extent that its claims are substantially identical with the original patent, shall constitute a continuation thereof and have effect continuously from the date of the original patent." 35 U.S.C. § 252. Of the claims at issue in this trial, Claim 4 of the RE'733 Patent is unamended from the '340 Patent and thus "substantially identical" under § 252. *See* JTX-1.14-15; *see also* JTX-3.1276-1278 (seeking PTE based on Claim 4). Therefore, imposing the RE'733 Patent's issue date on Claim 4 for purposes of patent term extension would be inconsistent with § 252's command to give substantially identical claims continuous effect "from the date of the original patent." 35 U.S.C. § 252. If, instead, a patent term

extension were calculated based on the date of reissue as Defendants propose, then none of the term lost for the identical claims of the '340 Patent would be restored. Defendants have offered no basis to conclude that Congress intended for § 156 to disrupt the continuous effect given to identical claims in a reissue patent, as has been the law for 100 years. *See Fresenius,* 721 F.3d at 1337.[8]

*d) The Parties' Examples of Absurd Results*

Notwithstanding these conflicts with § 251 and § 252, Defendants' interpretation also leads to results that Congress could not have intended. "Both the Supreme Court and [the Federal Circuit] . . . have repeatedly held over the years that [i]f a literal construction of the words of a statute be absurd, the act must be so construed as to avoid the absurdity." *Dupuch-Carron v. Sec'y of Health & Hum. Servs.*, 969 F.3d 1318, 1330 (Fed. Cir. 2020) (internal quotation omitted). As Merck posits, if the FDA had approved Merck's application three years *earlier* in 2012 (and thus after Merck applied for the RE'733 Patent but before the reissue was approved), Merck undoubtedly would be entitled to receive the full five years of restored term. *See* Pl. Br. at 19 ("If FDA approval came in December 2012, Merck would have applied for PTE on the original '340 patent because its reissue application, filed in March 2012, would have been pending. In that circumstance, the PTO would calculate PTE based on the issue date of the '340 patent, as it had done in every instance where a reissue application was pending at the time of the PTE application."); *see also* Trial Tr. 171:24-172:25 (Burke acknowledging the PTO determined PTE

[8] Defendants also argue Merck's proposed application of term extension to the entirety of the RE'733 Patent fails because § 252 gives continuous effect *only* to substantially identical claims in the reissue patent (and not newly added ones). *See, e.g.,* Closing Tr. 93:5-6. However, the Federal Circuit has explained that when it comes to term extension "[a] patent as a whole is extended even though its effect may be limited to certain of its claims." *Genetics Inst. LLC v. Novarties Vaccines & Diagnostics Inc.*, 655 F.3d 1291, 1301 (Fed. Cir. 2011); *see also Biogen Int'l GmbH v. Banner Life Scis. LLC*, 424 F. Supp. 3d 303, 308 (D. Del.) (same), *aff'd*, 956 F.3d 1351 (Fed. Cir. 2020).

based on the original issue date in every instance where a reissue application was pending at the time of the PTE application). That *more* FDA delay should result in *less* restored term, as Defendants argue here, cannot be squared with Congress' intent to restore "time lost in [a] patent term by reason of FDA delay" through § 156. *Kessler,* 80 F.3d at 1553; *see also infra* Section IV.B.

Merck highlighted an additional scenario at trial whereby a three-day change in the date the PTO approved reissue—from just one day before FDA approval to just two days after—would lead to drastically different amounts of patent term extension. *See* Closing Tr. 63:15-65:2 (detailing the dates and calculations).[9] In that circumstance, if the reissue occurred just before FDA approval it would lead to a *one-day* patent term extension. If, on the other hand, reissue occurred just after FDA approval, it would result in a patent term extension of the full five years. *See supra* n.9. To follow Defendants' reading of the statute would mean that a three-day change in the PTO's approval of reissue (which is out of the patentee's control) is the difference between a full five-year extension and a one-day extension.

[9] Merck's hypothetical proceeds as follows: in both of the following scenarios, the actual original issue date of December 30, 2003 and the FDA's actual approval date of Bridion® on December 15, 2015 remain unchanged. The first scenario assumes the PTO approved reissue on December 17, 2015. Merck would then receive the full five-year extension under Defendants' theory because the entire regulatory review period of 4,265 days occurred before the RE'733 Patent was approved, and so the only patent "in effect" to be plugged into § 156(c) would be the original '340 Patent. *See* 35 U.S.C. § 156(c) (directing restoration of "the time equal to the regulatory review period for the approved product which period occurs after the date the patent is issued"). But, on the other hand, in a scenario in which the PTO approved reissue just three days earlier—on December 14, 2015, or one day before FDA approval—Merck would now receive *one day* of restored term under Defendants' theory. This is because, with the RE'733 Patent being the operative patent at the time of FDA approval, "the time equal to the regulatory review period for the approved product which period occurs after the date the patent is issued" is reduced to just one day: December 14, 2015 (reissue approval) to December 15, 2015 (FDA approval). 35 U.S.C. § 156(c).

A statutory scheme that fluctuates so dramatically on variables outside the patentee's control appears contrary to a framework in which Congress provided patent term extensions to incentivize drug companies to invest in innovating new drugs. *See infra* Section IV.B. The balance which Congress struck is not for this Court to second-guess; yet there is little doubt Congress did not intend to create a system that would inhibit planning and disrupt settled expectations. *See Festo Corp. v. Shoketsu Kinzoku Kogyo Kabushiki Co.*, 535 U.S. 722, 739 (2002) ("[C]ourts must be cautious before adopting changes that disrupt the settled expectations of the inventing community."); MacMillan Dep. Tr. 158:9–159:1; 160:3–10 (Merck used original issue date because it is "self-evident" from concept of reissue). Therefore, in addition to being inconsistent with § 251 and § 252, Defendants' interpretation would lead to unworkable results that Congress could not have intended.[10]

*e) Summation of Statutory Analysis*

In contrast to Defendants' interpretation which conflicts with multiple provisions of the statutory scheme, Merck's interpretation gives effect to all relevant provisions without creating conflicts or illogical results. First, reading "the date the patent is issued" in § 156(c) to mean the

[10] Defendants offer a hypothetical of their own based on Merck's interpretation that would lead, in their view, to just as "strange" a result as the hypotheticals posed by Merck. Def. Br. at 20. They contend that "where a patent is broadened through reissue, it is possible that an original patent would not cover a drug but a reissue patent would. In such a case, under Merck's interpretation using the issue date of the original patent, the patentee would receive a PTE for a period of time (issuance of original through issuance of reissue) when it did not have a patent that covered the product at issue." *Id.* Putting aside that this scenario speaks to a *broadened* reissue (which has its own limitations per § 251(d)), the Court is not convinced that the statute would operate this way where the original patent does not cover the product at issue. And indeed, the PTO has expressly disclaimed this possibility in its most recent MPEP. *See* MPEP (Ninth Edition), § 2766 [R-07.2022] ("With respect to calculating the amount of extension to which the reissued patent is entitled to receive, *so long as the original patent claimed the approved product and the reissued patent claims the approved product*, the original patent grant date would be used to calculate the extension to which the reissued patent would be entitled.") (emphasis added).

original patent's issue date gives force to § 251's mandate that the PTO "reissue the [original] patent" and give the amended version the "unexpired part of the term of the original patent." 35 U.S.C. § 251(a). Second, this interpretation also provides a consistent reading of "term" across § 156 and § 251—as required by the Federal Circuit in *Yamazaki*—by maintaining the relationship between the reissued patent's term and the original patent's term. *See Yamazaki*, 702 F.3d at 1332. Third, Merck's interpretation gives the RE'733 Patent "the same effect and operation in law, on the trial of actions for causes thereafter arising, as if the same had been originally granted in such amended form." 35 U.S.C. § 252. As explained above, since Defendants filed their ANDAs in 2019 (approximately six years after reissue in January 2014), this is a "trial of actions for causes thereafter arising." *Id.* Consequently, using the '340 Patent's issue date for calculating PTE effectuates § 252 by treating the RE'733 Patent the way the '340 Patent would have been treated in this trial if the '340 Patent had been originally granted with the RE'733 Patent's additional 12 narrower claims. Fourth, Merck's interpretation gives RE'733's Claim 4, which is "substantially identical" to Claim 4 in the '340 Patent, continuous effect "from the date of the original patent," as further required by an additional part of § 252. *Id.* And finally, Merck's interpretation avoids the absurd results of (i) more FDA delay leading to less restoration, and (ii) drastic swings in PTE hinging on the mere sequencing of the end dates of independent PTO and FDA processes—both of which are outside the patentee's control.

Accordingly, understanding § 156(c) within its place in the statutory scheme and alongside other relevant provisions of the Patent Act—as this Court must—it is clear that, for reissue patents seeking patent term extensions, "the date the patent is issued" refers to the date the original patent issued.

**B. Purpose of the Hatch-Waxman Act and Patent Term Extension**

Merck also argues that using the original date the patent issued for purposes of § 156(c)

effectuates the statute's remedial purpose of restoring time lost to extended regulatory review. Pl. Br. at 11-14. In response, Defendants contend that "Merck has turned to broad policy appeals" which are outside the "judicial role" and, in any event, are "unduly one-sided." Def. Br. at 17-18. While the Court finds that the text of the relevant provisions of the Patent Act's statutory scheme unambiguously requires Merck's interpretation of § 156(c), *see supra* Section IV.A.2, the underlying purpose of the Hatch-Waxman Act further confirms the appropriateness of that interpretation, and would resolve any ambiguity to the extent it exists.

Under traditional rules of statutory construction, a statute that "is remedial in nature … should be read broadly." *Wells Fargo & Co. v. United States*, 827 F.3d 1026, 1036 (Fed. Cir. 2016). The Federal Circuit has further recognized that "[i]n expounding a statute, we must not be guided by a single sentence or member of a sentence, but look to the provisions of the whole law, and to its object and policy." *Warner-Lambert Co. v. Apotex Corp.*, 316 F.3d 1348, 1355 (Fed. Cir. 2003) (internal quotation omitted). That is, the Court "considers not only the bare meaning of the words, but also their placement and purpose in the statutory scheme." *Superior Fireplace Co. v. Majestic Prod. Co.*, 270 F.3d 1358, 1369 (Fed. Cir. 2001) (brackets altered). Affirming that an interpretation conforms with a statute's purpose thus reflects fundamental principles of statutory interpretation. *See Thompson v. Cherokee Nation of Oklahoma*, 334 F.3d 1075, 1088 (Fed. Cir. 2003), *aff'd and remanded sub nom. Cherokee Nation of Oklahoma v. Leavitt*, 543 U.S. 631 (2005) (rejecting interpretation "directly contrary to the purpose of the" statute).

As an initial matter, the relevant provisions here are all remedial. *See In re Doyle*, 293 F.3d 1355, 1358 (Fed. Cir. 2002) (holding that § 251 "is remedial in nature, based on fundamental principles of equity and fairness, and should be construed liberally); *Slimfold Mfg. Co. v. Kinkead Indus., Inc.*, 810 F.2d 1113, 1117 (Fed. Cir. 1987) (holding § 252 is a "remedial statute having as

its sole purpose the correction of errors"); *Medicines Co. v. Kappos*, 731 F. Supp. 2d 470, 478 (E.D. Va. 2010) ("Section 156 provides a remedy: an extended patent term to offset the loss of effective patent life during the period of regulatory review of a new drug product."); *In re Patent No. 4,146,029* (Comm'r Pat. July 12, 1988) at 3 ("Since § 156 was intended to restore a part of the effective patent life ..., § 156 can be viewed as remedial in nature."). In fact, the Federal Circuit has offered express guidance about the expansive construction § 156 is owed: "The statute contemplates a patentee receiving time lost in its patent term by reason of FDA delay, and the statute should be liberally interpreted to achieve this end." *Kessler*, 80 F.3d at 1552 (describing § 156). This initial examination of the nature of these statutes thus confirms that Merck's interpretation—the only one to "liberally interpret[]" § 156 to achieve restoration for time lost to extensive FDA review—effectuates their remedial purposes. Nevertheless, given Defendants' objection to the remedial statutes' canon as the "last redoubt of losing causes," Def. Br. at 18 (quoting *Dir., Off. of Workers' Comp. Programs, Dep't of Labor v. Newport News Shipbuilding & Dry Dock Co.*, 514 U.S. 122, 135 (1995)), the Court turns to a deeper examination of the context of the Hatch-Waxman Act.

When Congress enacted § 156 as part of the Hatch-Waxman Act in 1984, it "established a balance whereby the patent term extension is offset by facilitating generic entry when the extended term expires, yet preserving the innovation incentive." *Pfizer Inc. v. Dr. Reddy's Labs., Ltd.*, 359 F.3d 1361, 1366 (Fed. Cir. 2004). For the generics, that entailed the "freedom from infringement during production and testing of generic counterparts intended to be sold after patent expiration" and "the right to rely on the patentee's data and approved uses to support approval of their generic counterparts." *Id.* at 1364; *see also Kessler*, 80 F.3d at 1546 (noting the Hatch-Waxman Act "eliminated the pre-1984 requirement that a company seeking to market a generic version of a

patented drug had to conduct its own testing program"). On the other hand, the Act entitled innovator patentees to "restoration of some of the time lost on patent life while the product is awaiting pre-market approval." *Pfizer Inc.*, 359 F.3d at 1366 (quoting H.R.Rep. No. 98–857 at 15 (1984)). This extension to innovator patentees was intended to "ameliorate[] the loss incurred when patent terms tick away while the patented product is awaiting [FDA's] regulatory approval for marketing." *Kessler*, 80 F.3d at 1547 (quoting *Unimed, Inc. v. Quigg*, 888 F.2d 826, 829 (Fed. Cir.1989)). Balanced with the loosening of certain restrictions on generics, patent term extension was thus established by Congress "in recognition of the lengthy procedures associated with regulatory review of a new drug product . . . in order to preserve the economic incentive for development of new therapeutic products." *PhotoCure Asa v. Kappos*, 603 F.3d 1372, 1374 (Fed. Cir. 2010).

Against this context, using the original issue date to calculate a patent term extension aligns with the balance Congress established. As noted, the Hatch-Waxman Act was intended to create predictable incentives for innovator drug companies to invest in the costly process of developing new drugs. *See Medicines Co.*, 731 F. Supp. 2d at 472 ("The purpose of the Act is to encourage drug manufacturers to assume the increased costs of research and development of certain products which are subject to pre-marketing clearance.") (internal quotation and bracket omitted); H.R.Rep. No.98-857 at 41 ("By extending patents for up to five years for products developed in the future … the Committee expects that research intensive companies will have the necessary incentive to increase their research and development activities."). Not only would using Defendants' proposed reissue date for PTE calculation greatly reduce the incentive Congress provided here, the unpredictable nature of such a scheme would also frustrate Congress' intent to provide a predictable and workable system upon which brand names, generics, and the public could rely. *See*

*Festo Corp.*, 535 U.S. at 739 (warning courts about "adopting changes that disrupt the settled expectations of the inventing community"); *cf. Pfizer, Inc.*, 359 F.3d at 1364 (noting "the legislation was 'designed to benefit makers of generic drugs, research-based pharmaceutical companies, and not incidentally the public.'") (quoting *Eli Lilly & Co. v. Medtronic, Inc.,* 496 U.S. 661, 672 (1990)); *see also* MacMillan Dep. Tr. 158:9-159:25, 160:3-10 (explaining reliance on original issue date for PTE calculations). Defendants correctly respond that "the Hatch-Waxman Act is not a statute that is merely in favor of the brand innovator" but "a statute that was adopted as [a] balance by Congress." Closing Tr. at 101:22-23. Yet, under the circumstances presented here, Defendants' interpretation would unduly disrupt that balance in their favor. Notably, Defendants have already received their benefit of this "bargain," *Pfizer Inc.*, 359 F.3d at 1366, namely "freedom from infringement during production and testing" and "the right to rely on the patentee's data and approved uses." *Id.* at 1364*; see also* Final Pretrial Order 3.B-I (detailing stipulations regarding Defendants' ANDAs). Merck, on the other hand, despite holding a patent that covered sugammadex since 2003—both as originally issued and reissued—would not be able to avail itself of the statutory guarantee of 5-years' restoration, despite nearly 12 years of FDA review for sugammadex. Defendants, in turn, have not pointed to anything about the "balance" of the Hatch-Waxman Act that supports curtailing the amount of patent life based solely on the timing of the date of reissue approval by the PTO.

Accordingly, the remedial nature of the relevant provisions of the Patent Act—particularly § 156—and the purpose of the Hatch-Waxman Act further support using the original issue date for purposes of calculating patent term extension, as required by the statutory language and scheme. *See Novartis AG v. Lee*, 740 F.3d 593, 601 (Fed. Cir. 2014) (affirming PTO interpretation because its "construction is supported by the statutory purpose and other aspects of the statutory structure").

**C. The Patent and Trademark Office's Policy and Deference**

Merck maintains that § 156, when properly read within the statutory scheme, unambiguously supports using the original issue date when calculating PTE. Nevertheless, to the extent any ambiguity exists, Merck argues in the alternative that it "can and should be resolved by deference to the PTO's well-reasoned and consistent treatment of reissued patents." Pl. Br. at 2. Specifically, Merck contends that "the evidence at trial demonstrated that PTO policy treats reissued patents as if they were originally granted in amended form in all respects, and that the PTO consistently followed this policy to calculate PTE for reissued patents." *Id*. at 20 (citing Trial Tr. 153:12-23, 156:15-157:1 (Burke); *id.* 184:11-20, 195:21-204:14 (Mojica)). This, in turn, warrants *Skidmore* deference in Merck's view. Pl. Br. at 20. Defendants dispute the existence of such a policy, its application to patent term extension calculations, and whether the PTO has consistently applied it. *See* Def. Br. at 20. As such, Defendants assert that "there is no basis to defer to the Patent Office, as its practice on this issue has been both unreasoned and inconsistent." *Id.*; *see also* Closing Tr. 88:14-15 (Defendants' counsel noting "at most there's a tiny amount of deference and I don't even think it gets there").

1. The Patent and Trademark Office's Policy and Practice

Before turning to deference, the Court addresses the parties' dispute about the existence and scope of the PTO's policy and practice concerning reissued patents. For the reasons discussed below, the Court finds that the PTO has a policy of treating reissued patents as if they had been originally granted in amended form for purposes relevant to the PTO's administration of the Patent Act. And the PTO has applied that policy when determining PTE for a reissued patent by consistently using the original patent's issue date. This policy and practice, in turn, further reinforces the interpretation which is required by the statute's language and is confirmed by its purpose.

The PTO's policy is generally established by the MPEP, which outlines PTO office procedure. *See Nebraska, Dept. of Health & Human Services v. U.S. Dept. of Health and Human Services*, 340 F. Supp. 2d 1, 21 (D.D.C. 2004) (noting documents presenting the agency's "fair and considered judgment … constitute authoritative departmental positions") (quotation omitted). The parties recognize the MPEP is the authoritative source of guidance for all the PTO's responsibilities, even if it lacks the force of law. Trial Tr. 122:8-11 (Burke); *id.* 190:14-16 (Mojica describing the MPEP as "our Bible" and "what all the patent office looks to for policy and procedure"). The MPEP provides, in its guidance concerning reissued patents: "With respect to the Office treatment of the reissued patent, the reissued patent will be viewed as if the original patent had been originally granted in the amended form provided by the reissue." MPEP § 1460 (interpreting 35 U.S.C. § 252). As Ms. Mojica explained at trial, this means that for all of the PTO's purposes, the reissued patent "steps into the shoes of the original patent and is as though anything that came out of that reissue was issued on the date that the original patent is issued." Trial Tr. 203:8-21 (Mojica).[11] Further, the MPEP directs examiners to treat the claims in a reissue application "as if they had the same effective filing date as the original patent" because "a reissue patent replaces the original patent, and thus is merely continuing the patent privilege of the original patent as opposed to being an independent (regular) patent with its own privilege (and its own term)." MPEP § 1440 (citing *Grant v. Raymond,* 31 U.S. 218, 214 (1832)); *see also* Tr. 197:6–199:2 (Mojica).

[11] Relatedly, Ms. Mojica testified that the PTO tracks the reissue date for "administrative" purposes, rather than for any substantive function. Trial Tr. 204:4–14. Merck suggested at trial that the PTO records the reissue date "so that in other contexts, perhaps outside the patent office, including intervening rights, that date can be used." Closing Tr. 67:16-17. As explained above, the reissue date is relevant to issues surrounding intervening rights, but, importantly, the PTO does not administer issues concerning these rights. *See* § 252; Closing Tr. 67:18-20.

This broad directive carries over to many areas within the PTO's purview, including, *inter alia*: the PTO's use of the original filing date to assess prior art (MPEP § 1440); the PTO "transfer[ring] over" the term of the original patent to the reissue patent (Trial Tr. 199:5-21 (Mojica referencing MPEP § 1405)); the PTO's understanding that a terminal disclaimer shortens the term of the original patent rather than creates a new term (MPEP § 1490); the PTO's use of the original issue date to calculate maintenance fees for reissued patents (MPEP § 1415.01); and the PTO's practice of transferring a PTE application filed on an original patent to a reissued patent if the reissue application was pending at the time the patentee files for PTE (MPEP § 2766). *See also* Trial Tr. 197:6-199:2 (Mojica testimony on § 1440); *id.* 200:21-24 (Mojica on terminal disclaimers); *id.* 202:19-25 (Mojica testimony on maintenance fees); *id.* 208:14-209:11 (Mojica testimony on § 2766); *id.* 172:3-173:4 (Burke testimony on transferring PTE application when pending reissue application is approved). In fact, Defendants could not identify any PTO policy guidance using the *reissue date* for any purpose, nor could their expert point to any experience from her time at the PTO when the reissue date was used for any reason. *See, e.g.*, *id.* 178:9-179:14 (Burke). And while the MPEP did not have a specific provision applying this overarching policy to reissued patents seeking term extension at the time Merck sought PTE,[12] that is understandable given the paucity of instances in which this issue arose relative to the PTO's overall responsibilities and other issues pertaining to reissued patents. *See* Closing Tr. 90:22-91:4 ("[T]he reason you have a regulation for maintenance fees but not PTE is explained by how often that issue comes up. There are tens of thousands of reissued patents. All of them have maintenance fees…. But when we're talking about PTE calculations for reissued patents, it's only a couple of dozen."); *see also* PTX-130 (summary of Ms. Mojica's 36 identifications); DTX-75 (summary of Dr. Burke's 4

[12] *But see infra* (explaining the MPEP was subsequently modified to reflect this policy).

identifications).

Further, although the Court finds the PTO has this policy based on the evidence submitted at trial, the Court notes that the PTO has since updated the MPEP to reflect its practice. *See* MPEP (Ninth Edition), § 2766 [R-07.2022], Processing of Patent Term Extension Applications When Reissue Has Been Filed ("With respect to calculating the amount of extension to which the reissued patent is entitled to receive, so long as the original patent claimed the approved product and the reissued patent claims the approved product, the original patent grant date would be used to calculate the extension to which the reissued patent would be entitled."). Relatedly, there was testimony at trial that § 2766 specifically operated to formalize "longstanding policy" of the PTO. Trial Tr. 208:14-209:11 (Mojica addressing prior version of § 2766).

Turning to the application of this policy, the Court also finds that the PTO has a consistent practice of applying this broad policy to PTE calculation for reissued patents. At trial, the parties presented 40 instances where a patent term extension was granted on a reissued patent since the 1980s. In 36 of these—or 90% of the time—the PTO used the original issue date for its calculation. *See supra* Section I.E.2. In the four remaining cases, neither the PTO nor the patentee would have had reason to challenge using the reissue date for various reasons. *See id.* (detailing circumstances of four exceptions, including that in two cases the choice of date for PTE had no effect on the amount of extension and in two the patentee ultimately elected PTE on another patent); *see also* Trial Tr. 217:3-22; PTX-130. These four instances thus appear to be outliers with unique circumstances that diminished the importance of the issuance date, rather than persuasive evidence of inconsistency. But even including those four outliers in the applicable data set, the overwhelming use of the reissue date demonstrates the overall consistency of the PTO's practice. *Cf. Fed. Exp. Corp. v. Holowecki,* 552 U.S. 389, 399-400 (2008) (rejecting a charge of

inconsistency even though "the agency's implementation of [its] policy has been uneven").[13]

Therefore, after considering (i) the language of the MPEP directing the PTO to treat the reissued patent "as if the original patent had been originally granted in the amended form provided by the reissue," MPEP § 1460 (citing 35 U.S.C. § 252), (ii) the other provisions in the MPEP applying this overarching policy to specific PTO functions, (iii) the lack of any guidance or practice by the PTO using the reissue date for any purpose, and (iv) the PTO's consistent use of the original issue date when calculating PTE for reissued patents, the Court finds that the PTO has a policy and practice that further reinforces the interpretation required by the statutory language and confirmed by the purpose of the Hatch-Waxman Act.

2. Deference

Having determined the PTO has a policy and practice of using the original issue date for patent term extensions of reissued patents, the Court turns to whether this practice warrants deference. Merck asserts, in the alternative to its principal argument focused on construction, that any ambiguity created by attempting to interpret § 156 in isolation should be resolved by deferring to "the PTO's consistent policies and practice regarding reissue patents generally and PTE calculations specifically." Pl. Br. at 20. Though the parties dispute whether deference is appropriate here, both agree that to the extent deference is available, it would be under the precepts of *Skidmore v. Swift & Co.*, 323 U.S. 134 (1944). *See* Def. Br. at 3; Closing Tr. 36:4-5. Defendants, however, contend that even *Skidmore* deference is not justified here because the PTO has been inconsistent in choosing between the original issue date and the reissue date when determining

[13] Dr. Burke attempted to distinguish 9 cases, reducing the relevant data set in her view to 31 total cases. *See supra* Section I.E.2, n.5. Assuming *arguendo* that these 9 cases should be discredited, the difference in consistency between using the original issue date in 27 out of 31 cases (87%) and 36 out of 40 cases (90%) is negligible. *See Holowecki*, 552 U.S. at 399-400.

PTE, and, moreover, has never thoroughly explained its rationale for that choice, to the extent it has made such a choice. Def. Br. at 20-25. As explained below, the Court finds that under *Skidmore*'s sliding scale rubric, deference to the PTO is appropriate.

To start, the Court agrees that insofar as deference to the PTO is warranted here, it would constitute *Skidmore* deference. *See Kessler*, 80 F.3d at 1550 (holding that PTO's final determinations about patent term extension are entitled to *Skidmore*, rather than *Chevron*, deference). Under *Skidmore*, courts may defer to an agency's practice based on "the thoroughness evident in [the agency's] consideration, the validity of its reasoning, [and] its consistency with earlier and later pronouncements." *United States v. Mead Corp.*, 533 U.S. 218, 228 (2001) (quoting *Skidmore*, 323 U.S. at 140); *see also Kessler*, 80 F.3d at 1550 (explaining *Skidmore* deference results from the agency's "basic power to persuade if lacking power to control").[14] The Federal Circuit has also held that an agency's "specialized experience" may factor into *Skidmore* deference. *Heartland By-Products, Inc., v. United States*, 264 F.3d 1126, 1135-36 (Fed. Cir. 2001). Further, courts have understood "the *Skidmore* framework as a 'sliding-scale' test in which the level of weight afforded to an interpretation varies depending on [the] analysis of the enumerated factors." *Hagans v. Commr. of Soc. Sec.*, 694 F.3d 287, 304 (3d Cir. 2012) (citing *Mead,* 553 U.S. at 228); *Cathedral Candle Co. v. U.S. Intern. Trade Commn.*, 400 F.3d 1352, 1365–66 (Fed. Cir.

[14] Defendants also appear to question the force of *Skidmore* deference, suggesting, based on caselaw from other circuits that *Skidmore* "is of limited value" and merely "a statement of the obvious." *Id*. at 22 n.6 (quoting *Moore v. Hannon Food Serv., Inc.*, 317 F.3d 489, 497 n.14 (5th Cir. 2003) and *Hydro Res., Inc. v. U.S. E.P.A.*, 608 F.3d 1131, 1146 n.10 (10th Cir. 2010) (en banc)). The Federal Circuit, however, has expressly rejected this view. *See Cathedral Candle Co. v. U.S. Intern. Trade Commn.*, 400 F.3d 1352, 1366 (Fed. Cir. 2005) ("We are confident that the [Supreme] Court did not mean for [*Skidmore*] to reduce to the proposition that 'we defer if we agree.' If that were the guiding principle, Skidmore deference would entail no deference at all."); *accord Hagans v. Commr. of Soc. Sec.*, 694 F.3d 287, 305 (3d Cir. 2012) (affirming agency interpretation even though that interpretation "may not be the interpretation we would adopt if we were to engage in an independent review").

2005) (explaining that, under *Skidmore*, courts adjust "the degree of deference depending on the circumstances"); Kristin E. Hickman & Matthew D. Krueger, *In Search of the Modern Skidmore Standard*, 107 COLUM. L. REV. 1235, 1272 (2007) (concluding "the appellate courts overwhelmingly follow the sliding-scale approach"); *see also* Closing Tr. at 88:12-15 (discussing *Skidmore's* sliding scale).

As to Defendants' initial argument about inconsistency, the Court reiterates that with the exception of four outliers, the PTO has always used the original issue date for purposes of patent term extensions for reissued patents. *See supra* Section IV.C.1. In any event, an agency's interpretation may be persuasive under *Skidmore* notwithstanding the existence of distinguishable conflicting rulings. *See Honda of America Mfg., Inc. v. U.S.,* 607 F.3d 771, 775 (Fed. Cir. 2010) ("Honda also claims that Customs' decision deserves less deference because it conflicts with previous rulings. . . . Those rulings are distinguishable."). And here, the four outlier examples are indeed distinguishable. *See supra* Sections I.E.2, IV.C.1. As discussed above, in two, the choice was inconsequential—either the original or the reissue date would have led to the same amount of term restoration. *See supra* Section I.E.2 (discussing RE'30,811 and RE'34,712). In the other two, the PTO never awarded PTE based on the date of reissue because the patentee ultimately chose to elect PTE on another patent. *Id.* (RE'42,072 and RE'43,691). In all four, then, the patentee had no reason to seek reconsideration and thus there was no occasion for the PTO to reexamine its decision. Moreover, in contrast with the Notice of Final Determination for the RE'733 Patent, the Notices for the four outliers failed to expressly note that the subject patent seeking extension was reissued. *See* Closing Tr. 70:6-71:3; *see also* DTX-4, DTX-8, DTX-9, DTX-10, JTX-3.1798. This is especially pertinent because the PTO's practice flows from its understanding of § 252, whereby reissued patents should be treated as originally granted in amended form. Consequently, that the

PTO did not expressly acknowledge the subject patent was reissued in the four outliers at least suggests the possibility that the policy may have been mistakenly overlooked rather than inconsistently applied. *See Holowecki,* 552 U.S. at 400 ("Some degree of inconsistent treatment is unavoidable…."); *see also Heartland By-Products, Inc.*, 264 F.3d at 1136 (affording *Skidmore* deference despite "the ruling's lack of consistency with an earlier pronouncement"). On the whole, the PTO's use of the original issue date in the overwhelming majority of instances across the last four decades, paired with the distinguishable nature of the limited outliers, shows "consistency with earlier and later pronouncements." *Skidmore*, 323 U.S. at 140.

Defendants argue that deference is still unwarranted even if the PTO acted consistently, because the PTO has never sufficiently explained its reasoning behind the application of its policy concerning patent term extensions for reissued patents. *See* Def. Br. at 22 (citing *Packard v. Pittsburgh Transp. Co.*, 418 F.3d 246, 253 (3d Cir. 2005) (rejecting deference to agency's legal conclusions that "provide[d] no reasoning or analysis that a court could properly find persuasive")). Merck responds that the PTO's reasoning flows from its broad policy concerning reissued patents set forth in MPEP § 1460, which "the Patent Office follows [] in every single aspect of its practice." Closing Tr. 109:19-20. Because the PTO always views the reissued patent "as if the original patent had been originally granted in the amended form provided by the reissue," MPEP § 1460), Merck contends there was no compelling reason for the PTO to further elaborate in the context of PTE for reissued patents.

While the persuasive power of an agency's order is diminished when a relevant agency order "sets forth no reasoning in support of its conclusion," Def. Br. at 22 (quoting *Fed. Nat'l Mortg. Ass'n v. United States*, 379 F.3d 1303, 1308–09 (Fed. Cir. 2004)), deference to an agency decision is warranted even if the decision "does not explain the reasoning behind the [agency's]

adoption of its interpretation," so long as the reasons for the policy "are not difficult to discern" and the agency "consistently applie[s] this policy." *Hagans*, 694 F.3d at 305 (applying "an appropriately high level of deference under *Skidmore*" where the Social Security Administration "consistently applied [its] policy during the past 20 years"). The Court has already addressed the PTO's consistent application of its policy. As to whether the reasons for the policy "are not difficult to discern," as in *Hagans*, the PTO has elsewhere explained in detail that the language of § 252 requires this broad treatment for all the PTO's purposes. *See* MPEP § 1460; *see also id.* § 1440 (reasoning that *Grant* requires the claims in a reissued patent to be treated "as if they had the same effective filing date as the original patent" because "a reissue patent replaces the original patent, and thus is merely continuing the patent privilege of the original patent as opposed to being an independent (regular) patent with its own privilege (and its own term)"). In fact, neither expert identified another function of the PTO in which it uses the reissue date, confirming the widespread application of this principle. *See, e.g.,* Trial Tr. 176:10-14, 178:9-13 (Burke); *id.* 204:4-14 (Mojica). The reasonableness of the PTO's interpretation and explanation are further supported by the broad, unqualified language of § 252 and the PTO's analysis of longstanding precedent, including *Grant* (§ 1440).

In sum, the PTO has set forth a reasoned consideration of the broader principle concerning reissue patents, *see, e.g.,* MPEP §§ 1440, 1460, and applied that principle to all areas of its responsibilities. When combined with the PTO's institutional expertise and consistent practice on the precise question at issue here, the Court concludes deference is warranted. Even if the reasoning offered by the SSA in *Hagans* may have been more narrowly tailored to the underlying issue, *see* Def. Reply Br. at 9, *Skidmore*'s sliding-scale approach directs the Court to adjust "the degree of deference depending on the circumstances," rather than reject deference altogether.

*Cathedral Candle Co.*, 400 F.3d at 1366. Consequently, if anything, the "high level of deference" given in *Hagans* might suggest a slight discount in the present circumstances. Nevertheless, because these factors combine to have the "power to persuade," *Mead*, 533 U.S. at 219, the PTO is entitled to at least a substantial level of deference, assuming *arguendo* the Court had found ambiguity in the statutory scheme.

Accordingly, the PTO's policy and practice not only reinforces the interpretation required by the statute's language, but, even if ambiguity were found to exist, that policy and practice would be afforded *Skidmore* deference to resolve the question of statutory interpretation in Merck's favor.

## V. CONCLUSION

For the foregoing reasons, the Court finds that the PTO correctly used the original issue date to calculate PTE for the RE'733 Patent. Therefore, the Court holds that no portion of the PTE for the RE'733 Patent is invalid. An appropriate Order accompanies this Opinion.

**Dated**: June 13, 2023

**CLAIRE C. CECCHI, U.S.D.J.**

JOINT TRIAL EXHIBIT
JTX-1

RE 8636405

# THE UNITED STATES OF AMERICA

TO ALL TO WHOM THESE PRESENTS SHALL COME:

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office

March 02, 2020

THIS IS TO CERTIFY THAT ANNEXED HERETO IS A TRUE COPY FROM THE RECORDS OF THIS OFFICE OF:

U.S. PATENT: *RE44,733*
ISSUE DATE: *January 28, 2014*

By Authority of the
Under Secretary of Commerce for Intellectual Property
and Director of the United States Patent and Trademark Office

SYLVIA HOLLEY
Certifying Officer

US00RE44733E

(19) **United States**

(12) **Reissued Patent**
**Zhang et al.**

(10) **Patent Number: US RE44,733 E**

(45) **Date of Reissued Patent: *Jan. 28, 2014**

(54) **6-MERCAPTO-CYCLODEXTRIN DERIVATIVES:REVERSAL AGENTS FOR DRUG-INDUCED NEUROMUSCULAR BLOCK**

(75) Inventors: **Mingiang Zhang**, Montreal (CA); **Ronald Palin**, Banton (GB); **Jonathan Bennett**, Edinburgh (GB)

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( * ) Notice: This patent is subject to a terminal disclaimer.

(21) Appl. No.: **13/432,742**

(22) Filed: **Mar. 28, 2012**

**Related U.S. Patent Documents**

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PCT Filed: **Nov. 23, 2000**
PCT No.: **PCT/EP00/11789**
§ 371 (c)(1),
(2), (4) Date: **Aug. 19, 2002**
PCT Pub. No.: **WO01/40316**
PCT Pub. Date: **Jun. 7, 2001**

U.S. Applications:

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| ***A61K 31/715*** | (2006.01) |
| ***A61K 31/537*** | (2006.01) |
| ***A61K 31/452*** | (2006.01) |
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| ***A61P 25/00*** | (2006.01) |
| ***C08B 37/16*** | (2006.01) |

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USPC ..... **514/58**; 514/231.5; 514/316; 514/547; 536/103

(58) **Field of Classification Search**
None
See application file for complete search history.

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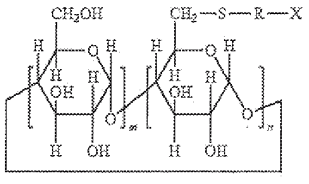
(57) **ABSTRACT**

Disclosed is a 6-mercapto-cyclodextrin derivative having general formula (I) wherein m is 0-7 and n is 1-8 and m+n=7 or 8; R is ($C_{1-6}$)alkylene, optionally substituated with 1-3 OH groups, or $(CH_2)_o$-phenylene-$(CH_2)_p$—; o and p are independently 0-4; X is COOH, $CONHR_1$, $NHCOR_2$, $SO_2OH$, $PO(OH)_2$, $O(CH_2—CH_2—O)_q—H$, OH or tetrazol-5-yl; $R_1$ is H or ($C_{1-3}$)alkyl; $R_2$ is carboxyphenyl; q is 1-3; or pharmaceutically acceptable salts thereof. The 6-mercaptocyclodextrin derivative is highly suitable for use in the reversal of drug-induced neuromuscular block.



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**21 Claims, No Drawings**

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# 6-MERCAPTO-CYCLODEXTRIN DERIVATIVES:REVERSAL AGENTS FOR DRUG-INDUCED NEUROMUSCULAR BLOCK

**Matter enclosed in heavy brackets [ ] appears in the original patent but forms no part of this reissue specification; matter printed in italics indicates the additions made by reissue.**

This is a National Stage filing under 35 USC 371 of PCT/EP00/11789, filed Nov. 23, 2000.

The invention relates to 6-mercapto-cyclodextrin derivatives, to their use for the preparation of a medicament for the reversal of drug-induced neuromuscular block, and to a kit for providing neuromuscular block and its reversal.

A neuromuscular blocking agent (NMBA, also called a muscle relaxant) is routinely used during the administration of anaesthesia to facilitate endotracheal intubation and to allow surgical access to body cavities, in particular the abdomen and thorax, without hindrance from voluntary or reflex muscle movement. NMBAs are also used in the care of critically-ill patients undergoing intensive therapy, to facilitate compliance with mechanical ventilation when sedation and analgesia alone have proved inadequate, and to prevent the violent muscle movements that are associated with electroconvulsive therapy treatment.

Based on their mechanisms of action, NMBAs are divided into two categories: depolarizing and non-depolarizing. Depolarizing neuromuscular blocking agents bind to nicotinic acetylcholine receptors (nAChRs) at the neuromuscular junction in a way similar to that of the endogenous neurotransmitter acetylcholine. They stimulate an initial opening of the ion channel, producing contractions known as fasciculations. However, since these drugs are broken down only relatively slowly by cholinesterase enzymes, compared to the very rapid hydrolysis of acetyl-choline by acetylcholinesterases, they bind for a much longer period than acetylcholine, causing persistent depolarization of the end-plate and hence a neuromuscular block. Succinylcholine (suxamethonium) is the best known example of a depolarizing NMBA.

Non-depolarizing neuromuscular blocking agents compete with acetylcholine for binding to muscle nAChRs, but unlike depolarizing NMBAs, they do not activate the channel. They block the activation of the channel by acetylcholine and hence prevent cell membrane depolarization, and as a result, the muscle will become flaccid. Most of the clinically-used NMBAs belong to the non-depolarizing category. These include tubocurarine, atracurium, (cis) atracurium, mivacurium, pancuronium, vecuronium, rocuronium and rapacuronium (Org 9487).

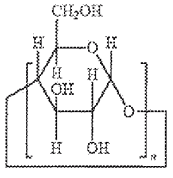
At the end of surgery or a period of intensive care, a reversal agent of NMBAs is often given to the patient to assist the recovery of muscle function. Most commonly used reversal agents are inhibitors of acetylcholinesterase (AChE), such as neostigmine, edrophonium and pyridostigmine. Because the mechanism of action of these drugs is to increase the level of acetylcholine at the neuromuscular junction by inhibiting the breakdown of acetylcholine, they are not suitable for reversal of depolarizing NMBAs such as succinylcholine. The use of AChE inhibitors as reversal agents leads to problems with selectivity, since neurotransmission to all synapses (both somatic and autonomic) involving the neurotransmitter acetylcholine is potentiated by these agents. This non-selectivity may lead to many side-effects due to the non-selective activation of muscarinic and nicotinic acetylcholine receptors, including bradycardia, hypotension, increased salivation, nausea, vomiting, abdominal cramps, diarrhoea and bronchoconstriction. Therefore in practice, these agents can be used only after or together with the administration of atropine (or glycopyrrolate) to antagonize the muscarinic effects of acetylcholine at the muscarinic receptors in the autonomic parasympathetic neuro-effector junctions (e.g. the heart). The use of a muscarinic acetylcholine receptor (mAChR) antagonist such as atropine causes a number of side-effects, e.g., tachycardia, dry mouth, blurred vision, difficulties in emptying the bladder and furthermore may affect cardiac conduction.



A further problem with anticholinesterase agents is that residual neuro-muscular activity must be present (>10% twitch activity) to allow the rapid recovery of neuromuscular function. Occasionally, either due to hyper-sensitivity of the patient or accidental overdose, administration of NMBAs can cause complete and prolonged block of neuromuscular function ("profound block"). At present, there is no reliable treatment to reverse such a 'profound block'. Attempts to overcome a 'profound block' with high doses of AChE inhibitors has the risk of inducing a "cholinergic crisis", resulting in a broad range of symptoms related to enhanced stimulation of nicotinic and muscarinic receptors.

In European Patent Application 99,306,411 (AKZO NOBEL N.V.) the use of chemical chelators (or sequestrants) as reversal agents has been disclosed. Chemical chelators capable of forming a guest-host complex for the manufacture of a medicament for the reversal of drug-induced neuromuscular block were described. The use of chemical chelators as reversal agents for NMBAs has the advantage that they are effective in reversing the action of both depolarizing and non-depolarizing NMBAs. Their use does not increase the level of acetylcholine and therefore they produce fewer side effects and none associated with the stimulation of muscarinic and nicotinic receptors seen with the AChE reversal agents. In addition, there is no need for the combined use of an AChE inhibitor and a mAChR antagonist (e.g., atropine), while the chemical chelators may further be safely employed for the reversal of 'profound block'. Examples of such chemical chelators, as disclosed in EP 99,306,411, were selected from various classes of, mostly cyclic, organic compounds which are known for their ability to form inclusion complexes with various organic compounds in aqueous solution, e.g. cyclic oligosaccharides, cyclophanes, cyclic peptides, calixarenes, crown ethers and aza crown ethers.

The cyclodextrins,



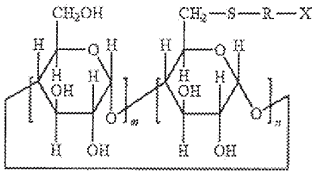

n = 6-9

a class of cyclic molecules containing six or more α-D-glucopyranose units linked at the 1,4 positions by α-linkages as in amylose, and derivatives thereof, were identified in EP 99306411 as particularly useful in the reversal of many of the commonly used neuromuscular blocking agents, or muscle relaxants, such as rocuronium, pancuronium, vecuronium,

rapacuronium, mivacurium, atracurium, (cis) atracurium, succinylcholine and tubocurarine.

It has now been found that 6-mercapto-cyclodextrin derivatives having the general formula I

Formula I



wherein m is 0-7 and n is 1-8 and m+n=7 or 8;

R is $(C_{1-6})$alkylene, optionally substituted with 1-3 OH groups, or $(CH_2)_o$-phenylene-$(CH_2)_p$—;

o and p are independently 0-4;

X is COOH, $CONHR_1$, $NHCOR_2$, $SO_2OH$, $PO(OH)_2$, $O(CH_2—CH_2—O)_q—H$, OH or tetrazol-5-yl;

$R_1$ is H or $(C_{1-3})$alkyl;

$R_2$ is carboxyphenyl;

q is 1-3;

or pharmaceutically acceptable salts thereof;

are highly active in vivo in the reversal of the action of neuromuscular blocking agents.

No protection per se is sought for the following 6-mercapto-cyclodextrin derivatives:

6-per-deoxy-6-per-(2-hydroxyethylthio)-β-cyclodextrin and

6-per-deoxy-6per-(2-hydroxyethylthio)-γ-cyclodextrin, which are described by Ling, C. and Darcy, R. (J. Chem. Soc. Chem Comm. 1993, (2), 203-205);

6-mono-deoxy-6-mono-(2-hydroxyethylthio)-β-cyclodextrin, which is disclosed by Fujita, K. et al. (Tetr. Letters 21, 1541-1544, 1980);

6-per-deoxy-6-per-(carboxymethylthio)-β-cyclodextrin, which is described by Guillo, F. et al. (Bull Chem. Soc. Chim. Fr. 132 (8), 857-866, 1995);

6-mono-deoxy-6-mono-(carboxymethylthio)-β-cyclodextrin, which is described by Akiie, T. et al. (Chem. Lett. 1994 (6), 1089-1092);

6A,6B-dideoxy-6A,6B-bis[(o-carboxyphenyl)thio}-β-cyclodextrin and 6A,6B-dideoxy-6A,6B-bis (carboxymethylthiol)-β-cyclodextrin, which are described by Tubashi, I. et al. (J. Am. Chem. Soc. 108, 4514-4518, 1986; and

6-per-deoxy-6-per-(2,3dihydroxypropylthio)-β-cyclodextrin, which is described by Baer, H. H. and Santoyo-González, F. (Carb. Res. 280, 315-321, 1996). These prior art 6-mercapto-cyclodextrin derivatives have been described in relation with different utilities in each instance.

However, the above mentioned prior art 6-mercapto-cyclodextrin derivatives do belong to the main aspect of the present invention which relates to the use of a 6-mercapto-cyclodextrin derivative according to the general formula I for the manufacture of a medicament for the reversal of drug-induced neuromuscular block.

In one embodiment the invention relates to 6-mercapto-cyclodextrin derivatives having the general formula I,

wherein m is 0-7 and n is 1-8 and m+n=7 or 8;

X is COOH, OH or $CONHCH_3$;

R is $(C_{1-6})$alkylene or $(CH_2)_o$-phenylene-$(CH_2)_p$;



o and p are independently 0-4; or a pharmaceutically acceptable salt thereof, with the exclusion of

6-per-deoxy-6-per-(2-hydroxyethylthio)-β-cyclodextrin;

6-mono-deoxy-6-mono-(2-hydroxyethylthio)-β-cyclodextrin;

6-per-deoxy-6-per-(2-hydroxyethylthio)-γ-cyclodextrin;

6-per-deoxy-6-per-(carboxymethylthio)-β-cyclodextrin;

6-mono-deoxy-6-mono-(carboxymethylthio)-β-cyclodextrin;

6A,6B-dideoxy-6A,6B-bis[(o-carboxyphenyl)thio]-β-cyclodextrin; and

6A,6B-dideoxy-6A,6B-bis(carboxymethylthiol)-β-cyclodextrin.

The term $(C_{1-6})$alkylene as used in the definition of formula I means a branched or straight chain bivalent carbon radical containing 1-6 carbon atoms, such as methylene, ethylene (1,2-ethandiyl), propylene (1-methyl-1,2-ethanediyl), 2-methyl-1,2-ethanediyl, 2,2-dimethyl-1,2-ethanediyl, 1,3-propanediyl, 1,4-butanediyl, 1,5-pentanediyl and 1,6-hexanediyl.

The term phenylene means a bivalent moiety the free valencies of which can be positioned either ortho, meta or para to one another.

The term $(C_{1-3})$alkyl means a branched or straight chain alkyl group containing 1-3 carbon atoms, i.e. methyl, ethyl, propyl and isopropyl.

The term carboxyphenyl means a phenyl group which is substituted at either the ortho-, the meta- or the para-position with a carboxy-group. The ortho-carboxyphenyl group is preferred.

Compounds according to formula I wherein n+m is 7 are derivatives of β-cyclodextrin, those wherein n+m is 8 are derived from γ-cyclodextrin.

Preferred are the 6-mercapto-cyclodextrin derivatives of formula I wherein X is COOH, or a pharmaceutically acceptable salt thereof.

More preferred are the 6-mercapto-γ-cyclodextrin derivatives of formula I wherein n is 8, R is $(C_{1-6})$alkylene and X is COOH.

Particularly preferred 6-mercapto-cyclodextrin derivatives of the invention are

6-per-deoxy-6-per-(2-carboxyethyl)thio-γ-cyclodextrin;

6-per-deoxy-6-per-(3-carboxypropyl)thio-γ-cyclodextrin;

6-per-deoxy-6-per-(4-carboxyphenyl)thio-γ-cyclodextrin;

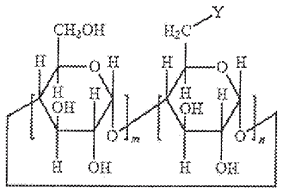
6-per-deoxy-6-per-(4-carboxyphenylmethyl)thio-γ-cyclodextrin;

6-per-deoxy-6-per-(2-carboxypropyl)thio-γ-cyclodextrin; and

6-per-deoxy-6-per-(2-sulfoethyl)thio-γ-cyclodextrin.

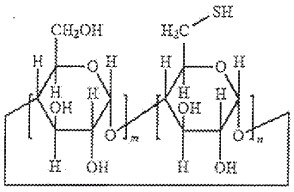
The 6-mercapto-cyclodextrin derivatives of formula I can be prepared by reacting a C6-activated cyclodextrin derivative of formula II with an alkylthiol, arylalkylthiol or arylthiol derivative corresponding to H—S—R—X, wherein R and X

have the meaning as previously defined, in the presence of an inorganic or organic base.



Formula TI wherein m is 0-7, n is 1-8, m+n=7 or 8 and Y is a leaving group which can be a halide (Cl, Br or I), sulfuric ester or a sulfonic ester function, such as a tosylate, a napthalenesulfonate or a triflate.

Conversely the 6-mercapto-cyclodextrin derivatives of formula I can also be prepared by reacting a 6-thiol γ- or β-cyclodextrin derivative of formula III with an alkylating agent, e.g., alkyl halide, arylalkyl halide, alkyl sulfonate, arylalkyl sulfonate, corresponding to Y—X—R, wherein Y, X and R have the meanings as previously defined, or with a double bond containing reagent, e.g., vinyl alkane, acrylate, etc., or an epoxide in the presence of an inorganic or organic base.



Formula III wherein m is 0-7, n is 1-8, m+n=7 or 8.

Alternative synthesis routes for the preparation of the 6-mercapto-cyclodextrin derivatives of the invention are known to the skilled person. The chemistry of the derivatisation of cyclodextrins is well documented (see for example: Comprehensive Supramolecular Chemistry, Volumes 1-11, Atwood J. L., Davies J. E. D., MacNicol D. D., Vogtle F., eds; Elsevier Science Ltd., Oxford, UK, 1996).

Pharmaceutically acceptable salts of 6-mercapto-cyclodextrin derivatives of formula I wherein X represents the carboxylic acid group COOH, the sulphonic acid group $SO_2OH$, the, phosphonic acid group $PO(OH)_2$ or the tetrazol-5-yl group, may be obtained by treating the acid with an organic base or a mineral base, like sodium-, potassium- or lithium hydroxide.

The 6-mercapto-cyclodextrin derivatives, or pharmaceutically acceptable salts or solvates thereof, for use in the invention are administered parenterally. The injection route can be intravenous, subcutaneous, intradermal, intramuscular, or intra-arterial. The intravenous route is the preferred one. The exact dose to be used will necessarily be dependent upon the needs of the individual subject to whom the medicament is being administered, the degree of muscular activity to be restored and the judgement of the anaesthetist/critical-care specialist. Exfracorporal application of the chemical chelators of the invention, for instance by mixing of the chemical chelator with the blood during dialysis or during plasmapheresis, is also contemplated.

In a further aspect the invention relates to a kit for providing neuromuscular block and its reversal comprising (a) a neuromuscular blocking agent, and (b) a 6mercapto-cyclodextrin derivative according to general formula I capable of forming a guest-host complex with the neuromuscular blocking agent. With a kit according to the invention is meant a formulation, which contains separate pharmaceutical preparations, i.e. the neuromuscular blocking agent and a 6-mercapto-cyclodextrin derivative of formula I, i.e. the reversal agent. The components of such a kit of parts are to be used sequentially, i.e. the neuromuscular blocking agent and a 6-mercapto-cyclodextrin derivative of formula I, i.e. the reversal agent. The components of such a kit of parts are to be used sequentially, i.e. the neuromuscular blocking agent is administered to a subject in need thereof, which is followed, at a point in time when restoration of muscle function is required, by the administration of the reversal agent, i.e. a 6-mercapto-cyclodextrin derivative of the present invention.

A preferred kit, according to the invention, contains a 6-mercapto-cyclodextrin derivative of formula I and a neuromuscular blocking agent which is selected from the group consisting of rocuronium, vecuronium, pancuronium, rapacuronium, mivacurium, atracurium, (cis)atracurium, tubocurarine and suxamethonium. A particularly preferred kit of the invention comprises rocuronium as the neuromuscular blocking agent.

Mixed with pharmaceutically suitable auxiliaries and pharmaceutically suitable liquids, e.g. as described in the standard reference, Gennaro et al., Remington's Pharmaceutical Sciences, (18th ed., Mack Publishing Company, 1990, Part 8: Pharmaceutical Preparations and Their Manufacture; see especially Chapter 84 on "Parenteral preparations", pp. 1545-1569; and Chapter 85 on "Intravenous admixtures", pp. 1570-1580) the 6-mercapto-cyclodextrin derivatives can be applied in the form of a solution, e.g. for use as an injection preparation.

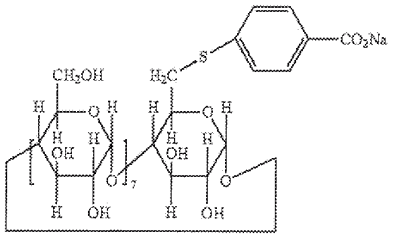
Alternatively, the pharmaceutical composition may be presented in unit-dose or multi-dose containers, for example sealed vials and ampoules, and may be stored in a freeze dried (lyophilised) condition requiring only the addition of the sterile liquid carrier, for example, water prior to use.

The invention further includes a pharmaceutical formulation, as hereinbefore described, in combination with packaging material suitable for said composition, said packaging material including instructions for the use of the composition for the use as hereinbefore described.

The invention is illustrated in the following examples.

## EXAMPLE 1

6-mono-Deoxy-6-mono-(4-carboxyphenyl)thio-γ-cyclodextrin, Sodium Salt



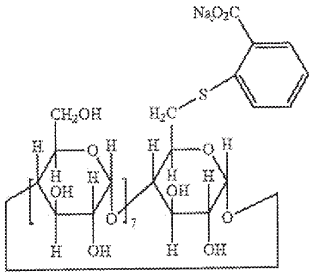
To a round bottom flask containing pyridine (120 ml) was added dry γ-cyclodextrin (2.0 g, 1.54 mmol) under nitrogen at

room temperature. After dissolution, 2-napthalenesulfonyl chloride (1.05 g, 4.64 mmol) in pyridine (20 ml) was added and the mixture stirred for 24 h. Quenched with water (50 ml) and evaporated to dryness to leave crude 6-mono-O-(2'-naphthalenesulfonyl)-γ-cyclodextrin.

Sodium hydride (0.38 g, 15.83 mmol) was suspended in dry dimethylformamide (20 ml). 4-Mercaptobenzoic acid (0.7 g, 4.55 mmol) was then added to the suspension and the resulting mixture was stirred for 20 minutes. γ-Cyclodextrin nosylate (3.2 g, 2.12 mmol) was added to the mixture and the reaction was heated to 100° C. for 90 minutes. After cooling, acetone was added to precipitate a solid, which was reprecipitated from water/acetone. This was then dissolved in water (20 ml), pH adjusted to 7.0 by adding 2N hydrochloric acid, then chromatographed on a Sephadex DEAE A-25 column. Appropriate fractions were combined, dialysed, then precipitated, twice from water/acetone to give 400 mg of the titled compound. $^1$H NMR in DMSO δ 7.4 to 7.8 (ArH), 5.0 to 5.2 (8H), 4.13 (1H), 3.7 to 4.0 (29H), 3.7 to 3.4 (17H), 3.25 (1H) ppm. $^{13}$C NMR in DMSO δ 129.9 and 127.5 (ArC), 103.3 and 102.9 (C1 and C1'), 85.0 (C4'), 81.6 (C4), 73.8 (C3), 73.5 (C2), 72.2 (C5), 70.8 (C5'), 60.6 (C6), 34.3 (C6') ppm. Electrospray MS $[M+H]^+$=1455.7 and $[M+Na]^+$ =1477.7.

## EXAMPLE 2

6mono-Deoxy-6-mono-(2-carboxyphenyl)thio-γ-cyclodextin, Sodium Salt

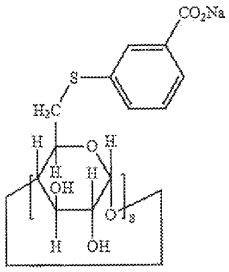


Sodium hydride (60% dispersed in oil, 0.18 g, 4.5 mmol) was added to thiosalicylic acid (0.34 g, 2.2 mmol) in DMF (25 ml) in one portion and stirred at room temperature for 30 min. To this was then added the crude solution of 6-mono-O-(2'-naphthalenesulfonyl)-γ-cyclodextrin (2.5 g, 1.45 mmol) in DMF (15 ml) and heated to 70° C. for 24 h. The mixture was cooled and quenched with water (20 ml) before evaporating to dryness. Water was then added to the residue and the resulting solution was poured into acetone (250 ml) to effect precipitation. The resulting solid was collected by filtration and dissolved in water (10 ml) before passing through a Sephadex DEAE A-25 column eluting with water then 0.2 N NaOH. Fractions containing the product were combined and evaporated to a low volume and dialysed (MWCO 1000) by changing the external water four times. Internal solution was evaporated to low volume and poured into acetone (100 ml). Solid was collected by filtration and dried under vacuum at 70° C. to leave the title compound (235 mg) as a white solid. $^1$H NMR ($D_2O$) δ 7.50-7.10 (4H, m, Ar—H), 5.14 (8H, m, CyD 1-H), 4.16 (1H, m, CyD 5-H), 3.98-3.85 (26H, m, CyD 3,5, 2,4-H), 3.70-3.61 (20H, m, CyD 2,3,4,6-H), 3.15 (1H, m, CyD 6-H) ppm; Electrospray MS m/z 1477.6 for $[M+Na]^+$, calcd for $C_{55}H_{83}NaO_{41}S$ M 1455.304.



## EXAMPLE 3

6-Per-deoxy-6-per-(3-carboxyphenyl)thio-γ-cyclodextrin, Sodium Salt

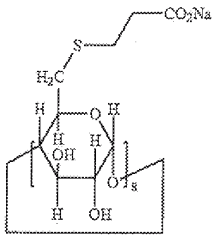


Triphenylphosphine (30.1 g, 15 eq) was dissolved with stirring in dry DMF (160 ml). To this was added iodine (30.5 g, 15.6 eq) over 10 min. with heat evolved. Dry γ-cyclodextrin (10 g, 7.7 mmol) was then added and the mixture was heated to 70° C. for 24 h. The mixture was allowed to cool, to which sodium methoxide (3.1 g sodium in 50 ml methanol) was added and the mixture was stirred for 30 min, before pouring onto methanol (800 ml) and evaporating to dryness. To the residue was added water (500 ml) and the solid was collected by filtration and washed with water (3×100 ml), then acetone (3×100 ml), and dried under vacuum at 70° C. to give 6-per-deoxy-6-per-iodo-γ-cyclodextrin as a yellow solid (16.2 g) which was used without further purification.

To a solution of 3-mercaptobenzoic acid (1.0 g, 10 eq) in DMF (30 ml) was added 60% sodium hydride dispersed in oil (476 mg, 22 eq) portionwise over 30 min. The mixture was cooled and 6-per-deoxy-6-per-iodo-γ-cyclodextrin (1.4 g) in DMF (30 ml) was added. The mixture was then stirred at 70° C. for 24 h. The mixture was allowed to cool to room temperature and quenched with the addition of water (20 ml) before evaporating to a low volume. The solution was poured into acetone (500 ml) and the precipitate was collected by filtration, dissolved in water (20 ml) and dialysed (MWCO 1000) by changing the external water four times. Internal solution was evaporated to low volume and poured into acetone (250 ml). The solid precipitate was collected by filtration and dried under vacuum at 70° C. to afford the title compound (1.45 g) as a white solid: $^1$H NMR ($D_2O$) δ 7.77 (8H, br s, Ar—H), 7.55 (8H, d, J=6.0 Hz, Ar—H), 7.71 (16H, m, Ar—H), 5.16 (8H, s, CyD 1-H), 4.00-3.94 (16H, m, CyD 3,5-H), 3.58-3.53 (16H, m, CyD 4,2-H), 3.43-3.40 (8H, m, CyD 6-H), 3.24-3.20 (8H, m, CyD 6-H); Electrospray m/z 1190.6 for $[M-8Na+6H]^{2-}$, calcd for $C_{104}H_{104}Na_8O_{48}S_8$ M 2562.39.

EXAMPLE 4

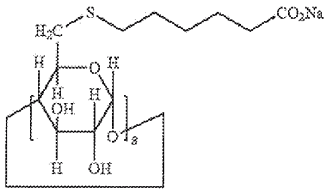
6-Per-deoxy-6-per-(2-carboxyethyl)thio-γ-cyclodextrin, Sodium Salt



3-Mercaptopropionic acid (1.22 ml, 14.0 mmol) was dissolved in dry DMF (45 ml) under $N_2$ at room temperature. To this solution was added in three portions sodium hydride (1.23 g, 30.8 mmol, 60%) and the mixture was stirred for a further 30 min. To this mixture was then added dropwise a solution of 6-per-deoxy6-per-iodo-γ-cyclodextrin (3.12 g, 1.40 mmol) in 45 ml dry DMF. After addition, the reaction mixture was heated at 70° C. for 12 h. After cooling, water (10 ml) was added to the mixture and the volume was reduced to 40 ml in vacuo, to which ethanol (250 ml) was added resulting in precipitation. The solid precipitate was collected by filtration and dialysed for 36 h. The volume was then reduced to 20 ml in vacuo. To this was added ethanol, and the precipitate was collected by filtration and dried to give the title compound as a white solid (1.3 g, 43%). $^1$H-NMR $D_2O$ δ 2.47-2.51 (m, 16H); 2.84-2.88 (m, 16H); 3.00-3.02 (t, 8H); 3.11-3.14 (t, 8H); 3.62-3.68 (m, 16H); 3.92-3.97 (m, 8H); 4.04-4.06 (m, 8H); 5.19 (m, 8H) ppm. MS FIA +ion at 2024.9 m/z.

EXAMPLE 5

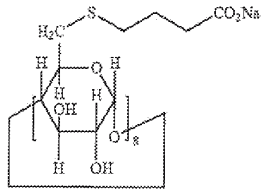
6-Per-deoxy-6-per-(5-carboxypentyl)thio-γ-cyclodextrin, Sodium Salt



The title compound was prepared in a similar way as described for Example 4 by reacting 6-mercaptohexanoic acid (1.34 g, 0.90 mmol) with 6-per-deoxy-6-per-iodo-γ-cyclodextrin. $^1$H-NMR $D_2O$ δ 1.40 (s, 16H); 1.57-1.64 (m, 32H); 2.17-2.21 (m, 16H); 2.67-3.00 (m, 16H); 2.85-2.90 (m, 8H); 3.15-3.20 (m, 8H); 3.52-3.59 (m, 8H); 3.60-3.63 (m, 8H); 3.87-3.93 (m, 16H); 5.16 (s, 8H) ppm. MS FIA +ions at 2362.2, 2213, 2065 and 1919 m/z.

EXAMPLE 6

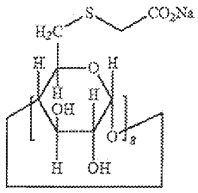
6-Per-deoxy-6-per-(3carboxypropyl)thio-γ-cyclodextrin, Sodium Salt



The title compound was prepared in a similar way as described for Example 4 by reacting 4-mercaptobutyric acid (1.10 g, 0.009 mol) with 6-per-deoxy-6-per-iodo-γ-cyclodextrin. $^1$H-NMR $D_2O$ δ 1.87-1.88 (m, 16H); 2.27-2.30 (m, 16H); 2.67-2.71 (m, 16H); 2.98-3.00 (m, 8H); 3.13-3.16 (m, 8H); 3.61-3.63 (m, 16H); 3.94-4.03 (m, 16H); 5.21 (s, 8H) ppm. MS FIA +ion at 2138.8 m/z.

EXAMPLE 7

6-Per-deoxy-6-per-carboxymethylthio-γ-cyclodextrin, Sodium Salt



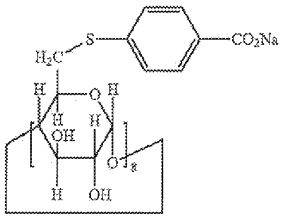
Sodium hydride (60% dispersion, 0.34 g, 8.60 mmol) was added to a stirred solution of ethyl 2-mercaptoacetate (0.92 ml, 8.40 mmol) in DMF (20 ml) under nitrogen at room temperature. After effervescence had ceased (15 min), per-6-deoxy-per-6-iodo-γ-cyclodextrin (2.17 g, 1.00 mmol) was added to the system. After a further 5 min, the temperature was raised to 70° C. and the reaction was left with stirring for 17 h. After cooling, DMF was removed in vacuo. Methanol (50 ml) was added and a creamy white solid slowly crystallised out of solution. This was filtered off under suction, washed with methanol and dried to give 6-per-deoxy-6-per-carbethoxymethylthio-γ-cyclodextrin as a solid (1.74 g, 82%). $\delta_H$ (d6-dmso) 4.95-4.85 (8H, m, 8×anomeric CH), 4.05 (16H, q, 8×$CH_2CH_3$), 3.85-3.75 (8H, m), 3.60-3.50 (8H, m), 3.40-3.20 (32H, bs, 8×$CH_2SCH_2$), 3.20-3.10 (8H, m), 2.95-2.85 (8H, m), 1.20 (24H, t, 8×$CH_2CH_3$).

To 1 M solution of sodium hydroxide (7 ml) was added 6-per-deoxy-6-per-carbethoxymethylthio-γ-cyclodextrin (1.00 g, 0.47 mmol) and the reaction was allowed to stir at room temperature. After 18 h, the clear solution was dialysed for 8 h, with water (2 L) being replaced every 2 h. After this time, the contents of the dialysis tubing was emptied into a flask and water evaporated in vacuo, giving the title com-

pound as a white solid (0.62 g, 64%). $\delta_H$ ($D_2O$) 5.21 (8H, d, 8×anomeric CH), 4.18-4.05 (8H, m), 4.00 (8H, dd), 3.78 (8H, dd), 3.70 (8H, $\overline{dd}$), 3.40 (16H, dd), 3.20 (8H, d), 3.02 (8H, dd). $\delta_C$ ($D_2O$) 178.1, 101.6, 82.8, 73.0, 72.7, 71.8, 39.0, 34.1 LC/MS TOF 1889 m/z.

EXAMPLE 8

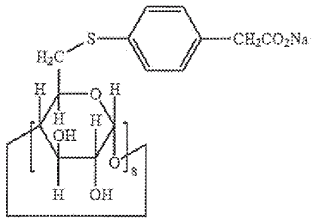
6-Per-deoxy-6-per-(4-carboxyphenyl)thio-γ-cyclodextrin, Sodium Salt



To a solution of 4-mercaptobenzoic acid (856 mg) in DMF (30 ml) was added 60% sodium hydride dispersed in oil (372 mg) portionwise over 30 min. The mixture was cooled and per-6-deoxy-per-6-bromo-γ-cyclodextrin (1.0 g) was added in one portion and the mixture was stirred at 70° C. for 24 h. The mixture was allowed to cool to room temperature and quenched with the addition of water (20 ml) before evaporating to a low volume. The solution was poured into ethanol (250 ml) and the precipitate was collected by filtration, dissolved in water (20 ml) and dialysed (MWCO 1000) by changing the external water four times. Internal solution was evaporated to low volume and poured into acetone (250 ml). The solid precipitate was collected by filtration and dried under vacuum at 70° C. to afford the title compound (1.2 g) as a white solid. $^1$H NMR ($D_2O$, 343K) δ 7.70 (16H, d, J=8.1 Hz, Ar—H), 7.23 (16H, d, J=7.3 Hz, Ar—H), 5.15 (8H, s, CyD 1-H), 4.00-3.96 (16H, m, CyD 3,5-H), 3.55-3.53 (24H, m, CyD 6',4,2-H), 3.15 (8H, m, CyD 6-H); MALDI-TOF m/z 2383.7 for [M–$Na_8$+$H_6$], calcd for $C_{104}H_{104}Na_8O_{48}S_8$ M 2562.39.

EXAMPLE 9

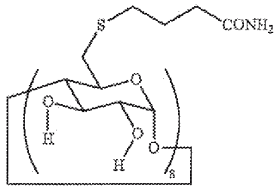
6-Per-deoxy-6-per-(4-carboxymethylphenyl)thio-γ-cyclodextrin, Sodium Salt



To a solution of 4-mercaptophenylacetic acid (10 eq) in DMF (50 ml) was added 60% sodium hydride in oil (22 eq) portionwise over 30 min. The mixture was cooled and per-6-deoxy-per-6-bromo-γ-cyclodextrin (1.0 g) was added in one portion and the mixture was stirred at 70° C. for 24 h. The mixture was allowed to cool to room temperature and quenched with the addition of water (20 ml) before evaporating to a low volume. The solution was then poured into acetone (250 ml) and the precipitate was collected by filtration, suspended in water (20 ml) and dialysed (MWCO 1000) by changing the external water four times. Internal solution was evaporated to low volume and poured into acetone (250 ml). The solid precipitate was collected by filtration and dried under vacuum at 70° C. to afford the title compound (1.44 g) as a white solid. $^1$HNMR ($D_2O$, 343K) δ 7.15 (16H, d, J=8.0 Hz, Ar—H), 6.99 (16H, d, J=8.0 Hz, Ar—H), 4.98 (8H, s, CyD 1-H), 3.90-3.72 (16H, m, CyD 3,5-H), 3.51-3.43 (16H, m, CyD 4,2-H), 3.28 (24H, m, $CH_2$—Ar, CyD 6'-H), 3.15-3.10 (1H, m, CyD 6-H); MALDI-TOF m/z 2495.8 for [M–$Na_8$+$H_6$], calcd for $C_{112}H_{120}Na_8O_{48}S_8$ M 2674.6.

EXAMPLE 10

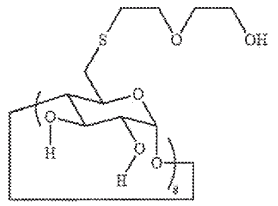
6-Per-deoxy-6-per(3-amidopropyl)thio-γ-cyclodextrin



To a mixture of 6-per-deoxy-6-per-thio-γ-cyclodextrin (500 mg; prepared as described in Example 17) and potassium iodide (5 mg) in DMF (10 ml) was added 4-chlorobutamide (673 mg; Fries et. al. Biochemistry 1975, 14, 5233). Caesium carbonate (1.8 g) was added and the reaction mixture was heated to 60° C. overnight. The resulting mixture was poured into acetone, filtered, washed with ethanol and water and then dried in-vacuo (118 mg; 16.2%). $^1$H NMR (DMSO/$D_2O$) δ 4.9 (1H, s), 3.8 (1H, m), 3.6 (1H, m), 3.4 (2H, m), 3.05 (1H, m), 2.85 (1H, m), 2.2 (2H, m), 1.75 (2H, m). Electrospray Mass Spectrum M–H (m/z) 2105.

EXAMPLE 11

6-Per-deoxy-6-per(5-hydroxy-3-oxa-pentyl)thio-γ-cyclodextrin



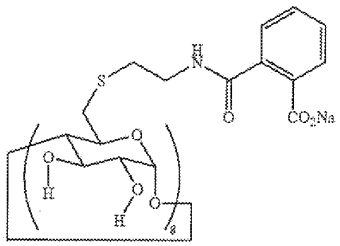
2-(2-Mercaptoethoxy)ethanol (1.4 g, 11.6 mmol) was dissolved in DMF (20 ml) and stirring commenced at room temperature under a nitrogen atmosphere. Per-6-bromo-γ-cyclodextrin (2 g, 1.12 mmol) and caesium carbonate (3.2 g,

9.86 mmol) were then added and the resultant suspension stirred at 60° C. overnight under a nitrogen atmosphere. After cooling to room temperature the suspension was poured into acetone (200 ml) and the insoluble material isolated by filtration, washed with acetone (×3) and dried in vacuo. The crude product was dissolved in de-ionised water (20 ml) and dialysed (10 h). The contents of the dialysis membrane were then concentrated in vacuo to yield 1 g of the desired product as a cream solid.

$^1$H NMR ($D_2O$, 400 MHz): δ 2.81-3.00 (m, 24H), 3.21-3.31 (d, 8H), 3.49 (t, 8H), 3.55-3.75 (m, 56H), 3.82 (t, 8H), 3.89 (t, 8H), 5.11 (d, 8H). ESI-MS: 2175 $(M-H)^-$.

EXAMPLE 12

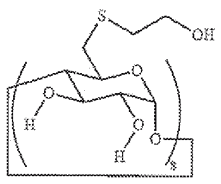
6-Per-deoxy-6-per[(2(2-carboxybenzoyl)amino) ethyl]thio-γ-cyclodextrin, Sodium Salt



Per-6-mercapto-γ-cyclodextrin (1 g, 0.7 mmol; see example 17) was dissolved in DMF (10 ml) and stirring commenced at room temperature under a nitrogen atmosphere. N-(2-Bromoethyl)phthalimide (1.57 g, 6.17 mmol) and caesium carbonate (2 g, 6.17 mmol) were added and the resultant suspension was stirred at 60° C. overnight under a nitrogen atmosphere. After cooling to room temperature the DMF was removed in vacuo and water (100 ml) was added with vigorous stirring. The precipitate was isolated by filtration, washed with water (×3) and dried in vacuo to yield 1.67 g of a cream solid. Aqueous sodium hydroxide (1M, 20 ml) was then added to the crude product (600 mg) and the resultant solution stirred at room temperature overnight under a nitrogen atmosphere. The solution was then dialysed with de-ionised water until constant pH and the contents of the dialysis membrane dried in vacuo to yield 500 mg of the desired product as a glassy solid. $^1$H NMR ($D_2O$, 400 MHz): δ 2.76-2.96 (m, 24H), 3.10-3.30 (m, 8H), 3.35-3.62 (m, 32H), 3.78-3.95 (m, 16H), 5.02 (d, 8H), 7.30-7.62 (m, 32H); ESI-MS: 1477 $(M-2H)^{2-}$.

EXAMPLE 13

6-Per-deoxy-6-per(2-hydroxyethyl)thio-γ-cyclodextrin



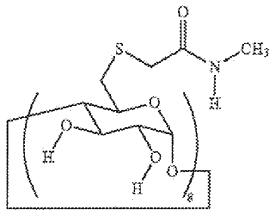
To a stirred solution of 2-mercaptoethanol (10.85 g, 10 eq) in DMF (500 ml) under nitrogen was added 60% sodium hydride dispersed in oil (11.7 g, 21 eq) portion-wise over 30 min. The mixture was stirred at room temperature for 90 minutes. Per-6-deoxy-6-per-bromo-γ-cyclodextrin (25.0 g) was added and the mixture heated to 70° C. for 24 h. The mixture was allowed to cool to room temperature and quenched by addition of water (50 ml) before evaporating to a low volume. The residue was taken up in water (100 ml) and poured onto 1:1 methanol/acetone (500 ml). The solid formed was collected by filtration, dissolved in water (500 ml) and dialysed (MWCO 1000) changing the external water four times. The internal solution was evaporated to low volume and then re-crystallised from hot water to afford the title compound (8.5 g) as white cross-shaped crystals.

$^1$H NMR (400 MHz; DMSO) δ 5.91 (16H, br s, 2,3-OH), 4.92 (8H, s, 1-H), 4.71 (8H, t, J 4.4 Hz, $SCH_2CH_2OH$), 3.75 [8H, t, J 8.0 Hz, 3-H (or 5-H)], 3.60-3.50 [24H, m, 5-H (or 3-H), $SCH_2CH_2OH$], 3.40-3.30 (16H, m, 4-H, 2-H), 3.08 (8H, d, J 13.6 Hz, 6-H), 2.82 (8H, dd, J 13.6, 6.8 Hz, 6-H), 2.66 (16H, t, J 6.8 Hz, $SCH_2CH_2OH$); m/z (electrospray) 1775.4 for $[M-H]^-$, calcd for $C_{64}H_{112}S_8O_{40}$ M 1776.45.

The preparation of this compound by a similar method has been published previously: J. Chem. Soc., Chem. Commun., 203 (1993).

EXAMPLE 14

6-Per-deoxy-6-per(N-methylamidomethyl)thio-γ-cyclodextrin



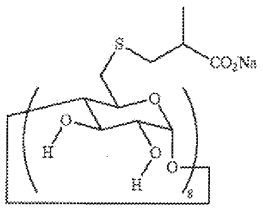
To a stirred solution of N-methylmercaptoacetamide (0.58 g, 10 eq) in DMF (30 ml) under nitrogen was added 60% sodium hydride dispersed in oil (0.22 g, 10 eq) portion-wise over 30 min. The mixture was stirred at room temperature for 30 minutes. Per-6-deoxy-6-per-bromo-γ-cyclodextrin (1.0 g) was added and the mixture heated to 60-70° C. for 48 h. The mixture was allowed to cool to room temperature and quenched by addition of water (20 ml) before evaporating to a low volume. The residual solution was poured onto ethanol (100 ml). The solid formed was collected by filtration, dissolved in water (200 ml) and dialysed (MWCO 1000), changing the external water four times. The internal solution was evaporated to low volume and poured onto ethanol (100 ml). The precipitate was collected by filtration and dried under vacuum to afford the title compound (0.55 g) as a white solid.

$^1$H NMR (400 MHz; $D_2O$) δ 5.29 (8H, d, J 4.0 Hz, 1-H), 4.10 (8H, br t, J 9.6 Hz, 5-H), 4.05 (8H, t, J 9.8 Hz, 3-H), 3.83 (8H, dd, J 10.0, 3.6 Hz, 2-H), 3.74 (8H, t, J 9.2 Hz, 4-H), 3.58-3.49 [16H, AB system, $SCH_2C(O)NHCH_3$], 3.36 (8H, br d, J 12.8 Hz, 6-H), 3.07 (8H, dd, J 14.0, 8.4 Hz, 6-H), 2.94

(24H, s, $SCH_2C(O)NHCH_3$); m/z (electrospray) 1991.7 for $[M-H]^-$, calculated for $C_{72}H_{120}N_8S_8O_{40}$ M 1992.54.

EXAMPLE 15

6-Per-deoxy-6-per(2-carboxypropyl)thio-γ-cyclodextrin, Sodium Salt



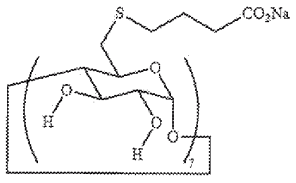
Sodium hydride (60% in oil) (0.44 g) was added to methyl 3-mercapto-2-methyl-propionate (1.474 g; J. Med. Chem., 1994, 1159) in dimethylformamide (25 ml). After 30 minutes per-6-deoxy-per-6-bromo-γ-cyclodextrin (2.25 g), dissolved in dimethylformamide (25 ml), was added. A crystal of sodium iodide was added and the mixture heated at 75° C. overnight. The solvent was distilled off and the residue crystallised from methanol to give the methyl ester (1.3 g). Mass spec. (M−H) 2224;

$^1$H NMR (dmso $D_6$): δ 1.41 (d, 24H), 2.68 (m, 16H), 2.80 (m, 16H), 3.00 (m, 8H), 3.61 (3, 24H), 3.79 (m, 8H), 4.95 (s, 8H).

This product was then stirred overnight with sodium hydroxide solution (M, 13 ml). The resulting mixture was filtered, dialysed to neutrality, and evaporated to dryness to give the title compound (1.13 g). Mass spec. (M−H) 2112; $^1$H NMR (D2O): δ 1.15 (d, 24H), 2.5 (m, 8H), 2.65 (m, 8H), 2.8-3.1 (m, 24H), 3.65 (16H), 4.0 (m, 16H), 5.2 (s, 8H).

EXAMPLE 16

6-Per-deoxy-6-per(3-carboxypropyl)thio-β-cyclodextrin, Sodium Salt



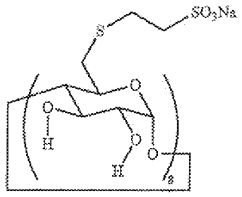
Per-6-deoxy-per-6-bromo-β-cyclodextrin (2.25 g), methyl-4-mercaptobutyrate (1.7 g; Tetrahedron 1998, 2652), cesium carbonate (4.24 g) and dimethylformamide (25 ml) were stirred and heated together for three days. The mixture was cooled, poured into water and filtered. The solid was washed with methanol and dried (2.1 g). This was stirred overnight with sodium hydroxide solution (M, 21 ml), filtered and the filtrate dialysed to neutrality. This was evaporated to dryness giving the title compound (1.7 g). Mass Spec. (M−H)



1848.8. $^1$H NMR ($D_2O$): δ 1.75 (m, 16H), 2.15 (m, 16H), 2.6 (m, 16H), 2.85 (m, 8H), 3.05 (m, 8H), 3.55 (m, 16H) 3.87 (m, 16H), 5.07 (s, 8H).

EXAMPLE 17

6-Per-deoxy-6-per(2-sulfoethyl)thio-γ-cyclodextrin, Sodium Salt



A: Per-6-deoxy-per-6-thio-γ-cyclodextrin

Per-6-deoxy-per-6-bromo-γ-cyclodextrin (20 g), thiourea (13.5 g) and dimethylformamide (100 ml) were heated together for three days at 65° C. and then ethanolamine (20 ml) was added and heating continued for two hours. The mixture was cooled, diluted with ice water and the product separated by centrifuge. The solid was washed twice with water and dried in vacuum at 65° C. giving the thiol (7.34 g).

Mass spec. (M−H) 1424. $^1$H NMR (dmso $D_6$): δ 2.82 (m, 8H), 3.20 (d, 8H), 3.35 (m, 16H), 6.65 (t, 8H), 7.75 (t, 8H), 5.0 (s, 8H).

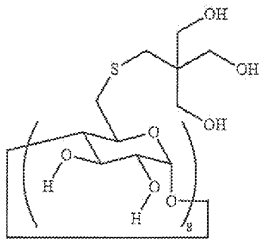
B: 6-Per-deoxy-6-per(2-sulfoethyl)thio-γ-cyclodextrin, Sodium Salt

The above per-thiol (1 g), 2-bromoethane sulphonic acid sodium salt (1.42 g), cesium carbonate (2.2 g) and dimethylformamide (10 ml) were stirred and heated overnight at 64° C. Most of the solvent was evaporated under vacuum and the residue dissolved in water. Sodium bicarbonate solution (5% w/w, 5 ml) was added and the solution dialysed three times with water. This solution was evaporated to dryness and the residue dissolved in sodium bicarbonate solution (10 ml), dialysed and evaporated as before. This process was repeated, the resulting solid was dissolved in a small volume of water and the product precipitated with methanol. This was dissolved in water and evaporated to dryness giving the title compound (1.18 g).

$^1$H NMR ($D_2O$): δ 3.9 (m, 24H), 3.2 (m, 24H), 3.55-3.65 (m, 16H), 3.9 (m, 8H), 4.05 (m, 8H), 5.15 (s, 8H).

EXAMPLE 18

6-Per-deoxy-6-per(2,2-di(hydroxymethyl)-3-hydroxy-propyl)thio-γ-cyclodextin

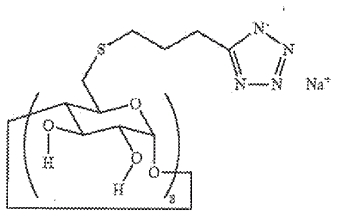


Per-6-deoxy-per-6-thio-γ-cyclodextrin (500 mg; Example 17), 3-bromo-2,2-dihydroxy-methylpropanol (670 mg), cesium carbonate (550 mg) and dimethyiformamide (10 ml) were heated and stirred for 35 days at 65° C. until analysis by LCMS showed conversion to the required product. The mixture was evaporated to dryness, dissolved in water, dialysed against water, evaporated to low, volume and precipitated with acetone. Drying under vacuum gave the title compound (550 mg).

Mass spec. FIA (M−H) 2369. $^1$H NMR ($D_2O$): δ 2.84 (m, 16H), 3.15 (m, 8H), 3.24 (m, 8H), 3.69 (s, 64H), 3.85-4.19 (m, 16H), 5.25 (s, 8H).

## EXAMPLE 19

### 6-Per-deoxy-6-per(3-(tetrazol-5-yl)propyl)thio-γ-cyclodextrin, Sodium Salt



Per-6-deoxy-per-6-thio-γ-cyclodextrin (1 g), 4-bromobutyronitrile (1 g), cesium carbonate (1 g) and dimethylformamide (10 ml) were stirred together at 60° C. over the weekend. The mixture was cooled, water added and the precipitate separated by centrifuge. After washing and drying the perbutyronitrile (1.4 g) was obtained. This product (1 g), sodium azide (1.3 g), triethylamine hydrochloride (2.8 g) and dimethylformamide (13 ml) were stirred and heated together for 7 days at 100° C. The mixture was cooled, diluted with water, acidified and the precipitated filtered off. This was washed with water, sonicated with methanol, separated by centrifuge, dried and dissolved in sodium hydroxide solution (M, 10 ml), filtered and dialysed to neutrality. This solution was evaporated to dryness to give the title compound (600 mg). Mass spec. (M−2H) 1152.8.

$^1$H NMR ($D_2O$); δ 1.95 (m, 16H), 2.55 (m, 16H), 2.85 (m, 24H), 3.05 (d, 8H), 3.5 (m, 8H), 3.6 (m, 8H), 3.9 (m, 16H), 5.06 (s, 8H).

## EXAMPLE 20

### Reversal of Neuromuscular Blockade in Anaesthetized Guinea Pigs in vivo

Male Dunkin-Hartley guinea pigs (bodyweight: 600-900 g) were anaesthetized by i.p. administration of 10 mg/kg pentobarbitone and 1000 mg/kg urethane. After tracheotomy, the animals were artificially ventilated using a Harvard small animal ventilator. A catheter was placed into the carotid artery for continuous monitoring of arterial blood pressure and the taking of blood samples for blood gas analysis. Heart rate was derived from the blood pressure signal. The sciatic nerve was stimulated (rectangular pulses of 0.5 ms duration at 10 s (0.1 Hz) intervals at a supramaximal voltage, using a Grass S88 Stimulator) and the force of M. gastrocnemius contractions was measured using a Grass FT03 force-displacement transducer. Contractions, blood pressure and heart rate were recorded on a multichannel Grass 7D recorder. Catheters were placed in both jugular veins. One catheter was used for the continuous infusion of a neuromuscular blocking agent. The infusion rate of the neuromuscular blocking agent was increased until a steady-state block of 85-90% was obtained. The other catheter was used for administration of increasing doses of the reversal agent. During continuous infusion of the neuromuscular blocking agent, single doses of increasing concentration of reversal agent were given. At the end of the experiment, the measured force of muscle contractions was plotted against the concentration of reversal agent, and using regression analysis techniques, the 50% reversal concentration was calculated. Results for the reversal of the neuromuscular block, induced by the muscle relaxant rocuronium bromide (Roc), by the 6-mercapto-cyclodextrin derivatives of Examples 1-19 are presented in Table I. For comparison, the reversal activity of the parent compounds β-cyclodextrin and γ-cyclodextrin are included as well.



TABLE 1

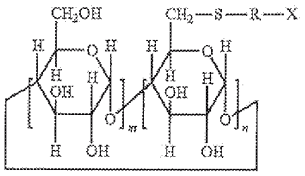
Dose ($ED_{50}$, μmol · kg$^{-1}$) producing 50% reversal of steady-state neuromuscular block in anaesthetized guinea pigs and concentration at maximum reversal.

| Compound | $ED_{50}$ μmol · kg$^{-1}$ | % max reversal at conc. (μmol · kg$^{-1}$) |
|---|---|---|
| γ-cyclodextrin (γ-CD) | 4 | 104 (47) |
| β-cyclodextrin (β-CD) | 20 | 93 (113) |
| 6-mono-deoxy-6-mono-(4-carboxyphenyl)-thio-γ-cyclodextrin, Na salt (example 1) | 0.94 | 102 (8.0) |
| 6-mono-deoxy-6-mono-(2-carboxyphenyl)-thio-γ-cyclodextrin (example 2) | 1.30 | 93 (11) |
| 6-per-deoxy-6-per-(3-carboxyphenyl)thio-γ-cyclodextrin (example 3) | 0.28 | 102 (1.28) |
| 6-per-deoxy-6-per-(2-carboxyethyl)thio-γ-cyclodextrin, Na salt (example 4) | 0.09 | 97 (0.53) |
| 6-per-deoxy-6-per-(5-carboxypentyl)thio-γ-cyclodextrin, Na salt (example 5) | 0.74 | 78 (2.5) |
| 6-per-deoxy-6-per-(3-carboxypropyl)thio-γ-cyclodextrin, Na salt (example 6) | 0.09 | 108 (0.48) |
| 6-per-deoxy-6-per-carboxymethylthio-γ-cyclodextrin, Na salt (example 7) | 0.21 | 88 (1.92) |
| 6-per-deoxy-6-per-(4-carboxyphenyl)thio-γ-cyclodextrin, Na salt (example 8) | 0.10 | 95 (0.48) |
| 6-per-deoxy-6-per-(4-carboxyphenylmethyl)-thio-γ-cyclodextrin, Na salt (example 9) | 0.13 | 100 (0.50) |
| 6-per-deoxy-6-per-(3-amidopropyl)thio-γ-cyclodextrin (example 10) | 0.57 | 94 (33) |
| 6-per-deoxy-6-per-(5-hydroxy-3-oxa-pentyl)-thio-γ-cyclodextrin (example 11) | 0.47 | 92 (2.1) |
| 6-per deoxy-6-per-[(2(2 carboxybenzoyl)-amino)ethyl]-thio-γ-cyclodextrin, sodium salt (example 12) | 0.085 | 95 (0.48) |
| 6-per-deoxy-6-per-(2-hydroxyethyl)thio-γ-cyclodextrin (example 13) | 0.20 | 96 (2.0) |
| 6-per-deoxy-6-per-(N-methylamidomethyl)-thio-γ-cyclodextrin (example 14) | 1.54 | 102 (7.3) |
| 6-per-deoxy-6-per-(2-carboxypropyl)thio-γ-cyclodextrin, sodium salt. (example 15) | 0.10 | 103 (0.48) |
| 6-per-deoxy-6-per-(3-carboxypropyl)thio-β-cyclodextrin, sodium salt (example 16) | 0.5 | 100 (3.2) |
| 6-per-deoxy-6-per-(2-sulfoethyl)thio-γ-cyclodextrin, sodium salt (example 17) | 0.055 | 106 (1.7) |
| 6-per-deoxy-6-per-(2,2,di(hydroxymethyl)-3-hydroxy-propyl)thio-γ-cyclodextrin (example 18) | 2.9 | 63 (4.9) |
| 6-per-deoxy-6-per-(3-(tetrazol-5-yl)-propyl)thio-γ-cyclodextrin, sodium salt (example 19) | 0.22 | 109 (1.2) |

What is claimed is:

1. A 6-mercapto-cyclodextrin derivative having the general formula I

Formula I



wherein m is 0-7 and n is 1-8 and m+n=7 or 8;

R is $(C_{1-6})$alkylene, optionally substituted with 1-3 OH groups, or $(CH_2)_o$-phenylene-$(CH_2)_p$;

o and p are independently 0-4;

X is COOH, $CONHR_1$, $NHCOR_2$, $SO_2OH$, $PO(OH)_2$, $O(CH_2—CH_2—O)_q—H$, OH or tetrazol-5-yl;

$R_1$ is H or $(C_{1-3})$alkyl;

$R_2$ is carboxyphenyl;

q is 1-3;

or pharmaceutically acceptable salts thereof; with the exclusion of

6-per-deoxy-6-per-(2-hydroxyethylthio)-β-cyclodextrin;

6-mono-deoxy-6-mono-(2-hydroxyethylthio)-β-cyclodextrin;

6-per-deoxy-6-per-(2-hydroxyethylthio)-γ-cyclodextrin;

6-per-deoxy-6-per-(carboxymethylthio)-β-cyclodextrin;

6-mono-deoxy-6-mono-(carboxymethylthio)-β-cyclodextrin;

6A,6B-dideoxy-6A,6B-bis((o-carboxyphenyl)thio)-β-cyclodextrin;

6A,6B-dideoxy-6A,6B-bis(carboxymethylthiol)-β-cyclodextrin and 6-per-deoxy-6-per-(2,3-dihydroxypropylthio)-β-cyclodextrin.

2. The 6-mercapto-cyclodextrin derivative according to claim 1, wherein R, m and n are defined as in claim 1 and X is COOH or $SO_2OH$; or a pharmaceutically acceptable salt thereof.

3. The 6-mercapto-cyclodextrin derivative according to claim 1, wherein m is 0; n is 8; R is $(C_{1-6})$alkylene or $(CH_2)_o$-phenylene-$(CH_2)_p$; o and p are independently 0-4; and X is COOH or $SO_2OH$; or a pharmaceutically acceptable salt thereof.

4. A 6-mercapto-cyclodextrin derivative according to claim 1 selected from the group consisting of:

6-per-deoxy-6-per-(2-carboxyethyl)thio-γ-cyclodextrin;

6-per-deoxy-6-per-(3-carboxypropyl)thio-γ-cyclodextrin;

6-per-deoxy-6-per-(4-carboxyphenyl)thio-γ-cyclodextrin;

6-per-deoxy-6-per-(4-carboxyphenylmethyl)thio-γ-cyclodextrin;

6-per-deoxy-6-per-(2-carboxypropyl)thio-γ-cyclodextrin; and

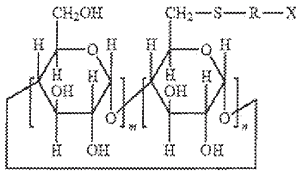
6-per-deoxy-6-per-(2-sulfoethyl)thio-γ-cyclodextrin;

or a pharmaceutically acceptable salt thereof.



5. A pharmaceutical composition comprising a 6-mercapto-cyclodextrin derivative having the general formula I

Formula I



wherein m is 0-7 and n is 1-8 and m+n=7 or 8;

R is $(C_{1-6})$alkylene, optionally substituted with 1-3 OH groups, or $(CH_2)_o$-phenylene-$(CH_2)_p$;

o and p are independently 0-4;

X is COOH, $CONHR_1$, $NHCOR_2$, $SO_2OH$, $PO(OH)_2$, $O(CH_2—CH_2—O)_q—H$, OH or tetrazol-5-yl;

$R_1$ is H or $(C_{1-3})$alkyl;

$R_2$ is carboxyphenyl;

q is 1-3;

or a pharmaceutically acceptable salt thereof, with the exclusion of

6-per-deoxy-6-per-(2-hydroxyethylthio)-β-cyclodextrin;

6-mono-deoxy-6-mono-(2-hydroxyethylthio)-β-cyclodextrin;

6-per-deoxy-6-per-(2-hydroxyethylthio)-γ-cyclodextrin;

6-per-deoxy-6-per-(carboxymethylthio)-β-cyclodextrin;

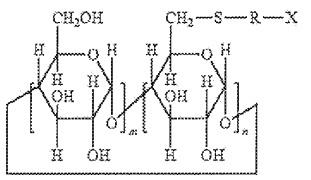
6-mono-deoxy-6-mono-(carboxymethylthio)-β-cyclodextrin;

6A,6B-dideoxy-6A,6B-bis((o-carboxyphenyl)thio)-β-cyclodextrin;

6A,6B-dideoxy-6A,6B-bis(carboxymethylthiol)-β-cyclodextrin and 6-per-deoxy-6-per-(2,3-dihydroxypropylthio)-β-cyclodextrin, in admixture with pharmaceutically acceptable auxilliaries.

6. A kit for providing neuromuscular block and its reversal comprising (a) a neuromuscular blocking agent, and (b) a 6-mercapto-cyclodextrin derivative according to the general formula I

Formula I



wherein m is 0-7 and n is 1-8 and m+n=7 or 8;

R is $(C_{1-6})$alkylene, optionally substituted with 1-3 OH groups, or $(CH_2)_o$-phenylene-$(CH_2)_p$;

o and p are independently 0-4;

X is COOH, $CONHR_1$, $NHCOR_2$, $SO_2OH$, $PO(OH)_2$, $O(CH_2—CH_2—O)_q—H$, OH or tetrazol-5-yl;

$R_1$ is H or $(C_{1-3})$alkyl;

$R_2$ is carboxyphenyl;

q is 1-3;

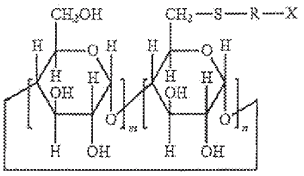
or a pharmaceutically acceptable salt thereof.

7. The kit according to claim 6, wherein the neuromuscular blocking agent is selected from the group consisting of rocuronium, vecuronium, pancuronium, rapacuronium, mivacurium, (cis)atracurium, tubocurarine and suxamethonium.

8. The kit according to claim 6, wherein the neuromuscular blocking agent is rocuronium.

9. A method for reversal of drug-induced neuromuscular block in a patient, which comprises parenterally administering to said patient an effective amount of a 6-mercaptocyclodextrin derivative according to the general formula I

Formula I



wherein m is 0-7 and n is 1-8 and m+n=7 or 8;

R is $(C_{1-6})$alkylene, optionally substituted with 1-3 OH groups, or $(CH_2)_o$-phenylene-$(CH_2)_p$;

o and p are independently 0-4;

X is COOH, $CONHR_1$, $NHCOR_2$, $SO_2OH$, $PO(OH)_2$, $O(CH_2—CH_2—O)_q—H$, OH or tetrazol-5-yl;

$R_1$ is H or $(C_{1-3})$alkyl;

$R_2$ is carboxyphenyl;

q is 1-3;

or a pharmaceutically acceptable salt thereof.

*10. The kit according to claim 6, wherein the neuromuscular blocking agent is vecuronium.*

*11. 6-Per-deoxy-6-per-(2-carboxyethyl)thio-γ-cyclodextrin, or a pharmaceutically acceptable salt thereof.*

*12. 6-Per-deoxy-6-per-(2-carboxyethyl)thio-γ-cyclodextrin, sodium salt.*



*13. A pharmaceutical composition comprising 6-per-deoxy-6-per-(2-carboxyethyl)thio-γ-cyclodextrin, or a pharmaceutically acceptable salt thereof, and a pharmaceutically suitable auxiliary.*

*14. A pharmaceutical composition comprising 6-per-deoxy-6-per-(2-carboxyethyl)thio-γ-cyclodextrin, sodium salt, and a pharmaceutically suitable auxiliary.*

*15. A kit for providing neuromuscular block and its reversal comprising (a) a neuromuscular blocking agent, and (b) 6-per-deoxy-6-per-(2-carboxyethyl)thio-γ-cyclodextrin, or a pharmaceutically acceptable salt thereof.*

*16. A kit for providing neuromuscular block and its reversal comprising (a) a neuromuscular blocking agent, and (b) 6-per-deoxy-6-per-(2-carboxyethyl)thio-γ-cyclodextrin, sodium salt.*

*17. The kit according to claim 15, wherein the neuromuscular blocking agent is selected from the group consisting of rocuronium, vecuronium, pancuronium, rapacuronium, mivacurium, (cis)atracurium, tubocurarine and suxamethonium.*

*18. The kit according to claim 15, wherein the neuromuscular blocking agent is rocuronium.*

*19. The kit according to claim 15, wherein the neuromuscular blocking agent is vecuronium.*

*20. A method for reversal of drug-induced neuromuscular block in a subject, which comprises parenterally administering to said subject an effective amount of 6-per-deoxy-6-per-(2-carboxyethyl)thio-γ-cyclodextrin, or a pharmaceutically acceptable salt thereof.*

*21. A method for reversal of drug-induced neuromuscular block in a subject, which comprises parenterally administering to said subject an effective amount of 6-per-deoxy-6-per-(2-carboxyethyl)thio-γ-cyclodextrin, sodium salt.*

* * * * *

PTO-1683
(Rev. 7-96)

**CERTIFICATE OF COMPLIANCE WITH TYPE-VOLUME LIMITATIONS**

I hereby certify that the foregoing complies with the word limitation of Fed. Cir. R. 32(b)(1) because it contains 13,651 words, excluding the parts of the brief exempted by Fed. R. App. P. 32(f) and Fed. Cir. R. 32(b)(2). This brief complies with the typeface requirements of Fed. R. App. P. 32(a)(5) and the type-style requirements of Fed. R. App. P. 32(a)(6) because it was prepared in Microsoft Word 365 using a proportionally spaced typeface (Book Antiqua) in 14-point font.

Dated: November 9, 2023 /s/ Deepro R. Mukerjee

**CERTIFICATE OF COMPLIANCE WITH FED. CIR. R. 25.1**

I hereby certify that the foregoing complies with Federal Circuit Rule 25.1 because 2 unique words are marked confidential in the confidential and redacted in the non-confidential version of this brief.

Dated: November 9, 2023 /s/ Deepro R. Mukerjee

## CERTIFICATE OF SERVICE

I hereby certify that I caused a copy of the foregoing document to be filed on November 9, 2023, with the Clerk of the Court for the United States Court of Appeals for the Federal Circuit using the Court's electronic filing system, which will send a notice of electronic filing to all attorneys appearing in this matter.

/s/ Deepro R. Mukerjee