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Attorneys for Defendants
GENENTECH USA, INC. and
GENENTECH, INC.

UNITED STATES DISTRICT COURT

NORTHERN DISTRICT OF CALIFORNIA

| | |
|---|---|
| ANDREW WILLIAMSON and BLUE CROSS AND BLUE SHIELD OF KANSAS CITY, on behalf of themselves and all others similarly situated,<br><br>Plaintiffs,<br><br>v.<br><br>GENENTECH, INC. and GENENTECH USA, INC.,<br><br>Defendants. | Case No. 3:20-cv-06695<br><br>**DEFENDANTS' NOTICE OF REMOVAL**<br><br>**JURY TRIAL DEMANDED** |

Pursuant to 28 U.S.C. §§ 1332(d), 1441, 1446 and 1453, Defendants Genentech, Inc. and Genentech USA, Inc. ("Genentech") hereby remove the above-captioned action from the Superior Court of the State of California in and for the County of San Mateo to the United States District Court for the Northern District of California.

## I. INTRODUCTION

1. On February 26, 2019, Plaintiff Andrew Williamson ("Williamson") filed a Class Action Complaint in the Superior Court of the State of California in and for the County of San Mateo captioned, *Andrew Williamson on behalf of himself and all others similarly situated, v. Genentech, Inc. and Genentech USA, Inc.*, San Mateo County Case No. 19-CIV-01022.

2. On April 5, 2019, Genentech filed a notice of removal to the United States District Court for the Northern District of California, No. 3:19-cv-01840-JSC, and the matter was assigned to the Honorable Jacqueline Scott Corley.

3. On May 17, 2019, Williamson filed a First Amended Class Action Complaint.

4. On June 7, 2019, Williamson filed a Second Amended Class Action Complaint.

5. On March 18, 2020, the case was remanded to San Mateo County Superior Court for lack of subject matter jurisdiction. In particular, the Court reasoned that Williamson "has not alleged, and cannot allege, that he would have paid any less if a smaller vial … had been provided … A patient who could actually allege that Genentech's practices caused him to personally pay more money, or the insurance company that paid for the medication, would likely have Article III standing." *Williamson v. Genentech*, No. 3:19-cv-01840-JSC, ECF 64 at 9:23-10:2 (March 18, 2020 Remand Order).

6. On August 26, 2020, Williamson filed a Third Amended Class Action Complaint ("TAC") to add Blue Cross and Blue Shield of Kansas City ("BCBSKC") as a plaintiff. A copy of the TAC is attached as Exhibit A.

7. Exhibits A and B are true and correct copies of "all process, pleadings, and orders served upon" Genentech as of September 24, 2020. *See* 28 U.S.C. § 1446(a).

## II. FACTUAL BACKGROUND

8. The TAC alleges that Genentech packages its medications in such a way that "needlessly costs patients with cancer and other serious diseases hundreds of millions of dollars a year for costly medicines that cannot be used and instead must be thrown away." TAC ¶ 1. Williamson and BCBSKC on behalf of themselves and other end payors seek "to recover the amounts they necessarily spent … on wasted medicine sold by Genentech." *Id.* ¶ 17. BCBSKC alleges that it "was the health insurer and payor for its subscriber, Williamson, and the medical and prescription drug plans of which he was a member." *Id.* ¶¶ 20, 105.

9. Plaintiffs' alleged class consists of "All end payors who, during the Class Period, paid for Avastin, Rituxan, Kadcyla or Xolair, a portion of which was discarded because the quantity in the vials exceed [sic] the patient's dose (the "Class")." *Id.* ¶ 116. Plaintiff further alleges "the total

number of Class Members is so numerous that joinder of all Class Members would be impracticable." *Id.* ¶ 121.

10. Plaintiffs seek an award of restitution, damages, disgorgement, costs and attorneys' fees in addition to an order enjoining Genentech from continuing to engage in the alleged unlawful and/or unfair business practices, and an order requiring Genentech to pay pre- and post-judgment interest. TAC, Prayer for Relief.

## III. REMOVAL UNDER CLASS ACTION FAIRNESS ACT

11. This Court has original jurisdiction over this action under 28 U.S.C. §§ 1332(d). Under the Class Action Fairness Act ("CAFA"), federal district courts have original jurisdiction when: (1) the putative class consists of at least 100 members; (2) the citizenship of at least one proposed member of the class is different from that of the defendant; and (3) the aggregated amount in controversy exceeds $5,000,000, exclusive of interest and costs. 28 U.S.C. § 1332(d). As set forth herein, all of the requirements for removal are satisfied.

### A. The Putative Class Consists of at Least 100 Members

12. CAFA's first requirement, that the proposed class contain of at least 100 members, 28 U.S.C. § 1332(d)(5), is satisfied.

13. Plaintiff purports to represent a class of: "All end payors who, during the Class Period, paid for Avastin, Rituxan, Kadcyla or Xolair, a portion of which was discarded because the quantity in the vials exceed [sic] the patient's dose (the "Class")." The purported class is not limited in geographic scope. TAC ¶ 116.

14. The "Class Period" is alleged as encompassing "the applicable period of limitations, as well as the period beginning with the filing of this lawsuit and ending on the date notice is sent to the class." *Id.* ¶ 117.

15. While the exact number of Class Members is currently unknown to Plaintiff, he alleges that "the total number of Class Members is so numerous that joinder of all Class Members would be impracticable." *Id.* ¶ 121.

16. Plaintiff has thus alleged a proposed class with at least 100 members, therefore satisfying the class size requirement.

**B. Minimal Diversity Exists Between the Parties**

17. CAFA's second requirement, that any one member of the proposed class be a citizen of a state different from any defendant, 28 U.S.C. § 1332(d)(2), is also satisfied.

18. Williamson alleges that he is a resident of Liberty, Missouri. TAC ¶ 19.

19. BCBSKC alleges that it is a duly organized and existing Missouri non-profit corporation with its primary place of business located in Kansas City, Missouri. *Id*. ¶ 20.

20. Genentech, Inc. is a corporation incorporated in Delaware with its principal place of business at 1 DNA Way, South San Francisco, CA 94080. *Id*. ¶ 21. Therefore, Genentech, Inc. is a citizen of Delaware and California.

21. Genentech USA, Inc. is a corporation incorporated in Delaware with its principal place of business at 1 DNA Way, South San Francisco, CA 94080. *Id*. ¶ 22. Therefore, Genentech USA, Inc. is a citizen of Delaware and California.

22. Plaintiffs are diverse from Defendants. 28 U.S.C. § 1332(d)(2). Moreover, given that Plaintiffs' purported class is not limited in geographic scope, it is virtually certain that one or more putative class members are not citizens of California or Delaware.

23. Minimal diversity exists between "any one member" of the proposed class and "any defendant" in satisfaction of 28 U.S.C. § 1332(d)(2).

**C. The Amount in Controversy Exceeds $5 Million**

24. CAFA's third requirement, that the aggregate amount in controversy exceed $5 million, exclusive of interest and costs, 28 U.S.C. § 1332(d)(2), is satisfied as well. To remove the case, a defendant need not prove that class recovery ***will*** exceed that figure, only that it ***could***. *Rea v. Michaels Stores Inc.*, 742 F.3d 1234, 1239 (9th Cir. 2014). For purposes of removal, defendants need only to make a "plausible allegation" that the amount in controversy exceeds $5 million. *Dart Cherokee Basin Operating Co., LLC v. Owens*, 574 U.S. 81, 89 (2014); *Fritsch v. Swift Transp. Co. of Arizona, LLC*, 899 F.3d 785, 788 (9th Cir. 2018).

25. Although Genentech disputes liability and damages, it is evident that Plaintiffs purport to allege claims for themselves and the proposed class for monetary relief that, if granted, would, in the aggregate, well exceed CAFA's $5 million requirement. Plaintiffs allege that they "bring this

lawsuit to obtain redress from a practice that needlessly costs patients with cancer and other serious diseases hundreds of millions of dollars a year for costly medicines that cannot be used and instead must be thrown away because of the wasteful way that Genentech packages them." TAC ¶ 1. Plaintiffs specifically allege "[t]he amount spent on wasted drugs for just one patient can total many thousands of dollars a year for Genentech's drugs." *Id*. ¶ 57. The TAC also contains an allegation that "Genentech's annual revenues from wasted subject medicines totaled $562 million with its existing vial sizes but would have been reduced to $125 million, a savings of $437 million, with the addition of one smaller vial for each drug." *Id*. ¶ 78.

26. On behalf of Plaintiffs and the putative class, the TAC seeks, *inter alia*, "restitution, damages, and disgorgement." TAC, Prayer for Relief.

27. Plaintiffs also seek an award of attorneys' fees. *Guglielmino v. McKee Foods Corp*., 506 F.3d 696, 700-701 (9th Cir. 2007) (attorneys' fees are included in amount in controversy determination); *Conrad Assocs. v. Hartford Acc. & Indem. Co.*, 994 F. Supp. 1196, 1198 (N.D. Cal. 1998) (noting that the amount in controversy includes attorneys' fees).

28. Assuming the truth of the allegations in the TAC, there is more than $5 million in controversy, as required for removal by 28 U.S.C. § 1332(d)(2).

29. Plaintiffs have therefore alleged an amount in controversy that exceeds $5 million, exclusive of interest and costs.

## IV. NO EXCEPTION TO CAFA JURISDICTION APPLIES

30. Genentech has carried its burden of establishing the satisfaction of CAFA's initial jurisdictional requirements. The burden shifts to Plaintiffs to establish the applicability of any express CAFA jurisdictional exception. *Allen v. Boeing Co.*, 784 F.3d 625, 628 (9th Cir. 2015). Any doubt as to the applicability of a CAFA exception is to be resolved in favor of removal. *See Arbuckle Mountain Ranch of Tex., Inc. v. Chesapeake Energy Corp.*, 810 F.3d 335, 337-38 (5th Cir. 2016); *Hood v. Gilster-Mary Lee Corp.*, 785 F.3d 263, 265 (8th Cir. 2015). The Ninth Circuit instructs that "CAFA should be read 'with a strong preference that interstate class actions should be heard in a federal court if properly removed by any defendant." *Bridgewell-Sledge v. Blue Cross of*

*Cal.*, 798 F.3d 923, 929 (9th Cir. 2015) (citations omitted). "[N]o antiremoval presumption attends cases invoking CAFA." *Id*.

## V. PROCEDURAL COMPLIANCE

31. Plaintiffs filed the TAC on August 26, 2020, in the Superior Court of the State of California for the County of San Mateo. Exhibit A.

32. On August 26, 2020, Plaintiffs served the TAC on Genentech. Genentech is timely filing this notice of removal within 30 days of that date. *See* 28 U.S.C. § 1446(b)(3).

33. A copy of this Notice of Removal is being filed with the Clerk of the Superior Court of the State of California for the County of San Mateo, and is being served on counsel of record pursuant to 28 U.S.C. §§ 1446(a) & (d).

Accordingly, Genentech hereby removes this action to the United States District Court for the Northern District of California.

Pursuant to Rule 38 of the Federal Rules of Civil Procedure, Genentech hereby requests trial by jury.

Dated: September 24, 2020

Respectfully submitted,

SHOOK, HARDY & BACON L.L.P.

By: */s/ Alicia J. Donahue*
ALICIA J. DONAHUE
JOAN R. CAMAGONG

Attorneys for Defendants
GENENTECH, INC. and GENENTECH USA, INC.

JS-CAND 44 (Rev. 06/17)

# CIVIL COVER SHEET

The JS-CAND 44 civil cover sheet and the information contained herein neither replace nor supplement the filing and service of pleadings or other papers as required by law, except as provided by local rules of court. This form, approved in its original form by the Judicial Conference of the United States in September 1974, is required for the Clerk of Court to initiate the civil docket sheet. *(SEE INSTRUCTIONS ON NEXT PAGE OF THIS FORM.)*

## I. (a) PLAINTIFFS

Andrew Williamson and Blue Cross and Blue Shield of Kansas City

**(b)** County of Residence of First Listed Plaintiff *(EXCEPT IN U.S. PLAINTIFF CASES)*
Clay County, Missouri

**(c)** Attorneys *(Firm Name, Address, and Telephone Number)*
Mike Arias, SBN 115385 / Elise R. Sanguinetti, SBN 191389 / Alfredo Torrijos, SBN 222458; ARIAS SANGUINETTI WANG & TORRIJOS, LLP, 6701 Center Drive West, 14th Floor, Los Angeles, CA 90045; Tel: 310.844.9696 [See attachment A]

## DEFENDANTS

Genentech, Inc. and Genentech, USA, Inc.

County of Residence of First Listed Defendant *(IN U.S. PLAINTIFF CASES ONLY)*

NOTE: IN LAND CONDEMNATION CASES, USE THE LOCATION OF THE TRACT OF LAND INVOLVED.

Attorneys *(If Known)*
Alicia J. Donahue, SBN 117412 / Joan R. Camagong, SBN 288217
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## II. BASIS OF JURISDICTION *(Place an "X" in One Box Only)*

- ☐ 1 U.S. Government Plaintiff
- ☐ 3 Federal Question *(U.S. Government Not a Party)*
- ☐ 2 U.S. Government Defendant
- ☒ 4 Diversity *(Indicate Citizenship of Parties in Item III)*

## III. CITIZENSHIP OF PRINCIPAL PARTIES *(Place an "X" in One Box for Plaintiff and One Box for Defendant)*

*(For Diversity Cases Only)*

| | PTF | DEF | | PTF | DEF |
|---|---|---|---|---|---|
| Citizen of This State | ☐ 1 | ☐ 1 | Incorporated *or* Principal Place of Business In This State | ☐ 4 | ☒ 4 |
| Citizen of Another State | ☒ 2 | ☐ 2 | Incorporated *and* Principal Place of Business In Another State | ☐ 5 | ☐ 5 |
| Citizen or Subject of a Foreign Country | ☐ 3 | ☐ 3 | Foreign Nation | ☐ 6 | ☐ 6 |

## IV. NATURE OF SUIT *(Place an "X" in One Box Only)*

**CONTRACT**
- ☐ 110 Insurance
- ☐ 120 Marine
- ☐ 130 Miller Act
- ☐ 140 Negotiable Instrument
- ☐ 150 Recovery of Overpayment Of Veteran's Benefits
- ☐ 151 Medicare Act
- ☐ 152 Recovery of Defaulted Student Loans (Excludes Veterans)
- ☐ 153 Recovery of Overpayment of Veteran's Benefits
- ☐ 160 Stockholders' Suits
- ☐ 190 Other Contract
- ☐ 195 Contract Product Liability
- ☐ 196 Franchise

**REAL PROPERTY**
- ☐ 210 Land Condemnation
- ☐ 220 Foreclosure
- ☐ 230 Rent Lease & Ejectment
- ☐ 240 Torts to Land
- ☐ 245 Tort Product Liability
- ☐ 290 All Other Real Property

**TORTS**

**PERSONAL INJURY**
- ☐ 310 Airplane
- ☐ 315 Airplane Product Liability
- ☐ 320 Assault, Libel & Slander
- ☐ 330 Federal Employers' Liability
- ☐ 340 Marine
- ☐ 345 Marine Product Liability
- ☐ 350 Motor Vehicle
- ☐ 355 Motor Vehicle Product Liability
- ☐ 360 Other Personal Injury
- ☐ 362 Personal Injury -Medical Malpractice

**PERSONAL INJURY**
- ☐ 365 Personal Injury – Product Liability
- ☐ 367 Health Care/ Pharmaceutical Personal Injury Product Liability
- ☐ 368 Asbestos Personal Injury Product Liability

**PERSONAL PROPERTY**
- ☒ 370 Other Fraud
- ☐ 371 Truth in Lending
- ☐ 380 Other Personal Property Damage
- ☐ 385 Property Damage Product Liability

**CIVIL RIGHTS**
- ☐ 440 Other Civil Rights
- ☐ 441 Voting
- ☐ 442 Employment
- ☐ 443 Housing/ Accommodations
- ☐ 445 Amer. w/Disabilities-Employment
- ☐ 446 Amer. w/Disabilities-Other
- ☐ 448 Education

**PRISONER PETITIONS**

**HABEAS CORPUS:**
- ☐ 463 Alien Detainee
- ☐ 510 Motions to Vacate Sentence
- ☐ 530 General
- ☐ 535 Death Penalty

**OTHER:**
- ☐ 540 Mandamus & Other
- ☐ 550 Civil Rights
- ☐ 555 Prison Condition
- ☐ 560 Civil Detainee - Conditions of Confinement

**FORFEITURE/PENALTY**
- ☐ 625 Drug Related Seizure of Property 21 USC 881
- ☐ 690 Other

**LABOR**
- ☐ 710 Fair Labor Standards Act
- ☐ 720 Labor/Management Relations
- ☐ 740 Railway Labor Act
- ☐ 751 Family and Medical Leave Act
- ☐ 790 Other Labor Litigation
- ☐ 791 Employee Retirement Income Security Act

**IMMIGRATION**
- ☐ 462 Naturalization Application
- ☐ 465 Other Immigration Actions

**BANKRUPTCY**
- ☐ 422 Appeal 28 USC § 158
- ☐ 423 Withdrawal 28 USC § 157

**PROPERTY RIGHTS**
- ☐ 820 Copyrights
- ☐ 830 Patent
- ☐ 835 Patent-Abbreviated New Drug Application
- ☐ 840 Trademark

**SOCIAL SECURITY**
- ☐ 861 HIA (1395ff)
- ☐ 862 Black Lung (923)
- ☐ 863 DIWC/DIWW (405(g))
- ☐ 864 SSID Title XVI
- ☐ 865 RSI (405(g))

**FEDERAL TAX SUITS**
- ☐ 870 Taxes (U.S. Plaintiff or Defendant)
- ☐ 871 IRS—Third Party 26 USC § 7609

**OTHER STATUTES**
- ☐ 375 False Claims Act
- ☐ 376 Qui Tam (31 USC § 3729(a))
- ☐ 400 State Reapportionment
- ☐ 410 Antitrust
- ☐ 430 Banks and Banking
- ☐ 450 Commerce
- ☐ 460 Deportation
- ☐ 470 Racketeer Influenced & Corrupt Organizations
- ☐ 480 Consumer Credit
- ☐ 490 Cable/Sat TV
- ☐ 850 Securities/Commodities/ Exchange
- ☐ 890 Other Statutory Actions
- ☐ 891 Agricultural Acts
- ☐ 893 Environmental Matters
- ☐ 895 Freedom of Information Act
- ☐ 896 Arbitration
- ☐ 899 Administrative Procedure Act/Review or Appeal of Agency Decision
- ☐ 950 Constitutionality of State Statutes

## V. ORIGIN *(Place an "X" in One Box Only)*

- ☐ 1 Original Proceeding
- ☒ 2 Removed from State Court
- ☐ 3 Remanded from Appellate Court
- ☐ 4 Reinstated or Reopened
- ☐ 5 Transferred from Another District *(specify)*
- ☐ 6 Multidistrict Litigation-Transfer
- ☐ 8 Multidistrict Litigation-Direct File

## VI. CAUSE OF ACTION

Cite the U.S. Civil Statute under which you are filing ***(Do not cite jurisdictional statutes unless diversity)***:
28 U.S.C. §§ 1446 and 1453

Brief description of cause:
Alleged violation of California's Unfair Competition Law

## VII. REQUESTED IN COMPLAINT:

☒ CHECK IF THIS IS A **CLASS ACTION** UNDER RULE 23, F.R.Cv.P.

**DEMAND $** Exceeds $75,000

CHECK YES only if demanded in complaint:
**JURY DEMAND:** ☒ Yes ☐ No

## VIII. RELATED CASE(S) IF ANY *(See instructions)*:

JUDGE Jacqueline Scott Corley

DOCKET NUMBER 3:19-cv-01840-JSC (previously assigned and remanded)

## IX. DIVISIONAL ASSIGNMENT (Civil Local Rule 3-2)

**(Place an "X" in One Box Only)** ☒ **SAN FRANCISCO/OAKLAND** ☐ **SAN JOSE** ☐ **EUREKA-MCKINLEYVILLE**

**DATE** September 24, 2020 **SIGNATURE OF ATTORNEY OF RECORD** /s/ *Alicia J. Donahue*

# INSTRUCTIONS FOR ATTORNEYS COMPLETING CIVIL COVER SHEET FORM JS-CAND 44

**Authority For Civil Cover Sheet.** The JS-CAND 44 civil cover sheet and the information contained herein neither replaces nor supplements the filings and service of pleading or other papers as required by law, except as provided by local rules of court. This form, approved in its original form by the Judicial Conference of the United States in September 1974, is required for the Clerk of Court to initiate the civil docket sheet. Consequently, a civil cover sheet is submitted to the Clerk of Court for each civil complaint filed. The attorney filing a case should complete the form as follows:

**I. a) Plaintiffs-Defendants.** Enter names (last, first, middle initial) of plaintiff and defendant. If the plaintiff or defendant is a government agency, use only the full name or standard abbreviations. If the plaintiff or defendant is an official within a government agency, identify first the agency and then the official, giving both name and title.

**b) County of Residence.** For each civil case filed, except U.S. plaintiff cases, enter the name of the county where the first listed plaintiff resides at the time of filing. In U.S. plaintiff cases, enter the name of the county in which the first listed defendant resides at the time of filing. (NOTE: In land condemnation cases, the county of residence of the "defendant" is the location of the tract of land involved.)

**c) Attorneys.** Enter the firm name, address, telephone number, and attorney of record. If there are several attorneys, list them on an attachment, noting in this section "(see attachment)."

**II. Jurisdiction.** The basis of jurisdiction is set forth under Federal Rule of Civil Procedure 8(a), which requires that jurisdictions be shown in pleadings. Place an "X" in one of the boxes. If there is more than one basis of jurisdiction, precedence is given in the order shown below.

(1) United States plaintiff. Jurisdiction based on 28 USC §§ 1345 and 1348. Suits by agencies and officers of the United States are included here.

(2) United States defendant. When the plaintiff is suing the United States, its officers or agencies, place an "X" in this box.

(3) Federal question. This refers to suits under 28 USC § 1331, where jurisdiction arises under the Constitution of the United States, an amendment to the Constitution, an act of Congress or a treaty of the United States. In cases where the U.S. is a party, the U.S. plaintiff or defendant code takes precedence, and box 1 or 2 should be marked.

(4) Diversity of citizenship. This refers to suits under 28 USC § 1332, where parties are citizens of different states. When Box 4 is checked, the citizenship of the different parties must be checked. (See Section III below; **NOTE: federal question actions take precedence over diversity cases.**)

**III. Residence (citizenship) of Principal Parties.** This section of the JS-CAND 44 is to be completed if diversity of citizenship was indicated above. Mark this section for each principal party.

**IV. Nature of Suit.** Place an "X" in the appropriate box. If the nature of suit cannot be determined, be sure the cause of action, in Section VI below, is sufficient to enable the deputy clerk or the statistical clerk(s) in the Administrative Office to determine the nature of suit. If the cause fits more than one nature of suit, select the most definitive.

**V. Origin.** Place an "X" in one of the six boxes.

(1) Original Proceedings. Cases originating in the United States district courts.

(2) Removed from State Court. Proceedings initiated in state courts may be removed to the district courts under Title 28 USC § 1441. When the petition for removal is granted, check this box.

(3) Remanded from Appellate Court. Check this box for cases remanded to the district court for further action. Use the date of remand as the filing date.

(4) Reinstated or Reopened. Check this box for cases reinstated or reopened in the district court. Use the reopening date as the filing date.

(5) Transferred from Another District. For cases transferred under Title 28 USC § 1404(a). Do not use this for within district transfers or multidistrict litigation transfers.

(6) Multidistrict Litigation Transfer. Check this box when a multidistrict case is transferred into the district under authority of Title 28 USC § 1407. When this box is checked, do not check (5) above.

(8) Multidistrict Litigation Direct File. Check this box when a multidistrict litigation case is filed in the same district as the Master MDL docket.

Please note that there is no Origin Code 7. Origin Code 7 was used for historical records and is no longer relevant due to changes in statute.

**VI. Cause of Action.** Report the civil statute directly related to the cause of action and give a brief description of the cause. **Do not cite jurisdictional statutes unless diversity.** Example: U.S. Civil Statute: 47 USC § 553. Brief Description: Unauthorized reception of cable service.

**VII. Requested in Complaint.** Class Action. Place an "X" in this box if you are filing a class action under Federal Rule of Civil Procedure 23.

Demand. In this space enter the actual dollar amount being demanded or indicate other demand, such as a preliminary injunction.

Jury Demand. Check the appropriate box to indicate whether or not a jury is being demanded.

**VIII. Related Cases.** This section of the JS-CAND 44 is used to identify related pending cases, if any. If there are related pending cases, insert the docket numbers and the corresponding judge names for such cases.

**IX. Divisional Assignment.** If the Nature of Suit is under Property Rights or Prisoner Petitions or the matter is a Securities Class Action, leave this section blank. For all other cases, identify the divisional venue according to Civil Local Rule 3-2: "the county in which a substantial part of the events or omissions which give rise to the claim occurred or in which a substantial part of the property that is the subject of the action is situated."

**Date and Attorney Signature.** Date and sign the civil cover sheet.

**ATTACHMENT A**

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*Counsel for Plaintiff Blue Cross and Blue Shield of Kansas City*

# Exhibit A

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*Attorneys for Plaintiff Andrew Williamson and the Proposed Class*

*[Additional Counsel listed on following page.]*

**SUPERIOR COURT OF THE STATE OF CALIFORNIA**
**FOR THE COUNTY OF SAN MATEO**

Andrew Williamson and Blue Cross and Blue Shield of Kansas City, on behalf of themselves and all others similarly situated,

Plaintiffs,

vs.

Genentech, Inc., and Genentech USA, Inc.,

Defendants.

Case No. 19-CIV-01022

HON. MARIE S. WEINER

**THIRD AMENDED CLASS ACTION COMPLAINT FOR**

1. **VIOLATION OF CALIFORNIA'S UNFAIR COMPETITION LAW (Bus. & Prof. Code §§ 17200, *et seq*.)**

JURY TRIAL DEMANDED

Gary D. McCallister (Admitted *Pro Hac Vice*)
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E. Documents provided by FDA in response to Williamson's FOIA request.

F. Spreadsheet reflecting Rituxan doses used, charges submitted to BCBSKC and amounts paid.

> *"The federal Medicare program and private health insurers waste nearly $3 billion every year buying cancer medicines that are thrown out because many drug makers distribute the drugs only in vials that hold too much for most patients, a group of cancer researchers has found."*[1]
>
> * * *
>
> *"The reduction of oncology drug wastage offers the potential to decrease pharmaceutical expenditures.... Decreasing waste is a desirable strategy to reduce expenditures on oncology drugs without affecting health outcomes or quality of care or limiting specific drug use."*[2]

COME NOW Andrew Williamson (individually referred to as "Williamson" ") and Blue Cross and Blue Shield of Kansas City, ("BCBSKC") (individually referred to as "BCBSKC") and collectively referred to as "End Payors"), individually and on behalf of all others similarly situated, and, for their Third Amended Complaint against Defendants Genentech, Inc., and Genentech USA, Inc. (collectively referred to as "Defendants" or "Genentech") alleges upon personal knowledge as to their own acts and upon information and belief (based on the investigation of counsel), as follows:

## INTRODUCTION

1. End Payors bring this lawsuit to obtain redress from a practice that needlessly costs patients with cancer and other serious diseases hundreds of millions of dollars a year for costly medicines that cannot be used and instead must be thrown away because of the wasteful way that Genentech packages them.

2. It is a truism that the increasing cost of healthcare in the United States is unsustainable and has a devastating effect on the American economy and on patients and their families in particular.[3]

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[1] Dr. Peter B. Bach, director of the Center for Health Policy and Outcomes at Memorial Sloan Kettering Cancer Center, quoted in Gardiner Harris, *Waste in Cancer Drugs Costs $3 Billion a Year, a Study Finds*, N.Y. Times, March 1, 2016, at B1 (Ex. C) ("Harris").

[2] Eli Lilly, as stated in Kristin M. Sheffield *et al.*, *Minimization of olaratumab drug waste using real-world data*, 74 Am. J. Health-Syst. Pharm. E270 (2017) ("Sheffield") (Ex. B).

[3] *See* Alex Kacik, *Healthcare costs increasing at unsustainable pace*, Modern Healthcare (6/13/2018), available at https://www.modernhealthcare.com/article/20180613/NEWS/1806199619 (accessed 2/18/2019); J. Sahadi, CNN Business, *Warren Buffet is right. Health care costs are swallowing the economy* (1/30/2018), available at https://money.cnn.com/2018/01/30/news/economy/health-care-costs-eating-the-economy/index.html (accessed 2/18/2019); Niek Stadhouders *et al.*, Effective healthcare cost-containment policies: A systematic review, 123 Health Policy 71 (2019).

A major culprit is the cost of cancer drugs and other drugs.[4] These drugs are a major burden on the economy and on individual patients and their families.

3. The IMS Institute for Healthcare Informatics recently found that "[t]he total cost of oncology therapeutics and supportive care drugs" for cancer worldwide in 2015 was $107 billion, of which 46% (or $49 billion) was spent in the United States.[5]

4. The cost of these drugs for individual patients and their families can be crushing. A recent study found that the average amount spent by patients with colorectal cancer was more than $63,000 during just the first year.[6] Of 13 cancer drugs introduced in 2012, 12 were priced above $100,000 per year, "and the situation has only gotten worse since."[7]

5. The prices of cancer drugs are increasing rapidly. The net price of branded oncology drugs increased by 21.8% from 2010 to 2015.[8] That is nearly three times the increase in overall inflation over that period, as measured by the Consumer Price Index.[9] "[E]ven the cost of existing cancer drugs has been increasing precipitously – well above the rate of inflation and much faster than other aspects of health care."[10]

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[4] Experts in Chronic Myeloid Leukemia, *The price of drugs for chronic myeloid leukemia (CML) is a reflection of the unsustainable prices of cancer drugs*, 121 Blood 4439 (2013); Linda A. Johnson, *AARP: Price hikes doubled average drug price over 7* years (2/29/16), available at https://apnews.com/3fabc10146aa4e3285cfbf829d8469c1 (accessed 2/18/2019); Peter Loftus, *Employers Battle Drug Costs*, Wall Street Journal, Dec. 18, 2015, available at http://www.wsj.com/articles/employers-battle-drug-costs-1450488416 (accessed 2/18/2019).

[5] Murray Aitken & Michael Kleinrock, Global oncology trend report. A review of 2015 and outlook to 2020. IMS Institute for Healthcare Informatics, June 2016, at 4.

[6] Christopher T. Chen *et al.*, Medicare Spending for Breast, Prostate, Lung, and Colorectal Cancer Patients in the Year of Diagnosis and Year of Death, Health Serv, Res., pre-publication version available at http://onlinelibrary.wiley.com/doi/10.1111/1475-6773.12745/abstract (accessed 2/18/2019).

[7] Paul Workman *et al.*, *How Much Longer Will We Put Up With $100,000 Cancer drugs*, 168 Cell 579, 579 (2017)

[8] *Id.* at 26, Chart 19.

[9] *See* the United States Bureau of Labor Statistics Inflation Calculator, at https://www.bls.gov/data/inflation_calculator.htm (accessed 2/18/2019), showing an increase in the Consumer Price Index over that period of 7.9%.

[10] Elie Dolgin, *Cancer's cost conundrum*, 555 Nature S26, S26 (2018).

6. In recent years, Defendants' drugs have risen even faster than that. Between May 2017 and February 2019, the Wholesale Acquisition Cost ("WAC"), meaning the manufacturer's list price in the United States, of the four drugs at issue herein increased by 26% (Avastin), 24% (Kadcyla), 30% (Rituxan) and 27% (Xolair). Those increases far outstripped both general inflation and medical care inflation, as measured by the government's Consumer Price Index ("CPI"). During that same time period, the CPI for all urban consumers, all items, increased by only 3%[11] and for medical care increased by only 4%.[12]

7. Cancer drugs have become so expensive that even middle-class patients have been forced to stop taking their medicines – at great risk to their survival – because they cannot afford them.[13] One recent study found that 39% of patients with cancer altered their care by not filling a prescription or taking less medication than prescribed because of treatment-related financial distress.[14] Moreover, those diagnosed with cancer are more than twice as likely to declare bankruptcy than non-cancer patients.[15]

8. The scientific literature refers to the impact on patients of the cost of cancer care as "financial toxicity."[16]

9. Another truism is that a reason for runaway healthcare costs is waste, fraud, and abuse. Many people think that those terms simply refer to individual actions by unscrupulous medical

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[11] *See* https://www.bls.gov/data/inflation_calculator.htm (accessed 2/22/2019).

[12] *See* https://fred.stlouisfed.org/series/CPIMEDSL (accessed 2/22/2019).

[13] *See, e.g.*, Joseph Walker, *Patients Struggle with High Drug Prices*, Wall Street Journal, Dec. 31, 2015, available at http://www.wsj.com/articles/patients-struggle-with-high-drug-prices-1451557981 (accessed 2/18/2019).

[14] Ryan D. Nipp *et al.*, *Identifying cancer patients who alter care or lifestyle due to treatment-related financial distress*, 25 Psycho-Oncology 719 (2016).

[15] S. Yousuf *et al.*, *The Utility of Cost Discussions Between Patients with Cancer and Oncologists*, 21 Am. J. Managed Care 607 (2015).

[16] This term was introduced in 2013 in S. Yousuf Zafar *et al.*, *The Financial Toxicity of Cancer Treatment: A Pilot Study Assessing*, 18 Oncologist 381 (2013). According to Google Scholar, this article had been cited by more than 1,600 scientific papers as of February 2019. *See* *https://scholar.google.com/scholar?hl=en&as_sdt=0%2C26&q=%22Financial+Toxicity%22&btnG=* (accessed 2/18/2019). The term "financial toxicity" had appeared in more than 900 scientific papers. *Id.*

providers to perform unnecessary services, overcharge, or provide services that do not meet the standard of care.[17]

10. But that is not a complete understanding of the situation as it pertains to drugs, particularly cancer drugs. In 2016, a paper published in the peer-reviewed journal BMJ (formerly the British Medical Journal) by a group of experts headed by Dr. Peter B. Bach, director of the Center for Health Policy and Outcomes of Memorial Sloan Kettering Cancer Center, revealed another more systemic source of waste. Pharmaceutical companies actually are selling cancer and other expensive drugs in vials that can be used only once but that provide more medicine than is appropriate for most patients, resulting in expensive products simply being thrown away at great cost to patients and their insurers.[18]

11. Dr. Bach's study projected that payments the United States in 2016 for the wasted portions of just 18 cancer drugs, including three manufactured by Genentech, would total $1.8 billion in revenues received by the pharmaceutical companies, with another $1 billion in markups paid to doctors and hospitals. For three Genentech products alone, the total was more than half a billion dollars, not counting wholesale and retail markups. And that is the cost of waste for just one year. But this practice is not new, and these amounts of waste can be multiplied many times over because of what has gone on since this practice began.

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[17] *See* "Addressing Fraud, Waste, and Abuse," at https://www.humana.com/about/legal/disclaimer-and-licensure/fraud-waste-and-abuse (accessed 2/18/2019); Centers for Medicare & Medicaid Services, *Health Care Fraud and Proram Integrity: An Overview for Providers*, available at https://dbhids.org/wp-content/uploads/2015/10/Health-Care-Fraud-and-Program-Integrity-An-Overview-for-Providers.pdf (accessed 2/18/2019); Nicole C. Lallemand, *Reducing Waste in Health Care* (Dec. 13, 2012), available at http://www.healthaffairs.org/healthpolicybriefs/brief.php?brief_id=82 (accessed 2/18/2019).

[18] Peter B. Bach *et al*., *Overspending driven by oversized single dose vials of cancer drugs*, 352 BMJ 788 (2016) (Ex. A).

12. As the New York Times stated in reporting on the BMJ study: "The federal Medicare program and private health insurers waste nearly $3 billion every year buying cancer medicines that are thrown out because many drug makers distribute the drugs only in vials that hold too much for most patients …."[19]

13. Most patients probably do not know that they are paying large amounts of money for medicines that do not, and cannot, treat them. The New York Times related what happened to Lena Haddad, 53, of Germantown, Maryland:

> On a recent day at Ms. Haddad's doctor's office in Bethesda, Md., a nurse, Patricia Traylor, took a vial of Velcade from a large drug cabinet. She injected a syringeful of saline into the vial and shook it, pushed a needle into the vial and withdrew about half the contents. Then she threw out the vial with the remaining medicine.
>
> "You can't use the remainder for the patient the next time she comes in or use it on another patient, so it has to be discarded as waste," Ms. Traylor said.
>
> Safety standards permit nurses to use drug leftovers in other patients only if used within six hours and only in specialized pharmacies.
>
> Told that she was using only about half of the drug that was purchased, Ms. Haddad said she was shocked.[20]

14. Dr. Bach and his co-authors proposed a simple fix for this serious problem. If each manufacturer, including Genentech, had offered just one additional smaller vial size (meaning a vial with less fill volume) for each of 18 different products, the amount of wasted medicine would have been reduced from $1.8 billion to $400 million per year, an annual savings of $1.4 billion, plus savings of another $600 million in markups to doctors and hospitals that would not have had to be paid. For each of the three Genentech products, the authors proposed one additional vial size that, if implemented, would have reduced the amounts paid for wasted drugs by than $400 million per year, plus associated markups.

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[19] Harris, *supra* (Ex. C).

[20] Harris, *supra*, at 2.

15. Dr. Bach's proposal is feasible. In Europe, drug companies, including Genentech, do just as Dr. Bach recommended. In Europe, Genentech's asthma drug Xolair (annual U.S. Sales: $1.8 billion[21]) is dosed in multiples of 75 mg. But until at least late 2018, Genentech sold Xolair only in 150 mg vials in the United States, leading to large amounts of waste for patients whose prescribed dose was 75, 225 or 375 mg. (In or about late 2018, it introduced 75 mg and 150 mg pre-filled syringes.) But because in Europe Genentech also sells Xolair in 75 mg vials, not one mg of Xolair ever went to waste there.

16. Since the Bach study was published, one company, Eli Lilly, substantially mitigated the problem for one of its cancer drugs. In March 2017, it added a smaller vial size to its existing 500 mg size of olaratumab (Brand Name: Lartruvo) and reported in a peer-reviewed study that this action reduced the amount of wasted product by 87.8%.[22] However, Genentech has not followed that responsible practice, and patients continue to pay hundreds of millions of dollars for medicine that necessarily is wasted.

17. Williamson and BCBSKC bring this case individually and on behalf of other end payors (patients, insurers, and other third-party payors) to recover the amounts they necessarily spent, through no fault of their own, on wasted medicine sold by Genentech.[23] Because absent this Court's intervention, Genentech's practice will undoubtedly continue unchecked for as long as there are cancer drugs. End Payors seek injunctive relief to put a stop to it.

18. Genentech's actions alleged in this Third Amended Complaint violate the California Unfair Competition Law ("UCL"), Cal. Bus. & Prof. Code §§ 17200, *et seq*.

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[21] https://www.fiercepharma.com/special-report/xolair (accessed 2/18/2019).

[22] Kristin M. Sheffield, Julie Kay Beyner, Ian A. Watson, *et al.*, *Minimization of olaratumab drug waste using real-world data*, 74 Am. J. Health-Syst. Pharm. E270 (2017) (Ex. B).

[23] Collectively, these medicines are referred to herein as "subject medicines." They include the medicines manufactured and sold by Defendants as identified in the "Parties" section of this Third Amended Complaint, as well as any other medicines that Defendants sell in quantities that lead to waste, as identified in discovery.

## PARTIES

**Plaintiffs**

19. Andrew Williamson is a resident of Liberty, Missouri, who was treated with Genentech's Rituxan at the University of Kansas Hospital, in Kansas City, Kansas, beginning in 2016.

20. BCBSKC is a duly organized and existing Missouri non-profit corporation with its primary place of business located in Kansas City, Missouri. Its service area covers Johnson and Wyandotte counties in the State of Kansas, including the location of the University of Kansas Hospital, where Andrew Williamson was treated. At all times relevant hereto, BCBSKC was the health insurer and payor for its subscriber, Williamson, and the medical and prescription drug plans of which he was a member. At all times relevant hereto, BCBSKC was also the payor for numerous other members treated with not only Rituxan, but also all other drugs manufactured, sold and distributed by the Defendants at issue in this Third Amended Complaint.

**Defendants**

21. Genentech, Inc., is a corporation incorporated in Delaware with its principal place of business at 1 DNA Way, South San Francisco, CA 94080. It is a subsidiary of the multinational pharmaceutical giant, Roche. Based in Switzerland, Roche claims to be the world's largest biotech company.[24]

22. Genentech USA, Inc., is a corporation incorporated in Delaware with its principal place of business at 1 DNA Way, South San Francisco, CA 94080. It is a wholly-owned subsidiary of Genentech, Inc.

23. These companies, collectively referred to as "Genentech," manufacture the following drugs that are sold in single-use vials resulting in large amounts of wasted medication.

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[24] *See* https://www.roche.com/about.htm (accessed 2/18/2019).

**Avastin**

24. Under the brand-name Avastin, Genentech sells the biologic product bevacizumab for treatment of colorectal cancer. FDA approved Avastin in 2004 under the license BLA #125085, and it has been sold in the United States ever since. Genentech classifies Avastin as a BioOncology drug.[25]

25. According to its product label,[26] Avastin is supplied in single-use vials as a solution in two sizes containing either 100 mg or 400 mg. The dosage of Avastin, which is administered by injection, is 5 or 10 mg/kg of body weight, depending on the other drug with which it is administered, for metastatic colorectal cancer. The dosage is 15 mg/kg for treatment of non-squamous non-small cell lung cancer. The dosage is 10 mg/kg for treatment of other cancers.

26. According to Dr. Bach's 2016 study, Avastin's sales in the United States in 2016 were expected to be $3.2 billion. That year, it was reported to be the seventh largest-selling drug in the world with $6.8 billion in sales.[27] As of February 2019, its WAC, meaning the manufacturer's list price in the United States, for the larger size was $ 3,732.00 per vial and for the smaller size was $ 933.00 per vial.

**Rituxan**

27. Under the brand-name Rituxan, Genentech sells the biologic product rituximab for treatment of Non-Hodgkin's Lymphoma ("NHL"), Chronic Lymphocytic Leukemia ("CLL"), and other conditions. FDA approved Rituxan in November 1997, under license numbers BLA # 103705 and BLA # 103737, and it has been sold in the United States ever since. Genentech classifies Rituxan as a BioOncology drug.[28]

28. According to its product label, Genentech supplies Rituxan in single-use vials as solutions in two sizes, 100 mg of Rituxan in 10 mL solution and 500 mg of Rituxan in 50 mL solution;

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[25] https://www.gene.com/medical-professionals/medicines (accessed 2/18/2019).

[26] https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/125085s323lbl.pdf (accessed 2/18/2019).

[27] http://www.genengnews.com/the-lists/the-top-15-best-selling-drugs-of-2016/77900868 (accessed 2/18/2019).

[28] https://www.gene.com/medical-professionals/medicines (accessed 2/18/2019).

these have the same concentration (10 mg/ml).[29] Its dosage, which is administered by injection, is 375 mg/m$^2$ of skin area for NHL and 375 mg/m$^2$ for CLL in the first cycle and 500 mg/m$^2$ in subsequent cycles.

29. According to Dr. Bach's 2016 study, Rituxan's sales in the United States in 2016 were expected to be $3.85 billion. That year, it was the fourth largest selling drug in the world with $8.6 billion in sales.[30] As of May 2017, the WAC for Rituxan was $ 1,084.06 per 10 mL vial and $ 5,420.28 per 50 mL vial.

**Kadcyla**

30. Under the brand-name Kadcyla, Genentech sells the biologic product ado-trastuzumab entansine for treatment of breast cancer. FDA approved Kadcyla on February 2013 under the license number BLA # 125514, and it has been sold in the United States ever since. Genentech classifies Kadcyla as a BioOncology drug.[31]

31. According to its product label, Kadcyla is supplied in single-use vials as a lyophilized powder in two sizes, 100 mg and 160 mg, both of which must be reconstituted with sterile water.[32] The dosage of Kadcyla, which is administered by injection, is 3.6 mg/kg of body weight.

32. According to Dr. Bach's 2016 study, Kadcyla's sales in the United States in 2016 were expected to be $414 million. As of May 2017, its WAC was $ 5,652.00 per 160 mg vial and $ 3,532.50 per 100 mg vial.

**Xolair**

33. Under the brand-name Xolair, Genentech co-developed and co-promotes with Novartis Pharmaceuticals Corporation the biologic product omalizumab for treatment of asthma, which Genentech sells in the United States. FDA approved Xolair in June 2003 under license number BLA

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[29] https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/103705s5451lbl.pdf (accessed 2/18/2019).

[30] http://www.genengnews.com/the-lists/the-top-15-best-selling-drugs-of-2016/77900868 (accessed 2/18/2019).

[31] https://www.gene.com/medical-professionals/medicines (accessed 2/18/2019).

[32] https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/125427s102lbl.pdf (accessed 2/18/2019).

#103976, and it has been sold in the United States ever since.

34. According to its product label, Xolair is supplied in single-use vials as a lyophilized powder to be reconstituted with water.[33] In the United States, each vial contains 150 mg. Xolair has an FDA-approved 75 mg vial size, which Genentech does not sell in the United States although that size is sold in Europe.[34] Xolair's dosage, which is administered by injection, is between 150 to 375 mg, depending on the patient's serum IgE level and body weight, according to charts on the product label.

35. In or about late 2018, Genentech introduced 75 mg and 150 mg prefilled syringes of Xolair in the United States. It did not introduce a 75 mg vial.[35]

36. Genentech's parent, Roche, reported that Xolair's sales in the United States in 2017 were 1,742 million Swiss francs,[36] or approximately $1.8 billion. As of May 2017, the WAC for Xolair, was $1,022.49 per vial in the United States.

**JURISDICTION AND VENUE**

37. This is a class action filed pursuant to Code of Civil Procedure Section 382. End Payors allege only state-law claims and allege no claims under federal law.

38. The California Superior Court has subject-matter jurisdiction over this action. *See* Code of Civil Procedure § 410.10.

39. This Court has personal jurisdiction over Defendants because their headquarters are located in California, and that is where they made the decisions and took actions at issue here.

40. Venue is proper in this judicial district pursuant to California Code of Civil Procedure section 395 because a substantial part of the events or omissions giving rise to the claims occurred and/or emanated from San Mateo County, where Genentech has its principal place of business, and

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[33] https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/103976s5231lbl.pdf (accessed 2/18/2019).

[34] Bach *et al.* (2016) at p. 2 or 7; http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/000606/WC500057298.pdf (accessed 2/18/2019).

[35] https://www.pharma.us.novartis.com/news/media-releases/novartis-announces-fda-approval-xolair-omalizumab-prefilled-syringe-formulation (accessed 2/18/2019).

[36] https://www.roche.com/dam/jcr:8476522e-ecb4-4c65-b91d-4a8301ccb14b/en/180201_IR_FY_release_en.pdf accessed 2/18/2019).

because Genentech has caused harm to class members residing in San Mateo County, California.

## FACTUAL ALLEGATIONS REGARDING GENENTECH'S LIABILITY

### The Bach Article

41. In early 2016, the peer-reviewed journal *The BMJ* (formerly the British Medical Journal) published a scientific paper entitled "*Overspending driven by oversized single dose vials of cancer drugs,*" which presented the results from a study by Peter Bach and colleagues at Memorial Sloan Kettering Cancer Center and the University of Chicago on wasteful healthcare spending.[37] *The BMJ* is one of the world's most prestigious scientific journals. In 2016, it ranked fourth in the world among general medical journals in "impact factor," a widely recognized measure of a journal's importance in its scientific field.[38]

42. Bach *et al.* (2016) reported on "the waste that can be created when expensive infused drugs are packed containing quantities larger than the amount needed." *Id.* at 1. As the authors stated:

> These drugs must be either administered or discarded once open, and because patients' body sizes are unlikely to match the amount of drug included in the vial, there is nearly always some left over. The leftover drug still has to be paid for, even when discarded, making it possible for drug companies to artificially increase the amount of drug they sell per treated patient by increasing the amount in each single dose vial relative to the typically required dose.

43. In their paper, Dr. Bach and his colleagues studied 20 cancer drugs, as well as two non-cancer drugs, including four drugs sold by Genentech: Avastin (generic name: bevacizuma); Rituxan (generic name: rituximab); Kadcyla (generic name: Ado-trastuzumab emtansine); and Xolair (generic name: omalizumab). Because these vials cannot be safely reused, any leftover amount must be discarded except in unusual circumstances. As a result, large amounts are not used and must be thrown away.

[37] Peter B. Bach *et al.*, *Overspending driven by oversized single dose vials of cancer drugs*, 352 BMJ 788 (2016) (Ex. A) ("the Bach study" or "Bach *et al.* (2016)").

[38] *See* http://www.bmj.com/about-bmj (accessed 2/18/2019).

44. The authors stated: "Regularly and systematically discarding expensive drugs is antithetical to efforts to reduce spending on healthcare services that provide no value." Bach *et al.* (2016) at 2.

45. Patients and their third-party payors pay substantial sums for the unused amounts in the vials.

46. According to Dr. Bach, as quoted in the *Washington Post*, patients and their third-party payors are "literally paying for drugs that go in the trash.... [Drug companies] are finding a way to charge patients and insurers for drugs that they don't even take."[39]

47. In their study, Bach and his colleagues "calculated the total amount of leftover drug and resulting 2016 US revenues for each drug ...." Bach *et al.* (2016) at 1. Their estimate was that for 20 cancer drugs manufacturers received, in the aggregate, $1.8 billion in annual revenues from discarded drugs. *Id.* at 1-2. Because of wholesale and retail markups, end payors paid much more than that for wasted drugs, in excess of $1 billion more. *Id.* at 2. Thus, the total amount that end payors paid for wasted amounts of these 20 drugs approached $3 billion in 2016 alone.

48. The authors made a simple and effective proposal for reducing the amount of waste: for each drug product, the seller would introduce one additional and smaller vial size. Their proposal would reduce the aggregate manufacturers' revenues for these drugs from $1.8 billion to $400 million per year and would save end payors approximately $2 billion a year. *Id.* at 2.

49. Bach *et al.* used the term "vial size" to refer not to the size of the vial or container, but to the amount of the drug in the vial (*i.e.*, the fill volume). For example, they referred to a "75 mg vial size" of one drug and "100 mg vial sizes" of another. *Id.* at 2, 5. Their reference to "vial size" is therefore not to the size of the container but to the amount of drug in the container. The containers of these drugs do not weigh 75 or 100 mg; the drug in the containers do. Similarly, in this Third Amended Complaint, End Payors use the term "vial size" to refer to the amount of drug in the vial.

[39] Laurie McGinley, "Americans are wasting $3 billion a year on discarded cancer drugs," March 1, 2016. (Ex. D.)

**Other Investigators Agree with Bach**

50. Other investigators agree on the financial impact of this wasteful practice. In 2017, the National Academy of Science published a Consensus Study Report entitled *Making Medicines Affordable: A National Imperative*.[40] Members of the committee that authored this work included academics, government officials, employees of insurers such as United Health and Blue Cross Blue Shield, and nonprofit health study groups such as the Henry J. Kaiser Family Foundation. The committee also included a former Chief Medical Officer of Merck & Co., Inc., and a former President and CEO of Genzyme Corporation, both manufactures of anti-cancer drugs.[41]

51. Chapter 3 of *Making Medicines Affordable* is entitled "Factors Influencing Affordability."[42] One of those factors is "Waste and Cost Due to Unused Drugs in the Supply Chain." Citing Bach *et al.* (2016), the authors stated:

> Every year drugs worth billions of dollars that have been purchased by health care organizations (e.g., retail pharmacies, hospitals, nursing homes) and patients are discarded. Some of this waste in the system could be eliminated by changing the way drugs are packaged and labeled. For example, vials of infused drugs are often available only in a single dose size that is sufficient to treat a physically large patient. As a result, the remaining drug must be discarded when a smaller patient is treated. Because 18 of the top 20 infused cancer drugs are sold in just one or two vial sizes, 10 percent of the purchased drug amount is discarded on average (Bach et al., 2016). Manufacturers propose dose sizes for marketing, and the FDA only reviews the request for safety considerations [citation omitted].[43]

52. Similarly, in 2017, the Organization for Economic Co-operation and Development ("OECD"), an organization of 35 countries (including the United States) devoted to "foster[ing] prosperity and fight[ing] poverty,"[44] published a report entitled *Tackling Wasteful Spending on*

[40] National Academies of Sciences, Engineering, and Medicine, *Making medicines affordable: A national imperative.* Washington, DC (2017) (*Making Medicines Affordable*).

[41] *Making Medicines Affordable* at vii-viii.

[42] *Making Medicines Affordable* at 73-124.

[43] *Making Medicines Affordable* at 99-100.

[44] *See* http://www.oecd.org/about/ (accessed 2/18/2019).

*Health.*[45] In a section entitled "Discard of unused pharmaceuticals and other medical supplies," the Report cited Bach *et al.* (2016) for the following:

> Discard of pharmaceuticals used in hospitals often occurs due to the too-large package size of single-dose drugs. This is particularly true for drugs whose dosage is based on a patient's body weight or size and come in single-dose packages. Such packaging means that these drugs must be either administered or discarded once open. When packaging is such that a patient's body size is unlikely to match the amount of drug in a single dose, some is nearly always left over. For example, a recent study estimates that unused leftover infused single-vial cancer drugs cost an additional USD 2 billion annually in the United States (Bach et al., 2016).[46]

53. In an editorial published in the peer-reviewed *Journal of Cancer* in September 2017, Dr. John Valgus of the University of North Carolina Medical Center, stated: "How significant is this problem of wasted cancer drugs? ... When formalized evaluations looking at the impact of cancer drug wastage are completed, the results are unanimous: the impact is significant."[47]

54. Writing in the peer-reviewed JAMA Oncology in early 2008, Daniel A. Goldstein of the Winship Cancer Institute at Emory University and his co-author stated: "Drug wastage is of economic importance. Of note, Bach et al recently estimated that over-sized vials for cancer drugs may lead to $3 billion of overspending each year. Real-world data from Canada have reinforced these claims, demonstrating the problems and potential solutions for drug wastage owing to oversized vials."[48]

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[45] OECD, *Tackling Wasteful Spending on Health* (2017) ("Tackling Wasteful Spending").

[46] Tackling Wasteful Spending at 163.

[47] John M.Valgus, Cancer Drug Wastage: *The Hidden Cost in Value-Based Cancer Care Delivery*, 123 Cancer 3445, 3445 (2017).

[48] Daniel A. Goldstein & Abigail Hirsch, *A Policy That Encourages Wastage of Expensive Medications—The JW Modifier*, 4 JAMA Oncol. 155, 155 (2018) (footnotes omitted).

55. At least one manufacturer of cancer drugs agrees with these principles and their importance. In a peer-reviewed 2017 paper, authors from Eli Lilly and Company stated: "The reduction of oncology drug wastage offers the potential to decrease pharmaceutical expenditures.... Decreasing waste is a desirable strategy to reduce expenditures on oncology drugs without affecting health outcomes or quality of care or limiting specific drug use."[49]

56. Two British researchers, writing in the journal *Applied Health Economics and Health Policy* in December 2018, could have been talking about Genentech when they stated that "where the larger vial is perfectly divisible by the smaller vial, i.e. one is a multiple of the other, wastage is higher. This is unsurprising, as vial sizes that are not divisible can create more combinations with no wastage.... Despite this seemingly obvious finding, many novel pharmaceuticals are available only with perfectly divisible vial sizes."[50] Those pharmaceuticals include Genentech's Avastin (400 mg and 100 mg) and Rituxan (500 mg and 100 mg).

**Amounts that Class Members Needlessly Spend on Unusable Mediations Are Substantial.**

57. The amount spent on wasted drugs for just one patient can total many thousands of dollars a year for Genentech's drugs.

**Avastin**

58. Avastin is sold in vials containing either 100 mg or 400 mg. The initial dosage of Avastin for patients with lung cancer at the outset of treatment is 15 milligrams per kilogram of body weight, or 1,218 mg for the average male patient and 1,013.1 for the average female patient (average weight: 81.20 kg for men and 67.54 kg for women). [51] To meet that dose, the average male patient must receive three 400 mg vials and one 100 mg vial (1,300 mg altogether), with 82 mg, or 82% of the 100 mg vial, being unused and thrown away. The average female patient would receive two 400 mg vials and three 100 mg vials (1,100 mg in total), with 86.1 mg, or 86.1% of the last 100 mg vial, being unused and going to waste.

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[49] Sheffield *et al.* at e269-e270 (2017).

[50] Anthony J. Hartswell & Joshua K. Porter, Reducing Drug Wastage in Pharmaceuticals Dosed by Weight or Body Surface Areas by Optimising Vial Sizes, Appl Health Econ Health Policy (2018).

[51] Sheffield *et al.*, (2017) at Table 3 (Ex. B).

59. The cost of those wasted amounts can run into many thousands of dollars per patient. The WAC – the published list price charged by the manufacturer – of a 100 mg vial of Avastin in February2019 was $933.00. But because 82 mg of the drug had to be discarded, Genentech received $756.06 for wasted drug from just that one treatment. Similarly, Genentech received $803.31 for wasted drug for the average female patient's treatment in May 2017.

60. Genentech's recommended course calls for the treatment to be repeated every three weeks.[52] Thus, for the average patient receiving Avastin for lung cancer, Genentech reaps $12,096.96 and $12,852.96, for males and females, respectively, in annual revenues for Avastin that must be thrown away.

61. Those amounts are just what the manufacturer receives. Patients and insurers must pay much more because of wholesale and retail mark-ups. *See* Bach *et al.* (2016) at 2 ("We have focused on how much money companies earn in terms of revenues from leftover drug, not how much payers and patients are spending on them, which is a larger number due to the fact that distributing intermediaries and treating doctors and hospitals mark-up drugs when they bill for them.").

62. In Table 1, Bach *et al.* (2016) list the manufacturers' expected 2016 revenue from wasted drug. For Avastin, that amount comes to $284.49 million per year.

**Rituxan**

63. Rituxan is sold in 100 and 500 mg vials. The dose for Non-Hodgkin's Lymphoma is 375 mg/m$^2$, or 637.5 mg for the typical patient, according to data presented by Bach *et al.* on BMJ's website.[53] The typical patient must be administered one 500 mg vial and two 100 mg vials, with 62.5 mg in the last vial going to waste.

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[52] *See* Avastin label at § 2.2, https://www.accessdata.fda.gov/drugsatfda_docs/label/2011/125085s225lbl.pdf (accessed 2/18/2019).

[53] BMJ 2016;352:i788, http://www.bmj.com/content/352/bmj.i788 (accessed 2/18/2019).

64. The WAC for the 100 mg vial of Rituxan in February 2019 was $1,084.06. Thus, Genentech reaped $677.54 from the wasted portion of 62.5 mg with that one treatment. Because the recommended course of treatment includes four, eight, or twelve doses over several weeks,[54] Genentech's revenue from the sale of unneeded drug for treatment of a typical patient is $2,710.16, $5,420.32, or $8,130.48.

65. According to Bach *et al.* (2016), Genentech receives $253.9 million in annual revenue from the wasted portions of all the Rituxan it sells in the United States.

**Kadcyla**

66. Genentech's Kadcyla is sold in 100 mg and 160 mg vials for breast cancer with a dose of 3.6 mg/kg. According to Sheffield *et al.* (2017), the average patient with breast cancer weighs 76.31 kg. That means that the average patient receives a dose of 274.716 mg, which requires three 100 mg vials, with 25.284 mg left over from the last vial.

67. The WAC in May 2017 for the 100 mg vial was $3,532.50; thus, Genentech received $893.16 per dose for the leftover amount of 25.284 mg from one treatment of a typical patient with Kadcyla. Genentech's total revenue for unneeded drug per typical patient is much more than that because Kadcyla is administered "every 3 weeks (21-day cycle) until disease progression or unacceptable toxicity."[55]

68. Bach *et al.* (2016) estimate that Genentech received $23.7 million per year for the total discarded amount of Kadcyla.

**Xolair**

69. In the United States, until at least late 2018, Genentech's asthma drug Xolair was sold only in 150 mg vials, even though FDA had approved the product in 75 mg vials. For many patients,

[54] *See* Rituxan label at § 2.2, https://www.accessdata.fda.gov/drugsatfda_docs/label/2014/103705s5432lbl.pdf (accessed 2/18/2019).

[55] *See* Kadcyla label at § 2.1, https://www.accessdata.fda.gov/drugsatfda_docs/label/2016/125427s096lbl.pdf (accessed 2/18/2019).

the Xolair dose is exactly 75 mg, 225 mg, or 375 mg, as shown in the following table, with the result that, for those patients, half of one vial invariably had to be discarded.[56]

| Patients 12 and older | | |
|---|---|---|
| **Dose (mg)** | **Weight (kg)** | **Pre-Treatment Serum IgE (IU/mL)** |
| 225 | >60-70 | >200-300 |
| 225 | >60-70 | >300-400 |
| 225 | >70-90 | >200-300 |
| 225 | >90-150 | >100-200 |
| 375 | 30-60 | >600-700 |
| 375 | >60-70 | >500-600 |
| 375 | >70-90 | >300-400 |
| | | |
| **Patients from 6 to younger than 12** | | |
| **Dose (mg)** | **Weight (kg)** | **Pre-Treatment Serum IgE (IU/mL)** |
| 75 | 20-40 | 30-100 |
| 225 | 20-25 | >300-500 |
| 225 | 20-25 | >700-1100 |
| 225 | >25-30 | >300-400 |
| 225 | >25-30 | >600-900 |
| 225 | >30-40 | >400-700 |
| 225 | >40-50 | >300-500 |
| 225 | >50-60 | >300-400 |
| 225 | >60-70 | >200-400 |
| 225 | >70-90 | >200-300 |
| 225 | >90-125 | >100-200 |
| 375 | >25-30 | >1200-1300 |
| 375 | >30-40 | >900-1100 |
| 375 | >40-50 | >700-900 |
| 375 | >50-60 | >600-700 |
| 375 | >60-70 | >500-600 |
| 375 | >70-90 | >400-500 |
| 375 | >125-150 | >200-300 |

[56] *See* Xolair's label, https://www.accessdata.fda.gov/drugsatfda_docs/label/2016/103976s5225lbl.pdf. (accessed 2/18/2019).

70. Patients in each of the above categories required 75 mg from one of their 150 mg vials, with 75 mg, or 50%, of that vial, being unused and discarded. Because the WAC for Xolair in May 2017 was $1,022.49, the manufacturer received $511.25 for the wasted portion of that one treatment.

71. The course of treatment for Xolair includes a dose every two or four weeks. Thus, the wasted amount for each treatment can be multiplied by 26 or by 13 to determine the amount the manufacturer received every year from each such patient or insurer for medicine that had to be thrown away ($13,292.37 or $6,646.19).

**How Genentech Could Have Easily Reduced the Amount of Waste**

72. Genentech could have substantially reduced the amount of waste by adding just one additional vial size per product. Bach *et al.* (2016) showed how to do it.

73. For example, if, as Bach *et al.* recommended, Genentech had added a 20 mg size to the existing 400 mg and 100 mg vials of its colorectal drug Avastin, the average male patient – who, as shown above, requires 1,218 mg – could have been treated with three 400 mg vials and one 20 mg vial (instead of a 100 mg vial to go with the three 400 mg vials). That would have reduced the amount of wasted medicine from 82 mg to only 2 mg, a reduction of 97.5%, while not increasing the number of vials per treatment. Similarly, the average female patient – who, as shown above, requires 1,013.1 mg – could have been treated with two 400 mg vials, two 100 mg vials and one 20 mg vial (replacing one 100 mg vial). That would have reduced the amount of wasted drug from 86.1 mg to 6.9 mg, a reduction of 92.0%. Again, it would not have increased the number of vials per treatment.

74. Bach *et al.* (2016) proposed one additional size for each of 18 cancer products including the three Genentech cancer products at issue in this case. In each instance, if Genentech had added that smaller size, there would have been a large reduction in the amount wasted. The table below shows the reduction in waste for the average or typical patient treated with Genentech's products (all quantities are mg except as noted):

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| Drug | Existing vial(s) | Added vial | Typical/ average dose | Existing wasted drug | Revised wasted drug | Pctg. reduction |
|---|---|---|---|---|---|---|
| Avastin | 400, 100 | 20 | 1,218 (m)<br>1,013.1 (f) | 82 (male)<br>86.1 (female) | 2 (male)<br>7.9 (female) | 98%<br>91% |
| Kadcyla | 160, 100 | 20 | 274.716 | 25.284 | 5.284 | 79% |
| Rituxan | 500. 100 | 40 | 637.5 | 62.5 | 2.5 | 96% |

75. The number of vials needed to provide the typical or average dose would not have been increased if Genentech had offered the added vial that Bach *et al.* (2016) recommended. As noted above, the average male and female patient would have needed four and five vials of Avastin, respectively, the same as with the existing vials. Similarly, the average or typical patient would have needed three vials of Kadcyla or three vials of Rituxan, the same as with the existing vials.

76. In the case of Xolair, if Genentech had introduced a 75 mg vial, it would not have increased the number of vials needed per treatment. Instead, it would have meant replacing one 150 mg vial with a 75 mg vial for patients who had Xolair go to waste. In each instance, that was 75 mg wasted out of a 150 mg vial.

77. Bach *et al.* (2016) showed the aggregate financial savings that would have resulted when all patients are considered. The following table, adapted from Bach *et al.*'s Table 3, shows those savings for Genentech's cancer drugs. The last two columns show the annual dollar value of the waste from existing vials and the lesser amount that would result from adding one more vial size (both in millions of dollars):

**Bach *et al.*'s proposed additional vial sizes to reduce the amount of waste on leftover drug**

| Name | Currently available vial sizes (mg) | Proposed Additional vial size | Estimated waste in 2016 ($million) | |
|---|---|---|---|---|
| | | | With existing vials | With additional vial |
| Avastin | 400, 100 | 20 | $284 | $60 |
| Kadcyla | 160, 100 | 20 | $24 | $12 |
| Rituxan | 500, 100 | 40 | $254 | $53 |
| Total | — | — | $562 | $125 |

78. The sums in the last two columns indicate that Genentech's annual revenues from wasted subject medicines totaled $562 million with its existing vial sizes but would have been reduced to $125 million, a savings of $437 million, with the addition of one smaller vial for each drug. These savings are understated because they do not account for doctor and hospital markups on these drugs. (The mark-ups would have been calculated on lower amounts for the smaller vials.) When lower

mark-ups are included, the total savings would have been even larger.

79. Rather than limiting Xolair to 150 mg vials, Genentech could have eliminated *all* waste of Xolair by marketing the already approved 75 mg vial size as it does in Europe or by doing as it did in or about late 2018 in marketing 75 mg prefilled syringes of Xolair in the United States.

**Two Manufacturers That Minimize Waste**

80. Minimizing waste is feasible. Two other manufacturers have minimized waste by making small vial sizes available.

**Treanda**

81. Cephalon, Inc., a subsidiary of Teva Pharmaceuticals, Ltd., sells its leukemia drug Treanda in four different single-use vial sizes. Two vial sizes contain a lyophilized powder, either 100 mg or 25 mg, that are to be reconstituted with sterile water. Two contain solutions with either 45 or 180 mg of the drug.[57]

82. When it was introduced in 2008, Treanda was sold in only one size, 100 mg.[58] The following year Cephalon added the 25 mg size[59] and subsequently the 45 mg and 180 mg sizes.

83. As Bach *et al.* (2016) report, this array of sizes enables medical providers to administer the drug without significant waste. Treanda's dosage is 100 mg/m$^2$. According to data presented by Bach *et al.* on BMJ's website, [60] that works out to a dose of 170 mg for a typical patient. As Bach *et al.* (2016) report, the medical provider can combine one vial each of the 100, 45, and 25 mg sizes to provide the exact dose for the typical patient with no waste (as well as either the exact dose or nearly the exact dose even for atypical patients). As a result, Bach *et al.* (2016) estimate that an average of only 1% of Treanda is wasted.

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[57] *See* October 2016 label, https://www.accessdata.fda.gov/drugsatfda_docs/label/2016/022249s022lbl.pdf (accessed 2/18/2019).

[58] *See* the original Treanda label at https://www.accessdata.fda.gov/drugsatfda_docs/label/2008/022249lbl.pdf (accessed 2/18/2019).

[59] *See* April 2009 label, https://www.accessdata.fda.gov/drugsatfda_docs/label/2009/022249s001lbl.pdf (accessed 2/18/2019).

[60] BMJ 2016;352:i788, http://www.bmj.com/content/352/bmj.i788 (accessed 2/18/2019).

84. There is no reason why Genentch could not have done (and could not now do for Avastin, Rituxan, and Kadcyla) the same thing for its four products at issue in this lawsuit by adding smaller sizes to reduce or eliminate waste.

**Lartruvo**

85. Another example of a company that responsibly sized a product to reduce waste is Eli Lilly, which introduced its Lartruvo biologic product (generic name: olaratumab) to treat soft tissue sarcoma and other cancers. FDA licensed Lartruvo in October 2016 pursuant to the license BLA # 761038.

86. As originally licensed, Lartruvo came in only 500 mg vials. However, as explained below, in March 2017, Eli Lilly added a smaller size vial of 190 mg.

87. In a peer-reviewed publication in the American Journal of Health-System Pharmacists, Eli Lilly's scientists reported on the study that led it to introduce that smaller size.[61] This journal "is the official publication of the American Society of Health-System Pharmacists" and "is the most widely recognized and respected clinical pharmacy journal in the world."[62]

88. In the introduction to their article, these Eli Lilly scientists explained the reason for their study: "The reduction of oncology drug wastage offers the potential to decrease pharmaceutical expenditures.... Decreasing waste is a desirable strategy to reduce expenditures on oncology drugs without affecting health outcomes or quality of care or limiting specific drug use." Sheffield *et al.* at e269-e270 (2017).

89. According to these Eli Lilly scientists, "available vial sizes often are not well suited to cost-efficient administration of the drug dosages possible across the distributions of patient weight and BSA [body surface area]." *Id.* at e270. The authors made clear where the solution to this problem lies: "Manufacturers can help reduce waste by producing appropriate and multiple vial sizes based on the distribution of body sizes across the targeted patient population." *Id.*

[61] Sheffield, *et al.*, (2017) (Ex. B).

[62] http://www.ajhp.org/content/mission-and-vision (accessed 2/18/2019).

90. To advance that process, the Eli Lilly scientists conducted a study to determine the weight and BSA data of patients with various forms of cancer. Eli Lilly then used the study results to determine the "optimal volume for a planned new olaratumab [brand-name: Lartruvo] vial size and quantify the reduction in drug waste with the addition of the new vial size." *Id.*

91. Based on the results of this study, Eli Lilly added a smaller, 190 mg-size vial in March 2017 to its existing 500 mg vial.[63] The addition of the smaller vial reduced waste by 87.6%. *Id.* at e269.

92. The authors indicated that Eli Lilly carefully selected a new vial size that would limit the number of vials needed per treatment to six or fewer. They stated:

> The objectives of waste minimization and vial minimization cannot be simultaneously optimized. At the extreme, producing very small vial sizes would allow for almost any dose with minimal waste. However, preparation would become unduly burdensome for the pharmacy to handle numerous vials. In addition, producing very small vial sizes may increase the potential for medication errors and microbial contamination. Therefore, to control pharmacy handling, we imposed a limit of no more than 6 vials to be opened for any given patient.

*Id.* at e275-e276 (footnote omitted). As noted above, if Genentech had followed Bach *et al.*'s recommendation, it would not have had to increase the number of vials per treatment for the average or typical patient.

93. The benefits of the 190 mg vial for Lartruvo can be seen by looking at patients of average weight with soft tissue sarcoma, which this study found to be 85.27 kg for male patients and 72.89 for female patients. *Id.* at e274, Table 3. Lartruvo's dose is 15 mg/kg. *Id.* at e271. Thus, the total dose for a male soft tissue sarcoma patient of average weight is 1,279.05 mg. If just 500 mg vials were available, that would require three vials, leaving 220.95 mg left over. However, a patient could be administered two 500 mg and two 190 mg vials for a total of 1,380 mg, with only 100.95 mg left over. The difference in price is considerable. In May 2017, the WAC for a 500 mg vial of Lartruvo was $2,360 or $7,080 for three vials. But the WAC for a 190 mg vial was only $896.80 per vial or

[63] *See* http://www.njsom.org/aws/NJSOM/asset_manager/get_file/152920 (accessed 2/18/2019) for introduction date.

$6,513.60 for two 500 mg vials and two 190 mg vials. With administration of two 500 mg vials and two 190 mg vials, there would be four vials but a savings of $566.40.

94. Female patients realized similar savings from the smaller vial of Lartruvo. The dose for soft tissue sarcoma in a female patient of average weight is 1,093.35 mg (72.89 kg times 15 mg/kg). With only 500 mg vials, that would require three vials, leaving 406.65 mg left over. But a female patient would get the correct dose from six 190 mg vials, providing a total of 1,140 mg, with only 46.65 left over. Again, the price difference is substantial. The WAC for three 500 mg vials, as shown above, is $7,080; for six 190 mg vials it is $5,380.80, representing a savings of $1,699.20.

95. Sheffield *et al.* (2017) states that one of its "key points" is that "[m]anufacturers can help reduce drug waste by producing multiple vial sizes based on weight and BSA distributions across the targeted patient population in actual clinical practice." *Id.* at e270. Yet, two years after the scientific literature described how Eli Lilly had altered its vial sizes and the consequences of doing so, Genentech has not followed Eli Lilly's example.

**Genentech Offered a Smaller Size of Xolair in Europe, but Not in the United States.**

96. Bach *et al.* (2016) report that many manufacturers are already doing in Europe, but not in the United States, what these authors and Eli Lilly recommend: selling smaller vial sizes to save money for patients and insurers. Dr. Leonard Saltz, a co-author of the Bach study, told the New York Times: "You have these incredibly expensive drugs, and you can only buy them in bulk. What's really interesting is that they're selling these drugs in smaller vials in Europe …."[64]

97. One example of this Europe-United States discrepancy was Genentech's asthma treatment Xolair. Xolair is sold in 75 mg vials in Europe,[65] but until in or about late 2018 only in 150 mg vials in the United States. Xolair is dosed in 75 mg increments (*i.e.*, 75 mg, 150 mg, 225 mg, etc.), depending on the patient's age, weight, and serum IgE level. This means that no amount of Xolair *ever* systematically goes to waste in Europe. But until at least late 2018 for all patients whose dose was not evenly divisible by 150, half a vial, or 75 mg, was wasted with every treatment in the United States.

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[64] Harris, *supra*, at 2.

[65] http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/000606/WC500057298.pdf (accessed 2/18/2019).

98. There is no legitimate reason why, before late 2018, Genentech could not have given U.S. patients the benefit of the smaller vial sizes that it gave to patients in Europe.

**FACTS RELATED TO WILLIAMSON'S TREATMENT WITH GENENTECH'S DRUGS, WILLIAMSON'S CHARGES AND END PAYORS' PAYMENTS**

99. Beginning in January 2016, Williamson was treated with Rituxan for Follicular Lymphoma at the University of Kansas Hospital in Kansas City, Kansas**.**

100. Between January 28, 2016 and June 16, 2016, Williamson was treated six times with Rituxan, each time with a dose of 772.5 mg. On each of these occasions, the hospital used either eight 100 mg vials or one 500 mg vial and three 100 mg vials; on each occasion, the total charges were $34,189.33 per treatment.

101. From September 15, 2016 until August 24, 2017, Williamson was given a second course of treatment, each time with a dose of 780 mg of Rituxan. On each of these occasions, the hospital used one 500 mg vial and three 100 mg vials. On the first four treatments during this course, the charges were $37,464.99 per treatment. On the last treatment during this course, the charges were $43,230.99.

102. Beginning on November 16, 2017, Williamson was given a third course, with treatments of 800 mg. On November 16, 2017 and March 1, 2018, the hospital used one 500 mg vial and three 100 mg vials, for which the charges were $43,230.99. Notably, this was the same charge that the hospital imposed for the treatment on August 24, 2017, even though the dose was 780 mg on August 24, 2017, and 800 mg for the later treatments.

103. Because Genentech supplies Rituxan in only 500 mg and 100 mg single-use vials, Willliamson's medical provider was forced to use vials totaling 800 mg for each treatment, even when the prescribed dosage was less than 800 mg. Thus, 27.5 mg had to be discarded for each of the treatments with a dose of 772.5 mg and 20 mg had to be discarded for each of the treatments with a dose of 780 mg. The charges for the unused portions of Rituxan totaled $11,878.82.

104. If Genentech had added a 40 mg vial of Rituxan, Williamson's doctors could have used one 500 mg vial, two 100 mg vials, and two 40 mg vials to reduce the amount of unused drug to 7.5 mg and 0 mg per treatment for the first two courses respectively. That vial configuration would have

meant that Williamson's treatment could have been accomplished with five vials, fewer vials than Eli Lilly's self-imposed limit of six vials. That vial configuration would have reduced the charges for unused Rituxan to $1,923.25, representing a savings of $9,955.67.

105. For each of these treatments, some or all of the hospital and treatment charges were paid by BCBSKC, Williamson's insurer. BCBSKC's payments for each of Williamson's treatment doses used are shown in the table attached as Exhibit F along with the above-referenced charges and savings that would have been realized if a 40 mg vial of Rituxan had been available. For the treatment of March 2, 2017, Williamson paid a $231.15 deductible out of his own pocket. All remaining payments were made by BCBSKC.

106. During the period March 1, 2012 until the present, BCBSKC has paid tens of millions of dollars for Avastin® (bevacizumab), Kadcyla® [ado-trastuzumab emtansine], Rituxan® [rituximab], and Xolair®- [omalizumab], which includes substantial overpayments for wasted drugs, as substantiated by the Bach calculation of waste during the relevant period of time, all of which exceeds the jurisdictional amount of this court.

**GENENTECH'S SCHEME ORIGINATED AND IS DIRECTED FROM CALIFORNIA**

107. On information and belief, Genentech made the decisions and took the actions that violated the UCL in California. This belief is based on the following:

108. California is the center of Genentech's business operations. According to Genentech's website, www.gene.com, Genentech maintains three facilities in California: its headquarters in South San Francisco; a research, manufacturing, and business center in Oceanside; and a manufacturing plant in Vacaville.

109. Genentech's campus in South San Francisco includes "multiple buildings that house an advanced research center, manufacturing operations and various business functions. The South San Francisco campus continues to serve as Genentech's corporate headquarters and is also the headquarters for Roche's pharmaceutical operations in the United States."[66] Roche is Genentech's parent.

[66] https://www.gene.com/contact-us/visit-us/s-san-francisco (accessed 2/18/2019).

110. The current labels of each of the subject medicines indicate that they were manufactured by Genentech, with an address in South San Francisco:

A. Avastin:

**Avastin® (bevacizumab)**
Manufactured by:
**Genentech, Inc.**
A Member of the Roche Group
1 DNA Way
South San Francisco, CA 94080-4990[67]

B. Kadcyla:

KADCYLA® [ado-trastuzumab emtansine]
Manufactured by:
**Genentech, Inc.**
A Member of the Roche Group
1 DNA Way
South San Francisco, CA 94080-4990
U.S. License No: 1048[68]

C. Rituxan:

**RITUXAN® [rituximab]**
Manufactured by:
**Genentech, Inc.**
A Member of the Roche Group
1 DNA Way
South San Francisco, CA 94080-4990
U.S. License No: 1048[69]

D. Xolair:

Manufactured by:
**Genentech, Inc.**
A Member of the Roche Group
1 DNA Way
South San Francisco, CA 94080-4990
U.S. License No: 1048[70]

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[67] https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/125085s323lbl.pdf (accessed 2/18/2019).

[68] https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/125427s102lbl.pdf (accessed 2/18/2019).

[69] https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/103705s5451lbl.pdf (accessed 2/18/2019).

[70] https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/103976s5231lbl.pdf (accessed 2/18/2019).

111. Most of Genentech's employees are located in California. On its website, www.gene.com, Genentech instructs readers to "Get to know us better. Check us out on ... LinkedIn" and links to Genentech's page on LinkedIn.[71] Genentech's page in turn links to a "jobs" page with a section titled "Where we work," which shows a total of 17,981 employees in the San Francisco area and 1,455 elsewhere in California, out of a total of 20,626 employees; thus, 94% of the total are in California, with 87% at the South San Francisco headquarters.[72]

112. Genentech made its decisions regarding the packaging of the products at issue at its headquarters in South San Francisco, where all of its principal executives are located.

113. Genentech has a seven-member Executive Committee.[73] All members of the Executive committee are based in California: Chief Executive Officer Bill Anderson; Ed Harrington, Chief Financial Officer;[74] Sandra Horning, Executive Vice President, Global Development and Chief Medical Officer;[75] Michael Varney, Executive Vice President, Genentech Research and Early Development;[76] Sean Johnston, Senior Vice President and General Counsel;[77] Kimball Hall, Senior Vice President, Manufacturing Biologics Drug Substance;[78] and Nancy Vitale, Senior Vice President of Human Resources, Genentech and Regional Human Resources Head, North America.[79]

114. Genentech's LinkedIn site shows that the following key employees responsible for Genentech's product development, product strategy, and marketing of the subject medicines are located in the San Francisco area: the Senior Vice President, Global Product Strategy Oncology[80]; the

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[71] https://www.gene.com/contact-us/connect-with-us (accessed 2/18/2019).

[72] https://www.linkedin.com/company/genentech/jobs/ (accessed 2/18/2019).

[73] https://www.gene.com/about-us/leadership/executive-committee (accessed 12/11/2018).

[74] https://www.linkedin.com/in/ed-harrington-190a894/ (accessed 2/18/2019).

[75] https://www.linkedin.com/in/sandra-horning-11090788/ (accessed 2/18/2019).

[76] https://www.linkedin.com/in/mike-varney-27114b1/ (accessed 2/18/2019).

[77] https://www.martindale.com/south-san-francisco/california/sean-a-johnston-271855-a/ (accessed 2/18/2019).

[78] https://www.linkedin.com/in/kimball-hall-a6133012/ (accessed 2/18/2019).

[79] https://www.linkedin.com/in/nancy-vitale-a144bb/ (accessed 2/18/2019).

[80] https://www.linkedin.com/in/cindy-perettie-69623b1/ (accessed 2/18/2019).

Senior Vice President, Global Strategy, Immunology[81]; the Vice President of Global Product Development, Hematology/Oncology;[82] the Vice President responsible for development of Avastin[83]; the Medical Director of Global Product Development[84]; the Marketing Director for Genentech BioOncology (Cancer Immunotherapy)[85]; the Senior Product Manager and Product Manager for Avastin Marketing[86]; the Director of Marketing for Genentech's "HER2" products, including Kadcyla[87]; the Senior Product Manager for Xolair Marketing[88]; and an employee with "[o]verall leadership to over 30 marketers accountable for all marketing aspects of Genentech Hematology, including for Rituxan.[89] Many other Genentech employees with responsibilities for product management, marketing, and development of the products at issue are located in the San Francisco area.[90]

115. According to Genentech's website, Genentech's Pharma Technical North America (PTNA) Operations group, headed by Genentech's Global Head of Technical Operations Tim Moore

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[81] https://www.linkedin.com/in/frank-lee-9b446b8/ (accessed 2/18/2019).

[82] https://www.linkedin.com/in/nancy-valente-m-d-46461bb/ (accessed 2/18/2019).

[83] https://www.linkedin.com/in/philippe-bishop-aratinga-bio/ (accessed 2/18/2019); he had this position from 2008-2009).

[84] https://www.linkedin.com/in/ted-omachi-a773964/.

[85] https://www.linkedin.com/in/william-f-waas-2a8331a/ (accessed 2/18/2019). As noted above, Avastin, Kadcyla and Rituxan are biooncology drugs.

[86] https://www.linkedin.com/in/brianjpetteys/ and https://www.linkedin.com/in/karyn-heffernan-66526267/ (accessed 2/18/2019).

[87] https://www.linkedin.com/in/michelle-kunkel-mba-b-s-75364413/ (accessed 2/18/2019).

[88] https://www.linkedin.com/in/manoj-warrier-078b913/ (accessed 2/18/2019).

[89] https://www.linkedin.com/in/nnazmi/ (accessed 2/18/2019).

[90] https://www.linkedin.com/in/erikhaghjoo/, https://www.linkedin.com/in/brooke-aghajani-2144277/, https://www.linkedin.com/in/thomasvanstavern/, https://www.linkedin.com/in/manoj-warrier-078b913/, https://www.linkedin.com/in/kerstin-schmidt-3ab0687/, https://www.linkedin.com/in/michaeltancer/, https://www.linkedin.com/in/tricia-kim-280212b/, https://www.linkedin.com/in/michelle-dinapoli-73593a5/, https://www.linkedin.com/in/nick-mascioli-3935625/, https://www.linkedin.com/in/angie-redmann-b636574/, https://www.linkedin.com/in/sinhabrownnisha/, https://www.linkedin.com/in/stephanie-wang-570baa5/, https://www.linkedin.com/in/lynn-siu-346575b/, https://www.linkedin.com/in/thomasvanstavern/, https://www.linkedin.com/in/karen-dittrich-003222a/, https://www.linkedin.com/in/uthragopal/, https://www.linkedin.com/in/venu-vittaladevuni-426408/, https://www.linkedin.com/in/wei-liu-b772025/ (all accessed 2/18/2019).

is responsible for packaging its products into vials.[91] Tim Moore is located in the San Francisco Bay area.[92]

**CLASS ACTION ALLEGATIONS**

116. End Payors bring this action on behalf of themselves and as representatives of all others similarly situated. This action has been brought and may be properly maintained on behalf of the class proposed herein under Section 382 of the California Code of Civil Procedure because this action satisfies the numerosity, commonality, typicality, adequacy, predominance, and superiority requirements of Section 382 of the Code of Civil Procedure. End Payors seek certification of the following class initially defined as follows:

> *All end payors who, during the Class Period, paid for Avastin, Rituxan, Kadcyla or Xolair, a portion of which was discarded because the quantity in the vials exceed the patient's dose (the "Class").*

117. For purposes of the above class definition, "Class Period" encompasses the applicable period of limitations, as well as the period beginning with the filing of this lawsuit and ending on the date notice is sent to the class.

118. Excluded from the Class is Genentech, any entity in which Genentech has a controlling interest, is a parent or subsidiary, or which is controlled by Genentech, and the officers, directors, affiliates, legal representatives, predecessors, successors, and assigns of Genentech. Also excluded from the Class are counsel and members of the immediate families of counsel for End Payors as well as the judges and court personnel in this case and any members of their immediate families.

119. End Payors reserve the right to amend or modify the above class definition with greater specificity or division into subclasses after having had an opportunity to conduct discovery.

120. This action has been brought and may be properly maintained on behalf of the Class proposed herein under Section 382 of the California Code of Civil Procedure.

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[91] https://www.gene.com/careers/professional-areas/technical-operations (accessed 2/18/2019).

[92] https://www.linkedin.com/in/timothy-moore-65282820/ (accessed 2/18/2019).

121. **Numerosity**. The exact number of Class Members is currently unknown to End Payors, but the total number of Class Members is so numerous that joinder of all Class Members would be impracticable.

122. **Commonality and Predominance**. There are questions of law and fact common to the Class that predominate over any questions affecting individual members of each respective class. These common questions of law and fact include, without limitation:

A. Does Genentech sell the subject medicines in vials that are too large for the needs of patients so that large portions must be thrown away?

B. Do patients and their third-party payors pay for the portions of the subject medicines that must be thrown away?

C. Can Genentech reduce the amount of waste by selling its products in smaller vial sizes?

D. Do Genentech's alleged practices violate the unlawful and/or unfairness prongs of California's Unfair Competition Law (Bus. & Prof. Code, §§ 17200, *et seq*.)?

E. Are End Payors and Class Members entitled to be reimbursed for the sums they paid for the portions of the subject medicines that must be discarded?

123. **Typicality**. End Payors' claims are typical of the claims of the Class they seek to represent. End Payors and all Class Members were exposed to uniform practices and sustained injuries arising out of and caused by Genentech's conduct.

124. **Adequacy of Representation.** End Payors are adequate representatives of the Class and have no conflict of interest with other class members. End Payors' attorneys are experienced in this type of litigation and will prosecute the action adequately and vigorously on behalf of the Class.

125. **Appropriateness of injunctive relief.** Because Genentech's practices apply to all patients who are administered the subject medicines, Genentech has acted on grounds that apply generally to the Class, so that final injunctive relief is appropriate respecting the Class as a whole.

126. **Superiority.** A class action is superior to other available methods for fairly and efficiently adjudicating the controversy. Since the amount of each individual Class Member's claim is small relative to the complexity of the litigation, and due to the financial resources of Genentech, no

Class Member could afford to seek legal redress individually for the claims alleged herein. Therefore, absent a class action, Class Members will continue to suffer losses and Genentech's misconduct will continue without remedy. Even if Class Members themselves could afford such individual litigation, the court system could not. Given the complex legal and factual issues involved, individualized litigation would significantly increase the delay and expense to all parties and to the Court. Individualized litigation would also create the potential for inconsistent or contradictory rulings. By contrast, a class action presents far fewer management difficulties, allows claims to be heard which might otherwise go unheard because of the relative expense of bringing individual lawsuits, and provides the benefits of adjudication, economies of scale and comprehensive supervision by a single court. Finally, End Payors know of no difficulty that will be encountered in the management of this litigation which would preclude its maintenance as a class action.

**FDA DOES NOT PREVENT GENENTECH FROM INTRODUCING SMALLER VIAL SIZES**

127. Genentech has not been constrained by any legal or regulatory restriction of the FDA from introducing vials for the products at issue with less fill volume.

128. As the facts alleged in this Third Amended Complaint demonstrate, introduction of a smaller vial size (*i.e.*, a vial with a smaller amount of fill) would not have "a substantial potential to have an adverse effect on the identity, strength, quality, purity, or potency of the product as they may relate to the safety or effectiveness of the product." 21 C.F.R. § 601.12(b)(1). Therefore, such a reduction would not be a "major change" requiring prior FDA approval under 21 C.F.R. § 601.12. Nor does FDA regulate the economics of drug use. For those reasons, FDA does not require or specifically permit Genentech to make its fill volumes so large that it leads to waste of medication.

129. FDA requires pre-approval of a change in a biological product only if it "has a substantial potential to have an adverse effect on the identity, strength, quality, purity, or potency of the product as they may relate to the safety or effectiveness of the product." 21 C.F.R. § 601.12(b)(1). These changes are called "major changes." 21 C.F.R. § 601.12(b).

130. A manufacturer need not obtain pre-approval of a change in a biological product if it would have only a moderate "potential to have an adverse effect on the identity, strength, quality,

purity, or potency of the product as they may relate to the safety or effectiveness of the product." 21 C.F.R. § 601.12(c)(1) A manufacturer may implement such a change on its own, without FDA prior approval, within 30 days of making a "supplement submission" to FDA unless FDA informs the manufacturer that prior approval is required or information required to be submitted is missing; such a submission is called "Supplement—Changes Being Effected in 30 Days" or a "CBE-30." *See* 21 C.F.R. § 601.12(c)(1) and (3).

131. Reducing the fill volumes in the products at issue would not be a "major" change because it would not have a substantial potential to have an adverse effect on the safety or effectiveness of the products. In fact, it would have no such effect.

132. For example, the Eli Lilly study that reported on the waste-reducing effect of the smaller vial size of Lartruvo stated: "Decreasing waste is a desirable strategy to reduce expenditures on oncology drugs without affecting health outcomes or quality of care or limiting specific drug use."[93]

133. Specifically, as shown below, reducing the amount of fill of the Genentech products at issue would not have a substantial potential to have an adverse effect on any of the characteristics specified in 21 C.F.R. § 601.12(b)(1) – the identity, strength, quality, purity, or potency of the product – as they may relate to the safety or effectiveness of the product.

134. With respect to identity, FDA requires manufacturers to test the final container of each filling of each lot for "identity." The regulation states: "The identity test shall be specific for each product in a manner that will adequately identify it as the product designated on final container and package labels and circulars, and distinguish it from any other product being processed in the same laboratory." 21 C.F.R. § 610.14. That test would identify the product as Avastin, Kadcyla, Rituxan, or Xolair regardless of the fill volume. Thus, reducing the fill volume of the Genentech products at issue would not have a substantial potential to have an adverse effect on the "identity" of the products as it relates to their safety or effectiveness.

135. Similarly, reducing the fill volume of the Genentech products at issue would not have a substantial potential to have an adverse effect on the "strength" of the products as it relates to their

[93] Sheffield *et al.* (2017) at e270.

safety or effectiveness. Subchapter F of FDA's regulations, the Subchapter that relates to Biologics, does not contain a definition of "strength." *See* 21 C.F.R. § 600.3 (containing definitions of terms used in Subchapter F and not containing a definition of "strength."). Thus, the appropriate definition is the one in FDA's Glossary of Terms, available at http://www.fda.gov/Drugs/InformationOnDrugs/ucm079436.htm#S (accessed 5/2/2019), which states "The strength of a drug product tells how much of the active ingredient is present in each dosage."

136. The quantity of the active ingredient present in each dosage of the products at issue would be the same regardless of the fill volume, and, therefore, their strength would be unaffected by a change in fill volume. For example, Williamson's dose of 772.5 mg of Rituxan from January until June 2016 did not depend on the amount of biologic in the vials (given that the dose was 772.5 mg regardless of the number of vials used). That is, he would have received the same dose regardless of the vials' fills, and, therefore, the strength would be unaffected.

137. Although FDA regulations contain other definitions of "strength," those definitions do not apply to Subchapter F related to biologics. For example, 21 C.F.R. § 314.3 contains a definition of strength, but it states that the definitions in that section apply *only* to Part 314 and Part 320 of the regulations, not to Part 601, which is where the regulation on changes to Biologics is located.

138. Similarly, reducing the fill volume of the Genentech products at issue would not have a substantial potential to have an adverse effect on the "quality" of the products as it relates to their safety or effectiveness. Neither Subchapter F of FDA's regulations related to Biologics nor FDA's Glossary of Terms contains a definition of "quality." Merriam-Webster's principal definition of "quality" is "peculiar and essential character."[94] The peculiar and essential character of the products at issue would not change, no matter how much biologic is in the vial. Thus, their quality would not change.

139. With respect to "purity," the regulations on Biologics define it as "relative freedom from extraneous matter in the finished product, whether or not harmful to the recipient or deleterious to the

[94] Merriam-Webster definition of "quality." https://www.merriam-webster.com/dictionary/quality (accessed 5/2/2019).

product. Purity includes but is not limited to relative freedom from residual moisture or other volatile substances and pyrogenic substances." 21 C.F.R. § 600.3(r). A reduction in fill volume of the products at issue would have no effect on their freedom from extraneous matter, and therefore it would have no effect on their purity as it may relate to safety or effectiveness.

140. With respect to "potency," FDA's definition states: "The word potency is interpreted to mean the specific ability or capacity of the product, as indicated by appropriate laboratory tests or by adequately controlled clinical data obtained through the administration of the product in the manner intended, to effect a given result." 21 C.F.R. § 600.3(s). Reducing the fill volume in the vials of the products at issue would not affect their ability or capacity to achieve their results, and therefore it would not have a substantial adverse effect on their potency, as it may relate to safety or effectiveness.

141. Nor would reducing the fill volume of the Genentech products at issue be a major change as one affecting product sterility assurance as provided in 21 C.F.R. § 601.12(b)(2)(vi). There are two reasons for that.

142. First, 21 C.F.R. § 601.12(b)(2)(vi) specifies that it is referring to methods and processes, such as sterilization methods. That provision refers to "Changes which may affect product sterility assurance, such as changes in product or component sterilization method(s), or an addition, deletion, or substitution of steps in an aseptic processing operation." *Id.* Genentech would not need to change a sterilization method or do anything to the steps in an aseptic processing operation to reduce the amount of fill in the vial.

143. Second, even if that regulation referred to the use of a different vial or container and stated that such a change would affect sterility assurance, there is no reason why the manufacturer could not use the same vial and simply fill it with a smaller amount. Indeed, that is what FDA would require in that situation. 21 C.F.R. § 601.12(a)(3) states, "Notwithstanding the requirements of paragraphs (b), (c), and (f) of this section, an applicant must make a change provided for in those paragraphs in accordance with a regulation or guidance that provides for a less burdensome notification of the change (for example, by submission of a supplement that does not require approval prior to distribution of the product or in an annual report)." Thus, if using a different vial would require prior approval, the manufacturer would be required to put the smaller fill volume in the

existing vial.

144. Reducing the fill volume of the Genentech products at issue would not have a substantial potential to have an adverse effect on the "quantitative formulation" of the products as it relates to their safety or effectiveness. Neither the regulations nor the FDA website contains a definition of "formulation" or "quantitative formulation," but Oxford Living Dictionaries defines "formulation" as "[a] material or mixture prepared according to a formula."[95] That has nothing to do with the amount of fill in the vial.

145. Furthermore, the way FDA refers to "formulation" shows that it relates to the chemical formulation of the drug, not the amount of the drug in the container. *See, e.g.*, 21 C.F.R. § 601.12(b)(2) ("quantitative formulation, including inactive ingredients"); FDA Glossary of Terms ("The Chemical Type represents the newness of a drug formulation or a new indication for an existing drug formulation. For example, Chemical Type 1 is assigned to an active ingredient that has never before been marketed in the United States in any form."):[96] FDA, Inactive Ingredient Search for Approved Drug Products: Frequently Asked Questions ("Alcohol is a good example of an ingredient that may be considered either active or inactive depending on the product formulation.").[97]

146. Reducing the fill volume of the Genentech products at issue would not be a major change because of a requirement to change their specifications. "Specification" as used in 21 C.F.R. § 601.12 is defined as:

> the quality standard (i.e., tests, analytical procedures, and acceptance criteria) provided in an approved application to confirm the quality of products, intermediates, raw materials, reagents, components, in-process materials, container closure systems, and other materials used in the production of a product. For the purpose of this definition, acceptance criteria means numerical limits, ranges, or other criteria for the tests described.

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[95] https://en.oxforddictionaries.com/definition/formulation (accessed 5/2/2019) (Definition 2; the first definition does not apply in this context).

[96] https://www.fda.gov/drugs/drug-approvals-and-databases/drugsfda-glossary-terms#C (accessed 5/2/2019).

[97] https://www.fda.gov/drugs/drug-approvals-and-databases/inactive-ingredient-search-approved-drug-products-frequently-asked-questions (accessed 5/2/2019).

21 C.F.R. § 600.3. Nothing in that definition says that the approved quantity of medicine filled into each container is a specification. Instead, it refers to "quality," which, as described above, would be unchanged with a smaller vial.

147. FDA does not prevent manufacturers from introducing smaller vial sizes to keep dosages to a single vial. Although an FDA Guidance document states that "[c]onsumers and/or health care providers should not be routinely required to use more than one vial to administer a typical single dose of the drug product,"[98] this is not a mandatory requirement. FDA states: "The use of the word "should" in Agency guidances means that something is suggested or recommended, but not required."[99].

148. Moreover, Genentech routinely ignores this recommendation and sizes its products so that multiple vials are needed for each treatment. As shown above, the typical or average patient needs four or five vials of Avastin and three vials of Kadcyla and Rituxan each per treatment.

149. Genentech has attempted to mislead the public into believing that it sizes its products to limit a single treatment to a single vial. After this lawsuit was filed, Genentech representative Emily Wang was quoted in the press as saying, "The FDA calls on companies to balance vial contents so that leftover drug is minimized yet also provide enough drug so that more than one vial is rarely needed for a single dose."[100] This is misleading because Genentech does not provide enough drug so that more than one vial is rarely needed for a single dose. More than one vial is invariably, or virtually invariably, needed to meet the dosage levels routinely prescribed to cancer patients using the biologics at issue in this suit.

150. Reducing the fill volume of the Genentech products at issue would not require pre-approval as a major change to the products' labels. To the contrary, the change would only need to be submitted in an annual report (and would not have to be submitted to the FDA before the change was made). The relevant regulation provides:

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[98] FDA Guidance, Allowable Excess Volume and Labeled Vial Fill Size in Injectable Drug and Biological Products Guidance for Industry, 2015 WL 4652905, at *3.

[99] *Id.* at *1.

[100] Hailey Konnath, Genentech Profits Off Wasteful Cancer Drug Vials, Suit Says, Law 360 (Feb. 28, 2019).

> An applicant shall submit any final printed package insert, package label, container label, or Medication Guide required under part 208 of this chapter incorporating the following changes in an annual report submitted to FDA each year as provided in paragraph (d)(1) of this section:
>
> ***
>
> (B) A change in the information on how the product is supplied that does not involve a change in the dosage strength or dosage form;

21 C.F.R. § 601.12.

151. A change in how the products at issue are supplied by reducing the fill volume in their vials would not involve a change in the dosage strength or dosage form because the dosage would remain the same; therefore, such a change would require only a minor amendment to the product labels, one required to be submitted only in an annual report.

152. End Payors filed this lawsuit rather than a citizen petition with FDA because FDA is powerless to afford End Payors the relief they seek. FDA regulates only the safety and effectiveness of drugs, not their economics or the fairness of how they are marketed. Under 42 U.S.C. § 262(a)(1)(C), its approval of a biologic license is limited to determining whether the product is "safe, pure and potent." FDA states: "All FDA-approved biological products, including reference, biosimilar, and interchangeable products, undergo a rigorous evaluation to ensure that patients can rely on their efficacy, safety, and quality."[101]

153. This fact was confirmed by the committee of the National Academy of Sciences quoted above, which said: "Manufacturers propose dose sizes for marketing, and the FDA only reviews the request for safety considerations [citation omitted]."[102] Members of that committee included a former Chief Medical Officer of the pharmaceutical company Merck & Co., Inc., and a former President and CEO of the pharmaceutical company Genzyme Corporation.

154. Furthermore, even if FDA were authorized to consider economics and the fairness of how a product is marketed, it would be powerless to compel Genentech to introduce smaller vial sizes. It can only approve or disapprove a manufacturer's application. It cannot order changes to the product.

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[101] Biosimilar Development, Review and Approval, https://www.fda.gov/drugs/biosimilars/biosimilar-development-review-and-approval (accessed 5/3/2019).

[102] Making Medicines Affordable at 99-100.

Nor could it award restitution to patients and third-party payers for the money they have spent on drugs that necessarily went to waste. All FDA could do would be to order the products taken off the market. End Payors do not seek to order these products off the market. They seek restitution and fair practices.

155. The example of Eli Lilly's biologic cancer drug Lartruvo confirms that a smaller vial size may be introduced without FDA's pre-approval. FDA first approved Lartruvo on October 19, 2016.[103] Its original label shows that it was supplied in only one vial size, 500 mg in 50 ml of solution (hereafter "500 mg" or "500 mg/50 ml").[104]

156. As alleged above, four-and-a-half months later, on March 6, 2017, Eli Lilly introduced a vial containing only 190 mg of Lartruvo in 19 ml of solution (hereafter "190 mg" or "190 mg/19 ml") to reduce the amount of product that went to waste.

157. According to a response by FDA to a Freedom of Information Act request received by Williamson's counsel on May 21, 2019, Eli Lilly submitted its request for approval of the vial containing 190 mg/19 mL of Lartruvo in a CBE-30 supplement on January 13, 2017. That was approximately three months after the initial approval of Lartruvo in a 500 mg vial.[105] FDA had not acted on that submission when Eli Lilly introduced and began to market the smaller, 190 mg, vial in March 2017.

158. On January 24, 2017, FDA acknowledged receipt of the submission "in the form of a '**Supplement – Changes Being Effected in 30 days'** as described in 21 CFR 601.12(c)." (Ex. E, p. 23 [bold-face in original].) It stated, "Continued use of the changes is subject to final approval of this supplement." (*Id.*)

159. Eli Lilly's CBE-30 submission regarding its smaller, 190 mg, vial size of Lartruvo was reviewed by at least six officials of FDA. The Division of Microbiology Assessment conducted a

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[103] https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm?event=overview.process&varApplNo=761038 (accessed 5/3/2019).

[104] https://www.accessdata.fda.gov/drugsatfda_docs/label/2016/761038lbl.pdf at 8 (accessed 5/3/2019).

[105] Documents provided by FDA in response to Williamson's FOIA request are attached hereto as Ex. E.

Microbiology/Virology Review, and the Office of Biotechnology Products conducted a Chemistry Review, both of which recommended approval. (Ex. E.)

160. In its Microbiology/Virology Review, dated February 10, 2017, the Division of Microbiology stated, "Stability data was provided for three commercial batches of 20 mL vials which were stored at 2-8ºC. These batches were acceptable for endotoxin, sterility, and container closure integrity." The review concluded, "The supplement was reviewed from a product quality microbiology perspective and is recommended for approval." (Ex. E, p. 13.) The reviewers added: "Product quality aspects other than microbiology should be reviewed by OBP." (*Id*.) [106]

161. The Office of Biotechnology Products conducted such a review. In a Memorandum of Review dated May 23, 2017, it provided the following justification for its recommendation of approval:

> The formulation for the proposed olaratumab [Lartrovo's generic name] Injection 190 mg/19 mL dosage form is identical to the formulation for the currently approved olaratumab Injection 500 mg/50 mL dosage form. No changes are introduced to the materials of the container closure system. The proposed changes to the manufacturing process are considered low risk. The provided data adequately support the analytical comparability between the 190 mg/19 mL and the 500 mg/50 mL dosage forms. The processing time limits are appropriately determined from the product quality perspective. The shipping process is adequately validated for the 190 mg/19 mL dosage form. (Ex. E, p. 9.)

162. This review confirms that the formulation of a biological product is not changed simply because a lower amount of fill is included in the vial; the review states that the formulation of the product was unchanged. It also demonstrates that what is important in terms of the container closure system is whether "changes are introduced to the materials of the container closure system."

163. FDA approved the CBE-30 for Lartruvo's 190 mg vial size on July 10, 2017. (Ex. E, pp. 4-5.) On that date, David Frucht, Ph. D., Director of FDA's Division of Biotechnology Review and Research II of the Office of Biotechnology Products and Office of Pharmaceutical Quality in the Center for Drug Evaluation and Research, wrote to Eli Lilly approving the "Changes Being Effected in

[106] OBP is the Office of Biotechnology Products. See https://www.fda.gov/media/77674/download (accessed 5/21/2019).

30 days supplemental biological application." (Ex. E, p. 4.) By then, the 190 mg vial size of Lartruvo had been on the market for approximately four months.

164. Similarly, Genentech would not have needed FDA's prior approval to introduce a smaller vial size of Avastin, Kadcyla, Rituxan or Xolair. Like Eli Lilly, it could make the change within 30 days of submitting a CBE-30.

## FIRST CLAIM FOR RELIEF
### Violation of California's Unfair Competition Law
### (By End Payors and the Class Against All Defendants)

165. End Payors reallege and incorporate by reference all preceding paragraphs of this Third Amended Complaint as though fully alleged in this paragraph.

166. End Payors bring this claim individually and on behalf of the members of the Class against Genentech under California law.

167. End Payors have standing to pursue this cause of action as End Payors have suffered injury in fact and have lost money or property as a result of Genentech's actions as delineated herein.

168. Genentech's scheme, as delineated herein, constitutes unlawful and/or unfair business practices in violation of California Business and Professions Code sections 17200, *et seq.*

169. Genentech's practices of selling drugs in quantities that inherently lead to wasted amounts of medicine, causing substantial injury to End Payors and the Class who are forced to purchase large amount of medications that they do not and cannot use. As set forth above, the financial injury to End Payors alone from Genentech's scheme runs into the millions of dollars. Genentech's scheme also means that there is no way for End Payors and the Class to avoid these losses since they must purchase the medication and can only purchase vials at the sizes that Genentech has decided to provide – regardless of the waste that will necessarily result. Likewise, the injuries suffered by End Payors are not outweighed by countervailing benefits to consumers or competition. In fact, there are no countervailing benefits to consumers or competition from supplying cancer and other medications in sizes that are too large for patients to fully use.

170. Genentech's business practices, as alleged herein, violate the "unlawful" prong of California Business & Professions Code sections 17200, *et seq.* because they violate, *inter alia*, Section 5(a)(1) of the FTC Act, 15 U.S.C. § 45(a)(1).

171. Genentech's business practices, as alleged herein, violate the "unfair" prong of California Business & Professions Code sections 17200, *et seq.* because, *inter alia*,: (i) the utility of Genentech's scheme is significantly outweighed by the gravity of the harm the scheme imposes on End Payors and the Class; (ii) the injury suffered by End Payors and the Class as a result of Genentech's scheme is substantial and is not one that End Payors and the Class could have reasonably avoided; and (iii) Genentech's scheme runs counter to legislatively declared and public policy.

172. These acts and practices of Genentech violate established public policy as expressed, *inter alia*, by the FTC's Policy Statement on Unfairness.

173. These acts and practices of Genentech are immoral, unethical, oppressive, unscrupulous, and/or substantially injurious to consumers

174. The consumer injury resulting from Genentech's acts and practices is substantial, not outweighed by any countervailing benefits to consumers or to competition, and not an injury that the consumers themselves could reasonably have avoided.

175. Accordingly, Genentech has violated, and continues to violate, California Business and Professions Code section 17200's proscription against engaging in unlawful business acts or practices.

176. As a direct and proximate result of Genentech's unlawful and/or unfair business practices, End Payors and the Class have suffered injury in fact and lost money or property, in that they spent money or property on medication that was unwanted and unneeded.

177. Pursuant to California Business and Professions Code section 17203, End Payors and the Class seek an order of this court enjoining Genentech from continuing to engage in unlawful and/or unfair business practices and any other act prohibited by law, including those acts set forth in this Third Amended Complaint.

178. End Payors and the Class also seek an order requiring Genentech to make full restitution of all monies wrongfully obtained from End Payors and the Class.

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**PRAYER FOR RELIEF**

WHEREFORE, End Payors, on behalf of themselves and the Class, pray judgment against Genentech as follows:

A. An order certifying appropriate Classes and/or Subclasses, designating End Payors as the class representatives and the undersigned counsel as class counsel;

B. An order enjoining Genentech from continuing to engage in the practices complained of herein, including but not limited to requiring that Genentech cease selling subject medicines only in quantities that necessarily lead to waste;

C. An award of restitution, damages, and disgorgement to End Payors and the Class in an amount to be determined at trial;

D. An order requiring Genentech to pay both pre- and post-judgment interest on any amounts awarded, as allowed by law;

E. An award of costs and attorneys' fees, as allowed by law, including but not limited to section 1021.5 of the Code of Civil Procedure; and

F. Such other or further relief as may be appropriate.

Dated: August 26, 2020

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**DEMAND FOR JURY TRIAL**

End Payors, individually and on behalf of all others similarly situated, hereby demand a trial by jury of any and all issues in this action so triable of right.

Dated: August 26, 2020

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ANALYSIS

# Overspending driven by oversized single dose vials of cancer drugs

**Peter B Bach and colleagues** call for an end to contradictory regulatory standards in the US that allow drug manufacturers to boost profits by producing single dose vials containing quantities that increase leftover drug

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Even though reducing waste in healthcare is a top priority, analysts have missed the waste that can be created when expensive infused drugs are packaged containing quantities larger than the amount needed.[1 2] This is particularly true for drugs for which dosage is based on a patient's weight or body size and that come in single dose packages. These drugs must be either administered or discarded once open, and because patients' body sizes are unlikely to match the amount of drug included in the vial, there is nearly always some left over. The leftover drug still has to be paid for, even when discarded, making it possible for drug companies to artificially increase the amount of drug they sell per treated patient by increasing the amount in each single dose vial relative to the typically required dose.

Increasing the amount of drug sold per treated patient also increases profits to doctors and hospitals in the United States. Under a system nicknamed "buy and bill," doctors and hospitals buy single dose vials of drugs and then bill insurers or patients when they are used. The bill includes a percentage based mark-up which can vary widely, but even low percentages can equate to large amounts of money given that many of the drugs cost thousands of dollars per vial.

Although doctors and hospitals sometimes use leftover drug to treat a subsequent patient, thus reducing the amount of leftover drug for which they bill, this practice is very limited. Safety standards from the US Pharmacopeial Convention permit sharing only if leftover drug is used within six hours, and only in specialised pharmacies.[3-5]

We analysed spending on cancer drugs that are packaged in single dose vials and dosed based on body size in the United States to estimate the extent of the problem. We focused on the US because, unlike in most other Western countries, the government plays no role in how drugs are priced and doctors and hospitals can profit from leftover drugs. Although similar problems exist with other drugs, cancer drugs are expensive and they constitute the largest single category of specialty drug spending.[6] Moreover, cancer drugs often have narrow therapeutic and toxicity windows, meaning that dosing is commonly based on a patient's body size.

## How big is the problem?

We examined the top 20 cancer drugs that are dosed by body size and packaged in single dose vials (based on 2016 projected sales), which collectively account for 93% of all sales of such drugs. We calculated the total amount of leftover drug and resulting 2016 US revenues for each drug using the method shown in fig 1⇓. In brief, we estimated how often vial sharing occurred by examining how often claims filed with the Medicare program included amounts of drug that did not total the full contents of the vial. We then calculated the most efficient way to combine available vial sizes to achieve the lowest US Food and Drug Administration approved dose in a representative sample of the US population derived from the National Health and Nutrition Examination Survey.[7] After correcting for vial sharing percentage, and adjusting the population to mirror a cancer patient population, we apportioned projected 2016 US revenues to administered or leftover drug.[8 9] When calculating the effect of vial sharing we assumed that doses that were not multiples of available vial sizes had no leftover drug, an assumption that made our estimates of leftover drug conservative.

Table 1⇓ shows the leftover drug from the packaging approaches for the 20 drugs. We estimate total US revenue from these drugs

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to be $18bn (£12.5bn; €16bn) in 2016, with 10% or $1.8bn from discarded drug. The extent and cost of leftover drug varies according to market size and available vial sizes. For example, in 2016, 7% of $3.9bn in rituximab sales will be on discarded drug, totaling $254m, while 33% of $697m in carfilzomib sales will be discarded, totaling nearly as much, $231m. Sensitivity analyses suggested our results were robust. If every person received the highest dose approved by the FDA, revenue from discarded drugs falls to $1.4bn; if every cancer patients weighed 10% less than the survey participants, the estimate rises to $2bn.

The proportion of drug left over varies from 1% to 33%. Between these extremes are drugs such as bevacizumab, which comes in both 100 mg and 500 mg vials, and ipilimumab, which comes in both 40 mg and 100 mg. About 9% and 7% of these drugs, respectively, is left over. Yet small percentages can still lead to large dollar amounts. The October 2015 Medicare Average Sales Price files show that a dose of ipilumumab might cost $29 000,[10] meaning that the 7% left over would generate an additional $2000 in revenue for the company for each vial sold.

## How drug quantity affects profits and waste

The effect of different approaches to packaging for single dose vials is illustrated by the two drugs bendamustine and bortezomib. Bendamustine, a drug for leukemia, is sold in a broad array of single dose vials (25, 45, 100, and 180 mg) that can be combined to reach its dose of 100 mg/m$^2$ nearly precisely (fig 2⇓). Vial combinations cover every 5 mg interval across the typical adult dose range of 110 mg to 310 mg, with the exception of 130 mg and 155 mg. We calculate that only 1% of bendamustine is wasted. Bortezomib on the other hand, a drug to treat multiple myeloma, is available in the US in only a 3.5 mg vial, much larger than the average required dose, which we calculate to be 2.5 mg based on the drug's dose of 1.3 mg/m$^2$ and the average weight of a cancer patient. Our estimate is that 27% to 30% of bortezomib sales in the US are related to leftover drug equating to $309m. The large vial size of bortezomib seems to be unique to the US market. The drug is sold in 1 mg vials in the UK.[11]

Pembrolizumab provides another example of how vial sizes can influence revenues. When it was initially approved in the US in September 2014, the drug was sold in 50 mg vials (as a powder that needs to be reconstituted into a liquid). But in February 2015 the manufacturer introduced a larger 100 mg vial (as a liquid) and stopped distributing the 50 mg vials to the US market. Five months later, in July 2015, pembrolizumab was approved in Europe, where it is sold in the smaller 50 mg vials as a powder.

The increased revenue from the change is substantial. Consider a 70 kg patient who requires a dose of 140 mg (the drug is dosed at 2 mg/kg). When the drug was sold in 50 mg vials, reaching the desired dose would require three 50 mg vials and leave 10 mg unused. But with only 100 mg vials available, 60 mg is left over. According to the Medicare Not Otherwise Classified October 2015 file, which lists Medicare's reimbursement rates for these drugs, each milligram of pembrolizumab costs around $50. In this example the change in vial size alone increases the revenues for the company from leftover drug by sixfold, from $500 to $3000, for a single dose. We estimate that the additional revenue to the company from the packaging change over the next five years will be $1.2bn, which comes on top of the $1.2bn they would have gained from leftover drug with the 50 mg package (table 2⇓). Similarly, by only selling bortezomib in the US in the larger 3.5 mg vials rather than the 1 mg vials sizes available in Europe, the manufacturer, Millennium, will increase its 2016 US revenues by $130m (data not shown).[11]

## Effect on hospitals and patients

We have focused on how much money companies earn in terms of revenues from leftover drug, not how much payers and patients are spending on them, which is a larger number due to the fact that distributing intermediaries and treating doctors and hospitals mark-up drugs when they bill for them. The mark-up varies considerably. In public insurance programs such as the Federal Medicare program the mark-up set by Congress is 6% and is currently 4%. For commercial insurance, which is the more common coverage in the United States, payers have reported that they pay mark-ups to doctors and hospitals in the order of 22% and 142%, respectively.[12] In hospitals that use the distribution channel 340B, mark-ups in the Medicare program have been estimated to be 58%.[13-15] The mark-up for commercially insured patients at these types of hospitals is even greater. So although it is hard to precisely estimate the additional profit that will come to doctors and hospitals from billing for leftover cancer drugs, our estimate is that it will almost certainly exceed $1bn in 2016.

The additional costs to patients, who are charged for leftover drug just as they are for drug they have received is also likely to be substantial. Medicare Part B, covering roughly half of cancer patients, includes 20% coinsurance with no upper limit, and 14% of beneficiaries have no additional coverage for their coinsurance.[16] Private insurance generally has out of pocket maximums that many patients with cancer reach regardless.

Although we focused on cancer, the problem of mismatched single dose vials and doses is not unique to the disease. The asthma drug omalizumab has approved doses in 75 mg intervals, but the company only sells 150 mg vials in the United States, even though it has an approved 75 mg vial size. The drug infliximab, one of the largest selling drugs in the United States with expected 2015 revenues of $4.3bn, is available in only 100 mg single dose vials. It is also dosed based on body size and using the same methods we applied to the cancer drugs, this packaging generates around $500m in additional revenues from leftover drug.

## How can we stop the waste?

Regularly and systematically discarding expensive drugs is antithetical to efforts to reduce spending on healthcare services that provide no value. Policy makers should therefore explore approaches that would reduce or eliminate paying for leftover drug. Current regulatory standards could be viewed as contradictory, or at least as ambiguous (box). The FDA calls on companies to balance vial contents so that leftover drug is minimized yet they should also provide enough drug that more than one vial is rarely needed for a single dose.[17] Guidance on vial sharing is also inconsistent. The Centers for Medicare and Medicaid Services essentially encourages it; the Centers for Disease Control and Prevention states that it is unsafe (box).[18 19]

Several policy options merit exploration. Regulators could require manufacturers to provide drugs in a reasonable set of size options to ensure the amount of wasted drug is low, say 3%. This is achievable, as table 3⇓ shows. If all of our suggestions were adopted, it would lower revenue from leftover drug from $1.8bn to $400m and, including the reductions to doctor and hospital mark-ups on leftover drug, would save around $2bn in total. An alternative would be to leave

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**Federal agency guidelines and advisories regarding proper drug quantity and use of drugs contained in single dose vials (SDVs)**

*FDA guideline*[20]—"Significantly more drug than is required for a single dose may result in the misuse of the leftover drug product. Similarly, the need to combine several single-dose vials for a single patient dose may lead to medication errors and microbial contamination"

*Centers for Medicare and Medicaid Services advisory*[21]—"It is permissible for healthcare personnel to administer repackaged doses derived from SDVs to multiple patients, provided that each repackaged dose is used for a single patient in accordance with applicable storage and handling requirements"

*Centers for Disease Control and Prevention guideline*[22]—"Vials labeled by the manufacturer as 'single dose' or 'single use' should only be used for a single patient. These medications typically lack antimicrobial preservatives and can become contaminated and serve as a source of infection when they are used inappropriately"

manufacturers free to select their vial sizes but also require them to refund the cost of leftover drug. This could be achieved through certified disposal and a virtual return.

One pattern sometimes seen in clinical practice is to round up doses to the quantity in the full vial, thus changing dosing from body sized based to "flat" or "fixed" dosing. The approach is problematic not only because it leads some patients to receive too high a dose and others too low when compared to the FDA approved dose, but also because it does not reduce spending on leftover drug. It merely changes clinician behavior from discarding leftover drug to infusing leftover drug into patients.

Policy makers should also revisit the current FDA guidance on the appropriate packaging of infused drugs in single dose vials and encourage the FDA, CDC, Centers for Medicare and Medicaid Services, and US Pharmacopeial Convention to reconcile their views on vial contents and vial sharing. Such steps could lead to savings for our healthcare system without sacrificing health outcomes. Opportunities to eradicate waste of this kind are rare.

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Competing Interests: We have read and understood BMJ policy on declaration of interests and declare the following interests: PBB reports personal fees from Association of Community Cancer Centers, America's Health Insurance Plans, AIM Specialty Health, American College of Chest Physicians, American Society of Clinical Oncology, Barclays, Defined Health, Express Scripts, Genentech, Goldman Sachs, McKinsey and Company, MPM Capital, National Comprehensive Cancer Network, Novartis, Biotechnology Industry Organization, *American Journal of Managed Care*, Boston Consulting Group, Foundation Medicine; LBS reports grants from Taiho Pharmaceuticals; RJM reports personal fees from Amgen, Hospira, Seattle Genetics, Sunesis, Amneal Biosciences, Magellan Medication Management System, and is an uncompensated member of the national clinical advisory committee for the Institute of Safe Medication Practices.

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**Key messages**

- Many infused cancer drugs are packaged in single dose vials but dosed based on body size, often resulting in leftover drug
- All the drug in the vial has to be paid for, making wasted drug a source of unnecessary spending
- Drug companies will earn around $1.8bn from leftover cancer drugs in the United States in 2016
- Manufacturers should be required to package drugs in quantities that allow better matching with required doses or enable virtual return of leftover drug

# Tables

**Table 1| Top 20 infused cancer drugs based on projected 2016 sales sold in single dose vials and dosed based on patient body size**

| Drug (brand name), year of FDA approval | Dose of first approved indication (highest approved dose at any time) | Amount of drug in available single dose vials (discontinued vial sizes)* | Vial sharing | | | 2016 expected sales ($m) | 2016 expected revenue from leftover drug ($m) |
|---|---|---|---|---|---|---|---|
| | | | % of leftover drug using only full vials | % doses with vial sharing | % of leftover drug adjusted for frequency of vial sharing† | | |
| Paclitaxel protein bound (Abraxane), 2005 | Breast 260 mg/m$^2$ | 100 | 9 | 16 | 8 | 960.77 | 76.72 |
| Brentuximab vedotin (Adcetris), 2011 | Lymphoma 1.8 mg/kg | 50 | 15 | 36 | 10 | 292.18 | 29.15 |
| Pemetrexed (Alimta), 2004 | Mesothelioma/lung 500 mg/ m$^2$ | 100, 500 | 5 | 16 | 4 | 1269.04 | 54.64 |
| Bevacizumab (Avastin), 2004 | Colorectal 5 (15) mg/kg | 100, 400 | 11 | 19 | 9 | 3159.32 | 284.49 |
| Ramucirumab (Cryamza), 2014 | Gastric 8 (10) mg/kg | 100, 500 | 7 | 16‡ | 6 | 471.55 | 28.78 |
| Cetuximab (Erbitux), 2004 | Head/neck 250 (400) mg/m$^2$ | 100, 200 | 6 | 19 | 5 | 570.22 | 29.18 |
| Asparaginase Erwinia chrysanthemi (Erwinaze), 2011 | All 25000 IU/ m$^2$ | 10000 | 10 | 16‡ | 8 | 170.40 | 14.13 |
| Eribulin (Halaven), 2010 | Breast 1.4 mg/ m$^2$ | 1 | 15 | 18 | 13 | 167.71 | 21.85 |
| Cabazitaxel (Jevtana), 2010 | Prostate 25 mg/m$^2$ | 60 | 23 | 12 | 21 | 127.96 | 26.89 |
| Ado-trastuzumab emtansine (Kadcyla), 2013 | Breast 3.6 mg/kg | 100, 160 | 7 | 16‡ | 6 | 413.96 | 23.66 |
| Pembrolizumab (Keytruda), 2014 | Melanoma 2 mg/kg | (50), 100 | 24 | 16‡ | 21 | 943.07 | 197.94 |
| Carfilzomib (Kyprolis), 2012 | Myeloma 20 (27) mg/ m$^2$ | 60 | 37 | 16‡ | 33 | 697.65 | 231.45 |
| Filgrastim (Neupogen), 1991 | Neutropenia 5 (10) µg/kg | 300, 480 | 17 | 0§ | 17 | 623.85 | 106.01 |
| Irinotecan liposome (Onivyde), 2015 | Pancreatic 70 mg/m$^2$ | 43 | 7 | 16 | 6 | 118.09 | 7.13 |
| Nivolumab (Opdivo), 2014 | Melanoma 3 mg/kg | 40, 100 | 4 | 16‡ | 3 | 2078.63 | 68.93 |
| Rituximab (Rituxan), 1997 | Non-Hodgkin's lymphoma 375 (500) mg/m$^2$ | 100, 500 | 7 | 0§ | 7 | 3852.75 | 253.85 |
| Bendamustine (Treanda), 2008 | Chronic lymphocytic leukemia 100 (120) mg/ m$^2$ | 25, 45, 100, 180 | 1 | 6 | 1 | 563.44 | 7.38 |
| Panitumumab (Vectibix), 2006 | Colorectal 6 mg/kg | 100, 200, 400 | 10 | 17 | 8 | 237.41 | 18.72 |
| Bortezomib (Velcade), 2003 | Myeloma:1.3 mg/ m$^2$ | 3.5 | 30 | 16 | 27 | 1160.64 | 308.74 |
| Ipilimumab (Yervoy), 2011 | Melanoma 3 mg/kg | 50, 200 | 10 | 22 | 7 | 620.22 | 46.47 |
| Total | — | — | — | — | — | 18 498.86 | 1836.11 |

*All amounts in mg except for filgrastim (µg) and asparaginase (IU). Filgrastim also sold in single dose prefilled syringes.

†Based on (discarded percentage assuming full vials×proportion of full vials)/((discarded percentage assuming full vials×proportion of full vials)+average dose).

‡Based on median of drugs for which there were available data.

§Billed in full vial or full prefilled syringe units.

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**Table 2| Projected revenue from sales of pembrolizumab comparing scenarios with revenue only from administered drug, revenue based on 50 mg vial sizes with reimbursement for leftover drug, and revenue based on 100 mg vial sizes with reimbursement for leftover drug. Data based on pooled analyst estimates compiled by Defined Health.**

| Year of sales | Revenue from dose only ($m) | Revenue from dose and leftover using 50 mg vials ($m) | Revenue from dose and leftover using 100 mg vials ($m) |
|---|---|---|---|
| 2016 | 762 | 862 | 964 |
| 2017 | 1335 | 1510 | 1690 |
| 2018 | 1991 | 2253 | 2520 |
| 2019 | 2346 | 2654 | 2969 |
| 2020 | 2687 | 3040 | 3401 |
| Total | 9121 | 10 320 | 11 544 |

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**Table 3| Proposed additional single dose vial sizes to reduce the amount of waste on leftover drug for 18 out of 20 top selling cancer drugs in our analysis for which we propose one additional size and estimation of effect on waste in 2016**

| Generic name | Currently available vial sizes (mg) | Proposed additional vial size | Estimated waste in 2016 ($m) | | Value of drug in additional vial ($)* |
|---|---|---|---|---|---|
| | | | With existing vials | With additional vial | |
| Paclitaxel protein bound | 100 | 30 | 77 | 8 | 293 |
| Brentuximab vedotin | 50 | 10 | 29 | 6 | 1193 |
| Pemetrexed | 500, 100 | 60 | 55 | 11 | 367 |
| Bevacizumab | 400, 100 | 20 | 284 | 60 | 139 |
| Ramucirumab | 500, 100 | 40 | 29 | 6 | 432 |
| Cetuximab | 200, 100 | 50 | 29 | 15 | 267 |
| Asparaginase Erwinia chrysanthemi | 10000† | 3000† | 14 | 2 | 1129 |
| Eribulin | 1 | 0.25 | 22 | 6 | 256 |
| Cabazitaxel | 60 | 2.5 | 27 | 3 | 372 |
| Ado-trastuzumab emtansine | 160, 100 | 20 | 24 | 12 | 584 |
| Pembrolizumab | 100, (50)‡ | 10 | 198 | 24 | 457 |
| Carfilzomib | 60 | 2.5 | 231 | 19 | 78 |
| Irinotecan liposome | 43 | 10 | 14 | 1 | 389 |
| Nivolumab | 100, 40 | 10 | 69 | 35 | 254 |
| Rituximab | 500, 100 | 40 | 254 | 53 | 300 |
| Panitumumab | 400, 200, 100 | 30 | 19 | 2 | 303 |
| Bortezomib | 3.5 | 0.25 | 309 | 48 | 117 |
| Ipilimumab | 200, 50 | 10 | 46 | 10 | 1388 |
| Total | — | — | 1843.11 | 434.25 | — |

*Based on October 2015 ASP files.[10]

†International Units.

‡No longer marketed.

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# Figures

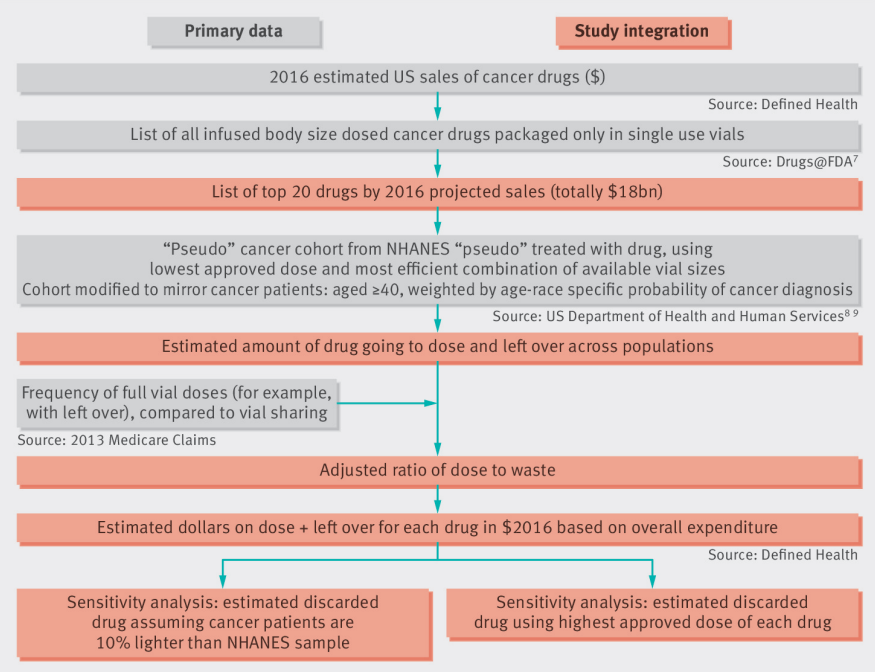


**Fig 1** Study flowchart

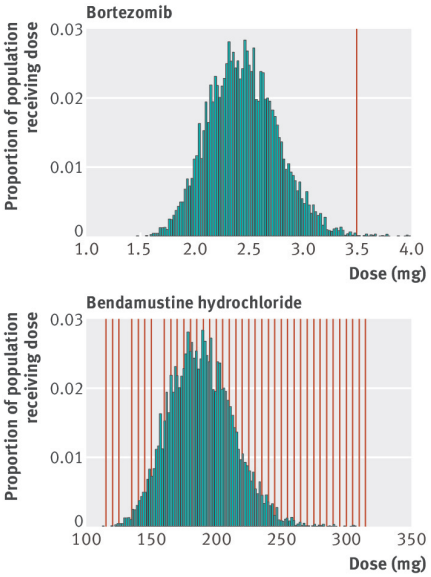


**Fig 2** Distribution of FDA approved dose (green histogram) in the US population of cancer patients, and available combinations of full vial contents (red lines) to achieve that dose for bortezomib (top) and bendamustine (bottom)

# Minimization of olaratumab drug waste using real-world data

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**Purpose.** Results of a study in which population-based body weight and body surface area (BSA) data were used for vial size optimization to reduce drug waste associated with administration of the i.v. anticancer agent olaratumab are reported.

**Methods.** A retrospective observational study was conducted to determine weight and BSA distributions in a large sample of U.S. oncology patients using data from a large electronic medical record database. Body weight and BSA values at the time of initial systemic anticancer therapy were used to compute olaratumab dose requirements in a cohort of patients with soft tissue sarcoma; those data were analyzed to derive estimates of drug waste likely to result from the use of various proposed olaratumab vial sizes in combination with an existing 500-mg size. Weight and BSA distributions were calculated for additional cohorts of patients with 7 other cancer types.

**Results.** Median weight values in men ($n$ = 1,179) and women ($n$ = 1,078) with soft tissue sarcoma were 82.55 kg (interquartile range [IQR], 72.58–95.53 kg) and 68.69 kg (IQR, 58.51–84.28 kg), respectively. Modeling of olaratumab dosing scenarios indicated that use of the 500-mg vial only would result in estimated average drug waste of 234 mg per patient per administration; analysis of various potential vial size combinations showed that waste could be reduced by 87.6% with the addition of a 190-mg vial size.

**Conclusion.** Analysis of real-world patient weight and BSA data allowed olaratumab vial size optimization to enable maximal dosing flexibility with minimal drug waste.

**Keywords:** antineoplastic agents/therapeutic use, body weight, drug packaging, drug waste, electronic health records, neoplasms/drug therapy

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The cost of cancer care in the United States is projected to increase to more than $157 billion by 2020.[1] A number of factors contribute to the growth in cancer care costs, including the increasing incidence and prevalence of cancer in an aging population, advancements in treatments and technology, and the adoption of novel targeted therapies.[1-3] With increasing costs of oncology care, cost-containment strategies are important. Cancer care facilities and providers are seeking to redirect resources toward higher-value care and minimize costs and wastage during the delivery of oncology care.[2-4]

The reduction of oncology drug wastage offers the potential to decrease pharmaceutical expenditures. Cancer care facilities and providers can incur serious economic losses as a result of inefficient drug usage and waste resulting from the disposal of unused or partially used ampules, vials, and prepared syringes.[5-8] Although the economic loss attributable to wastage of oncology drugs is not fre-

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quently reported, in some facilities drug wastage has been estimated to account for more than 8% of the annual drug expenditure,[9] and several facilities have reported savings of 4–5% of annual drug expenditures with the implementation of waste-minimization protocols.[6,10,11] Decreasing waste is a desirable strategy to reduce expenditures on oncology drugs without affecting health outcomes or quality of care or limiting specific drug use.[6]

Vial size and limited beyond-use dating (i.e., issues with stability and sterility) are often cited as the 2 main causes of oncology drug wastage.[5,6,9,12] Oncology drugs are frequently marketed in large vial sizes or even a single vial size.[5,13] However, it is common practice among clinicians to calculate doses to the nearest milligram according to body surface area (BSA) or weight, and available vial sizes often are not well suited to cost-efficient administration of the drug dosages possible across the distributions of patient weight and BSA.[6,7] In addition, many oncology drugs, especially monoclonal antibodies, are packaged preservative free and allow for only single uses with short expirations.[14,15] Unused partial vials can amount to considerable drug waste.

Physicians and pharmacists have called for cooperation with manufacturers to produce more suitable final vial sizes.[6,7] Manufacturers can help reduce waste by producing appropriate and multiple vial sizes based on the distribution of body sizes across the targeted patient population. However, vial size is typically determined prior to Phase III studies by coupling effective doses extrapolated from Phase I or II studies with mean BSA or weight data from trial populations. Little published literature with population-based estimates of BSA or weight for adult patients diagnosed with cancer is available, and estimates based on data from clinical trial participants may not be representative of current patients in real-world clinical practice. The weight and BSA values used in dosage calculations also can have important consequences for pharmacy budget projections, health technology assessments, and payer budget impact models.[13] Population-based weight and BSA distributions would enable better estimations of potential drug wastage and, more importantly, allow manufacturers to calculate and produce optimal vial sizes for a target patient population in actual clinical practice.

The first objective of the study described here was to provide healthcare providers, health technology assessors, payers, and manufacturers with population-based estimates of weight and BSA for U.S. patients with cancer using electronic medical record (EMR) data from outpatient community oncology practices. The cancers of interest were soft tissue sarcoma, multiple myeloma, and breast, colorectal, lung, ovarian, prostate, and gastric cancers. These results could be used as inputs to estimate wastage and drug costs as well as to determine dosage forms and vial sizes for drugs in development. The second objective of the study was to demonstrate the use of real-world BSA and weight data to optimize the size of a planned additional product container for olaratumab (Lartruvo, Eli Lilly and Company), a platelet-derived growth factor receptor α–blocking antibody that received accelerated Food and Drug Administration (FDA) approval in October 2016 for use (in combination with doxorubicin) for the treatment of patients with soft tissue sarcoma. Olaratumab dosing is based on patient weight (in milligrams per kilogram).[16]

At the time of our study, olaratumab was undergoing Phase III clinical testing. A 500-mg/50-mL vial size had already been evaluated and was in production, but a second vial size was explored with the goal of reducing drug waste and overall costs for institutions. The olaratumab research presented here illustrates how real-world weight data on patients with cancer were used to determine the optimal volume for a planned new olaratumab vial size and quantify the reduction in drug waste associated with the addition of the new vial size.

### KEY POINTS

- Population-based estimates of mean body weight and body surface area (BSA) values in oncology patients were derived for use in health economics evaluations of anticancer drugs.
- Manufacturers can help reduce drug waste by producing multiple vial sizes based on weight and BSA distributions across the targeted patient population in actual clinical practice.
- A case study of olaratumab dosing indicated that vial size optimization would result in an 87.6% reduction in drug waste associated with olaratumab administration to patients with soft tissue sarcoma.

## Methods

A retrospective observational study was conducted to describe the weight and BSA data of patients with cancer in EMRs in IMS Oncology (IMS Health, Danbury, CT), a commercial EMR database for capturing detailed, patient-level clinical data in primarily medium and large community-based oncology practices throughout the United States. The EMR weight data for patients with soft tissue sarcoma were then used to evaluate the various options for the second olaratumab vial size and determine the optimal vial volume for minimization of drug wastage.

**Study design.** Real-world patient weight and BSA data were retrieved from EMRs in the IMS Oncology database. At the time of study execution, the database included information on patients with cancer covering the period January 2000–June 2014, with more robust data available from 2004 on-

ward. The IMS data set included information on more than 840,000 patients with cancer representing a total of 840 facilities in all 50 states. Detailed clinical data available for these patients include but are not limited to cancer diagnosis; cancer stage; TNM Classification of Malignant Tumors notation; patient age, sex, and race; laboratory results and vital-sign data; injectable and oral medications, including chemotherapy and hormonal drugs; dosing; drug regimens; treatment intervals; weight; height; BSA; and body mass index values. Data in IMS Oncology are deidentified in compliance with the Health Insurance Portability and Accountability Act.

The index period for identification of cancer diagnoses was January 2004 through June 2014. The follow-up period for each patient consisted of all patient data collected from the index (i.e., cancer diagnosis) date through the end of the data set in June 2014.

**Inclusion criteria.** Weight and BSA records were retrieved from the oncology EMR database for patients with soft tissue sarcoma. The weight and BSA records of other patients with cancer were also reviewed, using *International Classification of Diseases, Ninth Revision, Clinical Modification* (*ICD-9-CM*) codes to identify each cancer type as soft tissue sarcoma (171.xx), female breast (174.xx), colorectal (153.xx, 154, 154.0, and 154.1), lung (162.2–162.9), ovarian (183.xx), prostate (185.xx), multiple myeloma (203.0x), or gastric (151.xx) cancer. Per the inclusion criteria, all patients in the study population were 18 years of age or older as of the index date and had at least 2 documented visits to a treating provider (the latter criterion was applied to exclude patients with a "rule-out," or uncertain, diagnosis. Patients' weight and BSA records at the time of the first systemic therapy (order for chemotherapy, biological, or anticancer hormonal agents) were reviewed for patients who had systemic therapy orders during the 30 days prior to the index diagnosis to any time thereafter.

**Study endpoints.** The key measures were patient weight and BSA at the time of the first dose of systemic anticancer therapy. Compared with BSA records, weight and height data are better populated in the EMR database for the majority of patients and at multiple time points. Therefore, our preference was to calculate each patient's BSA using his or her weight and height records and the method of Du Bois and Du Bois: BSA ($m^2$) = weight $(kg)^{0.425} \times$ height $(cm)^{0.725} \times 0.007184$. The height and weight values recorded in closest proximity to the date of the first systemic therapy were used. Only weights recorded within 30 days of the first systemic therapy were included in the analysis; height records recorded in the EMR at any time were included. If either eligible height or eligible weight data were missing, the patient's BSA record was used if the BSA record was available within 30 days of the first systemic therapy. If all of these records were missing, the patient's data were omitted from analyses of BSA; however, the data were retained for other analyses (e.g., analyses of patient demographic characteristics). Other variables of interest included age, race or ethnicity (white, black, Asian, Hispanic, or other), sex, cancer type, stage at diagnosis, and region of residence at the time of diagnosis.

**Statistical analysis.** Descriptive statistics were used to summarize baseline demographic characteristics (age, race, sex, stage at diagnosis, and region of residence) for the 8 cancer cohorts. The primary descriptive measures of weight and BSA at the time of first systemic therapy (both means ± S.D. values and medians with interquartile ranges) were stratified according to cancer type and sex. Descriptive statistics were generated using SAS software, version 9.2 (SAS Institute Inc., Cary, NC).

**Waste-minimization analysis.** The distribution of patient weights in the soft tissue sarcoma population was reviewed. Given the sample size and the division of weight into 1-pound intervals, the resulting histograms of patient weights exhibited considerable "noise." Therefore, the density function in the R program (version 2.15.2, R Core Team, Vienna, Austria) was used to smooth out the noise. Based on visual inspection, the smoothing bandwidth parameter was set to 10 pounds (about 4.5 kg), which produced population densities exhibiting increasing and then decreasing numbers of patients as the weight increased. American patient weights are systematically higher than patient weights in other regions, especially Europe and Asia. To not bias the waste calculation analysis toward heavier patients, who are less likely to be encountered globally, patient weight distributions were truncated at approximately 122 kg. For soft tissue sarcoma, this restriction excluded approximately 4% of patients and lowered the mean patient weight by approximately 1.4 kg.

After the bandwidth parameter was applied and data on patients weighing more than 122 kg were removed, the doses were computed. Olaratumab is being evaluated at a dose of 15 mg/kg and produced as a 10-mg/mL solution. The fractional distribution of weights for the study cohort of patients with soft tissue sarcoma was converted to a population of patients, and for each unique patient weight the dose required was computed. Based on the doses to be delivered, decisions were made regarding the largest and smallest vial sizes to be considered. The analysis constrained the number of vials per administration to a maximum of 6 to minimize or limit needed pharmacy manipulation during sterile compounding and to avoid an excessive number of vials for any given patient. All doses were rounded in increments of 10 mg. All possible vial size combinations were enumerated subject to the constraints described in this section. A C++ program that, for a given distribution of patient weights and a fixed dose per kilogram, computes the population-weighted average waste

**Table 1.** Cohort Attrition[a]

| Criterion | No. Patients Meeting Criterion | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | Soft Tissue Sarcoma | Female Breast Cancer[b] | Colorectal Cancer | Lung Cancer | Ovarian Cancer[b] | Prostate Cancer[b] | Multiple Myeloma | Gastric Cancer |
| Diagnosis of interest documented in EMR | 7,400 | 206,106 | 75,297 | 106,281 | 15,648 | 46,582 | 19,068 | 8,127 |
| Age ≥ 18 yr at index (diagnosis date) | 7,308 | 205,995 | 75,246 | 106,242 | 15,615 | 46,535 | 19,066 | 8,118 |
| ≥ 2 visits to treating provider documented in EMR | 6,647 | 191,472 | 68,863 | 97,771 | 14,438 | 41,810 | 18,209 | 7,464 |
| Documented systemic chemotherapy | 2,291 | 110,534 | 35,044 | 56,411 | 8,020 | 16,510 | 10,374 | 3,866 |
| BSA and height or weight values documented within 30 days of first systemic therapy | 2,285 | 110,210 | 35,008 | 56,354 | 8,005 | 16,360 | 10,349 | 3,853 |

[a]BSA = body surface area, EMR = electronic medical record.
[b]Attrition shows all patients (male and female). The entire patient sample consisted of 242,424 patients, of whom 177 patients had miscoded cancer diagnoses or sex in the EMR; data on these patients were not included for review in analyses of demographic and clinical characteristics, weight, or BSA.

associated with a given set of vial size combinations was written.

At the time of our study, olaratumab had already been formulated for administration as a 500-mg dose, produced as a 10-mg/mL solution in a 50-mL vial, for use in clinical trials. The manufacturer wanted to ensure that any dose considered was aligned with the manufacturer's current vial platform (vial sizes of 3, 5, 10, 20, and 50 mL). Due to the 6-vial constraint, dosage forms containing less than 10 mL were not considered. Other manufacturing considerations included meeting the minimum fill levels for the respective vial sizes, avoiding the appearance of underfill or overfill, and maintaining a fill volume that was "elegant" (i.e., a whole number rounded to the tens). The aforementioned calculations were performed combining doses with a 500-mg dose, and the waste and other characteristics were estimated from each combination.

Waste calculations are reported here as either a mean amount per patient or as a fraction or percentage of the total dose administered. A patient weighing 80 kg and administered a dose of 15 mg/kg would need 1,200 mg of a given drug. If only a single vial size (500 mg) were available, 3 500-mg doses would be ordered, with 1,200 mg administered to the patient and 300 mg (20% of the ordered dose) wasted.

## Results

**Patient body weight and BSA.** Table 1 displays cohort attrition for each cancer type according to the eligibility criteria. The majority of patients (>99%; 242,424 of 243,050 patients) who received systemic chemotherapy also had eligible weight, height, or BSA records. The entire patient sample consisted of 242,424 patients, of whom 177 had miscoded cancer diagnoses or sex in the EMR (i.e., 146 men had *ICD-9-CM* diagnosis codes for female breast cancer, 10 men had codes for ovarian cancer, and 21 women had codes for prostate cancer). Table 2 shows demographic characteristics and cancer stage at di-

**Table 2.** Cohort Demographics and Clinical Characteristics

| Variable | Soft Tissue Sarcoma (*n* = 2,285) | Female Breast Cancer[a] (*n* = 110,041) | Colorectal Cancer (*n* = 35,008) | Lung Cancer (*n* = 56,354) | Ovarian Cancer[a] (*n* = 7,995) | Prostate Cancer[b] (*n* = 16,335) | Multiple Myeloma (*n* = 10,349) | Gastric Cancer (*n* = 3,853) |
|---|---|---|---|---|---|---|---|---|
| Mean ± S.D. age at diagnosis, yr | 60 ± 15 | 60 ± 12 | 63 ± 12 | 66 ± 10 | 63 ± 12 | 71 ± 8 | 66 ± 11 | 63 ± 12 |
| Female, no. (%) | 1,095 (47.9) | 110,041 (100.0) | 16,164 (46.2) | 26,296 (46.7) | 7,995 (100.0) | . . .[c] | 4,627 (44.7) | 1,341 (34.8) |
| Race/ethnicity, no. (%) | | | | | | | | |
| White | 1,277 (55.9) | 66,277 (60.2) | 19,140 (54.7) | 31,225 (55.4) | 4,561 (57.0) | 9,368 (57.3) | 5,629 (54.4) | 1,663 (43.2) |
| Black | 216 (9.5) | 8,540 (7.8) | 2,732 (7.8) | 3,061 (5.4) | 457 (5.7) | 1,325 (8.1) | 1,229 (11.9) | 414 (10.7) |
| Asian | 21 (0.9) | 1,231 (1.1) | 388 (1.1) | 365 (0.6) | 85 (1.1) | 84 (0.5) | 80 (0.8) | 120 (3.1) |
| Hispanic | 20 (0.9) | 847 (0.8) | 264 (0.8) | 166 (0.3) | 61 (0.8) | 109 (0.7) | 73 (0.7) | 80 (2.1) |
| Other | 136 (6.0) | 5,793 (5.3) | 1,852 (5.3) | 2,294 (4.1) | 411 (5.1) | 791 (4.8) | 732 (7.1) | 310 (8.1) |
| Unknown | 615 (26.9) | 27,353 (24.9) | 10,362 (30.4) | 19,243 (34.1) | 2,420 (30.3) | 4,658 (28.5) | 2,606 (25.2) | 1,266 (32.9) |
| U.S. Census region, no. (%)[d] | | | | | | | | |
| Northeast | 233 (10.2) | 12,076 (11.0) | 4,244 (12.1) | 6,837 (12.1) | 1,013 (12.7) | 2,080 (12.7) | 1,321 (12.8) | 571 (14.8) |
| Midwest | 264 (11.6) | 11,817 (10.7) | 4,359 (12.5) | 7,236 (12.8) | 1,177 (14.7) | 1,685 (10.3) | 1,269 (12.3) | 421 (10.9) |
| South | 1,539 (67.4) | 74,307 (67.5) | 22,160 (63.3) | 36,751 (65.2) | 4,522 (56.6) | 10,411 (63.7) | 6,556 (63.3) | 2,383 (61.8) |
| West | 238 (10.4) | 11,387 (10.4) | 4,045 (11.6) | 5,305 (9.4) | 1,250 (15.6) | 2,099 (12.9) | 1,165 (11.3) | 457 (11.9) |
| Unknown | 11 (0.5) | 454 (0.4) | 200 (0.6) | 225 (0.4) | 33 (0.4) | 60 (0.4) | 38 (0.4) | 21 (0.5) |
| Stage at diagnosis, no. (%)[e] | | | | | | | | |
| 0 | 1 (0.0) | 1,496 (1.4) | 19 (0.05) | 6 (0.01) | 2 (0.03) | 3 (0.02) | 0 (0.0) | 1 (0.03) |
| I | 12 (0.5) | 25,540 (23.2) | 638 (1.8) | 2,014 (3.6) | 452 (5.7) | 140 (0.9) | 16 (0.2) | 131 (3.4) |
| II | 11 (0.5) | 22,469 (20.4) | 3,728 (10.6) | 1,899 (3.4) | 265 (3.3) | 1,113 (6.8) | 14 (0.1) | 338 (8.8) |
| III | 31 (1.4) | 8,430 (7.7) | 7,919 (22.6) | 6,455 (11.5) | 1,565 (19.6) | 403 (2.5) | 13 (0.1) | 384 (10.0) |
| IV | 63 (2.8) | 6,872 (6.3) | 8,030 (22.9) | 11,570 (20.5) | 1,227 (15.3) | 4,180 (25.6) | 24 (0.2) | 1,048 (27.2) |
| Unknown[f] | 2,167 (94.8) | 45,234 (41.1) | 14,674 (41.9) | 34,410 (61.1) | 4,484 (56.1) | 10,496 (64.3) | 10,282 (99.4) | 1,951 (50.6) |

[a]Data are for women only (miscoded cases in men excluded from analysis).
[b]Data are for men only (miscoded cases in women excluded from analysis).
[c]Not applicable.
[d]The four regions are based on U.S. Census rules: Northeast (Connecticut, Maine, Massachusetts, New Hampshire, Rhode Island, Vermont, New Jersey, New York, and Pennsylvania); Midwest (Illinois, Indiana, Michigan, Ohio, Wisconsin, Iowa, Kansas, Minnesota, Missouri, Nebraska, North Dakota, and South Dakota); South (Delaware, Florida, Georgia, Maryland, North Carolina, South Carolina, Virginia, Washington D.C., West Virginia, Alabama, Kentucky, Mississippi, Tennessee, Arkansas, Louisiana, Oklahoma, and Texas); and West (Arizona, Colorado, Idaho, Montana, Nevada, New Mexico, Utah, Wyoming, Alaska, California, Hawaii, Oregon, and Washington).
[e]Stage closest to diagnosis (i.e., within 120 days of index date). In some cases in which cancers were documented as "stage X" or staging data were missing, cancers were recoded as stage IV on the basis of TNM Classification of Malignant Tumors notations.
[f]Includes cases in which staging data were not documented and cases involving notations of "stage X," "limited," "extensive," or "occult."

**Table 3.** Cohort Data on Body Weight and Body Surface Area[a]

| Variable | Soft Tissue Sarcoma (*n* = 2,285) | Female Breast Cancer[b] (*n* = 110,041) | Colorectal Cancer (*n* = 35,008) | Lung Cancer (*n* = 56,354) | Ovarian Cancer[b] (*n* = 7,995) | Prostate Cancer[c] (*n* = 16,335) | Multiple Myeloma (*n* = 10,349) | Gastric Cancer (*n* = 3,853) |
|---|---|---|---|---|---|---|---|---|
| *Results of Weight Analysis Stratified by Sex* | | | | | | | | |
| Male, no. | 1,179 | . . .[d] | 18,524 | 29,446 | . . . | 16,061 | 5,660 | 2,465 |
| Mean ± S.D. weight, kg | 85.27 ± 18.62 | . . . | 85.69 ± 18.82 | 81.20 ± 17.33 | . . . | 86.18 ± 17.84 | 86.13 ± 17.53 | 79.31 ± 18.17 |
| Median (IQR) weight, kg | 82.55 (72.58–95.53) | . . . | 83.46 (72.94–95.71) | 79.38 (69.13–91.08) | . . . | 83.92 (73.94–96.16) | 83.92 (73.94–95.71) | 76.66 (67.59–88.72) |
| Female, no. | 1,078 | 108,505 | 15,911 | 25,711 | 7,925 | . . . | 4,559 | 1,321 |
| Mean ± S.D. weight, kg | 72.89 ± 19.93 | 76.31 ± 18.50 | 71.17 ± 18.71 | 67.54 ± 16.96 | 71.87 ± 18.67 | . . . | 71.74 ± 18.24 | 65.43 ± 16.82 |
| Median (IQR) weight, kg | 68.69 (58.51–84.28) | 73.48 (63.05–86.18) | 68.04 (57.97–80.92) | 64.86 (55.70–76.66) | 68.04 (58.51–81.65) | . . . | 68.95 (58.97–81.60) | 62.60 (53.07–74.53) |
| *Results of BSA Analysis Stratified by Sex* | | | | | | | | |
| Male, no. | 1,170 | . . . | 18,391 | 29,297 | . . . | 15,541 | 5,614 | 2,453 |
| Mean ± S.D. BSA, $m^2$ | 2.01 ± 0.22 | . . . | 2.01 ± 0.22 | 1.96 ± 0.21 | . . . | 2.01 ± 0.21 | 2.01 ± 0.21 | 1.93 ± 0.22 |
| Median (IQR) BSA, $m^2$ | 2.00 (1.86–2.14) | . . . | 2.00 (1.86–2.14) | 1.95 (1.82–2.09) | . . . | 2.00 (1.86–2.14) | 2.00 (1.87–2.14) | 1.92 (1.79–2.06) |
| Female, no. | 1,073 | 107,237 | 15,797 | 25,528 | 7,873 | . . . | 4,512 | 1,315 |
| Mean ± S.D. BSA, $m^2$ | 1.76 ± 0.22 | 1.80 ± 0.20 | 1.74 ± 0.21 | 1.70 ± 0.20 | 1.75 ± 0.21 | . . . | 1.74 ± 0.21 | 1.67 ± 0.20 |
| Median (IQR) BSA, $m^2$ | 1.73 (1.61–1.90) | 1.78 (1.66–1.93) | 1.72 (1.59–1.87) | 1.69 (1.56–1.82) | 1.73 (1.60–1.88) | . . . | 1.73 (1.59–1.87) | 1.65 (1.52–1.80) |

[a]IQR = interquartile range, BSA = body surface area.
[b]Data are for women only (miscoded cases in men excluded from analysis).
[c]Data are for men only (miscoded cases in women excluded from analysis).
[d]Not applicable.

agnosis for the cohorts. The mean age of patients in the soft tissue sarcoma cohort was 60 years; the mean ages ranged from 60 to 71 years across the other cancer cohorts. While the majority of patients whose race or ethnicity was documented in the EMR were white, race or ethnicity was not recorded for 25–34% of patients. The study cohorts were disproportionately (57–68%) composed of patients residing in the South versus other U.S. Census regions. Depending on the cohort, stage at diagnosis was unknown in 41–99% of patients.

Table 3 shows weight and BSA for patients at the time of systemic therapy, stratified by cancer type and sex. There were distinct differences across cancer types; patient weights and BSA values were, on average, lower in the lung cancer and gastric cancer cohorts and higher in the female breast cancer cohort relative to cohorts with other cancer types. Across all cancer types, as expected, men tended to have higher weight and BSA values than females. Within each cancer type and sex, the mean and median weight values were largely similar, although the means tended to be slightly higher than the medians because of extreme weight and BSA values in some patients. Across all cancers and for both sexes, patients were consistently heavier in the Midwest than in other U.S. Census regions (data not shown). Patient weights were also consistently higher in patients younger than 65 years compared with those 65 or older (data not shown).

**Waste calculation.** By applying the analytic methods to the weight data from the 2,285 patients with soft tissue sarcoma, the estimated average waste associated with dispensing of olaratumab to a population of patients with soft tissue sarcoma, assuming the use of only 500-mg/50-mL vials, was approximately 234 mg per patient per administration.

Table 4 shows the waste calculation results for hypothetical scenarios for the use of various potential vial sizes in combination with the existing

500-mg vial. In terms of waste avoidance, the optimal dosage form was 210 mg/21 mL, which yielded a population average waste of 28.68 mg; however, due to the previously described vial size constraints, this was not selected as an appropriate alternative vial size. Instead, it was determined that the best feasible combination was a 10-mg/mL solution (190 mg/19 mL) delivered in a 20-mL vial; we calculated that the use of that vial size in combination with the existing 500-mg/50-mL vials would result in a population-weighted average waste value of just 29 mg per patient per administration, an 87.6% reduction in waste relative to use of 500-mg vials exclusively.

Assuming use of a combination of 190- and 500-mg vials, it was calculated that drug wastage would occur in 65% of olaratumab administrations (Table 4), while 35% of administrations would result in no or negligible waste. We determined that the worst-case scenario of waste generation would occur in a patient weighing 51.3 kg. Dosed at 15 mg/kg, that patient would need 770 mg of olaratumab; the best combination of 190- and 500-mg doses (2 doses of 190 mg and 1 dose of 500 mg, for a total dose of 880 mg) would generate waste of 110 mg. Similar waste generation would result from administration of a dose of 580 mg to a patient weighing 38.7 kg. However, these worst-case scenarios must be placed into context by considering the entire population. Table 4 shows a population-weighted average waste of 29 mg per patient per administration, and we expect that over the long term waste at individual treatment centers will approach the average.

Figure 1 illustrates the combined picture of the real-world weight data from the soft tissue sarcoma population with the 190- and 500-mg olaratumab vials and also demonstrates how combinations of 190- and 500-mg vials can cover the anticipated dose range of olaratumab at 15 mg/kg and displays those doses that can be covered exactly.

## Discussion

Reduction of drug waste offers the potential to reduce drug expenditures within a relatively short period without negatively affecting quality of care or limiting specific drug use.[6] Manufacturers can contribute to the reduction of drug waste through the production of multiple appropriate vial sizes for parenteral drugs. However, the selection of appropriate vial sizes depends greatly on the weight and BSA distributions of the targeted cancer patient populations. In this study, we demonstrated how real-world data on patient weight was used to determine the optimal second vial size for olaratumab, which was granted FDA approval in October 2016 for use in patients with soft tissue sarcoma.

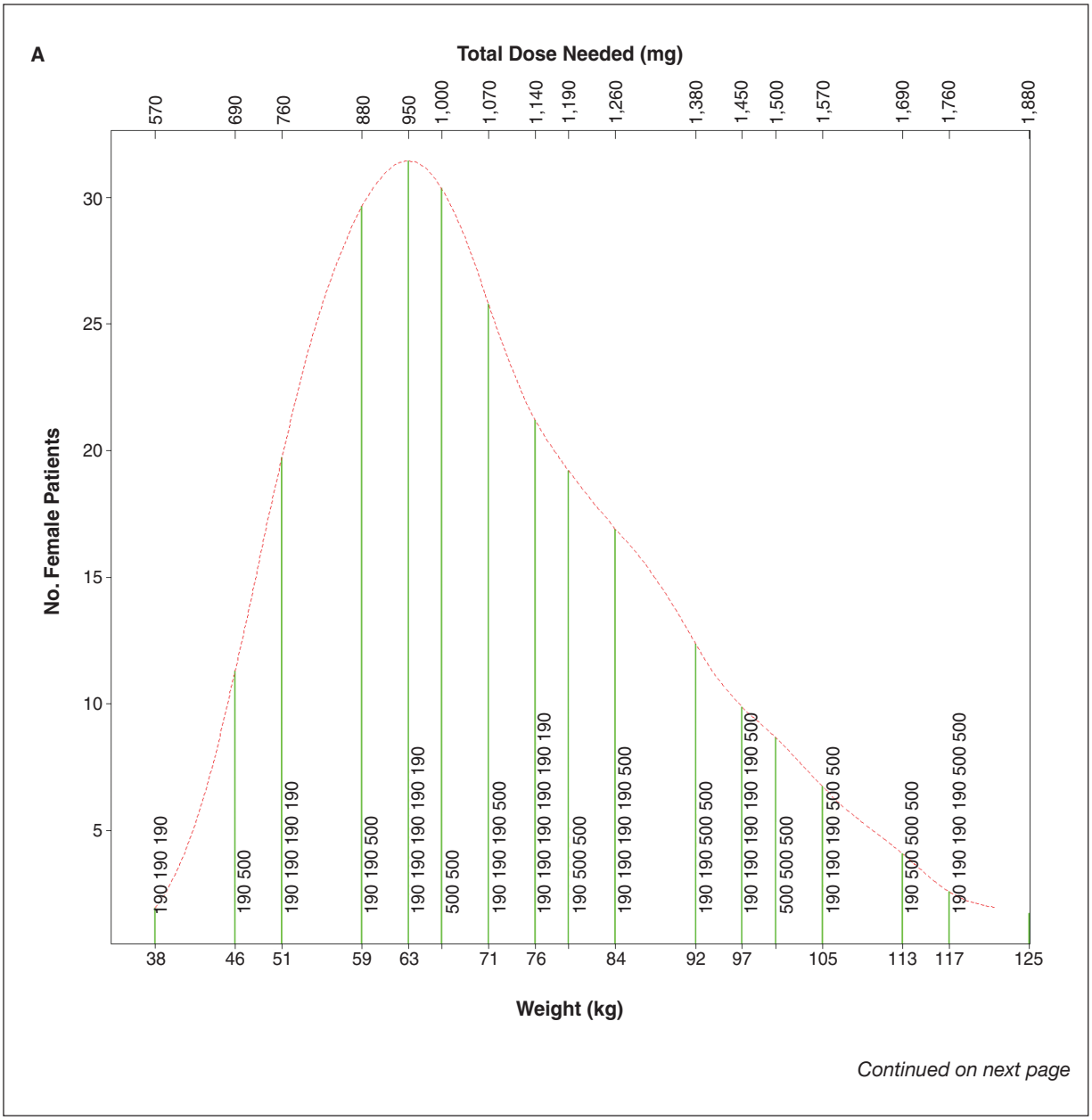
In many instances, manufacturers do not have a financial incentive to proactively produce smaller vial sizes for the commercial market after a product launch. Mindful of the potential impact of drug waste on pharmacy budgets, an opportunity to significantly reduce wastage for a clinically promising investigational agent was explored through the introduction of an additional vial size. Our analyses indicated that the addition of a 190-mg vial size would reduce the population average waste per patient per administration by 87.6%, to just 29 mg.

The waste calculation analyses presented here included a number of considerations and constraints. For example, an important constraint was the need to minimize the number of vials that would have to be manipulated per olaratumab administration. The objectives of waste minimization and vial minimization cannot be simultaneously optimized. At the extreme, producing very small vial sizes would allow for almost any dose with minimal waste. However, preparation would become unduly burdensome for the pharmacy to handle numerous vials. In addition, producing very small vial sizes may increase the potential for medication errors and microbial contamination.[17] Therefore, to control pharmacy handling, we imposed

**Table 4.** Estimates of Drug Waste and Waste Reduction With Various Olaratumab Vial Sizes

| Outcome | Potential Vial Size | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | 210 mg | 190 mg | 140 mg | 220 mg | 150 mg | 90 mg | 110 mg | 180 mg |
| Population average waste per patient per administration (mg) | 28.68 | 29.02 | 30.29 | 31.61 | 33.71 | 35.98 | 36.25 | 37.65 |
| Mean no. vials needed | 3.89 | 4.19 | 4.14 | 4.17 | 4.64 | 4.24 | 4.31 | 3.66 |
| % Cases involving waste | 60.66 | 64.72 | 65.59 | 65.54 | 66.50 | 69.69 | 68.91 | 65.82 |
| % Waste reduction relative to use of 500-mg vial only | 87.74 | 87.60 | 87.06 | 86.49 | 85.59 | 84.63 | 84.51 | 83.91 |

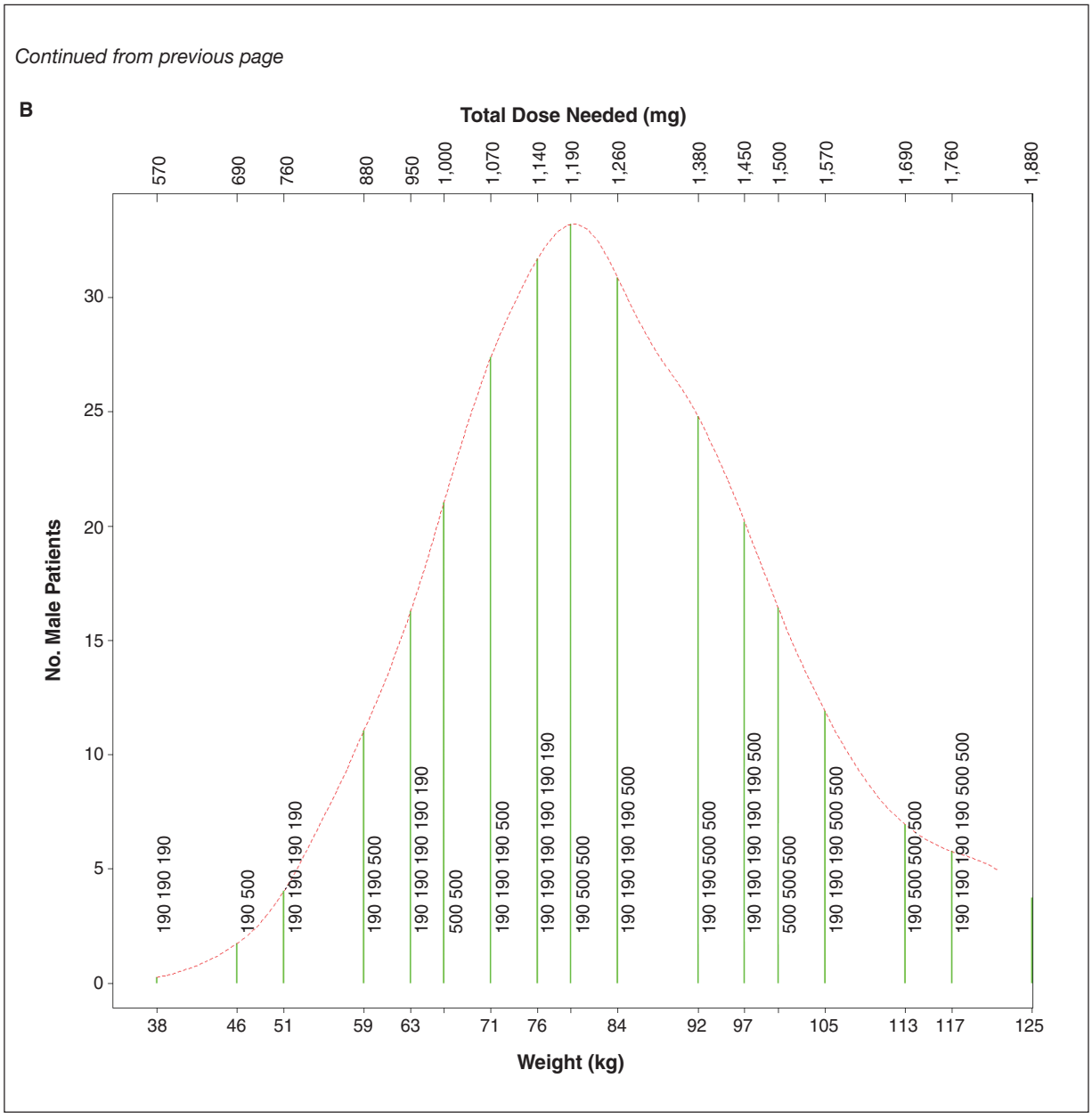
**Figure 1.** Results of modeling of olaratumab dosing requirements and combinations of 190- and 500-mg vials needed to treat a real-world population of patients with soft tissue sarcoma in relation to various weight values (green lines) and weight distribution (dotted red line) in adult female (panel A) and male (panel B) patients with soft tissue sarcoma.




*Continued on next page*

a limit of no more than 6 vials to be opened for any given patient. Another consideration involved the inclusion and evaluation of atypical vial sizes. In our waste calculations, we found that combinations of vial volumes that are not multiples of each other produce less waste because their use can accommodate a greater variety of doses and offers inherent advantages with regard to applications in other populations (e.g., non-U.S. patients). The ability to accommodate a greater variety of doses is particularly important given the differences in the distributions of body weight and height across regions of the world. In the case of olaratumab administration at a dose of 15 mg/kg, doses of 880, 950, 1,000, 1,070, 1,140, 1,190, and 1,260 mg can all be achieved with 6 or fewer vials containing 500 mg/50 mL or 190 mg/19 mL, whereas with vials containing 500 mg/50 mL and 200 mg/20 mL,

**Figure 1.** *Continued.*




only doses in milligram quantities that are multiples of 100 could be prepared without wastage. In fact, the combination of a 500-mg/50 mL vial and a 190-mg/19 mL vial reduced wastage by 22% compared with a combination of a 500-mg/50 mL vial and a 100-mg/10 mL vial. Finally, it was important to consider assumptions about dose rounding. Dose rounding to the nearest 5–10% has been reported as a frequent and viable waste mitigation strategy by cancer care facilities and providers.[6,9,14,15,18-20] In sensitivity analyses, we assumed dose rounding of 1–5% and found minimal differences in mean population waste and mean number of vials required. Drug waste-minimization calculations must factor in real-world pharmacy and manufacturing contexts in order to be useful for decision-making.

A strength of the study was the use of the entire weight distribution

of 2,285 patients with soft tissue sarcoma rather than reliance on mean or median weight values. This approach accounted for the considerable variability in weight, dosing, and potential waste across the patient population.

Another important strength of the study was the use of real-world patient data versus clinical trial patient data. In the Phase II study of olaratumab for soft tissue sarcoma,[16] several patients with large weight values caused the overall population ($n$ = 178 patients) weight distribution to be heavier than the real-world patient weights from the IMS Oncology EMR database. Hence, having a larger sample size of representative patients is an important consideration for the waste calculations from a payer perspective.

In addition to using real-world data to optimize vial sizes, with this study we aimed to provide healthcare providers, health technology assessors, payers, and manufacturers with population-based estimates of weight and BSA for U.S. patients with cancer. The use of BSA- and weight-based dosing is relevant to health technology assessment (HTA) agencies, healthcare systems, and payers that need to estimate the average yearly cost of a particular anticancer agent for their patient populations.[13] Cost-effectiveness analyses and budget impact models rely on accurate assessments of BSA or weight to estimate mean dose per administration of i.v. drug per patient[13] and associated costs, and increasingly, these models attempt to model or account for waste. According to a recent systematic review, drug wastage was considered in the primary, or base-case, analysis of parenteral therapies for hematologic malignancies in 2 of the 3 HTA reports reviewed, and consideration of wastage in the model changed the calculated incremental cost-effectiveness ratio.[21]

There is no standard BSA or weight on which to base dosing and estimate the number of vials needed (and costs) for each drug administration.[13] As a result, varying BSA values have been used by manufacturers and evidence review groups in the evaluation of new agents. Even small differences in dose estimates could have a significant impact on cost projections when accounting for partial use of additional vials and the associated drug wastage. The weight and BSA values and distributions used in dosage calculations can have important consequences for pharmacy budgets and reimbursement decisions. However, a literature search revealed that only 2 pertinent studies (using data from real-world clinical practice in the United Kingdom) have been conducted within the last 10 years.[13,22] The patients in our U.S. cancer cohorts had somewhat greater weight and BSA values than patients in the U.K. cancer cohorts, although neither of these studies assessed weight in patients with soft tissue sarcoma.

Our study had several limitations. In the absence of robust histology data, cases of soft tissue sarcoma are difficult to identify using real-world data. We identified patients with soft tissue sarcoma in the EMR data by searching for an *ICD-9-CM* diagnosis code of 171.xx, which will not identify sarcomas occurring in organs or other tissues that are classified under other, tumor location–specific codes. Also, weight loss is a common occurrence during the course of systemic therapy, but our waste calculations captured only weight at initiation of systemic therapy rather than weight changes over time. In addition, we did not distinguish between neoadjuvant, adjuvant, and palliative systemic therapies. However, a prior study found no differences in mean BSA results among patients receiving those forms of therapy, even though the palliative chemotherapy included second- and later-line regimens.[13] Moreover, our study included a large sample, but patients from the South were overrepresented in the EMR data set (they constituted approximately 67% of the soft tissue sarcoma cohort); therefore, our cohorts may not be representative of the U.S. cancer population as a whole. Finally, the formula of DuBois and DuBois was used to calculate BSA, although some pharmacies may use the Mosteller formula; however, no practical differences in the resulting waste-minimization calculations would be expected.

Two objectives were achieved in this study. First, the study provided estimates for weight and BSA for a large sample of men and women with cancer receiving systemic therapy in U.S. outpatient oncology clinics. These real-world patient weight and BSA estimates are important inputs for calculating the cost impact or cost-effectiveness of new cancer therapies in pharmacy budget projections, HTA initiatives, and budget impact models. In addition, the olaratumab study demonstrated how real-world patient weight estimates may be used during drug development and manufacturing to optimize drug vial sizes and reduce drug waste. Based on the weight distribution of patients with soft tissue sarcoma, it was determined that adding a 190-mg vial to the existing product line would reduce anticipated olaratumab waste by 87%; this vial size is now available in the United States. The study demonstrated how optimizing vial sizes is inseparably linked to knowing the population weight and BSA distribution; the choice should not be made in isolation from real-world data if such data are available. The olaratumab study also shows how a seemingly minor change to drug vial sizes can have a significant populationwide impact on drug waste. Using real-world data, manufacturers may implement practices to select vial sizes that will significantly reduce drug waste.

## Conclusion

Analysis of real-world patient weight and BSA data allowed olaratumab vial size optimization to enable maximal dosing flexibility with minimal drug waste.

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## Disclosures

Dr. Sheffield, Ms. Beyrer, Dr. Watson, Ms. Stafford, and Mr. Mills are employees of Eli Lilly and Company and own stock in the company. Dr. Ale-Ali participated on Eli Lilly and Company advisory boards during the study and is currently an employee of the company. The authors have declared no other potential conflicts of interest.

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The New York Times | http://nyti.ms/1UvzN9h

HEALTH

# Waste in Cancer Drugs Costs $3 Billion a Year, a Study Says

By **GARDINER HARRIS** MARCH 1, 2016

WASHINGTON — The federal Medicare program and private health insurers waste nearly $3 billion every year buying cancer medicines that are thrown out because many drug makers distribute the drugs only in vials that hold too much for most patients, a group of cancer researchers has found.

The expensive drugs are usually injected by nurses working in doctors' offices and hospitals who carefully measure the amount needed for a particular patient and then, because of safety concerns, discard the rest.

If drug makers distributed vials containing smaller quantities, nurses could pick the right volume for a patient and minimize waste. Instead, many drug makers exclusively sell one-size-fits-all vials, ensuring that many smaller patients pay thousands of dollars for medicine they are never given, according to researchers at Memorial Sloan Kettering Cancer Center, who published a study on Tuesday in BMJ, formerly known as the British Medical Journal.

Some of these medicines are distributed in smaller vial sizes in Europe, where governments play a more active role than the United States does in drug pricing and distribution.

"Drug companies are quietly making billions forcing little old ladies to buy

enough medicine to treat football players, and regulators have completely missed it," said Dr. Peter B. Bach, director of the Center for Health Policy and Outcomes at Memorial Sloan Kettering and a co-author of the study. "If we're ever going to start saving money in health care, this is an obvious place to cut."

The researchers analyzed the waste generated by the top 20 selling cancer medicines and concluded that insurers paid drug makers $1.8 billion annually on discarded quantities and then spent about $1 billion on markups to doctors and hospitals.

Some non-cancer drugs also generate considerable waste, including Remicade, an arthritis drug sold by Johnson & Johnson for which an estimated $500 million of the drug's $4.3 billion in annual sales comes from quantities that are thrown away, researchers found. But such non-cancer drugs were not included in the study's estimates of total waste.

In one example, the study said that in the United States Takeda Pharmaceuticals sells Velcade, a drug for the treatment of multiple myeloma and lymphoma, only in 3.5-milligram vials that sell for $1,034 and hold enough medicine to treat a person who is 6 feet 6 inches tall and who weighs 250 pounds. If a patient is smaller, then a quantity of the precious powder is thrown away.

Lena Haddad, 53, of Germantown, Md., who has been living with multiple myeloma for four years, now gets a weekly dose of 1.8 milligrams of Velcade. On a recent day at Ms. Haddad's doctor's office in Bethesda, Md., a nurse, Patricia Traylor, took a vial of Velcade from a large drug cabinet. She injected a syringeful of saline into the vial and shook it, pushed a needle into the vial and withdrew about half the contents. Then she threw out the vial with the remaining medicine.

"You can't use the remainder for the patient the next time she comes in or use it on another patient, so it has to be discarded as waste," Ms. Traylor said.

Safety standards permit nurses to use drug leftovers in other patients only if used within six hours and only in specialized pharmacies.

Told that she was using only about half of the drug that was purchased, Ms. Haddad said she was shocked.

“No wonder my premiums keep going up,” she said.

Medicare and many private insurers charge patients drug co-payments of as much as 20 percent, which can add up to tens of thousands of dollars annually for the latest drugs; much is spent on cancer medicines that patients never receive, according to the study.

Dr. Dixie-Lee Esseltine, vice president for oncology clinical research at Takeda, wrote in an email that the pharmaceutical firm “worked closely with the F.D.A. to establish the Velcade vial size of 3.5 mg to ensure that one vial of Velcade would provide an adequate amount of the drug for a patient of almost any size.”

Velcade is sold in Britain in both 1-milligram and 3.5-milligram vials.

Takeda is expected to earn $309 million this year on supplies of Velcade that are discarded, an amount that represents 30 percent of the drug’s overall sales in the United States, the cancer researchers estimated. If Takeda provided an additional vial size of 0.25 milligram, waste would be slashed by 84 percent, also reducing Velcade’s sales in the United States by $261 million annually, the researchers calculated.

“You have these incredibly expensive drugs, and you can only buy them in bulk,” said Dr. Leonard Saltz, who leads the pharmacy and therapeutics committee at Memorial Sloan Kettering and was a co-author of the study. “What’s really interesting is they’re selling these drugs in smaller vials in Europe, where regulators are clearly paying attention to this issue.”

Christopher Kelly, a spokesman for the Food and Drug Administration,

said the agency objected to companies' proposed vial sizes only if it believed that an excessively large volume of medicine "could lead to medication errors or safety issues due to inappropriate multiple dosing."

In other words, as long as nurses are not tempted to do anything but discard additional quantities, the drug agency is fine with extra-large, one-size-fits-all packaging. Congress has not given the drug agency the authority to consider cost in its decisions.

"Companies propose the vial sizes that they would like to market," Mr. Kelly said.

Rising drug prices have been a concern for many years, and high initial prices and subsequent increases are an industrywide phenomenon. The last 10 cancer drugs approved before July 2015 have an average annual price of $190,217, and major drug makers routinely increase the prices of big sellers 10 percent or more each year, far above the rate of inflation.

The industry explains that high prices are needed to fund research, but companies such as Pfizer and Merck spend just 17 percent of their revenues finding new drugs, according to their financial statements. Far more goes to marketing and profits.

For decades, cancer doctors largely ignored the issue of pricing, but as their patients became impoverished, some began to speak up. In 2012, Dr. Bach and Dr. Saltz wrote an Op-Ed article in The New York Times announcing that their hospital would not purchase a new cancer drug that was twice as expensive as but no more effective than an existing medicine. The maker of the drug slashed its price.

Dr. Bach and Dr. Saltz say they have since become concerned that prices of new cancer medicines have almost no connection with their lifesaving potential. Dr. Bach recently unveiled a complex calculator of drug value.

But there was nothing complex about measuring the value of a drug that was thrown away, Dr. Saltz said, since the value to the patient was zero.

The two doctors have proposed that the government either mandate that drug makers provide medicines in enough vial sizes to minimize waste, or mandate that drug makers refund the government for wasted quantities.

Dr. Saltz first noticed the problem of waste when he was considering adding Keytruda, a new drug for metastatic lung cancer and melanoma, to the hospital's list of drugs to be used on patients. Although a 150-pound patient would need 136 milligrams of the drug, Dr. Saltz noticed that Merck, its manufacturer, sold the medicine only in 50-milligram vials — ensuring waste.

"I thought that was really cynical," Dr. Saltz said in an interview. "And then it got worse."

In February 2015, Merck introduced 100-milligram vials and stopped selling Keytruda in 50-milligram vials, ensuring far larger amounts of waste. The company still sells 50-milligram vials of the drug in Europe.

Pamela L. Eisele, a Merck spokeswoman, said the company hoped to persuade the F.D.A. to approve a fixed dose of 200 milligrams of Keytruda for all patients, higher than the dose presently given to nearly all patients. In studies given to the drug agency, there was no evidence that the higher dose was more effective, Ms. Eisele said, but the fixed dose "will eliminate wastage."

Since the extra medicine does nothing to help patients, Dr. Bach said that the company was advocating that waste be injected into patients rather than thrown away.

Under its present dosing, Merck would earn $2.4 billion over the next five years from discarded quantities of Keytruda, half of which would result from switching to 100-milligram vials, the researchers estimated.

Some cancer drugs have little waste.

Treanda, which is used to treat leukemia and non-Hodgkin's lymphoma and is manufactured by Teva Pharmaceuticals, is packaged in four separate dosages so only 1 percent of the drug is wasted, on average.

But 18 of the top 20 cancer medicines are sold in just one or two vial sizes, so on average 10 percent of the volume of cancer drugs purchased by doctors and hospitals is discarded, the researchers say.

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A version of this article appears in print on March 1, 2016, on page B1 of the New York edition with the headline: Researchers Describe Costly Waste in Cancer Drugs.

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The Washington Post

To Your Health

# Americans are wasting $3 billion a year on discarded cancer drugs

By Laurie McGinley March 1

Almost $3 billion a year in expensive cancer drugs are wasted because their single-use packages contain more medication than is needed -- and the leftover drug is thrown away for safety reasons, according to a new analysis by researchers.

The study focused on 20 cancer drugs that are infused -- administered intravenously or injected -- by doctors' offices or hospitals. These come in dosages based on patients' weights and body sizes, but often the doses are too large and the remainder is tossed out, the analysis found.

"It's literally paying for drugs that go in the trash," said Peter Bach, director of the Center for Health Policy and Outcomes at Memorial Sloan Kettering Cancer Center in New York. Bach co-authored the study, which was published Tuesday in BMJ, formerly known as British Medical Journal. To increase profits, pharmaceutical companies "are finding a way to charge patients and insurers for drugs that they don't even take," he said.

The study concluded that Medicare and private insurers, as well as patients, pay companies about $1.8 billion a year for medications that are thrown away. They pay another $1 billion to doctors and hospitals as price markups on those discarded medications, according to the study. The analysis was conducted against the backdrop of rapidly rising price increases in both new and older cancer drugs.

"This study reveals that billions of dollars are wasted on expensive cancer drugs, due to the way they are packaged in single doses. This practice greatly inflates profits but is waste that we can no longer afford," John Rother, president and chief executive of the National Coalition on Health Care, said in an email.

But Allyson Funk, senior director of communications at the trade group Pharmaceutical Research and Manufacturers of America noted in a statement that developing and manufacturing cancer medications remains extremely complex and subject to strict regulation by the Food and Drug Administration.

"Decisions regarding vial size are tied to a product's initially approved dosage and labeled use, taking into account that different patients will have different needs," she said. "Vial fill size must be approved by FDA as part of the sponsor's drug application and any excess volume must meet FDA standards outlined in regulations." Any change in vial sizes requires FDA approval, which can take months, she said.

The FDA, which regulates the safety and effectiveness of drugs, doesn't have authority to weigh cost in considering medications, and Bach said he didn't think the agency could order drug companies to use certain vial sizes. But he said he thinks it could, and should, encourage the companies to sell their products in various vial sizes to minimize leftover medication.

An FDA statement noted that officials had not yet reviewed the article but that the agency "works with firms to make sure the proposed vial size is appropriate for the intended use of the product, especially where there are safety concerns about medication errors or the potential that excess drug could be used inappropriately to treat multiple patients from the same vial (which raises concerns about cross-contamination)."

The researchers who did the analysis also said government agencies should develop a consistent policy on whether a vial can be used on more than one patient. Though the Centers on Medicare and Medicaid Services encourages such "vial sharing," they said, the Centers for Disease Control and Prevention considers it unsafe.

**Read more:**

Scientists think anti-oxidants may boost cancer, not restrain it.

Tapeworms can transmit cancer cells to humans: CDC

# Exhibit E

# CENTER FOR DRUG EVALUATION AND RESEARCH

## Approval Package for:

## *APPLICATION NUMBER:*

## 761038Orig1s001

| | |
|---|---|
| ***Trade Name:*** | LARTRUVO |
| ***Generic or Proper Name:*** | olaratumab |
| ***Sponsor:*** | Eli Lilly and Company |
| ***Approval Date:*** | July 10, 2017 |
| ***Indication:*** | Lartruvo is indicated, in combination with doxorubicin, for the treatment of adult patients with soft tissue sarcoma (STS) with a histologic subtype for which an anthracycline-containing regimen is appropriate and which is not amenable to curative treatment with radiotherapy or surgery.<br>This indication is approved under accelerated approval. Continued approval for this indication may be contingent upon verification and description of clinical benefit in the confirmatory trial. |

# CENTER FOR DRUG EVALUATION AND RESEARCH

# 761038Orig1s001

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# CENTER FOR DRUG EVALUATION AND RESEARCH

***APPLICATION NUMBER:***

# 761038Orig1s001

# APPROVAL LETTER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Silver Spring, MD 20993

**APPROVAL LETTER**

BLA 761038/1

Eli Lilly and Company
Attention: Lisa Wenzler, Ph.D.
Research Advisor, CMC Regulatory, Global Regulatory Affairs-US
Lilly Corporate Center
Drop Code 2543
Indianapolis, IN 46285

Dear Dr. Wenzler:

Please refer to your Supplemental Biologics License Application (sBLA) dated January 13, 2017 and received January 13, 2017, submitted under section 351(a) of the Public Health Service Act for Lartruvo™ (Olaratumab) for Injection, 500 mg/50 mL.

This "Changes Being Effected in 30 days" supplemental biological application proposes to introduce a new vial presentation of 190 mg/19 mL for Lartruvo (Olaratumab) drug product.

We have completed our review of this supplemental biologics application. This supplement is approved.

This information will be included in your biologics license application file.

If you have any questions, call Kelly Ballard, Regulatory Business Process Manager, at (301) 348-3054.

Sincerely,

*{See appended electronic signature page}*

David Frucht, Ph.D.
Director
Division of Biotechnology Review and Research II
Office of Biotechnology Products
Office of Pharmaceutical Quality
Center for Drug Evaluation and Research

David Frucht

Digitally signed by David Frucht
Date: 7/10/2017 11:30:13AM
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# CENTER FOR DRUG EVALUATION AND RESEARCH

***APPLICATION NUMBER:***

# 761038Orig1s001

# LABELING

LARTRUVO™ (olaratumab) injection

**HIGHLIGHTS OF PRESCRIBING INFORMATION**

These highlights do not include all the information needed to use LARTRUVO safely and effectively. See full prescribing information for LARTRUVO.

**LARTRUVO** (olaratumab) injection, for intravenous use
**Initial U.S. Approval: 2016**

**—INDICATIONS AND USAGE—**

LARTRUVO™ is a platelet-derived growth factor receptor alpha (PDGFR-α) blocking antibody indicated, in combination with doxorubicin, for the treatment of adult patients with soft tissue sarcoma (STS) with a histologic subtype for which an anthracycline-containing regimen is appropriate and which is not amenable to curative treatment with radiotherapy or surgery. (1)
This indication is approved under accelerated approval. Continued approval for this indication may be contingent upon verification and description of clinical benefit in the confirmatory trial. (14)

**—DOSAGE AND ADMINISTRATION—**

- Administer LARTRUVO at 15 mg/kg as an intravenous infusion over 60 minutes on Days 1 and 8 of each 21-day cycle until disease progression or unacceptable toxicity. (2.1)
- For the first 8 cycles, LARTRUVO is administered with doxorubicin. (2.1)
- Premedicate with diphenhydramine and dexamethasone intravenously, prior to LARTRUVO on Day 1 of cycle 1. (2.2)
- For intravenous infusion only. Do not administer as an intravenous push or bolus. (2.4)

**—DOSAGE FORMS AND STRENGTHS—**

Injection: 500 mg/50 mL (10 mg/mL) or 190 mg/19 mL (10 mg/mL) solution in a single-dose vial (3)

**—CONTRAINDICATIONS—**

None. (4)

**—WARNINGS AND PRECAUTIONS—**

- Infusion-Related Reactions: Monitor for signs and symptoms during and following infusion. Discontinue LARTRUVO for Grade 3 or 4 infusion-related reactions. (2.3, 5.1)
- Embryo-Fetal Toxicity: Can cause fetal harm. Advise females of potential risk to the fetus and to use effective contraception during treatment with LARTRUVO and for 5 months after the last dose. (5.2, 8.1, 8.3)

**—ADVERSE REACTIONS—**

The most common (≥25%) adverse reactions of LARTRUVO plus doxorubicin are nausea, fatigue, musculoskeletal pain, mucositis, alopecia, vomiting, diarrhea, decreased appetite, abdominal pain, neutropenia, and headache. (6.1)
The most common (≥25%) laboratory abnormalities were lymphopenia, neutropenia, thrombocytopenia, hyperglycemia, elevated aPTT, hypokalemia, and hypophosphatemia. (6.1)

To report **SUSPECTED ADVERSE REACTIONS**, contact **Eli Lilly** and Company at **1-800-LillyRx** (1-800-545-5979) or **FDA** at **1-800-FDA-1088** or **www.fda.gov/medwatch**.

**—USE IN SPECIFIC POPULATIONS—**

Lactation: Advise women not to breastfeed. (8.2)

**See 17 for PATIENT COUNSELING INFORMATION.**

Revised: 09/2017

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**FULL PRESCRIBING INFORMATION**

**1 INDICATIONS AND USAGE**

LARTRUVO™ is indicated, in combination with doxorubicin, for the treatment of adult patients with soft tissue sarcoma (STS) with a histologic subtype for which an anthracycline-containing regimen is appropriate and which is not amenable to curative treatment with radiotherapy or surgery.
This indication is approved under accelerated approval [see Clinical Studies (14)]. Continued approval for this indication may be contingent upon verification and description of clinical benefit in the confirmatory trial.

**2 DOSAGE AND ADMINISTRATION**

**2.1 Recommended Dosage**

The recommended dose of LARTRUVO is 15 mg/kg administered as an intravenous infusion over 60 minutes on Days 1 and 8 of each 21-day cycle until disease progression or unacceptable toxicity. For the first 8 cycles, LARTRUVO is administered with doxorubicin [see Clinical Studies (14)].

Refer to doxorubicin prescribing information for dosing, and dose modifications.

**2.2 Premedication**

- Premedicate with diphenhydramine 25 to 50 mg intravenously and dexamethasone 10 to 20 mg intravenously prior to LARTRUVO on Day 1 of cycle 1.

**2.3 Dosing Modifications**

*Infusion-Related Reactions*

- Permanently discontinue LARTRUVO for Grade 3 or 4 infusion-related reactions [see Dosage and Administration (2.3) and Warnings and Precautions (5.1)].
- Interrupt infusion of LARTRUVO for Grade 1 or 2 infusion-related reactions (IRR). After resolution, resume LARTRUVO infusion at 50% of the initial infusion rate, [see Warnings and Precautions (5.1)]

*Neutropenia*

- For neutropenia (neutrophil count < 1,000/mcL) or Grade 4 neutropenia lasting longer than 1 week, discontinue administration of LARTRUVO until the absolute neutrophil count is 1,000 /microliter or greater and then permanently reduce the dose to 12 mg/kg.

**2.4 Preparation and Administration**

*Preparation*

- Inspect vial contents for particulate matter and discoloration prior to dilution [see Description (11)]. Discard the vial if particulate matter or discolorations are identified.
- Withdraw calculated dose and further dilute with 0.9% Sodium Chloride Injection, USP to a final volume of 250 mL for intravenous infusion. Do not use dextrose-containing or other solutions.
- Gently invert but do not shake.
- DO NOT FREEZE the diluted solution.
- Store the diluted solution for up to 24 hours under refrigeration at 2°C to 8°C (36°F to 46°F) and for up to an additional 4 hours at room temperature (below 25°C (77°F)). Storage times include the duration of infusion. If refrigerated, allow the diluted solution to come to room temperature prior to administration.
- Discard vial with any unused portion of LARTRUVO.

*Administration*

- Do not administer LARTRUVO as an intravenous push or bolus. Do not co-infuse with electrolytes or other medications through the same intravenous line.
- Visually inspect the diluted solution for particulate matter and discoloration prior to administration. If particulate matter or discolorations are identified, discard the solution.
- Administer diluted solution as an intravenous infusion over 60 minutes. Flush the line with 0.9% Sodium Chloride Injection, USP at end of infusion.

**3 DOSAGE FORMS AND STRENGTHS**

Injection: 500 mg/50 mL (10 mg/mL) or 190 mg/19 mL (10 mg/mL) clear to slightly opalescent, colorless to slightly yellow solution in a single-dose vial.

**4 CONTRAINDICATIONS**

None.

**5 WARNINGS AND PRECAUTIONS**

**5.1 Infusion-Related Reactions**

Infusion-related reactions (IRR) occurred in 70 (14%) of 495 patients who received at least one dose of LARTRUVO across clinical trials. For 68 of these 70 patients (97%), the first occurrence of IRR was in the first or second cycle. Grade ≥3 IRR occurred in 11 (2.5%) of 495 patients, with one (0.2%) fatality. Symptoms of IRR included flushing, shortness of breath, bronchospasm, or fever/chills, and in severe cases symptoms manifested as severe hypotension, anaphylactic shock, or cardiac arrest.
Infusion-related reactions required permanent discontinuation in 0.2% of patients and interruption of infusion in 10% of patients. All 68 patients with Grade 1 or 2 IRR resumed LARTRUVO. 12 (20%) of these patients had a Grade 1 or 2 IRR with rechallenge. The incidence of IRR in the overall safety database (N = 495) was similar (14% versus 12%) between those who did (68%) and those who did not (44%) receive premedication.
Monitor patients during and following LARTRUVO infusion for signs and symptoms of IRR in a setting with available resuscitation equipment. Immediately and permanently discontinue LARTRUVO for Grade 3 or 4 IRR [see Dosage and Administration (2.3, 2.4) and Adverse Reactions (6.1)].

**5.2 Embryo-Fetal Toxicity**

Based on animal data and its mechanism of action, LARTRUVO can cause fetal harm when administered to a pregnant woman. Animal knockout models link disruption of platelet-derived growth factor receptor alpha (PDGFR-α) signaling to adverse effects on embryo-fetal development. Administration of an anti-murine PDGFR-α antibody to pregnant mice during organogenesis caused malformations and skeletal variations. Advise pregnant women of the potential risk to a fetus. Advise females of reproductive potential to use effective contraception during treatment with LARTRUVO and for 5 months after the last dose [see Use in Specific Populations (8.1, 8.3)].

**6 ADVERSE REACTIONS**

The following adverse drug reactions are described elsewhere in the labeling:
- Infusion-Related Reactions [see Warnings and Precautions (5.1)]

**6.1 Clinical Trials Experience**

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.
The data in the Warnings and Precautions section reflect exposure to LARTRUVO in 495 patients from three randomized, open-label, active-controlled clinical trials. These trials enrolled 256 patients with various tumors who received LARTRUVO in combination with chemotherapy (127 patients) or as a single agent (129 patients) and 239 patients who received chemotherapy alone. The majority of patients (n = 361) received LARTRUVO in combination with doxorubicin and two trials, including Trial 1, which enrolled 133 patients with soft tissue sarcoma who received LARTRUVO at doses of 15 mg/kg in combination with doxorubicin (129 patients) or LARTRUVO as a single agent (64 patients). Among the 495 patients, 81% were exposed to LARTRUVO for ≥6 months and 9% were exposed for ≥12 months.
The data described below reflect exposure to LARTRUVO in 64 patients with metastatic soft tissue sarcoma enrolled in Trial 1, a multicenter, randomized (1:1), open-label, active-controlled trial comparing LARTRUVO plus doxorubicin with doxorubicin as a single agent. LARTRUVO was administered at 15 mg/kg as an intravenous infusion on Days 1 and 8 of each 21-day cycle until disease progression or unacceptable toxicity [see Clinical Studies (14)]. All patients received doxorubicin 75 mg/m² as an intravenous infusion on Day 1 of each 21-day cycle for a maximum of eight cycles and received dexrazoxane, prior to doxorubicin in cycles 1 to 4. In Trial 1, no patients had received a prior anthracycline-containing regimen. The trial excluded patients with an ECOG performance status ≥2, left ventricular ejection fraction (LVEF) below the institutional lower limit of normal, or prior cumulative doxorubicin exposure greater than 400 mg/m².
The baseline demographics and disease characteristics were: median age 58 years (range 27 to 86); 45% male; 97% White, 9% Black, 3% Asian, 2% Other; 91% ECOG PS 0, 39% ECOG PS 1, and 1% ECOG PS 2. The median duration of exposure to LARTRUVO was 5 months (range 21 days to 25.4 months). 36 (56%) patients receiving LARTRUVO for ≥6 months and 10 (16%) patients receiving LARTRUVO for ≥12 months. The median cumulative doxorubicin dose was 489 mg/m² in the LARTRUVO plus doxorubicin arm and 300 mg/m² in the doxorubicin arm.
In Trial 1, adverse reactions resulting in permanent discontinuation of LARTRUVO occurred in 9% (5/64) of patients. The most common adverse reaction leading to LARTRUVO discontinuation was infusion-related reaction (3%). Dose reductions of LARTRUVO for adverse reactions occurred in 23% (15/64) of patients. The most common adverse reaction leading to dose reduction was Grade 3 or 4 neutropenia (25%). Dose delays of LARTRUVO for adverse reactions occurred in 52% (33/64) of patients. The most common adverse reactions leading to dose delay were neutropenia (25%), thrombocytopenia (5%), and anemia (5%).
Table 1 summarizes adverse reactions that occurred in at least 10% of patients receiving LARTRUVO in the randomized portion of the study. The most common adverse reactions reported in at least 20% of patients receiving LARTRUVO plus doxorubicin were nausea, fatigue, musculoskeletal pain, mucositis, alopecia, vomiting, diarrhea, decreased appetite, abdominal pain, neutropenia, and headache.

**Table 1: Adverse Reactions Occurring in ≥10% (All Grades) of Patients in the LARTRUVO plus Doxorubicin Arm and at a Higher Incidence than in the Doxorubicin Arm (Between Arm Difference of ≥5% for All Grades or ≥2% for Grades 3 and 4) (Trial 1)**

| Adverse Reactions | LARTRUVO plus Doxorubicin N=64 | | Doxorubicin N=65 | |
|---|---|---|---|---|
| | All Grades (%) | Grade 3-4 (%) | All Grades (%) | Grade 3-4 (%) |
| **Gastrointestinal Disorders** | | | | |
| Nausea | 73 | 2 | 62 | 0 |
| Mucositis | 52 | 8 | 26 | 0 |
| Vomiting | 35 | 0 | 19 | 0 |
| Diarrhea | 34 | 5 | 23 | 0 |
| Abdominal Pain* | 23 | 5 | 14 | 0 |
| **General Disorders and Administration Site Conditions** | | | | |
| Fatigue† | 69 | 8 | 60 | 2 |
| Infusion-Related Reactions | 16 | 5 | 5 | 0 |
| **Musculoskeletal and Connective Tissue Disorders** | | | | |
| Musculoskeletal Pain‡ | 64 | 8 | 25 | 2 |
| **Skin and Subcutaneous Tissue Disorders** | | | | |
| Alopecia | 50 | 0 | 46 | 0 |
| **Metabolic and Nutritional Disorders** | | | | |
| Decreased Appetite | 31 | 2 | 20 | 0 |
| **Nervous System Disorders** | | | | |
| Neuropathy | 22 | 0 | 11 | 0 |
| Headache | 20 | 0 | 9 | 0 |
| **Psychiatric Disorder** | | | | |
| Anxiety | 11 | 0 | 3 | 0 |
| Eye Disorder | | | | |
| Dry Eyes | 11 | 0 | 3 | 0 |

* Abdominal pain includes: abdominal pain, lower abdominal pain, and upper abdominal pain.
† Fatigue includes: asthenia and fatigue.
‡ Musculoskeletal pain includes: arthralgia, back pain, bone pain, flank pain, groin pain, musculoskeletal chest pain, musculoskeletal pain, myalgia, muscle spasms, neck pain, and pain in extremity.

In Trial 1, the most common laboratory abnormalities (≥25%) were lymphopenia, neutropenia, thrombocytopenia, hyperglycemia, elevated aPTT, hypokalemia, and hypophosphatemia as shown in Table 2.

**Table 2: Laboratory Abnormalities Worsening from Baseline in ≥ 50% (All Grades) of Patients in the LARTRUVO plus Doxorubicin Arm and Occurring at a Higher Incidence than in the Doxorubicin Arm (Between Arm Difference ≥5% for All Grades or ≥2% for Grades 3 and 4) (Trial 1)**

| Laboratory Abnormality | LARTRUVO plus Doxorubicin* | | Doxorubicin* | |
|---|---|---|---|---|
| | All Grades (%) | Grades 3-4 (%) | All Grades (%) | Grades 3-4 (%) |
| **Chemistry** | | | | |
| Hyperglycemia | 50 | 3 | 28 | 3 |
| Increased aPTT† | 38 | 6 | 15 | 0 |
| Hypokalemia | 31 | 8 | 15 | 5 |
| Hypophosphatemia | 31 | 6 | 7 | 0 |
| Increased Alkaline Phosphatase | 16 | 0 | 7 | 0 |
| Hyponatremia | 16 | 0 | 9 | 5 |
| **Hematology** | | | | |
| Lymphopenia | 77 | 44 | 72 | 51 |
| Neutropenia | 50 | 48 | 60 | 58 |
| Thrombocytopenia | 58 | 8 | 44 | 11 |

* The incidence is based on the number of patients who had both baseline and at least one on-study laboratory measurement: LARTRUVO plus doxorubicin arm (range 46 to 63 patients) and doxorubicin arm (range 56 to 62 patients).
† aPTT = activated partial thromboplastin time

**6.2 Immunogenicity**

As with all therapeutic proteins, there is the potential for immunogenicity. In clinical trials, 12/370 (3.2%) of evaluable LARTRUVO-treated patients tested positive for treatment-emergent anti-olaratumab antibodies by an enzyme-linked immunosorbent assay (ELISA). Neutralizing antibodies were detected in all patients who tested positive for treatment-emergent anti-olaratumab antibodies. The effects of anti-olaratumab antibodies on efficacy, safety, and exposure could not be assessed due to the limited number of patients with treatment-emergent anti-olaratumab antibodies.
The ELISA was not drug tolerant at concentrations ≤ 50 mcg/mL of olaratumab in the assay. Additionally, the observed incidence of antibody (including neutralizing antibody) positivity in an assay may be influenced by several factors including assay methodology, sample handling, timing of sample collection, concomitant medications, and underlying disease. For these reasons, comparison of incidence of antibodies to LARTRUVO with the incidence of antibodies to other products may be misleading.

**8 USE IN SPECIFIC POPULATIONS**

**8.1 Pregnancy**

*Risk Summary*

Based on animal data and its mechanism of action, LARTRUVO can cause fetal harm [see Clinical Pharmacology (12.1)]. There are no available data on LARTRUVO use in pregnant women. No animal studies using olaratumab have been conducted to evaluate its effect on female reproduction and embryo-fetal development. Animal knockout models link disruption of platelet-derived growth factor receptor alpha (PDGFR-α) signaling to adverse effects on embryo-fetal development. Administration of an anti-murine PDGFR-α antibody to pregnant mice during organogenesis at exposures less than the exposure at the maximum recommended human dose caused malformations and skeletal variations [see Data].
In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2-4% and 15-20%, respectively.

*Data*

*Animal Data*

No animal studies have been conducted using olaratumab to evaluate the effect of blocking PDGFR-α signaling on reproduction and embryo-fetal development. In PDGFR-α knockout mice, disruption of PDGFR-α signaling resulted in embryo-fetal lethality and teratogenicity, including cleft face and axial bifida. Intravenous administration of an anti-murine PDGFR-α antibody once every 3 days to pregnant mice during organogenesis at 50 and 150 mg/kg resulted in increased malformations, abnormal ocular development and skeletal variations (additional cranial/facial ossification sites in the frontal/parietal skull, increased post-zygapophysis ossification) at doses of 5 mg/kg. The effects on fetal development in mice administered this antibody occurred at exposures less than the AUC exposure at the maximum recommended human dose of 15 mg/kg LARTRUVO.

**8.2 Lactation**

*Risk Summary*

There are no data on the presence of olaratumab in human milk, or its effects on the breastfed infant or on milk production. Because of the potential risk for serious adverse reactions in breastfeeding infants from olaratumab, advise women not to breastfeed during treatment with LARTRUVO and for 5 months following the last dose.

**8.3 Females and Males of Reproductive Potential**

*Contraception*

*Females*

Based on its mechanism of action, LARTRUVO can cause fetal harm when administered to a pregnant woman [see Use in Specific Populations (8.1)]. Advise females of reproductive potential to use effective contraception during treatment with LARTRUVO and for 5 months after the last dose.

*Infertility*

*Males*

Based on animal models, LARTRUVO may impair male fertility [see Nonclinical Toxicology (13.1)].

**8.4 Pediatric Use**

The safety and effectiveness of LARTRUVO in pediatric patients have not been established.

**8.5 Geriatric Use**

Clinical studies of LARTRUVO did not include sufficient numbers of patients aged 65 years and older to determine whether they respond differently from younger patients.

**11 DESCRIPTION**

Olaratumab is a recombinant human IgG1 monoclonal blocking antibody that binds specifically to human platelet-derived growth factor receptor alpha (PDGFR-α). LARTRUVO has an approximate molecular weight of 154 kDa. LARTRUVO is produced in genetically engineered mammalian NS0 cells.
LARTRUVO is a sterile, preservative-free, clear to slightly opalescent, and colorless to slightly yellow solution. LARTRUVO injection is supplied in single-dose vials for intravenous use following dilution. Each vial contains 500 mg LARTRUVO (10 mg/mL) or 190 mg LARTRUVO (10 mL (10 mg/mL). Each mL contains 10 mg olaratumab, glycine (7.5 mg), L-histidine (0.5 mg), L-histidine monohydrochloride (1.7 mg), mannitol (15.7 mg), polysorbate 20 (0.2 mg), sodium chloride (2.9 mg), and water for injection, USP, pH 6.2 to 6.8.

**12 CLINICAL PHARMACOLOGY**

**12.1 Mechanism of Action**

Olaratumab is a human IgG1 antibody that binds platelet-derived growth factor receptor alpha (PDGFR-α). PDGFR-α is a receptor tyrosine kinase expressed on cells of mesenchymal origin. Signaling through this receptor plays a role in cell growth, chemotaxis, and mesenchymal stem cell differentiation. The receptor has also been detected on some tumor and stromal cells, including sarcomas, where signaling can contribute to cancer cell proliferation, metastasis, and maintenance of the tumor microenvironment. The interaction between olaratumab and PDGFR-α prevents binding of the receptor to the PDGF-AA and -BB ligands as well as PDGF-AA, -BB, and -CC-induced receptor activation and downstream PDGFR-α pathway signaling. Olaratumab exhibits in vitro and in vivo anti-tumor activity against selected sarcoma cell lines and disrupted the PDGFR-α signaling pathway in in vivo tumor implant models.

**12.2 Pharmacodynamics**

Olaratumab exposure-response relationships and the time course of the pharmacodynamics response are unknown.

**12.3 Pharmacokinetics**

*Distribution*

The volume of distribution (CV%) at steady-state ($V_{ss}$) is 7.7 L (15%).

*Elimination*

The mean clearance (CV%) for olaratumab was 0.36 L/day (33%). The estimated elimination half-life was approximately 11 days (range 6 to 24 days).

*Specific Populations*

Age (22 to 90 years), sex (47% females), race (86% Whites), mild to moderate renal impairment (calculated creatinine clearance (CLcr) 30-89 mL/min as estimated by the Cockcroft-Gault formula (C-G)), and mild (total bilirubin within upper limit of normal (ULN) and AST greater than ULN or total bilirubin greater than 1.0 and up to 1.5 times ULN and any AST) to moderate (total bilirubin greater than 1.5 and up to 3.0 times ULN and any AST) hepatic impairment had no clinically important effect on the pharmacokinetics of olaratumab. The pharmacokinetics of olaratumab in patients with severe renal impairment (CLcr 15-29 mL/min as estimated by C-G) or with severe hepatic impairment (total bilirubin greater than 3.0 times ULN and any AST) are unknown. Body weight (range 37 to 151 kg) correlates with clearance and volume of distribution of olaratumab.

*Drug Interaction Studies*

No clinically relevant changes in the exposure of either olaratumab or doxorubicin were observed when LARTRUVO 15 mg/kg and doxorubicin 75 mg/m² were co-administered in patients with solid tumors.

**13 NONCLINICAL TOXICOLOGY**

**13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility**

No studies have been performed to assess the potential of olaratumab for carcinogenicity or genotoxicity.
Fertility studies have not been performed with olaratumab; however, in animal knockout models, loss of PDGFR-α pathway signaling resulted in progressive reduction in testicular size, Leydig cell loss, and spermatogenic arrest.

**14 CLINICAL STUDIES**

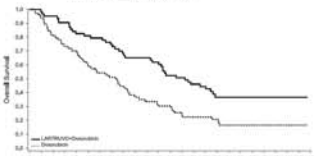
The efficacy of LARTRUVO was demonstrated in Trial 1, an open-label, randomized, active-controlled study. Eligible patients were required to have soft tissue sarcoma (STS) with a histologic subtype for which an anthracycline-containing regimen was appropriate but not amenable to curative treatment with surgery or radiotherapy, a histologic type of sarcoma for which an anthracycline-containing regimen was appropriate but had not been administered, ECOG PS of 0-2, and tumor specimen available for assessment of PDGFR-α expression by an investigational use assay. Patients were randomized (1:1) to receive LARTRUVO in combination with doxorubicin or doxorubicin as a single agent. PDGFR-α expression (positive versus negative), number of previous lines of treatment (0 versus 1 or more), histological tumor type (leiomyosarcoma versus synovial sarcoma versus all others), and ECOG PS (0 versus 1 versus 2) were used as stratification factors. LARTRUVO was administered at 15 mg/kg as an intravenous infusion on Days 1 and 8 of each 21-day cycle for the first 8 cycles in combination with doxorubicin or as a single agent. Doxorubicin 75 mg/m² as an intravenous infusion on Day 1 of each 21-day cycle for a maximum of eight cycles and dexrazoxane 75 mg/m² as an intravenous infusion on Day 1 of each 21-day cycle for a maximum of eight cycles and were permitted to receive dexrazoxane prior to doxorubicin in Cycles 5 to 8. Patients randomized to receive doxorubicin as a single agent were offered LARTRUVO at the time of disease progression. The efficacy outcome measures were overall survival (OS), and progression-free survival (PFS) and objective response rate (ORR) as assessed by investigator and by independent review according to RECIST v1.1.
A total of 133 patients were randomized, 66 patients to the LARTRUVO plus doxorubicin arm and 67 patients to the doxorubicin arm. Baseline demographics and disease characteristics were: median age of 56 years (range 22 to 86); 44% men; 89% White, 4% Black, 3% Asian, and 2% Other; 56% ECOG PS 0 and 39% ECOG PS 1; 85% no prior chemotherapy (excluding adjuvant and neoadjuvant therapy); 39% leiomyosarcoma, 1.5% synovial sarcoma, and 61% other histologies (17% liposarcoma (9% dedifferentiated, 4% myxoid, 3% well-differentiated), 1.5% pleomorphic, 1% liposarcoma not otherwise specified (NOS), 11% undifferentiated pleomorphic sarcoma (UPS)/malignant fibrous histiocytoma (MFH), 4% gastrointestinal stromal sarcoma, 3% rhabdomyosarcoma, 3% malignant solitary fibrous tumor, 2% endometrial stromal sarcoma, 1.5% chondrosarcoma, 1.5% epithelioid sarcoma, 1.5% fibrosarcoma, 1.5% low-grade fibromyxoid sarcoma, and 5% other histologies with one patient each). All patients had metastatic disease and were enrolled at U.S. sites. Among patients randomized to doxorubicin, 30 (45%) patients received LARTRUVO as a single agent at the time of disease progression.
Trial 1 demonstrated a significant improvement in overall survival. The efficacy results are summarized in Table 3 and Figure 1.

**Table 3: Efficacy Results in Trial 1**

| | LARTRUVO + Doxorubicin N=66 | Doxorubicin N=67 |
|---|---|---|
| **Overall Survival** | | |
| Number of deaths (%) | 39 (59%) | 52 (78%) |
| Median, months (95% CI) | 25.5 (20.8, 31.7) | 14.7 (12.2, 17.1) |
| Hazard Ratio (95% CI)* | 0.52 (0.34, 0.79) | |
| 2-sided p-value† | p=0.00 | |
| **Progression-Free Survival‡** | | |
| Number of events (%) | 37 (56%) | 54 (81%) |
| Median, months (95% CI) | 8.2 (5.5, 8.9) | 4.6 (3.1, 7.4) |
| Hazard Ratio (95% CI)* | 0.74 (0.48, 1.16) | |
| **Objective Response Rate (CR + PR)§** | | |
| (95% CI) | 18.2% (9.4, 29.8) | 7.9% (2.3, 18.8) |
| CR, n (%) | 3 (4.5%) | 1 (1.5%) |
| PR, n (%) | 9 (13.6%) | 4 (6%) |

Abbreviations: CI = confidence interval, CR = complete response, PR = partial response
* Unstratified Cox model
† Based on independent review

**Figure 1: Kaplan-Meier Curves of Overall Survival**




Number at Risk

| | | | | | | | | | | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| LARTRUVO+Doxorubicin | 66 | 62 | 60 | 57 | 52 | 51 | 50 | 47 | 43 | 41 | 41 | 39 | 33 | 32 | 29 | 26 | 19 | 16 | 15 | 8 | 3 | 3 | 1 | 1 | 0 |
| Doxorubicin | 67 | 61 | 53 | 49 | 43 | 37 | 34 | 32 | 28 | 23 | 21 | 18 | 16 | 15 | 13 | 13 | 10 | 7 | 6 | 6 | 5 | 3 | 2 | 1 | 0 |

**16 HOW SUPPLIED/STORAGE AND HANDLING**

LARTRUVO is supplied in single-dose vials as a sterile, preservative-free, clear to slightly opalescent and colorless to slightly yellow solution.

- NDC 0002-7190-01
  190 mg/19 mL (10 mg/mL) single-dose vial, individually packaged in a carton
- NDC 0002-8809-01
  500 mg/50 mL (10 mg/mL) single-dose vial, individually packaged in a carton

Store vials in a refrigerator at 2°C to 8°C (36°F to 46°F) until time of use. Keep the vial in the outer carton to protect from light. **DO NOT FREEZE OR SHAKE** the vials.

**17 PATIENT COUNSELING INFORMATION**

*Infusion-Related Reactions*

Advise patients to report signs and symptoms of infusion reactions [see Dosage and Administration (2.3) and Warnings and Precautions (5.1)].

*Embryo-Fetal Toxicity*

Advise pregnant women of the potential risk to the fetus. Advise females of reproductive potential of the potential risk to the fetus, to use effective contraception during treatment with LARTRUVO and for 5 months after the last dose, and to inform their healthcare provider of a known or suspected pregnancy [see Use in Specific Populations (8.1, 8.3)].

*Lactation*

Advise patients not to breastfeed during treatment with LARTRUVO and for 5 months after the last dose [see Use in Specific Populations (8.2)].

**Eli Lilly and Company, Indianapolis, IN 46285, USA**
**US License No. 1891**



LAR-0002-USPI-20170213

# CENTER FOR DRUG EVALUATION AND RESEARCH

***APPLICATION NUMBER:***

# 761038Orig1s001

# CHEMISTRY REVIEW(S)

**Department of Health and Human Services**
**Food and Drug Administration**
**Center for Drug Evaluation and Research**
**Office of Biotechnology Products**

# Memorandum of Review:

| | |
|---|---|
| **STN:** | 761038 |
| **Subject:** | CBE-30, introduction of a new presentation for drug product |
| **Date:** | 1/13/2017 |
| **Review/Revision Date:** | 5/23/2017 |
| **Primary Reviewer:** | Chikako Torigoe, PhD |
| **Secondary Reviewer:** | William Hallett, PhD |
| **Assigned RPM:** | Kelly Ballard |
| **Applicant:** | Eli Lilly and Company |
| **Product:** | Olaratumab |
| **Indication:** | Soft-tissue sarcoma |
| **Filing Action Date:** | 3/14/2017 |
| **Action Due Date:** | 7/13/2017 |

**I. Summary Basis of Recommendation:**

**a. Recommendation:** I recommend the approval of this supplement.

**b. Justification:** The formulation for the proposed olaratumab Injection 190 mg/19 mL dosage form is identical to the formulation for the currently approved olaratumab Injection 500 mg/50 mL dosage form. No changes are introduced to the materials of the container closure system. The proposed changes to the manufacturing process are considered low risk. The provided data adequately support the analytical comparability between the 190 mg/19 mL and the 500 mg/50 mL dosage forms. The processing time limits are appropriately determined from the product quality perspective. The shipping process is adequately validated for the 190 mg/19 mL dosage form.

**II. Language for Action Letter:** This "Changes Being Effected in 30 days" supplemental biological application proposes to introduce a new vial presentation of 190 mg/19 mL for Lartruvo (olaratumab) drug product.

We have completed our review of this supplemental biologics application. This supplement is approved.

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William Hallett

Digitally signed by William Hallett
Date: 5/23/2017 04:05:21PM
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# CENTER FOR DRUG EVALUATION AND RESEARCH

***APPLICATION NUMBER:***

# 761038Orig1s001

# MICROBIOLOGY/VIROLOGY REVIEW(S)

U.S. FOOD & DRUG ADMINISTRATION

Center for Drug Evaluation and Research
Office of Pharmaceutical Quality
Office of Process and Facilities
Division of Microbiology Assessment
WO Building 22
10903 New Hampshire Ave.
Silver Spring, MD 20993

**Date:** February 10, 2017
**To:** Administrative File, **STN** 761038/1
**From**: Aimee Cunningham, Ph.D., Reviewer, CDER/OPQ/OPF/DMA/ Branch IV
**Endorsement:** Natalia Pripuzova, Ph.D., Reviewer, CDER/OPQ/OPF/DMA/Branch IV
**Subject**: CBE-30: New Vial Presentation of 190 mg/19 mL (FEI: 1819470)
**US License:** 1891
**Applicant:** Eli Lilly and Co.
**Facility:** Lilly Corporate Center, Indianapolis, IN, 46285, USA (FEI: 1819470)
**Product:** LARTRUVO™ (Olaratumab)
**Dosage:** 10 mg/mL, solution for intravenous infusion (190 mg/19 mL)
**Indication:** Advanced Soft Tissue Carcinoma
**Due date**: 07/13/2017

**Recommendation on Approvability –** The supplement (CBE-30) was reviewed from a drug product quality microbiology control perspective and is recommended for approval.

**Summary:** In this submission, Eli Lilly is seeking the approval of a new vial presentation (190 mg/19 mL) of Olaratumab. The BLA currently is approved for a 500 mg/50 mL vial presentation.

**Product Quality Microbiology Information Reviewed**

| Submission Type | Sequence number | Sequence date |
|---|---|---|
| Original CBE-30 submission | 0104 | 13-January-17 |
| Response to IR | 0117 | 8-February-17 |

# Drug Product Review

## Module 3.2

### P.1 Description and Composition of the Drug Product

Olaratumab injection solution for i.v. infusion is a sterile solution at 10 mg/mL intended for single use. The DP composition has not changed, but is now being presented at 190 mg/19 mL in addition to the previously approved 500 mg/50 mL. The unit formula for each presentation is below:

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The post-approval stability commitment has not changed from the previous BLA, and remains one lot annually from each approved vial presentation. With the addition of the 20 mL vial presentation, Lilly commits to test at least two lots annually.

SATISFACTORY

## P.8.3 Stability Data

Stability data was provided for three commercial batches of 20 mL vials which were stored at 2-8°C. These batches were acceptable for endotoxin, sterility, and container closure integrity.

SATISFACTORY

## CGMP Status

The assessment of manufacturing facilities is documented in panorama.

## Conclusion

I. The supplement was reviewed from a product quality microbiology perspective and is recommended for approval.

II. Product quality aspects other than microbiology should be reviewed by OBP.

III. No inspection follow-up items were identified.

AIMEE CUNNINGHAM
(REVIEWER)
02/10/2017

NATALIA PRIPUZOVA
(SECONDARY REVIEWER)
02/10/2017

# CENTER FOR DRUG EVALUATION AND RESEARCH

***APPLICATION NUMBER:***

# 761038Orig1s001

# OTHER REVIEW(S)

# PRODUCT QUALITY (Biotechnology)
## FILING REVIEW FOR BLA/NDA Supplements (OBP & DMPQ)

| BLA/NDA Number: | Applicant: | Stamp Date: |
|---|---|---|
| STN 761038/1 | Eli Lilly and Company | January 13, 2017 |
| Established/Proper Name: Lartruvo™ (Olaratumab) | BLA/NDA Type: CBE30 | |

| | |
|---|---|
| **Brief description of the change:** | Introduction of a new vial presentation of 190 mg/19 mL, which includes revisions to the relevant sections of the USPI |
| **Reviewer:** | Chikako Torigoe |
| **Office/Division:** | OBP |

On **initial** overview of the BLA/NDA **supplement** for filing:

The following was submitted in support of the change (check all that apply):

| | |
|---|---|
| x | A detailed description of the proposed change |
| x | Identification of the product(s) involved |
| x | A description of the manufacturing site(s) or area(s) affected |
| x | A description of the methods used and studies performed to evaluate the effect of the change on the identity, strength, quality, purity, or potency of the product as they may relate to the safety or effectiveness of the product |
| x | The data derived from such studies |
| x | Relevant validation protocols and data |
| N/A | A reference list of relevant standard operating procedures (SOP's) |

**IS THE PRODUCT QUALITY SECTION OF THE SUPPLEMENT FILEABLE? Yes**

Chikako Torigoe 3/13/2017

Product Quality Reviewer Date

William Hallett

3/13/2017

Branch Chief/Team Leader/Supervisor Date

CC: Review Team, Review Team TLs, OBP Deputy Div Director

# CENTER FOR DRUG EVALUATION AND RESEARCH

***APPLICATION NUMBER:***

# 761038Orig1s001

# ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

BLA 761038/1

**INFORMATION REQUEST**

Eli Lilly and Company
Attention: Lisa Wenzler, Ph.D.
Research Advisor, CMC Regulatory, Global Regulatory Affairs-US
Lilly Corporate Center
Drop Code 2543
Indianapolis, IN 46285

Dear Dr. Wenzler:

Please refer to your Supplemental Biologics License Application (sBLA) dated and received January 13, 2017, submitted under section 351(a) of the Public Health Service Act for Lartruvo™ (Olaratumab).

We are reviewing your submission and have the following information request. We request a prompt written response by COB April 14, 2017 in order to continue our evaluation of your application.

Provide the following information on the shipping validation studies for olaratumab drug product 190 mg/19 mL dosage form.

a) In your Drug Product Shipping Validation studies, single values are reported for product quality results. Provide the information on how many vials were selected for the product quality attribute tests and how the results are reported (e.g. averaged, single vial). In addition, provide the information on how the vials were selected for the tests.

b) High Molecular Weight Species (HMWS) is one of the quality attributes that may be impacted by the shipping stress. Provide the justification for not performing SE-HPLC in the quality attribute tests.

c) In Table 3.2.P.3.5.3.1.2-1, the data from only one small ISC configuration are provided. Provide the data for both maximum and minimum load configurations.

If you have questions, call me, at (301) 348-3054.

Sincerely,

*{See appended electronic signature page}*

Kelly Ballard, MS
Regulatory Business Process Manager
Office of Program and Regulatory Operations
Office of Pharmaceutical Quality
Center for Drug Evaluation and Research

Kelly Ballard

Digitally signed by Kelly Ballard
Date: 4/07/2017 08:01:17AM
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DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

BLA 761038/1

**INFORMATION REQUEST**

Eli Lilly and Company
Attention: Lisa Wenzler, Ph.D.
Research Advisor, CMC Regulatory, Global Regulatory Affairs-US
Lilly Corporate Center
Drop Code 2543
Indianapolis, IN 46285

Dear Dr. Wenzler:

Please refer to your Supplemental Biologics License Application (sBLA) dated and received January 13th, 2017, submitted under section 351(a) of the Public Health Service Act for Lartruvo™ (Olaratumab).

We are reviewing your submission and have the following information request. We request a prompt written response by COB February 9th, 2017 in order to continue our evaluation of your application.

Please refer to ***3.2.P.3.5,*** *Process Validation and Evaluation*, submitted on 13 January 2017, sequence 0104. Please provide the following additional information to support the new 190 mg/19 mL vial presentation:

1. If the filling operation for the 190 mg/19 mL presentation will use (b) (4) , please clarify whether the sterilization validation data provided in the BLA also covers the (b) (4) .
2. Provide the following additional information for the media fills referenced in Tables 3.2.P.3.5.2.4.2-1 and 3.2.P.3.5.2.4.2-2:
    a. The medium used.
    b. The total time for the fill and the number of units filled.
    c. The number of units filled but not incubated. Briefly explain why these units were excluded.
    d. Compare the media fill conditions to those used for routine production (belt speed, number of personnel and shift changes, duration of fill, number of containers filled, interventions, etc.) and explain how (b) (4)

3. Regarding the qualification of the vial depyrogenation, please clarify the sub-process parameters used in validation in comparison to production parameters for 10 mL and 50 mL vials used to qualify 20 mL vials.

If you have questions, call me, at (301) 348-3054.

Sincerely,

*{See appended electronic signature page}*

Kelly Ballard, MS
Regulatory Business Process Manager
Office of Program and Regulatory Operations
Office of Pharmaceutical Quality
Center for Drug Evaluation and Research

Kelly Ballard

Digitally signed by Kelly Ballard
Date: 2/02/2017 08:15:04AM
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DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

BLA 761038/1

**CBE 30 CMC SUPPLEMENT - ACKNOWLEDGEMENT & FILING**

Eli Lilly and Company
Attention: Lisa Wenzler, Ph.D.
Research Advisor, CMC Regulatory, Global Regulatory Affairs-US
Lilly Corporate Center
Drop Code 2543
Indianapolis, IN 46285

Dear Dr. Wenzler:

We have received your Supplemental Biologics License Application (sBLA) submitted under section 351 of the Public Health Service Act for the following:

| | |
|---|---|
| **BLA SUPPLEMENT NUMBER:** | 761038/1 |
| **PRODUCT NAME:** | Lartruvo™ (Olaratumab) |
| **REASON FOR THE SUBMISSION:** | Provides for a new vial presentation of 190mg/19mL which includes revisions to the relevant sections of the USPI |
| **DATE OF SUBMISSION:** | January 13, 2017 |
| **DATE OF RECEIPT:** | January 13, 2017 |

This acknowledgment recognizes that your submission is in the form of a "**Supplement--Changes Being Effected in 30 Days**" as described under 21 CFR 601.12(c). Continued use of the changes is subject to final approval of this supplement.

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, we will file the application on March 14, 2017 in accordance with 21 CFR 601.2(a).

If the application is filed, the goal date will be July 13, 2017.

**SUBMISSION REQUIREMENTS**

Cite the application number listed above at the top of the first page of all submissions to this application. Send all submissions, electronic or paper, including those sent by overnight mail or courier, to the following address:

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Biotechnology Products
5901-B Ammendale Road
Beltsville, MD 20705-1266

All regulatory documents submitted in paper should be three-hole punched on the left side of the page and bound. The left margin should be at least three-fourths of an inch to assure text is not obscured in the fastened area. Standard paper size (8-1/2 by 11 inches) should be used; however, it may occasionally be necessary to use individual pages larger than standard paper size. Non-standard, large pages should be folded and mounted to allow the page to be opened for review without disassembling the jacket and refolded without damage when the volume is shelved. Shipping unbound documents may result in the loss of portions of the submission or an unnecessary delay in processing which could have an adverse impact on the review of the submission. For additional information, see http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/DrugMasterFilesDMFs/ucm073080.htm.

This acknowledgment does not mean that this supplement has been approved nor does it represent any evaluation of the adequacy of the data submitted. Following a review of this submission, we shall advise you in writing as to what action has been taken and request additional information if needed.

If you have questions, call me, at (301) 348-3054.

Sincerely,

*{SSeappSndSdeSlSctronicesignaturSepagS}*

Kelly Ballard, MS
Regulatory Business Process Manager
Office of Program and Regulatory Operations
Office of Pharmaceutical Quality
Center for Drug Evaluation and Research

Kelly
Ballard

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Date: 1/24/2017 07:44:32AM
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# Exhibit F

EXHIBIT F

| Date | Dose | Total in vials (mg) | Hospital charges | Amount paid by BCBSKC | $ Charged/ mg in vial | $ Paid/mg in vial | Amt unused (mg) | Chg for unused portion | Paid for unused portion | Amt unused w/40 mg vial | Chg for unused w/40 mg vial | Paid for unused w/40 mg vial | Savings on Charges | Savings on Paid Amount |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 1/28/2016 | 772.5 | 800 | $34,189.32 | $5,851.50 | $42.74 | $7.31 | 27.5 | $1,175.26 | $201.15 | 7.5 | $320.52 | $54.86 | $854.73 | $146.29 |
| 2/25/2016 | 772.5 | 800 | $34,189.32 | $5,851.50 | $42.74 | $7.31 | 27.5 | $1,175.26 | $201.15 | 7.5 | $320.52 | $54.86 | $854.73 | $146.29 |
| 3/24/2016 | 772.5 | 800 | $34,189.32 | $6,056.30 | $42.74 | $7.57 | 27.5 | $1,175.26 | $208.19 | 7.5 | $320.52 | $56.78 | $854.73 | $151.41 |
| 4/21/2016 | 772.5 | 800 | $34,189.32 | $6,056.30 | $42.74 | $7.57 | 27.5 | $1,175.26 | $208.19 | 7.5 | $320.52 | $56.78 | $854.73 | $151.41 |
| 5/19/2016 | 772.5 | 800 | $34,189.32 | $6,056.30 | $42.74 | $7.57 | 27.5 | $1,175.26 | $208.19 | 7.5 | $320.52 | $56.78 | $854.73 | $151.41 |
| 6/16/2016 | 772.5 | 800 | $34,189.32 | $6,056.30 | $42.74 | $7.57 | 27.5 | $1,175.26 | $208.19 | 7.5 | $320.52 | $56.78 | $854.73 | $151.41 |
| 9/15/2016 | 780 | 800 | $37,464.99 | $6,283.45 | $46.83 | $7.85 | 20 | $936.62 | $157.09 | 0.0 | $0.00 | $0.00 | $936.62 | $157.09 |
| 12/8/2016 | 780 | 800 | $37,464.99 | $6,283.45 | $46.83 | $7.85 | 20 | $936.62 | $157.09 | 0.0 | $0.00 | $0.00 | $936.62 | $157.09 |
| 3/2/2017 | 780 | 800 | $37,464.99 | $6,534.74 | $46.83 | $8.17 | 20 | $936.62 | $163.37 | 0.0 | $0.00 | $0.00 | $936.62 | $163.37 |
| 5/25/2017 | 780 | 800 | $37,464.99 | $6,534.74 | $46.83 | $8.17 | 20 | $936.62 | $163.37 | 0.0 | $0.00 | $0.00 | $936.62 | $163.37 |
| 8/24/2017 | 780 | 800 | $43,230.99 | $0.00 | $54.04 | $0.00 | 20 | $1,080.77 | $0.00 | 0.0 | $0.00 | $0.00 | $1,080.77 | $0.00 |
| 11/16/2017 | 800 | 800 | $43,230.98 | $0.00 | $54.04 | $0.00 | 0 | $0.00 | $0.00 | 0.0 | $0.00 | $0.00 | $0.00 | $0.00 |
| 3/1/2018 | 800 | 800 | $43,230.99 | $7,068.07 | $54.04 | $8.84 | 0 | $0.00 | $0.00 | 0.0 | $0.00 | $0.00 | $0.00 | $0.00 |
| | | | | | | | | | | | | | | |
| **Total** | **10,135** | **10,400** | **$484,688.84** | **$68,632.65** | **N/A** | **N/A** | **265** | **$11,878.82** | **$1,875.94** | **45** | **$1,923.15** | **$336.83** | **$9,955.67** | **$1,539.11** |

**PROOF OF SERVICE**

I, Alfredo Torrijos, hereby declare as follows:

I am employed in the County of Los Angeles, State of California, I am over the age of 18 and I am not a party to this action.

On August 26, 2020, I served the following document(s):

**THIRD AMENDED CLASS ACTION COMPLAINT**

On the following interested parties:

***Counsel for Defendants Genentech USA, Inc. and Genentech, Inc.:***

Alicia J. Donahue
adonahue@shb.com
Joan R. Camagong
jcamagong@shb.com
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***Counsel for Blue Cross and Blue Shield of Kansas City:***

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425 S. Perry Street
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Eric I. Unrein
eunrein@cavlem.com
**CAVANAUGH, BIGGS & LEMON, P.A.**
2942A SW Wanamaker Drive, Suite 100
Topeka, KS 66614
Tel: (785) 440-4000
Fax: (785) 400-3900

By the following means of service:

[ ] **VIA U.S. MAIL –** I deposited such envelop(s) with the United States Postal Service, enclosed in a sealed envelope, for collection and mailing with the United States Postal Service where it would be deposited for first class delivery, postage fully prepared, in the United States Postal Service that same day in the ordinary course of business. I am readily familiar with my employer's business practice for collection and processing of correspondence for mailing with the United States Postal Service.

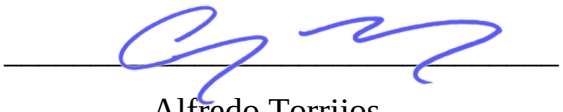
[X] **VIA E-MAIL** – Based on and in accordance with the Court's July 20, 2020 Case Management Order #2 requiring all parties and their counsel to accept service of documents electronically in conformity with Code of Civil Procedure section 1010.6, I caused a true copy of the above listed document(s) as scanned into an electronic file in Adobe PDF format to be sent to the persons at the corresponding electronic address indicated above on the date of this proof of service. My electronic notification address is alfredo@aswtlawyers.com.

[ ] **VIA OVERNIGHT DELIVERY SERVICE** – I caused such envelope to be deposited with an overnight delivery service (Overnite Express/Federal Express) for delivery the next court day.

[ ] **VIA FACSIMILE TRANSMISSION** – By use of facsimile machine, I served a copy of the document(s) to the fax numbers of the persons on the attached Service List. The transmissions were reported as complete and without error.

I declare under penalty of perjury under the laws of the State of California that the foregoing is true and correct.

Executed on August 26, 2020.



Alfredo Torrijos

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