IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE

GENENTECH, INC. and CITY OF HOPE, Plaintiffs, v. AMGEN, INC., Defendant.	C.A. No. 18-924-CFC [redacted] PUBLIC VERSION FILED: July 19, 2019

EXHIBITS 49-114 TO THE DECLARATION OF NORA Q.E. PASSAMANECK

VOLUME 2 OF 3

Date: July 10, 2019

Of Counsel:

William F. Lee
Lisa J. Pirozzolo
Emily R. Whelan
Kevin Prussia
Andrew J. Danford
WILMER CUTLER PICKERING
HALE AND DORR LLP
60 State Street
Boston, MA 02109
(627) 526-6000
william.lee@wilmerhale.com
lisa.pirozzolo@wilmerhale.com
emily.whelan@wilmerhale.com
kevin.prussia@wilmerhale.com
andrew.danford@wilmerhale.com

Robert J. Gunther Jr.
WILMER CUTLER PICKERING
HALE AND DORR LLP
7 World Trade Center
250 Greenwich Street
New York, NY 10007
(212) 230-8800
robert.gunther@wilmerhale.com

Daralyn J. Durie
Adam R. Brausa
DURIE TANGRI LLP
217 Leidesdorff St.
San Francisco, CA 94111
(415) 362-6666
ddurie@durietangri.com
abrausa@durietangri.com

MCCARTER & ENGLISH LLP

/s/ Michael P. Kelly

Michael P. Kelly (#2295)
Daniel M. Silver (#4758)
Alexandra M. Joyce (#6423)
Renaissance Centre
405 N. King Street, 8th Floor
Wilmington, Delaware 19801
Tel.: (302) 984-6300
Fax: (302) 984-6399
mkelly@mccarter.com
dsilver@mccarter.com
ajoyce@mccarter.com

Attorneys for Plaintiffs Genentech, Inc. and City of Hope

EXHIBIT 49

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EXHIBIT 57

List of Cleared or Approved Companion Diagnostic Devices (In Vitro and Imaging Tools)

A *companion diagnostic device* can be in vitro diagnostic device or an imaging tool that provides information that is essential for the safe and effective use of a corresponding therapeutic product.

The use of an IVD companion diagnostic device with a specific therapeutic product is stipulated in the instructions for use in the labeling of both the diagnostic device and the corresponding therapeutic product, as well as in the labeling of any generic equivalents and biosimilar equivalents of the therapeutic product.

This table lists devices in the order of approval, with most recently approved device at the top.

Diagnostic Name	PMA/ 510(k)/ HDE	Diagnostic Manufacturer	Trade Name (Generic) - NDA/BLA
BRACAnalysis CDx	P140020/S016	Myriad Genetic Laboratories, Inc.	Breast Cancer • Lynparza (olaparib) - NDA 208558 • Talzenna (talazoparib) – NDA 211651 Ovarian Cancer • Lynparza (olaparib) - NDA 208558 • Rubraca (rucaparib) – NDA 209115
therascreen EGFR RGQ PCR Kit	P120022/S018	Qiagen Manchester, Ltd.	Non-small cell lung cancer • Iressa (gefitinib) - NDA 206995 • Gilotrif (afatinib)- NDA 201292 • Vizimpro (dacomitinib)- NDA 211288
cobas EGFR Mutation Test v2	P120019/S019	Roche Molecular Systems, Inc.	Non-small cell lung cancer (tissue and plasma) • Tarceva (erlotinib) - NDA 021743 • Tagrisso (osimertinib) - NDA 208065 • Iressa (gefitinib) - NDA 206995
PD-L1 IHC 22C3 pharmDx	P150013/S011	Dako North America, Inc.	Non-small cell lung cancer, gastric or gastroesophageal junction adenocarcinoma, cervical cancer, and urothelial carcinoma • Keytruda (pembrolizimab) - BLA 125514

Diagnostic Name	PMA/ 510(k)/ HDE	Diagnostic Manufacturer	Trade Name (Generic) - NDA/BLA
VENTANA PD-L1(SP142) Assay	P160002/S006	Ventana Medical Systems, Inc.	Non-small cell lung cancer and urothelial carcinoma • Tecentriq (atezolizumab) – sBLA 761034/S012
Abbott RealTi*me* IDH1	P170041	Abbott Molecular, Inc.	Acute myeloid leukemia • Tibsovo (ivosidenib) - NDA 211192
MRDx BCR-ABL Test	K173492	MolecularMD Corporation	Chronic myeloid leukemia • Tasigna (nilotinib) - NDA 022068/S026
FoundationOne CDx	P170019	Foundation Medicine, Inc.	Non-small cell lung cancer • Gilotrif (afatinib) - NDA 201292 • Iressa (gefitinib) - NDA 206995 • Tarceva (erlotinib) - NDA 021743 • Tagrisso (osimertinib) NDA 208065 • Alecensa (alectinib) - NDA 208434 • Xalkori (crizotinib) - NDA 202570 • Zykadia (ceritinib) - NDA 205755 • Tafinlar (dabrafenib) - NDA 202806 in combination with Mekinist (trametinib) - NDA 204114 Melanoma • Tafinlar (dabrafenib) - NDA 202806 • Zelboraf (vemurafenib) - NDA 202429 • Mekinist (trametinib) - NDA 204114 or Cotellic (cobimetinib) - NDA 206192 in combination with Zelboraf (vemurafenib) - NDA 202429 Breast cancer • Herceptin (trastuzumab) - BLA 103792 • Perjeta (pertuzumab) - BLA 125409 • Kadcyla (ado-trastuzumab emtansine) - BLA 125427

Diagnostic Name	PMA/ 510(k)/ HDE	Diagnostic Manufacturer	Trade Name (Generic) - NDA/BLA
			Colorectal cancer • Erbitux (cetuximab) - BLA 125084 • Vectibix (panitumumab) - BLA 125147 Ovarian cancer • Rubraca (rucaparib) - NDA 209115
VENTANA ALK (D5F3) CDx Assay	P140025/S006	Ventana Medical Systems, Inc.	Non-small cell lung cancer • Zykadia (ceritinib) - NDA 205755 • Xalkori (crizotinib) - NDA 202570 • Alecensa (alectinib) - NDA 208434
Abbott RealTi*me* IDH2	P170005	Abbott Molecular, Inc.	Acute myeloid leukemia • Idhifa (enasidenib) – NDA 209606
Praxis Extended RAS Panel	P160038	Illumina, Inc.	Colorectal cancer • Vectibix (panitumumab) – NDA 125147
Oncomine Dx Target Test	P160045	Life Technologies Corporation	Non-small cell lung cancer • Tafinlar (dabrafenib) - NDA 202806 • Mekinist (trametinib) - NDA 204114 • Xalkori (crizotinib) - NDA 202570 • Iressa (gefitinib) - NDA 206995
LeukoStrat CDx FLT3 Mutation Assay	P160040	Invivoscribe Technologies, Inc.	Acute myelogenous leukemia • Rydapt (midostaurin) – NDA 207997 • Xospata (gilterinib) – NDA 211349
FoundationFocus CDx*BRCA* Assay	P160018	Foundation Medicine, Inc.	Ovarian cancer • Rubraca (rucaparib) – NDA 209115
Vysis CLL FISH Probe Kit	P150041	Abbott Molecular, Inc.	B-cell chronic lymphocytic leukemia • Venclexta (venetoclax) – NDA 208573
***KIT* D816V Mutation Detection by PCR for Gleevec Eligibility in Aggressive Systemic Mastocytosis (ASM)**	H140006	ARUP Laboratories, Inc.	Aggressive systemic mastocytosis • Gleevec (imatinib mesylate) – NDA 021335

Diagnostic Name	PMA/ 510(k)/ HDE	Diagnostic Manufacturer	Trade Name (Generic) - NDA/BLA
***PDGFRB* FISH for Gleevec Eligibility in Myelodysplastic Syndrome / Myeloproliferative Disease (MDS/MPD)**	H140005	ARUP Laboratories, Inc.	Myelodysplastic syndrome/myeloproliferative disease • Gleevec (imatinib mesylate) – NDA 021335
cobas KRAS Mutation Test	P140023	Roche Molecular Systems, Inc.	Colorectal cancer • Erbitux (cetuximab) - BLA 125084 • Vectibix (panitumumab) - BLA 125147
therascreen KRAS RGQ PCR Kit	P110030 P110027	Qiagen Manchester, Ltd.	Colorectal cancer • Erbitux (cetuximab) - BLA 125084 • Vectibix (panitumumab) - BLA 125147
Dako EGFR pharmDx Kit	P030044/S002	Dako North America, Inc.	Colorectal cancer • Erbitux (cetuximab) - BLA 125084 • Vectibix (panitumumab) - BLA 125147
FerriScan	DEN130012/K124065	Resonance Health Analysis Services Pty Ltd	Non-transfusion-dependent thalassemia • Exjade (deferasirox) – NDA 021882
Dako c-KIT pharmDx	P040011	Dako North America, Inc.	Gastrointestinal stromal tumors • Gleevec (imatinib mesylate) – NDA 021335 • Glivec (imatinib mesylate) – NDA 021588
INFORM HER-2/neu	P940004	Ventana Medical Systems, Inc.	Breast cancer • Herceptin (trastuzumab) - BLA 103792
PathVysion HER-2 DNA Probe Kit	P980024	Abbott Molecular Inc.	Breast cancer • Herceptin (trastuzumab) - BLA 103792
PATHWAY anti-Her2/neu (4B5) Rabbit Monoclonal Primary Antibody	P990081/S001-S028	Ventana Medical Systems, Inc.	Breast cancer • Herceptin (trastuzumab) - BLA 103792

Diagnostic Name	PMA/ 510(k)/ HDE	Diagnostic Manufacturer	Trade Name (Generic) - NDA/BLA
InSite Her-2/neu KIT	P040030	Biogenex Laboratories, Inc.	Breast cancer • Herceptin (trastuzumab) - BLA 103792
SPOT-LIGHT HER2 CISH Kit	P050040/S001-S003	Life Technologies Corporation	Breast cancer • Herceptin (trastuzumab) - BLA 103792
Bond Oracle HER2 IHC System	P090015	Leica Biosystems	Breast cancer • Herceptin (trastuzumab) - BLA 103792
HER2 CISH pharmDx Kit	P100024	Dako Denmark A/S	Breast cancer • Herceptin (trastuzumab) - BLA 103792
INFORM HER2 Dual ISH DNA Probe Cocktail	P100027	Ventana Medical Systems, Inc.	Breast cancer • Herceptin (trastuzumab) - BLA 103792
HercepTest	P980018/S018	Dako Denmark A/S	Breast cancer • Herceptin (trastuzumab) - BLA 103792 • Perjeta (pertuzumab) - BLA 125409 • Kadcyla (ado-trastuzumab emtansine) - BLA 125427 Gastic and gastroesophogeal cancer • Herceptin (trastuzumab) - BLA 103792
HER2 FISH pharmDx Kit	P040005/S009	Dako Denmark A/S	Breast cancer • Herceptin (trastuzumab) - BLA 103792 • Perjeta (pertuzumab) - BLA 125409 • Kadcyla (ado-trastuzumab emtansine) - BLA 125427 Gastic and gastroesophogeal cancer • Herceptin (trastuzumab) - BLA 103792

Diagnostic Name	PMA/ 510(k)/ HDE	Diagnostic Manufacturer	Trade Name (Generic) - NDA/BLA
THXID BRAF Kit	P120014	bioMérieux Inc.	Melanoma • Braftovi (encorafenib) in combination with Mektovi (binimetinib) – NDA 210496 and NDA 210498 • Mekinist (tramatenib) - NDA 204114 • Tafinlar (dabrafenib) – NDA 202806
Vysis ALK Break Apart FISH Probe Kit	P110012	Abbott Molecular Inc.	Non-small cell lung cancer • Xalkori (crizotinib) – NDA 202570
cobas 4800 BRAF V600 Mutation Test	P110020/S016	Roche Molecular Systems, Inc.	Melanoma • Zelboraf (vemurafenib) - NDA 202429 • Cotellic (cobimetinib) - NDA 206192 in combination with Zelboraf (vemurafenib) - NDA 202429
VENTANA PD-L1(SP142) Assay	P160002/S009	Ventana Medical Systems, Inc.	Triple-Negative Breast Carcinoma (TNBC), Non-small cell lung cancer and urothelial carcinoma • Tecentriq (atezolizumab) – sBLA 761034/S012

EXHIBIT 58

Dako

HercepTest™

Code K5204

11th edition

For immunocytochemical staining.

The kit is for 35 tests (70 slides).

Intended Use

For in vitro diagnostic use.

HercepTest™ is a semi-quantitative immunocytochemical assay to determine HER2 protein overexpression in breast cancer tissues routinely processed for histological evaluation and formalin-fixed, paraffin-embedded cancer tissue from patients with metastatic gastric or gastroesophageal junction adenocarcinoma. HercepTest™ is indicated as an aid in the assessment of breast and gastric cancer patients for whom Herceptin® (trastuzumab) treatment is being considered and for breast cancer patients for whom PERJETA™ (pertuzumab) treatment or KADCYLA™ (ado-trastuzumab emtansine) treatment is being considered (see Herceptin®, PERJETA™ and KADCYLA™ package inserts).

NOTE for breast cancer only: All of the patients in the Herceptin® clinical trials were selected using an investigational immunocytochemical clinical trial assay (CTA). None of the patients in those trials were selected using the HercepTest™. The HercepTest™ was compared to the CTA on an independent set of samples and found to provide acceptably concordant results. The actual correlation of the HercepTest™ to Herceptin® clinical outcome has not been established.

NOTE for gastric cancer only: All of the patients in the phase III BO18255 (ToGA) study sponsored by Hoffmann-La Roche were selected using Dako HercepTest™ (IHC) and Dako *HER2* FISH pharmDx™ Kit (FISH). However, enrollment in the BO18255 study was limited to patients whose tumors were HER2 protein overexpressing (IHC 3+) or gene amplified (FISH+; HER2/CEN-17 ratio ≥ 2.0). No patients were enrolled whose tumors were not gene amplified but HER2 protein weakly to strongly overexpressing [FISH(-)/IHC 2+], therefore it is unclear if patients whose tumors are not gene amplified but HER2 protein overexpressing [i.e., FISH(-), IHC 2+ or 3+] will benefit from Herceptin® treatment. The study also demonstrated that gene amplification and protein overexpression (IHC) are not as correlated as with breast cancer, therefore a single method should not be used to determine HER2 status.

Gastric or gastroesophageal junction adenocarcinoma is also referred to as gastric cancer in this document.

For breast cancer application, please refer to pages 5-27.
For gastric cancer application, please refer to pages 28-50.

Important: Please note for breast cancer tissue and gastric cancer tissue differences especially in the Interpretation of Staining Sections.

Summary and Explanation - Breast

Background
The human *HER2* gene (also known as *ERBB2* or *NEU*) encodes a protein often referred to as HER2 protein or $p185^{HER2}$. The HER2 protein is a membrane receptor tyrosine kinase with homology to the epidermal growth factor receptor (EGFR or HER1) (1-8). The HER2 protein is a normal component expressed by a variety of epithelial cell types (8).

In a fraction of patients with breast cancer, the HER2 protein is overexpressed as part of the process of malignant transformation and tumor progression (9). Overexpression of the HER2 protein on the surface of breast cancer cells suggested that it could be a target for an antibody therapeutic. Herceptin® (trastuzumab) is a humanized monoclonal antibody (10) that binds with high affinity to the HER2 protein and has been shown to inhibit the proliferation of human tumor cells that overexpress HER2 protein in vitro and in vivo (11-13).

Pertuzumab is a recombinant humanized monoclonal antibody that binds to sub-domain II of the extracellular part of the HER2 protein thereby blocking its ability to form heterodimers with other members of the HER family including HER1 (EGFR), HER3, and HER4 (14-16). PERJETA™ (pertuzumab) has shown to be effective and safe in treatment of breast cancer patients with HER2 protein overexpression. During clinical studies of pertuzumab, HER2 overexpression was demonstrated directly by IHC or indirectly evidenced through correlation of HER2 gene amplification to protein overexpression as demonstrated by FISH. However, in the randomized trial, data were available for a limited number of patients (8/808) for whom the FISH results were positive but the IHC results were negative (0, 1+) (17, 18).

Ado-trastuzumab emtansine is a novel antibody–drug conjugate specifically designed for the treatment of HER2-positive cancer. It is composed of the potent cytotoxic agent DM1 (a thiol-containing maytansinoid anti-microtubule agent) conjugated to trastuzumab via a linker molecule. Ado-trastuzumab emtansine binds to HER2 with an affinity similar to that of trastuzumab; such binding is required for its anti-tumor activity. It is hypothesized that after binding to HER2, ado-trastuzumab emtansine undergoes receptor-mediated internalization, followed by intracellular release of DM1 and subsequent cytotoxicity (19). A number of clinical studies have shown that trastuzumab emtansine is effective and safe in treatment of HER2-positive breast cancer patients (20-23).

Characteristics
HercepTest™ was developed to provide an alternative to the investigational CTA used in the Herceptin® clinical studies. The performance of HercepTest™ for determination of HER2 protein overexpression was evaluated in an independent study comparing the results of the HercepTest™ to the CTA on 548 breast tumor specimens, none of which were obtained from patients in the Herceptin® clinical studies. The results indicated a 79% concordance between the results from the two assays on these tissue specimens.

The concordance data also indicates that a 3+ reading with HercepTest™ was highly likely to correspond with a positive reading on the CTA, which would have met the entry criteria for the trial (2+ or 3+). A finding of 2+ on HercepTest™ did not correlate as well with the CTA results. Approximately 42% (53/126) of HercepTest™ 2+ results were negative by CTA (0 - 1+) which would not have allowed entry into the Herceptin® clinical trials.

HercepTest™ is interpreted as negative for HER2 protein overexpression (0 and 1+ staining intensity), weakly positive (2+ staining intensity), and strongly positive (3+ staining intensity). HercepTest™ is not intended to provide prognostic information to the patient and physician and has not been validated for that purpose.

EXHIBIT 59

English

Bond™ Oracle™ HER2 IHC System for Leica BOND-MAX System Instructions For Use

For use on Leica Biosystems' BOND-MAX fully automated, advanced staining system.

Product Code TA9145 is designed to stain 60 tests (150 slides):
60 test slides with HER2 Primary Antibody
60 test slides with HER2 Negative Control
15 HER2 Control Slides with HER2 Primary Antibody
15 positive in-house tissue controls with HER2 Primary Antibody

IVD CE

Leica Biosystems Newcastle Ltd
Balliol Business Park
Benton Lane
Newcastle Upon Tyne NE12 8EW
United Kingdom
✆ +44 191 215 4242

Leica Biosystems Canada
71 Four Valley Drive
Concord, Ontario L4K 4V8
Canada
✆ +1 800 248 0123

Leica Biosystems Inc
1700 Leider Lane
Buffalo Grove IL 60089
USA
✆ +1 800 248 0123

Leica Biosystems Melbourne Pty Ltd
495 Blackburn Road
Mt Waverly VIC 3149
Australia
✆ +61 2 8870 3500

English

Intended Use

For in vitro diagnostic use

Bond Oracle HER2 IHC System for BOND-MAX is a semi-quantitative immunohistochemical (IHC) assay to determine HER2 (Human Epidermal Growth Factor Receptor 2) oncoprotein status in formalin-fixed, paraffin-embedded breast cancer tissue processed for histological evaluation following automated staining on the BOND-MAX slide staining instrument. The Bond Oracle HER2 IHC System for BOND-MAX is indicated as an aid in the assessment of patients for whom Herceptin® (trastuzumab) treatment is being considered.

Note: All of the patients in the Herceptin® clinical trials were selected using an investigational immunohistochemical Clinical Trial Assay (CTA). None of the patients in those trials were selected using the Bond Oracle HER2 IHC System for BOND-MAX. The Bond Oracle HER2 IHC System for BOND-MAX has been compared to the Dako HercepTest™ on an independent set of samples and found to provide acceptably concordant results. The actual correlation of the Bond Oracle HER2 IHC System for BOND-MAX to clinical outcome has not been established.

Summary and Explanation

Background

The Bond Oracle HER2 IHC System for BOND-MAX contains the mouse monoclonal anti-HER2 antibody, clone CB11. Clone CB11, originally developed by Corbett et al (1) and manufactured by Novocastra Laboratories Ltd (now Leica Biosystems Newcastle Ltd), is directed against the internal domain of the HER2 oncoprotein.

In a proportion of breast cancer patients, the HER2 oncoprotein is overexpressed as part of the process of malignant transformation and tumor progression (2). Overexpression of the HER2 oncoprotein found in breast cancer cells suggests HER2 as a target for an antibody-based therapy. Herceptin® is a humanized monoclonal antibody (3) that binds with high affinity to the HER2 oncoprotein and has been shown to inhibit the proliferation of human tumor cells that overexpress HER2 oncoprotein both in vitro and in vivo (4–6).

Since the first immunoperoxidase technique, reported by Nakane and Pierce (7), many developments have occurred within the field of immunohistochemistry, resulting in increased sensitivity. A recent development has been the use of polymeric labeling. This technology has been applied to both primary antibodies and immunohistochemical detection systems (8). The Compact Polymer™ detection system utilized by the Bond Oracle HER2 IHC System for BOND-MAX is part of a family of novel, controlled polymerization technologies that have been specifically developed to prepare polymeric HRP-linked antibody conjugates. As this polymer technology is utilized in the Oracle product range, the problem of nonspecific endogenous biotin staining, which may be seen with streptavidin/biotin detection systems, does not occur.

Expression of HER2

The HER2 oncoprotein is expressed at levels detectable by immunohistochemistry in up to 20% of adenocarcinomas from various sites. Between 10% and 20% of invasive ductal carcinomas of the breast are positive for HER2 oncoprotein (9). 90% of cases of ductal carcinoma in situ (DCIS) of comedo type are positive (10), together with almost all cases of Paget's disease of the breast (11).

Clinical Concordance Summary

The Bond Oracle HER2 IHC System for BOND-MAX was developed to provide an alternative to the investigational Clinical Trial Assay (CTA) used in the Herceptin® clinical studies. The performance of the Bond Oracle HER2 IHC System for BOND-MAX for determination of HER2 oncoprotein overexpression was evaluated in an independent study comparing the results of the Bond Oracle HER2 IHC System for BOND-MAX to the Dako HercepTest on 431 breast tumor specimens, of US origin. None of these tumor specimens were obtained from patients in the Herceptin® clinical trials. The results indicated a 92.34% concordance in a 2x2 analysis (95% confidence intervals of 89.42% to 94.67%) and 86.54% in a 3x3 analysis (95% confidence intervals of 82.95% to 89.62%) between the results from the two assays.

and the quality control requirements of the CAP Certification Program for Immunohistochemistry and/or CLSI (formerly NCCLS) Quality Assurance for Immunocytochemistry, Approved Guideline (12). These quality control procedures should be repeated for each new antibody lot, or whenever there is a change in assay parameters. Human invasive (infiltrating) ductal breast carcinoma with known HER2 oncoprotein staining intensities from 0 to 3+ and other suitably negative tissues are appropriate for assay verification.

Interpretation of Staining

For the determination of HER2 oncoprotein expression, only membrane staining pattern and intensity should be evaluated using the scale presented in Table 4. A pathologist using a bright-field microscope should perform slide evaluation. For evaluation of the immunohistochemical staining and scoring, an objective of 10x magnification is appropriate. The use of 20–40x objective magnification should be used in the confirmation of the score. Cytoplasmic staining should be considered as nonspecific staining and is not to be included in the assessment of membrane staining intensity (14). To aid in the differentiation of 0, 1+, 2+, and 3+ staining, refer to the Bond Oracle HER2 IHC System for BOND-MAX Interpretation Guide for representative images of the staining intensities. Only specimens from patients with invasive breast carcinoma should be scored. In cases with carcinoma *in situ* and invasive carcinoma in the same specimen, only the invasive component should be scored.

Immunohistochemical Staining Pattern	Score	Assessment
No staining is observed or membrane staining is observed in less than 10% of the tumor cells.	0	Negative
Faint/barely perceptible membrane staining is detected in more than 10% of the tumor cells. The cells are only stained in part of their membrane.	1+	Negative
Weak to moderate complete membrane staining is observed in more than 10% of the tumor cells.	2+	Equivocal (Weakly Positive)
Strong complete membrane staining is observed in more than 10% of the tumor cells.	3+	Strongly Positive

Table 4. Interpretation of HER2 staining

Bond Oracle HER2 IHC System for BOND-MAX staining results are interpreted as negative for HER2 oncoprotein expression with scores of 0 and 1+ staining intensity, equivocal (weakly positive) with a score of 2+ staining intensity, and strongly positive with a score of 3+ staining intensity. Bond Oracle HER2 IHC System for BOND-MAX is not intended to provide prognostic information to the patient and/or physician and has not been validated for that purpose. For each staining assessment, slides should be examined in the order presented below to determine the validity of the staining run and enable semi-quantitative assessment of the staining intensity of the sample tissue.

EXHIBIT 60

VENTANA®

PATHWAY anti-HER-2/neu (4B5) Rabbit Monoclonal Primary Antibody

REF 790-2991

05278368001

IVD Σ 50

INDICATIONS AND USE

Intended Use

This antibody is intended for in vitro diagnostic use.

Ventana Medical Systems, Inc.'s (Ventana) PATHWAY anti-HER-2/*neu* (4B5) Rabbit Monoclonal Primary Antibody (PATHWAY HER2 (4B5)) is a rabbit monoclonal antibody intended for laboratory use for the semi-quantitative detection of HER2 antigen in sections of formalin-fixed, paraffin-embedded normal and neoplastic tissue on a VENTANA automated immunohistochemistry slide staining device. It is indicated as an aid in the assessment of breast cancer patients for whom Herceptin treatment is considered.

Note: All of the patients in the Herceptin clinical trials were selected using a clinical trial assay. None of the patients in those trials were selected using PATHWAY anti-HER-2/*neu* (4B5). PATHWAY anti-HER-2/*neu* (4B5) was compared to PATHWAY HER-2 (clone CB11) Primary Antibody on an independent sample set and found to provide acceptably concordant results. The actual correlation of PATHWAY anti-HER-2/*neu* (4B5) to clinical outcome has not been established.

The *VIAS* Image Analysis System is an adjunctive optional computer-assisted image analysis system functionally connected to an interactive microscope. It is intended for use as an aid to the pathologist in the detection, classification and counting of cells of interest based on marker intensity, size and shape using appropriate controls to assure the validity of the *VIAS* scores.

Prescription use only.

Summary and Explanation

PATHWAY anti-HER-2/*neu* is a rabbit monoclonal antibody (clone 4B5) directed against the internal domain of the c-erbB-2 oncoprotein (HER2). c-erbB-2 oncoprotein was cloned and characterized by Akiyama, et al in 1986.[1] It is an approximately 185 kD transmembrane glycoprotein which is structurally similar to epidermal growth factor receptor (EGFR). The protein is associated with tyrosine kinase activity similar to that of several growth factor receptors, and to that of the transforming proteins of the *src* family. The coding sequence is consistent with an extracellular binding domain and an intracellular kinase domain. This suggests that HER2 may be involved in signal transduction and stimulation of mitogenic activity.[1]

Clone 4B5 has been shown to react with a 185 kD protein from SK-BR-3 cell lysates via Western blotting. SK-BR-3 is a breast carcinoma cell line, which has a 128-fold over expression of HER2 mRNA.[2] The size of the band identified correlates well with that reported by Akiyama et al for HER2 protein (185 kD).[1] Immunohistochemistry has been used to detect specific antigens in cells or tissue since 1950.[3] The use of enzymes and peroxidase as markers for immunohistochemistry was reported by Nakane and Pierce in 1967.[4] The increased sensitivity of the avidin-biotin-peroxidase detection system over the enzyme labeled antibody method was documented by Hsu et al in 1981.[5]

The HER2 protein is expressed at a level detectable by immunohistochemistry in up to 20 percent of adenocarcinomas from various sites. Between 15 and 30 percent of invasive ductal cancers are positive for HER2.[6] Almost all cases of Paget's disease of breast[7] and up to 90 percent of cases of ductal carcinoma *in situ* of comedo type are positive.[6] The immunohistochemical detection of HER2 protein overexpression is also used as an aid in determination of patients for whom Herceptin therapy is indicated.[8]

Staining results in normal tissues, neoplastic tissues, and 322 cases of breast carcinoma with PATHWAY HER2 (4B5) were evaluated by Ventana. In the normal tissues tested, expression was consistent with the published literature in that there was no unexpected specific cytoplasmic/membrane staining, with the following exceptions: two cases of tonsil showing with epithelial cell membrane staining, one case of parathyroid, and one case of esophageal epithelium. Of the neoplastic tissues tested, cytoplasmic/membrane staining was seen in cancer cells of the breast, colon and ovary. Three hundred twenty-two (322) breast carcinomas were evaluated with VENTANA PATHWAY HER2 (4B5) in a method comparison study with PATHWAY HER-2 (CB11). There is a significant correlation of staining between these two tests. See Summary of Expected Results section for further information. Additional information on PATHWAY HER2 (4B5) can be found in the References section, 25-31.

VENTANA PATHWAY HER2 (4B5) in combination with VENTANA *i*VIEW DAB Detection Kit, utilizes biotinylated secondary antibodies to locate the bound PATHWAY HER2 (4B5) primary antibody (produced by using a synthetic peptide corresponding to a site on the internal domain of the HER2 protein). This is followed by the binding of an avidin/streptavidin-enzyme conjugate to the biotin. The complex is then visualized using a precipitating enzyme generated product.

The use of VENTANA pre-diluted PATHWAY HER2 (4B5) and ready-to-use *i*VIEW DAB and *ultra*View Universal DAB Detection Kits, in combination with a VENTANA automated slide stainer, reduces the possibility of human error and inherent variability resulting from individual reagent dilution, manual pipetting, and manual reagent application.

CLINICAL SIGNIFICANCE

Breast cancer is the most common carcinoma occurring in women, and the second leading cause of cancer related death. In North America, a woman's chance of contracting breast cancer is one in eight.[9] Early detection and appropriate treatment therapies can significantly affect overall survival.[10] Small tissue samples may be easily used in routine immunohistochemistry (IHC), making this technique, in combination with antibodies that detect antigens important for carcinoma interpretation, an effective tool for the pathologist in their diagnosis and prognosis of disease. One important marker in breast cancer today is c-erbB-2 oncoprotein (HER2).

HER2 is an intracellular membrane protein detected in the cellular membrane.[11] It is closely related to EGFR and, like EGFR, has tyrosine kinase activity.[1] Gene amplification and the corresponding overexpression of c-erbB-2 has been found in a variety of tumors, including breast carcinomas.[11,12]

The therapeutic drug Herceptin has been shown to benefit some breast carcinoma patients by arresting, and in some cases reversing the growth of their cancer.[8] The drug is a humanized monoclonal antibody that binds to HER2 protein on cancer cells. Thus only patients with HER-2/*neu* positive breast carcinomas should benefit from treatment with Herceptin. *In vitro* diagnostics for the determination of HER2 status in breast carcinomas are important to aid the clinician in determination of therapy with Herceptin.

Interpretation of the results of any detection system for HER2 must take into consideration the fact that HER2 is expressed in both breast cancer tumors and healthy tissue, albeit at differing levels and with different patterns of expression.[13] Histological tissue preparations have the advantage of intact tissue morphology to aid in the interpretation of the HER2 positivity of the sample. All histological tests should be interpreted by a specialist in breast cancer morphology, and/or pathology, and the results should be complemented by morphological studies and proper controls and used in conjunction with other clinical and laboratory data.

Principles and Procedures

PATHWAY HER2 (4B5) is a rabbit monoclonal antibody, which binds to HER2 in paraffin-embedded tissue sections. The specific antibody can be localized by either a biotin conjugated secondary antibody formulation that recognizes rabbit immunoglobulins followed by the addition of a streptavidin-horseradish peroxidase (HRP) conjugate (*i*VIEW DAB Detection Kit) or a secondary antibody-HRP conjugate (*ultra*View Universal DAB Detection Kit). The specific antibody-enzyme complex is then visualized with a precipitating enzyme reaction product. Each step is incubated for a precise time and temperature. At the end of each incubation step, the VENTANA automated slide stainer washes the sections to stop the reaction and to remove unbound material that would hinder the desired reaction in subsequent steps. It also applies Liquid Coverslip, which minimizes evaporation of the aqueous reagents from the specimen slide.

Clinical cases should be evaluated within the context of the performance of appropriate controls. Ventana recommends the inclusion of a positive tissue control fixed and processed in the same manner as the patient specimen (for example, a weakly positive breast carcinoma). In addition to staining with PATHWAY HER2 (4B5), a second slide should be stained with CONFIRM Negative Control Rabbit Ig. For the test to be considered valid, the positive control tissue should exhibit membrane staining of the tumor cells. These components should be negative when stained with CONFIRM Negative Control Rabbit Ig. In addition, it is recommended that a negative tissue control slide (for example, a HER-2/*neu* negative breast carcinoma) be included for every batch of samples processed and run on the VENTANA automated slide stainer. This negative tissue control should be stained with PATHWAY HER2 (4B5) to ensure that the antigen enhancement and other pretreatment procedures did not create false positive staining.

The *VIAS* is an interactive histology imaging device that performs image processing using a microscope, digital color video camera, computer, and image analysis software to

VENTANA®

staining procedure performed. This tissue could contain both positive staining cell/tissue components and negative cell/tissue components and serve as both the positive and negative control tissue. Control tissue should be fresh autopsy/biopsy/surgical specimens prepared and fixed as soon as possible in a manner identical to test sections. Such tissue may monitor all steps of the analysis, from tissue preparation through staining. Use of a tissue section fixed or processed differently from the test specimen provides control for all reagents and method steps except fixation and tissue preparation. A tissue with weak positive staining is more suitable than strong positive staining for optimal quality control and to detect minor levels of reagent degradation. Ideally a tissue which is known to have weak but positive staining should be chosen to ensure that the system is sensitive to small amounts of reagent degradation or problems with the IHC methodology. Generally, however, neoplastic tissue that is positive for HER-2/*neu* is strongly positive due to the nature of the pathology (overexpression). An example of a positive control for PATHWAY HER2 (4B5) is a known weak HER-2/*neu* positive invasive breast carcinoma (for example ductal or lobular). The positive staining tissue components (cytoplasmic membrane of neoplastic cells) are used to confirm that the antibody was applied and the instrument functioned properly.

A known weak HER-2/*neu* positive invasive breast carcinoma tissue may contain both positive and negative staining cells or tissue components and may serve as both the positive and negative control tissue.

Known positive tissue controls should be utilized only for monitoring the correct performance of processed tissues and test reagents, and not as an aid in determining a specific diagnosis of patient samples.

Negative Tissue Control

The same slide used for the positive tissue control (ductal or lobular invasive breast carcinoma) may be used as the negative tissue control. The non-staining components (surrounding stroma, lymphoid cells and blood vessels) should demonstrate absence of specific staining and provide an indication of specific background staining with the primary antibody. Alternatively, normal breast tissue is an adequate negative control tissue. Use a tissue known to be fixed, processed and embedded in a manner identical to the patient sample(s) with each staining run to verify the specificity of PATHWAY HER2 (4B5) for demonstration of HER-2/*neu*, and to provide an indication of specific background staining (false positive staining).

Negative Reagent Control

A negative reagent control must be run for every specimen to aid in the interpretation of results. A negative reagent control is used in place of the primary antibody to evaluate nonspecific staining. The slide should be stained with CONFIRM Negative Control Rabbit Ig. The incubation period for the negative reagent control should equal the primary antibody incubation period.

Unexplained Discrepancies

Unexplained discrepancies in controls should be referred to your local support representative immediately. If quality control results do not meet specifications, patient results are invalid. See the Troubleshooting section of this insert. Identify and correct the problem, then repeat the patient samples.

Assay Verification

Prior to initial use of an antibody or staining system in a diagnostic procedure, the specificity of the antibody should be verified by testing it on a series of tissues with known immunohistochemistry performance characteristics representing known positive and negative tissues (refer to the Quality Control Procedures previously outlined in this section of the product insert and to the Quality Control recommendations of the College of American Pathologists Laboratory Accreditation Program, Anatomic Pathology Checklist,[15] or the CLSI Approved Guideline[16] or both documents). These quality control procedures should be repeated for each new antibody lot, or whenever there is a change in assay parameters. Breast cancer tissues with known HER2 status are suitable for assay verification.

Interpretation of Results

The VENTANA automated immunostaining procedure causes a brown colored (DAB) reaction product to precipitate at the antigen sites localized by PATHWAY HER2 (4B5). A qualified pathologist experienced in immunohistochemical procedures must evaluate controls and qualify the stained product before interpreting results.

Positive Controls

The stained positive tissue control should be examined first to ascertain that all reagents are functioning properly. The presence of an appropriately colored reaction product within the membrane of the target cells is indicative of positive reactivity. Depending on the incubation length and potency of the hematoxylin used, counterstaining will result in a pale to dark blue coloration of cell nuclei. Excessive or incomplete counterstaining may compromise proper interpretation of results.

If the positive tissue control fails to demonstrate positive staining, any results with the test specimens should be considered invalid.

Negative Tissue Controls

The negative tissue control should be examined after the positive tissue control to verify the specific labeling of the target antigen by the primary antibody. The absence of specific staining in the negative tissue control confirms the lack of antibody cross reactivity to cells or cellular components. The staining of normal breast is an adequate negative control tissue. Intact stromal and ductal elements should show no intense staining in the membrane, indicating that staining did not occur. If the tissue is counterstained, there may be staining around the outside of the cell, i.e., the interstitial spaces. If specific staining occurs in the negative tissue control, results with the patient specimen should be considered invalid.

Negative Reagent Controls

Nonspecific staining, if present, will have a diffuse appearance. Sporadic light staining of connective tissue may also be observed in tissue sections that are excessively formalin fixed. Intact cells should be used for interpretation of staining results, as necrotic or degenerated cells often stain nonspecifically.

Patient Tissue

Patient specimens should be examined last. Positive staining intensity should be assessed within the context of any background staining of the negative reagent control. As with any immunohistochemical test, a negative result means that the antigen in question was not detected, not that the antigen is absent in the cells or tissue assayed. The morphology of each tissue sample should also be examined utilizing a hematoxylin and eosin stained section when interpreting any immunohistochemical result. The patient's morphologic findings and pertinent clinical data must be interpreted by a qualified pathologist.

A qualified pathologist who is experienced in immunohistochemical procedures must evaluate positive and negative controls and qualify the stained product before interpreting results.

Scoring Conventions for the Interpretation of PATHWAY HER2 (4B5)

Breast carcinomas that are considered positive for HER-2 protein overexpression must meet threshold criteria for intensity of staining (2+ or greater on a scale of 0 to 3+) and percent positive tumor cells (greater than 10%). Staining must also localize to the cellular membrane. Cytoplasmic staining may still be present, but this staining is not included in the determination of positivity. Three fields within the well preserved and well stained region of the tissue should be examined for intensity of staining and determination of completeness of the cytoplasmic membrane stain. Staining that completely encircles the cytoplasmic membrane should be scored as an intensity of "2+" or "3+". Partial staining of the membrane should be scored as a "1+". It may be necessary to examine borderline cases at 400X or higher magnification to discriminate between intensities of "1+" and "2+". In contrast to cases scored as an intensity of 3+, the staining scored as 2+ has a crisper and more clearly delineated ring, while cases scored as 3+ exhibit a very thick outline. Below is a quick reference chart for staining criteria. Refer to VENTANA Interpretation Guide for PATHWAY HER-2/neu (4B5) for a more detailed description with photographs of staining with PATHWAY HER2 (4B5).

Table 4. Criteria for Intensity and Pattern of Cell Membrane Staining with PATHWAY HER2 (4B5).

Staining Pattern	Score (Report to Treating Physician)	HER2 Staining Assessment
No membrane staining is observed	0	Negative
Faint, partial staining of the membrane in any proportion of the cancer cells	1+	Negative
Weak complete staining of the membrane, greater than 10% of cancer cells	2+	Weakly Positive
Intense complete staining of the membrane, greater than 10% of cancer cells	3+	Positive

EXHIBIT 61

Dako

HER2 IQFISH pharmDx

Code K5731

11th edition

HER2 IQFISH pharmDx is a direct fluorescence in situ hybridization (FISH) assay designed to quantitatively determine *HER2* gene amplification in formalin-fixed, paraffin-embedded (FFPE) breast cancer tissue specimens and FFPE specimens from patients with metastatic gastric or gastroesophageal junction adenocarcinoma.

HER2 IQFISH pharmDx is indicated as an aid in the assessment of breast and gastric cancer patients for whom Herceptin® (trastuzumab) treatment is being considered and for breast cancer patients for whom PERJETA™ (pertuzumab) or KADCYLA™ (ado-trastuzumab emtansine) treatment is being considered (see Herceptin®, PERJETA™ and KADCYLA™ package inserts).

For breast cancer patients, results from the *HER2* IQFISH pharmDx are intended for use as an adjunct to the clinicopathologic information currently used for estimating prognosis in stage II, node-positive breast cancer patients.

The kit contains reagents sufficient for 20 tests.

Contents

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Intended Use

HER2 IQFISH pharmDx is a direct fluorescence in situ hybridization (FISH) assay designed to quantitatively determine *HER2* gene amplification in formalin-fixed, paraffin-embedded (FFPE) breast cancer tissue specimens and FFPE specimens from patients with metastatic gastric or gastroesophageal junction adenocarcinoma.

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For breast cancer patients, results from the *HER2* IQFISH pharmDx are intended for use as an adjunct to the clinicopathologic information currently used for estimating prognosis in stage II, node-positive breast cancer patients.

NOTE for gastric cancer only: All of the patients in the phase III BO18255 (ToGA) study sponsored by Hoffmann-La Roche were selected using Dako HercepTest™ (IHC) and Dako *HER2* FISH pharmDx Kit (FISH). However, enrollment in the BO18255 study was limited to patients whose tumors were HER2 protein overexpressing (IHC 3+) or gene amplified (FISH+; *HER2*/CEN-17 ratio ≥ 2.0). No patients were enrolled whose tumors were not gene amplified but HER2 protein weakly to strongly overexpressing [FISH(-)/IHC 2+], therefore it is unclear if patients whose tumors are not gene amplified but HER2 protein-overexpressing [i.e., FISH(-), IHC 2+ or 3+] will benefit from Herceptin® treatment. The study also demonstrated that gene amplification (FISH) and protein overexpression (IHC) are not as correlated as with breast cancer, therefore a single method should not be used to determine HER2 status.

Gastric or gastroesophageal junction adenocarcinoma is also referred to as gastric cancer in this document.

For breast cancer application, please refer to pages 5-38.

For gastric cancer application, please refer to pages 39-69.

Important: Please note differences for breast cancer tissue and gastric cancer tissue especially in the Interpretation of Staining Sections.

Summary and Explanation - Breast

The human *HER2* gene (also known as *ERBB2* or *NEU*) is located on chromosome 17 and encodes the HER2 protein or $p185^{HER2}$. The HER2 protein is a membrane receptor tyrosine kinase with homology to the epidermal growth factor receptor (EGFR or HER1) (1-2). The *HER2* gene is present in 2 copies in all normal diploid cells.

In a fraction of patients with breast cancer, the *HER2* gene is amplified as part of the process of malignant transformation and tumor progression (3-8). *HER2* gene amplification generally leads to overexpression of the HER2 protein on the surface of breast cancer cells (9).

Amplification of the *HER2* gene and/or overexpression of its protein have been demonstrated in 20-25% of breast cancers (10). This up-regulation is associated with poor prognosis, increased risk of recurrence, and shortened survival. Several studies have shown that HER2 status correlates with sensitivity or resistance to certain chemotherapy regimens (11).

Demonstration of high HER2 protein overexpression or *HER2* gene amplification is essential for initiating therapy with Herceptin®, a monoclonal antibody to HER2 protein. Clinical studies have shown that patients whose tumors have high HER2 protein overexpression and/or amplification of the *HER2* gene benefit most from Herceptin® (12).

Pertuzumab is a recombinant, humanized monoclonal antibody that binds to subdomain II of the extracellular part of the HER2 protein thereby blocking its ability to form heterodimers with other members of the HER family including HER1 (EGFR), HER3, and HER4 (13-15)). PERJETA™ (pertuzumab) has shown to be effective and safe in treatment of breast cancer patients with HER2 protein overexpression. During clinical studies of pertuzumab, HER2 overexpression was demonstrated directly by IHC or indirectly evidenced through correlation of *HER2* gene amplification to protein overexpression as demonstrated by FISH. However, in the randomized trial, data were available for a limited number of patients (8/808) for whom the FISH results were positive but the IHC results were negative (0, 1+) (16-17).

Ado-trastuzumab emtansine is a novel antibody–drug conjugate specifically designed for the treatment of HER2-positive cancer. It is composed of the potent cytotoxic agent DM1 (a thiol-containing maytansinoid anti-microtubule agent) conjugated to trastuzumab via a linker molecule. Ado-trastuzumab emtansine binds to HER2 with an affinity similar to that of trastuzumab; such binding is required for its anti-tumor activity. It is hypothesized that after binding to HER2, ado-trastuzumab emtansine undergoes receptor-mediated internalization, followed by intracellular release of DM1 and subsequent cytotoxicity (18). A number of clinical studies have shown that ado-trastuzumab emtansine is effective and safe in treatment of HER2-positive breast cancer patients (19-22).

Principle of Procedure - Breast

HER2 IQFISH pharmDx contains all key reagents required to complete a FISH procedure for formalin-fixed, paraffin-embedded tissue section specimens.

After deparaffinization and rehydration, specimens are heated in Pre-Treatment Solution for 10 minutes. The next step involves a proteolytic digestion using ready-to-use Pepsin at room temperature for 5-15 minutes, at 37 °C for 3-5 minutes or by immersing the slides into Pepsin solution at 37 °C for 20-30 minutes. Following the heating and proteolytic pre-treatment steps, this kit employs a ready-to-use FISH Probe Mix based on a combination of PNA (peptide nucleic acid) (23) and DNA technology. This Probe Mix consists of a mixture of Texas Red-labelled DNA probes covering a 218 kb region including the *HER2* gene on chromosome 17, and a mixture of fluorescein-labelled PNA probes targeted at the centromeric region of chromosome 17 (CEN-17). The specific hybridization to the two targets results in formation of a distinct red fluorescent signal at each *HER2* gene locus and a distinct green fluorescent signal at each chromosome 17 centromere. After a stringent wash, the specimens are mounted with

Fluorescence Mounting Medium containing DAPI and coverslipped. Using a fluorescence microscope equipped with appropriate filters (see Appendix 3), tumor cells are located, and enumeration of the red *(HER2*) and green (CEN-17) signals is conducted. Then the *HER2*/CEN-17 ratio is calculated. Normal cells in the analyzed tissue section will serve as an internal positive control of pre-treatment and hybridization efficiency.

For details see the Interpretation of Staining section.

EXHIBIT 62

PathVysion HER-2 DNA Probe Kit

en

REF 02J01

30-608377/R7

PathVysion
HER-2 DNA Probe Kit
REF 02J01
30-608377/R7

Key to Symbols Used

	Manufacturer
REF	Reference Number
IVD	In Vitro Diagnostic Medical Device
Σ	Contains sufficient for <n> tests
-20°C / -20°C	Temperature limitation
25°C / -20°C	Temperature limitation
	Biological Risks
	Danger
	Danger
	Danger
	Consult instructions for use
	Use by
EC REP	Authorized representative in the European Community

PATHVYSION HER-2 DNA PROBE KIT

Part No. 30-161060, List No. 02J01-030 (20 assays)/
Part No. 35-161060, List No. 02J01-035 (50 assays)/
Part No. 36-161060, List No. 02J01-036 (100 assays)

PROPRIETARY NAME

PathVysion HER-2 DNA Probe Kit

COMMON OR USUAL NAME

Fluorescence in situ hybridization (FISH) reagents

INTENDED USE

The PathVysion HER-2 DNA Probe Kit (PathVysion Kit) is designed to detect amplification of the HER-2/*neu* gene via fluorescence in situ hybridization (FISH) in formalin-fixed, paraffin-embedded human breast cancer tissue specimens. Results from the PathVysion Kit are intended for use as an adjunct to existing clinical and pathologic information currently used as prognostic factors in stage II, node-positive breast cancer patients. The PathVysion Kit is further indicated as an aid to predict disease-free and overall survival in patients with stage II, node-positive breast cancer treated with adjuvant cyclophosphamide, doxorubicin and 5-fluorouracil (CAF) chemotherapy.

The PathVysion Kit is indicated as an aid in the assessment of patients for whom HERCEPTIN® (Trastuzumab) treatment is being considered (see HERCEPTIN package insert).

Warning:

HERCEPTIN therapy selection

NOTE: All of the patients in the HERCEPTIN clinical trials were selected using an investigational immunohistochemical assay (CTA). None of the patients in those trials were selected using the PathVysion assay. The PathVysion assay was compared to the CTA on a subset of clinical trial samples and found to provide acceptably concordant results. The actual correlation of the PathVysion assay to HERCEPTIN clinical outcome in prospective clinical trials has not been established.

Adjuvant therapy selection

The PathVysion Kit is not intended for use to screen for or diagnose breast cancer. It is intended to be used as an adjunct to other prognostic factors currently used to predict disease-free and overall survival in stage II, node-positive breast cancer patients and no treatment decision for stage II, node-positive breast cancer patients should be based on HER-2/*neu* gene amplification status alone.

Selected patients with breast cancers shown to lack amplification of HER-2/*neu* may still benefit from CAF (cyclophosphamide, doxorubicin, 5-fluorouracil) adjuvant therapy on the basis of other prognostic factors that predict poor outcome (eg, tumor size, number of involved lymph nodes, and hormone receptor status). Conversely, selected patients with breast cancers shown to contain gene amplification may not be candidates for CAF therapy due to pre-existing or intercurrent medical illnesses.

Required Training

Abbott Molecular will provide training in specimen preparation, assay procedure, and interpretation of FISH testing of the HER-2 gene for inexperienced users. It is also recommended that a laboratory that has previously received training but now has new personnel performing the assay request training for the new users.

SUMMARY AND EXPLANATION

Among all cancers in the United States there were approximately 2,591,855 women alive who had a history of cancer of the breast in 2007. This includes any person alive who had been diagnosed with cancer of the breast at any point prior to 2007 and includes persons with active disease and those who are cured of their disease.[1] After surgery, breast cancers with positive axillary nodes, which account for 30% of all breast cancers,[2] are associated with a shorter disease-free survival[3,4] and a shorter overall survival[5] than node-negative breast cancers. It has been generally accepted that patients with breast cancer and positive axillary nodes at diagnosis should be offered adjuvant systemic treatment.

Amplification or overexpression of the HER-2/*neu* gene has been shown to be an indicator of poor prognosis in node-positive breast cancer.[6-10] In one study, the prognostic value of HER-2/*neu* appears to be stronger among patients treated with chemotherapy.[7] However, in predicting disease-free and overall survival in individual patients, other established prognostic factors such as tumor size, number of positive lymph nodes, and steroid receptor status must also be taken into consideration.

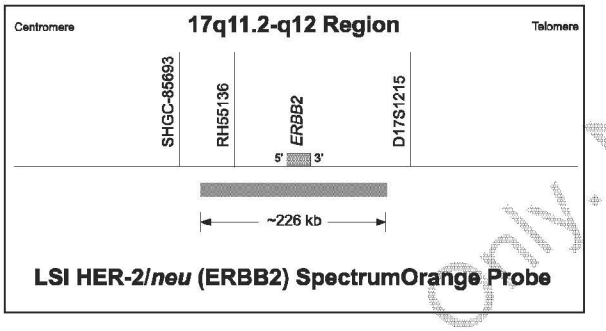
The FISH technique has been used to detect HER-2/*neu* gene amplification in human breast carcinoma cell lines in both interphase and metaphase cells.[11-14] FISH appears to be an alternative technique capable of overcoming many of the inherent technical and interpretative limitations of other techniques, such as immunohistochemistry.[15] For quantification of HER-2/*neu* gene amplification, FISH assesses not only the level of HER-2/*neu* gene amplification directly in the tumor cells while retaining the characteristic morphology of the tissue studied, but also the spatial distribution of oncogene copies in individual uncultured primary breast carcinomas.

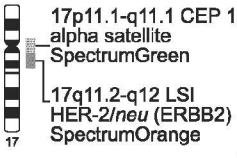
PRINCIPLES OF THE PROCEDURE

In situ hybridization is a technique that allows the visualization of specific nucleic acid sequences within a cellular preparation. Specifically, DNA FISH involves the precise annealing of a single-stranded, fluorescently-labeled DNA probe to complementary target sequences. The hybridization of the probe with the cellular DNA site is visible by direct detection using fluorescence microscopy.

The Locus Specific Identifier (LSI) HER-2/*neu* DNA probe is a 226 Kb SpectrumOrange directly-labeled, fluorescent DNA probe specific for the HER-2/*neu* gene locus (17q11.2-q12). The Chromosome Enumeration Probe (CEP) 17 DNA probe is a 5.4 Kb SpectrumGreen directly-labeled, fluorescent DNA probe specific for the alpha satellite DNA sequence at the centromeric region of chromosome 17 (17p11.1-q11.1). The probes are pre-mixed and pre-denatured in hybridization buffer for ease of use. Unlabeled blocking DNA is also included with the probes to suppress sequences contained within the target loci that are common to other chromosomes. This PathVysion Kit is designed for the detection of HER-2/*neu* gene amplification in formalin-fixed, paraffin-embedded human breast tissue specimens by FISH. The assay is rapid, non-radioactive, requires little tumor material, and is capable of detecting as few as 2 to 8 copies of the oncogene.

Formalin-fixed, paraffin-embedded tissue specimens are placed on slides. The DNA is denatured to single-stranded form and subsequently allowed to hybridize with the PathVysion probes. Following hybridization, the unbound probe is removed by a series of washes and the nuclei are counterstained with DAPI (4,6 diamidino-2-phenylindole), a DNA-specific stain that fluoresces blue. Hybridization of the PathVysion probes is viewed using a fluorescence microscope equipped with appropriate excitation and emission filters allowing visualization of the intense orange and green fluorescent signals. Enumeration of the LSI HER-2/*neu* and CEP 17 signals is conducted by microscopic examination of the nucleus, which yields a ratio of the HER-2/*neu* gene to chromosome 17 copy number.





REAGENTS AND INSTRUMENTS

Materials Provided

This kit contains sufficient reagents to process approximately 20, 50, or 100 assays dependent on product ordered. An assay is defined as one 22 mm × 22 mm target area.

1. LSI HER-2/neu SpectrumOrange (low copy number E. coli vector)/ CEP 17 SpectrumGreen DNA Probe (E. coli plasmid)

Part Number: 30-171060/35-171060

Quantity: 200 µL/500 µL/500 µL × 2 for the 100 assay kit

Storage: -20°C / -20°C – 20°C in the dark

Composition: SpectrumGreen fluorophore-labeled alpha satellite DNA probe for chromosome 17, SpectrumOrange fluorophore-labeled DNA probe for the HER-2/*neu* gene locus and blocking DNA, pre-denatured in hybridization buffer.

2. DAPI Counterstain

Part Number: 30-804840/30-804860/30-804960

Quantity: 300 µL/600 µL/1000 µL

Storage: -20°C / -20°C – 20°C in the dark

Composition: 1000 ng/mL DAPI (4,6-diamidino-2-phenylindole) in phenylenediamine dihydrochloride, glycerol, and buffer.

3. NP-40

Part Number: 30-804820

Quantity: 4 mL (2 vials)

Storage: 25°C / -20°C – 20 to 25°C

Composition: Igepal (NP-40 substitute) [Octyl phenoxy] polyethoxyethanol.

4. 20X SSC salts

Part Number 30-805850

Quantity: 66 g for up to 250 mL of 20X SSC solution

Storage: 25°C / -20°C – 20 to 25°C

Composition: Sodium chloride and sodium citrate.

Storage and Handling

Store the unopened PathVysion Kit as a unit at –20°C, protected from light and humidity. The 20X SSC salts and NP-40 may be stored separately at room temperature. Expiration dates for each of the components are indicated on the individual component labels. These storage conditions apply to both opened and unopened components.

Exposure to light, heat or humidity may affect the shelf life of some of the kit components and should be avoided. Components stored under conditions other than those stated on the labels may not perform properly and may adversely affect the assay results.

Materials Required But Not Provided

Laboratory Reagents

- ProbeChek HER-2/*neu* Normal Control Slides (Normal Signal Ratio) Part No. 30-805093, List No. 02J05-030 (manual assay) or Part No. 32-805093, List No. 02J05-010 (for use with Vysis AutoVysion System) Formalin-fixed, paraffin-embedded, cultured human breast cancer cell line (MDA-MB-231; normal LSI HER-2/*neu*:CEP 17 ratio) applied to glass microscope slides. Quantity: 5 slides. Store the control slides at 15 to 30°C in a sealed container with desiccant to protect them from humidity.
- ProbeChek HER-2/*neu* Cutoff Control Slides (Weakly Amplified Signal Ratio) Part No. 30-805042, List No. 02J04-030 (manual assay) or Part No. 32-805042, List No. 02J04-010 (for use with Vysis AutoVysion System) Formalin-fixed, paraffin-embedded, cultured human breast cancer cell line (Hs 578T; low level HER-2/*neu* amplification) applied to glass microscope slides. Quantity: 5 slides. Store the control slides at 15 to 30°C in a sealed container with desiccant to protect them from humidity.
- Vysis Paraffin Pretreatment Reagent Kit (Part No. 32-801200, List No. 02J02-032) which includes:
  - Vysis Pretreatment Solution (NaSCN) Quantity: 5 × 50 mL
  - Vysis Protease (Pepsin (Activity 1:3000 to 1:3500) Quantity: 5 × 25 mg

  NOTE: Pepsin digests not less than 3000 and not more than 3500 times its weight of coagulated egg albumin.
  - Vysis Protease Buffer (NaCl solution, pH 2.0) Quantity: 5 × 50 mL
  - Vysis Wash Buffer (2X SSC, pH 7.0) Quantity: 2 × 250 mL
- Neutral buffered formalin solution (4% formaldehyde in PBS)
- Hemo-De clearing agent (Scientific Safety Solvents #HD-150)
- Hematoxalin and eosin (H & E)
- Immersion oil appropriate for fluorescence microscopy. Store at room temperature (15 to 30°C).
- Ultra-pure, formamide.
- Ethanol (100%). Store at room temperature.
- Concentrated (12N) HCl

EXHIBIT 63

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EXHIBIT 64

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EXHIBIT 67

Efficacy and safety of ABP 980 compared with reference trastuzumab in women with HER2-positive early breast cancer (LILAC study): a randomised, double-blind, phase 3 trial

Gunter von Minckwitz, Marco Colleoni, Hans-Christian Kolberg, Serafin Morales, Patricia Santi, Zorica Tomasevic, Nan Zhang, Vladimir Hanes

Summary

Background ABP 980 (Amgen Inc, Thousand Oaks, CA, USA) is a biosimilar of trastuzumab, with analytical, functional, and pharmacokinetic similarities. We compared the clinical safety and efficacy of ABP 980 with that of trastuzumab in women with HER2-positive early breast cancer.

Methods We did a randomised, multicentre, double-blind, active-controlled equivalence trial at 97 study centres in 20 countries, mainly in Europe and South America. Eligible women were aged 18 years or older, had histologically confirmed HER2-positive invasive early breast cancer, an Eastern Cooperative Oncology Group performance status score of 0 or 1, and were planning to have surgical resection of the breast tumour with sentinel or axillary lymph node dissection and neoadjuvant chemotherapy. After four cycles of run-in anthracycline-based chemotherapy, patients were assigned 1:1 to receive ABP 980 or trastuzumab with a permuted block design (blocks of four) computer-generated randomisation schedule. Patients received neoadjuvant therapy with a loading dose (8 mg/kg) of ABP 980 or trastuzumab plus paclitaxel 175 mg/m² in a 90 min intravenous infusion, followed by three cycles of 6 mg/kg intravenous ABP 980 or trastuzumab plus paclitaxel 175 mg/m² every 3 weeks in 30 min intravenous infusions (or 80 mg/m² paclitaxel once per week for 12 cycles if that was the local standard of care). Randomisation was stratified by T stage, node status, hormone receptor status, planned paclitaxel dosing schedule, and geographical region. Surgery was completed 3–7 weeks after the last dose of neoadjuvant treatment, after which adjuvant treatment with ABP 980 or trastuzumab was given every 3 weeks for up to 1 year after the first dose in the study. Patients had been randomly assigned at baseline to continue APB 980, continue trastuzumab, or switch from trastuzumab to APB 980 as their adjuvant treatment. The co-primary efficacy endpoints were risk difference and risk ratio (RR) of pathological complete response in breast tissue and axillary lymph nodes assessed at a local laboratory in all patients who were randomly assigned and received any amount of neoadjuvant investigational product and underwent surgery. We assessed safety in all patients who were randomly assigned and received any amount of investigational product. This trial is registered with ClinicalTrials.gov, number NCT01901146 and Eudra, number CT 2012-004319-29.

Findings Of 827 patients enrolled, 725 were randomly assigned to receive ABP 980 (n=364) or trastuzumab (n=361). The primary endpoint was assessable in 696 patients (358 who received ABP 980 and 338 who received trastuzumab). Pathological complete response was recorded in 172 (48%, 95% CI 43–53) of 358 patients in the ABP 980 group and 137 (41%, 35–46) of 338 in the trastuzumab group (risk difference 7·3%, 90% CI 1·2–13·4; RR 1·188, 90% CI 1·033–1·366), with the upper bounds of the CIs exceeding the predefined equivalence margins of 13% and 1·318, respectively. Pathological complete response in the central laboratory assessment was seen in 162 (48%) of 339 patients assigned to ABP 980 at baseline and 138 (42%) of 330 assigned to trastuzumab at baseline (risk difference 5·8%, 90% CI −0·5 to 12·0, and RR 1·142, 90% CI 0·993 to 1·312). Grade 3 or worse adverse events during the neoadjuvant phase occurred in 54 (15%) of 364 patients in the ABP 980 group and 51 (14%) of 361 patients in the trastuzumab group, of which the most frequent grade 3 or worse event of interest was neutropenia, occurring in 21 (6%) patients in both groups. In the adjuvant phase, grade 3 or worse adverse events occurred in 30 (9%) of 349 patients continuing ABP 980, 11 (6%) of 171 continuing trastuzumab, and 13 (8%) of 171 who switched from trastuzumab to ABP 980, the most frequent grade 3 or worse events of interest were infections and infestations (four [1%], two [1%], and two [1%]), neutropenia (three [1%], two [1%], and one [1%]), and infusion reactions (two [1%], two [1%], and three [2%]). Two patients died from adverse events judged to be unrelated to the investigational products: one died from pneumonia while receiving neoadjuvant ABP 980 and one died from septic shock while receiving adjuvant ABP 980 after trastuzumab.

Interpretation Although the lower bounds of the 90% CIs for RR and risk difference showed non-inferiority, the upper bounds exceeded the predefined equivalence margins when based on local laboratory review of tumour samples, meaning that non-superiority was non-conclusive. In our sensitivity analyses based on central laboratory evaluation of tumour samples, estimates for the two drugs were contained within the predefined equivalence margins, indicating similar efficacy. ABP 980 and trastuzumab had similar safety outcomes in both the neoadjuvant and adjuvant phases of the study.

Lancet Oncol 2018

Published Online
June 4, 2018
http://dx.doi.org/10.1016/S1470-2045(18)30241-9

See Online/Comment
http://dx.doi.org/10.1016/S1470-2045(18)30290-0

German Breast Group, Neu-Isenburg, Germany (Prof G von Minckwitz MD); Divisione di Senologia Medica, Division of Medical Senology, Milan, Italy (M Colleoni MD); Marienhospital Bottrop, Klinik fur Gynakologie und Geburtshilfe, Bottrop, Germany (H-C Kolberg MD); Hospital Universitario Arnau de Vilanova, Lleida, Spain (S Morales MD); Centro de Estudos de Hematologia e Oncologia, Sao Paulo, Brazil (P Santi MD); Institute for Oncology and Radiology of Serbia, Belgrade, Serbia (Z Tomasevic MD); and Amgen, Thousand Oaks, CA, USA (N Zhang PhD, V Hanes MD)

Correspondence to:
Prof Gunter von Minckwitz, c/o GBG Forschungs, 63263 Neu-Isenburg, Germany
vonMinckwitz@gbg.de

Funding Amgen.

Introduction

Trastuzumab is approved in many countries for the treatment of metastatic breast cancer, early breast cancer, and metastatic gastric cancer,[1,2] and it is the standard of care for patients with HER2-overexpressing breast cancers.[3–5] Trastuzumab is a monoclonal antibody that binds to the extracellular domain of HER2, blocking receptor activation and the subsequent proliferation of cells expressing HER2. It also induces the downstream effects of antibody-dependent cellular cytotoxicity in and cellular phagocytosis of HER2-expressing cells.[6]

Several trastuzumab biosimilars are in development. Guidelines for the development of biosimilars recommend a totality of evidence approach with stepwise development to ensure comprehensive analytical characterisation. Studies should include structural and functional assessments followed by phase 1 pharmacokinetic and, if feasible, pharmacodynamic studies to show similarity to the reference product.[7,8] At least one comparative clinical study in a representative population with sensitive endpoints (ie, are clinically relevant, readily assessible, and show a size of treatment effect that is large enough to detect differences between similar treatments if any exist) is also needed to confirm similarities in safety, efficacy, and immunogenicity.[9]

Results from phase 3 studies have shown clinical similarity to trastuzumab reference product for CT-P6 (Celltrion, Incheon, South Korea),[10] MYL-1401O (Biocon, Bangalore, India, and Mylan, Canonsburg, PA, USA),[11] and SB3 (Samsung Bioepis, Incheon, South Korea and Merck, Kenilworth, NJ, USA).[12] Two studies were done in the neoadjuvant setting[10,12] and one in the metastatic setting.[11] No studies, however, have been designed to assess the effect of switching from the trastuzumab reference product to the biosimilar. The trastuzumab biosimilar ABP 980 (Amgen Inc, Thousand Oaks, CA, USA) is analytically similar to trastuzumab with respect to structure, function, and pharmacokinetic profile,[13] which suggests that there should be no clinically meaningful differences between these drugs in efficacy, safety, or immunogenicity.

We assessed the clinical similarity of ABP 980 and trastuzumab in women with HER2-positive early breast cancer in the neoadjuvant and adjuvant settings, based on the proportion of patients achieving a pathological complete response. We compared safety, tolerability, and immunogenicity, including after switching treatment from trastuzumab to ABP 980 to generate data about clinical use.

Research in context

Evidence before this study

We searched PubMed on June 11, 2012, for papers on trastuzumab in the neoadjuvant treatment of early breast cancer with the search terms ("trastuzumab" AND "neoadjuvant" AND "breast"). We identified 220 papers that included clinical studies and reviews of trastuzumab and papers on other topics that discussed trastuzumab. We selected studies in which data were collected for HER2-positive patients; neoadjuvant treatment included at least epirubicin or doxorubicin and cyclophosphamide in combination with a taxane (docetaxel or paclitaxel) for at least 18 weeks; pertuzumab or lapatinib were not allowed; the definition of pathological complete response was consistent with that proposed for this study; and patients received neoadjuvant trastuzumab treatment for at least 18 weeks. We also included data from an abstract presented at the Annual Meeting of the American Society of Clinical Oncology, Chicago, IL, USA, June 3–7, 2011, and two studies that were unpublished at the time of the literature search but have since been published. Together, the studies showed that trastuzumab was safe and effective for the neoadjuvant treatment of early breast cancer.

Added value of this study

In this randomised, double-blind, phase 3 comparative trial, we assessed ABP 980 (Amgen Inc, Thousand Oaks, CA, USA) as a potential biosimilar to trastuzumab for the treatment of HER2-positive early breast cancer. We assessed safety based on pathological complete response in breast tissue and axillary lymph nodes. During the adjuvant phase some patients in the trastuzumab group switched to ABP 980, which allowed assessment of the clinical safety and immunogenicity. We were also able to assess the feasibility of central independent pathological review of response in a large multicentre study. To our knowledge, these are novel study design features. Our results add to the totality of evidence generated in analytical, functional, and pharmacokinetic studies and support clinical similarity of ABP 980 to the trastuzumab reference product.

Implications of all the available evidence

All the data indicate that there are no clinically meaningful differences between ABP 980 and trastuzumab. Our findings add to the growing body of evidence supporting the potential clinical usefulness of ABP 980. Additionally, switching from trastuzumab to a biosimilar seems to be safe. The use of trastuzumab biosimilars could expand treatment options for clinicians, mitigate cost barriers for payers, and increase patients' access to important therapy.

Methods

Study design and participants

We designed a randomised, multicentre, double-blind, active-controlled, phase 3 equivalence trial to compare ABP 980 with trastuzumab in adult women with HER2-positive early breast cancer. Patients were recruited from 97 study centres in 20 countries, mainly in Europe and South America (appendix pp 14–16).

Eligible patients were women aged 18 years or older with histologically confirmed invasive breast cancer and an Eastern Cooperative Oncology Group performance status score of 0 or 1, who were planning to have surgical resection of their breast tumour with sentinel or axillary lymph node dissection and neoadjuvant chemotherapy. Inclusion criteria were HER2-positive disease confirmed by a central laboratory before randomisation (defined as 3+ overexpression on immunohistochemistry or HER2 amplification on fluorescence in situ hybridisation), known oestrogen-receptor and progesterone-receptor status at study entry, measurable disease in the breast after diagnostic biopsy (defined as longest tumour diameter ≥2·0 cm), and left ventricular ejection fraction (LVEF) of at least 55% on a two-dimensional echocardiogram. Exclusion criteria were presence of bilateral breast cancer or known distant metastases; previous treatment for primary breast cancer, including chemotherapy, a biological agent, radiotherapy, or surgery; concomitant active malignancy; and malignant disease in the previous 5 years, except treated basal-cell carcinoma of the skin or carcinoma in situ of the cervix.

The protocol was reviewed and approved by the relevant independent ethics committees for each centre. All patients provided written informed consent. This study was done in accordance with the terms of the Declaration of Helsinki, Good Clinical Practice guidelines, and all applicable regulatory requirements.

Randomisation and masking

All patients had to complete screening and a 12-week run-in period of chemotherapy to be eligible for randomisation. After run-in, patients were randomly assigned 1:1 to receive ABP 980 or trastuzumab. Randomisation was stratified by T stage (<T4 *vs* T4), node status (yes *vs* no), hormone receptor status (positive for oestrogen receptor, progesterone receptor, or both *vs* negative for oestrogen receptor and progesterone receptor), planned paclitaxel dosing schedule (once weekly for 12 weeks *vs* every 3 weeks for four cycles), and geographical region (eastern Europe *vs* western Europe *vs* other). Sentinel lymph node assessment was not a stratification factor.

We used a computer-generated randomisation schedule with a permuted block design (blocks of four) in each stratum, which was prepared by PRA International (Paris, France) before the start of the study, to assign patients to treatment groups. At the start of screening, each patient received a unique identification number before undergoing any study procedures. This number was used for individual patient identification throughout the study, although it was not necessarily the same as the randomisation number. Upon completion of run-in chemotherapy, researchers at the study sites used an interactive voice and web response system (IXRS, Almac, Souderton, PA, USA) to receive a centrally assigned unique randomisation number that was used for central randomisation of each patient to treatment group and treatment allocation. Patients were randomly assigned to receive ABP 980 throughout the study, trastuzumab throughout the study, or neoadjuvant trastuzumab followed by adjuvant ABP 980.

See Online for appendix

The pharmacists who prepared investigational products were aware of treatment allocation. Patients, physicians, the sponsor, investigators, and study site staff were masked to treatment allocation until the final database was locked. The pathologists who assessed complete response at the local and central laboratories were also masked to treatment allocation.

Procedures

During the 28-day screening period, we took patients' medical histories, did physical examinations, electrocardiograms, two-dimensional echocardiograms, and laboratory testing in blood samples, assessed vital signs, serious adverse events, and disease progression or recurrence, and established Eastern Cooperative Oncology Group performance status score (assessed locally) and HER2 and hormone receptor statuses (assessed centrally).

After screening, patients entered the 24-week neoadjuvant treatment phase. This phase began with a 12-week run-in chemotherapy period (during which clinical response was not assessed) when patients received intravenous epirubicin 90 mg/m² and cyclophosphamide 600 mg/m² every 3 weeks for four cycles. After run-in chemotherapy and surgery, patients with adequate cardiac function, assessed by left ventricular ejection fraction on two-dimensional echocardiograms, were randomly assigned to one of three treatment groups: ABP 980, trastuzumab, or neoadjuvant trastuzumab followed by adjuvant ABP 980. Neoadjuvant treatment began with one cycle of 8 mg/kg investigational product (ie, either ABP 890 or trastuzumab) given in an intravenous infusion over 90 min as a loading dose; administration as a push or bolus dose was not allowed. Trastuzumab and ABP 980 were received in 150 g vials of lysophilised sterile powders that were qualitatively and quantitatively the same. The containers, however, differed in appearance, and to achieve masking the products were reconstituted with 7·2 mL sterilised water for injection, yielding 7·4 mL solutions containing approximately 21 mg/mL of either drug, and transferred to intravenous bags labelled with patients' randomisation numbers.

If the loading dose was tolerated, patients received three cycles of trastuzumab or ABP 980 6 mg/kg given as 30 min intravenous infusions once every 3 weeks. All

patients also received intravenous paclitaxel 175 mg/m² with all doses of investigational product (or 80 mg/m² every week for 12 cycles if that was the local standard of care). Patients were observed to check for infusion-related symptoms for at least 6 h after the start of the first infusion and for 2 h after the start of subsequent infusions. Interruption or slowing of the rate of the infusion was allowed if infusion-related symptoms occurred, and could be resumed at the 30 min infusion rate once symptoms abated.

Patients underwent surgery (lumpectomy or mastectomy with sentinel or axillary lymph node dissection) within 3–7 weeks of receiving the last dose of neoadjuvant investigational product, then entered the adjuvant phase. During the adjuvant phase, patients either continued with ABP 980 or trastuzumab (dose 6 mg/kg) or switched from trastuzumab to ABP 980 6 mg/kg intravenous infusions given over 30 min every 3 weeks for up to 1 year after the first dose of neoadjuvant treatment.

Laboratory assessments were done during screening (visit 1), during treatment (neoadjuvant phase visits 2–9 and adjuvant phase visits 10–22), and at the end of the study, 30 days after the end of treatment (visit 23). These assessments were serum chemistry (visits 1, 2–9, 14, 18, 22, and 23), haematology (visits 1, 2–9, 10–22, and 23), measurements of antibodies against the investigational product (immunogenicity; visits 1, 5, 9, 10, 14, 18, 22, and 23); and pharmacokinetics (visits 5–9, 10, 14, 18, 22, and 23).

Patients could withdraw from the study at any time and for any reason. Safety concerns (eg, due to an adverse event, failure to use contraception, or protocol requirements) and disease progression or recurrence were clinically assessed at each visit as potential causes for withdrawing patients from the investigational product or procedural assessments per protocol.

We did not allow investigational product dose adjustments, but if LVEF decreased from the value seen on echocardiograms after chemotherapy run-in and before randomisation by 10 percentage points or more and to less than 50%, treatment was suspended and a repeat LVEF assessment was done within approximately 3 weeks. If LVEF had not improved or had declined further, the investigational product was discontinued. If symptomatic cardiac failure developed, it was treated according to local standard of care. Administration of an investigational product could be delayed or discontinued for decreases in LVEF, symptomatic cardiac failure, or other adverse events.

Based on the known safety profile of trastuzumab, we prespecified cardiac failure, neutropenia, infusion reactions, pulmonary toxicity, hypersensitivity, and infections and infestations as events of interest. We used Standardized MedDRA Queries to retrieve relevant system organ classes and preferred terms in the Medical Dictionary for Regulatory Activities version 19.0, if available. If no standardised query was available for a given event of interest, we used a customised search strategy to identify relevant terms. Investigators graded adverse events according to Common Terminology Criteria for Adverse Events version 4.0. Previous and concomitant medications were coded with the WHO Drug Dictionary version 2015 DEC01.

Adverse events and disease progression or recurrence were assessed at all visits during the neoadjuvant and the adjuvant phases. Two-dimensional echocardiography was done at screening, and at visits 5 and 9 of the neoadjuvant phase, and results were assessed before administration of the investigational product. During the adjuvant phase, we assessed patients for adverse events, concomitant medications, and disease progression or recurrence at all visits and did two-dimensional echocardiograms at visits 14 and 18.

The efficacy analysis was done after the last patient had had surgery and been assessed for pathological complete response or had withdrawn from the study. Here we present the pathological complete response efficacy analysis and the safety and immunogenicity data from the final database lock. All tumour samples were assessed by local pathologists. Representative tumour samples were sent to the central laboratory for assessment by two independent central pathologists who were unaware of each other's findings. The pathologists determined the samples as adequate or inadequate for evaluation based on the presence or absence of tumour bed and integrity or loss of nuclear detail. The central pathology findings were documented on worksheets specifically developed for the study and included the following items: adequate or inadequate specimen quality; presence or absence of tumour bed; presence or absence of invasive breast cancer; results differing from the local assessment for the number of blocks with invasive breast cancer present; results differing from the local assessment for the estimated percentage of viable residual tumour; presence or absence of ductal carcinoma in situ; presence or absence of lymph nodes; and presence or absence of lymph-node-invasive cancer. If the central results were concordant, those from first central pathologist were entered into the database and were deemed to be representative. If results were discordant, the worksheets were reviewed by an adjudicating pathologist who made a final independent interpretation, which was entered into the database.

Assays validated according to FDA guidance[14] were used to detect antibodies against the investigational products. All samples were first tested in an electrochemiluminescence-based bridging immunoassay that used ABP 980 as antigen to detect binding antibodies. Samples were then tested to confirm specificity of response. Those that showed signal inhibition greater than the drug depletion cutoff point in the presence of excess soluble drug were reported as positive for binding antibodies against investigational products. Positive samples were tested in a non-cell-based, time-resolved, fluorescence-based competitive target-binding assay to determine neutralising activity. A confirmatory assay was done on

all samples to determine whether the inhibition of drug activity was due to neutralising antibodies to ABP 980. A post-treatment sample was defined as positive for neutralising antibodies if it was simultaneously positive for binding antibodies and neutralising activity.

We recorded the numbers and percentages of patients in each treatment group who had pre-existing or developed binding and neutralising binding antibodies against investigational products. Pre-existing antibody incidence was defined as the number of patients with positive antibody results at the time of or before the first dose of investigational product divided by the number of patients with an immunoassay result on or before the first dose. We defined patients who developed antibodies as the number of patients with a negative antibody result or no result available at or before baseline and a positive antibody result at any time after the first dose of investigational product divided by the number of patients with at least one immunoassay result after baseline. A transient antibody result was defined as a positive result after baseline with a negative result at the patient's last time tested within the study period.

Outcomes

The co-primary efficacy endpoints were risk difference and risk ratio (RR) of pathological complete response, defined as the absence of invasive tumour cells in the breast tissue and in axillary lymph nodes regardless of ductal carcinoma in situ (as defined by the FDA).[15] The primary analysis was based on local laboratory findings in patients with assessable tumour samples. We did sensitivity analyses based on central pathology findings to reduce variability between pathologists at the local level. Efficacy results are reported for the neoadjuvant phase (ABP 980 and trastuzumab groups).

Secondary efficacy endpoints were risk differences and RRs for pathological complete response in breast tissue (absence of invasive tumour cells, regardless of residual ductal carcinoma in situ); risk differences and RRs for pathological complete response in breast tissue and axillary lymph nodes in the absence of ductal carcinoma in situ (defined as the absence of invasive tumour cells in breast tissue and axillary lymph nodes and absence of ductal carcinoma). These results will be reported separately.

Safety assessments reported in this Article are the incidence of treatment-emergent adverse events, changes in LVEF, exposure to investigational product and paclitaxel, and formation of antibodies against an investigational product (immunogenicity). Safety results are presented for the neoadjuvant phase (ABP 980 and trastuzumab groups) and adjuvant phase (ABP 980, trastuzumab, and switching groups). Other safety outcomes that will be reported elsewhere were on-study event-free survival, overall survival, pharmacokinetics, concomitant medications, laboratory tests (including serum chemistry and haematology), vital signs, and physical examination.

Subgroup analyses done in prespecified groups for the neoadjuvant phase, adjuvant phase, and entire study. These included age group, race, T stage, axillary lymph node involvement, hormone receptor status, paclitaxel dosing schedule, and geographical region, and will be reported separately.

Statistical analysis

The primary efficacy hypothesis was that ABP 980 would be equivalent to trastuzumab when each was given in combination with standard-of-care neoadjuvant cancer treatment (paclitaxel). The planned sample size was 808 to ensure that 768 patients (384 in each group) were randomly assigned treatment. We calculated that this number would achieve 90% power to show equivalence when assessed by RR for pathological complete response with 5% dropout during run-in chemotherapy phase. This sample size was also calculated to provide at least 90% power to show equivalence when assessed by risk difference between groups for pathological complete response with margins of −13% and 13% and a two-sided 0·05 significance level. We assumed that the proportion of patients who would achieve a pathological complete response would be approximately 42·5% in the ABP 980 and trastuzumab groups.[16]

We initially used a sequential testing method to test similarity between ABP 980 and trastuzumab by comparing the two-sided 90% CI for risk difference between the ABP 980 and trastuzumab groups with statistical margins of −13% and 13%. If the test on the risk difference was successful, similarity was then tested by RR of pathological complete response at a two-sided significance level of 0·05 by comparing the two-sided 90% CI between the ABP 980 and trastuzumab groups with statistical margins of 0·759 and 1·318.

The population assessable for pathological complete response was defined as all randomised patients who received any amount of investigational product, underwent surgery, and had an available pathological complete response assessment from the local laboratory. The safety analysis population consisted of all patients who were randomised and received any amount of investigational product. We did sensitivity analyses in the intention-to-treat and per-protocol populations (data not shown). The intention-to-treat population included all patients randomly assigned to a study group, regardless of whether they received any investigational product. The per-protocol population included all patients who were randomised, had local laboratory pathological complete response results, and had no protocol deviations that prevented assessment of the primary objective.

All statistical analyses were done with SAS version 9.1.3 or later. This study is registered with ClinicalTrials.gov, number NCT01901146, and Eudra, number CT 2012-004319-29.

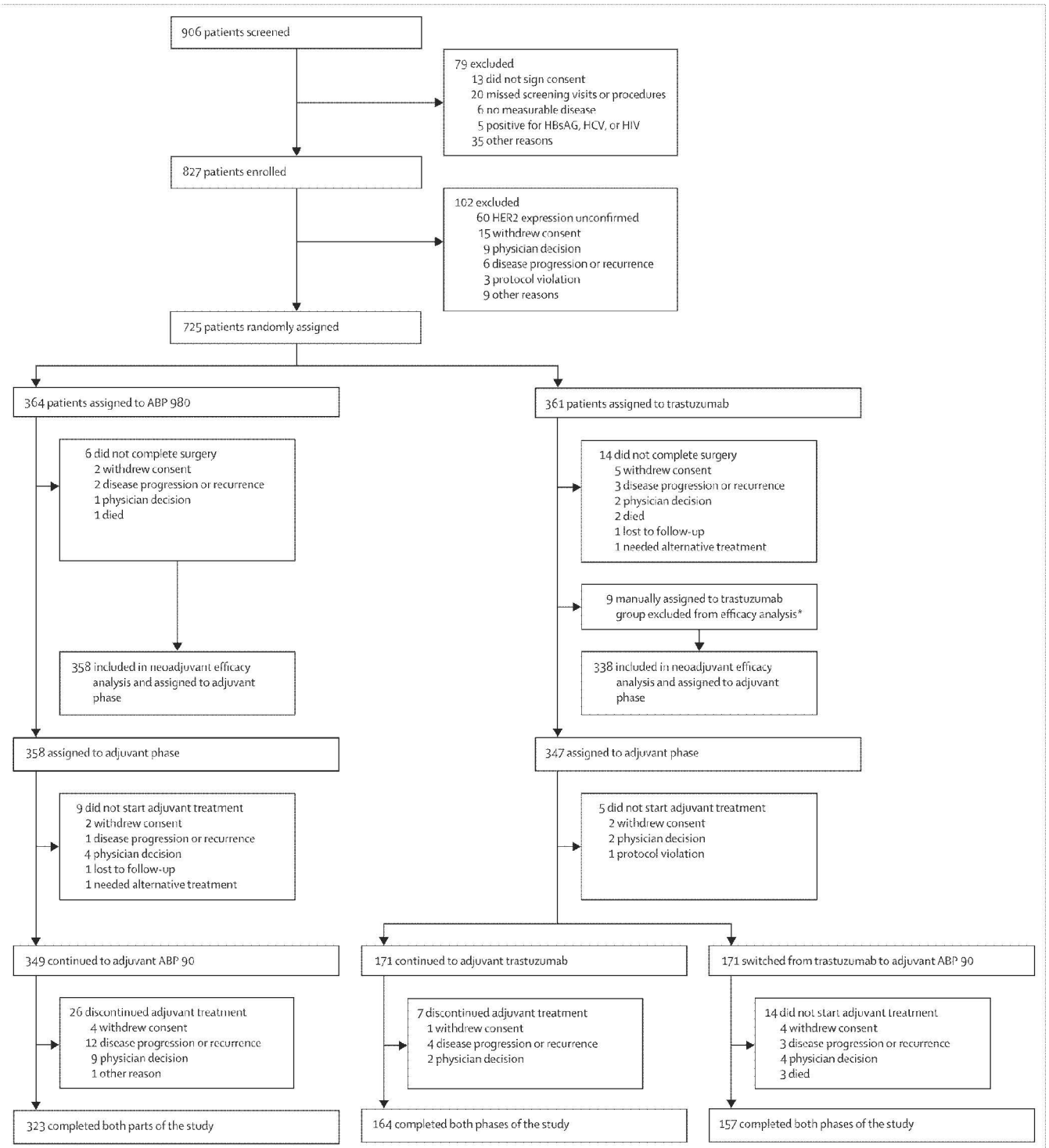

Figure 1: **Trial profile**
HBsAg=hepatitis B surface antigen. HCV=hepatitis C virus. *Nine patients were assigned to the trastuzumab group because of a delay in manufacturing of ABP 980 at the start of the study. These patients were excluded from the primary efficacy analysis but included in the final safety analysis.

Role of the funding source

The funder had a role in study design, data analysis, data interpretation, and writing of the report, and had access to the raw data, but had no role in data collection. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

We enrolled patients between April 29, 2013, and Sept 29, 2015. The data cutoff for the primary analysis was May 5, 2016, and the database lock for the final analysis was March 29, 2017. Of 906 patients screened, 79 were excluded (figure 1). 827 patients were enrolled and 725 were randomised (figure 1). The treatment groups were well balanced in terms of baseline characteristics (table 1). The baseline distribution of sentinel lymph node biopsies was balanced the two groups (39 [11%] patients in the ABP 980 group and 29 [9%] in the trastuzumab group). Lymph node surgery was not done in 13 patients after neoadjuvant treatment because they had negative or only up to two positive sentinel nodes; these patients were equally distributed between the two treatment groups of the neoadjuvant phase (six [2%] of 358 patients in the ABP 980 group *vs* seven [2%] of 338 in the trastuzumab group). Patients' exposure to investigational products is shown in table 2. Exposure to paclitaxel during the neoadjuvant phase was similar in the ABP 980 and trastuzumab groups. Paclitaxel was administered only in the neoadjuvant phase. The mean cumulative dose for patients receiving paclitaxel every 3 weeks was 686·0 (SD 65·2) mg/m² in the ABP 980 group and 679·0 (83·0) mg/m² in the trastuzumab group. For patients who received paclitaxel weekly, the mean cumulative dose was 913·0 (SD 131·2) mg/m² in the ABP 980 group and 906·0 (132·8) mg/m² in the trastuzumab group. Median follow-up was 12 months (IQR 1·04–1·08) in patients who only received ABP 980, 12 months (1·04–1·07) in those who only received trastuzumab, and 12 months (1·04–1·08) in the patients who switched from trastuzumab to ABP 980 in the adjuvant phase.

All patients who underwent surgery were assessable for the primary endpoint of pathological complete response (696 patients in total; 358 of whom received ABP 980 and 338 who received trastuzumab). 172 (48%, 95% CI 43–53) of 358 patients who received neoadjuvant ABP 980 and 137 (41%, 35–46) of 338 patients who received neoadjuvant trastuzumab achieved a pathological complete response in breast tissue and axillary nodes based on local laboratory assessments. The risk difference (ABP 980 minus trastuzumab) of pathological complete response was 7·3% (90% CI 1·2–13·4). The RR (ABP 980 *vs* trastuzumab) of pathological complete response was 1·188 (90% CI 1·033–1·366). The primary endpoint, however, was not met, because the upper boundaries of the 90% CIs for risk difference and RR exceeded the predefined equivalence margins (figure 2).

	ABP 980 (n=364)	Trastuzumab (n=190)	Switched from adjuvant trastuzumab to ABP 980 (n=171)
Age (years)	53·0 (46·0–60·0)	53·0 (45·0–60·0)	53·0 (44·0–62·0)
Ethnicity			
White	331 (91%)	175 (92%)	158 (92%)
Black or African American	10 (3%)	2 (1%)	2 (1%)
Other	23 (6%)	13 (7%)	11 (6%)
Weight (kg)	70·6 (61·60–81·00)	70·2 (62·00–79·00)	73·3 (62·20–81·30)
Geographical region			
Eastern Europe	271 (75%)	141 (74%)	132 (77%)
Western Europe	43 (12%)	24 (13%)	22 (13%)
Other	50 (14%)	25 (13%)	17 (10%)
ECOG performance status score			
0	298 (82%)	163 (86%)	149 (87%)
1	66 (18%)	27 (14%)	22 (13%)
Tumour stage			
<T4	282 (78%)	147 (77%)	134 (78%)
T4	82 (23%)	43 (23%)	37 (22%)
Axilla lymph node involvement			
Yes	277 (76%)	136 (72%)	130 (76%)
No	87 (24%)	54 (28%)	41 (24%)
Hormone receptor status			
Positive for ER, PR, or both	265 (73%)	140 (74%)	128 (75%)
Negative for ER and PR	99 (27%)	50 (26%)	43 (25%)
Histological grade			
1	8 (2%)	1 (1%)	0
2	174 (48%)	93 (49%)	80 (47%)
3	120 (33%)	67 (35%)	65 (38%)
Unknown	62 (17%)	29 (15%)	26 (15%)
Left ventricular ejection fraction (%)	65 (61·0–68·0)	65 (60·0–68·0)	65 (60·0–68·0)

Data are median (IQR) or n (%). Percentage values might not total 100% because of rounding. ECOG=Eastern Cooperative Oncology Group. ER=oestrogen receptor. PR=progesterone receptor.

Table 1: **Baseline characteristics of safety population**

In the sensitivity analyses based on central pathology review of tumour samples, 162 (48%, 95% CI 42–53) of 339 patients in the ABP 980 group and 138 (42%, 36–47) of 330 in the trastuzumab group showed pathological complete response in breast tissue and axillary nodes. The risk difference between groups and RR of ABP 980 versus trastuzumab were within the predefined equivalence margins (figure 2).

The overall incidence of adverse events in the two treatment groups during both the neoadjuvant and adjuvant phases was similar (tables 3, 4, appendix pp 3–7). In the neoadjuvant phase, 19 (5%) of 364 patients in the ABP 980 group and 23 (6%) of 361 in the trastuzumab group had adverse events that led to dose delays of investigational products, three (1%) and two (1%), respectively, had events that led to discontinuation of treatment, and four (1%) and two (1%), respectively, had events that led to withdrawal from the study. In the adjuvant phase, 16 (5%) of 349 patients in the

	Neoadjuvant treatment		Adjuvant treatment		
	ABP 980 (n=364)	Trastuzumab (n=361)	ABP 980 (n=349)	Trastuzumab (n=171)	Switched from adjuvant trastuzumab to ABP 980 (n=171)
Total number of doses of investigational product administered					
Neoadjuvant					
1–3	7 (2%)	9 (3%)	0	0	0
4	357 (98%)	352 (98%)	0	0	0
Adjuvant					
1–10	0	0	41 (12%)	12 (7%)	17 (10%)
11–13	0	0	308 (88%)	159 (93%)	154 (90%)
Weight-based average dose (mg/kg)*	6·5 (6·5–6·5)	6·5 (6·5–6·5)	6·2 (6·17–6·18)	6·2 (6·15–6·17)	6·2 (6·15–6·18)
Weight-based cumulative dose (mg/kg)*	26·0 (26·0–26·0)	26·0 (26·0–26·0)	74·0 (68·0–76·0)	74·0 (74·0–80·0)	74·0 (70·0–80·0)
Total cumulative dose (mg)*†	1820·0 (1605·5–2106·0)	1830·0 (1612·0–2080·0)	5106·0 (4399·6–5920·0)	5200·0 (4440·0–5920·0)	5208·0 (4514·00–6142·00)

Data are number (%) or median (IQR). Percentage values might not total 100% because of rounding. *For visits where partial loading or reloading doses were indicated on the electronic case report form, 4 mg/kg was given, and for visits where maintenance doses were indicated on the form, 3 mg/kg was used. †Calculated with use of the patient's weight at screening.

Table 2: **Investigational product exposure in the safety analysis population**

ABP 980 group, six (4%) of 171 in the trastuzumab group, and eight (5%) of 171 in the switching group had adverse events that led to dose delay of investigational products, seven (2%), three (2%), and four (2%), respectively, had events that led to treatment discontinuation, and seven (2%), two (1%), and two (1%), respectively, had events that led to withdrawal from the study.

Grade 3 or worse adverse events during the neoadjuvant phase occurred in 54 (15%) of 364 patients in the ABP 980 group and 51 (14%) of 361 patients in the trastuzumab group, of which the most frequent grade 3 or worse event of interest was neutropenia, occurring in 21 (6%) patients in both groups. In the adjuvant phase, grade 3 or worse adverse events occurred in 30 (9%) of 349 continuing ABP 980, 11 (6%) of 171 continuing trastuzumab, and 13 (8%) of 171 who switched from trastuzumab to ABP 980; the most frequent grade 3 or worse events of interest were infections and infestations (four [1%], two [1%], and two [1%]), neutropenia (three [1%], two [1%], and one [1%]), and infusion reactions (two [1%], two [1%], and three [2%]).

We recorded no differences in the incidence of events of interest between treatment groups in the neoadjuvant or adjuvant phases (tables 5, 6). Overall, the incidence of adverse events of interest was lower in the adjuvant phase than in the neoadjuvant phase (tables, 5, 6). In patients who initially received neoadjuvant trastuzumab, the incidence of adverse events of interest did not differ between patients who continued receiving trastuzumab in the adjuvant phase and those who switched to ABP 980 in the adjuvant phase (table 6).

A complete list of treatment-emergent serious adverse events is provided in the appendix (pp 8–10). In the neoadjuvant phase, serious adverse events occurred in 18 (5%) of 364 patients in the ABP 980 group and five (1%) of 361 in the trastuzumab group. The most common were infections and infestations. Three (<1%) of 364 patients in the ABP 980 group and two (<1%) of 361 patients in the trastuzumab group had serious adverse events that were judged to be related to the investigational products. In the adjuvant phase, 18 (5%) of 349 patients in the ABP 980 group, six (4%) of 171 in the trastuzumab group, and six (4%) of 171 in the switching group had serious adverse events. One (<1%) of 171 patients in the switching group had a serious adverse event (ventricular extrasystoles) that was judged to be related to the investigational product. Six patients in the ABP 980 treatment group and one in the trastuzumab group had serious adverse events from accidents or surgery that were deemed to be unrelated to the investigational products. The most common serious treatment-emergent adverse events during the adjuvant therapy phase were gastrointestinal disorders, injury, poisoning, and procedural complications, and infections and infestations (appendix pp 8–10).

Six patients died during the study, among whom four died before or more than 30 days after treatment with an investigational product. Two patients died from adverse events not judged to be related to the investigational products. One patient in the ABP 980 group died from pneumonia during the neoadjuvant phase and the other, in the switching group, died from septic shock in the adjuvant phase.

Overall, the incidence of adverse events was lower in the adjuvant phase, when there was no run-in chemotherapy, than in the neoadjuvant phase, which was preceded by chemotherapy (tables 3, 4). Switching patients from trastuzumab to ABP 980 did not affect safety; the incidence of adverse events in the switching

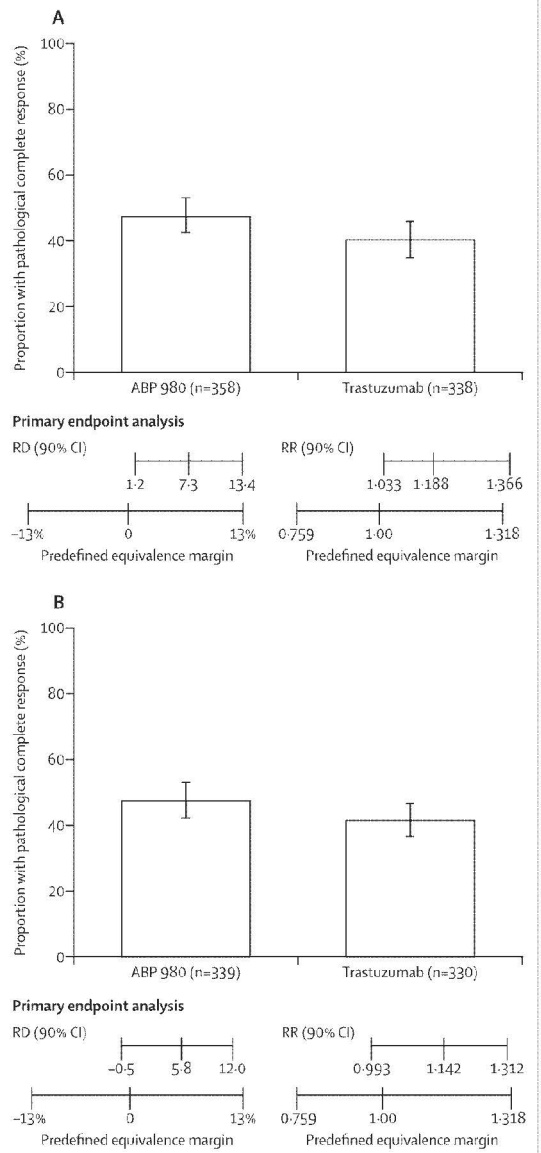

Figure 2: **Proportions of patients with pathological complete responses**
(A) Local laboratory review. (B) Central laboratory review. Data are percentages and the error bars represent 95% CIs. RD=risk difference. RR=risk ratio.

	ABP 980 (n=364)			Trastuzumab (n=361)		
	Grade 1–2	Grade 3	Grade 4	Grade 1–2	Grade 3	Grade 4
Arthralgia	63 (17%)	1 (<1%)	0	55 (15%)	0	0
Asthenia	53 (15%)	1 (<1%)	0	59 (16%)	0	0
Neuropathy peripheral	48 (13%)	3 (1%)	0	36 (10%)	7 (2%)	0
Anaemia	38 (10%)	2 (1%)	0	35 (10%)	3 (1%)	0
Neutropenia	37 (10%)	12 (3%)	4 (1%)	25 (7%)	14 (4%)	6 (2%)

The table shows grade 1–2 events that occurred in ≥10% of patients in any group and grade 3 and 4 adverse events that occurred in >2% of patients in any group; none of the events were grade 5. A complete list of adverse events is available in the appendix (pp 3–7). Adverse events were classified with Medical Dictionary for Regulatory Activities version 19.0 codes. Only treatment-emergent adverse events are summarised. Patients are included only once, even if they had multiple events in a category.

Table 3: **Adverse events during neoadjuvant treatment in the safety analysis population**

group was consistent with that reported in patients who continued receiving trastuzumab in the adjuvant phase (appendix pp 3–10).

The incidence of LVEF decline from the value after chemotherapy run-in and before randomisation by at least 10 percentage points and to less than 50% ranged from 1·8% to 3·5% across the treatment groups (appendix p 11), and the median LVEF values did not change in any treatment group over the full course of the study (data not shown). The trastuzumab and switching groups had similar LVEF results (appendix p 11).

Of the seven patients who had cardiac failure adverse events during the neoadjuvant phase (six [2%] of 364 patients in the ABP 980 group and one [<1%] of 361 in the trastuzumab group), none experienced cardiac failure coincident with LVEF decline of at least 10 percentage points and to less than 50%. All cardiac failure events were grade 1 or 2, and patients completed all planned doses of investigational product with no worsening of the cardiac failure event. During the adjuvant phase, two (1%) of 349 patients in the ABP 980 group, one (1%) of 171 in the trastuzumab group, and one (1%) of 171 in the switching group had cardiac failure events. One patient in the switching group had a grade 3 cardiac failure event and all others were grade 1 or 2. One patient in the trastuzumab group had a cardiac failure event that was coincident with LVEF decline of at least 10 percentage points and to less than 50%. No patients discontinued investigational products due to cardiac failure in the adjuvant phase.

Two patients in the ABP 980 group and two in the trastuzumab group developed binding antibodies during the neoadjuvant phase. Neither of these patients tested positive for neutralising antibodies.

During the course of the entire study, eight patients (two [1%] in the ABP 980 group, two [1%] in the trastuzumab group, and four [2%] in the switching group) tested positive for binding antibodies at any time during the study (appendix p 12). No patients tested positive for neutralising antibodies. Two (1%) patients in the ABP 980 group, one (1%) in the trastuzumab group, and two (1%) in the switching group who were negative for binding antibodies at baseline later had positive results, all of which were transient (ie, results were negative at the last time the patient was tested). None of these patients tested positive for neutralising antibodies after baseline.

Discussion

We designed this equivalence study to compare the effects of the biosimilar ABP 980 with those of reference product trastuzumab on pathological complete response in women with HER2-positive early breast cancer in the

	ABP 980 (n=349)			Trastuzumab (n=171)			Switched from adjuvant trastuzumab to ABP 980 (n=171)		
	Grade 1–2	Grade 3	Grade 4	Grade 1–2	Grade 3	Grade 4	Grade 1–2	Grade 3	Grade 4
Neutropenia	22 (6%)	2 (1%)	1 (<1%)	10 (6%)	0	0	5 (3%)	1 (1%)	0
Arthralgia	20 (6%)	0	0	9 (5%)	0	0	9 (5%)	0	0
Asthenia	17 (5%)	1 (<1%)	0	7 (4%)	0	0	10 (6%)	0	0
Anaemia	17 (5%)	0	0	7 (4%)	0	0	10 (6%)	0	0
Neuropathy peripheral	8 (2%)	0	0	3 (2%)	0	0	2 (1%)	0	0

The table shows grade 1–2 adverse events that occurred in >10% of patients in any group and grade 3 and 4 adverse events that occurred in >2% of patients in any group; none of the events were grade 5. A complete list of adverse events is provided in the appendix (pp 3–7). Adverse events were classified with Medical Dictionary for Regulatory Activities version 19.0 codes. Only treatment-emergent adverse events are summarised. Patients are only included once, even if they had multiple events in a category.

Table 4: **Adverse events during adjuvant treatment in the safety analysis population**

	ABP 980 (n=364)				Trastuzumab (n=361)			
	Grade 1–2	Grade 3	Grade 4	Grade 5	Grade 1–2	Grade 3	Grade 4	Grade 5
Infusion reactions	73 (20%)	7 (2%)	0	0	61 (17%)	7 (2%)	0	0
Neutropenia	48 (13%)	16 (4%)	5 (1%)	0	36 (10%)	15 (4%)	6 (2%)	0
Infections and infestations	44 (12%)	4 (1%)	2 (1%)	1 (<1%)	53 (15%)	1 (<1%)	1 (<1%)	0
Hypersensitivity	22 (6%)	2 (1%)	0	0	17 (5%)	2 (1%)	0	0
Cardiac failure	6 (2%)	0	0	0	1 (<1%)	0	0	0
Pulmonary toxicity	1 (<1%)	0	0	0	1 (<1%)	0	0	0

Adverse events were classified with Medical Dictionary for Regulatory Activities version 19.0 codes. Only treatment-emergent adverse events of interest are summarised. Patients are only included once, even if they had multiple events in a category.

Table 5: **Adverse events of interest during neoadjuvant treatment in the safety analysis population**

	ABP 980 (n=349)				Trastuzumab (n=171)				Switched from adjuvant trastuzumab to ABP 980 (n=171)			
	Grade 1–2	Grade 3	Grade 4	Grade 5	Grade 1–2	Grade 3	Grade 4	Grade 5	Grade 1–2	Grade 3	Grade 4	Grade 5
Infusion reactions	26 (8%)	2 (1%)	0	0	12 (7%)	2 (1%)	0	0	17 (10%)	2 (1%)	1 (1%)	0
Neutropenia	35 (10%)	2 (1%)	1 (<1%)	0	14 (8%)	2 (1%)	0	0	12 (7%)	1 (1%)	0	0
Infections and infestations	50 (14%)	4 (1%)	0	0	15 (9%)	2 (1%)	0	0	21 (12%)	1 (1%)	0	1 (1%)
Hypersensitivity	11 (3%)	0	0	0	7 (4%)	0	0	0	8 (5%)	0	0	0
Cardiac failure	2 (1%)	0	0	0	1 (1%)	0	0	0	0	1 (1%)	0	0
Pulmonary toxicity	4 (1%)	0	0	0	1 (1%)	1 (1%)	0	0	0	1 (1%)	0	0

Adverse events were classified with Medical Dictionary for Regulatory Activities version 19.0 codes. Only treatment-emergent adverse events of interest are summarised. Patients are only included once, even if they had multiple events in a category.

Table 6: **Adverse events of interest during adjuvant treatment in the safety analysis population**

neoadjuvant setting. Although the primary efficacy endpoint of our study was not met because, based on local laboratory review of tumour samples, the upper bounds of the 90% CIs for RR and risk difference exceeded the predefined equivalence margins, our sensitivity analyses based on central laboratory evaluation of tumour samples indicated similar efficacy of the two drugs, with both risk estimates contained within the predefined equivalence margins. ABP 980 and trastuzumab had similar safety outcomes in both the neoadjuvant and adjuvant phases of the study. The incidence of serious adverse events was slightly higher in the ABP 980 group than in the trastuzumab group during the neoadjuvant phase, including a higher number of infectious adverse events, but many adverse events were probably confounded by concomitant paclitaxel or were surgical complications or trauma unrelated to the investigational products. The numbers of patients with serious adverse events in the neoadjuvant phase judged to be related to investigational products were similar in the two groups. Similarly, most of the serious adverse events in the adjuvant phase were unrelated to investigational products, and only one patient in the switching group had a serious event that was associated with treatment. Overall, therefore, the safety profiles of ABP 980 and trastuzumab for adverse events, serious

adverse events, and events of interest were similar. The frequencies, types, and severities of adverse events were consistent with the historical safety profile of trastuzumab.[1,2]

We chose women with early-stage breast cancer as the study population for this trial because this population is more homogeneous than patients who have metastatic disease, and, therefore, is more suitable for an equivalence study.[15,17] We selected pathological complete response as the primary efficacy endpoint to be consistent with previous studies of trastuzumab and because it is a clinically meaningful and validated endpoint that is directly associated with increased event-free survival.[18] The proportions of patients in the ABP 980 and the trastuzumab groups were consistent with those previously reported for trastuzumab,[19–23] but, despite clinically similar efficacy, in the local review of tumours the risk difference and RR for pathological complete response between the two groups slightly exceeded the upper statistical margins for equivalence. In the central review of tumour samples, however, the point estimates for risk difference and RR were lower and fell within the similarity margins.

A potential limitation of the study is that we did not assess clinical response of breast cancer to the neoadjuvant treatment; clinical tumour response is highly variable and there is no validated standard method to differentiate between two very similar products. Histopathological assessment of pathological complete response remains the standard method to investigate whether breast cancer patients have residual disease after receiving neoadjuvant treatment. The choice of locally reviewed pathological complete response as the primary endpoint is another potential limitation of this study. Central assessment is generally more conservative and reduces variability, which provides greater confidence in the results. We chose to base the primary endpoint on local review of tumour samples partly because of concerns about potential logistical difficulties associated with transfer of tissue across the four different regions in which the study was done (eg, ensuring integrity of the samples is maintained during international transport). Use of local laboratories increased the likelihood that we would have sufficient tissue from patients to make meaningful comparisons of treatment effects, despite the risk of higher variability. We found, however, that transport of samples for central review was feasible and did prespecified sensitivity analyses of the central findings to address the issue of pathologist variability at the local level. In most cases, the amount and integrity of the samples that were transported to the central laboratory were adequate to assess pathological complete response. To our knowledge, this study is the first to show that including central pathology review of pathological complete response is feasible in a large, international, multicentre clinical trial.

Treatment with trastuzumab has been associated with an increased risk of cardiac toxicity, possibly due to previous exposure to anthracyclines.[24] Therefore, we carefully assessed LVEF and cardiac adverse events. We found no change in median LVEF values over the course of the study, and decreases in LVEF were seen in few patients, with the frequencies being similar across treatment groups. The frequency of cardiac disorders was low throughout the study and none resulted in discontinuation of investigational product. Only seven patients had cardiac failure in the neoadjuvant phase, and all events were grade 1 or 2. Moreover, all seven patients received the planned doses of investigational products, which suggests resolution or no worsening of cardiac failure. Furthermore, LVEF decline and a cardiac failure adverse event coincided in only one patient in the adjuvant phase, which suggests very low cardiac toxicity in this study.

To our knowledge, this is the first study of a trastuzumab biosimilar encompassing a single-switch design from the reference product to a biosimilar, which allowed us to assess the clinical safety and immunogenicity of this approach to treatment. Safety and immunogenicity were similar in patients who were switched and in those who continued to receive trastuzumab as adjuvant therapy.

Safety, efficacy, and clinical outcomes did not differ for the biosimilar ABP 980 and trastuzumab reference product in women with HER2-positive early breast cancer. The frequencies, types, and severities of adverse events, including cardiac events, did not differ between treatment groups and were consistent with the known safety profile of trastuzumab. Immunogenicity was low for both drugs. Similarities persisted in the neoadjuvant and adjuvant phases, and switching from trastuzumab to ABP 980 did not lead to any new or unexpected safety signals. Overall, our results add to the evidence from analytical, functional, and pharmacokinetic studies supporting the clinical similarity of ABP 980 and trastuzumab.

Contributors

GvM, NZ, and VH conceived and designed the study and analysed the data. MC, H-CK, SM, PS, and ZT acquired patients' data. All authors reviewed the study results and interpreted the data, contributed substantially to development of the manuscript, and reviewed and approved the final version for submission.

Declaration of interests

GvM is a consultant for Amgen. MC is a consultant for AstraZeneca, Celldex, Novartis, OBI Pharma, Pfizer, Pierre Fabre, and Puma Biotechnology. H-CK is a consultant for Amgen, Carl Zeiss Meditec, Genomic Health, GSK, Janssen, LIV Pharma, Novartis, Pfizer, Roche, SurgVision, TEVA, and Theraclion. NZ and VH are employees and stockholders of Amgen. The other authors declare no competing interests.

Acknowledgments

The study was funded by Amgen. We thank the patients and all those who participated in the study. Medical writing support to develop drafts, tables, and figures in consultation with the authors, copyediting, fact checking, and referencing) was funded by Amgen and provided by Pasquale Iannuzzelli, Innovation Communications Group, under the direction of Monica Ramchandani, Amgen.

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SIDLEY AUSTIN LLP
Vernon M. Winters (SBN 130128)
555 California Street, Suite 2000
San Francisco, CA 94104-1503
Telephone: (415) 772-1200
Facsimile: (415) 772-7400
vwinters@sidley.com

PAUL, WEISS, RIFKIND, WHARTON & GARRISON LLP
Nicholas Groombridge (*pro hac vice*)
Eric Alan Stone (*pro hac vice*)
Jennifer H. Wu (*pro hac vice*)
Jennifer Gordon
Peter Sandel (*pro hac vice*)
Michael T. Wu (*pro hac vice*)
1285 Avenue of the Americas
New York, NY 10019-6064
Telephone: (212) 373-3000
Facsimile: (212) 757-3990
ngroombridge@paulweiss.com

AMGEN INC.
Wendy A. Whiteford (SBN 150283)
Lois M. Kwasigroch (SBN 130159)
One Amgen Center Drive
Thousand Oaks, CA 91320-1789
Telephone: (805) 447-1000
Facsimile: (805) 447-1010
wendy@amgen.com

Attorneys for Plaintiffs Amgen Inc.
and Amgen Manufacturing, Limited

UNITED STATES DISTRICT COURT
NORTHERN DISTRICT OF CALIFORNIA

AMGEN INC. and AMGEN MANUFACTURING, LIMITED, Plaintiffs, vs. SANDOZ INC., SANDOZ INTERNATIONAL GMBH, and SANDOZ GMBH, Defendants.	Case No. 3:14-cv-04741-RS **NOTICE OF MOTION AND MOTION BY AMGEN FOR A PRELIMINARY INJUNCTION** Date: March 2, 2015 Time: 1:30 PM Location: Courtroom 3, 17th Floor

1. Irreparable Harm to Research and Development

Amgen—unlike Sandoz—is an innovator. It invests substantially to develop novel, potentially life-saving products through primary research and development. Revenue for that research comes from Amgen's commercial products, including Neupogen® and Neulasta®. That research will be immediately and irreversibly harmed if Sandoz's biosimilar filgrastim draws sales from Amgen's products. *See* Philipson Report ¶¶ 20-59, 83-101. The missed opportunities in research or development of a product could not be remedied later by an injunction or an award of damages. In addition, Sandoz's entry into the market could cause Amgen to have to lay off the highly skilled research and development scientists whose projects would now go unfunded. This is irreparable harm: "[D]amage caused by a loss in personnel and the impact this would have on [a] company are indeed significant and unquantifiable." *AstraZeneca LP* v. *Apotex, Inc.*, 623 F. Supp. 2d 579, 612 (D.N.J. 2009), *supplemented*, 623 F. Supp. 2d 615 (D.N.J. 2009) and *aff'd*, 633 F.3d 1042 (Fed. Cir. 2010).

In the preliminary injunction context, the law must guard against that outcome. In *Bio-Technology Gen. Corp.* v. *Genentech, Inc*., the Federal Circuit affirmed the finding of irreparable harm based in part on Genentech's being "required to reduce its research and development activities" and because of the loss of revenue that would occur absent an injunction. 80 F.3d 1553, 1566 (Fed. Cir. 1996). Another court noted that "a significant disruption or loss of research that otherwise would have been sponsored or completed by [plaintiff] as well as a scaling back of investment in research and development which otherwise would not have occurred" are losses that cannot be "adequately compensated by a monetary payment." *Eli Lilly & Co*. v. *Teva Pharm. USA, Inc.*, 609 F. Supp. 2d 786, 812 (S.D. Ind. 2009). Irreparable harm has also been found in the context of a permanent injunction when "a reduction of revenue would subsequently impact [a pharmaceutical company's] ability to allocate its resources to product development." *Pozen Inc.* v. *Par Pharm., Inc.*, 800 F. Supp. 2d 789, 824 (E.D. Tex. 2011) *aff'd*, 696 F.3d 1151 (Fed. Cir. 2012).

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What Are "Biologics" Questions and Answers

What is a biological product?

Biological products include a wide range of products such as vaccines, blood and blood components, allergenics, somatic cells, gene therapy, tissues, and recombinant therapeutic proteins. Biologics can be composed of sugars, proteins, or nucleic acids or complex combinations of these substances, or may be living entities such as cells and tissues. Biologics are isolated from a variety of natural sources - human, animal, or microorganism - and may be produced by biotechnology methods and other cutting-edge technologies. Gene-based and cellular biologics, for example, often are at the forefront of biomedical research, and may be used to treat a variety of medical conditions for which no other treatments are available.

How do biological products differ from conventional drugs?

In contrast to most drugs that are chemically synthesized and their structure is known, most biologics are complex mixtures that are not easily identified or characterized. Biological products, including those manufactured by biotechnology, tend to be heat sensitive and susceptible to microbial contamination. Therefore, it is necessary to use aseptic principles from initial manufacturing steps, which is also in contrast to most conventional drugs.

Biological products often represent the cutting-edge of biomedical research and, in time, may offer the most effective means to treat a variety of medical illnesses and conditions that presently have no other treatments available.

Contact FDA

(800) 835-4709
(301) 827-1800
ocod@fda.hhs.gov (mailto:ocod@fda.hhs.gov)

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Division of Communication and Consumer Affairs
Office of Communication, Outreach and Development
Food and Drug Administration
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Suite 200N/HFM-47
Rockville, MD 20852-1448

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EXHIBIT 79

IN THIS SECTION

←

Biosimilar and Interchangeable Products

Biological products are the fastest-growing class of therapeutic products in the United States. When patients are prescribed a biological product, biosimilar and interchangeable products can offer additional treatment options, potentially lowering health care costs.

(/drugs/biosimilars/biosimilar-development-review-and-approval)Learn more about biologics, biosimilars, interchangeable products, and other related terms below.

- What is a biological product?
- What is a reference product?
- What is a biosimilar product?
- What does it mean to be “highly similar”?
- What does it mean to have “no clinically meaningful differences”?
- What is an interchangeable product?
- What is the difference between a biosimilar and an interchangeable product?
- Are biosimilars the same as generic drugs?

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What is a biological product?

Biological products are regulated by the Food and Drug Administration (FDA) and are used to diagnose, prevent, treat, and cure diseases and medical conditions. Biological products are a diverse category of products and are generally large, complex molecules. These products may be produced through biotechnology in a living system, such as a microorganism, plant cell, or animal cell, and are often more difficult to characterize than small molecule drugs. There are many types of biological products approved for use in the United States, including therapeutic proteins (such as filgrastim), monoclonal antibodies (such as adalimumab), and vaccines (such as those for influenza and tetanus).

The nature of biological products, including the inherent variations that can result from the manufacturing process, can present challenges in characterizing and manufacturing these products that often do not exist in the development of small molecule drugs. Slight differences between manufactured lots of the same biological product (i.e., acceptable within-product variations) are normal and expected within the manufacturing process. As part of its review, FDA assesses the manufacturing process and the manufacturer's strategy to control within-product variations. These control strategies are put in place to help ensure that manufacturers produce biological products with consistent clinical performance.

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What is a reference product?

A reference product is the single biological product, already approved by FDA, against which a proposed biosimilar product is compared. A reference product is approved based on, among other things, a full complement of safety and effectiveness data. A proposed biosimilar product is compared to and evaluated against a reference product to ensure that the product is highly similar and has no clinically meaningful differences.

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What is a biosimilar product?

A biosimilar is a biological product that is highly similar to and has no clinically meaningful differences from an existing FDA-approved reference product. These two standards are described further below.

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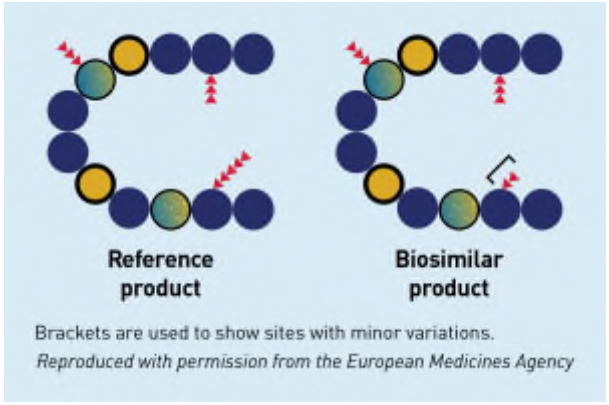
What does it mean to be "highly similar"?



Minor differences between the references product and the proposed biosimilar product in clinically inactive components are acceptable.

A manufacturer developing a proposed biosimilar demonstrates that its product is highly similar to the reference product by extensively analyzing (i.e., characterizing) the structure and function of both the reference product and the proposed biosimilar. State-of-the-art technology is used to compare characteristics of the products, such as purity, chemical identity, and bioactivity. The manufacturer uses results from these comparative tests, along with other information, to demonstrate that the biosimilar is highly similar to the reference product.

Minor differences between the reference product and the proposed biosimilar product in clinically inactive components are acceptable. For example, these could include minor differences in the stabilizer or buffer compared to what is used in the reference product. Any differences between the proposed biosimilar product and the reference product are carefully evaluated by FDA to ensure the biosimilar meets FDA's high approval standards.

As mentioned above, slight differences (i.e., acceptable within-product variations) are expected during the manufacturing process for biological products, regardless of whether the product is a biosimilar or a reference product. For both reference products and biosimilars, lot-to-lot differences (i.e., acceptable within-product differences) are carefully controlled and monitored.

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What does it mean to have "no clinically meaningful differences"?

A manufacturer must also demonstrate that its proposed biosimilar product has no clinically meaningful differences from the reference product in terms of safety, purity, and potency (safety and effectiveness). This is generally demonstrated through human pharmacokinetic (exposure) and pharmacodynamic (response) studies, an assessment of clinical immunogenicity, and, if needed, additional clinical studies.

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What is an interchangeable product?

An interchangeable product is a biosimilar product that meets additional requirements outlined by the Biologics Price Competition and Innovation Act. As part of fulfilling these additional requirements, information is needed to show that an interchangeable product is expected to produce the same clinical result as the reference product in any given patient. Also, for products administered to a patient more than once, the risk in terms of safety and reduced efficacy of switching back and forth between an interchangeable product and a reference product will have been evaluated.

An interchangeable product may be substituted for the reference product without the involvement of the prescriber. FDA's high standards for approval should assure health care providers that they can be confident in the safety and effectiveness of an interchangeable product, just as they would be for an FDA-approved reference product.

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What is the difference between a biosimilar and an interchangeable product?

As mentioned above, an interchangeable product, in addition to being biosimilar, meets additional requirements based on further evaluation and testing of the product. A manufacturer of a proposed interchangeable product will need to provide additional information to show that an interchangeable product is expected to produce the same clinical result as the reference product in any given patient. Also, for a product that is administered to a patient more than once, a manufacturer will need to provide data and information to evaluate the risk, in terms of safety and decreased efficacy, of alternating or switching between the products.

As a result, a product approved as an interchangeable product means that FDA has concluded it may be substituted for the reference product without consulting the prescriber. For example, say a patient self-administers a biological product by injection to treat their rheumatoid arthritis. To receive the biosimilar instead of the reference product, the patient may need a prescription

from a health care prescriber written specifically for that biosimilar. However, once a product is approved by FDA as interchangeable, the patient may be able to take a prescription for the reference product to the pharmacy and, depending on the state, the pharmacist could substitute the interchangeable product for the reference product without consulting the prescriber. Note that pharmacy laws and practices vary from state to state.

FDA undertakes a rigorous and thorough evaluation to ensure that all products, including biosimilar and interchangeable products, meet the Agency's high standards for approval.

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Are biosimilars the same as generic drugs?

Biosimilars and generic drugs are versions of brand name drugs and may offer more affordable treatment options to patients. Biosimilars and generics are each approved through different abbreviated pathways that avoid duplicating costly clinical trials. But biosimilars are not generics, and there are important differences between biosimilars and generic drugs.

For example, the active ingredients of generic drugs are the same as those of brand name drugs. In addition, the manufacturer of a generic drug must demonstrate that the generic is bioequivalent to the brand name drug.

By contrast, biosimilar manufacturers must demonstrate that the biosimilar is highly similar to the reference product, except for minor differences in clinically inactive components. Biosimilar manufacturers must also demonstrate that there are no clinically meaningful differences between the biosimilar and the reference product in terms of safety and effectiveness.

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EXHIBIT 80

Implementation of the Biosimilar Pathway: Economic and Policy Issues

Henry Grabowski,[*] *Genia Long,*[**] *& Richard Mortimer*[***]

[*] Professor of Economics and Director of the Program in Pharmaceuticals and Health Economics, Duke University, grabow@econ.duke.edu.

[**] Managing Principal, Analysis Group, Inc., glong@analysisgroup.com.

[***] Vice President, Analysis Group, Inc., rmortimer@analysisgroup.com.

I. INTRODUCTION

The Biologics Price Competition and Innovation Act of 2009 (BPCIA), enacted as part of the Patient Protection and Affordable Care Act of 2010 (PPACA), created an abbreviated pathway for the FDA to approve biosimilars.[1] This legislation broadly complements the twenty-five-year-old Drug Price Competition and Patent Term Restoration Act of 1984 (generally referred to as the Hatch-Waxman Act),[2] which provides a clear path for generic drug entry in the case of new chemical entities (NCEs) approved under the Food, Drug, and Cosmetic Act (FD&C Act)[3] through the Abbreviated New Drug Application (ANDA) process.[4] Through the ANDA process, generic drugs demonstrated to be bioequivalent to off-patent reference drugs may be approved without the submission of clinical-trial data.[5] The Hatch-Waxman Act, however, does not apply to most large-molecule biologic medicines, which generally are regulated under the Public Health Service Act and had no corresponding provision to the ANDA prior to passage of the BPCIA.[6] Although some biologics were approved under the FD&C Act for historical reasons, and therefore already exposed to potential generic competition, most biotech drugs

[1] Patient Protection and Affordable Care Act (PPACA), Pub. L. No. 111-148, § 7001–03, 124 Stat. 119, 804–21 (2010) [hereinafter BPCIA]. Applications under this pathway are to demonstrate that "the biological product is biosimilar to the reference product," utilizing the same mechanism(s) of action as the reference product (if known), and is to be used for the same condition(s) with the same route of administration, dose, and strength as the reference product. § 7002.

[2] Pub. L. No. 98-417, 98 Stat. 1585.

[3] Pub. L. No. 75-717, 52 Stat. 1040 (codified as amended in 21 U.S.C. § 355 (Supp. IV 2010)).

[4] 21 U.S.C. §§ 355(j).

[5] To obtain approval of an ANDA, manufacturers must establish that the generic drug product is bioequivalent to the reference drug and has the same active ingredient(s), route of administration, dosage form, strength, previously approved conditions of use, and labeling (with some exceptions). § 355(j)(2)(A). Bioequivalence is defined as "the absence of a significant difference in the rate and extent to which the active ingredient or active moiety in pharmaceutical equivalents or pharmaceutical alternatives becomes available at the site of drug action when administered at the same molar dose under similar conditions in an appropriately designed study" (with some exceptions). 21 C.F.R. § 320.1 (2010). For bioequivalence to be established, the pharmacokinetic studies should find that the generic product is within a confidence interval of 80% to 125% of the branded drug in terms of bioequivalence (a non-binding recommendation). U.S. DEP'T OF HEALTH AND HUMAN SERVS., FOOD & DRUG ADMIN., GUIDANCE FOR INDUSTRY: BIOAVAILABILITY AND BIOEQUIVALENCE STUDIES FOR ORALLY ADMINISTERED DRUG PRODUCTS—GENERAL CONSIDERATIONS 20 (2003), *available at* http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatory Information/Guidances/ucm070124.pdf.

[6] *See* 42 U.S.C. § 262 (Supp. IV 2010).

will face competition from products coming to market through an expedited approval process—relying at least in part on the innovator's package of data and/or a prior FDA approval for the first time as a result of the BPCIA.[7]

Some of the key provisions of the new legislation are:

Similarity and Interchangeability: A biosimilar does not have to be chemically identical to its reference product, but there must be "no clinically meaningful differences . . . in terms of safety, purity, and potency."[8] The FDA can find that a biosimilar is interchangeable with its reference product if it can be shown that switching between the products produces no additional risk in terms of safety or efficacy beyond that posed by the reference product alone.[9] The first biosimilar shown to be interchangeable is entitled to a one-year exclusivity period during which no other product may be deemed interchangeable with the same reference product.[10]

Regulatory Review: The FDA will determine whether a product is biosimilar to a reference product based on analytical, animal-based, and clinical studies (including the assessment of immunogenicity and pharmacokinetics or pharmacodynamics).[11] The FDA may waive the need for any of these studies in individual cases.[12] The FDA may, but is not required to, conduct rulemaking or issue guidance before reviewing or approving a specific application.[13] It may also conclude that based on the state of science and experience, biosimilars to certain products or in a certain class of products will not be approved.[14]

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[7] The FDA's review and eventual approval of two "biosimilar-like" applications were both for products approved under the FD&C Act: an ANDA for enoxaparin sodium, referencing Sanofi-Aventis's Lovenox, and a § 505(b)(2) application for Omnitrope. *See infra* Part III.A.

[8] 42 U.S.C. § 262(i)(2)(B) (Supp. IV 2010).

[9] § 262(i)(3).

[10] § 262(k)(6). Other litigation-related provisions apply. Exclusivity is the earliest of: one year after the first commercial marketing for the first-approved biosimilar found to be interchangeable; or 18 months after a final court decision, including appeal on all patents in a suit against the first interchangeable biologic, or the dismissal of a suit against the first interchangeable biologic; or 42 months after the approval of the first interchangeable biologic if litigation is still ongoing; or 18 months after approval of the first interchangeable biologic if the applicant has not been sued. *Id.*

[11] § 262(k)(2)(A)(i)(I).

[12] § 262(k)(2)(A)(ii).

[13] § 262(k)(8). The FDA may issue general or class-specific standards or guidelines (as the European Medicines Agency does) after a public comment period, but it is not required to do so. *Id.* If the FDA issues guidelines, it must include the criteria it will use to determine interchangeability and similarity. *Id.*

[14] § 262(k)(8)(E).

Exclusivity for the Innovative Biologic: Biosimilar applications may be submitted beginning four years after FDA approval of the reference innovative product.[15] Before the FDA can approve a biosimilar using the abbreviated pathway, however, there is a twelve-year period of exclusivity following FDA approval of the innovative biologic.[16] An additional six months of exclusivity is available for the reference innovative biologic if pediatric-study requirements are met, which applies to both the four- and twelve-year exclusivity periods.[17] There has been controversy surrounding the most appropriate terminology for these provisions and discussion regarding the Congressional intent of the innovator biologic exclusivity periods in the BPCIA. Therefore, in this Article, we refer to the four-year, twelve-year, and six-month exclusivity periods defined in the statute collectively, simply as new-biologic-entity exclusivity (NBE exclusivity) and to new innovative (rather than interchangeable or biosimilar) biologics as NBEs.[18]

Anti-Evergreening Provisions: Several types of licensures or approvals are not eligible for NBE exclusivity, including: (1) a supplemental biologics license application (sBLA) for the reference biologic product; (2) a subsequent BLA filed by the same sponsor, manufacturer, or other related entity as the reference biologic product that does not include structural changes in a biologic's formulation (i.e., a new indication, route of administration, dosing schedule, dosage form, deli-

[15] § 262(k)(7)(B).

[16] § 262(k)(7)(A).

[17] § 262(m).

[18] In a recent letter to the FDA, members of Congress noted that these provisions should be distinguished from and do not offer "market exclusivity for innovator products," which would "prohibit or prevent another manufacturer from developing its own data to justify FDA approval of a similar or competitive product." Letter from Representatives Anna Eshoo, Jay Inslee & Joe Barton, U.S. House of Representatives, to the Food & Drug Admin. (Dec. 21, 2010), *available at* http://www.hpm.com/pdf/EIB%20Ltr%20FDA%20DEC%202010.pdf. A letter using similar language was submitted by several senators, stating that "It (the Act) does not prohibit or prevent another manufacturer from developing its own data to justify FDA approval of a full biologics license application rather than an abbreviated application that relies on the prior approval of a reference product." Letter from Senators Kay Hagan, Orrin Hatch, Michael Enzi & John Kerry, U.S. Senate, to Dr. Margaret Hamburg, Comm'r, Food & Drug Admin. (Jan. 7, 2011), *available at* http://www.hpm.com/pdf/1-7-11%20Senate%20Biologics%20letter%20to%20FDA.pdf. A third letter was submitted to the FDA by several other senators, noting their opposition to "statutory interpretations which, if implemented by the FDA, could result in generic competition being delayed well beyond the 12 year exclusivity period in statute." Letter from Senators Sherrod Brown, John McCain, Charles Schumer & Tom Harkin, U.S. Senate, to Dr. Margaret Hamburg, Comm'r, Food & Drug Admin., (Jan. 24, 2011), *available at* http://www.hpm.com/pdf/1-24-11%20BPCIA%20Excl%20Letter%20to%20Hamburg.pdf.

very system, delivery device, or strength); or (3) a subsequent BLA filed by the same sponsor, manufacturer, or other related entity as the reference biologic product and reflecting structural changes in a biologic's formulation that does not result in improved safety, purity, or potency.[19]

Reimbursement: A potential disincentive for biosimilar adoption is mitigated by setting the reimbursement for a biosimilar under Medicare Part B at the sum of its Average Selling Price (ASP) and six percent of the ASP of the biological reference product.[20]

Patent Provisions: The BPCIA requires a series of potentially complex private information exchanges among the biosimilar applicant, reference product sponsor, and patent owners, followed by negotiations and litigation, if necessary.[21] In contrast to the patent provisions for new chemical entities under the Hatch-Waxman Act, there is no public listing akin to the Orange Book, no thirty-month stay when a patent infringement suit is brought, and no 180-day exclusivity awarded to the first firm to file an abbreviated application and achieve a successful Paragraph IV patent challenge.[22]

In this Article, we consider a number of demand- and supply-side economic factors that will affect how competition between branded biologics and biosimilars may evolve over the foreseeable future. These factors are based on current market dynamics, the provisions of the new law, initial European biosimilar experience, and experience under the Hatch-Waxman Act, taking into account differences between biologics and chemically-synthesized drugs and between the two regulatory frameworks.

Biologics are typically more complex molecules than small-molecule chemical drugs. They are not manufactured through clinical synthesis but instead, are produced through biological processes involving manipulation of genetic material and large-scale cultures of living cells, where even small changes to the manufacturing process can lead to significant changes in safety and efficacy.[23] As a result, establishing that a biosimilar is "similar enough" to achieve comparable therapeutic effects in patients is a much more challenging task for

[19] § 262(k)(7)(C).

[20] *Id.* § 1395w-3a(b)(8).

[21] *Id.* § 262(l).

[22] *Id.* § 355(j); *see also* 21 C.F.R. § 314.107(b)(3)(i)(A) (2010).

[23] *See* Henry Grabowski et al., *The Market for Follow-on Biologics: How Will it Evolve?*, 25 HEALTH AFFS. 1291, 1291–1301 (2006).

companies and regulators than establishing bioequivalence for generic chemical entities.[24]

FDA regulatory requirements for biosimilar approval will affect the investment necessary to gain market approval, the number of potential competitors, and how competition will evolve in terms of both price and product differentiation.[25] Other important factors influencing market competition include reimbursement for, and access to, biosimilars by government and private insurers, as well as patent disclosure and resolution provisions, and future intellectual property litigation.[26] NBE exclusivity provisions in the new Act will have a long-term impact on incentives for investment in innovation and the development of new biologic therapies.[27] As with any new legislation, a

[24] *Assessing the Impact of a Safe and Equitable Biosimilar Policy in the United States: Hearing Before the H. Subcomm. on Health, and H. Comm. on Energy and Commerce*, 110th Cong. 22 (2007) (statement of Janet Woodcock, M.D., Deputy Comm'r, Chief Med. Officer, FDA), available at http://www.fda.gov/NewsEvents/Testimony/ucm154017.htm; Asher Mullard, *Hearing Shines Spotlight on Biosimilar Controversies*, 9 NAT. REVS. DRUG DISCOVERY 905, 905–06 (2010). On the one hand, subtle changes in manufacturing have resulted in changes in the characteristics of finished product: Raptiva produced according to the same protocol by Genentech, and its partner XOMA exhibited different pharmacokinetic profiles; Genzyme's scale-up for Myozyme from 160 liters to a 2,000 liter production capacity was associated with glycosylation profile changes, resulting in a separate BLA requirement for the 2,000 liter product; the introduction of an uncoated rubber stopper in the prefilled syringes for Eprex is thought to have been associated with a number of cases of red blood cell aplasia. *See, e.g.*, Katia Boven et al., *The Increased Incidence of Pure Red Cell Aplasia with an Eprex Formulation in Uncoated Rubber Stopper Syringes*, 67 KIDNEY INT'L 2346 (2005) (scientific study finding that the use of rubber syringe stoppers was associated with an increased incidence of pure red cell aplasia with Eprex); *Genentech and XOMA Obtain Results from Xanelim™ (Efalizumab) Pharmacokinetic Study*, GENENTECH (Apr. 5, 2002), http://www.gene.com/gene/news/press-releases/display.do?method=detail&id=4947; *Myozyme Produced at the 2000 L Bioreactor Scale to Receive Accelerated Approval*, UNITED POMPE FOUNDATION (Feb. 28, 2009), http://www.unitedpompe.com/articles2.cfm?Article_Selected=528. Others have cited Amgen's change in manufacturing process from the previous "roller ball" manufacturing process to a bioreactor process and associated change in master cell bank for Aranesp, which entailed a new Phase III study and significant Phase IV post-marketing study follow-up. *See* Interview with Mark McCamish, Global Head of Biopharmaceutical Dev., Sandoz Int'l, *available at* http://www.iirusa.com/upload/wysiwyg/2010-P-Div/P1586/Podcast/Podcast Script_MarkMcCamish.pdf. On the other hand, not all changes that might appear to be significant ex ante prove to have a significant clinical effect; in gaining approval for Avonex, Biogen was able to rely on clinical studies conducted in entirely different cell lines (Biogen produced Avonex in a unique CHO cell line). *See* Günter Blaich et al., *Overview: Differentiating Issues in the Development of Macromolecules Compared with Small Molecules*, in HANDBOOK OF PHARM. BIOTECHNOLOGY 109–10 (Shane Cox Gad ed., 2007).

[25] *See* Grabowski et al., *supra* note 23, at 1294.

[26] *See id.* at 1295–98.

[27] *Id.* at 1298–99.

range of strategic responses by manufacturers of innovative biologics and biosimilars will emerge. In this Article, we examine each of these interrelated factors as they affect supply- and demand-side incentives.

II. FDA REGULATIONS AND THE EXPENSE OF DEVELOPING A BIOSIMILAR

The new law authorizing biosimilars gives broad latitude to the FDA to define the process and standards it will apply to biosimilar-marketing approvals.[28] FDA decisions will have an impact on both the demand for, and supply, of biosimilars:

- The level of clinical trial and other evidence required to establish either interchangeability or similarity will affect not only regulatory approval but also adoption, as greater levels of evidence will increase physician, payer, and patient confidence in a biosimilar medicine. As a result, the level of evidence required will have an impact on the costs of market entry, number of biosimilar entrants, and assets and capabilities required to compete successfully;[29]
- Naming conventions and pharmacovigilance requirements for biosimilars will have an impact on entry and perceptions of substitutability by physicians, payers, and patients;[30]
- Whether data on one indication can be extrapolated to others—absent additional clinical trials in that patient population—safely and without creating a potential for "off-label" liability will have an impact on entry decisions, perceptions of substitutability, and biosimilar uptake;[31]
- Definitions of what will constitute changes in "safety, purity, or potency," as they are applied to determine whether NBE exclusivity is to be authorized for next-generation

[28] 42 U.S.C. § 262(a), (k)(3)–(6), (k)(8) (Supp. IV 2010).

[29] *See* Grabowski et al., *supra* note 23, at 1296–98. This includes whether foreign data will be accepted that use non-U.S.-licensed biologic products as comparators. *Id.*

[30] *Id.* at 1298. The FDA notes that patient-safety protection will require distinguishing among the reference product, related biological products that have not been demonstrated to be biosimilar, biosimilar products, and interchangeable products. *See* U.S. DEP'T OF HEALTH & HUMAN SERVS, FOOD & DRUG ADMIN., DOCKET NO. FDA-2010-N-0477, APPROVAL PATHWAY FOR BIOSIMILAR AND INTERCHANGEABLE BIOLOGICAL PRODUCTS; PUBLIC HEARING; REQUEST FOR COMMENTS 64–101 (2010) [hereinafter FOOD & DRUG ADMIN. HEARING].

[31] *See* Grabowski et al., *supra* note 23, at 1296–98.

products will have an impact on biotech-investor incentives.[32]

The FDA conducted a two-day public hearing in November 2010 to solicit comments on these and other issues.[33] In addition to the points noted above, the FDA panel also gathered input on the phenomenon of "drift" (i.e., post-market changes to the reference product caused by manufacturing changes) and the effect of the drift on the consideration of interchangeability ratings.[34] On the one hand, some expressed concern as to whether the potential for drift calls into question whether products can ever be considered interchangeable, given that drift will result in both the reference product and the biosimilar changing separately over time following biosimilar approval, potentially increasing initial dissimilarities between the drugs.[35] On the other hand, some argued that the FDA's process for assessing the changes in a reference product over time, due to drift, through comparability studies recognizes that a marketed reference product may differ from the version of the reference product used in clinical trials for approval, and supports the idea of weaker standards for interchangeability ratings for biosimilars.[36] One proposal for dealing with these challenges is establishing a post-marketing system to monitor interchangeability.[37] This system could require strong pharmacovigilence and reporting standards and could potentially allow biosimilars to achieve interchangeability status after the product has been observed on the market for some period of time.[38] In particular, the FDA requirements for evidence submitted as part of a biosimilar application will have far-reaching effects on the development of the biosimilar and innovative biotech markets. The law specifies that in reviewing biosimilar applications, the FDA will rely on the results of analytic, animal testing, and clinical-trial data, but it is left to the agency to determine in a particular instance precisely what studies it will require.[39] For a given biosimilar application, therefore, the FDA could theoretically require a manufacturer to conduct, at one extreme, only a bioequivalence study (similar to what is required for

[32] *See* 42 U.S.C. § 262(k)(2)(A)(i)(I)(cc), (k)(7)(C)(ii)(II) (Supp. IV 2010).

[33] FOOD & DRUG ADMIN. HEARING, *supra* note 30.

[34] *Id.* at 251–70.

[35] *Id.*

[36] *Id.*

[37] *Id.* at 41.

[38] *See* Chad Landmon & Elizabeth Retersdorf, *Challenges of FDA's Nascent Biosimilar Regime*, LAW360 (Nov. 17, 2010), http://www.law360.com/web/articles/208593.

[39] BPCIA, Pub. L. No. 111-148, § 7002(k)(2)(A), 124 Stat. 119, 805 (2010).

generic approval under Hatch-Waxman Act[40]) or, at the other extreme, when science and experience do not allow it, a full program of clinical studies equivalent to that included in a biologic licensing application (BLA).[41] For the foreseeable future, the FDA is likely to apply requirements that reflect the relative state of knowledge and complexity of the molecule under review. Current FDA Commissioner Margaret Hamburg signaled this position when she stated, "there will not be a 'one-size-fits-all' approach. There will, rather, be a science-driven, case-by-case decision-making process rooted in the regulatory studies that I would encourage your [Generic Pharmaceutical Association] industry to support."[42]

Also, the FDA will need to determine what evidence the applicant must submit to achieve a rating of interchangeability with the reference biologic,[43] versus a finding of biosimilarity.[44] Achieving an FDA finding of interchangeability may be associated with far greater development costs than achieving a determination of biosimilarity, or it may be limited initially to a select few examples where molecules meet certain tests for establishing "sameness" through differentiated characterization or other technology being available and validated.[45] For instance, the FDA's recent approval of Sandoz's ANDA for generic enoxaparin sodium (referencing Lovenox), although not a biosimilar (Momenta and Sandoz describe Lovenox, a chemically synthesized product derived from natural sources, as a complex mixture),[46] may give some insight into the FDA's current approach, and it may also apply to more complex molecules and to findings of interchangeability.[47]

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[40] Pub. L. No. 98-417, 98 Stat. 1585 (1984).

[41] 42 U.S.C. § 262(a) (Supp. IV 2010).

[42] Margaret A. Hamburg, Comm'r, Food & Drug Admin., Remarks at Generic Pharm. Ass'n Annual Meeting (Feb. 18, 2010), *available at* http://www.fda.gov/NewsEvents/Speeches/ucm201833.htm.

[43] § 262(k)(4).

[44] § 262(k)(2)(A)(i)(I).

[45] *See infra* Part III.A.

[46] *See, e.g.*, *Generic*, MOMENTA, http://www.momentapharma.com/pipeline/generic.html (last visited Mar. 6, 2011).

[47] *See FDA Approves First Generic Enoxaparin Sodium Injection*, FOOD & DRUG ADMIN. (July 23, 2010), http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm220092.htm; *see also* Letter from Keith Webber, Deputy Dir., Office of Pharm. Sci., Ctr. for Drug Evaluation and Research, FDA, to Marcy Macdonald, Dir., Regulatory Affairs, Sandoz Int'l (July 23, 2010), *available at* http://www.accessdata.fda.gov/drugsatfda_docs/appletter/2010/077857s000ltr.pdf (approving the ANDA). The five criteria the FDA applied in its review are summarized in Part III.

The European Union has had a well-defined regulatory pathway for biosimilars in place for several years which provides one model that could inform how the FDA will elect to proceed.[48] The European Medicines Agency (EMA) adopted a framework that includes an overarching set of principles;[49] general guidelines on quality, safety and efficacy;[50] and product class-specific guidelines.[51] To date, the EMA has issued guidelines in six therapeutic classes[52] and has approved biosimilars in three major biologic-product classes—erythropoietins (alpha and zeta), somatropin, and granulocyte-colony

[48] *See* Eur. Meds. Agency [EMA], *Guideline on Similar Biological Medicinal Products*, EMEA Doc. No. CHMP/437/04 (Oct. 30, 2005), *available at* http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500003517.pdf.

[49] *Id.*

[50] *Id.*

[51] *Multidisciplinary: Biosimilar*, EUR. MEDS. AGENCY, http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general_content_000408.jsp (last visited Mar. 6, 2011).

[52] The product-specific biosimilar guidelines include recombinant Erythropoietins, low-molecular-weight heparins, recombinant interferon alpha, Recombinant Granulocyte-Colony Stimulating Factor, Somatropin, and Recombinant Human Insulin. *See generally* EMA, *Guideline on Clinical and Non-Clinical Development of Similar Biological Medicinal Products Containing Recombinant Erythropoietins (Revision)*, EMEA Doc. No. CHMP/BMWP/301636/2008 (Mar. 18. 2010), *available at* http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2010/04/WC500089474.pdf; EMA, *Guideline on Clinical and Non-Clinical Development of Similar Biological Medicinal Products Containing Low-Molecular-Weight Herapins*, EMEA Doc. No. CHMP/BMWP/118264/07 (Mar. 16, 2009) [hereinafter EMA, EMEA/CHMP/BMWP/118264/07], *available at* http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500003927.pdf; EMA, *Non-clinical and Clinical Development of Similar Biological Medicinal Products Containing Recombinant Interferon Alfa*, EMEA Doc. No. CHMP/BMWP/102046/2006 (Apr. 23, 2009) [hereinafter EMA, EMEA/CHMP/BMWP/102046/2006], *available at* http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500003930.pdf; EMA, *Annex to Guideline on Similar Biological Medicinal Products Containing Biotechnology-Derived Proteins as Active Substance: Non-Clinical and Clinical Issues: Guidance on Similar Medicinal Products Containing Recombinant Granulocyte-Colony Stimulating Factor*, EMEA Doc. No. CHMP/31329/2005 (Feb. 22, 2006), *available at* http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500003955.pdf; EMA, *Annex to Guideline on Similar Biological Medicinal Products Containing Biotechnology-Derived Proteins as Active Substance: Non-Clinical and Clinical Issues: Guidance on Similar Medicinal Products Containing Somatropin*, EMEA Doc. No. CHMP/94528/2005 (Feb. 22, 2006), *available at* http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500003956.pdf; EMA, *Annex to Guideline on Similar Biological Medicinal Products Containing Biotechnology-Derived Proteins as Active Substance: Non-Clinical and Clinical Issues: Guidance on Similar Medicinal Products Containing Recombinant Human Soluble Insulin*, EMEA Doc. No. CHMP/32775/05 (Feb. 22, 2006), *available at* http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500003957.pdf.

stimulating factors (G-CSFs).[53] Guidance for three other major types of biologics are under development; the EMA has circulated a draft guideline for monoclonal antibodies[54] and concept papers for recombinant follicle stimulation hormone and recombinant interferon beta.[55] Among monoclonal antibodies are significant biologics, some of which, such as Rituxan, face expiry of important patents in the next several years.[56] The global market for monoclonal antibodies is estimated to have totaled $36 billion in 2009 and to exceed $60 billion in 2015.[57] In anticipation of European and U.S. developments, Teva Pharmaceuticals began clinical trials for its biosimilar to Rituxan, TL011, in both severe rheumatoid arthritis and CD20-positive diffuse b-cell non-Hodgkin's lymphoma.[58]

The EMA has required at least one Phase II or III clinical trial for biosimilars to demonstrate similar safety and efficacy as their reference molecules and has left questions of substitution to the member states.[59] If the FDA also requires significant clinical-trial evidence, this will mean a much higher investment to obtain approvals for biosimilars as compared to generics. The cost for biosimilar approval will depend on the number and size of the necessary clinical trials,

[53] Ben Hirschler, *EU Prepares for Biosimilar Antibody Drugs*, REUTERS (October 1, 2010 1:05 EDT), http://www.reuters.com/article/2010/10/01/us-medicines-europe-biosimilars-idUSTRE69047620101001. The EMA issued a draft guideline for interferon alpha and have followed this with a reflection paper (April 2009). *See* EMA, EMEA/CHMP/BMWP/118264/07, *supra* note 52; EMA, EMEA/CHMP/BMWP/102046/2006, *supra* note 52.

[54] *See generally* EMA, *Guideline on Similar Biological Medicinal Products Containing Monoclonal Antibodies (Draft)*, Nov. 18, 2010, EMEA Doc. No. CHMP/BMWP/403543/2010 (2010), *available at* http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2010/11/WC500099361.pdf (circulated November 2010 and open for comments through May 2011).

[55] EMA, *Concept Paper on Similar Biological Medicinal Products Containing Recombinant Follicle Stimulation Hormone*, EMEA Doc. No. CHMP/BMWP/94899/2010 (Mar. 18, 2010); EMA, *Similar Biological Medicinal Products Containing Recombinant Interferon Beta*, EMEA Doc. No. CHMP/BMWP/86572/2010 (Mar. 18, 2010), *available at* http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2010/04/WC500089208.pdf.

[56] *See* Table 3 for a list of biologics facing expiry of important patents in the next few years. Other clinically and economically significant monoclonal antibodies include Avastin, Remicade, Herceptin, and Lucentis. *See* DATAMONITOR, PHARMAVITAE: MONOCLONAL ANTIBODIES: 2010, at 1 (2010).

[57] DATAMONITOR, *supra* note 56, at 22.

[58] *See* Naomi Kresge, *Teva Targets Roche's $5 Billion Rituxan Cancer Drug in Biosimilar Trial*, BLOOMBERG (May 25, 2010), http://www.bloomberg.com/news/2010-05-25/teva-targets-roche-s-5-billion-rituxan-cancer-drug-in-biosimilar-trial.html.

[59] *See* FALK EHMANN, BIOSIMILARS—REGULATION STRATEGIES AND PATHWAY IN THE EU (AND US) 25 (2010), *available at* http://www.dvfa.de/files/die_dvfa/kommissionen/life_science/application/pdf/2_Falk_Ehmann_EMEA.pdf.

the number of indications involved, and other specific FDA requirements. The current requirement for a BLA is typically two large-scale Phase III pivotal trials.[60] If the FDA requires at least one Phase II/III type study comparable to those undertaken by innovators, then the out-of-pocket costs likely will be in the range of $20 to $40 million for the studies alone.[61] In addition, the pre-clinical costs associated with biosimilars may actually be higher for biosimilars than for innovative products as they entail modifying the production process in order to achieve a very specific profile that closely approximates the reference product.[62] Others have estimated that for very complex biologics, biosimilar development costs could total $100 to $150 million and take eight or more years to bring a product to market.[63] By contrast, the cost of completing bioequivalence studies for generic drugs is estimated to be only $1 to $2 million.[64]

There are important differences between the European and U.S. health care systems, however, that suggest biosimilar market development (and share uptake) may differ between the two regions. Among others, the U.S. environment is more litigious than Europe, and so the FDA may decide to proceed more cautiously and require more clinical data than the EMA has in the past. Nevertheless, in the United States, the FDA approved M-Enoxaparin as a fully substitutable generic, which required no clinical evidence.[65] By contrast, the EMA would require clinical data to approve a biosimilar application for a low molecular weight heparin.[66] Costs of an FDA submission for U.S. approval could be lower for biosimilars already on the market in

[60] *See* Lisa M. Schwartz & Steven Woloshin, *Lost in Transmission—FDA Drug Information that Never Reaches Clinicians*, 361 NEW ENG. J. MED. 1717, 1717 (2009).

[61] T. Oldham, Presentation at the IBC Conference, Brussels, Belgium: Working Out the Profit Potential for Follow-On Biologics (Mar. 1–4 2005); ELMAR SCHÄFER, OPPORTUNITIES FOR FOBS IN EUROPE: A RISK BENEFIT ANALYSIS WITH EPO 16 (2005), *available at* http://www.biogenerix.com/publications/21_Schaefer.pdf. Schäfer finds an upper bound of $80 million, but this estimate assumes two large-scale pivotal trials typically required for a new molecular entity. *Id.*

[62] *See* Interview with Mark McCamish, *supra* note 24.

[63] *See* Ludwig Burger, *Battle over Biosimilar Drugs is only for the Brave*, REUTERS (July 2, 2010 11:44 AM BST), http://uk.reuters.com/article/idUKLNE66102R20100702?rpc=401&feedType=RSS&feedName=stocksNews&rpc=401.

[64] *See* David Reiffen & Michael R. Ward, *Generic Drug Industry Dynamics* 6 (FTC Working Paper, 2002), *available at* http://www.ftc.gov/be/workpapers/industrydynamicsreiffenwp.pdf. Reiffen and Ward estimate that the cost of applying for an ANDA was approximately $1.3 million in the early 1990s. *Id.*

[65] *See* Letter from Keith Webber, *supra* note 47.

[66] *See Generic Enoxaparin Questions and Answers*, FOOD & DRUG ADMIN., http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm220037.htm (last visited Mar. 6, 2011).

Europe if the biosimilar can rely on previously undertaken European clinical trials when compiling an FDA submission. The FDA, however, has not taken a position yet on whether it will accept clinical studies undertaken for approval in other jurisdictions.[67] The ability to rely on non-U.S. clinical studies for FDA approval of biosimilars may be an important influence on the U.S. costs of biosimilar approval, at least for some products. At a minimum, the FDA may require some level of "bridging" data to justify the relevance of non-U.S. studies for FDA approval, given that the BPCIA specifies that an applicant must demonstrate that its product is biosimilar to a U.S.-approved reference product,[68] and also given that biologics licensed in different regions may have different characteristics.[69]

The ongoing cost of manufacturing biological entities is also significantly higher than for chemical entities.[70] Biosimilar manufacturers would either need to construct expensive plants or obtain long-term lease or purchase agreements with third-parties that have an FDA-approved facility if they do not already have excess suitable manufacturing capacity.[71] In any event, the cost of entry for biosimilars is likely to be an order of magnitude higher than for generic drug products and may be closer to two orders of magnitude higher. The high capital costs of entry together with other features discussed below in Part IV will likely restrict the number and types of entrants, at least initially. Further, initial entry is likely to be targeted to the biologics with largest revenues as well as those where scientific and market feasibility have been demonstrated in Europe.

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[67] Currently, the FDA is considering comments from the November 2010 public hearing on "to what extent, if any, should animal or clinical data comparing a proposed biosimilar product with a non-U.S.-licensed comparator product be used to support a demonstration of biosimilarity to a U.S.-licensed reference product." Approval Pathway for Biosimilar and Interchangeable Biological Products; Public Hearing; Request for Comments, 75 Fed. Reg. 61,497, 61,499 (Oct. 5, 2010).

[68] 42 U.S.C. § 262(i)(4) (Supp. IV 2010). Reference product "means the single biological product licensed under subsection (a) against which a biological product is evaluated in an application submitted under subsection (k)." *Id.*; § 262(k)(2)(A)(i)(I).

[69] The FDA's inquiry into the use of bridging data, *see supra* note 67, to justify the use of non-U.S. approved reference products may reflect concerns that non-U.S. approved reference products could possess different characteristics than the U.S. approved counterpart.

[70] *A Brief Primer on Manufacturing Therapeutic Proteins*, BIOTECHNOLOGY INDUS. ORG., http://www.bio.org/healthcare/pmp/factsheet1.asp (last visited Mar. 6, 2011).

[71] *Id.*

III. INTERCHANGEABILITY AND DEMAND SIDE ECONOMIC FACTORS

A. Regulatory Requirements for Interchangeability

Another key regulatory issue will be the analytical and clinical evidence necessary for the FDA to deem a biosimilar interchangeable with its reference product, thus enabling automatic substitution without physician approval, subject to relevant state laws. For a biosimilar to be interchangeable, an applicant must demonstrate that the product is biosimilar to the U.S. reference product and that it "can be expected to produce the same clinical result as the reference product in any given patient."[72] Taken to the extreme, no product could demonstrate the same result in literally every patient, so the FDA's guidance on how to interpret this requirement will be an important, and likely contentious, factor. For products used more than once by patients (the majority of biologic products), this will require a demonstration that switching between the biosimilar and reference product poses no additional risk of reduced safety or efficacy beyond that posed by the reference product alone.[73] This will likely require crossover trial designs in which patients in clinical trials switch between the products over time. It can be difficult to recruit patients for these trials and potentially expensive to perform at a scale necessary to obtain statistical significance. It is also unclear what factors the FDA will consider in evaluating the potential risks related to alternating or switching between the biosimilar(s) and the reference product. Many firms may elect not to make the investments necessary to pursue interchangeability initially, given the current state of uncertainty and scientific knowledge regarding biosimilars. This is in contrast to generics, where an "A" rating by the FDA recognizes the products as therapeutically equivalent and eligible for substitution by pharmacists without physician approval, subject to state substitution laws, thus driving rapid share loss by the branded reference product.[74]

While there have not yet been any approvals under a new biosimilar pathway in the United States, the FDA has approved two more complex molecules that share some characteristics with biologics, enoxaparin sodium and somatropin, by relying in part on a reference product's safety and efficacy data.[75] These approvals may shed light

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[72] BPCIA, Pub. L. No. 111-148, § 7002(k)(4)(A)(ii), 124 Stat. 119, 806 (2010).

[73] § 7002(a).

[74] *See* THOMAS BROWN, HANDBOOK OF INSTITUTIONAL PHARMACY PRACTICE 482 (4th ed. 2006).

[75] The FDA approved Momenta's enoxaparin sodium as a generic version of Sanofi-Aventis's Lovenox through the ANDA pathway, s*ee supra* note 47, and approved

on how the FDA will review biosimilars and evaluate interchangeability. The recent FDA approval of Sandoz's and Momenta's enoxaparin sodium ANDA and its comments associated with that approval suggest that the FDA will evaluate biosimilarity and interchangeability on a case-by-case basis, dependent on the state of scientific knowledge in each class of medicines.[76] In the case of relatively less complex and better-characterized biologics, some biosimilar manufacturers may elect to pursue an interchangeability rating.

Enoxaparin is a chemically-synthesized product, derived from naturally-sourced porcine [or pig] heparin.[77] In summarizing its reasoning in assigning an AP rating[78] of interchangeability with respect to the reference product Lovenox and Sandoz and Momenta's enoxaparin sodium, the FDA cited five criteria, some of which are unique to enoxaparin and thus would not apply to recombinant DNA biotechnology products:[79] (1) equivalence of heparin source material and mode of depolymerization, (2) equivalence of physiochemical properties, (3) equivalence of the elements that constitute the enoxaparin molecule (i.e., the disaccharide building blocks, fragment mapping, and sequence of oligosaccharide species), (4) equivalence in biological and biochemical assays, and (5) equivalence of in vivo pharmacodynamic profile.[80] The first three criteria ensure that the heparin source material, the chemical reaction used in the production process, and the structure of the active ingredient are equivalent to that of the reference product; the fourth and fifth criteria ensure that the biosimilar has the same degree of therapeutic activity as the reference product. Based on these five criteria, the FDA found the products to be interchangeable and did not require any clinical stu-

Novartis's growth hormone Omnitrope through the § 505(b)(2) pathway. *See* Letter from Robert Meyer, Dir., Office of Drug Evaluation II, Ctr. for Drug Evaluation & Research, to Beth Brannan, Sandoz Int'l (May 30, 2006), *available at* http://www.accessdata.fda.gov/drugsatfda_docs/appletter/2006/021426s000LTR.pdf (approving the § 505(b)(2) application).

[76] *See supra* note 75 and accompanying text.

[77] *Establishing Active Ingredient Sameness for a Generic Enoxaparin Sodium, a Low Molecular Weight Heparin*, FOOD & DRUG ADMIN., http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm220023.htm (last visited Mar. 7, 2011) [hereinafter FOOD & DRUG ADMIN., *Generic Enoxaparin Sodium*].

[78] For an explanation on FDA ratings, see *Orange Book Preface*, FDA, http://www.fda.gov/Drugs/DevelopmentApprovalProcess/ucm079068.htm (last visited Mar. 7, 2011).

[79] FOOD & DRUG ADMIN., *Generic Enoxaparin Sodium*, *supra* note 77.

[80] *Id.*

dies.[81] This is in contrast to the situation in Europe, where the EMA guideline adopts a biosimilar approach to low-molecular-weight heparins, such as Lovenox, and requires clinical studies for approval but does not consider interchangeability with Lovenox.[82]

Prior to the M-Enoxaparin approval decision, in June 2006, the FDA approved Novartis's growth hormone, Omnitrope, as a follow-on protein to Pfizer's Genotropin.[83] Because some older biologics such as human recombinant insulin and growth hormone were approved as new drugs through the New Drug Application (NDA) process under the FD&C Act, the § 505(b)2 pathway under that Act allows the FDA to rely on published scientific literature or its previous findings for similar products as the basis for approval.[84] The FDA narrowly limited Omnitrope's approval as applying to protein products approved as NDAs, which also had a single active ingredient, a well-understood mechanism of action, and could be well-characterized by existing technology.[85] While Omnitrope met all these criteria, the FDA did not find sufficient data to rate the product therapeutically equivalent or interchangeable with Genotropin or other approved human growth hormones.[86]

The approval of M-Enoxaparin and Omnitrope may have limited lessons for, and applicability to, the expected FDA requirements for biosimilar approval for more complex biologics with expiring patents in the near future, including the G-CSFs, erythropoietin, and interfe-

[81] *Generic Enoxaparin Questions and Answers*, FOOD & DRUG ADMIN., http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm220037.htm (last visited Mar. 7, 2011).

[82] *Id.*

[83] *See* Letter from Robert Meyer, *supra* note 75.

[84] *Follow-on Protein Products: Hearing Before the H. Comm. on Oversight and Gov't Reform*, 110th Cong. (2007) (statement of Janet Woodcock, Deputy Comm'r, Chief Med. Officer, FDA), *available at* http://www.fda.gov/NewsEvents/Testimony/ucm154070.htm.

[85] *Omnitrope (somatropin [rDNA origin]) Questions and Answers,* FOOD & DRUG ADMIN. (accessed through Wayback Machine), http://replay.waybackmachine.org/20090513141602/http://www.fda.gov/cder/drug/infopage/somatropin/qa.htm (last visited Mar. 7, 2011) [hereinafter FOOD & DRUG ADMIN., *Omnitrope Q&A*]; *see also* Letter from Steven Galson, Dir., Ctr. for Drug Evaluation & Research, FOOD & DRUG ADMIN., to Kathleen Sanzo, Morgan, Lewis & Bockius LLP, Stephan Lawton, Biotechnology Indus. Org., and Stephen Juelsgaard, Genentech 7–8 (May 30, 2006),. *available at* http://www.fda.gov/ohrms/dockets/dockets/04P0231/04P-0231-pdn0001.pdf (denying various Citizen Petitions that opposed approval of Omnitrope).

[86] FOOD & DRUG ADMIN., *Omnitrope Q&A*, *supra* note 85.

ron beta.[87] For the foreseeable future, applications for biosimilars in these classes of more complex biologics are likely to require some clinical-trial data for approval and, even more complicated, costly clinical trials to satisfy the law's requirements to be approved as an interchangeable product. The scope and extent of evidence necessary to demonstrate similarity is likely to evolve over time in accordance with Commissioner Hamburg's statement of a case-by-case regulatory process, which reflects ongoing scientific and technological developments.[88]

B. Patient and Physician Perspectives

The rate of biosimilar penetration is expected to vary by disease indication, patient type, physician specialty, and other factors. As noted, rates of patient and physician acceptance of biosimilars are expected to be lower when the biosimilar lacks an interchangeability rating. In addition, rates of biosimilar acceptance may vary according to such physician and patient-focused factors as: whether the physician specialty is historically more price-sensitive or exhibits greater levels of brand loyalty in therapy choice (e.g., primary care physicians versus specialists, allergists versus rheumatologists); whether the biosimilars will be used over long periods of time as maintenance therapy or only once or twice during a narrow clinical window of treatment opportunity (particularly if long-term clinical data is not available); whether the indication is life-threatening or the implications of therapeutic non-response or adverse reactions are perceived to be very serious; or whether the difference in ease-of-use or out-of-pocket cost to the patient of the brand instead of the biosimilar is expected to be high.[89]

When patients are stable on a given maintenance therapy, biosimilar substitution may tend to be concentrated among new patient starts. As a result, the penetration of biosimilars for indications with a

[87] As noted earlier, following both the FDA approval of M-Enoxaparin and Omnitrope, the FDA specified that those approvals did not necessarily set precedents for future approvals of other biologic therapies. It is therefore, the authors' opinion that the approvals of M-Enoxaparin and Omnitrope may provide limited guidance on potential FDA requirements for biosimilar approval of more complex biologics where less may be known about the structure of the molecule and the mechanism of action.

[88] *See* Hamburg, *supra* note 42.

[89] *See generally* Henry Grabowski et al., The Effect on Federal Spending of Legislation Creating a Regulatory Framework for Follow-on Biologics: Key Issues and Assumptions (Aug. 2007) (unpublished White Paper, Duke Univ. Dep't of Econ.), *available at* http://econ.duke.edu/Papers/PDF/0907_H_Grabowski_I_Cockburn_G_Long_et_al_Effect_on_Federal_Spending_of_Follow_on_Biologics.pdf.

low rate of turnover in the patient populations may be more limited if products are not interchangeable. The degree of biosimilar uptake will also depend on cost differences and incentives to utilize biosimilars employed by managed care and government payers, as discussed below.[90] These financial incentives, however, are likely to be tempered if existing patients are responding well to an established therapy. This factor, together with additional factors—specialists' brand loyalty, clinically-vulnerable patient populations, and physician conservatism in switching stable patients to new therapies—are likely to constrain rates of biosimilar uptake for existing patients below levels observed for new patients.[91]

Another important demand-side factor is the perspective of specialist physicians and patient groups concerning biosimilars. Physicians who have years of experience with the reference biologic may be reluctant to substitute a biosimilar even for new patients until sufficient experience has accumulated in clinical practice settings, as opposed to clinical trials, provided there is patient access to the reference product.[92] In order to stimulate demand, it may be necessary for biosimilar firms to establish "reputation bonds" with physicians through strategies similar to those employed by branded firms that communicate information to establish brand value through physician detailing, publications, advertising, and education programs.[93] In addition, patient assistance programs and contracts with health plans, pharmacy benefit managers (PBMs), hospitals, or provider groups, which will exercise control over therapy choice, may be used in a targeted way to strengthen the economic proposition associated with biosimilar adoption. These tactics will increase the cost of drug distribution and marketing for biosimilars compared to generics where such marketing and sales costs are minimal and demand is purely driven by lower price and pharmacy contracts for availability.

C. Reimbursement and Payer Considerations

Even if biosimilars are viewed as therapeutic alternatives rather than equivalents, hospital or insurer pharmacy and therapeutic (P&T) committees may determine that they are similar enough to institute various incentives to encourage biosimilar utilization, at least for new patients. This cost sensitivity may vary across different payer groups, including private insurers, Medicaid, and Medicare.

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[90] *See infra* Part III.C.

[91] *See* Grabowski et al., *supra* note 89, at 36.

[92] *See id.* at 36–37.

[93] *See id.* at 36.

1. Private Insurers

Historically, managed care plans have been reluctant to restrict access or pursue aggressive cost-control measures[94] because many biologic therapies are targeted to cancer and other diseases that are life-threatening or involve serious disability, and have often been without close substitutes. In addition, biologics are often managed within plans as medical benefits rather than pharmacy benefits, and are typically less subject to centralized controls or formulary restrictions.[95] This has been changing over the last several years, particularly in indications where there is a choice between multiple brand-name biologics. The introduction of biosimilars can be expected to accelerate these trends toward more active management of biologic choice, costs, and utilization.

The relatively high price of biologic treatments, and their growing utilization, indicates that payers have substantial incentives to actively manage access to these therapies and implement access restrictions and incentives that encourage the use of lower-priced biologics and biosimilars. Over the past decade, even with respect to non-interchangeable branded biologics, public and private health insurance plans have begun to develop and put into place medical management, network design, and benefit design strategies to control access to, and utilization of, biologic therapies. Prior authorization or step-edit requirements and formulary tiering with preferred products are used by commercial health insurance plans to manage specialty pharmaceuticals.[96] The use of specialty tiers—in which patient financial contribution is in the form of coinsurance rather than co-payment—has also been growing and the introduction of lower-priced biosimilars may further accelerate a trend towards multiple specialty tiers and preferred specialty therapies.[97]

[94] *See* Grabowski et al., *supra* note 23, at 1295.

[95] *See id.*

[96] *See* Debbie Stern & Debi Reissman, *Specialty Pharmacy Cost Management Strategies of Private Health Care Payers*, 12 J. MANAGED CARE PHARMACY 736, 741 (2006) (citing HEALTH STRATEGY GRP., MCO TRENDS IN SPECIALTY PHARMACY MANAGEMENT (2004)), *available at* http://www.amcp.org/data/jmcp/736-744.pdf). *See generally* C. Daniel Mullins et al., *Health Plan's Strategies for Managing Outpatient Specialty Pharmaceuticals*, 25 HEALTH AFFS. 1332 (2006).

[97] *See* Stern & Reissman, *supra* note 96, at 740–41.

2. Medicare

Medicare reimburses biologics under either the Part B or the Part D program, depending largely on the mode of administration.[98] Many biologic drugs are currently dispensed in a physician's office, clinic, or hospital as infused agents.[99] The use of these biologics for Medicare patients is covered under the Medicare Part B program, while self-injectable biologics dispensed in pharmacies (including by specialty pharmacy or mail-order programs) are covered by the Part D program.[100]

i. Medicare Part B

In designing the new abbreviated pathway for biosimilars, Congress was concerned that the current Medicare rules for reimbursement of drugs administered under Part B would provide inadequate financial incentives for providers to utilize lower-priced biosimilars.[101] Part B drugs are often purchased through a "buy and bill" approach by providers who also make decisions about which therapies are appropriate for a given patient.[102] The provider is reimbursed by Medicare for administering a Part B drug, and the level of reimbursement is based on the weighted average selling price (ASP) for the category to which the drug belongs (the "J-code"), plus six percent.[103] When generics are assigned to the same J-code as their reference new chemical entity, the physician receives the same level of reimbursement, the volume-weighted average ASP for all manufacturers' products, regardless of whether he or she uses the generic or the reference product.[104] This may provide a strong incentive for physicians to util-

[98] CTRS. FOR MEDICARE & MEDICAID SERVS., U.S. DEP'T OF HEALTH & HUMAN SERVS., YOUR MEDICARE BENEFITS 21 (2011), *available at* http://www.medicare.gov/Publications/Pubs/pdf/10116.pdf.

[99] *Id.*

[100] *Medicare Part B (Medical Insurance)*, MEDICARE.GOV, http://www.medicare.gov/navigation/medicare-basics/medicare-benefits/part-b.aspx (last visited Mar. 6, 2011); *Medicare Part D (Medicare Prescription Drug Coverage)*, MEDICARE.GOV, http://www.medicare.gov/navigation/medicare-basics/medicare-benefits/part-d.aspx (last visited Mar. 6, 2011).

[101] *See* MEDICARE PAYMENT ADVISORY COMM'N, REPORT TO THE CONGRESS: IMPROVING INCENTIVES IN THE MEDICARE PROGRAM 124–29 (2009).

[102] *See, e.g.*, CTRS. FOR MEDICARE & MEDICAID SERVS., U.S. DEP'T OF HEALTH & HUMAN SERVS., COMPETITIVE ACQUISITION PROGRAM (CAP) FOR PART B DRUGS (2005), *available at* https://www.cms.gov/transmittals/downloads/R777CP.pdf.

[103] BPCIA, Pub. L. No. 111-148, § 3139, 124 Stat. 119, 439 (2010).

[104] MEDICARE PAYMENT ADVISORY COMM'N, *supra* note 101, at 118–19; *see also* CONG. BUDGET OFFICE, PUB NO. 4043, EFFECTS OF USING GENERIC DRUGS ON MEDICARE'S PRESCRIPTION DRUG SPENDING (2010).

ize the lower-cost generic product, depending on the net-acquisition cost of both products to the physician, reflecting any contracts that may be in place with the brand manufacturer and the pricing strategy of the generic entrant.[105] Biosimilars may not be deemed interchangeable by the FDA, however, and therefore would not be assigned to the same J-code as the brand product.[106] Legislators were concerned that in such instances reimbursement incentives would encourage utilizing the more expensive (higher ASP) reference product for patients, as reimbursement is based on ASP plus six percent.[107]

To mitigate potential financial disincentives for physicians to adopt biosimilars, the new legislation sets biosimilar reimbursement under Medicare Part B at the sum of the biosimilar's ASP and six percent of the ASP of the reference biologic product.[108] The reference biologic product will continue to be reimbursed at its own ASP plus six percent.[109] By basing the six percent payment to providers on the reference brand's ASP, the legislation seeks to mitigate provider disincentives to adopt lower cost biosimilars when they are not deemed to be interchangeable and are placed in separate J-codes.[110] Whether this reimbursement provision will be sufficient to overcome physician experience and loyalty to the reference biologic, as well as other financial incentives, is an open question. Stronger financial incentives had been proposed by some, including two forms of reference pricing that have had only limited use in the Medicare program, least costly alternative (LCA) requirements and functional equivalents.[111] A recent case involving Part B inhalation drugs constrained the authority of the Centers for Medicare & Medicaid Services (CMS) and its regional carriers to apply LCA requirements without statutory

[105] MEDICARE PAYMENT ADVISORY COMM'N, *supra* note 101, at 107.

[106] *Id.* at 107–08.

[107] *Id.* at 115–16. An individual provider's incentives will depend upon the relative net-acquisition cost of the brand and biosimilar versions of the product. Brand manufacturers selectively lower the acquisition costs for providers through contracting, depending upon volume or other criteria, which in turn affects ASP. *Id.* at 130 n.13.

[108] BPCIA § 3139.

[109] *Id.*

[110] Others have raised concerns over shared J-codes due to "track and trace" public health requirements. *See, e.g.*, The Deficit Reduction Act of 2005, Pub. L. No 109-171, § 6002, 120 Stat. 4, 59 (2005) (requiring physicians to include the National Drug Code (NDC) in addition to the J-code on Medicaid reimbursement forms). Without the NDC code, Medicaid is unable to identify the corresponding manufacturer on shared J-code claims and therefore, is unable to request Medicaid rebates from the manufacturer.

[111] MEDICARE PAYMENT ADVISORY COMM'N, *supra* note 101, at 124–29.

changes, concluding that the statutory direction to CMS reimbursement using ASP precluded its using LCA policies.[112] A functional equivalent approach had been used by CMS in its 2003 hospital outpatient payment rule, reimbursing both darbepoetin alfa and epoetin alfa at the same rate, based on a finding that "the two products are functionally equivalent" and "produce the same clinical result."[113] Later, the Medicare Prescription Drug, Improvement, and Modernization Act of 2003 (MMA) limited the application of the functional equivalent standard and prohibited its use for other drugs and biologics in determining hospital outpatient payments.[114] While biosimilar reimbursement methodology is specified under the new statute, coverage decisions by regional carriers may vary and also could prove to be important, as suggested by the LCA example.

ii. Medicare Part D

Privately offered Medicare Part D drug programs cover retail drugs including self-injectable biologics.[115] Biologics accounted for only six percent of total prescription drug costs in the Medicare Part D program in 2007;[116] however, spending for biologics within the Part D program is expected to increase rapidly over the coming years. Between 2006 and 2007, biologic prescription drug costs within the Part D program grew by thirty-six percent, exceeding the overall Part D expenditure growth of twenty-two percent.[117] Expenditures for self-injected biologics are expected to continue to grow rapidly in the future, as they are increasingly used to treat a wide range of diseases, such as rheumatoid arthritis, and given the large number of new biologics currently under development. The high price of self-injected biologics relative to traditional new chemical entities (NCEs) also suggests that biologics will comprise an increasing share of Part D expenditures in the future. This may lead payers to pursue pharmacy

[112] *See, e.g.*, Hays v. Sebelius, 589 F.3d 1279, 1282 (D.C. Cir. 2009).

[113] Changes to the Hospital Outpatient PPS and Calendar Year 2003 Payment Rates, 67 Fed. Reg. 66,718, 66,758, (Nov. 1, 2002) (to be codified at CFR 42 pts. 405, 419).

[114] *See* Patricia Seliger Keenan et al., *Biotechnology and Medicare's New Technology Policy: Lessons from Three Case Studies*, 25 HEALTH AFFS. 1260, 1262 (2006), *available at* http://content.healthaffairs.org/cgi/reprint/25/5/1260.

[115] MEDICARE PAYMENT ADVISORY COMM'N, *supra* note 101, at 120; *Medicare Part D (Medicare Prescription Drug Coverage)*, *supra* note 100.

[116] JOAN SOKOLOVSKY & HANNAH MILLER, MEDICARE PAYMENT ADVISORY COMM'N, MEDICARE PAYMENT SYSTEMS AND FOLLOW-ON BIOLOGICS 8 (2009), *available at* http://www.medpac.gov/transcripts/followon%20biologics.pdf.

[117] *Id.*

management techniques aimed at controlling utilization of these biologics.[118]

Many Medicare Part D plan designs include a specialty-drug tier, with average coinsurance rates increasing from twenty-five percent in 2006 to thirty-three percent in 2009.[119] Coinsurance plan designs could produce strong incentives to utilize biosimilars if substantial discounts emerge for biologic products with expensive courses of treatment for patients.[120] Preferred specialty drugs might be subject to lower rates of coinsurance, to a copayment rather than to coinsurance, or to lower patient out-of-pocket costs at the same coinsurance rate.

One limiting factor to formulary incentives for biologics in Medicare Part D is that enrollees with low-income subsidies make up a disproportionately large share of the market for biologics under the Part D program.[121] Given that these individuals are subject to limited cost sharing, other instruments such as step therapy and prior authorization may be employed to incentivize the use of biosimilars.[122]

Finally, there is uncertainty as to whether biosimilars will be treated as brands or generics for purposes of mandated manufacturer pricing, and therefore patient costs, during the transition period under the federal health care reform law to eliminate the coverage gap or "donut hole" in the Part D program.[123] Starting in 2011, brand products are required to be sold at a 50% price discount to enrollees when their spending is in the coverage gap.[124] Generic products are subject to no such requirement.[125] Plan cost-sharing requirements over the 2011 to 2020 period also differ between brand and generic products. It is currently unclear how CMS will treat biosimilars with respect to spending in the coverage gap, and whether they will face the same price discount and cost-sharing requirements as branded

[118] *See* Grabowski et al., *supra* note 23, at 1294–95.

[119] 2009 plan designs were applied to 2008 plan enrollments for calculations. *See* ELIZABETH HARGRAVE ET AL., KAISER FAMILY FOUND., MEDICARE PART D 2008 DATA SPOTLIGHT: SPECIALTY TIERS (2007), *available at* http://www.kff.org/medicare/upload/7711.pdf; JACK HOADLEY ET AL., MEDICARE PAYMENT ADVISORY COMM'N, MEDICARE PART D BENEFIT DESIGNS AND FORMULARIES, 2006–2009 (2008), *available at* http://www.medpac.gov/transcripts/MedPAC%20Formulary%20Presentation%20-%20Hoadley%2012-05-08%20revised.pdf.

[120] HARGRAVE ET AL., *supra* note 119.

[121] CONG. BUDGET OFFICE, *supra* note 104, at 4 fig.1 (2010).

[122] *Id.* at 6.

[123] *Id.* at 21.

[124] *Id.* at 3.

[125] *Id.*; *see id.* at tbl.1.

drugs, or if they will be treated similarly to generics in this respect and face no price discount requirements.[126] If CMS were to categorize biosimilar drugs with generics for this purpose, there could be circumstances during the transition years in which it is economically attractive for patients and plans to utilize the reference brand over biosimilars, taking into account the "donut hole" discounts by brands relative to biosimilar discounts, the cost-sharing requirements for brands and generics, and related economic factors.[127] CMS has not announced how biosimilars will be categorized for the purpose of the Part D "donut hole" discounting requirement.

3. Medicaid

Medicaid Preferred Drug Lists (PDLs) reflect preferred biologic products in a number of therapeutic categories. Preferred drugs typically can be dispensed without undergoing access controls such as prior authorization which are applied to non-preferred drugs. For example, on-line PDLs for Florida, Illinois, New York, Ohio, Pennsylvania and Texas, indicate that current rheumatoid arthritis (RA), hepatitis C (HCV), and human growth hormone formularies in these six large states preferred two or three RA agents (of six), one or two HCV agents (of five), and between two and five human growth hormones (of nine agents/forms).[128] Medicaid programs can be expected to encourage biosimilars through PDLs and other medical management instruments. States with managed Medicaid programs apply formulary and access management techniques common in commercial insurance plans.[129]

[126] *Id.* at 20–21.

[127] CONG. BUDGET OFFICE, *supra* note 104, at 20–21.

[128] *See* FLA. AGENCY FOR HEALTH CARE ADMIN., FLORIDA MEDICAID PREFERRED DRUG LIST (2011), *available at* http://ahca.myflorida.com/Medicaid/Prescribed_Drug/pharm_thera/pdf/pdl.pdf; ILL. MEDICAID, PREFERRED DRUG LIST (2011), *available at* http://www.hfs.illinois.gov/assets/pdl.pdf; OHIO MEDICAID, PREFERRED DRUG LIST (2010), *available at* http://jfs.ohio.gov/ohp/bhpp/PDLQuicklist.pdf; PA. MEDICAID, MEDICAL ASSISTANCE FEE-FOR-SERVICE PREFERRED DRUG LIST (2010), *available at* http://www.providersynergies.com/services/documents/PAM_PDL_20110215.pdf; TEX. HEALTH & HUMAN SERVS., TEXAS MEDICAID PREFERRED DRUG LIST (2011), *available at* http://www.txvendordrug.com/downloads/pdl/TXPDL_012011.pdf; *NYS Medicaid Pharmacy Prior Authorization Programs*, MAGELLAN MEDICAID ADMIN., https://newyork.fhsc.com/enrollees/PDP_about.asp (last visited Mar. 6, 2011).

[129] ROBERT NAVARRO, MANAGED CARE PHARMACY PRACTICE 77 (2d ed. 2009).

4. Hospitals

Hospitals typically bear the costs of biologics used during inpatient hospital stays as part of a fixed global reimbursement payment scheme that includes other services and products. Consequently, these hospitals have incentives to implement access restrictions and other mechanisms that encourage the use of lower-priced biologics and biosimilars.[130] As a result, for biologics that are generally used in hospital settings, hospitals will play a larger role than insurance companies in affecting the demand for biosimilar therapies. In the hospital sector, P&T committees review the drugs that are stocked, on standing order forms, and which can be used by physicians. Hospitals also rely on Group Purchasing Organizations (GPOs) to gain leverage in negotiating discounts from suppliers, including biologic manufacturers.[131] Because the hospital GPO market is highly concentrated, favorable contracts with a handful of suppliers can have an important effect on product selection. In addition, fixed diagnosis-related group-based reimbursement creates strong incentives for input-cost reductions where possible.[132] To the degree that biologics used in the inpatient hospital setting are included in diagnosis-related groups (DRGs), depending on how significant a portion of spending they represent, hospitals may be aggressive in implementing financial incentives and access controls to favor the utilization of some biosimilars if biosimilar prices are not countered by the brand name manufacturers.

[130] *See, e.g.*, CTRS. FOR MEDICARE & MEDICAID SERVS., U.S. DEP'T OF HEALTH & HUMAN SERVS., MEDICARE CLAIMS PROCESSING MANUAL, CHAPTER 17: DRUGS AND BIOLOGICS (2010) (outlining the incentive structure for biologics), *available at* https://www.cms.gov/manuals/downloads/clm104c17.pdf.

[131] *See, e.g.*, OFFICE OF THE INSPECTOR GEN., U.S. DEP'T OF HEALTH & HUMAN SERVS., REVIEW OF REVENUE FROM VENDORS AT THREE GROUP PURCHASING ORGANIZATIONS AND THEIR MEMBERS (2005), *available at* http://oig.hhs.gov/oas/reports/region5/50300074.pdf.

[132] DRGs are used to classify the type of treatment that a patient receives while admitted at a hospital for inpatient care. The specific DRG assigned to a case is determined based on diagnoses, procedures, discharge status, and patient characteristics for that episode of care. For most cases, Medicare reimburses hospitals a fixed amount for an inpatient episode of care based on the assigned DRG irrespective of the actual costs incurred by the hospital for that specific patient. *See e.g.*, U.S. DEP'T OF HEALTH & HUMAN SERVS., ACUTE CARE HOSPITAL INPATIENT PROSPECTIVE PAYMENT SYSTEM (2010) (fact sheet regarding Medicare payments to facilities providing acute hospital inpatient care), *available at* http://www.cms.gov/MLNProducts/downloads/AcutePaymtSysfctsht.pdf.

5. Health Care Reform Initiatives

More widespread adoption of comparative- and cost-effectiveness analyses across the U.S. health care system could further influence adoption of biologics in the future. Formal cost-effectiveness reviews by payers have been well-established in geographies outside the United States in the form of Health Technology Assessments (HTAs).[133] In the United Kingdom, for example, the National Institute of Health and Clinical Excellence's (NICE) coverage recommendations have been based on strict reviews of cost-effectiveness calculations relative to an implied standard of an acceptable cost per quality-adjusted life year (QALY).[134] The creation of the new Patient-Centered Outcomes Research Institute (PCORI) as part of the recently enacted U.S. health reform legislation may contribute to further increases in cost- and comparative-effectiveness pressures.[135]

Finally, longer-term changes in reimbursement policies may further shift financial incentives toward the use of biosimilars. For example, the adoption of global-payment strategies, rather than fee-for-service reimbursement, or some form of shared savings, could strengthen the link between physician and/or hospital compensation and use of lower-priced biologics. Global payment strategies provide incentives for the adoption of lower-cost treatments (and potentially encourage greater price competition) by setting a fixed-payment level for a patient/episode of care, with all, or a portion of, cost savings accruing to the care providers.[136] Several states are considering implementing global-payment strategies, and it has been suggested that government programs such as Medicaid could be the first to implement these strategies.[137]

[133] *See, e.g.*, *Measuring Effectiveness and Cost Effectiveness: The QALY*, NAT'L INST. OF HEALTH & CLINICAL EXCELLENCE (Apr. 20, 2010), http://www.nice.org.uk/newsroom/features/measuringeffectivenessandcosteffectivenesstheqaly.jsp.

[134] *See id.*

[135] BPCIA, Pub. L. No. 111-148, § 7002, 124 Stat. 119, 804 (2010) (codified at 42 U.S.C. § 262 (Supp. IV 2010)).

[136] *See* HOSPITAL ACUTE INPATIENT SERVICES PAYMENT SYSTEM, MEDPAC 1 (2010), *available at* http://www.medpac.gov/documents/MedPAC_Payment_Basics_10_hospital.pdf.

[137] See, e.g., Liz Kowalczyk, *Massachusetts Recasting Health Payments: Officials Draft Plans for New System to Compensate Doctors, Hospitals*, BOSTON GLOBE, Sept. 27, 2010, at Metro 1.

IV. BIOSIMILAR COMPETITION VERSUS GENERIC COMPETITION

A. Generic Competition

Since the passage of the Hatch-Waxman Act twenty-five years ago, generic competition has become the main instrument of price competition in the U.S. pharmaceutical market.[138] Generic products in 2009 accounted for three-quarters of all U.S. prescriptions,[139] compared to only nineteen percent in 1984.[140] The growth of generic utilization has been accelerated by various formulary and utilization management techniques such as tiered formularies, prior authorization and step edits, higher reimbursements to pharmacies for dispensing generics, and maximum allowable cost (MAC) programs.[141]

A distinctive pattern of generic competition has been observed in various economic studies.[142] There is a strong positive relationship both between a product's market sales and the likelihood of a patent challenge, and between the number of generic entrants and the intensity of generic price competition once the exclusivity period has expired.[143] An increasing number of products are now subject to patent challenges earlier in their product life cycle, as generic firms seek out the 180-day exclusivity period awarded to the first firm to file an ANDA with a successful Paragraph IV challenge.[144] Significant products typically experience multiple entrants within the first several months after patent expiration, and generic price levels drop toward marginal costs rapidly as generic entry increases.[145]

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[138] *See* Henry Grabowski et al., *Entry and Competition in Generic Biologics*, 28 MANAGERIAL & DECISION ECON. 439, 447 (2007).

[139] Gary Gatyas, *IMS Health Reports U.S. Prescription Sales Grew 5.1 Percent in 2009, to $300.3 Billion*, IMS HEALTH (Apr. 1, 2010), http://www.imshealth.com/portal/site/imshealth/menuitem.a46c6d4df3db4b3d88f611019418c22a/?vgnextoid=d690a27e9d5b7210VgnVCM100000ed152ca2RCRD.

[140] FED. TRADE COMM'N, GENERIC DRUG ENTRY PRIOR TO PATENT EXPIRATION: AN FTC STUDY I (2002).

[141] *See generally* Murray Aitken et al., *Prescription Drug Spending Trends in the United States: Looking Beyond the Turning Point* 28 HEALTH AFFS. w151 (2009) (discussing recent trends in drug spending and the importance of biosimilars in the market).

[142] Henry Grabowski, *Competition Between Generic and Branded Drugs*, *in* PHARMACEUTICAL INNOVATION: INCENTIVES, COMPETITION, AND COST-BENEFIT ANALYSIS IN INTERNATIONAL PERSPECTIVE 153, 153–73 (Frank A. Sloan & Chee-Ruye Hsieh eds., 2007).

[143] *Id.* at 158.

[144] *Id.*

[145] *Id.* at 158, 161.

B. Theoretical Models of Biosimilar Competition

Given the much higher costs of entry for biosimilars compared to generic drugs, as well as the other demand- and supply-side factors discussed above, the pattern of biosimilar competition is expected to differ from current generic competition.[146] In particular, fewer entrants and less intensive price discounting are expected and competition may resemble branded competition more than generic competition. This is currently the case in the human growth hormone market, where there are eight products that compete both through price and product delivery differentiation, such as more convenient pen dispensers.[147] In 2006, Sandoz entered the market with Omnitrope but has struggled to gain market share. Initially, Omnitrope was priced at a thirty-percent discount based on wholesale acquisition cost (WAC) compared to the most widely used biologic in this class, Genetropin.[148] By 2008, Omnitrope's discount had increased to forty percent.[149] Despite these discounts, Omnitrope's share of somatropin use remained below two percent.[150] These outcomes may not be reflective of the substitution potential for biosimilars generally, given that the human growth hormone market is a mature one with a number of competitors, in which an important factor in a product's success is its delivery system.[151] Many of the established brands have invested in more sophisticated pen- or needle-free delivery systems compared to the delivery systems used by recent lower-priced entrants.

To date, some theoretical analyses have attempted to model the likely scenarios for biosimilar competition in the U.S. market. Henry Grabowski, David Ridley, and Kevin Schulman focus on how the higher costs of biosimilar entry will influence the number of entrants and the expected discounts.[152] Using a simulation approach, they project a relatively small number of entrants even for larger-selling biologic products, and more modest discounts on biosimilars, than in the case of generics. Devin Chauhan, Adrian Towse, and Jorge Me-

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[146] *See* Grabowski et al., *supra* note 23, at 1292–1300.

[147] *See* Grabowski et al., *supra* note 89, at 45.

[148] Paul Heldman, Potomac Research Grp., Presentation to the Federal Trade Commission: Follow-on Biologic Market: Initial Lessons and Challenges Ahead (Nov. 21, 2008), *available at* http://www.ftc.gov/bc/workshops/hcbio/docs/fob/pheldman.pdf.

[149] *See* Grabowski et al., *supra* note 89, at 45.

[150] *See* Heldman, *supra* note 148.

[151] *See generally* Grabowski et al., *supra* note 89.

[152] *See generally* Grabowski et al., *supra* note 138.

stre-Ferrandiz propose a segmented model of biosimilar competition, in which they expect biosimilars to be utilized significantly in the price-sensitive portion of the market but less so in the non-price-sensitive portion of the market (given the reluctance of many providers to utilize biosimilars until considerable clinical experience has accumulated).[153] Average price discounts will depend on the relative size of these market segments. The authors expect that, given a relatively small number of branded biosimilar competitors, the innovator will discount prices from pre-entry levels but not to the same level as the biosimilar entrants. This is in contrast to generic competition where branded firms typically do not lower prices post-entry but may license an authorized generic when only a small number of generic competitors are expected as a result of a successful paragraph IV entry with a 180-day exclusivity award.[154]

C. Empirical Studies of Generic Drug Analogues

Other researchers have attempted to predict how biosimilar competition will emerge by considering analogous situations, including the U.S. generic market for certain products which share some characteristics suggestive of biologics. Grabowski et al. divided small molecule drugs into two classes, non-complex and complex, with complex drugs being those that meet two of the following criteria: black box warnings, narrow therapeutic index, prescribed by specialists, oncology products, or manufacturing technology that is available to only a limited number of firms. [155]

They analyzed price and quantity data from IMS Health Inc. for thirty-five conventional (i.e., non-biologic) drugs that experienced generic entry between 1997 and 2003 and found that complex drugs are associated with lower levels of generic share and price discounts.[156] Figure 1 compares the average generic share over time for drugs with two or more of the above complex characteristics to drugs with one or none of these characteristics.[157] One year after initial generic entry, the mean generic share for drugs with two or more complex characteristics was forty-five percent, while drugs with one or no

[153] DEVEN CHAUHAN ET AL., THE MARKET FOR BIOSIMILARS: EVOLUTION AND POLICY OPTIONS, 45 OFFICE OF HEALTH & ECON. BRIEFING 12–14 (2008).

[154] Ernst R. Berndt et al., *Authorized Generic Drugs, Price Competition, and Consumers' Welfare*, 26 HEALTH AFFS. 790, 792–97 (2007).

[155] *See* Grabowski et al., *supra* note 89, at 42.

[156] *Id.*

[157] *Id.*

complex characteristics had a mean generic share of seventy-eight percent (1.7 times higher).[158]

FIGURE 1[159]

Average Generic Share of the Molecule by Complex Drug Characteristics

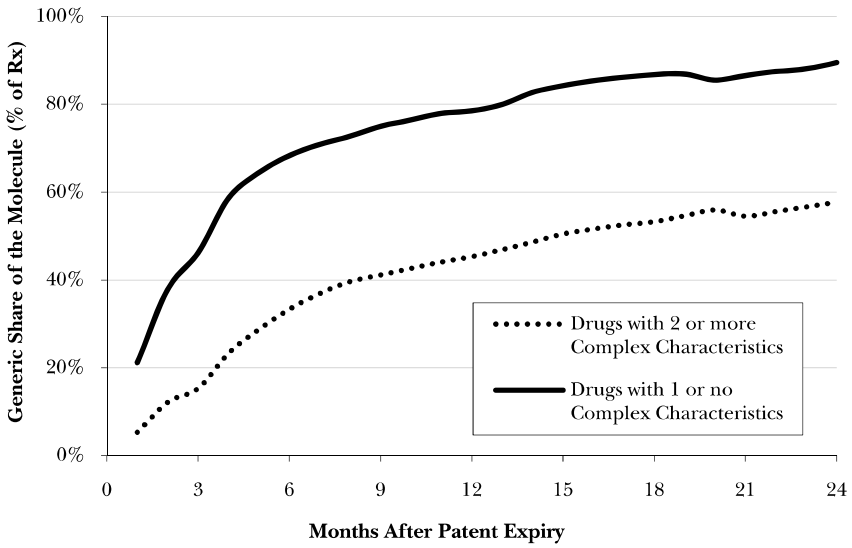


Figure 2 compares the generic price discounts from the brand over time for drugs with two or more of the above complex characteristics to drugs with one or none of these characteristics.[160] One year after initial generic entry, the generic price discount for drugs with two or more complex characteristics was thirty-five percent, while drugs with one or no complex characteristics had a generic discount of fifty-eight percent (1.6 times higher). The lower mean levels of generic shares and price discounts for drugs with two or more complex characteristics are also reflected in a lower number of generic entrants. On average, drugs with two or more characteristics faced 2.5 generic entrants one year following initial generic entry, while

[158] *Id.* at 42–43.

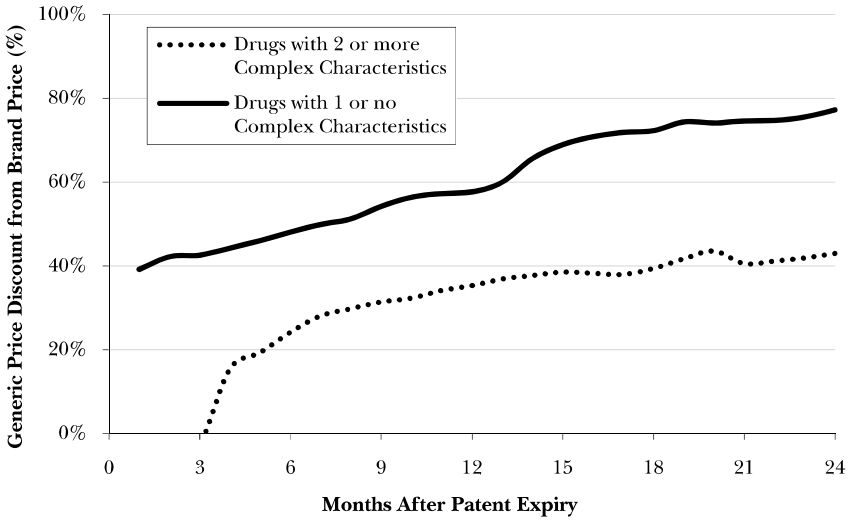
[159] Figure 1 represents the authors' calculations from a sample of 35 drugs experiencing generic entry between 1997 and 2003. The pharmaceutical sales data come from IMS National Sales Perspectives Data. A description of the data source is available at, IMS HEALTH, http://www.imshealth.com/portal/site/imshealth/menuitem.a46c6d4df3db4b3d88f611019418c22a/?vgnextoid=1cb0eec5accb2210VgnVCM100000ed152ca2RCRD&cpsextcurrchannel=1 (last visited Apr. 12, 2011). The determination of complex characteristics for each drug is based on the authors' research.

[160] *Id.* at 43, 53 fig.2.

drugs with one or no characteristics faced an average of 8.5 generic entrants.

FIGURE 2[161]

Average Generic Price Discount from Brand Price for the Molecule by Complex Drug Characteristics



While the data from conventional generics should not be directly applied to estimate biosimilar shares following market entry in the biologics market, they suggest that biosimilar uptake will be significantly lower than is observed today in the case of generic drugs.[162] Even these more complex generic drugs are nevertheless rated therapeutically equivalent (i.e., have an FDA rating of A) and, therefore, benefit from some automatic substitution.[163] In order to avoid substitution, physicians need to specify in "do not substitute" orders that prescriptions are to be dispensed as written.[164] At least initially, most biosimilars will not likely be rated therapeutically equivalent and,

[161] Figure 2 represents the authors' calculations from a sample of 35 drugs experiencing generic entry between 1997 and 2003. The pharmaceutical sales data come from IMS National Sales Perspectives Data. A description of the data source is available at, IMS HEALTH, http://www.imshealth.com/portal/site/imshealth/menuitem.a46c6d4df3db4b3d88f611019418c22a/?vgnextoid=1cb0eec5accb2210VgnVCM100000ed152ca2RCRD&cpsextcurrchannel=1 (last visited Apr. 12, 2011). The determination of complex characteristics for each drug is based on the authors' research.

[162] *Id.* at 43.

[163] *Id.*

[164] *See* Grabowski et al., *supra* note 89, at 43.

therefore, will not be subject to automatic substitution.[165] The recent FDA approval of generic enoxaparin, rated as therapeutically equivalent to branded Lovenox (which has an AP rating), will provide important data about competitive pricing strategy and market acceptance of a complex, "biologic-like" product in which only a few competitors are anticipated, based on the technical similarity and manufacturing requirements involved.[166] Currently, the FDA has approved only a single manufacturer's ANDA,[167] Momenta's generic enoxaparin, and sales of generic enoxaparin are robust.[168]

Table 1 summarizes other market share and price discount analyses generally based on selective aspects of the U.S. generic market. Most notably, as part of the evaluation of the proposed legislation regarding biosimilars, the Congressional Budget Office (CBO) predicted penetration ratios consistent with the analyses of complex drugs in Figures 1 and 2, but expected a longer phase-in period for biosimilar drugs.[169] By year four after market launch, the CBO expects a penetration rate of 35% with price discounts by biosimilars of 40%.[170] Other estimates on market penetration from a pharmacy benefit management firm, Express Scripts, as well as by Avalere Health, a consulting firm, tend to be somewhat higher than either the Grabowski et al. or CBO values, with penetration in the 50% to 60% range, and somewhat higher discounts in the case of the Avalere study (50% by year three).[171]

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[165] *Id.*

[166] *See Generic Enoxaparin Questions and Answers*, *supra* note 81.

[167] The FDA has also reviewed Teva's ANDA for generic enoxaparin and responded with a "Minor Deficiency" letter. Press Release, Teva, Teva Receives FDA Action Letter for Generic Lovenox (Jan. 25, 2011), *available at* http://www.tevapharm.com/pr/2011/pr_988.asp. Teva states that prior to final approval of its ANDA it needs to respond to a short list of questions contained on the Minor Deficiency letter and that it plans to submit a response to the FDA in the near future. *Id.*

[168] According to analysts, Momenta's generic enoxaparin generated $292 million in sales in its first sixty-nine days on the market. *See Generic Lovenox Feud Back in Spotlight*, RTT NEWS (Oct. 26, 2010), http://www.rttnews.com/content/topstories.aspx?Id=1457134&pageNum=1.

[169] *See* Cong. Budget Office, S. 1695 Biologics Price Competition and Innovation Act of 2007, at 7 (2008).

[170] *Id.*

[171] *See infra* tbl.1.

TABLE 1
Biosimilar Competition U.S. Market Share and Price Discount Evidence

Source	Peak Biosimilar Penetration	Biosimilar Discount to Pre-Entry Brand Price	Basis
Grabowski (2007) [172]	10% – 45%	10%–30% (year 1)	Higher estimates correspond to complex small molecules
CBO (2008) [173]	10% (year 1) 35% (year 4)	20% (year 1) 40% (year 4)	Similar market situations
Express Scripts (2007) [174]	49%	25% (year 1)	Therapeutic alternatives
Avalere Health (2007) [175]	60%	20% (year 1) 51% (year 3)	Average small molecule generic drug penetration rates

D. Empirical Evidence from Biosimilars in the European Union

Germany has exhibited the highest level of aggregate demand for biosimilar products thus far.[176] Experience in other European countries has been less strong. While evidence from experiences in Germany or other European countries with biosimilar substitution are not directly applicable to the U.S. market, given differences in the markets and reimbursement systems, they nevertheless suggest that over time significant biosimilar share is possible and payers, physicians, and patients will accept biosimilars.[177] In Germany, the biosimilar erythropoietin's sales accounted for nearly 60% of total biosimilar

[172] *See* Grabowski et al., *supra* note 89, at 9.

[173] *See* CONG. BUDGET OFFICE, *supra* note 169, at 7.

[174] *See* STEVE MILLER & JONAH HOUTS, POTENTIAL SAVINGS OF BIOGENERICS IN THE UNITED STATES 2 (2007), *available at* http://www.express-scripts.com/research/studies/pharmacybenefitresearch/specialtypharmacyservices/docs/potentialSavingsBiogenericsUS.pdf.

[175] *See* RONALD KING, AVALERE HEALTH, MODELING FEDERAL COST SAVINGS FROM FOLLOW-ON BIOLOGICS (2007), *available at* http://www.avalerehealth.net/research/docs/Follow_on_Biologic_Modeling_Framework.pdf. Biosimilar penetration estimates are for the largest selling products. Avalere Health is conducting further analysis.

[176] *See* Melanie Senior, *European Biosimilars' Market Performance Mirrors US Legislative Progress: Slow but Steady*, BIOPHARMA TODAY (May 19, 2009), http://www.biopharmatoday.com/2009/05/european-biosimilars-market-performance-mirrors-us-legislative-progress-slow-but-steady-.html.

[177] TED BUCKLEY, BIOSIMILARS: THE POTENTIAL FOR THE U.S. MARKET 9–15 (2010).

and reference product sales within two years of biosimilar launch; biosimilar G-CSF's accounted for almost 30% of combined biosimilar reference product sales.[178] These biosimilars have been far less successful in France, however, where the biosimilar erythropoietin has less than a 10% share and the biosimilar G-CSF has slightly less than a 20% share.[179] Table 2 summarizes the biosimilar share experiences in Germany and France. Germany's diverse payer environment (where there are hundreds of individual sickness funds) and relatively heavy reliance on generic drugs may suggest greater parallels with the United States. Future research comparing biosimilar market attitudes and experience in various European countries, the United States, and the BRIC countries (Brazil, Russia, India, and China) is needed.

TABLE 2

Biosimilar Competition Germany and France Market Share Evidence[180]

Biosimilar Shares	Share of Class		Share of Reference Product	
	Germany	France	Germany	France
Erythropoietin				
Q4/07	3.0%	–	8.1%	–
Q1/09	27.2%	0.3%	55.1%	1.5%
Q4/09	28.2%	1.4%	58.3%	6.4%
G-CSFs				
Q4/08	1.5%	–	1.8%	–
Q2/09	23.4%	3.6%	28.1%	4.9%
Q4/09	23.5%	13.0%	27.8%	17.8%

V. PROJECTED SAVINGS TO CONSUMERS

The Congressional Budget Office estimated that the provisions in the current health care law establishing a biosimilar pathway will reduce federal budget deficits by $7 billion over the 2010 to 2019 pe-

[178] *Id.* at 11–12; *see also* FED. TRADE COMM'N, HOSPIRA RESPONSES TO FTC QUESTIONS ON BIOSIMILARS (May 19, 2009), *available at* http://www.ftc.gov/os/comments/healthcarecompissues/090519hospirasupplementonbiosimilars.pdf (indicating that one year following the launch of biosimilar EPO in Germany, the biosimilar had almost a fifty-percent share of the EPO market and the biosimilar was priced at a thirty-seven percent discount compared to the average brand price prior to biosimilar entry).

[179] BUCKLEY, *supra* note 177, at 12–13.

[180] *See id.* at 11–13.

riod.[181] This finding is consistent with a 2008 CBO study of a similar Senate bill,[182] where it estimated a reduction in federal budget deficits of $6.6 billion and a reduction in biologic drug spending of $25 billion for the 2009 to 2018 period.[183] Over the full ten-year period, the $25 billion in reduced biologic drug spending would account for roughly 0.5% of national spending on prescription drugs, valued at wholesale prices.[184] The bulk of these estimated savings accrue in the last five years of the ten-year time ranges analyzed. Savings beyond the ten-year period may increase substantially as more biologics lose patent and NBE-exclusivity protections, and as scientific advances are made that both improve the ability to produce biosimilar versions of innovative drugs and reduce the cost of developing biosimilars.[185]

Over the next six years, a number of the largest selling biologic products may face losses of some key patent and/or NBE-exclusivity protections. Determining the effective patent expiry date for any given biologic is subject to interpretation, and opinions surely will differ considerably for some patents and products. A number of significant unknowns affect the precision of any such analysis, including the identification of all the patents in the portfolio protecting an individual biologic, the strength of those patents in the face of challenges, and the ability of biosimilar manufacturers to work around existing patents.[186] Based on a review of patent expiry information reported in manufacturers' financial reports and supplemented with additional public information from academic literature, research reports, patent filings, and court documents, the earliest publicly reported potential

[181] Letter from Douglas W. Elmendorf, Cong. Budget Office, to the Honorable Nancy Pelosi, Speaker, U.S. House of Representatives (Mar. 20, 2010), *available at* http://www.cbo.gov/ftpdocs/113xx/doc11379/AmendReconProp.pdf.

[182] Both the current health care law and the earlier Senate bill (S. 1695) allow for a twelve-year exclusivity period for the innovator biologic. *See* CONG. BUDGET OFFICE, *supra* note 169, at 4; *see also* 42 U.S.C. § 262(k)(7)(A) (Supp. IV 2010).

[183] *See* CONG. BUDGET OFFICE, *supra* note 169, at 1.

[184] *Id.* at 5.

[185] *See generally* CONG. BUDGET OFFICE, *supra* note 169. (estimates increase monotonically over time for the ten years projected from 2009 to 2018). The study identifies the increasing size of the biologic market at risk for biosimilar entry as one factor contributing to increased cost savings over time. *See id.* The size of the biologic market at risk for biosimilar entry is likely to continue to grow following 2018, and, in combination with technological advances for production of biosimilars and changes in the market acceptance of biosimilars, may result in further increases in savings. *See id.*

[186] Henry Grabowski et al., *Data Exclusivity for Biologics*, 10 NAT. REVS. DRUGS DISCOVERY 15, 15–16 (2011).

patent expiry dates are reported in Table 3.[187] We find that nine top-selling biologic drugs approved through a BLA may experience the loss of key patent protection by 2016. It is unknown when these biologics may experience biosimilar market entry under BPCIA, which will depend on many technical, market, regulatory, and legal factors, whether entry will be at risk, and the outcome of patent litigation that is sure to ensue.[188] Table 3 lists those nine biologics, their annual U.S. sales as of 2009, and the year of the earliest publicly reported key patent expiry, as described above.[189] The biologics that may face patent expiry between 2012 and 2013 alone had combined 2009 U.S. revenues exceeding $10.4 billion.

TABLE 3

Earliest Publicly Reported Year of Potential Patent Expiry for Selected Top-Selling Branded Biologics[190]

Drug	Company	2009 U.S. Sales ($Mil)	Earliest Publicly Reported Year of Key Patent Expiry
Enbrel	Amgen	$3,283	2012
Neupogen	Amgen	$901	2013
Epogen, Procrit	Amgen, J&J	$3,827	2013–2015
Rebif[191]	Merck Serono	$940	2013
Avonex	Biogen Idec	$1,406	2013

[187] Patent expiration dates are per the manufacturers' Form 10-K and annual reports except in the cases of Rebif and Remicade, where the patent expiration dates were not reported in the companies' financial statements. For patent expiration dates for both Rebif and Remicade, the authors relied on a report prepared for the U.S. Department of Health and Human Services and confirmed those dates using alternative publicly available sources. *See* LEWIN GROUP & i3 INNOVUS, ECONOMIC ANALYSIS OF AVAILABILITY OF FOLLOW-ON PROTEIN PRODUCTS (July 2009) (prepared for Dep't of Health and Human Servs., Office of the Assistant Sec'y for Planning and Evaluation). Results have not been vetted with individual manufacturers. Results of future patent litigation are unknown and projected dates may change.

[188] Other top-selling biologic drugs, including Humalog, Novolog, and Lantus, may lose protection from key patents by 2016, but were approved through NDAs.

[189] Results have not been vetted with individual manufacturers. The results of future patent litigation are unknown, and therefore projected dates may change.

[190] The potential year of patent expiry reflects company financial report disclosures when available and are supplemented with analyst reports and other public sources. Results have not been vetted with individual manufacturers. Results of future patent litigation are unknown and projected dates may change. *See also supra* note 187.

[191] The BLA for Rebif received FDA approval in 2002, indicating that the 12-year component of NBE exclusivity will end in 2014.

Drug	Company	2009 U.S. Sales ($Mil)	Earliest Publicly Reported Year of Key Patent Expiry
Remicade[192]	Johnson & Johnson	$3,088	2014–2018
Neulasta	Amgen	$2,527	2015
Rituxan[193]	Biogen Idec	$2,666	2015–2018
Humira[194]	Abbott	$2,519	2016–2018

VI. INNOVATION INCENTIVES

As with the Hatch-Waxman Act, Congress attempted to balance the objectives of achieving cost savings from an abbreviated pathway for biosimilars with preserving innovation incentives for new biologics. The law differs from Hatch-Waxman in the length of the exclusivity period for innovators: the BPCIA establishes twelve years after the approval of an innovative biologic during which the FDA cannot approve a biosimilar referencing it, versus the Hatch-Waxman Act, which establishes five years after approval of a NCE during which an abbreviated application for a generic drug referencing the NCE cannot be submitted.[195] Furthermore, as discussed earlier, the process for resolving patent disputes is very different for biologics under the BPCIA than for new chemical entities under Hatch-Waxman. This Part considers the growing importance of biological innovation for the healthcare sector, the innovation process in biotechnology, and how the provisions of the new law are expected to affect innovation incentives.

A. The Importance of Pharmaceutical Innovation

The biotech industry is a relatively new source of medical innovation with its first new drug product approvals coming in the early 1980s. It has, however, become a major source of novel drug introductions and overall industry growth in recent years. Grabowski and Y. Richard Wang examined the quantity and quality of new drug introductions worldwide between 1982 and 2003 and found that biotech drugs are the fastest growing segment of new therapeutics, accounting for 4% of new drug introductions in the 1982 to 1992

[192] The manufacturer relies on MAb technology that may be protected by Genentech's Cabilly II patent until the year 2018, subject to ongoing litigation. The extent to which licensing this MAb technology protects against biosimilar entry is uncertain.

[193] *Id.*

[194] *Id.*

[195] *Compare* 42 U.S.C. § 262(k)(7)(A) (Supp. IV. 2010), *with* 35 U.S.C. § 156(d)(5)(E)(i) (Supp. IV 2010).

period, but increasing to 16% in the 1993 to 2003 period.[196] U.S. firms are the dominant source of biotech drugs, originating more than half of all worldwide biopharmaceutical introductions from 1982 to 2003.[197]

One of the key indicators of drug quality or novelty in the study was whether the entity was a first-in-class introduction. New biological entities had a significantly higher likelihood of being a first-in-class or novel introduction compared to new drug introductions.[198] New biologics have been particularly focused on oncology and immunology in recent years. In particular, the oncology class has recently experienced the introduction of breakthrough monoclonal antibodies and targeted biological agents resulting from increased knowledge of the molecular mechanisms for cancer—these breakthrough products include rituximab (Rituxan), trastuzumab (Herceptin), and bevacuzimab (Avastin).[199]

Several new biological entities have had rapid diffusion and are among the leading drug therapies in their class. Substantial improvements in survival, morbidity, and patients' quality of life have been documented in diseases previously resistant to successful treatment, including cancers such as aggressive HER-2 positive breast cancer.[200] Improvements were also made in the prevention of disease progression, functional decline, joint destruction, and disability associated with rheumatoid arthritis.[201]

The prospects of future advances are further enhanced by a robust pipeline of more than 600 biotech drugs under development in a variety of therapeutic areas.[202] These include novel approaches to

[196] Henry Grabowski et al., *The Quantity and Quality of Worldwide New Drug Introductions 1992-2003*, 25 HEALTH AFFS. 452, 458 (2006).

[197] *Id.*

[198] *Id.*

[199] Joseph A. DiMasi & Henry G. Grabowski, *The Economics of New Oncology Drug Development*, 25 J. CLINICAL ONCOLOGY 209, 214–15 (2007).

[200] Ian Smith et al., *2-Year Follow-Up of Trastuzumab After Adjuvant Chemotherapy in HER2-Positive Breast Cancer: A Randomized Controlled Trial*, 369 THE LANCET 29, 33 (2007).

[201] *See generally* A.L. Weaver, *The Impact of New Biologicals in the Treatment of Rheumatoid Arthritis*, 43 RHEUMATOLOGY iii17 (2004) (describing studies on the impact of biologics in the treatment of rheumatoid arthritis).

[202] *See* PhRMA, 2008 REPORT: MEDICINES IN DEVELOPMENT—BIOTECHNOLOGY: BIOTECHNOLOGY RESEARCH CONTINUES TO BOLSTER ARSENAL AGAINST DISEASE WITH 633 MEDICINES IN DEVELOPMENT 1 (2008), *available at* http://www.phrma.org/sites/default/files/422/biotech2008.pdf.

conditions with large unmet medical need and societal disease burdens, including more than 250 biotech drugs for cancer alone.[203]

John Calfee and Elizabeth DuPré have identified two important features of competition involving new biological entities.[204] First, after proof of principle has been established for a new biological, multiple therapeutic interventions are possible in the biological cascade of proteins that often influence the same ultimate target (e.g., a particular receptor or dysfunctional enzyme).[205] In the case of Herceptin, for example, in 2008 there were fifty-one molecular targeted therapies in Phase II or III trials for breast cancer, many targeting the HER-2 receptor, other members of the HER family, or one of the other proteins downstream from HER-2.[206] The tumor necrosis factor inhibitors for rheumatoid arthritis and the angiogenesis inhibiting drugs for cancer are also experiencing similar forms of competition involving the same-targeted pathways, but with different specific modes of action.[207]

A second important feature of competition for new biological entities involves new indications associated with the same or related pathways.[208] For example, drugs initially approved for rheumatoid arthritis have been, or are being, investigated for a number of anti-inflammatory conditions that may be related to the same dysfunctional pathway. Two of the leading rheumatoid arthritis drugs have already received subsequent approval for psoriasis (Enbrel) and Crohn's disease (Remicade).[209] Michael Flanagan finds that as of the mid-2000s Avastin had 15 Phase III and 105 Phase II clinical trials in progress for more than twenty different types of cancer and different stages of cancer.[210]

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[203] *Id.*

[204] John E. Calfee & Elizabeth DuPré, *The Emerging Market Dynamics of Targeted Therapeutics*, 25 HEALTH AFFS. 1302, 1305–06 (2006).

[205] *Id.* at 1306.

[206] DATAMONITOR, PIPELINE INSIGHT: BREAST CANCER—RECENT APPROVALS INCREASE PRESSURE ON PIPELINE CANDIDATES 4 (Apr. 2008); *see generally* Laura Tookman & Rebecca Roylance, *New Drugs for Breast Cancer*, 96 BRIT. MED. BULL. 111 (2010) (discussing the targeted drug therapies for HER-2 positive breast cancer, including trastuzumab).

[207] DATAMONITOR, PIPELINE INSIGHT: DISEASE MODIFICATION IN RHEUMATOID ARTHRITIS—NEW DRUG TARGETS COMPETE IN CROWDED MARKET 67 (Oct. 2009).

[208] Calfee & DuPré, *supra* note 204, at 1306.

[209] *Id.* at 1307.

[210] M. Flanagan, *Avastin's Progression*, BIOCENTURY, March 6, 2006, at A4.

B. NBE Exclusivity and Patent Protection

The process of discovering and developing a new biologic is a long, costly, and risky venture. Joseph DiMasi and Grabowski have estimated that the development of a typical new biologic costs $1.2 billion in capitalized R&D costs.[211] This compares with an earlier study of the cost of an NCE, estimated at roughly $800 million.[212] DiMasi and Grabowski found that biologics cost more in the discovery phase, take longer to develop, and require greater capital investment in manufacturing plants.[213] They found that the probability of success is higher for biologics than NCEs, but biologics that fail do so later in the R&D life cycle.[214] After adjustment for inflation and the different time periods studied, the cost of developing a biologic and an NCE are roughly comparable in value.[215]

The development of new medicines requires large and risky up-front capital investments. Intellectual property protection in the form of patents and exclusivity provisions in the BPCIA and Hatch Waxman Acts ("NBE/NCE exclusivity periods") are the primary policy instruments used in the United States with the aim of allowing investors to recoup sufficient profits from successful innovations to encourage risky investment in R&D for new medicines.[216] NBE/NCE exclusivity and patents have separate but complementary roles. The U.S. government awards patents for inventions based on well-known criteria: novelty, utility, and non-obviousness.[217] Patents are the main policy instrument for encouraging invention of, and innovation in, new products in the U.S. economy. NBE/NCE exclusivity, including data exclusivity, which protects investment in safety and efficacy data from use or reference by others in their abbreviated applications for a period of time, and market exclusivity, which prohibits competitors from marketing for a period of time, recognizes that after invention—typically before clinical trials—a long, risky, and costly R&D process remains in the United States for the development of new

[211] Joseph A. DiMasi & Henry G. Grabowski, *The Cost of Biopharmaceutical R&D: Is Biotech Different?*, 28 MANAGERIAL & DECISION ECON. 469, 475 (2007).

[212] Joseph A. DiMasi et al., *The Price of Innovation: New Estimates of Drug Development Costs*, 22 J. HEALTH ECON. 151, 166 (2003).

[213] DiMasi & Grabowski, *supra* note 211, at 473, 477.

[214] *Id.* at 472, 473 fig.1.

[215] *Id.* at 477.

[216] Henry Grabowski, *Follow-on Biologics: Data Exclusivity and the Balance Between Innovation and Competition*, 7 NAT. REVS. DRUG DISCOVERY 479, 479–87 (2008); *see also* Grabowski et al., *supra* note 186, at 15–16.

[217] Grabowski, *supra* note 216, at 479.

medicines.[218] Effective patent life is often uncertain because significant patent time elapses before FDA approval and because there is uncertainty associated with the resolution of any patent challenges.[219] As a result, NBE/NCE exclusivity provides a more predictable period of protection. It essentially acts as an "insurance policy" in instances where patents are narrow, uncertain, or near expiry.

The protection afforded by NBE exclusivity may be particularly important for innovation incentives in biologics because some have asserted that patents in biologics may be either narrower in scope than those for small-molecule drugs or potentially at greater risk of being successfully challenged or circumvented.[220] Biologics often rely only on formulation, or process, patents.[221] Given that a biosimilar will be slightly different in its composition and/or manufacturing process, a court may determine that it does not infringe the innovator's patent.[222] This has the potential to lead to a seemingly contradictory outcome where a biosimilar may be "different enough" not to infringe the innovator's patents, but, on the other hand, it may be "similar enough" to qualify for approval through an abbreviated approval pathway.[223]

C. Economic Insights Regarding a Reasonable NBE Exclusivity Period

The new law grants twelve years of exclusivity for innovative biologics during which the FDA may not approve biosimilars referencing them, compared to five years of exclusivity for NCEs under the Hatch-Waxman Act during which an abbreviated application referencing them cannot be submitted (plus a stay on generic entry of up to thirty months when there is a patent challenge to allow for resolution of litigation).[224] By contrast, the European Union (EU) has harmonized across member states a ten-year exclusivity period for both

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[218] See generally id. at 479–87.

[219] *Id.* at 479.

[220] See e.g., Bruce S. Manheim Jr. et al., *'Follow-On Biologics': Ensuring Continued Innovation in the Biotechnology Industry*, 25 HEALTH AFFS. 394, 398–99 (2006).

[221] *See id.* at 400.

[222] *Id.* at 398–400.

[223] *Id.* at 401.

[224] *See* BPCIA, Pub. L. No. 111-148, § 7002, 124 Stat. 119, 804 (2010); Drug Price Competition and Patent Term Restoration Act of 1984, Pub. L. No. 98-417, § 101, 98 Stat. 1585; U.S. DEP'T OF HEALTH & HUMAN SERVS, GUIDANCE FOR INDUSTRY: COURT DECISIONS, ANDA APPROVALS, AND 180-DAY EXCLUSIVITY UNDER THE HATCH-WAXMAN AMENDMENTS TO THE FEDERAL FOOD, DRUG, AND COSMETIC ACT (2000), *available at* http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072868.pdf.

NCEs and NBEs.[225] The EU also provided for an additional year of exclusivity for entities with significant new indications that are approved within the first eight years after the original molecule's approval.[226]

The NBE-exclusivity period was the focus of substantial debate by legislators, the 111th Congress considered bills with exclusivity periods ranging from five to fourteen years.[227] To provide economic analysis to support the consideration of NBE-exclusivity periods, Grabowski developed a breakeven financial analysis using historical data on R&D costs and revenues for new biologics and the risk-adjusted market return on investment in the industry.[228] Under this model, a representative portfolio of biologic candidates would be expected to "break even" (or recover the average costs of development, manufacturing, promotion, and the industry's cost of capital) between 12.9 and 16.2 years after launch.[229] This analysis provided support for a NBE-exclusivity period at the longer end of the spectrum considered by legislators. It should be noted that NBE exclusivity only extends overall market exclusivity for the molecule when effective patent lifetimes are either expected to be relatively limited (because of a longer-than-average development path) or vulnerable to patent challenges or "work arounds" (given the potentially narrower scope of many biologic patents). NBE exclusivity, thus, serves as an "insurance policy" to maintain incentives for the development of promising therapeutic candidates in cases where patent protection is inadequate because of these circumstances.

In a 2009 report, the Federal Trade Commission saw little need for a NBE-exclusivity period, claiming that patents alone should be sufficient to encourage biologic innovation in most circumstances.[230] Furthermore, the report argued that even when effective patent life was limited, early-mover competitive advantages should be sufficient to maintain innovation incentives, given relatively few expected biosimilar entrants, physician loyalty to the brand, and the likelihood

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[225] EMA, *Pre and Post-Authorisation Procedural Advice, Human Medicines*, EMEA No. CHMP/225411/2006 (July 2, 2008), *available at* http://www.fdalawyersblog.com/files/EMA%20Regulatory%20and%20Procedural%20Guidance.pdf.

[226] Grabowski, *supra* note 216, at 479.

[227] *Id.*

[228] *Id.* at 479–88.

[229] *Id.* at 486.

[230] *See generally* FED. TRADE COMM'N, EMERGING HEALTH CARE ISSUES: FOLLOW-ON BIOLOGIC DRUG COMPETITION (2009), *available at* http://www.ftc.gov/os/2009/06/P083901biologicsreport.pdf.

that biosimilars will not be interchangeable with the originator's brand, as is the case with generic drugs.[231]

To evaluate these claims, Grabowski, Long, and Mortimer, in a recent paper, extend the original model in a number of directions.[232] First, they examine how substantial brand retention of revenues after biosimilar entry affects breakeven lifetimes for innovators, assuming different market exclusivity periods. Second, using a Monte Carlo simulation approach, they examine the interaction between a NBE-exclusivity period and patent protection under different scenarios to highlight the circumstances where each is important in maintaining innovation incentives.[233] An advantage of this simulation approach is that it allows one to consider variations in several of the model's core parameters simultaneously, such as the contribution margin and cost of capital as well as the innovator's share and price.

The results of this new analysis are generally consistent with Congress's determination that a NBE-exclusivity period that includes twelve years during which FDA may not approve a biosimilar to the innovative reference biologic, appropriately balances objectives for potential cost savings from biosimilar-price competition with long-run incentives for investment in innovative biologics.[234] They find that when biologic patents are relatively less certain and expected to have shorter effective lifetimes, a NBE-exclusivity period including twelve years greatly enhances investment incentives.[235] On the other hand, if biologic patents provide relatively strong protection with significant effective patent life remaining at approval, patents alone will be sufficient to maintain investment incentives in most cases.[236] In those instances, however, the NBE-exclusivity period has only a minimal effect on the timing of potential biosimilar entry and consequently, on health care costs.[237]

One interesting question for future research is the impact disparate exclusivity periods for NCEs and NBEs will have on innovation incentives. As noted, biologic introductions and sales revenues have been growing rapidly over the last decade, and biologics have an in-

[231] *Id.* at iii–vi.

[232] Grabowski et al., *supra* note 186, at 15.

[233] In their paper, Grabowski, Long, and Mortimer use the term "data-exclusivity period" to represent the same concept as the term "NBE-exclusivity period" used in this Article.

[234] *Id.* at 16.

[235] *Id.*

[236] *Id.*

[237] *Id.*

creasing presence in R&D pipelines. It remains an open question whether the longer period for NBE-exclusivity compared to NCE exclusivity will further tilt R&D incentives toward large molecules and whether Congress should revisit the NCE-exclusivity period and consider harmonizing these periods, as is currently the case in the EU.

D. The Resolution of Patent Challenges

One of the most important developments under the Hatch-Waxman generic drug framework became the importance of the paragraph IV 180-day exclusivity provisions, under which generic manufacturers could challenge the legitimacy of branded manufacturers' patents or claim that generic entry would not infringe them.[238] Over time, as the law and economic benefits to generics were established, the likelihood of paragraph IV challenges increased and most drugs became subject to challenges.[239] In designing the patent disclosure provisions of the new law for biologics, Congress attempted to reduce the uncertainty and economic costs associated with litigation, but it remains to be seen what the eventual effects may be and whether this objective will be met.

Under the new law, an abbreviated application for a biosimilar can be filed after four years.[240] The filing of an application triggers a series of potentially complex private information exchanges among the biosimilar applicant, reference product sponsor, and patent owners.[241] These exchanges of information are followed by negotiations and a process for instituting litigation on the core patents when necessary. Congress has crafted these patent provisions while eliminating the incentive for litigation associated with a 180-day exclusivity period for the first filer in a successful challenge, as well as the automatic thirty-month stay on entry in Hatch-Waxman.[242] By instituting this potentially very complex structured process for biologics, the hope is that patent disputes will be resolved prior to the expiration of the twelve-year NBE-exclusivity period so that biosimilars can enter in a timely fashion. Whether these rules will achieve their intended effects remains unknown. Some companies have indicated that they may find it more attractive to develop evidence to support a full BLA,

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[238] Drug Price Competition and Patent Term Restoration Act of 1984, Pub. L. No. 98-417, § 101, 98 Stat. 1585, 1586.

[239] *See* Berndt et al., *supra* note 154, at 791.

[240] 42 U.S.C. § 262(k)(7)(B) (Supp. IV 2010).

[241] § 262(l).

[242] Drug Price Competition and Patent Term Restoration Act of 1984, Pub. L. No. 98-417, § 101, 98 Stat. 1585.

rather than an abbreviated biosimilar application,[243] which would avoid the information disclosures about manufacturing process and formulations under the patent challenge provisions.[244] In some cases, pursuing a full BLA instead of an abbreviated application would also allow companies to come to market in advance of the required twelve-year NBE-exclusivity period for the reference product.[245]

VII. SUMMARY AND CONCLUSIONS

The BPCIA established an abbreviated pathway for biosimilars that is expected to lead to a number of competitors for several leading biologic products over the next decade. In contrast to generic competition, there are likely to be fewer entrants into the market for particular molecules initially due to higher development, approval, and production costs, up to $150 million for very complex biologics,[246] compared to only a few million for generic drugs.[247] In addition, many biosimilars are likely to be therapeutic alternatives rather than therapeutic equivalents (i.e., they will not be rated as interchangeable by the FDA).[248] The penetration of the market will also be tempered by the reluctance of many physicians and patients to switch to biosimilars until experience in clinical settings has been established. This is likely to be particularly true for existing patients that are responding well to maintenance therapy on the reference product as well as for patients with a limited therapeutic window for successful response (e.g., certain cancer patients).[249] Therapeutic areas with serious clinical and economic consequences associated with loss

[243] *See, e.g., Sandoz Will Steer Clear of U.S. Biosimilars Pathway, Use Other Applications*, PINK SHEET, May 3, 2010, *available at* http://sis.windhover.com/buy/abstract.php?id=00720180006&utm_source=toc&utm_medium=website.

[244] Michael McCaughan, *Follow-On Biologics: Is There a Pathway?*, IN VIVO BLOG (May 20, 2010, 5:30 PM), http://invivoblog.blogspot.com/2010/05/follow-on-biologics-is-there-pathway.html.

[245] *Id.*

[246] Ludwig Burger, *Battle over Biosimilar Drugs is Only for the Brave*, REUTERS (July 2, 2010), http://uk.reuters.com/article/idUKLNE66102R20100702?rpc=401&feedType=RSS&feedName=stocksNews&rpc=401.

[247] *See* Reiffen & Ward, *supra* note 64, at 6.

[248] See, for example, the transcripts from the FDA two-day public hearing on "Approval Pathway for Biosimilar and Interchangeable Biologic Products Public Meeting." FOOD & DRUG ADMIN. HEARING, *supra* note 30.

[249] *See supra* Part III.B. In some therapeutic areas (e.g., immunology, oncology) physicians are unlikely to switch a patient who is responding well to a particular therapy. Similarly, the physician may have greater confidence initiating a new patient on therapies with which they have substantial experience. In the case of biosimilars it will take some time for physicians to gain experience with those particular therapies and consequently impact their choice of therapy.

of clinical effectiveness and low patient turnover are likely to experience lower rates of biosimilar penetration compared to those therapeutic areas with higher percentages of new patients—particularly, therapeutically vulnerable patients may be less likely to be prescribed biosimilars.[250] One pivotal factor affecting the degree of entry and price competition will be the FDA requirements to receive approval as a biosimilar. Based on preliminary statements from the FDA, regulatory requirements are likely to proceed on a case-by-case basis that is science-driven and subject to change over time as the science and technology evolves.[251] Since the biosimilar industry is global and there are already biosimilars present in Europe for some leading biologic products, the extent to which foreign trials and experience are accepted by the FDA, including when the reference products differ from those in the United States, could also be an important determinant of how many biosimilars enter the U.S. market and the corresponding extent of biosimilar competition.

Another pivotal factor affecting biosimilar penetration involves the reimbursement procedures and financial incentives employed by both government and private payers to encourage biosimilar utilization.[252] In the case of self-injectable drugs typically managed as part of the pharmacy benefit, more cost-sensitive Medicare Part D and commercial plans are likely to employ a number of existing techniques to encourage biosimilars, including tiered formularies, prior authorization, and step-therapy requirements. In the case of biologics dispensed in physician clinics and hospitals, as infused or physician-supervised injected therapies, and typically managed as part of the medical benefit, ASP-based reimbursement algorithms under Medicare Part B and commercial plans will influence physician adoption of lower cost biosimilars.[253] The statutory provision setting the six

[250] Physicians may be all the more hesitant to experiment with a biosimilar rather than use a branded biologic, with which they have a great deal of experience, if even small differences between the brand and the biosimilar could lead to important impacts on patient health. *See supra* Part III.B.

[251] *See supra* text accompanying note 42.

[252] Reimbursement procedures that increase the cost of the branded biologic to the patient (e.g., coinsurance payments or copayments), constrain physician prescribing (e.g., step therapy, prior-authorization requirements), or impact the financial incentives for physicians to select one therapy over another (e.g., limitations and regulations on physicians ability to buy-and-bill infused agents) can all influence the choice of therapy and the resulting biosimilar penetration. *See supra* Part III.C.

[253] Physicians may earn a margin on physician administered drugs through "buy and bill" reimbursement policies and procedures. To the extent that reimbursement policies provide financial incentives for the physician to use either the biosimilar or

percent of Medicare Part B reimbursement at an equivalent amount for both the biosimilar and the reference product will help to mitigate provider disincentives for biosimilar adoption. In addition, movement away from historical "buy and bill" physician reimbursement arrangements, including requirements that certain drugs be managed and delivered through specialty pharmacy providers, is also likely to have an important effect on the utilization of biosimilars. Coverage decisions and requirements at the regional level by Medicare contractors also could be important considerations.

The new law is designed to balance the objectives of achieving cost savings in the current period, and preserving incentives for continued innovation in the future. A number of leading biologic products with significant sales in the United States are expected to experience some patent expiration in the next decade, so cost savings could grow to meaningful values depending on how other factors such as regulation, reimbursement, and intellectual property litigation play out over this period.[254]

In terms of maintaining incentives for future innovation, the law provides for a NBE-exclusivity period in which a biosimilar can be approved utilizing an abbreviated pathway—sooner than twelve years following approval of the innovator product.[255] NBE exclusivity provides an important "insurance policy" to the patent system and could be important in the case of biologics where patents may prove to be narrower in scope than those for new chemical entities or easier to circumvent. Analysis of a portfolio of representative biological products indicates that twelve years or more of market exclusivity from patents or NBE exclusivity is generally necessary to achieve breakeven returns that provide a risk-adjusted return on capital and R&D investments.

A number of important issues remain for future research, including how the new law will affect industry structure and incentives for undertaking R&D for biologics versus new chemical entities. As was the case with the Hatch-Waxman Act, change may be gradual at first, but over time the new law could lead to profound changes in the economics and organization of the biopharmaceutical industry.

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the brand, this may impact the physician's choice of therapy and the resulting rate of biosimilar penetration. *See supra* text accompanying notes 101–114.

[254] *See supra* tbl.3 (illustrating biologics with combined 2009 U.S. revenues exceeding $11.5 billion for which some key patents may expire by the end of 2013, including Enbrel, Neupogen, Epogen/Procrit, Rebif, and Avonex).

[255] *See supra* text accompanying note 224.

EXHIBIT 81

FDA's Overview of the Regulatory Guidance for the Development and Approval of Biosimilar Products in the US

Leah Christl, Ph.D.
Associate Director for Therapeutic Biologics
OND Therapeutic Biologics and Biosimilars Team/CDER/FDA

Overview of Presentation

- Overview
  - Background
  - Definitions
  - Approval Pathway for Biosimilars – General Requirements

- Development of Biosimilars
  - FDA Guidance Documents
  - Approach to Development
  - Specific Development Concepts

Overview

Background

- The **Biologics Price Competition and Innovation Act of 2009 (BPCI Act)** was passed as part of health reform (Affordable Care Act) that President Obama signed into law on March 23, 2010.

- BPCI Act creates an ***abbreviated licensure pathway for biological products shown to be biosimilar to or interchangeable with*** an FDA-licensed reference product.

What is an Abbreviated Licensure Pathway for Biological Products?

- A biological product that is demonstrated to be "***highly similar***" to an FDA-licensed biological product (the reference product) may rely for licensure on, among other things, publicly-available information regarding FDA's previous determination that the reference product is safe, pure and potent.

- This licensure pathway permits a biosimilar biological product to be licensed under 351(k) of the Public Health Service Act (PHS Act) based on **less than a full complement of product-specific preclinical and clinical data** → **abbreviated** licensure pathway**.**

Definition: Biosimilarity

Biosimilar or **Biosimilarity** means:

- that the biological product is **highly similar** to the reference product notwithstanding minor differences in clinically inactive components; and

- there are **no clinically meaningful differences** between the biological product and the reference product in terms of the safety, purity, and potency of the product.

Definition: Reference Product

Reference Product means:

- the **single biological product, licensed under section 351(a) of the PHS Act,** against which a biological product is evaluated in an application submitted under section 351(k) of the PHS Act.

Note: A biological product, in a 351(k) application, may not be evaluated against more than 1 reference product.

Definition: Interchangeability

Interchangeable or **Interchangeability** means**:**

- the biological product is **biosimilar** to the reference product;
- it can be expected to produce the **same clinical result** as the reference product **in any given patient**; and
- for a product that is administered more than once to an individual, the risk in terms of **safety or diminished efficacy of alternating or switching** between use of the product and its reference product is not greater than the risk of using the reference product without such alternation or switch.

Note: The interchangeable product **may be substituted** for the reference product without the intervention of the health care provider who prescribed the reference product.

General Requirements

A 351(k) application must include information demonstrating that the biological product:

- Is **biosimilar** to a reference product;
- Utilizes the **same mechanism(s) of action** for the proposed condition(s) of use -- but only to the extent the mechanism(s) are known for the reference product;
- **Condition(s) of use** proposed in labeling **have been previously approved** for the reference product;
- Has the **same route of administration**, **dosage form**, and **strength** as the reference product; and
- Is manufactured, processed, packed, or held in a facility that **meets standards** designed to assure that the biological product continues to be safe, pure, and potent.

General Requirements: 351(k) Application

The PHS Act requires that a 351(k) application include, among other things, **information demonstrating biosimilarity based upon data derived from**:

- **Analytical studies** demonstrating that the biological product is "highly similar" to the reference product notwithstanding minor differences in clinically inactive components;
- **Animal studies** (including the assessment of toxicity); and
- A **clinical study or studies** (including the assessment of immunogenicity and pharmacokinetics (PK) or pharmacodynamics (PD)) that are sufficient to demonstrate safety, purity, and potency in 1 or more appropriate conditions of use for which the reference product is licensed and for which licensure is sought for the biosimilar product.

FDA may determine, in its discretion, that an element described above is unnecessary in a 351(k) application.

Standard for Licensure

- FDA shall license the biological product under section 351(k) of the PHS Act if—
  - FDA determines that the **information submitted in the application (or supplement) is sufficient to show** that the biological product—
    - (i) is **biosimilar** to the reference product; or
    - (ii) meets the standards described in 351(k)(4), and therefore is **interchangeable** with the reference product; and
  - Applicant (or other appropriate person) consents to inspection of the facility, in accordance with section 351(c).

- Note: BPCI Act does not require that FDA promulgate guidance or regulation before reviewing or approving a 351(k) application.

Non-US-Licensed Comparator Products

- The PHS Act defines the "reference product" for a 351(k) application as the "single biological product licensed under section 351(a) against which a biological product is evaluated."
- Data from animal studies and certain clinical studies comparing a proposed biosimilar product with a non-US-licensed product may be used to support a demonstration of biosimilarity to a US-licensed reference product.
- Sponsor should provide adequate data or information to scientifically justify the relevance of these comparative data to an assessment of biosimilarity and to establish an acceptable bridge to the U.S.-licensed reference product.

Support for Use of Non-US-Licensed Comparator

- Type of bridging data needed would include:
  - Direct physico-chemical comparison of all 3 products (proposed biosimilar to US-licensed reference product; proposed biosimilar to non-US-licensed comparator product; US-licensed reference product to non-US-licensed comparator product)
  - Likely 3-way bridging clinical PK and/or PD study

- All three pair-wise comparisons should meet the pre-specified acceptance criteria for analytical and PK and/or PD similarity.

Overview of FDA's Approach to the Development of Biosimilars - Specific Development Concepts

FDA Biosimilars Draft Guidances

1. Scientific Considerations in Demonstrating Biosimilarity to a Reference Product (2012)
2. Quality Considerations in Demonstrating Biosimilarity to a Reference Protein Product (2012)
3. Biosimilars: Questions and Answers Regarding Implementation of the Biologics Price Competition and Innovation Act of 2009 (2012)
4. Formal Meetings Between the FDA and Biosimilar Biological Product Sponsors or Applicants (2013)
5. Clinical Pharmacology Data to Support a Demonstration of Biosimilarity to a Reference Product (2014)

FDA Guidance

- Focus on therapeutic protein products
- Discusses general scientific principles
- Outlines a stepwise approach to generating data and the evaluation of residual uncertainty at each step
- Introduces the *totality-of-the-evidence* approach

Key Development Concepts

Goals of "Stand-alone" and Biosimilar Development are Different

- The goal of "stand-alone" development is to demonstrate that the proposed product is safe and efficacious
- Drug development starts with preclinical research, moves to Phase 1, 2 and culminates in Phase 3 "pivotal" trials to show safety and efficacy

- The goal is to **demonstrate biosimilarity** between the proposed product and a reference product
- The goal is not to independently establish safety and effectiveness of the proposed product

What does this difference mean from a development perspective?

Stepwise Evidence Development

- FDA has outlined a **stepwise approach** to generate data in support of a demonstration of biosimilarity
  - Evaluation of residual uncertainty at each step
- *Totality-of-the-evidence* approach in evaluating biosimilarity
  - There is no one "pivotal" study that demonstrates biosimilarity
- Apply a step-wise approach to data generation and the evaluation of residual uncertainty
- When considering designing a study, **evaluate** and **understand** the question being answered
  - What is the residual uncertainty?
  - What differences have been observed and how best to evaluate the potential impact?
  - What will the data tell you? Will it answer the question?

Totality of the Evidence

- No "one size fits all" assessment

- FDA scientists will evaluate the applicant's integration of various types of information to provide an overall assessment that a biological product is biosimilar to a US-licensed reference product.

Analytical Similarity Data - The Foundation of a Biosimilar Development Program

- Extensive **structural and functional characterization** is necessary
- **Understand** the molecule and function
- Identify **critical quality attributes** and clinically active components
- **Understanding the relationship** between quality attributes and the clinical safety & efficacy profile aids ability to determine **residual uncertainty** about biosimilarity and to predict expected "clinical similarity" from the quality data.

Generating Analytical Similarity Data

- Characterize reference product variability and product quality characteristics
- Characterize proposed biosimilar product quality characteristics
- Identify and evaluate impact of differences
  - The potential effect of the **differences** on safety, purity, and potency should be addressed and supported by appropriate data
  - Must be highly similar **and** no clinically meaningful differences

Assessing Analytical Similarity

- Important factors for consideration in assessing analytical similarity, including:
  - Expression System
  - Manufacturing Process
  - Assessment of Physicochemical Properties
  - Functional Activities
  - Receptor Binding and Immunochemical Properties
  - Impurities
  - Reference Product and Reference Standards
  - Finished Drug Product
  - Stability

Choice of Analytics

- It is expected that appropriate analytical test methods will be selected based on:
  - the nature of the protein being characterized,
  - knowledge regarding the structure, and
  - heterogeneity of the reference product and proposed biosimilar product including
    - known and potential impurities, and
    - characteristics that are critical to product performance

Animal Data

- Animal toxicity data are useful when uncertainties remain about the safety of the proposed product prior to initiating clinical studies.

- The scope and extent of animal toxicity studies will depend on publicly available information and/or data submitted in the biosimilar application regarding the reference product and the proposed biosimilar product, and the extent of known similarities or differences between the two.

- A comparison of PK/PD in an animal model may be useful.

Clinical Studies

- The nature and scope of clinical studies will depend on the extent of residual uncertainty about the biosimilarity of the two products **after** conducting extensive structural and functional characterization and, where relevant, animal studies.

Type of Clinical Data

- As a scientific matter, FDA expects an adequate clinical PK, and PD if relevant, comparison between the proposed biosimilar product and the reference product.

- As a scientific matter, at least 1 clinical study that includes a comparison of the immunogenicity of the proposed and reference product generally will be expected.

- As a scientific matter, a comparative clinical study will be necessary to support a demonstration of biosimilarity if there are **residual uncertainties** about whether there are clinically meaningful differences between the proposed and reference products based on structural and functional characterization, animal testing, human PK and PD data, and clinical immunogenicity assessment.

Comparative Human PK and PD Data

- Comparative human PK (and PD) data :
  - Demonstrate PK (and PD) **similarity**
  - Assess clinically meaningful differences between the proposed biosimilar and the reference product
- PK and/or PD is generally considered the most sensitive clinical study/assay in which to assess for differences, should they exist
- Support a demonstration of biosimilarity with the assumption that similar exposure (and pharmacodynamic response) provides similar efficacy and safety (i.e., an exposure-response relationship exists)
- Clinical PK data generally will be expected; PD data desirable (case by case consideration)

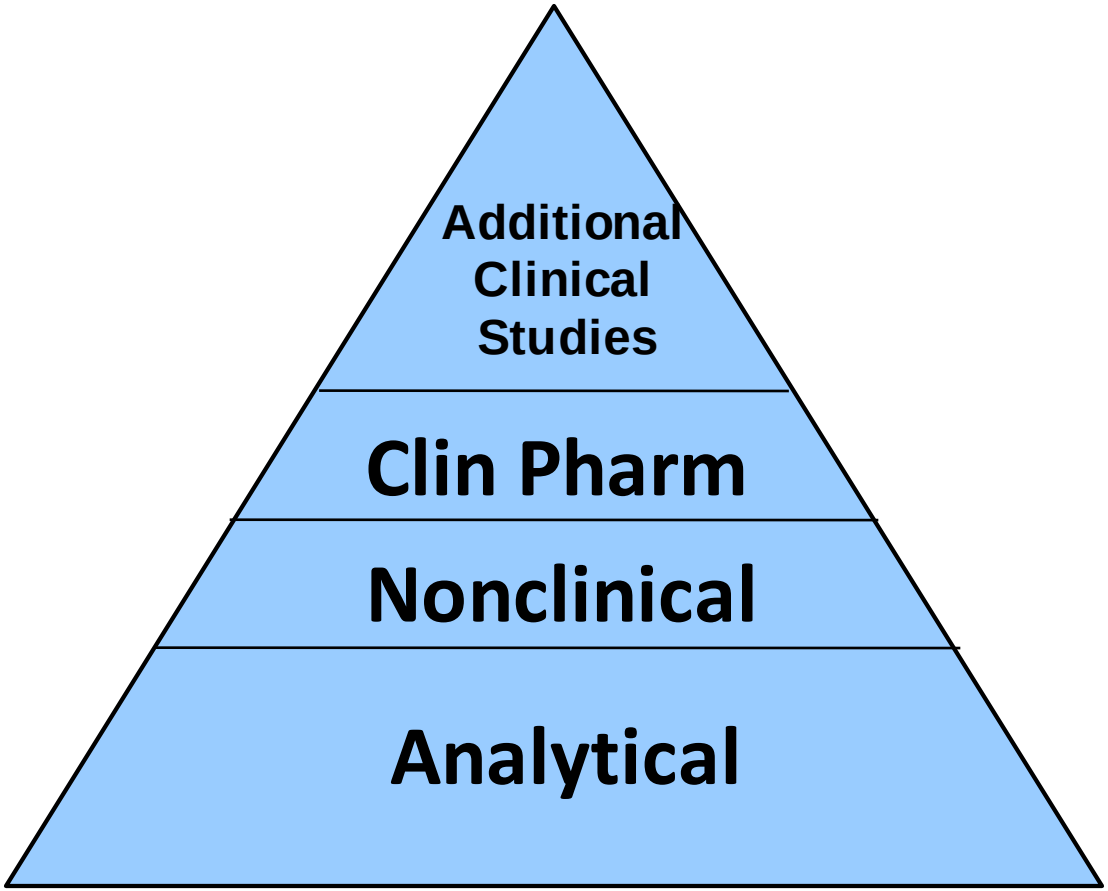
Human PK and PD Study Considerations

- **Study Design**
  - Study population: an adequately sensitive population to detect any differences, should they exist
  - PD endpoint: Reflect the biological effect(s) of the drug, they may (or may not) be on mechanistic path of MOA or disease process
  - Route of administration: all routes vs. a single route
- **Data analysis plan**
  - Acceptance range: 80-125% (90% CI for PK and PD), scientifically justify use of other ranges
  - Choice of primary endpoints (e.g., PK—AUC, C_{max}; PD—AUEC)
- **Others**
  - Incidence of immunogenicity

Comparative Clinical Study Considerations

- A comparative clinical study for a biosimilar development program should be designed to investigate whether there are clinically meaningful differences between the proposed product and the reference product.
- Consider the adequacy of population, sample size and study duration to detect differences, should they exist.
- The goal of the study is to support a demonstration of no clinically meaningful differences.
  - Typically, an equivalence design with symmetric inferiority and superiority margins would be used, but other designs may be justified depending on product-specific and program-specific considerations.

Highly Similar Analytical and PK/PD Data Assumes Lower Risk of Clinical Differences



Totality of the evidence to demonstrate biosimilarity

Extrapolation

- The potential exists for a biosimilar product to be approved for one or more conditions of use for which the US-licensed reference product is licensed based on extrapolation of data intended to demonstrate biosimilarity in one condition of use.

- Sufficient scientific justification for extrapolating data is necessary.

Extrapolation Considerations

- FDA guidance outlines factors/issues that should be considered when providing scientific justification for extrapolation including, for example*,
  - The MOA(s) in each condition of use for which licensure is sought
  - The PK and bio-distribution of the product in different patient populations
  - The immunogenicity of the product in different patient populations
  - Differences in expected toxicities in each condition of use and patient population
- <u>Differences between conditions of use do not necessarily preclude extrapolation</u>

*This list is a subset of the issues outlined in the FDA guidance document

Summary of Key Concepts

- Demonstrating biosimilarity is different from "stand-alone" product development
  - A "stand-alone"-like program will **not** demonstrate biosimilarity
  - The approach and the development program should and will be different based on the intended outcome to demonstrate biosimilarity
- **Analytical similarity data is the foundation** of biosimilar development
  - **Understanding the relationship** between quality attributes and the clinical safety & efficacy profile aids ability to determine **residual uncertainty** about biosimilarity and to predict expected "clinical similarity" from the quality data.

Summary of Key Concepts

- The nature and scope of clinical studies will depend on the extent of residual uncertainty about the biosimilarity of the two products **after** conducting an extensive analytical similarity assessment.
- Comparative clinical study(ies) will be necessary to support a demonstration of biosimilarity if there are **residual uncertainties** about whether there are clinically meaningful differences between the proposed biosimilar and reference product
- Scientific justification must be provided to support extrapolation to other conditions of use
- The content of a biosimilar development program is based on stepwise development and approvability is based on the totality of the evidence submitted by the sponsor

Thank you for your attention.

EXHIBIT 82

Biosimilars: Considerations for Payers

James Smeeding, RPh, MBA; Daniel C. Malone, RPh, PhD; Monica Ramchandani, PhD; Bradley Stolshek, PharmD; Larry Green, PharmD; and Philip Schneider, MS

Keywords: Biosimilars, pharmacoeconomics, affordability and access, managed care, payers, benefit management

INTRODUCTION

Biosimilars are similar versions of originator biologics. Biologics are complex molecules that are manufactured using living cells and used in the treatment of several chronic inflammatory diseases and cancer. Access to biologics is limited, and the availability of biosimilars has the potential to provide additional biologic drug options and to decrease the overall cost burden to the health care system.[1,2] The European Union (EU) pioneered the establishment of a regulatory pathway for the development and approval of biosimilars, with the first biosimilar approved in 2006. To create a regulatory pathway for biosimilars in the U.S., Congress passed the Biologics Price Competition and Innovation Act of 2009 (BPCIA), authorizing the Food and Drug Administration (FDA) to implement an abbreviated regulatory pathway (i.e., section 351(k) under the Public Health Service Act) for the development and approval of biosimilars.[1] A biosimilar is defined in the statute as a biologic that (1) is "highly similar to the reference product notwithstanding minor differences in clinically inactive components" and (2) has "no clinically meaningful differences" from the reference product in terms of safety, purity, or potency.[1]

Although biosimilars have been available in the EU for more than a decade, the initial market uptake of the products was slow.[3-5] Many reasons for this have been cited, including a lack of provider confidence in these similar biologics, potential minor differences from the reference products, uncertainty about substitution, certain financial incentives favoring the use of originator biologics (e.g., higher reimbursement limits for reference biologics), and a lack of patient awareness and education.[3,5-7] Although uptake has been slow, more than 40 biosimilars have been authorized for use in the EU, with three having been withdrawn.[8,9] As of October 10, 2018, 12 biosimilars have been approved in the U.S.: filgrastim-sndz (ZARXIO®, Sandoz Inc.), infliximab-dyyb (INFLECTRA®, Hospira, Celltrion, Inc.), etanercept-szzs (Erelzi™, Sandoz Inc.), adalimumab-atto (AMJEVITA™, Amgen Inc.), infliximab-abda (RENFLEXIS™, Merck Sharp & Dohme Corp., manufactured by Samsung Bioepis Co., Ltd.), adalimumab-adbm (CYLTEZO®, Boehringer Ingelheim International GmbH), bevacizumab-awwb (MVASI™, Amgen Inc.), trastuzumab-dkst (Ogivri™, Mylan GmbH), infliximab-qbtx (IXIFI™, Pfizer Inc), epoetin alfa-epbx (RETACRIT®, Hospira), pegfilgrastim-jmdb (Fulphila™, Mylan GmbH), and filgrastim-aafi (NIVESTYM™, Pfizer Inc., manufactured by Hospira, Inc.) (see Table 1),[10-21] although not all of them are currently commercially available. More U.S. approvals are expected in the near future.

This review discusses key considerations about biosimilars that are relevant to different U.S. payers, including private payers (e.g., pharmacy benefit managers [PBMs], private insurers) and Medicare perspectives. We explore factors promoting the uptake of biosimilars, cost considerations, a broader perspective on value beyond price reduction, and the current U.S. experience.

UPTAKE OF BIOSIMILARS

Although acquisition-cost considerations are likely the primary factor driving the uptake of biosimilars, additional considerations are also important in deciding to select a biosimilar over the reference biologic or another biosimilar of the same reference biologic (Table 2). For all stakeholders, maintaining overall quality, safety, and clinical efficacy is a major consideration. Additional considerations for physicians, patients, and payers include manufacturer reliability (e.g., the dependability of supply without disruptions), reimbursement rates set by Medicare or commercial payers, and support services for health care professionals and patients. Many patients rely on assurance from their providers about the efficacy and safety of their medicines, and also look for ways to reduce their out-of-pocket expenses. When considering the selection of a biosimilar, PBMs evaluate the contracts, rebates, and supply timelines associated with biosimilar use. It is also important to consider the impact of patient out-of-pocket expenses on adherence, as this can affect clinical outcomes. Understanding how these factors contribute to the use of biosimilars is important, and we seek to address these issues for all stakeholders.

TOTALITY OF EVIDENCE FOR BIOSIMILARS

To appreciate the challenges and potential of biosimilars, it helps to understand the complexities of their development, manufacturing, and regulatory approval. The regulatory review process for biosimilars is based on the totality of evidence generated to support the claim of biosimilarity.[22,23] The successful biosimilar development program is designed to minimize potential differences between the proposed

Mr. Smeeding is at JeSTARx Group in Dallas, Texas; Dr. Malone is at the College of Pharmacy at the University of Arizona in Tucson; Drs. Ramchandani, Stolshek, and Green are at Amgen Inc. in Thousand Oaks, California; and Mr. Schneider is currently at MediHealthInsight in Scottsdale, Arizona, but was based at the Phoenix Biomedical Campus, University of Arizona when this work was completed.

Disclosure: Mr. Smeeding reports no competing interests in regard to this article. Dr. Malone has received remuneration for consulting services unrelated to this paper and topic from Amgen Inc., AstraZeneca, Astellas, GlaxoSmithKline, Mallinckrodt, and Sanofi. Mr. Schneider is advisory board chair for the Alliance for Safe Biologic Medicines. Drs. Ramchandani, Stolshek, and Green are employees of Amgen Inc. and own Amgen stock. Editorial support was provided by Miranda Tradewell, Meghan Johnson, and James Balwit from Complete Healthcare Communications, LLC (North Wales, PA), a CHC Group company, whose work was funded by Amgen Inc. under the guidance of Dr. Ramchandani (Amgen Inc.).

Table 1 Biosimilars Approved in the United States[14-16,18-21,87-91]

Nonproprietary Name	Trade Name	Indication
Filgrastim-sndz	ZARXIO®	• Decrease the incidence of infection, as manifested by febrile neutropenia, in patients receiving myelosuppressive anti-cancer drugs • Reduce the time to neutrophil recovery and the duration of fever following chemotherapy • Reduce the duration of neutropenia and neutropenia-related clinical sequelae in patients with nonmyeloid malignancies undergoing myeloablative chemotherapy followed by bone marrow transplantation • Mobilize autologous hematopoietic progenitor cells into the peripheral blood for collection • Reduce the incidence and duration of sequelae of severe neutropenia in symptomatic patients with congenital neutropenia, cyclic neutropenia, or idiopathic neutropenia
Infliximab-dyyb	INFLECTRA®	• Crohn's disease • Pediatric Crohn's disease • Ulcerative colitis • Rheumatoid arthritis • Ankylosing spondylitis • Psoriatic arthritis • Plaque psoriasis
Etanercept-szzs	Erelzi™	• Rheumatoid arthritis • Polyarticular juvenile idiopathic arthritis • Ankylosing spondylitis
Adalimumab-atto	AMJEVITA™	• Rheumatoid arthritis • Juvenile idiopathic arthritis • Psoriatic arthritis • Ankylosing spondylitis • Adult Crohn's disease • Ulcerative colitis • Plaque psoriasis
Infliximab-abda	RENFLEXIS™	• Crohn's disease • Pediatric Crohn's disease • Ulcerative colitis • Rheumatoid arthritis • Ankylosing spondylitis • Psoriatic arthritis • Plaque psoriasis
Adalimumab-adbm	CYLTEZO®	• Rheumatoid arthritis • Juvenile idiopathic arthritis • Psoriatic arthritis • Ankylosing spondylitis • Adult Crohn's disease • Ulcerative colitis • Plaque psoriasis
Bevacizumab-awwb	MVASI™	• Metastatic colorectal cancer • Nonsquamous non–small-cell lung cancer • Glioblastoma • Metastatic renal cell carcinoma • Cervical cancer
Trastuzumab-dkst	Ogivri™	• HER2-overexpressing breast cancer • HER2-overexpressing metastatic gastric or gastroesophageal junction adenocarcinoma
Infliximab-qbtx	IXIFI™	• Crohn's disease • Pediatric Crohn's disease • Ulcerative colitis • Rheumatoid arthritis • Ankylosing spondylitis • Psoriatic arthritis • Plaque psoriasis

table continues

Table 1 Biosimilars Approved in the United States[14-16,18-21,87-91] (continued)

Nonproprietary Name	Trade Name	Indication
Epoetin alfa-epbx	RETACRIT®	• Anemia due to chronic kidney disease • Anemia due to zidovudine in patients with HIV-infection • Anemia due to the effects of concomitant myelosuppressive chemotherapy • Reduction of allogeneic red blood cell transfusions in patients undergoing elective, noncardiac, nonvascular surgery
Pegfilgrastim-jmdb	Fulphila™	• Decrease the incidence of infection, as manifested by febrile neutropenia, in patients receiving myelosuppressive anti-cancer drugs
Filgrastim-aafi	NIVESTYM™	• Decrease the incidence of infection, as manifested by febrile neutropenia, in patients receiving myelosuppressive anti-cancer drugs • Reduce the time to neutrophil recovery and the duration of fever following chemotherapy • Reduce the duration of neutropenia and neutropenia-related clinical sequelae in patients with nonmyeloid malignancies undergoing myeloablative chemotherapy followed by bone marrow transplantation • Mobilize autologous hematopoietic progenitor cells into the peripheral blood for collection • Reduce the incidence and duration of sequelae of severe neutropenia in symptomatic patients with congenital neutropenia, cyclic neutropenia, or idiopathic neutropenia

biosimilar and its reference product, and to establish robust manufacturing processes that can consistently and reliably produce a biosimilar product that meets preset specifications.

Producing a biosimilar is more complicated than replicating a traditional, small-molecule generic drug manufactured via chemical synthesis (i.e., a medication created to be the same as a marketed brand-name drug in dosage, safety, strength, administration, quality, and intended use). Manufacturing biosimilars requires an in-depth understanding of the reference product's physiochemical, biological, and clinical attributes, establishing a target profile, and evaluating potential differences in analytical, functional, and clinical safety and efficacy. This process is accomplished via side-by-side comparison of the proposed biosimilar with the reference product, using an iterative approach (e.g., quality by design) that "begins with predefined objectives and emphasizes product and process understanding and process control, based on sound science and quality risk management."[24] Manufacturers initially develop a quality target-product profile, which is a prospective summary of quality characteristics that ideally will be achieved, to ensure quality and account for the safety and efficacy of the product.[24]

In the first step toward evaluating biosimilarity, comparative analytical and functional *in vitro* assays are used to assess the above-mentioned quality objectives and to compare the proposed biosimilar with its reference product regarding structure and functional activity.[22,23] This serves as the foundation of the stepwise process for establishing biosimilarity. Manufacturing a product with the knowledge and understanding of the amino acid sequence of the reference product does not guarantee that the structural and functional properties of that product will be similar to the reference product. A broad array of physiochemical and functional properties also must be characterized and compared (e.g., primary, secondary, tertiary, and quaternary structures; posttranslational modifications such as glycosylation; and binding and biological activity such as antibody-dependent cellular cytotoxicity).

After assessment for analytical and functional similarity has been completed, preclinical studies specific to the proposed biosimilar are considered. These analyses may include but are not limited to pharmacokinetic and pharmacodynamic assays, as well as toxicology and interspecies cross-reactivity studies.[22,23] These assessments help alleviate some of the uncertainty concerning the proposed biosimilar and may potentially minimize the extent of in-human testing needed.

The ultimate development goal is to demonstrate that a proposed biosimilar is similar to the reference product based on analytical assessments, and that it does not have clinically meaningful differences from the reference molecule, which is achieved by conducting comparative clinical studies. The extent of the clinical development plan is dependent on the results of the analytical and preclinical assessments, including physiochemical, functional, pharmacologic, pharmacokinetic, and pharmacodynamic studies. Finally, at least one comparative clinical trial designed to address residual uncertainty regarding the similarity of safety, efficacy, and immunogenicity in a representative indication is recommended.[23] The goal of the biosimilar clinical program is to demonstrate that the proposed biosimilar is not different from the reference product with respect to clinical performance. To this end, clinical study designs select endpoints that may differ from those selected for pivotal clinical trials for new biologics; comparative biosimilar clinical studies are conducted in a representative population using sensitive endpoints (i.e., clinically relevant, readily assessable, and in which the size of the treatment effect is large enough to detect differences between similar treatments), such that the overall treatment effect between two very similar products may be identified. Clinical trials designed to assess biosimilarity aim to help resolve whether any residual, clinically meaningful differences might exist between a proposed biosimilar and its reference product (Figure 1).[22,23,25,26]

A unique component of the biosimilar development program is the concept of extrapolation.[22,23] This supports the use of an approved biosimilar product in indications that the reference product is approved for but in which the biosimilar product was not evaluated clinically. The justification for extrapolation is expected to address whether the same mechanism of action

Table 2 Key Considerations for Evaluating Biosimilar Uptake

Key Considerations	Supporting Points
Clinical efficacy	• Patient outcomes • Clinically meaningful differences between products • Drug exposure
Toxicity and immunogenicity	• Toxicology • Interspecies cross-reactivity • Occurrence of adverse events
Supplier manufacturing capability	• Size of operation • Supply chain security • Counterfeit protection
Supplier reliability	• Experience • History of on-time production and delivery • Logistics • Positive history with respect to recalls
Cost savings to payer	• Price negotiations • Government intervention • Accountable Care Organization (ACO) incentives • Medicare Part B reimbursement • Rebates • Deductibles • Copays
Dosage format for target population	• Medication delivery system is patient-friendly • Different dosage strengths are easily distinguishable
Patient adherence	• Willingness of patients to take medication routinely • Ease of medication administration • Side effects are manageable to allow repeat dosing

applies in each indication and in the similarity of the products' pharmacokinetic, biodistribution, and immunogenicity profiles in different patient populations. It is also expected to identify potential toxicities for each indication or patient population and any other factors that may affect the safety and efficacy for each new indication or patient population.[22] However, in the U.S., a biosimilar may not be approved for any indication of the reference product protected by regulatory exclusivity, such as orphan drug or pediatric exclusivity.

Although the extrapolation of data collected for a biosimilar reduces the need for duplicative clinical studies, it must be justifiably supported by scientific data, and thus regulatory agencies may differ in their approval decisions.[27] For example, Korean regulators in 2012, the European Medicines Agency (EMA) in 2013, and the FDA in 2016 granted approval for the biosimilar infliximab (Remsima, Celltrion, Inc., also known as Inflectra) for the full range of indications of the reference product, although it had only been studied in rheumatoid arthritis and ankylosing spondylitis, whereas Health Canada did not initially support the extrapolation of clinical data to Crohn's disease or ulcerative colitis in its approval in 2014.[27] However, after the sponsor provided additional data, Health Canada extended approval of their infliximab biosimilar in 2016 for gastrointestinal indications, including Crohn's disease, fistulizing Crohn's disease, and ulcerative colitis.[27]

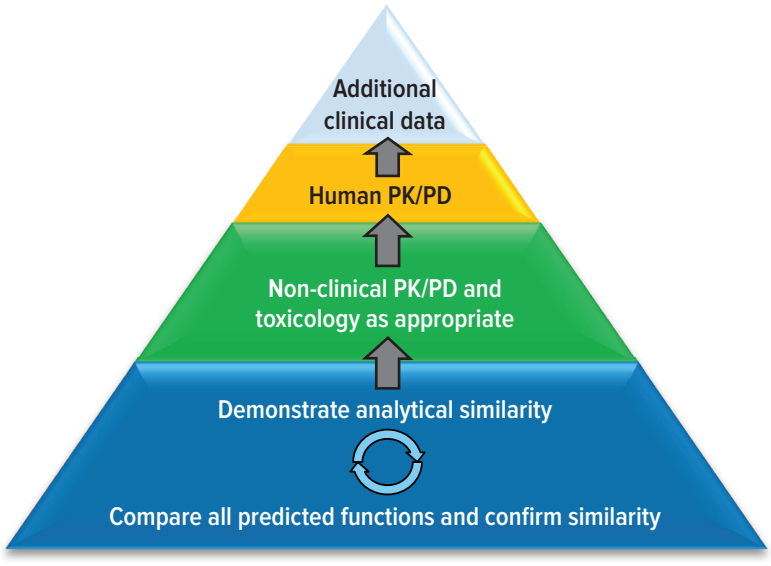
As biologic molecules, biosimilars have the potential to induce an immune response. The immunogenic potential of a biologic can be affected by differences in manufacturing processes, delivery components, or formulation,[28,29] which can lead to slight structural differences (e.g., glycosylation profiles) or differences in agglutination.[30] Therefore, demonstrating a similar immunogenic profile (e.g., infusion reactions, neutralizing antibodies) is critical for establishing biosimilarity. Immunogenicity is assessed during clinical assessments that evaluate immunogenic responses, typically first in healthy subjects as the most sensitive model—often during phase 1 pharmacokinetic/pharmacodynamic studies—then in patients who are usually enrolled in phase 3 studies. However, these studies designed to assess biosimilarity may not detect infrequent immunogenic events that are related to potential differences between a biosimilar and its reference product.[31-33] Thus, data on newly introduced products may initially be limited, and ongoing safety monitoring (pharmacovigilance) is needed.[32-35] Manufacturers are expected to closely monitor their products postmarket, and to further aid postmarketing surveillance, the Biologics and Biosimilars Collective Intelligence Consortium was established.[36] This task force engages in epidemiologic studies, sequential data analysis, and data mining to monitor biosimilar safety and efficacy through ongoing comparisons to their reference products.[36]

When generating the totality of evidence to support biosimilarity, it is important to bear in mind that the greater the level and quality of evidence provided at each step of the development pyramid (Figure 1), the greater will be the confidence of regulatory agencies in these products.[37] For example, two biosimilar candidates—Alpheon (BioPartners GmbH), a recombinant human interferon alfa-2a product, and Solumarv (Marvel LifeSciences Ltd.), a human insulin product—were refused approval by the EMA because of weaknesses in the evidence provided to support biosimilarity.[38a,38b]

INTERCHANGEABILITY

Interchangeability is an FDA designation unique to the U.S. that provides the basis for one-to-one substitution by a pharmacist without notification of, or permission from, the prescriber. Manufacturers decide if they wish to pursue this optional designation, which requires additional supporting evidence beyond that required for biosimilars without the designation. To earn interchangeability designation, federal law requires manufacturers to demonstrate that their product is "expected to produce the same clinical result as the reference product in any given patient" and, if the product is administered more than once to an individual, the sponsor must demonstrate that "the risk in terms of safety or diminished efficacy of alternating or switching between the use of the biological product and the reference product is not greater than the risk of using the reference product without such alternation or

Figure 1 Stepwise Process for Demonstrating Biosimilarity



PD = pharmacodynamics; PK = pharmacokinetics

(Adapted with permission from Markus R et al. Developing the totality of evidence for biosimilars: regulatory considerations and building confidence for the healthcare community. *BioDrugs* 2017;31(3):175–187.[23])

switch."[39] An interchangeability designation requires approval of the product as a biosimilar as well as additional biosimilar clinical switching studies (i.e., studies evaluating multiple switches between products).[39,40] According to the 2017 FDA Guidance for Industry on Interchangeability, simply providing postmarketing data that have been collected for products licensed as biosimilars without including corresponding data derived from appropriately designed, prospective, controlled switching studies with at least three switches, would generally not be considered sufficient to support the interchangeability designation.[39]

Autonomous substitution by pharmacists is the practice whereby a pharmacist may dispense a biosimilar product instead of the prescribed biologic without requiring prior approval from the prescriber. Although the FDA has not yet granted an interchangeable designation to any licensed biosimilar, most states and Puerto Rico have passed state-specific legislation regulating substitution.[41] These laws generally require that (1) biosimilars are first approved by the FDA with the interchangeable designation, (2) prescribers are permitted to prevent substitution by writing "dispense as written" or "brand medically necessary" on prescriptions, (3) the dispensing pharmacy must notify both prescribers and patients if an allowable substitution is made, and (4) records are retained by pharmacies and prescribers. A few states have included provisions to ensure that pharmacists who make compliant substitutions of biologics have immunity from prosecution. Also, pharmacists must explain the cost/price of both the reference biologic and the interchangeable biosimilar to patients.[41,42]

The potential for substitution may lead to the practice of alternating between reference products and biosimilars, particularly for treatments with a long course of therapy. The potential risks (e.g., immunogenicity, diminished efficacy) associated with switching between related biologics are evaluated in switching studies. A recently published, systematic literature review identifying publications on switching studies conducted before June 30, 2017, evaluated the possibility that switching from reference products to biosimilars could alter clinical safety or efficacy outcomes.[43] This analysis identified 90 publications with primary data on proteins that were available for review.[43] Although the analysis suggested there were low safety and efficacy risks associated with switching to biosimilars, its conclusion is limited by a small final sample size, the inclusion of a large number of abstracts or letters (n = 36) versus articles (n = 54), and the inclusion of more studies based on real-world evidence (n = 47) rather than randomized, controlled trials (n = 40).[43] Furthermore, the majority of these studies were single-switch studies and were not powered to detect switch-related differences.[43]

To our knowledge, four studies evaluating multiple switches between biosimilars and their reference products have been conducted or initiated[44-47], but three were completed before publication of the draft FDA guidance for demonstrating interchangeability and they do not meet all the recommendations (e.g., primary endpoints are clinical efficacy measures rather than pharmacokinetic/pharmacodynamic measures). The remaining study is the only one initiated to date that was designed to demonstrate interchangeability after publication of the guidance.[47] Also notable is that a few phase 3 clinical studies have included a single transition in their study designs.[48-50] However, although these provide information on the efficacy, safety, and particularly, immunogenicity after a single transition from the reference product to the proposed biosimilar, the FDA considers them insufficient to support the interchangeability designation. The current paucity of multiple-switch trials may be because "substitution" is essentially permitted in hospitals under the purview of pharmacy and therapeutics (P&T) committees; manufacturers may decide to launch their new biosimilars after receiving regulatory approval, and determine if interchangeability studies are needed at a later date. It is noteworthy that an interchangeability designation, because it pertains to automatic pharmacy substitution, would have little or no impact on medical benefit products and would only affect retail pharmacy products, for which there is a possibility that pharmacists might alternate between reference products and biosimilars.

As with generics, retail and specialty pharmacists may engage in substitution consistent with state laws. Drug substitution laws ultimately fall within the authority of individual states. In some states, substituting a lower-cost medicine is required

(i.e., not optional) unless the prescriber affirmatively prohibits substitution, such as by marking "do not substitute" on the prescription. If a biosimilar is identified as interchangeable, then changing from one product to another for reasons other than the patient's health or safety[51] may occur. In these instances, pharmacists may use their medical knowledge to inform the responsible use of limited resources to dispense the pharmacy's preferred biologic for its cost-effectiveness or another pharmacy-determined benefit, independently of what was prescribed, without required approval from the prescriber.[41] In a hospital or health system with a P&T committee, the selection of a biosimilar based on formulary considerations can occur within the confines of that specific institution without the need for an interchangeability designation.[32,52,53]

Payers should evaluate the incorporation of biosimilars into formularies based on numerous factors, including product characteristics and evidence, manufacturer supply, dosage-form suitability for the covered population, patient adherence, and the economic impact on payers and patients.[42] For patients with new prescriptions, incorporating biosimilars into treatment regimens will likely be relatively uncomplicated, but additional challenges exist for patients who are in the middle of treatment and stable on their current medications. As discussed, biosimilars are approved based on the totality of evidence, including extrapolated data, in comparison with their reference product, and are unlikely to be formally evaluated against other biosimilars of the same reference product.[54] As each biosimilar varies uniquely from the same reference product, biosimilarity is not transitive among biosimilars. Therefore, biosimilars should not be treated like generic small-molecule drugs, and further evaluation and consideration on a case-by-case basis may be necessary to support alternating among biosimilars. This consideration is particularly relevant for health care organizations that periodically change preferences among multiple biosimilars of the same reference product, thus exposing patients to biosimilars that have never been directly compared with each other and potentially increasing the risk of immunogenicity, depending on the type of biologic in question.

NAMING

The FDA's 2017 guidance stipulated that licensed biologic products should be assigned distinguishable, nonproprietary names.[55] For each originator biologic product, related biologic product, or biosimilar, the nonproprietary name will consist of the core name and an FDA-designated, distinguishable suffix of four letters, which is devoid of meaning.[55] The addition of the distinguishable suffix to the naming convention facilitates the accurate identification of biologic products by health care providers and patients, thus assisting with pharmacovigilance. These suffixes also help minimize the inadvertent substitution of products that are not deemed interchangeable.[55] Physician and pharmacist surveys have indicated the importance of clear labeling with regard to interchangeability.[56,57] More than 50% of physicians and pharmacists surveyed assumed that even without an interchangeability designation, two biologics that share the same name (1) could be considered identical, (2) could be expected to produce the same clinical results, (3) could be safely substituted for one another, and (4) would be approved for the same indications.[56,57]

ECONOMIC CONSIDERATIONS

Biosimilars are expected to increase market competition, and thereby reduce health care expenditure. The expected reductions in acquisition costs in the U.S. generally range from 10% to 40%.[42,58-60] Although this is lower than the reduction seen over time with generic drugs, the overall magnitude in terms of absolute savings may be similar owing to the higher cost of reference products. The wide range of expected cost reductions illustrates the lack of consensus on the extent of potential savings;[61] however, the impact of these considerations remains to be determined. Regulatory changes that simplify the development processes for biosimilars versus reference biologics (e.g., fewer preclinical and clinical trials required) may ultimately translate to lower overall product costs (e.g., $100–$250 million for biosimilars vs. an average pre-tax cost of $2.6 billion for originator biologics).[62,63] Given these differences, an estimated $44 billion in direct cost savings for biologics is expected between 2014 and 2024,[64] which should help offset the incremental costs associated with introducing new and innovative medicines that are likely to be approved in the future. Ultimately, cost and cost savings will be key factors for biosimilar acceptance in the market.[37,40,42,65]

PRICE NEGOTIATIONS

Despite the expected differences in unit cost between biosimilars and originators, payers may still need to negotiate with manufacturers to get the projected savings beyond the originator. For drugs covered under the retail pharmacy benefit, rebates and discounts[66] for biosimilars may be set through negotiations between payers and manufacturers. Other avenues, such as government payment policies[37] and accountable care organization (ACO) incentives,[37] may also have an impact on unit cost.[66,67]

MEDICARE CONSIDERATIONS

The Affordable Care Act (ACA) requires the Medicare Part B reimbursement value for a biosimilar to be based on the sum of the drug's average selling price plus a fixed percentage of the reference product's price (6% at present).[42] This was intended to put Medicare payment for biosimilars on a level playing field with reference products. In July 2015, the Centers for Medicare & Medicaid Services (CMS) published a proposed rule in the Federal Register to have all biosimilars share the same reimbursement code (i.e., J-code).[35,40] However, CMS recently issued new guidance on reimbursement for biosimilars;[68,69] as of January 1, 2018, all approved biosimilars receive their own healthcare common procedure coding system (HCPCS) reimbursement code. This was implemented to encourage more biosimilar development, although its effect on prices remains to be seen. The full impact of this change probably will not be realized for several years, but these changes combined with distinguishable names will likely assist with pharmacovigilance using claims data.[69]

PBMs AND PRIVATE INSURER CONSIDERATIONS

Because of the market power of drugs covered under the retail pharmacy benefit, PBMs are likely to obtain significant rebates with respect to biologics paid for by the plans they administer. For example, one large U.S. PBM has already

included biosimilars for filgrastim and insulin in its formulary to take advantage of lower pricing.[70] Of note, insulin and low-molecular weight heparin currently are not considered biologics/biosimilars in the U.S. However, in draft guidance issued in March 2016, the FDA stated that by 2020, these "transitional products" will be treated as biologics under the Public Health Service Act, and thus some products could be subject to biosimilar guidances.[71] Additional considerations for the use of biosimilars include the overall strength of the data supporting similar efficacy, safety, and potency between the biosimilar and its reference product; prescriber and patient education; and potential drug delivery advantages.

PHYSICIAN CONSIDERATIONS

For drugs covered under the medical benefit, which are often administered and billed for by physicians, payment policies have been shown to be significantly correlated with uptake by physicians;[7,72] however, there is a need for real-world evidence to truly evaluate biosimilar costs in relation to patient outcomes. One initiative developed through the ACA is the development of alternative payment models such as ACOs,[73] which are groups of doctors, hospitals, and other health care providers that provide coordinated care to their Medicare patients and share cost savings.[74] If a physician is part of an ACO, then the associated risk sharing may drive preferences. Furthermore, for specialists within large groups such as oncology practices or their own purchasing group, the group's choice will likely drive utilization. If the ACO is part of the CMS Medicare Shared Savings Program, then these choices may be driven by contracts created between the ACO and public or private payers who issue rewards for controlling the cost of care, provided the quality of care is met and maintained.[75,76] If successful, the ACOs receive part of the savings achieved by CMS through these policies.[75,76] Together, these incentives may create a barrier to biosimilars being used in clinical practice, thereby limiting the overall savings that could be realized with biosimilars in these settings.

PATIENT CONSIDERATIONS

The reduced acquisition cost of a biosimilar compared with the reference product will primarily affect patients with high-deductible plans or those with coinsurance where out-of-pocket expenses are calculated as a percentage of the drug's list price instead of a fixed copay.[77] In such situations, it is likely that patients seeking to reduce their out-of-pocket costs will drive providers to prescribe biosimilars over the reference biologic.[77] In the absence of a price differential, as it affects patients' out-of-pocket costs, patients may be more likely to choose the branded originator product. Prescribers and pharmacists will likely support the patient's drug choice if copay benefits and professional assurance are in place. Patients for Biologics Safety and Access (PBSA) is a national coalition of more than 20 patient advocacy organizations that aims to ensure that the voices and interests of patients are heard, as the FDA considers approval of biosimilars.[78] PBSA believes that patients must have access to safe and effective biologic and biosimilar medicines and all the information necessary to make a fully informed choice about whether to use a biosimilar. PBSA also aims to support the appropriate tracking of adverse events (AEs) and the use of unique names. Such efforts help to instill more confidence about biosimilar safety and efficacy in the patients who receive them.[79]

VALUE BEYOND PRICE REDUCTION

A payer's decision to adopt a biosimilar for formulary inclusion should be based on the quality and overall value as opposed to the price alone.[5,32,42,53,60,61] Elements that contribute to the value of a drug include product quality established through extensive analytical and functional assessments during product development; provider-focused education; provider engagement; manufacturer reliability of quality and the supply chain; and additional services such as, for example, anticounterfeit protection).[32,42,60,61]

Manufacturing considerations, supply chain security, and logistics are also important when determining the relative value of a biosimilar.[32,53,80] The strength of manufacturer records for quality is vital for developing brand acceptance, trust, and reliability,[32] and for maintaining consistency in treatment. In addition, physicians may develop a preference for biosimilars from reliable manufacturers with a low likelihood of supply disruptions, a positive history regarding recalls, safe handling practices, supply chain security, and counterfeit protection.[32,80,81] It is also important to consider potential differences between delivery devices for biosimilars and reference products that may provide added benefit to patients and health care providers.

As with generic medications, the reduced price of a biosimilar may also translate to other benefits in addition to cost savings. These may include improved medication adherence associated with lower copays, and enhanced motivation for originator and biosimilar manufacturers to invest in innovation to differentiate themselves in an increasingly competitive market.[82]

EXPERIENCE IN THE UNITED STATES

Currently, there are a number of challenges for all stakeholders[40,42] that could limit the immediate uptake of biosimilars.[61,83] Major considerations include provider and patient education, and an understanding of the regulatory approval process; differences in state and regional adoption practices and laws (especially as they relate to interchangeability and substitution); and administration strategies, the documentation of AE concerns, and cost or insurance coverage barriers.[84,85] Educational opportunities (e.g., data on approval requirements, clinical study regulations, immunogenicity considerations) for physicians, patients, and payers are needed to facilitate the incorporation of biosimilars into formulary decision-making. Without education to increase biosimilar familiarity, physicians may be less inclined to prescribe this new category of biologics and may not be aware of which biosimilars are available on a payer formulary. Furthermore, laws, regulations, and guidance for biosimilar usage and substitution vary at state and regional levels and are influenced by factors including state board of pharmacy requirements, state insurance options, and state legislative and regulatory structures. Together, these factors affect pricing and reimbursement strategies.[72,86] For biosimilars to be adopted into health care practice, pricing needs to be sufficiently low.[72]

CONCLUSION

There are many important considerations in addition to cost that payers should weigh when evaluating biosimilars. These include the totality-of-evidence approach for demonstrating biosimilarity (e.g., analytical/functional similarity, efficacy, and safety); the potential added value beyond cost; and manufacturing considerations, including the reliability of supply and logistics. Also, it is important that payers consider the impact of state laws regarding substitution, including how interchangeable biosimilars may be used. In the U.S., further real-world experience with biosimilars is needed to more fully appreciate their broader value and potential for increasing patient access to life-saving biologics.

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EXHIBIT 83


GLOSSARY (/glossary)
FAQs (/faqs)
LET'S SEE HOW
BIOSIMILARS ARE DEVELOPED

A rigorous process

The process for biosimilar medicine development involves rigorous analytical studies to establish a comprehensive understanding of the similarity of the biosimilar to the reference product. Assessments of toxicity and clinical studies are also used to further establish similarity. Ultimately, the goal is to demonstrate that there are no clinically meaningful differences between the reference product and the biosimilar based on the findings from all of these studies.

BUILDING ON THE ESTABLISHED CLINICAL PROFILE OF THE REFERENCE BIOLOGIC.

Using multiple state-of-the-art-methods, protein structures can be extensively characterized so that the reference product and biosimilar can be directly compared, helping to ensure comparability of both functional integrity and performance in vivo. These comparisons, with respect

to the structure and function of the molecule, will provide the foundation for development, which builds on the clinical experience with the reference biologic.

Biosimilar development requires substantial time and financial investment

Development of biosimilar medicines begins with substantial investment in the specialized infrastructure, expertise, and technology required to create the product, verify that it is biosimilar, and ultimately to maintain quality production.

INVESTING IN THE FUTURE

While biosimilars have the potential to provide additional treatment options at lower cost,

development of biosimilars requires significant investment. Development of a biosimilar may take 5 to 9 years at a cost of over $100 million, not including regulatory fees. A generic version of a small-molecule drug, on the other hand, costs $1 million to $2 million and takes approximately 2 years to develop.

DRUG DEVELOPMENT COMPARISON

GLOSSARY (/glossary) FAQs (/faqs)

New Medicine

(including cost of failures)

Development time:
>10 years
Cost: ~$2.6 billion

DISCOVERY

DEVELOPMENT

NONCLINICAL

PHASE 1

Biosimilar

(cost of failures not available)

Development time:
~5 to 9 years
Cost: ~$135 million*

*Not including regulatory fees.

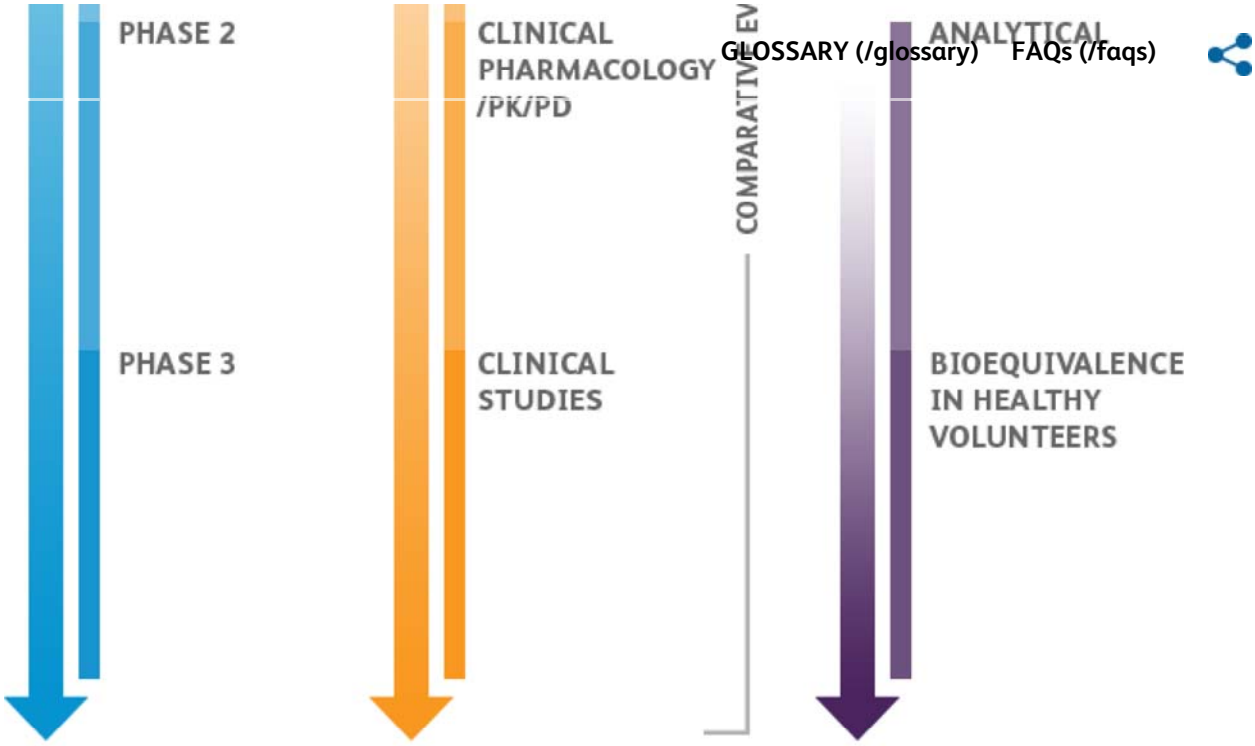
ANALYTICAL

NONCLINICAL

VALUATIONS

Small-molecule Generic

Development time: ~2 years
Cost: ~$1-2 million



The development processes for biologics and biosimilars are considerably more rigorous than the development process for small-molecule generics.

(/characteristics-of-biosimilars)
PREVIOUS: Characteristics of biosimilars (/characteristics-of-biosimilars)
NEXT: Regulatory pathway (/biosimilars-regulatory-pathway)
(/biosimilars-regulatory-pathway)

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SITEMAP (/SITEMAP) **GLOSSARY (/GLOSSARY)**

The information provided in this site is intended for residents of the United States.

The health information contained herein is provided for educational purposes only and is not intended to replace discussions with a health care provider.
All decisions regarding patient care must be made with a health care provider, considering the unique characteristics of the patient.

June 2017 PP-BIO-USA-0325-02

(http://www.pfizer.com/)

EXHIBIT 84

VOLUME 36 · NUMBER 12 · APRIL 20, 2018

JOURNAL OF CLINICAL ONCOLOGY

ASCO SPECIAL ARTICLE

American Society of Clinical Oncology Statement: Biosimilars in Oncology

Gary H. Lyman, Edward Balaban, Michael Diaz, Andrea Ferris, Anne Tsao, Emile Voest, Robin Zon, Michael Francisco, Sybil Green, Shimere Sherwood, R. Donald Harvey, and Richard L. Schilsky

Author affiliations and support information (if applicable) appear at the end of this article.

Published at jco.org on February 14, 2018.

R.D.H. and R.L.S. contributed equally as co-senior authors.

Corresponding author: Gary H. Lyman, MD, MPH, Hutchinson Institute for Cancer Outcomes Research Fred Hutchinson Cancer Research Center, 1100 Fairview Ave N, MS-B232, Seattle, WA 98109-1024; e-mail: glyman@fredhutch.org.

0732-183X/18/3612w-1260w/$20.00

ABSTRACT

As many biosimilars come to market in the next several years, their use in oncology will play an important role in the future care of patients with cancer. ASCO is committed to providing education and guidance to the oncology community on the use of biosimilars in the cancer setting; therefore, ASCO has developed this statement to offer guidance in the following areas: (1) naming, labeling, and other regulatory considerations, (2) safety and efficacy of biosimilars, (3) interchangeability, switching, and substitution, (4) value of biosimilars, and (5) prescriber and patient education.

J Clin Oncol 36:1260-1265. © 2018 by American Society of Clinical Oncology

INTRODUCTION

Despite considerable advances in cancer care, rising health care costs have prompted the need for cost-containment strategies.[1] This is especially true with regard to new oncology pharmaceuticals—eight of the 10 most expensive drugs on the market are cancer drugs. Since the enactment of the Biologics Price Competition and Innovation Act (BPCIA) in 2010, biosimilars have been developed and marketed as competitive, lower-cost alternatives to newer biologic treatments. In 2013, the Virginia Generally Assembly defined a biological product as a virus, therapeutic serum, toxin, antitoxin, vaccine, blood, blood component or derivative, allergenic product, protein other than a chemically synthesized polypeptide, or analogous product, or arsphenamine or any derivative of arsphenamine or any other trivalent organic arsenic compound, applicable to the prevention, treatment, or cure of a disease or condition of human beings. Biosimilar was defined as a biologic product that is highly similar to a specific reference biologic product, notwithstanding minor differences in clinically inactive compounds, such that there are no clinically meaningful differences between the reference biologic product and the biologic product that has been licensed as a biosimilar pursuant to 42 USC section 262(k) in terms of safety, purity, and potency of the product.

To date, the US Food and Drug Administration (FDA) has approved eight biosimilar products for use in the United States, including one product for use as a supportive care agent in the cancer setting (filgrastim-sndz, for use as an alternative to filgrastim) and two products for use in the treatment of cancer (bevacizumab-awwb, for use as an alternative to bevacizumab, and trastuzumab-dkst, for use as an alternative to trastuzumab). With the expiration of several biologic patents, a wave of biosimilars is expected in the United States, and cancer treatments are likely to consist of a significant proportion of the approved biosimilars. In fact, oncology biologic products with patents scheduled to expire by 2020 total global annual spending of more than $20 billion. The biosimilars for these products are expected to take over the majority of this market share.[2]

Whereas access to biosimilars could potentially reduce the cost of cancer therapies, inconsistent use and a lack of understanding of the terminology, evolving regulatory guidance, and questions about how biosimilars may be prescribed and dispensed, have contributed to an uncertain environment for all stakeholders. Moreover, there is growing concern that existing statutes regarding the regulation of generic drugs may be misapplied to biologic products, which has led several states to amend older state laws to address the complex molecular characteristics of biologics and biosimilars. ASCO, along with many other organizations, has commented on the evolving regulatory framework for biosimilars.[3,4] In addition, it has been noted in prior publications that physicians were initially concerned about the use of generic drugs and even the first monoclonal antibody therapies[5]; therefore, ASCO

ASSOCIATED CONTENT

Appendix
DOI: https://doi.org/10.1200/JCO.2017.77.4893

DOI: https://doi.org/10.1200/JCO.2017.77.4893

has developed this statement to provide education and guidance to the oncology community on the assessment of the safety and efficacy of biosimilars in the cancer setting. In doing so, ASCO offers guidance on the following issues:

- Safety and efficacy of biosimilars: Clinical standards and postmarket evidence development are essential components of the ongoing development of new products to ensure the safe and effective delivery of care. Oncologists play a critical role in the gathering and reporting of robust postmarket evidence. Sustained postmarket evidence development is necessary to enhance patient and provider confidence in biosimilars and to supplement the evidence supporting the safe and effective use of biosimilar products.
- Interchangeability, switching, and substitution: The ability of oncologists and patients to decide which biologic product will provide optimal treatment is key to providing high-quality, high-value cancer care. The interchangeability of a product is determined at the federal level after FDA review; however, substitution will be regulated at the state level. As individual states work to regulate the use of biosimilars, in accordance with the FDA designation, oncologists and patients must be aware of the regulations, authorities, and responsibilities that may affect their treatment choices.
- Naming, labeling, and other regulatory considerations: To effectively choose, prescribe, or administer biosimilars, it is important that providers understand the comparative risks and benefits of biologic products. Biosimilarity refers to similarity to a reference product, and does not imply similarity to other biosimilars. With biosimilars, the name alone may not be enough to help providers differentiate between products. The naming and labeling of biosimilars, considered together, will help to ensure that oncologists, pharmacists, and other providers have all the necessary information to ensure they are using their chosen therapy as intended.
- Value of biosimilars: Oncologists recognize the effect of cost and reimbursement in making treatment decisions. Biosimilars provide an opportunity to both obtain desired outcomes and manage the cost of care for patients with cancer. Coverage and reimbursement policies vary by payer, patient, and setting. In addition, use management policies are often used as a way to manage cost, without necessarily considering clinical information.
- Prescriber and patient education: Continuous provider education is critical to inform, promote, and use biosimilar products in a medically appropriate and cost-effective way to treat cancer. Also important is patient education about biosimilars provided by a knowledgeable health care professional. Public awareness and education, and the use of standardized, publicly available materials from professional societies, government sources, and patient advocacy groups will help to ensure understanding of biosimilars.

SAFETY AND EFFICACY OF BIOSIMILARS: CLINICAL STANDARDS AND POSTMARKET EVIDENCE DEVELOPMENT

Confidence in the safety and efficacy of biosimilars is of the utmost importance in clinical practice. The FDA approval process for biosimilars makes it less likely that large, phase III trials will be undertaken for all approved indications of the reference product. In fact, if the same level of evidence was required for biosimilars as that for original biologics, the potential for cost reduction would not likely be realized; therefore, approval of the biosimilar for other indications must largely be based on extrapolation, and the appropriate incorporation of biosimilars into practice is left largely to clinical experience and judgement. Product drift—product changes that can occur over time as a result of manufacturing changes, processing, and packaging—may result in differences in both biosimilars and the originator biologic over time. Currently, when there are postapproval changes to either the reference product or the biosimilar, the FDA requires data to demonstrate that any postapproval changes to the product do not result in clinically meaningful changes in safety or efficacy.

Given that regulatory review of biosimilars, compared with reference products, relies less on clinical data and more on structural, functional, and pharmacologic data, there will be a greater reliance on postmarket evidence development to demonstrate the value of these products to stakeholders. Indeed, postmarket research will provide additional data on the risks and benefits of switching biologic therapies.

Clinicians play an essential role in postmarket surveillance efforts. Postmarket surveillance is necessary to generate data on use, efficacy, and safety, which may not have been apparent during premarket trials and informs the optimal use of the drug in diverse populations. This process educates patients, clinicians, and regulators, and, importantly, may result in changes to product labels, compendia, or clinical pathways and practice guidelines.

However, the United States has and will continue to have significant challenges with collecting these data, given the fragmented nature of the US health care system. The Food and Drug Administration Amendment Acts of 2007 required the FDA to create a postmarket surveillance system to assess the safety of approved medical products. The Sentinel Initiative aims to enable the FDA to actively query electronic health record systems, administrative and insurance claims databases, and registries to evaluate possible medical product safety issues in a rapid and secure manner. The Sentinel system is still in development and has not yet facilitated rapid drug safety assessment or improved drug utilization. Although the FDA maintains that the Sentinel program holds promise for regulatory decisions on the basis of big data tools to organize and evaluate evidence and to maintain standards of safety and efficacy, alternative big data options are being explored. ASCO's big data initiative, CancerLinQ, represents a major effort in the development of an integrated real-time data resource for clinical oncology practice, quality performance assessment, and identification of safety concerns in a real-world setting. CancerLinQ also has the potential to contribute valuable information on biosimilar use and effectiveness.

INTERCHANGEABILITY, SWITCHING, AND SUBSTITUTION

A biosimilar is a biologic product that is highly similar to a specific reference biologic product. When a product is deemed biosimilar, there are no clinically meaningful differences between the reference biologic product and the product licensed as a biosimilar. Whereas there may be minor differences in the inactive compounds of

a biosimilar, the safety, purity, and potency of the product is highly similar to the reference biologic product. It is important to note that, unlike the relationship between generics and innovator brand products, the biosimilarity of a product is based on its similarity to the reference product and not to other biosimilars (Fig 1).

The biosimilarity and interchangeability of a product are determined after FDA review, whereas prescribing, dispensing, and the substitution of biologic products are regulated at the state level in a regulatory process that is similar to that of the dispensing and substitution of innovator drugs and generics. Generally, FDA approval of a biosimilar product is an indication that safety and efficacy are not meaningfully different from the reference product.

BPCIA allows substitution—the practice of dispensing an interchangeable product—to any given patient at the pharmacy level without consulting the prescriber. State laws generally uphold the authority of the physician to make final treatment decisions, including determinations of medical necessity and non-substitution. Although the FDA designation of interchangeable means that the biologic product may be substituted without the intervention of the prescribing provider, physicians and patients should be aware of potential product substitutions so that they can make informed treatment decisions.

For a biosimilar to be deemed interchangeable by the FDA, it has to be "expected to produce the same clinical result as the reference product in any given patient"[10(p3)] and fulfill necessary safety requirements as outlined by the FDA, including the evaluation of the safety and efficacy of switching back and forth between an interchangeable product and a reference product that will be administered more than once. When a product is deemed interchangeable, the data, analytics, and methodologies used to test and compare biosimilars with reference products provide scientific justification for expecting the same clinical outcomes.

Currently, no biosimilar has been approved by the FDA as being interchangeable with its reference product. State regulation, which relies on the federal determination, will dictate how and when biosimilars may be substituted for originator biologics. Regulations will vary from state to state and are currently in various stages of development.

NAMING, LABELING, AND OTHER REGULATORY CONSIDERATIONS

To ensure high-quality cancer care, oncologists, prescribers, patients, and pharmacists must be able to easily identify biologic products and ensure that patients receive the intended therapy. The complexity of biosimilars, including the manufacturing process, requires a naming and labeling scheme that is different from the naming and labeling of conventional drug products. At a basic level, oncologists must understand the significance of the name of each specific biosimilar that is being considered for use as treatment, as well as the clinical information associated with the biosimilar product.

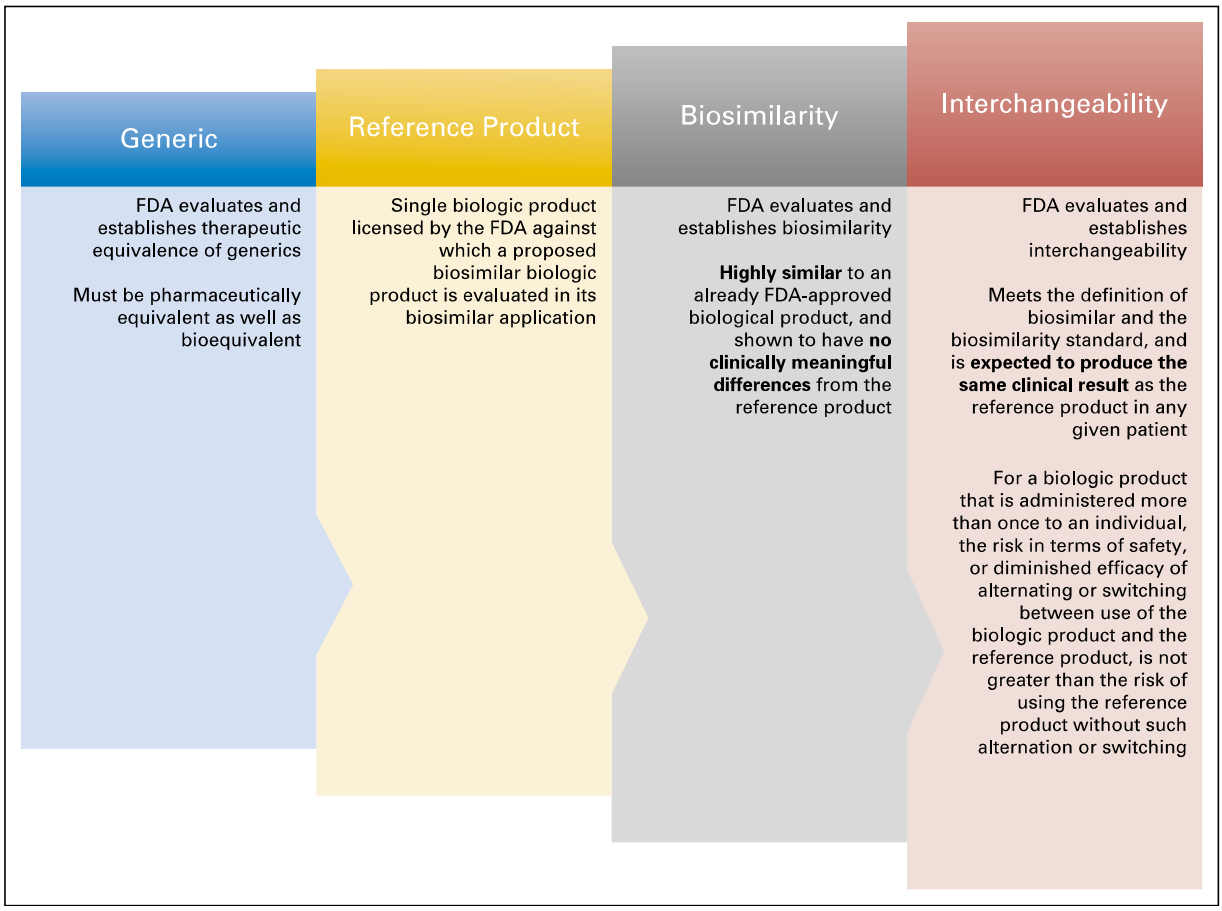

Fig 1. Definitions. FDA, US Food and Drug Administration.

Although physicians are familiar with the chemical and pharmacologic characteristics of drugs and biologics, the identification of the product is often associated with a single name that is universally recognized by providers, payers, and other clinicians. Thus, products are usually identified by a proper name that reflects the chemical and pharmacologic properties of a product or a proprietary/trademarked name. In the case of biosimilars, by definition, the products bear some differences that may warrant different clinical decisions (Table 1).

In its final guidance to the industry on the nonproprietary naming of biologic products, FDA guidance instructs manufacturers to assign a nonproprietary name that includes the core name of the product plus a distinguishing FDA-designated suffix that is devoid of meaning and composed of four lowercase letters.[11] The unique four lowercase-letter suffix affixed to a shared core name indicates a relationship among biologic products and is intended to be constant over time. As guidance on interchangeability has not been finalized, the FDA is continuing to consider the appropriate suffix format for interchangeable products.

Another aspect of providing optimal care and choosing the correct therapeutic product is the availability of accurate, scientific, and balanced information about the therapeutic characteristics of a product, which are included in the product labeling. Product labeling largely reflects the results of clinical studies that support the safety and efficacy of a product and may be used by providers to learn about the product and make clinical decisions. In the case of biosimilars, this information may also convey subtle, but important differences between the biosimilar and the reference biologic, including whether a biosimilar is interchangeable with the reference biologic.

The FDA has issued draft guidance on the proposed labeling requirements of biosimilar products.[12] Labels for biosimilars include a biosimilarity statement that describes the relationship to the reference product, (ie, Biosimilar X is biosimilar to Reference Product Y for the indications listed). The labels also include a footnote that defines the term, biosimilar, and indications and usage as well as adverse reactions and immunogenicity information. In the proposed guidance, the FDA maintains the presumption that the biosimilar designation is sufficient to support manufacturer claims of safety and efficacy. As such, merely citing the reference product in the labeling would be appropriate and could convey all necessary information for therapeutic decision making. However, in instances in which the indications, dosing, storage, etc, for a reference product and biosimilar may be different, statements that highlight these differences and additional details that explain the clinical aspects of these differences are necessary to facilitate the appropriate use of biosimilars. In addition, as the FDA continues to develop policies to designate the interchangeability of products, the inclusion of information related to interchangeability will be important. Distinction and clarity on the naming and labeling of biosimilar products before, during, and after use are critical to avoid unintended alternating or switching of biologic products that have not been deemed interchangeable by the FDA.

VALUE OF BIOSIMILARS: REIMBURSEMENT, COVERAGE, AND COST

Biosimilars have the potential to decrease the overall cost of care for complex medical conditions. Medicare, Medicaid, and commercial payers all have approached the reimbursement of biosimilars differently; however, it is clear that reasonable compensation, fair and medically appropriate coverage, and transparency of cost will serve to ensure a true value benefit to patients and society and promote access to new and innovative therapies.

BPCIA provides authority to the Centers for Medicare & Medicaid Services (CMS) to implement reimbursement policies for biosimilars. Many biologics and biosimilar products are reimbursed under a patient's medical benefit rather than the pharmacy benefit; therefore, CMS reimbursement for reference biologics is the same as that for all other drugs covered under Medicare Part B—that is, average sales price (ASP) plus a fixed percentage mark-up, which is currently 6% of the ASP, or ASP + 6%. As such, each reference biologic is given its own unique Healthcare Common Procedure Code.

Table 1. Selected Clinical and Pharmacologic Characteristics of Reference Agents and Selected Biosimilars in Development

Agent	Pharmacokinetics*	Target Binding Assay†	Cell Proliferation Assay‡	ORR§	Ratio of ORR¶	Vial Size, mg	Manufacturer
Trastuzumab (Herceptin; Genentech)[6,7]	Reference	Reference (HER2)	Reference	146 (64%) of 228	Reference	150 and 420	Genentech
Ogivri (trastuzumab-dkst)[7]	95.7 (89.7 to 101.5)	99.94 to 100.08	99.87 to 100.01	161 (70%) of 230	1.09 (0.98 to 1.22)	420	Mylan/Biocon
Bevacizumab (Avastin; Genentech)[8]	Reference	Reference (VEGF-A)	Reference	131 (42%) of 314	Reference	100 and 400	Genentech
Mvasi (bevacizumab-awwb)[9]	98.3 (94.0 to 102.9)	97.07 to 104.18	99.45 to 105.2	128 (39%) of 328	0.93 (0.8 to 1.09)	100 and 400	Amgen

Abbreviations: HER2, human epidermal growth factor receptor 2; ORR, overall response rate; VEGF-A, vascular endothelial growth factor A.
*The ratio of the measure of exposure (area under the plasma concentration-time curve from time 0 [predose] extrapolated to infinity [$AUC_{0-\infty}$] Geometric Mean Ratio with 90% CI) of the reference product divided by the AUC of the biosimilar after a single dose in healthy volunteers. For trastuzumab, 8 mg/kg; and for bevacizumab, 3 mg/kg. Equivalence is defined as including 100.
†90% CI for the range of the mean difference (target binding and cell proliferation assays) or mean ratio (ORR) between the biosimilar and the reference product. Equivalence for assays is defined as including 100 and, for ORR, 1.0.
‡90% CI for the range of the mean difference (target binding and cell proliferation assays) or mean ratio (ORR) between the biosimilar and the reference product. Equivalence for assays is defined as including 100 and, for ORR, 1.0.
§Trastuzumab with taxane breast cancer response at week 24, bevacizumab with carboplatin, and paclitaxel in non–small-cell lung cancer over six cycles.
¶90% CI for the range of the mean difference (target binding and cell proliferation assays) or mean ratio (ORR) between the biosimilar and the reference product. Equivalence for assays is defined as including 100 and, for ORR, 1.0.

Initially, CMS set reimbursement for biosimilars at the volume-weighted ASP of all biosimilar products within the same billing and payment code, plus an additional amount of 6% of the ASP of the reference product. The policy, which is similar to that for the reimbursement of multisource generics, was problematic for stakeholders, because the ASP of the reference biologic was not included in the weighted ASP of the biosimilars. However, beginning January 2018, for newly approved biosimilar products, biosimilars with a common reference product will no longer be grouped into the same billing code. CMS will code each biosimilar separately and reimburse at the current rate, which is ASP + 6%.

CMS also shares authority with states to regulate the coverage and reimbursement of drugs and biologics in the Medicaid program. The Medicaid program currently views biosimilars as single-source products and reimbursement methodologies reflect state-specific reimbursement for single-source products rather than methodologies that govern the reimbursement of multisource products. This means that each biosimilar may have a different reimbursement rate.

Commercial payers, including Medicare Part D plans, provide coverage for oral biologics under the pharmacy benefit of health insurance plans. Individual plan structure dictates the level of coverage and may also impose various cost-sharing and utilization management strategies in an effort to control costs. Such policies often result in higher out-of-pocket costs for single-source or nonpreferred products. On one hand, biosimilars and their relationship to biologics call for policies that are associated with generics that would tend to limit out-of-pocket costs; however, if a biosimilar is not interchangeable, it could stand alone as a single-source product and could therefore be subject to policies that are associated with single-source and nonpreferred products. ASCO principles for coverage and utilization management policies should be used to ensure the delivery of high-quality care that is most appropriate for patients while also ensuring patient access to medically necessary care.[13]

PRESCRIBER AND PATIENT EDUCATION

Given the novelty of biosimilar development in the United States and its reduced emphasis on clinical testing, there is greater need for education among providers regarding biosimilar products and their appropriate use. ASCO will continue to work to provide education that is focused on clarifying the difference between biosimilars and generic drugs; defining interchangeability, switching, and substitution; explaining naming and labeling issues; and emphasizing the need for postmarket safety surveillance. A broad range of educational materials, sources, and formats developed through a peer-review process, including appropriate conflict of interest provisions, must be readily available to all stakeholders (Appendix Table A1, online only). Practice guidelines for how biosimilars are prescribed, administered, and dispensed will be an important facet of educating oncologists.

Examples of such efforts include developing Webcasts, online practice guidelines, and social media updates potentially via ASCO University. Incorporating education sessions on biosimilars at scientific meetings, especially at the ASCO Annual Meeting as well as collaborating with ASCO's State Affiliates Council to elaborate and provide comparisons of the differing state prescribing regulations for biosimilars are needed. Education resources could be developed and maintained on ASCO's patient resource Web site and annual meeting repository, Cancer.net and ASCO's Meeting Library, respectively. Finally, ASCO's big data initiative, CancerLinQ, provides an opportunity to collect postmarket information on biosimilars that can be leveraged as real-time, rapid-learning educational tools in the health care setting.

For patients, the best source of patient education is the treating physician, regardless of the prescribed drug. However, as few resources exist that serve to educate patients on the use of biosimilar products, ASCO is committed to working with oncologists and other stakeholders to provide a wide range of educational materials tailored for patient use to facilitate patient understanding and acceptance of biosimilar products as appropriate treatment options.

The FDA has recently announced a series of educational Webinars designed to help health care professionals better understand FDA regulation and medication safety. The first Webinar is intended to provide an overview of the regulatory framework for biosimilar products, including the general requirements of the approval pathway for biosimilars and the approach and scientific concepts used by the FDA to review biosimilar products.

These educational materials—developed by professional societies and government entities in conjunction with patients or patient advocacy organizations—should provide all information relevant to the patient, including patient safety and efficacy concerns about biosimilars and any concerns regarding interchangeability and cost. These resources should be readily available for providers to share with patients in a timely manner and, when appropriate, to facilitate a dialog between the patient and the provider.

In conclusion, biosimilars will play an important role in the future care of patients with cancer and will improve access to valuable medicines. Whereas many biosimilars in oncology will be available in the next several years, their use and effect on patient care and health care costs will largely depend on patient and provider acceptance on the basis of an adequate understanding of the safety and efficacy of these agents in cancer care. This statement affirms ASCO's commitment to ensure the availability of biologics that are necessary in the delivery of high-quality, high-value care. To enhance patient and provider confidence in biosimilars, it is necessary to educate oncology providers and continue to advocate for federal and state policies that ensure the efficient approval, unrestricted access, and appropriate use of biosimilars.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Disclosures provided by the authors are available with this article at jco.org.

AUTHOR CONTRIBUTIONS

Conception and design: All authors
Collection and assembly of data: All authors
Data analysis and interpretation: All authors
Manuscript writing: All authors
Final approval of manuscript: All authors
Accountable for all aspects of the work: All authors

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Affiliations

Gary H. Lyman, Hutchinson Institute for Cancer Outcomes Research, Fred Hutchinson Cancer Research Center, Seattle, WA; **Edward Balaban**, University of Pennsylvania Medical College, Philadelphia, PA; **Michael Diaz**, Florida Cancer Specialists and Research Institute, St Petersburg, FL; **Andrea Ferris**, Lungevity Foundation, Bethesda, MD; **Anne Tsao**, The University of Texas MD Anderson Cancer Center, Houston, TX; **Emile Voest**, The Netherlands Cancer Institute, Amsterdam, the Netherlands; **Robin Zon**, Michiana Hematology Oncology, Mishawaka, IN; **Michael Francisco**, **Sybil Green**, **Shimere Sherwood**, and **Richard L. Schilsky**, American Society of Clinical Oncology, Alexandria, VA; and **R. Donald Harvey**, Emory University School of Medicine, Atlanta, GA.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

American Society of Clinical Oncology Statement: Biosimilars in Oncology

The following represents disclosure information provided by authors of this manuscript. All relationships are considered compensated. Relationships are self-held unless noted. I = Immediate Family Member, Inst = My Institution. Relationships may not relate to the subject matter of this manuscript. For more information about ASCO's conflict of interest policy, please refer to www.asco.org/rwc or ascopubs.org/jco/site/ifc.

Gary H. Lyman
Leadership: Generex Biotechnology
Consulting or Advisory Role: Halozyme, G1 Therapeutics, Coherus Biosciences, Mylan
Research Funding: Amgen (Inst)

Edward Balaban
No relationship to disclose

Michael Diaz
Employment: Florida Cancer Specialists
Leadership: Florida Cancer Specialists
Stock or Other Ownership: Florida Cancer Specialists
Consulting or Advisory Role: Janssen Pharmaceuticals

Andrea Ferris
No relationship to disclose

Anne Tsao
Honoraria: Novartis, Boehringer Ingelheim, AstraZeneca, Genentech, Bristol-Myers Squibb, Epizyme, EMD Serono, ARIAD Pharmaceuticals, Imedex, Eli Lilly, Novartis
Consulting or Advisory Role: Novartis, Boehringer Ingelheim, Astellas Pharma, Genentech, MedImmune, Imedex, Eli Lilly, Bristol-Myers Squibb, Epizyme, AstraZeneca, ARIAD Pharmaceuticals, EMD Serono
Research Funding: MedImmune (Inst), Merck (Inst), Genentech (Inst), Seattle Genetics, Millennium Pharmaceuticals, Bristol-Myers Squibb (Inst), Boehringer Ingelheim (Inst), Polaris

Emile Voest
Consulting or Advisory Role: InteRNA, Biogeneration Ventures
Research Funding: Novartis (Inst), GlaxoSmithKline (Inst), Genentech (Inst), Pfizer (Inst), AstraZeneca (Inst), Eisai (Inst), Pfizer (Inst), Bristol-Myers Squibb (Inst), Merck (Inst)

Robin Zon
Consulting or Advisory Role: Medical Protective Malpractice Insurance Company
Research Funding: Agendia (Inst)
Other Relationship: Medical Protective Advisory Board

Michael Francisco
No relationship to disclose

Sybil Green
No relationship to disclose

Shimere Sherwood
No relationship to disclose

R. Donald Harvey
No relationship to disclose

Richard L. Schilsky
Research Funding: AstraZeneca (Inst), Bayer (Inst), Bristol-Myers Squibb (Inst), Genentech (Inst), Eli Lilly (Inst), Merck (Inst), Pfizer (Inst)

Acknowledgment

We thank the FDA for their guidance and support in the development of this paper.

Appendix

Table A1. Terminology

Term	Equivalence Determination	Definition	Reference Product (comparison)	Substitution Statute*	MD-Initiated Change†	Pharmacist-Initiated Change‡	Source§
Generic	FDA evaluates and establishes the therapeutic equivalence of generics	Must be pharmaceutically equivalent and bioequivalent	Innovator brand: All products deemed equivalent to a brand may also be deemed equivalent to other therapeutic equivalents	State-regulated authorization of generic substitution	Yes	Yes, in most states	Orange book
Reference Product		Single licensed biologic product against which a biologic product is evaluated in a 351(k) application					
Biosimilar	FDA evaluates and establishes biosimilarity	Highly similar to an already FDA-approved biologic product, and shown to have no clinically meaningful differences from the reference product	Reference biologic: Biosimilars are deemed biosimilar to the reference product only		Yes	No	Purple book
Interchangeable	FDA evaluates and establishes interchangeability	Meets the definition of biosimilars and the biosimilarity standard, and is expected to produce the same clinical result as the reference product in any given patient for a biologic product that is administered more than once to an individual, and the risk in terms of safety, or diminished efficacy of alternating or switching between use of the biologic product and the reference product, is not greater than the risk of using the reference product without such alternation or switching	Reference biologic: Interchangeability of a product indicates interchangeability with the reference biologic only	BPCIA; FDA-deemed interchangeable products may be dispensed in place of the reference product	Yes	Yes	Purple book

Abbreviations: BPCIA, Biologics Price Competition and Innovation Act; FDA, US Food and Drug Administration.
*Varies from state to state.
†The physician may always choose which products to prescribe, administer, or dispense to the patient. Product selection is not regulated by any federal or state body, but rather reflects the physician's judgement regarding which product will result in desired outcomes—that is, physicians may use data, FDA determinations, etc, to understand equivalence and expected clinical outcomes.
‡The most-restrictive states prohibit any substitution without express consent of the physician. The least-restrictive states mandate substitution if there is an FDA-approved therapeutic equivalent. Most states require patient notification in any situation in which a product is substituted.
§The orange book does not establish substitution.

EXHIBIT 85

REPORT

Opportunities and Challenges in Biosimilar Uptake in Oncology

Carina Dolan, PharmD, BCOP

ABSTRACT

There are now 10 approved biosimilars in the United States, including 3 oncology drugs, and at least 16 others in late-stage development. The introduction of competition into the biologic space launches a new era in the treatment of cancer, possibly increasing access to the extremely costly biologics. The most important and influential stakeholders for biosimilar acceptance and usage are healthcare providers, such as pharmacists and physicians, as well as patients. Gaining their support requires extensive education, postmarketing pharmacovigilance, resolving concerns about immunogenicity, and allowing interchangeability and substitution. Patients require education on the basic definition of biosimilars versus generic drugs, how biosimilars are tested and approved, costs, and availability of clinical trials. Meanwhile, payers may need to find ways to incentivize physicians to prescribe biosimilars over biologics, as well as to provide information on cost and quality directly to patients in order to drive uptake. Finally, legal challenges to approved and pending biosimilars have limited the market access of these agents.

Am J Manag Care. 2018;24(11):S237-S243

For author information and disclosures, see end of text.

Since 2015, when the FDA approved the first biosimilar under the Biologics Price Competition and Innovation Act of 2009, 9 additional biosimilars have received agency approval, including 3 with an oncology indication.[1] Although tbo-filgrastim was approved under the traditional drug approval pathway, many viewed this approval as an example of what biosimilars would look like in the United States following the first approved biosimilar in the European Union. By January 2018, at least 60 biosimilars were enrolled in the FDA's biosimilar development program, with FDA commissioner Scott Gottlieb, MD, reporting that the agency had received requests for meetings to discuss biosimilars for 27 distinct reference biologics.[2]

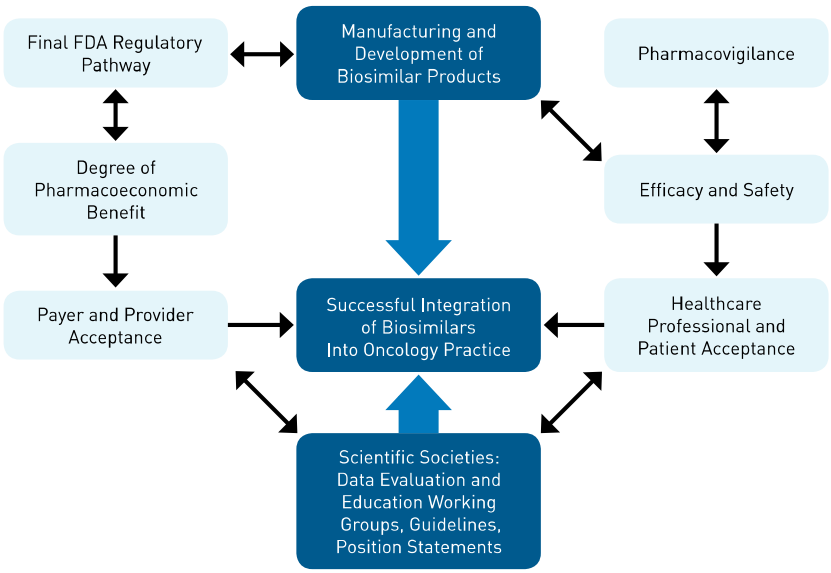
Most recently, pegfilgrastim-jmdb was approved by the FDA to decrease the incidence of infection with febrile neutropenia in patients receiving myelosuppressive chemotherapy similar to its reference product. Bevacizumab-awwb, for the treatment of adult patients with certain colorectal, lung, brain, kidney, and cervical cancers; and trastuzumab-dkst, for the treatment of certain breast and stomach cancers, are approved biosimilars that will have the greatest impact in the oncology arena. The expected lower costs of these drugs are likely to increase access to these therapies, which are among the most expensive drugs in the United States and are often out of reach for the patients who need them most.[3-5]

The successful uptake of biosimilars in the practice of oncology, however, rests on numerous factors, involving clinicians, patients, payers, legislators, and manufacturers. These include the number and timing of entrants into the market; patient and provider acceptability; development costs; competition and litigation involving reference product manufacturers; market size and share; pricing; payer coverage and utilization policies; cost sharing; and regulatory policies around interchangeability (**Figure 1**).[6,7]

Clinician and Patient Uptake of Biosimilars in Oncology

The most important and influential stakeholders for biosimilar acceptance and usage are physicians and patients. However, there is evidence of significant gaps in knowledge for both audiences.

FIGURE 1. Parameters Influencing the Successful Uptake and Integration of Biosimilars Into US Oncology Practices[7]



Recreated from *Seminars in Oncology*, vol 41, suppl 3. Rak Tkaczuk KH, Jacobs IA. Biosimilars in oncology: from development to clinical practice, pages S3-S12, Copyright 2014, with permission from Elsevier.

Physician Barriers

A survey of 376 US oncologists (part of a larger survey that included 1245 oncologists total from the United States, Europe, and Latin America) found that they lacked technical knowledge and understanding of the effects of biologics and biosimilars sharing the same nonproprietary name, and misunderstanding if biologics and biosimilars are structurally and therapeutically identical.[8] Earlier surveys also found significant knowledge gaps regarding all aspects of biosimilars (chemical structure, difference from reference product, approval process, availability of biosimilars in the United States, etc) among clinicians of various specialties.[9-12]

Gaining physician support for and confidence in biosimilars will require evidence demonstrating that the biosimilar provides similar efficacy and safety to the reference product. Still, some aspects of the biosimilar concept remain unclear to practitioners surrounding the biosimilar approval process, required clinical trials, and pharmacovigilance. A 2018 statement by the American Society of Clinical Oncology (ASCO) on the appropriate use of biosimilars in clinical practice highlighted the need for postmarketing evidence development to enhance physician and patient confidence in their use. The authors noted that this was particularly important because regulatory review of biosimilars relies less on clinical data and more on structural, functional, and pharmacologic data. ASCO also noted the challenges of such postmarketing evidence, given the fragmentation of the US healthcare system. It suggested that its CancerLinQ database, which provides data on millions of de-identified patients, and the pending FDA surveillance system, Sentinel, designed to monitor safety issues in clinical trials, could be used to collect these data.[13]

As with any biologic, physicians also have concerns about immunogenicity. Given that biosimilars will, by necessity, be manufactured in a slightly different manner from their reference product, there is concern that switching patients from a biologic to a biosimilar, or vice versa, could result in hypersensitivity reactions. To evaluate that possibility, some clinical trials have included product switching, although assessing immunogenicity often depends on the molecule and the indications studied.[14]

An important issue affecting physician uptake of biosimilars is interchangeability and substitution. To receive interchangeability designation, the manufacturer must demonstrate not only that the biosimilar has similar efficacy and safety to the biologic, but also that there is no greater risk in switching between the biologic and biosimilar than remaining on the reference product.[15] The advantage to the manufacturer is some level of exclusivity.[16] The FDA announced a pathway to interchangeability in January 2017 and is expected to designate the first interchangeable products within the next 2 years.[17]

An interchangeability designation allows the biosimilar to be substituted for the reference product at the pharmacy level similar to the way generic products are substituted for brand drugs today. The physician can still reserve the right to designate the drug by name. Substitution, however, is controlled at the state level. By March 2018, nearly all states, the District of Columbia, and Puerto Rico had passed some type of legislation allowing substitution of biosimilars, although the details vary by state.[18]

The aforementioned survey of 376 US oncologists found that 80% believed it is critically or very important that they be notified if a biosimilar is substituted for the prescribed reference drug. They were also more likely than their Latin American or European peers to believe that patients could switch biologics mid-treatment and expect the same results.[8]

Early experience with the filgrastim biosimilar showed that providers were slower to incorporate biosimilars into their practice until they gained experience and felt comfortable prescribing the biosimilar. One health plan in the United States reported that 30% of filgrastim prescriptions were for the biosimilar, while another reported that prescriptions for the biologic had dropped by a third since the biosimilars entered the market, disclosing initial hesitation from oncologists to prescribe them. Today, many payers are beginning to give biosimilars preferred status on their formularies.[19]

Oncologists also tend to be more comfortable with trying new therapies for patients and adding newly approved drugs to their armamentarium fairly quickly. Moreover, practitioners are feeling pressure from patients about high-cost biologic therapies, causing many physicians to speak out about the cost of therapies.[20]

Patient Knowledge Gaps

Patients need to understand the concept of biosimilars and their place in the treatment continuum. To accomplish this level of awareness requires education, so patients can make an informed decision on their care. A 2015 American Autoimmune-Related Diseases Association survey of 362 of its members, 96% of whom have an autoimmune disease, found that more than 80% did not know what biosimilar medicines were, while about half understood the difference between biologics and biosimilars.[21]

In another consumer-focused survey from the consulting firm PricewaterhouseCoopers conducted in 2015, 67% of consumers did not know what a biosimilar was, while just 17% chose the correct definition from several choices.[22]

Patients require education on the basic definition of biosimilars versus generic drugs; how they are tested and approved; costs; and availability of clinical trials.[14] The ASCO recommendations call for healthcare professionals to educate patients, and for medical societies, government sources, and patient advocacy organizations to provide public awareness and education programs, as well as use standardized, publicly available materials.[13]

Payers may also target patients directly with information about lower costs for biosimilars compared with the biologic medication. Medicare patients today pay a 20% co-payment for Part B drugs, which can be a significant cost for the higher priced biologics.[23] In addition, a growing percentage of commercially insured individuals have high-deductible health plans.[24] Thus, patients are becoming more aware of the cost of their healthcare.[25-27]

Payers and Reimbursement

The majority of cancer biologics are administered in an outpatient setting and paid for under the medical rather than pharmacy benefit (Part B for Medicare). Medicare typically reimburses for medication administered in a physician office or infusion clinic at a rate of the average sales price (ASP) plus 6% as an administrative fee.[28] To incentivize the prescribing of biosimilars, CMS set the administrative fee for the biosimilar based on the ASP of the reference product plus 6% of the reference product's ASP. How individual states will handle reimbursement under their Medicaid programs remains to be seen.[29] Moreover, in January 2018, CMS finalized a ruling on the hospital outpatient prospective payment system (OPPS) for 340b hospitals, adjusting reimbursement to ASP minus 22.5%.[30] This may impact the utilization of biosimilars in the ambulatory setting.

In the acute-care setting, biosimilars can be incorporated through the pharmacy and therapeutics (P&T) committee within the institution. This committee is primarily responsible for approving the pharmacy formulary system for the hospital and includes pharmacists, physicians, hospital administrators, nurses, and additional staff who support the medication use process. Many factors are taken into consideration when reviewing a drug to be placed on the formulary, including clinical effectiveness, operational objectives, cost, and product supply chain. Policies and procedures are approved that can include automatic substitution for medications to match the hospital formulary. Furthermore, the P&T committee can assist and direct staff educational programs that reflect changes to the formulary.

Additional payer reimbursement and requirements may also affect biosimilar uptake. Germany, which has one of the strongest uptakes of biosimilars in the world, incentivizes its doctors to prescribe biosimilars through quotas, budgeting, and monitoring programs, while key opinion leaders and medical associations provide education and integrate the use of biosimilars into their guidelines.[30] Providing similar incentives for clinicians could drive uptake in the United States and, with the movement toward value-based reimbursement, may help drive the utilization of biosimilars. For instance, payers could offer higher in-office payments for clinicians who meet certain prescribing levels for biosimilars versus biologics.[25]

Another potential barrier to the clinical integration of biosimilars may be the temporal and financial investment required to make the distribution change from the current biologic to a biosimilar. It is important to take into consideration the fine details that participants in the supply chain, such as manufacturers, pharmacy benefit managers, and specialty pharmacies, have in place to encourage continued prescribing of the reference product.[14]

Finally, although there are now 10 approved biosimilar drugs, only 3 are currently on the market. These delays in launching the biosimilar products are a result of pending litigation from the reference drug manufacturer. This presents a challenge for the ability of the biosimilars to penetrate the market in a timely fashion. Furthermore, brand suppliers are bringing new products to the market by enhancing the original biologic, otherwise known as follow-on biologics or "biobetters."[31] These new molecular entities are altered versions of approved biologics designed to improve their method of administration, safety, efficacy, or manufacturing.[32] All of these issues may limit the potential cost savings from biosimilar use in the next several years, although their use will likely increase over time due to supply and demand factors.[33]

The Economic Implications of Biosimilars in Cancer Therapy

Historically, when a generic drug enters the market, the cost is less than that of the brand manufacturer. However, payers should not

FIGURE 2. Biologic Market Relationships[6]

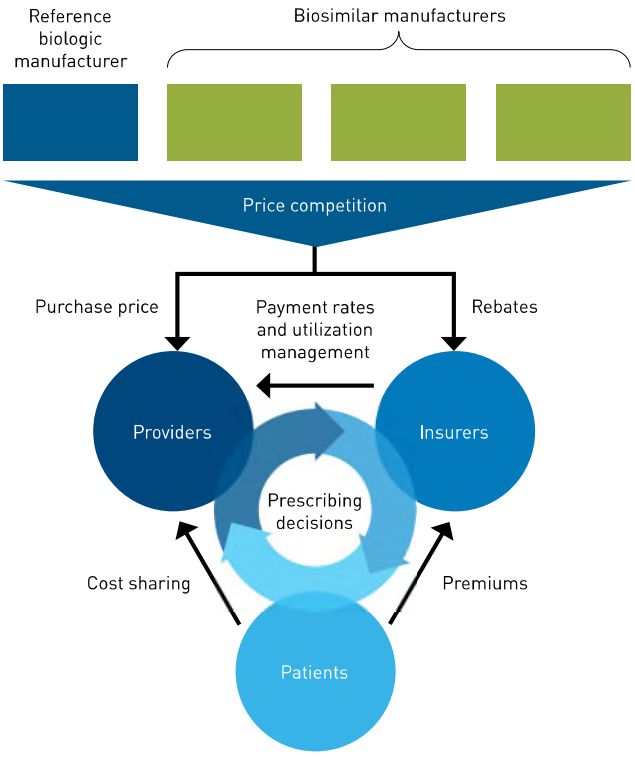


Figure adapted from Mulcahy AW, Hlávka JP, Case SR. *Biosimilar Cost Savings in the United States: Initial Experience and Future Potential.* Santa Monica, CA: RAND Corporation; 2017. www.rand.org/pubs/perspectives/PE264.html.

expect this level of price differential when it comes to biologics and biosimilars, nor even the 50% price differential they had hoped for.[31] There are several reasons for this, including the higher cost of bringing a biosimilar to market. This can cost more than $100 million and take 5 years or more compared with the $2 million to $5 million and 2 years required for a generic.[33]

Other barriers to lower pricing include complex, high-cost manufacturing processes; direct marketing to clinicians to share clinical data and highlight the efficacy and safety of the biosimilar compared with the original drug; development of a sales force in a new therapeutic arena; the need for phase 4 studies to demonstrate real-world safety and efficacy; and the likelihood that there may be a limited number of biosimilars in a given category.[34]

At the same time, rebates provided by pharmacy benefit managers and manufacturers that are tied to utilization of the reference drug may also mitigate any price reductions. Missing out on those rebates if patients are switched to biosimilars could make the reference drug much costlier, wiping out any savings from the biosimilar.[31]

A 2017 analysis from the RAND Corporation estimated that biosimilars would reduce direct spending on biologic drugs by $54 billion between 2017 and 2026, or about 3% of the total estimated biologic spending over the same period, with a range of $24 billion to $150 billion. The researchers cautioned, however, that the actual savings are dependent on industry, regulatory, prescriber, and insurer decisions, as well as potential future policy changes to strengthen the biosimilar market (**Figure 2**).[6]

As part of its analysis, RAND provided a case study on the uptake and cost savings of filgrastim-sndz and tbo-filgrastim. By the end of 2016, these 2 biosimilar-related products held a third of the total filgrastim market and were marketed at a 30% (tbo-filgrastim) and 45% (filgrastim-sndz) discount. RAND also noted that total spending on all 3 products (including filgrastim reference drug) dropped significantly between 2013 and 2016, suggesting the impact of the biosimilars. In addition, while the net price of filgrastim did not change during this time, both biosimilar-related drugs experienced large price decreases following their launch, likely due to competition in the marketplace, demonstrating that biosimilars could also increase access to more expensive drugs.[6,35,36]

A 2017 simulation analysis of the cost savings resulting from the use of filgrastim-sndz versus filgrastim on 20,000 patients with follicular lymphoma found a per-cycle cost savings between $327 and $915, depending on the length of the cycle, yielding a savings between $6.54 million (5-day cycle) and $18.3 million (14-day cycle). The authors estimated that the savings would generate expanded access to the biologic obinutuzumab, approved for relapsed/refractory follicular lymphoma and previously untreated chronic lymphocytic leukemia, to between 60 and 169 patients in a budget-neutral manner.[37]

The same analysis showed that switching patients from pegfilgrastim to filgrastim-sndz yielded savings of between $55.9 million for 5 days of treatment and $16.7 million for a 14-day cycle. The savings would expand access to obinutuzumab treatment for patients in a budget-neutral manner.[37]

New and Emerging Cancer Biosimilar Agents

Several oncologic biosimilars to trastuzumab, rituximab, cetuximab, and bevacizumab are in late-stage clinical trials (**Table**[38-51]).

Trastuzumab. The trastuzumab biosimilar CT-P6 demonstrated similar efficacy and safety in a head-to-head trial with trastuzumab (both combined with paclitaxel) in HER2-positive metastatic breast cancer (MBC) as well as in the neoadjuvant setting in women with early-stage breast cancer.[38,39] The biosimilar BCD-022 also demonstrated similar efficacy and safety in the MBC setting.[40] Another trastuzumab biosimilar candidate, SB3, was also studied in the neoadjuvant study in patients with early-stage breast cancer. It demonstrated equivalence based on pathologic clinical response rate, safety, pharmacokinetics, and immunogenicity.[41]

Rituximab. Several biosimilars are under investigation for rituximab, including CT-P10 in patients with follicular lymphoma. Early results from an ongoing randomized clinical trial in patients with late-stage disease demonstrated CT-P10's similar efficacy, safety,

TABLE. Investigational Oncology Biosimilars[38-51]

Biosimilar	Clinical Trial	Outcome
Trastuzumab		
CT-P6	Phase 3 in 475 patients with HER2-positive MBC	Similar ORR and TTP in combination with paclitaxel
	Phase 3 in neoadjuvant setting in 549 women with early-stage breast cancer in conjunction with neoadjuvant docetaxel and FEC	Similar PCR and safety between the 2 cohorts
BCD-022	Phase 3 in 46 patients with HER2-positive MBC randomized to BCD-022 or trastuzumab, both with paclitaxel	Noninferiority to trastuzumab with similar safety, tolerability, and immunogenicity
SB3	Phase 3 in 800 HER2-positive patients in the neoadjuvant setting who also received docetaxel and FEC	Equivalence by ratio of breast PCR rates; similar safety, pharmacokinetics, and immunogenicity
HLX02	Untreated MBC	Ongoing
CT-P10	Phase 3 in 140 patients with newly diagnosed, advanced-stage follicular lymphoma	No significant differences in efficacy, pharmacokinetics, or safety. Application pending with the FDA
BCD-020	Phase 3 in 92 patients with non-Hodgkin lymphoma	Similar ORR and adverse event profile between both arms
HLX01	Phase 3 study in combination with CHOP in previously untreated patients with CD20+ DLBCL	Ongoing
GP2013	Phase 3 study in 629 patients with previously untreated advanced follicular lymphoma (both arms also received cyclophosphamide, vincristine, and prednisone)	Demonstrated equivalence in ORR with similarity for efficacy and for PK and PD parameters. Application pending with FDA
Rituximab		
HD201	Phase 3 in patients with MBC	Ongoing
Bevacizumab		
BCD-021	Phase 3 in 138 patients with nonsquamous NSCLC in combination with carboplatin plus paclitaxel	Demonstrated similar ORR, safety, and immunogenicity
SB8	Phase 3 in patients with advanced nonsquamous NSCLC	Ongoing
MB02	Phase 3 in patients with stage IIIB/IV NSCLC	Ongoing
BEVZ92	Phase 3 in patients with previously untreated mCRC	Ongoing
HD204	Phase 3 in patients with advanced nonsquamous NSCLC	Ongoing
BCD-021	Phase 3 in patients with NSCLC in combination with paclitaxel and carboplatin	Ongoing
Cetuximab		
STI-001	Phase 3 of biosimilar with irinotecan in 501 patients with colorectal cancer against irinotecan monotherapy	Significant improvement compared with chemotherapy alone in ORR, PFS, and OS according to press release; no published results yet

CHOP indicates cyclophosphamide, hydroxydaunomycin, vincristine, prednisolone; DLBCL, diffuse large B-cell lymphoma; FEC, 5-fluorouracil, epirubicin, and cyclophosphamide; HER2, human epidermal growth factor receptor 2; MBC, metastatic breast cancer; mCRC, metastatic colorectal cancer; NSCLC, non-small cell lung cancer; ORR, overall response rate; OS, overall survival; PCR, pathological complete response; PD, pharmacodynamics; PFS, progression-free survival; PK, pharmacokinetics; TTP, time to progression.

and pharmacokinetic equivalence to rituximab.[42] Meanwhile, the biosimilar BCD-020 demonstrated significant difference in overall relapse rate and safety compared with rituximab in 92 patients with follicular or marginal zone non-Hodgkin lymphoma.[43] A third rituximab biosimilar, RTX-M83, demonstrated comparable efficacy to rituximab in terms of tumor response, pharmacokinetic profile, pharmacodynamic activity, safety, and immunogenicity in patients with previously untreated CD20+ diffuse large B-cell lymphoma.[44]

Bevacizumab. Bevacizumab biosimilar candidates include BCD-021, studied in patients with advanced nonsquamous non–small cell lung cancer (NSCLC) in combination with paclitaxel plus carboplatin. There were no significant differences in efficacy or safety between the biosimilar and the reference product.[45] At least 5 other bevacizumab biosimilars are in late-stage clinical trials.[46]

Cetuximab. One of the first biosimilars to be studied against a drug other than the reference biologic, STI-001, was investigated in EGFR-expressing metastatic colorectal cancer patients in combination with irinotecan versus irinotecan alone. The combination therapy showed significant improvement compared with chemotherapy alone with an overall response rate of 32.9% versus 12.8%, a

progression-free survival rate of 5.6 versus 3.2 months, and overall survival of 14.1 versus 13.4 months.[47] The manufacturer also reported significantly fewer adverse events than in studies of the reference product, with no hypersensitive reaction compared with more than 10% of patients in the cetuximab trials. The manufacturer attributed the difference to a different production method. However, the results have not yet been published, only announced in a 2016 press release. Several other cetuximab biosimilars are in early development.[48]

Conclusions

As more patents begin to expire on oncologic biologics, the pace of biosimilar development in this therapeutic arena will pick up speed. At least 16 biosimilars are now in late-stage development and 2 are already approved (albeit not on the market as of March 2018). Their uptake in the oncology community, however, remains unclear. Challenges include physician and patient understanding of biosimilars versus biologics, particularly in terms of approval process; concerns over immunogenicity; pricing; interchangeability and substitution; cost; and supply chain issues. The option biosimilars offer, even at a 15% discount, will likely overcome these barriers as they move into the market and offer some promise for future treatments. ■

Additional Resources	
FDA	fda.gov
European Medicines Agency	ema.europa.eu/ema
The Center for Biosimilars	centerforbiosimilars.com
Generics and Biosimilars Initiative	gabionline.net

Author affiliation: Director of Clinical Oncology and Pharmaceutical Outcomes, Center for Pharmacy Practice Excellence, Vizient, Irving, TX.

Funding source: This activity is supported by educational funding provided by Amgen Inc.

Author disclosure: Dr Dolan is an employee of Vizient in Irving, TX.

Authorship information: Concept and design, drafting of the manuscript, and critical revision of the manuscript for important intellectual content.

Address correspondence to: carina.dolan@vizientinc.com.

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EXHIBIT 86

Follow The Pill:
Understanding the U.S. Commercial Pharmaceutical Supply Chain

Prepared for The Kaiser Family Foundation by:

The Health Strategies Consultancy LLC

March 2005

Table of Contents

I. Executive Summary

The pharmaceutical supply chain is the means through which prescription medicines are delivered to patients. Pharmaceuticals originate in manufacturing sites; are transferred to wholesale distributors; stocked at retail, mail-order, and other types of pharmacies; subject to price negotiations and processed through quality and utilization management screens by pharmacy benefit management companies (PBMs); dispensed by pharmacies; and ultimately delivered to and taken by patients. There are many variations on this basic structure, as the players in the supply chain are constantly evolving, and commercial relationships vary considerably by geography, type of medication, and other factors.

The intent of this paper is to demystify the U.S. pharmaceutical supply chain. The first section of the paper describes each of the key players (i.e., industry segments) involved in the process of supplying prescription drugs to consumers. The section begins with a discussion of what each player does and the role that it plays in the flow of pharmaceuticals from manufacturer to patient. The second section of the paper describes the financial relationships between each of these key players and how the dollars flow between and among the segments, including the consumer.

Highlights from this paper about the key players and their financial relationships include:

Pharmaceutical Manufacturers:

- A relatively few large, multinational firms comprise the bulk of the brand pharmaceutical manufacturing industry today – the 10 largest pharmaceutical corporations, as measured by U.S. sales, accounted for almost 60 percent of total U.S. sales in 2004.
- Pharmaceutical manufacturers have the most influence over pharmaceutical prices, assessing expected demand, future competition, and projected marketing costs to establish the wholesale acquisition cost (WAC), which is the baseline price at which wholesale distributors purchase drug products. Discounts and rebates may be applied, based on market share, volume, and prompt payment.

Wholesale Distributors:

- The wholesale distribution industry has consolidated in the last 30 years, with the number of wholesale distributors in the U.S. declining from approximately 200 in 1975 to fewer than 50 in 2000. The top 3 wholesale distributors account for almost 90 percent of the wholesale market.
- Wholesale distributors typically sell drugs to pharmacies at WAC plus some negotiated percentage. They may facilitate discounts negotiated between manufacturers and other customers.

Pharmacies:

- Although comprising a small overall percentage of total prescriptions filled (approximately 6.1 percent in 2004), mail-order pharmacy sales were the fastest-growing sector of the U.S. prescription drug retail market in 2004, increasing by 18 percent over the previous year.

- Pharmacies may negotiate with manufacturers or wholesalers for discounts and rebates based on volume sales or market share, and they may negotiate with PBMs for inclusion in their networks and for their reimbursement (drug cost plus dispensing fee).

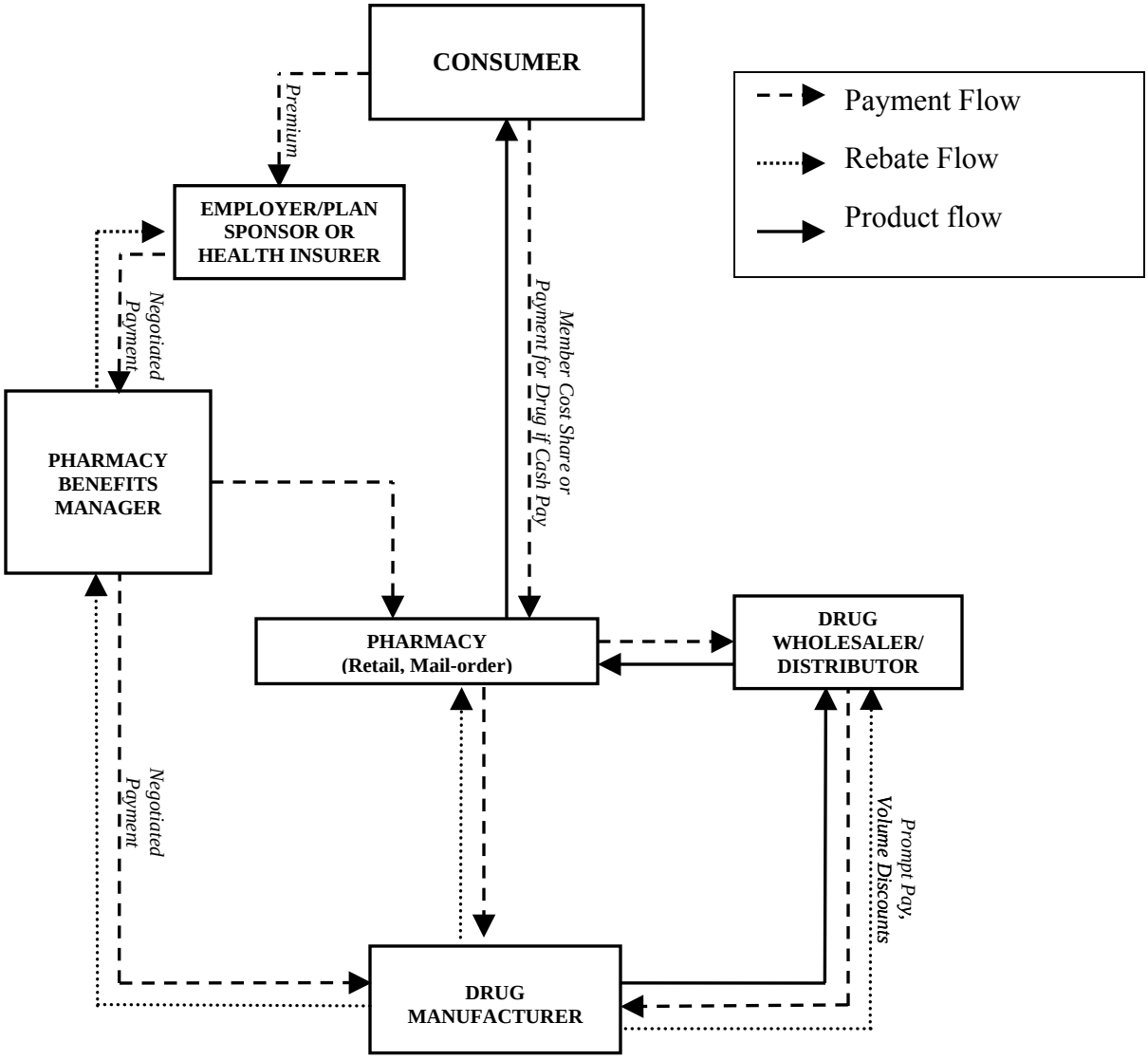
Pharmacy Benefit Managers (PBMs):

- Approximately two-thirds of all prescriptions written in the U.S. are processed by a PBM.
- PBMs may achieve savings for their customers by negotiating discounts and through cost containment programs, including use of formularies and cost sharing.

The Appendix briefly describes: (A) special pricing rules applicable to Medicaid and some other federal programs, and (B) the roles physicians, large employers, and health plans have in the pharmaceutical supply chain.

The pharmaceutical supply system is complex, and involves multiple organizations that play differing but sometimes overlapping roles in drug distribution and contracting. This complexity results in considerable price variability across different types of consumers, and the supply chain is not well understood by patients or policymakers. Increased understanding of these issues on the part of policymakers should assist in making rational policy decisions for the Medicare and Medicaid programs.

Exhibit 1. Flow of Goods and Financial Transactions Among Players in the U.S. Commercial Pharmaceutical Supply Chain



Source: The Health Strategies Consultancy LLC

II. The Flow of Goods from Manufacturers to Consumers in the U.S. Pharmaceutical Supply Chain

Pharmaceutical Manufacturers

Manufacturers are the source of the prescription drugs in the pharmaceutical supply chain. The pharmaceutical manufacturing industry is composed of two distinct business models: manufacturers of brand-name drugs (e.g., Pfizer, Merck, and Novartis) and manufacturers of generic drugs (e.g., Mylan, Roxane, and Barr). There are a few pharmaceutical companies that participate in both the branded and generic parts of the industry, and both models focus on the manufacturing and packaging of pharmaceutical products, but there are other important differences. Most brand manufacturers devote a portion of their expenses to the scientific research and development of new drug therapies. Generic drug manufacturers typically do not develop new drug therapies, but instead manufacture generic compounds that compete directly with the original branded version of a drug once the brand product's patent protection has expired.

Manufacturers manage the actual distribution of drugs from manufacturing facilities to drug wholesalers, and in some cases, directly to retail pharmacy chains, mail-order and specialty pharmacies, hospital chains, and some health plans. Manufacturers may also distribute products directly to government purchasers, such as the Veterans Administration, AIDS Drug Assistance Programs (ADAPs), and Vaccines for Children (VFC), which typically receive the largest price discounts. In a few rare cases, a manufacturer may distribute drugs directly to a self-insured employer with an on-site pharmacy, but the typical employer-sponsored plan does not follow this path. Wholesale distributors are the manufacturers' largest purchasers. Very few drugs are distributed directly to consumers.

At the most basic economic level, a pharmaceutical manufacturer supplies a quantity of its products that is equal to the demand for its products from consumers/patients (of course, consumer demand in this market is expressed through the medium of a prescribing physician or other licensed health care provider). Manufacturers also play roles in stimulating demand for drug products through underwriting clinical studies designed to demonstrate the value proposition of pharmaceutical treatments compared to one another or compared to no clinical treatment at all; by engaging in the promotion and marketing of products to health care providers (including health plans and PBMs) and direct-to-consumer advertising; and by administering patient assistance programs that provide the firm's products at nominal cost to low-income consumers.

Manufacturers also play an important role in ensuring the safety of the pharmaceutical supply chain by producing informational labeling for prescribers and consumers that is consistent with the terms and conditions of a drug's approval by the U.S. Food and Drug Administration (FDA), and by using electronic bar-coding technology on drug packaging that may be used to track individual production lots, and to prevent prescribing errors.

Overview of Pharmaceutical Manufacturing Industry

Pharmaceutical manufacturing is a large global industry. In 2003, worldwide pharmaceutical industry sales totaled $491.8 billion, an increase in sales volume of 9 percent over the preceding year.[1] The U.S. represents the largest single national market for pharmaceuticals, accounting for 44 percent of global industry sales in 2003, or a total of $216.4 billion, which was an increase of approximately 12 percent from the previous year's figure.[2]

After a decade of significant mergers and acquisitions by drug companies, a relatively few large, multinational firms comprise the bulk of the brand pharmaceutical manufacturing industry today. The ten largest pharmaceutical corporations, as measured by U.S. sales, accounted for almost 60 percent of total U.S. sales in 2004:

Exhibit 2. Top 10 Pharmaceutical Corporations by U.S. Sales, 2004

Rank	Corporation	U.S. Sales ($ Billions)	% Growth Over Previous Year	% Market Share
1	Pfizer	$30.7	5	13.1
2	GlaxoSmithKline	18.8	1	8.0
3	Johnson & Johnson	16.2	7	6.9
4	Merck & Co.	15.0	8	6.4
5	AstraZeneca	11.3	12	4.8
6	Novartis	10.2	7	4.3
7	Sanofi-Aventis	10.0	13	4.3
8	Amgen	9.5	23	4.1
9	Bristol-Myers Squibb	9.2	-4	3.9
10	Wyeth	8.2	11	3.5
	Total, Top 10	139.1	--	59.3

Source: IMS Health, IMS National Sales Perspectives,™ February 2005, accessed 2/28/05 at http://www.imshealth.com/ims/portal/front/articleC/0,2777,6599_49695983_69891374,00.html

[1]IMS Health, "Bruised But Triumphant," *Medical Marketing and Media*, May 2004, accessed at http://www.imshealth.com/vgn/images/portal/cit_40000873/23/12/55250930BruisedTriumphant081804.pdf

[2]IMS Health, "IMS Reports 11.5 Percent Dollar Growth in '03 U.S. Prescription Sales," February 17, 2004, accessed at http://www.imshealth.com/ims/portal/front/articleC/0,2777,6599_3665_44771558,00.html. Prescription sales figures reported by IMS Health represent manufacturer prices.

When measured by prescription volume, the "top 10" list is similar but not identical, as a few generic drug manufacturers appear on the list:

Exhibit 3. Top 10 Pharmaceutical Corporations by Total U.S. Dispensed Prescriptions, 2004

Rank	Corporation	U.S. Prescriptions (Millions)	% Growth Over Previous Year	% Market Share
1	Pfizer	360.7	-4	10.2
2	Novartis	225.5	-2	6.4
3	Teva*	221.2	7	6.3
4	Mylan Labs*	215.2	4	6.1
5	Watson*	175.6	7	5.0
6	GlaxoSmithKline	138.8	-13	3.9
7	Merck & Co.	129.5	3	3.7
8	AstraZeneca	100.4	11	2.9
9	Johnson & Johnson	95.6	-9	2.7
10	Abbott	91.5	-4	2.6
	Total, Top 10	1754.0.		49.8

* Generic drug manufacturers
Source: IMS Health, National Prescription Audit™Plus, January 2005, accessed 2/28/05 at http://www.imshealth.com/ims/portal/front/articleC/0,2777,6599_49695974_68913574,00.html

Exhibit 4 provides a description of the generic pharmaceutical market:

Exhibit 4. Top 10 Generic Manufacturers by Total Global Sales, 2003

Rank	Corporation	Global Sales ($ Millions)	% Growth Over Previous Year
1	Sandoz	$4,004.0	
2	Teva Pharmaceutical Industries Limited	3,276.4	30.1
3	IVAX Corporation	1,420.3	18.6
4	Mylan Laboratories Inc.	1,269.2	15.0
5	Alpharma Inc.	1,297.3	4.8
6	Andrx Corporation	1,046.3	35.7
7	Barr Pharmaceuticals, Inc.	902.9	-24.1
8	Par Pharmaceutical Companies, Inc.	661.7	73.4
9	American Pharmaceutical Partners, Inc.	351.3	26.6
10	Eon Labs, Inc.	329.5	34.9

Source: Hoover's, Inc. Hoover's Online, accessed 1/03/2005.

To convey the size of the pharmaceutical manufacturing industry from the perspective of individual products, the following tables present data on the biggest selling pharmaceutical products in the United States in 2004, measured by prescriptions dispensed and by sales in dollars. Exhibits 5 and 6 are for individual drug products, while Exhibits 7 and 8 are for broader therapeutic classes of drugs.

Exhibit 5. Top 10 Products by Total U.S. Dispensed Prescriptions, 2004

Rank	Product	Manufacturer	Prescriptions (Millions)	% Growth Over Previous Year	% Market Share
1	Lipitor	Pfizer	74.8	9	2.1
2	HYCD/APAP	Mallinckrodt	49.5	12	1.4
3	Synthroid	Abbott	47.4	-5	1.3
4	Norvasc	Pfizer	38.3	5	1.1
5	Toprol-XL	AstraZeneca	35.0	18	1.0
6	Zoloft	Pfizer	33.1	1	0.9
7	Zocor	Merck	29.6	1	0.8
8	HYCD/APAP	Watson	29.0	-2	0.8
9	Albuterol	Warrick	26.8	0	0.8
10	Amoxicillin	Teva	26.2	-5	0.7

Source: IMS Health, National Prescription Audit™Plus, January 2005, accessed 2/28/05 at http://www.imshealth.com/ims/portal/front/articleC/0,2777,6599_49695974_68913594,00.html

Exhibit 6. Top 10 Products by U.S. Sales, 2004

Rank	Product	Manufacturer	U.S. Sales ($ Billions)	% Growth Over Previous Year	% Market Share
1	Lipitor	Pfizer	$7.7	14	3.3
2	Zocor	Merck	4.6	4	1.9
3	Prevacid	TAP	3.8	-5	1.6
4	Nexium	AstraZeneca	3.8	23	1.6
5	Procrit	Ortho Biotech	3.2	-3	1.4
6	Zoloft	Pfizer	3.1	8	1.3
7	Epogen	Amgen	3.0	-4	1.3
8	Plavix	Sanofi-Synthelabo	3.0	33	1.3
9	Advair Diskus	GlaxoSmithKline	2.9	26	1.2
10	Zyprexa	Eli Lilly	2.8	-10	1.2

Source: IMS Health, IMS National Sales Perspectives,™ February 2005, accessed 2-28-05 at http://www.imshealth.com/ims/portal/front/articleC/0,2777,6599_49695983_69890133,00.html

Exhibit 7. Top 10 Therapeutic Classes by Total U.S. Dispensed Prescriptions, 2004

Rank	Therapeutic Class	Total Prescriptions (Millions)	% Growth over Previous Year	% Market Share
1	Codeine	157.6	5	4.5
2	SSRIs/SNRIs	147.4	4	4.2
3	ACE Inhibitors	143.8	5	4.1
4	HMG-COA Reductase Inhibitors (Statins)	139.8	11	4.0
5	Beta Blockers	120.6	7	3.4
6	Proton Pump Inhibitors	93.1	-2	2.6
7	Thyroid Hormone, Synthetic	90.0	6	2.6
8	Calcium Blockers	88.4	0	2.5
9	Seizure Disorders	84.8	7	2.4
10	Oral Contraceptives	82.5	-3	2.3

Source: IMS Health, National Prescription Audit™Plus, January 2005, accessed 2/28/05 at http://www.imshealth.com/ims/portal/front/articleC/0,2777,6599_49695974_68914714,00.html

Exhibit 8. Top 10 Therapeutic Classes by U.S. Sales, 2004

Rank	Therapeutic Class	U.S. Sales ($ Billions)	% Growth Over Previous Year	% Market Share
1	HMG-COA Reductase Inhibitors (Statins)	$15.5	12	6.6
2	Proton Pump Inhibitors	12.5	-3	5.3
3	SSRIs/SNRIs	11.0	1	4.7
4	Antipsychotics, Other	9.1	12	3.8
5	Seizure Disorders	8.2	19	3.5
6	Erythropoietins	8.0	8	3.4
7	Antiarthritics, COX-2 Inhibitors	5.3	0	2.3
8	Calcium Channel Blockers	4.4	1	1.9
9	Angiotensin II Antagonists	4.4	24	1.9
10	Ace Inhibitors	3.9	-5	1.7

Source: IMS Health, IMS National Sales Perspectives,™ February 2005, accessed 2/28/05 at http://www.imshealth.com/ims/portal/front/articleC/0,2777,6599_49695983_69891394,00.html

Wholesale Distributors

Wholesale distributors purchase pharmaceutical products from manufacturers and distribute them to a variety of customers, including pharmacies (retail and mail-order), hospitals, and long-term care and other medical facilities (e.g., community clinics, physician offices and diagnostic labs). Some wholesalers sell to a broad range of potential clients while others specialize in sales of particular products (e.g., biologic products) or sales to particular types of customers (e.g., nursing homes).

Exhibit 9. Wholesale Distribution Industry

In 2004, the wholesaler distributor industry is valued at approximately $212 billion in annual U.S. sales. The following three wholesalers represent 88% of the market:

1) McKesson

- Merged with health-care software giant HBO & Co. in 1998
- Rolling 12-month sales as of September 2004: $72.2 billion**;** Market Share: 34.1%

2) Cardinal Health

- From 1999 – 2002, Cardinal merged with many other wholesalers including Allegiance Corporation and Bindley Western Industries
- Rolling 12-month sales as of September 2004: $63.3 billion**;** Market Share: 29.9%

3) AmerisourceBergen

- Began operations in August 2001 following merger of AmeriSource Health Corporation and Bergen Brunswig Corporation
- Rolling 12-month sales as of September 2004: $52.4 billion**;** Market Share: 24.8%

Source: *GICS Sub-Industry Revenue Share (09/04/2004).*

In the past, wholesalers limited their operations to a traditional distribution function. They provided the link between manufacturers and pharmacies (and other entities, e.g., government sites and physicians) by warehousing products and managing inventory. While "traditional" distribution services remain the cornerstone of the business, the industry has developed a more comprehensive list of services in response to the evolving

marketplace. Today, wholesale distributors provide a number of specialized services, including specialty drug distribution, drug repackaging, electronic order services, reimbursement support, and drug buy-back programs.[3]

The wholesale distribution industry has gone through significant change and consolidation in the last 30 years, due in part to the increasing pressures to lower costs. Between 1975 and 2000, the number of wholesale distributors in the U.S. declined from approximately 200 to fewer than 50.[4] The top three wholesale distributors, McKesson, Cardinal Health, and Amerisource-Bergen, account for almost 90 percent of the entire wholesale drug market.[5]

This consolidation has forced the industry to change its revenue model, evolving its core distribution business into a low-margin enterprise that makes money by maximizing economies of scale, creating physical efficiencies in the distribution system (such as "just-in-time" deliveries to customers), and realizing financial efficiencies (such as retaining discounts for prompt payment). The industry has also extended and augmented its business model by moving into specialty pharmacy and disease management services.

Pharmacies

Pharmacies are the final step on the pharmaceutical supply chain before drugs reach the consumer/patient. Pharmacies purchase drugs from wholesalers, and occasionally directly from manufacturers, and then take physical possession of the drug products. After purchasing pharmaceuticals, pharmacies assume responsibility for their safe storage and dispensing to consumers. Pharmacy operations include maintaining an adequate stock of drug products, providing information to consumers about the safe and effective use of prescription drugs, and facilitating billing and payment for consumers participating in group health benefit plans.

Pharmacies also serve as a vital information link between PBMs, drug manufacturers, and wholesale distributors. Unlike most other sectors of the health care delivery system in the U.S., the pharmaceutical supply chain is highly automated and virtually all claims transactions are handled electronically, rather than on paper. Since they are the final point of sale for pharmaceuticals and the interface between the supply chain and the consumer, pharmacies generate the prescription drug claims information that PBMs, as well as heath plans, employers, governments, and other payers, rely upon to measure consumer activity. Other types of information, both quality-focused (e.g., drug-drug interaction warnings) and utilization management-based (e.g., formulary compliance

[3] Drug buy-back programs are offered by manufacturers and are facilitated by wholesale distributors. Buy-back programs are intended to minimize the financial risk that pharmacies must assume in stocking products by allowing them to sell unused products or products with near-term expiration dates back to the manufacturer.
[4] Goldman Sachs Industry Report: Health Care Technology & Distribution, February 27, 2003.
[5] Standard & Poor's, *GICS Sub-Industry Revenue Share,* September 4, 2004.

messaging) can originate from other parts of the supply chain, in particular from PBMs, to the pharmacy as a prescription is being dispensed. As the final actor in the supply chain, it is up to the pharmacy to take action based on the information provided. For example, the pharmacy is expected to contact the prescribing physician if the drug prescribed is not on the patient's health plan's formulary or if a lower-cost therapeutic alternative is available.

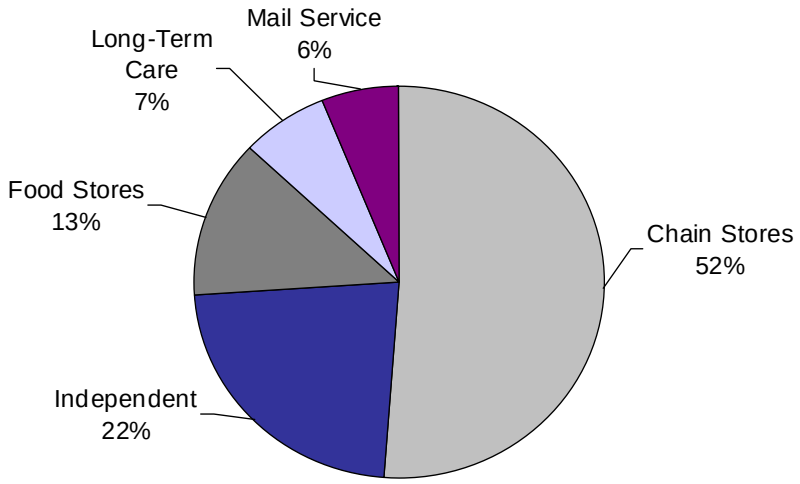
There are several types of pharmacies, including independent pharmacies, chain drug stores, pharmacies in supermarkets and other large retail establishments, and mail-order pharmacies. Most pharmacies purchase their drug supply from a wholesale distributor, although in some cases, large institutional and retail chain pharmacies, specialty pharmacies, and mail-order pharmacies obtain drugs directly from a manufacturer. These organizations can deal directly with manufacturers because they already possess the operational infrastructure necessary to bypass wholesalers – warehousing facilities, distribution vehicles, and inventory control systems. Once a pharmacy takes possession of the drug products, it distributes the products to physicians or directly to consumers. In addition, there are specialty pharmacies, which specialize in the distribution of high-cost and more complex drug therapies (e.g., self-injectable drugs and biologics).

In 2003, there were 55,000 community retail pharmacies, including 19,000 independent drug stores, 21,000 chain drug stores, and 16,000 pharmacies in supermarkets and other retail merchants.[6] In 2004, there were 3.5 billion prescriptions dispensed in the United States through community pharmacies, including about 1.8 billion filled at chain drug stores, 780 million filled at independent pharmacies, and 470 million filled in supermarkets. Another 214 million prescriptions were filled through the mail.[7]

[6] National Association of Chain Drug Stores, http://www.nacds.org/user-assets/PDF_files/Retail_Outlets2003.pdf.
[7] IMS Health, National Prescription Audit™Plus, January 2005, accesses 2/28/05 at http://www.imshealth.com/ims/portal/front/articleC/0,2777,6599_49695974_68913551,00.html

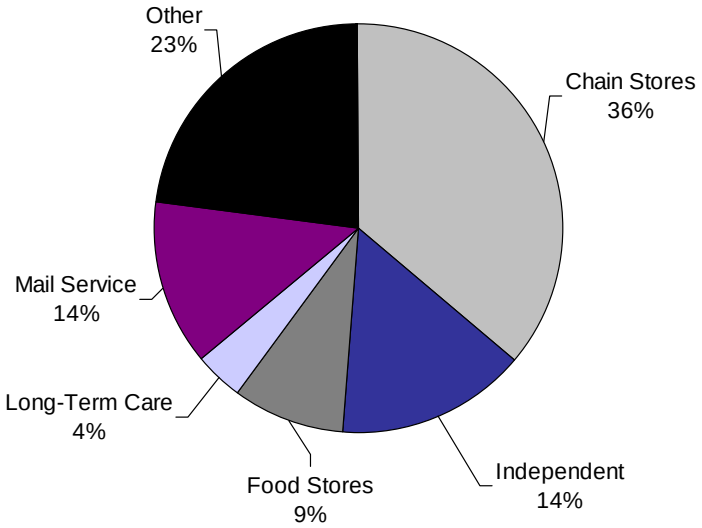
Exhibits 10 and 11 depict the distribution of pharmaceuticals in the U.S. through the various types of "retail" pharmacy channels:

Exhibit 10. Number of Prescriptions by Pharmacy Distribution Channel, 2004



Note: Represents total dispensed prescriptions, including insulin dispensed through chain, food store, independent, long term care, and mail service pharmacies.
Source: IMS Health, National Prescription Audit™ Plus, January 2005, accessed 2/28/05 at www.imshealth.com/ims/portal/front/articleC/0,2777,6599_49695974_68913551,00.html

Exhibit 11. Drug Sales by Pharmacy Distribution Channel, 2004



Note: Represents wholesale prices. Sales include prescription products only.
Source: IMS Health, IMS National Sales Perspectives,™ February 2005, accessed 2/28/05 at http://www.imshealth.com/ims/portal/front/articleC/0,2777,6599_49695983_69891354,00.html

Like all other parts of the pharmaceutical supply chain, the pharmacy industry has gone through significant consolidation as well as diversification of its businesses over the past five to ten years. Several retail pharmacy chains have merged, primarily as a way to gain buying power for use in negotiations with drug manufacturers and wholesale distributors.

As shown in Exhibit 12, Walgreens, CVS, and Rite Aid were the top three retail pharmacy chains based on market capitalization:

Exhibit 12. Top 5 Retail Pharmacy Chains in the U.S., By Market Capitalization

Rank	Pharmacy Chain	2004 Market Cap
1	Walgreens Company	$35.2 bil.
2	CVS Corporation	$16.1 bil.
3	Rite Aid	$2.6 bil.
4	Longs Drug Stores	$0.7 bil.
5	Duane Reade	$0.4 bil.
	Total for Industry	$103.0 bil.

Source: Health Strategies Consultancy analysis of Pharmacy/Drug Store Industry based on market cap data obtained from Dow Jones (factiva.com)[8]

In addition to traditional retail pharmacy services, consumers have increasingly been using specialty and mail-order pharmacies over the past several years. Growth in the use of these types of pharmacies is expected to increase rapidly for the foreseeable future, as more payers adopt the view that these specialized retail distribution channels can be important components of their strategies to manage the rate of growth in their pharmacy benefit expenditures. Residents of long-term care facilities (LTC) rely almost exclusively on dedicated LTC pharmacies.

- ***Specialty pharmacies*** serve patients with chronic diseases by dispensing high-cost biotechnology drugs. Specialty pharmaceuticals typically are administered by injection or infusion (intravenously), and often, are administered by a clinical professional in a doctor's office. The diseases treated with specialty pharmaceuticals range from relatively common conditions, some of which are treated with multiple drug therapies, such as HIV/AIDS, multiple sclerosis, cancer, and rheumatoid arthritis, to rare diseases that are treated with a single drug therapy, such as hemophilia and growth hormone deficiency. The specialty pharmacy industry today is dynamic, with new companies entering continuously. Types of firms in the market range from publicly-traded stand-alone firms to subsidiaries of PBMs, retail pharmacies, and home health companies.[9,10]

[8] Market capitalization is the value of a company's outstanding shares of stock, which is measured by multiplying the number of shares outstanding by the current share price. Speaking very generally, the larger the market capitalization, the more financially stable the company.
[9] Credit Suisse First Boston, "Pharmacy Benefit Managers and Specialty Pharmacies: Initiating Coverage," July 14, 2003, p. 22.
[10] Raymond James & Associates, Inc., "Specialty Drug Distribution," July 16, 2002, p. 3.

- ***Mail-order pharmacies*** receive prescriptions by mail, fax, phone, or Internet at a central location; process the prescription in large, mostly automated centers; and mail the prescribed drugs back to the consumer. An aging population, convenience, and the recent upswing in pharmaceutical treatments for common chronic ailments, such as diabetes and depression, are some of the driving forces behind the rapid growth in the use of mail-order pharmacies.[11] While representing a small overall percentage of total prescriptions filled (approximately 6.1 percent in 2004[12]), mail-order pharmacy sales remained the fastest-growing sector of the U.S. prescription drug retail market in 2004, increasing by 18 percent over the previous year.[13] The majority of mail-order facilities are owned and operated by PBMs, and a number of the large retail pharmacy chains also own mail-order pharmacies.[14]

- ***Long-term care pharmacies***, sometimes called institutional pharmacies, are a third type of specialized retail pharmacy. Long-term care pharmacies address the special needs of nursing homes, providing packaging for controlled administration (called unit-dose supply or bubble packs), and special services that are more extensive than those provided by retail pharmacies. These special services include: quality assurance checks, emergency drug kits and medication carts, regular and emergency (24-hour-a-day) delivery services, and in-service training programs for nurse aides, nurses, and other professional nursing facility staff. Four national chains provide the bulk of institutional pharmacy services to nursing homes: Omnicare, PharMerica, NeighborCare, and Kindred Healthcare. In 2003, these four chains served over two-thirds of all nursing home beds and had collective revenues of more than $6 billion.[15] The two largest national long-term care pharmacies, Omnicare and PharMerica (which is a subsidiary of AmerisourceBergen, a wholesale distributor), provide drugs to over half of the nursing home beds in the United States. Omnicare is the largest provider with over $3 billion in 2003 revenues.[16]

Pharmacy Benefit Managers (PBMs)

According to one leading report on the PBM industry, PBMs currently manage prescription drug benefits for as much as 57 percent of the U.S. population,[17] and the

[11] National Health Policy Forum, *The ABCs of PBMs*, October 1999.
[12] IMS Health, National Prescription Audit™Plus, January 2005, accessed 2/28/05 at http://www.imshealth.com/ims/portal/front/articleC/0,2777,6599_49695974_68913551,00.html
[13] IMS Health, IMS National Sales Perspectives,™ February 2005, accessed 2/28/05, at http://www.imshealth.com/ims/portal/front/articleC/0,2777,6599_49695983_69891354,00.html
[14] California Health Care Foundation, *Navigating the Pharmacy Benefits Marketplace*, January 2003.
[15] Long-Term Care Pharmacy Association, 2003.
[16] Omnicare Annual Report, 2003.
[17] Atlantic Information Services (AIS), Inc., *A Guide to Drug Cost Management Strategies (2nd Edition)*, 2004, p. 329. AIS states that its data are based on a quarterly survey that the firm has been using to track all publicly-traded and privately-held PBMs since 2000.

National Association of Chain Drug Stores estimates that approximately two-thirds of all prescriptions written in the U.S. are processed by a PBM.[18] While not a direct link in the physical supply chain for pharmaceutical products (PBMs in most instances do not take possession or control of prescription drugs), PBMs have become an integral part of most consumer drug purchases. PBMs work with third party payers (private insurers, self-funded employers and public health programs) to manage consumer drug purchases by defining which drugs will be paid for and the amounts that the pharmacy will receive and the consumer must pay out-of-pocket when the prescription is filled.

PBMs have evolved over the last three decades from basic claims administrators to more complex organizations offering a wide range of prescription drug management tools. In addition to offering their basic services – claims processing, record keeping, and reporting programs – PBMs offer their customers a wide range of services including drug utilization review, disease management, and consultative services. PBMs also assist clients with establishing their benefit structure. Options for plan design include: developing and maintaining a prescription drug formulary; developing a network of pharmacy providers; and providing mail order fulfillment services. A PBM's core services and tools include:

- ***Formularies:*** PBMs use formularies to negotiate deeper price discounts with manufacturers, set cost-sharing levels to influence beneficiary utilization rates, and encourage beneficiaries to use a mix of preferred or lower-cost covered products.

- ***Rebates:*** PBMs negotiate with pharmaceutical manufacturers for rebates on products selected for the formulary. Rebate amounts are based on the contracts negotiated between the PBM and plan sponsors and the PBM and manufacturers. Typically, contracts are structured so that PBMs retain a portion of the rebate in exchange for developing the formulary and negotiating with manufacturers.

- ***Pharmacy Networks:*** Pharmacy networks consist of pharmacies that have agreed to dispense prescription drugs and provide pharmacy services to a health plan's enrollees under specified terms and conditions. Pharmacy networks can be broad or narrow. These networks allow PBMs to lower prescription drug prices by negotiating the reimbursement rate and dispensing fee with pharmacies.

- ***Mail-Order Pharmacy Service:*** Almost all PBMs offer mail-order pharmacy service, especially targeted toward individuals with chronic medical conditions who take maintenance medications. The medications are dispensed typically in 90-day amounts per prescription, as opposed to the usual 30-day supply per prescription dispensed by a retail pharmacy. PBMs are able to lower the cost of pharmaceuticals to consumers and payers by using mail-order services to more successfully drive market share for particular products, based on the terms of

[18] Ibid., p. 331.

contracts negotiated with pharmaceutical manufacturers (e.g., encouraging generic and branded therapeutic substitution and other forms of managing formulary compliance), and (relative to the typical retail pharmacy operation) by automating dispensing processes.

- ***Claims Adjudication:*** All PBMs use a real-time, point-of-sale system linked to retail and mail-order pharmacies and distribution centers. This process provides verification of coverage, formulary restrictions, drug interactions, and individual co-pay information. This process also provides prescription drug information back at the PBM data warehouse, where it can be used for customized reporting and quality-focused clinical and intervention programs.

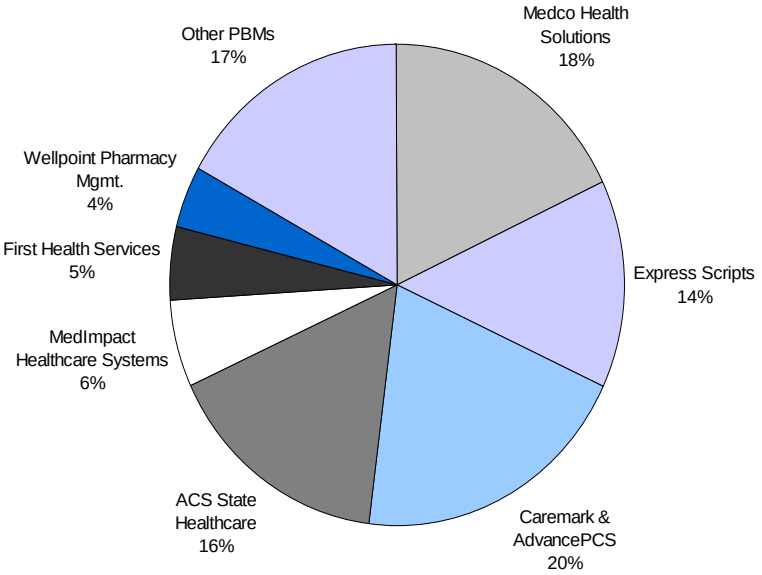
- ***Generic and Therapeutic Substitution:*** Generic substitution promotes the shift from brand to chemically equivalent generic drugs as a cost savings device. Therapeutic interchange programs promote the use of preferred drugs (i.e., drugs on a plan's formulary) that are determined to be clinically similar.

- ***Quality-Focused Programs:*** PBMs develop programs that provide disease management, compliance strategies, and other clinical expertise promoting the safe, educated use of prescription drugs.

PBMs generally do not take physical possession of prescription drugs when performing their core pharmaceutical management functions. However, in their mail-order and specialty-pharmacy businesses, PBMs buy drugs from wholesalers or manufacturers and dispense them directly to patients in a manner similar to other pharmacies.

During the 1990s, there was a great deal of jockeying within the PBM market, a highly penetrated market compared to just a decade ago. In order to remain competitive, PBMs have merged and acquired new businesses. Most recently, in March 2004, Caremark acquired AdvancePCS; in 2001, Express Scripts acquired National Prescription Administrators; in 2000, Medco Health Solutions acquired Provantage; and in 1998, Express Scripts acquired Value Rx. As shown in Exhibit 13, the PBMs that controlled the most market share measured by prescriptions per year in 2003 were Medco Health Solutions, ACS State Healthcare, AdvancePCS/Caremark, and Express Scripts.[19]

Exhibit 13. PBM Market Share by Number of Prescriptions per Year, 2003



*Note: Caremark acquired AdvancePCS in March 2004.
Source: AIS, *A Guide to Drug Cost Management Strategies*, 2nd Edition (2004), Fig. 12.13.

[19] Atlantic Information Services, Inc., *A Guide to Drug Cost Management Strategies*, 2nd Edition, 2004.

III. The Flow of Money and Key Financial Relationships in the U.S. Pharmaceutical Supply Chain

The flow of money between manufacturers and end-users is more complex than the physical distribution of drugs. The manufacturer typically interacts with three primary entities when dealing with price: wholesale distributors, retail pharmacies, and pharmacy benefit managers. Pharmaceutical manufacturers negotiate separate contracts with these entities and offer various discounts and rebates based largely on the entities' varying ability to influence the quantity of drugs that are sold. This section looks at these financial relationships and charts the flow of funds among the key players, starting with manufacturers, who play by far the most important role in establishing prices.

Pharmaceutical Manufacturers

Manufacturers have the most influence over pharmaceutical prices. They develop algorithms to account for expected demand for the product, future competition for the product, and projected marketing costs, and use those algorithms to establish the "wholesale acquisition cost" (WAC), which is the baseline price at which wholesale distributors purchase products. After the WAC is established, the average wholesale price (AWP), or the retail list price, is established either by the manufacturer or by one of the companies that publishes price compendia. The AWP, and sometimes the WAC, is listed in drug compendia published by a small number of private firms, such as the Red Book, published by Thomson Medical Economics, and First DataBank. The AWP has two purposes: (1) it is often used by public and private third-party payers as the basis for reimbursement, and (2) it often serves as the base price for negotiations between manufacturers and private sector purchasers of drugs (e.g., health plans, pharmacy benefit managers, self-insured employers, etc.).

The negotiation process and the price points on which negotiations are based are different for brand and generic manufacturers. Brand manufacturers typically offer discounts based on a percentage of AWP or WAC, depending upon the purchaser. End purchasers can typically acquire brand drug products for a price in a range of AWP minus 5 to 40 percent, depending upon their purchasing power or that of their designated agent, such as a PBM. Generic pharmaceutical manufacturers operate in a more aggressive and dynamic negotiation environment than brand manufacturers and thus the prices for generic drugs change much more frequently, sometimes daily, in response to market forces. The most common kinds of discounts and rebates include: retroactive rebates based on market share (i.e., rebates paid by the manufacturer to the pharmacy or PBM based on its ability to direct consumers to certain products); volume discounts (discounts that are triggered when predetermined sales volume targets are met); and "prompt pay" discounts (discounts that are triggered when the purchaser reimburses the manufacturer in an expedited fashion).

Pricing for prescription drugs purchased and dispensed by certain federal programs, including Medicaid and the Veterans Administration, are subject to special rules which

generally result in those programs getting lower prices than other purchasers. These rules are outlined in the Appendix.

PRICING TERMS DEFINED

- ***Average Manufacturer Price (AMP)***: The average price paid to a manufacturer by wholesalers for drugs distributed to retail pharmacies. AMP was a benchmark created by Congress in 1990 in calculating Medicaid rebates and is not publicly available. (See Appendix for additional discussion of pharmaceutical pricing in Medicaid).
- ***Average Sales Price (ASP***: The weighted average of all non-Federal sales to wholesalers net of chargebacks, discounts, rebates, and other benefits tied to the purchase of the drug product, whether it is paid to the wholesaler or the retailer. The basis for reimbursement for products covered under Medicare Part B changed under the Medicare Modernization Act of 2003 from AWP to ASP.
- ***Average Wholesale Price (AWP)***: Although not defined in statute, AWP is recognized as retail list price (sometimes referred to as a "sticker" price) and is currently used by some public and private third-party payers as the basis for reimbursement (e.g., AWP minus 5 or 25 percent). AWP has been widely criticized as a price that is (1) not reflective of the true market price, and (2) easily manipulated. The basis for reimbursement for products covered under Medicare Part B changed under the Medicare Modernization Act of 2003 from AWP to average sales price (ASP).
- ***Estimated Acquisition Cost (EAC)***: EAC is a state Medicaid Agency's best estimate of the price generally paid by pharmacies for a particular drug.
- ***Maximum Allowable Cost (MAC)***: MAC lists are designed to cap reimbursement for certain generic and multi-source brand products. States and private payers with MAC programs typically publish lists of selected generic and multi-source brand drugs along with the maximum price at which the program will reimburse for those drugs. In general, pharmacies will receive payment no higher than the MAC price when billing for drugs on a MAC list.
- ***Wholesale Acquisition Cost (WAC)***: The price paid by a wholesaler for drugs purchased from the wholesaler's supplier, typically the manufacturer of the drug. Publicly disclosed or listed WAC amounts may not reflect all available discounts.

Wholesale Distributors

Wholesale distributors purchase drugs from manufacturers. For branded products, the purchase price is fairly uniform, with little negotiation on the part of the wholesale distributor. The distributor typically purchases branded products for a discounted rate off of WAC. Examples of discounts for branded products include volume discounts, prompt pay discounts, and discounts related to the sale of short-dated products (because the wholesaler is assuming a risk that the product will expire before it can be resold). The wholesale distributor then sells the product to its end consumer, typically a pharmacy, at WAC plus some negotiated percentage.

For generic products, the purchase price is highly variable, largely depending upon competition in the class and the ability of the wholesale distributor to drive market share or increase the volume sold. In this case, wholesale distributors play a larger role in the negotiation of the price of the product. The price to the end consumer also is highly elastic depending upon the negotiated contracts with the retail pharmacies.

In some cases, the wholesale distributor may facilitate discounts negotiated between manufacturers and other customers. For example, wholesaler A may distribute drugs to pharmacy B based on negotiations between pharmacy B and manufacturer C. Although wholesaler A directly distributes the drugs to pharmacy B, it plays a minimal part in pricing negotiations for these drugs. In this case, wholesalers use an important pricing mechanism, *chargeback*, which allows them to carry products destined for customers paying very different prices to manufacturers. The wholesaler keeps track of sales to various customers under prices negotiated between the manufacturer and the customer. The wholesaler then "charges back" the manufacturer for any difference between the negotiated prices paid by the customer and the wholesaler's cost of goods (WAC).

Pharmacies

Payment for prescription drugs flow from the pharmacy to the manufacturer according to a negotiated contract involving manufacturers, PBMs, and pharmacies. Retail pharmacies negotiate with manufacturers for discounts and rebates based on the pharmacy's ability to sell specific volumes of certain drugs or achieve a certain share of a specified market. As discussed in the wholesale distributor section, pharmacies may be able to negotiate discounts with manufacturers that are more substantial than the wholesale distributor's cost. In these instances, the wholesale distributor facilitates the discount and "charges back" the manufacturer for any difference between the negotiated prices paid by the customer and the wholesaler's cost of goods (WAC). Pharmacies also negotiate with PBMs for inclusion in a PBM's pharmacy network and for reimbursement for the cost of the drug plus dispensing fees.

Manufacturers may offer volume discounts on selected drugs to pharmacies when they achieve predetermined market share targets. These discounts provide an incentive for pharmacists to work with patients and physicians to switch products from a prescribed non-preferred drug to a preferred drug.

Pharmacies contract with PBMs to join their pharmacy network. This structure provides pharmacies with guaranteed, stable reimbursement from private payers and access to a greater number of customers. The network consists of a group of retail and independent pharmacies and serves to offer plan members with lower prescription drug costs. As part of the pharmacy network contract, retail pharmacies must agree to a guaranteed reimbursement formula for prescription drugs. For brand-name medications, the reimbursement formula is usually determined by subtracting a negotiated percentage from the drug's AWP and adding the dispensing fee. For generic drugs, reimbursement may be determined in the same way as for a brand drug (for less competitive generic drug classes), but more often is based on an amount specified referred to as the maximum allowable cost (MAC).

Smaller retail stores, such as independent pharmacies and smaller retail chains, either purchase directly from wholesalers – at a price significantly higher than retail pharmacies – or join group-purchasing organizations (GPOs). As members of a GPO, small

pharmacies receive the benefits of volume purchasing by leveraging their combined purchasing power to negotiate discount pricing from wholesalers or even in some cases from manufacturers. Some of these groups further reduce their costs through direct rebate deals offered by manufacturers.

Mail-order and specialty pharmacy services are increasingly becoming a more attractive and demanded option for health plan sponsors and other payers seeking to rein in pharmaceutical expenditures for their members. Mail-order and specialty pharmacies are able to generate increased savings by driving market share, streamlining the distribution chain, and automating drug dispensing processes.

- ***Specialty Pharmacy:*** Most specialty pharmacy providers manage the cost of specialty pharmaceuticals by negotiating directly with manufacturers and by running quality-focused programs intended to improve patient care and lower costs. Large PBMs or retail pharmacy chains own a number of the specialty pharmacies, and in some cases these entities are able to negotiate greater discounts with manufacturers.[20] Nearly all specialty pharmacies also administer programs designed to enforce patient compliance. Industry representatives claim that these programs save the patient and health plan money by averting acute incidences.

- ***Mail-Order Pharmacy:*** In 2000, the U.S. Department of Health and Human Services estimated that mail-order pharmacies were able to generate savings between two and 35 percent compared to retail pharmacies.[21] Representatives from the mail-order industry attribute these savings to their ability to "manage" prescriptions because the majority of mail-order prescriptions are filled in 90-day units (the equivalent of three prescriptions).[22] The considerable lead time associated with filling a 90-day prescription gives the pharmacists and other clinical staff at a mail-order pharmacy the time to analyze whether the prescribed drug is on the client's (i.e., insurer's or health plan's) approved formulary, if there is a generic equivalent available, and if there are any potential interactions of the prescribed drug with other medications the member's physician or physicians may have also prescribed.

- ***Long-Term Care Pharmacy:*** LTC pharmacies have long-term, almost exclusive contracts with nursing homes to provide medications and services for residents. LTC pharmacies capture a large volume of customers in this way. LTC pharmacy chains have developed formularies and use them in many states that do not have Medicaid preferred drug lists (PDLs) applicable in the nursing home setting. The large LTC pharmacy chains negotiate rebates with manufacturers in exchange for

[20] Berg, Kevin I. "Health Care Industry Report: The Down Low," *First Albany Corporation* 6 (2003): 1-153.
[21] Department of Health and Human Services, *Report to the President: Prescription Drug Coverage: Spending Utilization and Prices*, April 2000.
[22] California HealthCare Foundation, *Navigating the Pharmacy Benefits Marketplace*, January 2003.

moving market share on their formularies. In addition to receiving rebates, many pharmacies are reimbursed at higher rates than acquisition costs, because they purchase drugs through wholesalers and group purchasing organizations.

Pharmacy Benefit Managers (PBMs)

Although PBMs are a relatively unknown entity to the end consumer, they play a fundamental role in negotiating the price that is ultimately paid for the product through their relationships with other entities in the supply chain.

PBMs contract with health plans to manage their prescription drug costs. Each contract is different between health plans and PBMs; however, there are generally three basic components of the payment negotiated between PBMs and their sponsors. First, PBMs receive payment for the services they provide. These services may include claims adjudication processing and disease management services. Second, PBMs typically assume some type of performance risk in the contracts they negotiate. Performance metrics can include: customer service (e.g., adequacy of pharmacy networks, timeliness of reporting), clinical quality measures (e.g., the number of people averted from taking inappropriate medications), and cost management techniques (e.g., the number of generic substitutions made in a given time period). Third, PBMs also retain a portion of rebates they secure from manufacturers.

PBMs do not typically assume full insurance risk for drugs. This type of risk is assumed when an insurer takes full or partial financial responsibility for claims incurred under a specified benefit. Insurance risk can further be segmented into three sub-categories: price, utilization, and selection risk. PBMs do not typically guarantee either the unit prices of drugs, the volume of drugs (utilization) or the kinds of patients that sign up for the drug plan (selection). Insurance risk for drugs is often assumed by self-insured entities in the context of a full medical benefit. For an entitiy to assume insurance risk, the entity must demonstrate that it has adequate financial reserves, be licensed and overseen by state insurance regulators, and be prepared for underwriting cycles.

While performance risk arrangements are very common for PBMs, insurance risk arrangements are not. During the mid-1990s, some PBMs experimented with risk contracts. ValueHealth, PCS, and Medco had contracts in which the PBM assumed full insurance risk. The contracts typically contained actuarial carve-outs for new biotechnology products and unexpected changes in demographics, but put the PBM at risk for other drug utilization and cost. Many of these contracts were with large manufacturing clients who were self-insured, concerned about drug spending, and bid out the pharmacy benefit competitively to multiple vendors. The experience was uniformly negative from the PBM perspective. The PBMs consistently lost money because they under-estimated the development and diffusion of new technology. Many were able to negotiate out of these contracts, but some contracts persisted until the late 1990s. Most, if not all, are now gone.

PBM relationships with manufacturers are governed under guidance from the Department of Health and Human Services (HHS) Office of the Inspector General, and subject to oversight by the Department of Justice for compliance with federal anti-kickback statutes. PBMs are further regulated in many states under consumer protection statutes. In recent years, some industry practices, for example switching of medications and associated pricing issues, have come under scrutiny by state Attorneys General and the Department of Justice. Allegations have also included accepting undisclosed incentives from pharmaceutical manufacturers, not passing manufacturer rebates through to plan sponsors, and driving beneficiaries unnecessarily to mail-order services for the benefit of the PBM. False Claim Act lawsuits also have been filed by the federal government and several states. Medco Health Solutions settled in April 2004 with twenty State Attorneys General on a case involving therapeutic interchange and price disclosure. While this legal scrutiny has focused on a few industry practices, the typical business practices of PBMs have also been heavily scrutinized by plan sponsors, such as health plans and self-insured employers. Further guidance from the HHS Office of the Inspector General on PBM operations and safe harbors under the anti-kickback statute is expected.[23]

According to a January 2003 study conducted by the federal Government Accountability Office (GAO), PBMs achieved significant discounts for drugs purchased at retail pharmacies (in comparison to cash-paying customers) and offered even greater discounts for their mail-order services.[24] However, cost savings are largely driven by how restrictive or open the cost-containment programs are. This is a point usually negotiated between the health plans and PBMs. For example, open formularies (where consumers are free to access all prescription drugs) typically yield lower cost savings than closed formularies (where consumers are limited to certain drugs). Cost sharing differences by the type of formulary also increase members' sensitivity to prescription drug costs and provides an incentive to use lower-cost or preferred products on the formulary. Common private-sector, cost sharing tools include flat copayments, percent copayments with a minimum/maximum dollar amount, and front-end deductibles with a benefit maximum and/or stop loss.[25]

- ***Manufacturer-PBM Relationship:*** As discussed above, the relationship between manufacturers and PBMs is centered around inclusion of a drug on a plan's formulary and the PBM's ability to increase a manufacturer's market share for certain drugs through inclusion or exclusion on a formulary. Manufacturers pay rebates to PBMs retroactively based on the PBM's ability to meet both of these goals. These rebates are passed in whole or in part back to the employer. According to the California HealthCare Foundation, PBMs are often able to secure rebates of 5-25 percent for branded drugs.[26]

[23] For more information about the Medco settlement, see *The Pink Sheet*, May 3, 2004, pages 22-30.
[24] U.S. Government Accountability Office, "Federal Employees' Health Benefits: Effects of Using Pharmacy Benefit Managers on Health Plans, Enrollees, and Pharmacies," GAO-03-196, January 2003.
[25] Joanne Sica, "Managing prescription drug costs," *Employee Benefits Journal*, March 2001, pp. 35-40.
[26] California HealthCare Foundation, *Navigating the Pharmacy Benefits Marketplace*, January 2003.

- ***PBM-Pharmacy Relationship:*** As discussed above, PBMs negotiate with pharmacies for drug reimbursement and dispensing. The pharmacies negotiate for inclusion in a PBM's pharmacy network. There is often significant tension between the two entities because (1) in general, pharmacies are reimbursed by PBMs at levels below uninsured cash-paying customers and other government payers, like Medicaid, and (2) pharmacies are often required to perform more administrative tasks when filling a prescription for a PBM customer.

IV. Conclusion

Pharmaceuticals are a vital part of patient care, and their importance will only grow as the population ages and pharmaceutical innovation continues. Understanding current pharmaceutical issues (including the sources of prescription drugs, pricing and discounts, cost containment methods, and brand/generic questions) requires knowledge about the various actors in the supply chain. State and federal policymakers increasingly are looking to private sector financing strategies to shape the ways in which individuals with public coverage receive medications. Passage of the Medicare Modernization Act of 2003 (MMA) makes knowledge about the pharmaceutical chain even more important as the large public Medicare program and its beneficiaries begin to access the chain, and pharmaceutical chain entities make changes in response to the new coverage.

The pricing of prescription drugs and the flow of money among the various links in the pharmaceutical supply chain is more complex than the physical distribution of drugs through the chain. This complexity can result in substantial variations in what different purchasers pay for the same drugs. As we have shown, the price of prescription drugs paid by the consumer is determined by a constellation of negotiated contracts between manufacturers, PBMs, wholesale distributors, pharmacies, and plan sponsors. The price charged by each entity in the chain is largely driven by the ability of contracting entities to sell specific volumes of certain drugs or achieve a certain share of a specified market. It is also affected by the value each entity brings to the subsequent actors in the supply chain.

Rapid increases in spending on pharmaceuticals in recent years have led policymakers to more closely scrutinize drug pricing and the relationships among key actors in the marketplace, and the greatly enhanced federal role in the market brought about through the MMA will only intensify public interest in these areas. Experiences with the Medicare price comparison website for the drug discount card has increased consumer and government interest in internet-based price comparisons. The price differences highlighted by these and other analyses lead to questions about the basis for these pricing differentials. Medicare's activities to detect and remedy fraud and abuse will also require continued oversight and need for transparency and fiscal accountability. Public policy discussions regarding transparency and price disclosure are thus likely to continue to be active over the coming years.

V. Appendix

This Appendix briefly describes: (A) special pricing rules applicable to Medicaid and some other federal programs, and (B) the roles physicians, large employers, and health plans have in the pharmaceutical supply chain.

A. Special Pricing Rules Applicable to Federal Programs

Several federal programs that are significant purchasers of prescription drugs have special rules for pricing.

Medicaid

Federal rules require that states pay for brand name prescription drugs based on the lower of (1) the estimated acquisition cost (EAC) of a drug (the method most states use); or (2) the usual or customary charge to the public. Most Medicaid programs use a drug's AWP to calculate the EAC, generally AWP minus some percentage. An additional limit, known as the Federal Upper Limit (FUL), applies to the purchase of generic drugs. Manufacturers who want to have their drugs covered by Medicaid also must provide rebates to state Medicaid programs. For brand name drugs, the basic rebate is the larger of (1) 15.1% of the AMP (the average price paid to manufacturers by wholesalers for drugs distributed to retail pharmacies; the AMP is usually lower than the AWP); or (2) the difference between the AMP and the lowest price the manufacturer offers to most other purchasers. An additional rebate is required if the price of brand name drugs rises faster than the change in Consumer Price Index. Rebates for generic drugs are calculated by multiplying the AMP by 11%.

Department of Veterans Affairs, Department of Defense, Public Health Service, Coast Guard

The Department of Veterans Affairs (VA) administers a program known as the Federal Supply Schedule (FSS), through which the VA and certain other government agencies can purchase prescription drugs at prices that are equal to or lower than the prices that drug manufacturers charge their "most-favored" private customers. In addition, manufacturers must sell brand-name drugs to these agencies at a minimum of 24% off the AMP (known as the federal ceiling price).

Section 340B Drug Pricing Program

Section 340B of the Public Health Service Act requires drug manufacturers, as a condition of having their drugs covered by Medicaid, to provide prescription drugs to certain nonfederal entities (public and disproportionate share hospitals, community health centers, certain grantees of Federal agencies, and health centers that serve migrant, homeless, public housing, and Native American populations)

at prices that are equal to or below the AMP reduced by the applicable Medicaid rebate percentage.

B. The Role of Physicians, Employers and Health Plans in Supply Chain

Physicians

Physicians play an important role in the pharmaceutical supply chain. They are the first to interact with the consumer (i.e., patient), the end-user in the supply chain. Doctors typically diagnose a patient's illnesses and prescribe a medication. The physician is also responsible for ensuring the appropriate quantity and dosage of the prescribed medication. If the prescribed drug is not covered under the patient's health plan, the physician may have to submit additional information substantiating the necessity of the specific medication for the treatment of the injury or illness. This is called "prior authorization." Once a drug is prescribed, patients typically fill prescriptions at their local retail pharmacies. In some cases, the physician may administer the drug in their office (e.g., chemotherapy).

Historically, patient compliance with whatever treatment the doctor ordered was assumed as part of the physician-patient relationship; increasingly, however, patients are becoming more proactive in their interaction with physicians, particularly in the area of prescription drug treatment decisions. Greater access to health information (fueled, in part, by widespread use of the Internet), the loosening of "direct-to-consumer" (DTC) advertising restrictions on drug manufacturers, and a general increase in the public's awareness of health care issues have helped transform many once-passive patients into inquiring and demanding consumers.[27] This trend has affected physician choices of specific medications prescribed and the modes of delivery used, and it has increased the complexity of the information transmitted to physicians and consumers. Now more than ever, physicians and patients/consumers play a large role in driving the market demand for pharmaceuticals.

Large Employers

Large employers that self insure their employees for health benefits generally negotiate contracts with PBMs (and sometimes with specialty pharmacy companies as well) to provide pharmaceutical coverage to employees. Employers exercise control over the supply chain through the contracts they set with PBMs. The contracts govern the prices of pharmaceuticals paid by the employer, the cost sharing to the insured population, the type of formularies that will be applied, the network standard for pharmacies, and what types of drug utilization review will be applied. Employers pay PBMs either on an administrative services basis, or by

[27] *Health Affairs*, March/April 2000.

allowing the PBMs to retain a portion of manufacturer rebates. Employers retain audit rights to exercise oversight of PBM operations.

Health Plans

Health plans employ the use of a range of strategies to manage prescription drug benefits, most of which involve the use of a PBM or PBM-like strategies. There are a few remaining plans that compensate pharmacies on a fee-for-service basis, but plans are using this method less frequently, as it does not allow for use of cost-containment strategies to lower prescription drug costs. More commonly, plans do one of the following: (1) outsource management to an external PBM, (2) operate their own PBM, or (3) outsource claims administration only. Notable exceptions include certain group models, such as that of Kaiser Permanente, which has maintained control of pharmaceutical procurement. Kaiser streamlines the distribution process by purchasing pharmaceuticals from manufacturers and dispensing the medications to consumers at on-site pharmacies.

Regardless of the strategy used, health plans often influence the cost-containment strategies utilized by PBMs. For example, managed care organizations may negotiate a more restrictive formulary or more competitive pharmacy networks. Managed care companies a greater ability to enforce formulary compliance and to drive consumers to a smaller number of pharmacies.

VI. Key Acronyms and Glossary of Key Terms

AMP – Average Manufacturer Price
ASP – Average Sales Price
AWP – Average Wholesale Price
EAC – Estimated Acquisition Cost
MAC – Maximum Allowable Cost
PBM – Pharmacy Benefit Manager
WAC – Wholesaler Acquisition Cost

Average Manufacturer Price (AMP) – The average price paid to a manufacturer by wholesalers for drugs distributed to retail pharmacies. AMP was a benchmark created by Congress in 1990 in calculating Medicaid rebates and is not publicly available.

Average Sales Price (ASP) – The weighted average of all non-Federal sales to wholesalers net of chargebacks, discounts, rebates, and other benefits tied to the purchase of the drug product, whether it is paid to the wholesaler or the retailer. The basis for reimbursement for products covered under Medicare Part B changed under the Medicare Modernization Act of 2003 from AWP to ASP.

Average Wholesale Price (AWP) – A national average of list prices charged by wholesalers to pharmacies. AWP is sometimes referred to as a "sticker price" because it is not the actual price that larger purchasers normally pay.

Estimated Acquisition Cost (EAC) – EAC is a state Medicaid Agency's best estimate of the price generally paid by pharmacies for a particular drug

Maximum Allowable Cost (MAC) – MAC is a cap set by payers on reimbursement for certain generic and multi-source brand products. States and private payers with MAC programs typically publish lists of selected generic and multi-source brand drugs along with the maximum price at which the program will reimburse for those drugs. In general, pharmacies will receive payment no higher than the MAC price when billing for drugs on a MAC list.

Medicaid Best Price – The lowest price paid to a manufacturer for a brand name drug, taking into account rebates, chargebacks, discounts, or other pricing adjustments, excluding nominal prices. Best price is a variable used in the Medicaid rebate statute to calculate manufacturer rebates owed to State Medicaid agencies. Prices charged to certain governmental purchasers are statutorily excluded from best price including prices charged to the Veterans Administration, Department of Defense, Indian tribes, the Federal Supply Schedule, State Pharmaceutical Assistance Programs, Medicaid, Public Health Service "340B" entities, and Medicare Part D prescription drug plans (starting in 2006). Best price data are reported by manufacturers to CMS, but are not publicly available.

Reference Pricing – System of fixed reimbursement for pharmaceuticals, in which the government or other third party payers establish a level at which they are willing to reimburse "interchangeable" products. Manufacturers may charge above the reference price, but patients must pay the excess cost.

Wholesale Acquisition Cost (WAC) – The price paid by a wholesaler for drugs purchased from the wholesaler's supplier, typically the manufacturer of the drug. Publicly disclosed or listed WAC amounts may not reflect all available discounts.

The Henry H. Kaiser Family Foundation
2400 Sand Hill Road
Menlo Park, CA 94025
Phone: 650-854-9400 Fax: 650-854-4800

Washington Office:
1330 G Street, NW
Washington, DC 20005
Phone: 202-347-5270 Fax: 202-347-5274

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EXHIBIT 87

Herceptin Distribution

Authorized Distributors and Specialty Pharmacies

Genentech has contracted with a network of authorized specialty distributors to service practices choosing to purchase Herceptin through the buy and bill model. Customers can purchase Herceptin through authorized specialty distributors and wholesalers that have made a commitment to product integrity. These partners have agreed to distribute only products purchased directly from Genentech and not to distribute Herceptin through secondary channels.

Important Safety Information & Indication See More

Indications

Adjuvant Breast Cancer

Herceptin is indicated for adjuvant treatment of HER2-overexpressing node-positive or node-negative (ER/PR-negative or with one high-risk feature*) breast

Herceptin Access Solutions works with SPs to help patients receive their medicines. SPs can dispense Genentech medicines to your office. The SPs can also provide coverage and reimbursement support.

Distributors for Federal Accounts +

Distributors for Hospitals +

Distributors for Physician Offices and Federally Qualified Health Centers +

Distributors for Authorized Specialty Pharmacies +

Distributors for Puerto Rico +

Specialty Pharmacies +

Genentech does not influence or advocate the use of any one specialty distributor or specialty pharmacy. We make no representation or guarantee of service or coverage of any item.

Learn About Treatment With Herceptin >
(http://www.herceptin.com/hcp/)

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Indications

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Herceptin is indicated for adjuvant treatment of HER2-overexpressing node-positive or node-negative (ER/PR-negative or with one high-risk feature*) breast

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Herceptin is indicated for adjuvant treatment of HER2-overexpressing node-positive or node-negative (ER/PR-negative or with one high-risk feature*) breast

EXHIBIT 88

FRIDAY, OCTOBER 14, 2016

Follow the Vial: The Buy-and-Bill System for Distribution and Reimbursement of Provider-Administered Outpatient Drugs

By reader request, below is a channel flow chart illustrating the buy-and-bill process for provider-administered drugs. It complements Follow the Dollar: The U.S. Pharmacy Distribution and Reimbursement System, which focuses on patient-administered outpatient drugs.

This post is adapted from Section 3.1.2. of our *The 2016–17 Economic Report on Pharmaceutical Wholesalers and Specialty Distributors*. Friendly reminder: Discounted pricing for the report ends today!

PROVIDER-ADMINSTERED DRUGS

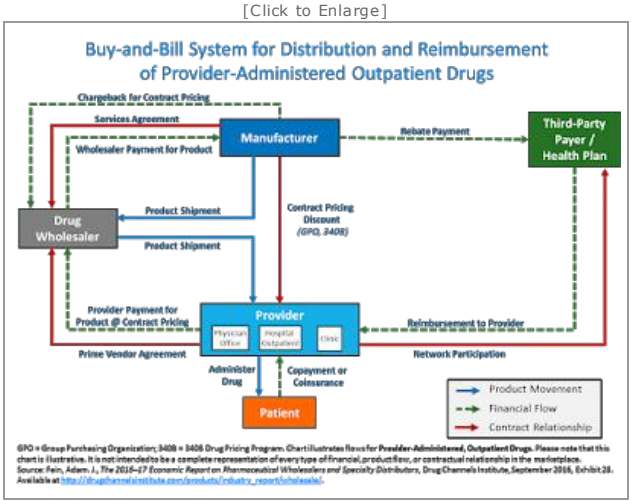
Physician offices and hospital outpatient clinics are the primary sites of administration for such provider-administered drugs as biologicals, injectables, IVIG, immunoglobulins, and other products. Oncology drugs and related products are the largest share of spend. These medications are typically covered under a patient's medical benefit.

More than half of outpatient commercial medical benefit drug spending occurred in hospital outpatient locations. Remaining spending occurred primarily in a physician's office or clinic. Medicare is the primary government payer of provider-administered specialty drugs. Its Part B program covers provider-administered injectable and certain other drugs. In contrast to the commercial payers, about one-third of Part B spending occurred in hospital outpatient locations. For details and pretty charts, see Section 3.1.1. in our 2016-17 wholesaler report .

BUY-AND-BILL

Most provider-administered outpatient drugs are governed by the buy-and-bill process, which is illustrated in the chart below. Click here to download the chart as a PDF file.

[Click to Enlarge]



In the buy-and-bill process for provider-administered outpatient drugs, a healthcare provider purchases, stores, and then administers the product to a patient. After the patient receives the drug and any other medical care, the provider submits a claim for reimbursement to a third-party payer. The process is called buy-and-bill, because the medical claim is submitted after the provider has purchased and administered the drug.

Drug Channels is written by Adam J. Fein, Ph.D. Dr. Fein is CEO of Drug Channels Institute, a subsidiary of Pembroke Consulting, Inc. Read More...

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Thus, in the buy-and-bill system, the provider is responsible for:

- Ordering and purchasing the drug
- Managing drug inventory at the practice
- Prescribing and administering the drug to a patient
- Submitting reimbursement claims for a drug and related professional services
- Collecting a patient's share of drug reimbursement—the copayment or coinsurance

Community-based physician practices typically purchase drugs from a specialty distributor. Hospital outpatient clinics and hospital-based practices typically receive products from a hospital pharmacy, which purchases drugs from a full-line pharmaceutical wholesaler. The distributor is responsible for:

- Purchasing products from manufacturers
- Negotiating the drug's cost with the provider
- Delivering the specialty drug to the provider's location
- Collecting payment from the provider

Some additional comments:

- The chart above shows a rebate payment from manufacturers to third-party payers. This line does not apply to Medicare Part B, which has no statutorily mandated rebates. However, more than half of payers received rebates for provider-administered injectable and infused drugs billed under the medical benefit for commercial members.
- Pharmacies—via white and brown bagging—have displaced buy-and-bill distribution channels for about one-quarter of oncology products. For simplicity, I have omitted these flows from the chart. See How Specialty Pharmacy Is Penetrating Buy-and-Bill Oncology Channels.
- The reimbursement approaches that commercial payers use permit hospitals to get paid two to three times as much as physician offices—and to inflate drug costs by thousands of dollars per claim See New Data: How Outrageous Hospital Markups Hike Drug Spending.
- For more on Medicare Part B and the wonderful world of J-codes, see Sections 3.1.3. and 4.5.2. of our 2016-17 wholesaler report
- For relaxing times, make it Suntory time.

Print Friendly and PDF Posted by Adam J. Fein, Ph.D. on Friday, October 14, 2016
2 Comments
Labels: Average Sales Price (ASP), Buy-and-Bill, Channel Management, Costs/Reimbursement, Hospitals, Physicians, Specialty Drugs, Wholesalers

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INDUSTRY NEWS AND BLOGS

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Chain Drug Review
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Fierce Pharma
Procter & Gamble shows up in force at Lions Health, serving notice to consumer health rivals

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Understanding Price Growth in the Market for Targeted Oncology Therapies

Pharmaceutical Commerce
DHL Supply Chain is spending $150 million to expand its North American operations

Biosimilars Review & Report
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PCMA
PCMA: Pharmacy Benefit Managers Increase Rx Access and Affordability for New Yorkers

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EXHIBIT 89

exclude any individual or entity that it determines has committed an act described in section 1128B(b) of the Act.

(2) With respect to acts described in section 1128B of the Act, the OIG—

(i) May exclude any individual or entity that it determines has knowingly and willfully solicited, received, offered or paid any remuneration in the manner and for the purposes described therein, irrespective of whether the individual or entity may be able to prove that the remuneration was also intended for some other purpose; and

(ii) Will not exclude any individual or entity if that individual or entity can prove that the remuneration that is the subject of the exclusion is exempted from serving as the basis for an exclusion.

(b) *Length of exclusion.* (1) The following factors will be considered in determining the length of exclusion in accordance with this section—

(i) The nature and circumstances of the acts and other similar acts;

(ii) The nature and extent of any adverse physical, mental, financial or other impact the conduct had on program beneficiaries or other individuals or the Medicare, Medicaid and all other Federal health care programs;

(iii) Whether the individual or entity has a documented history of criminal, civil or administrative wrongdoing (The lack of any prior record is to be considered neutral);

(iv) The individual or entity has been the subject of any other adverse action by any Federal, State or local government agency or board, if the adverse action is based on the same set of circumstances that serves as the basis for the imposition of the exclusion; or

(v) Any other facts bearing on the nature and seriousness of the individual's or entity's misconduct.

(2) It will be considered a mitigating factor if—

(i) The individual had a documented mental, emotional, or physical condition before or during the commission of the prohibited act(s) that reduced the individual's culpability for the acts in question;

(ii) The individual's or entity's cooperation with Federal or State officials resulted in the—

(A) Sanctioning of other individuals or entities, or

(B) Imposition of a civil money penalty against others; or

(iii) Alternative sources of the type of health care items or services provided by the individual or entity are not available.

[57 FR 3330, Jan. 29, 1992, as amended at 63 FR 46689, Sept. 2, 1998; 67 FR 11933, Mar. 18, 2002]

§ 1001.952 Exceptions.

The following payment practices shall not be treated as a criminal offense under section 1128B of the Act and shall not serve as the basis for an exclusion:

(a) *Investment interests.* As used in section 1128B of the Act, ''remuneration'' does not include any payment that is a return on an investment interest, such as a dividend or interest income, made to an investor as long as all of the applicable standards are met within one of the following three categories of entities:

(1) If, within the previous fiscal year or previous 12 month period, the entity possesses more than $50,000,000 in undepreciated net tangible assets (based on the net acquisition cost of purchasing such assets from an unrelated entity) related to the furnishing of health care items and services, all of the following five standards must be met—

(i) With respect to an investment interest that is an equity security, the equity security must be registered with the Securities and Exchange Commission under 15 U.S.C. 781 (b) or (g).

(ii) The investment interest of an investor in a position to make or influence referrals to, furnish items or services to, or otherwise generate business for the entity must be obtained on terms (including any direct or indirect transferability restrictions) and at a price equally available to the public when trading on a registered securities exchange, such as the New York Stock Exchange or the American Stock Exchange, or in accordance with the National Association of Securities Dealers Automated Quotation System.

(iii) The entity or any investor must not market or furnish the entity's items or services (or those of another

services are reimbursed by the same Federal health care program using the same methodology and the reduced charge is fully disclosed to the Federal health care program and accurately reflected where appropriate, and as appropriate, to the reimbursement methodology;

(iii) A reduction in price applicable to one payer but not to Medicare, Medicaid or other Federal health care programs;

(iv) A routine reduction or waiver of any coinsurance or deductible amount owed by a program beneficiary;

(v) Warranties;

(vi) Services provided in accordance with a personal or management services contract; or

(vii) Other remuneration, in cash or in kind, not explicitly described in paragraph (h)(5) of this section.

(i) *Employees.* As used in section 1128B of the Act, ''remuneration'' does not include any amount paid by an employer to an employee, who has a bona fide employment relationship with the employer, for employment in the furnishing of any item or service for which payment may be made in whole or in part under Medicare, Medicaid or other Federal health care programs. For purposes of paragraph (i) of this section, the term *employee* has the same meaning as it does for purposes of 26 U.S.C. 3121(d)(2).

(j) *Group purchasing organizations.* As used in section 1128B of the Act, ''remuneration'' does not include any payment by a vendor of goods or services to a group purchasing organization (GPO), as part of an agreement to furnish such goods or services to an individual or entity as long as both of the following two standards are met—

(1) The GPO must have a written agreement with each individual or entity, for which items or services are furnished, that provides for either of the following—

(i) The agreement states that participating vendors from which the individual or entity will purchase goods or services will pay a fee to the GPO of 3 percent or less of the purchase price of the goods or services provided by that vendor.

(ii) In the event the fee paid to the GPO is not fixed at 3 percent or less of the purchase price of the goods or services, the agreement specifies the amount (or if not known, the maximum amount) the GPO will be paid by each vendor (where such amount may be a fixed sum or a fixed percentage of the value of purchases made from the vendor by the members of the group under the contract between the vendor and the GPO).

(2) Where the entity which receives the goods or service from the vendor is a health care provider of services, the GPO must disclose in writing to the entity at least annually, and to the Secretary upon request, the amount received from each vendor with respect to purchases made by or on behalf of the entity. Note that for purposes of paragraph (j) of this section, the term *group purchasing organization* (GPO) means an entity authorized to act as a purchasing agent for a group of individuals or entities who are furnishing services for which payment may be made in whole or in part under Medicare, Medicaid or other Federal health care programs, and who are neither wholly-owned by the GPO nor subsidiaries of a parent corporation that wholly owns the GPO (either directly or through another wholly-owned entity).

(k) *Waiver of beneficiary coinsurance and deductible amounts.* As used in section 1128B of the Act, ''remuneration'' does not include any reduction or waiver of a Medicare or a State health care program beneficiary's obligation to pay coinsurance or deductible amounts as long as all of the standards are met within either of the following two categories of health care providers:

(1) If the coinsurance or deductible amounts are owed to a hospital for inpatient hospital services for which Medicare pays under the prospective payment system, the hospital must comply with all of the following three standards—

(i) The hospital must not later claim the amount reduced or waived as a bad debt for payment purposes under Medicare or otherwise shift the burden of the reduction or waiver onto Medicare, a State health care program, other payers, or individuals.

(ii) The hospital must offer to reduce or waive the coinsurance or deductible

EXHIBIT 90

National Purchasing Group

What We Do

WHAT WE DO (/WHAT-WE-DO)

HOW IT WORKS (/HOW-IT-WORKS)

First, some clerical housekeeping:

- PBG = Physician Buying Group
- GPO = Group Purchasing Organization

The difference between PBGs and GPOs is a frequent topic of confusion, so today we're going to set the record straight.

PBGs & GPOs have the same function

Both of these types of organizations help medical practices gain previously unrealized saving by aggregating purchasing volume and using that leverage to negotiate discounts with suppliers.

Medical practices can become members of either type of organization in much the same way, and the financial structures at play in both cases are extremely similar.

So PBGs and GPOs do essentially the same things. But there is one major difference in their capabilities.

PBGs & GPOs have different capabilities

THE LIMITATIONS OF GPOS

GPOs specialize in aggregate purchasing for large medical practices, such as hospitals. They do not accept new member practices unless they meet certain size requirements. These, of course, vary from one GPO to another, but generally, only large practices are able to work with GPOs.

THE FLEXIBILITY OF PBGS

PBGs can also meet all of the needs of large hospitals and healthcare centers, but their powers do not stop there. PBGs can also serve the needs of even the smallest medical practices.

PBGs can aggregate the supply needs of a large group of small practices to negotiate volume discounts with suppliers. These are the very same discounts that larger practices enjoy.

So, to put it simply, PBGs do everything that GPOs do, except that they can work with small businesses too

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EXHIBIT 91

United States Government Accountability Office

Report to Congressional Requesters

October 2014

GROUP PURCHASING ORGANIZATIONS

Funding Structure Has Potential Implications for Medicare Costs

through the Healthcare Group Purchasing Industry Initiative (HGPII). We issued five reports between 2002 and 2012 related to these issues.[5]

You raised questions about GPOs' contracting practices and about the effects of the GPO funding structure.[6] This report examines

1. GPO contracting practices and the reported effects of these practices; and
2. how GPOs are funded and the reported effects of this funding structure.

To address these objectives, we sent a questionnaire to representatives of the five largest national GPOs by purchasing volume about their contracting practices and sources of revenue, including administrative fees collected from vendors.[7] We also conducted a review of the literature regarding the effects of the GPO funding structure. In addition, we reviewed documentary evidence of the factors that GPOs consider when contracting for products and services, and reviewed published articles in economic and law journals, as well as analyses of the healthcare market. We also reviewed laws, legislative history, regulations, and guidance

[5]See GAO, *Group Purchasing Organizations: Pilot Study Suggests Large Buying Groups Do Not Always Offer Hospitals Lower Prices*, GAO-02-690T (Washington, D.C.: April 30, 2002); *Group Purchasing Organizations: Use of Contracting Processes and Strategies to Award Contracts for Medical-Surgical Products*, GAO-03-998T (Washington, D.C.: July 16, 2003); *Group Purchasing Organizations: Research on Their Pricing Impact on Health Care Providers*, GAO-10-323R (Washington, D.C.: Jan. 29, 2010); *Group Purchasing Organizations: Services Provided to Customers and Initiatives Regarding Their Business Practices*, GAO-10-738 (Washington D.C.: Aug. 24, 2010); *Group Purchasing Organizations: Federal Oversight and Self-Regulation,* GAO-12-399R (Washington, D.C.: March 30, 2012).

[6]You also raised questions about the number of shortages of generic injectable drugs in recent years and noted that some experts had raised concerns that GPO contracting practices were a primary cause of these shortages. We issued a report and a testimony on drug shortages in February 2014 and have ongoing work focused on the causes and management of drug shortages. See GAO, *Drug Shortages: Public Health Threat Continues, Despite Efforts to Help Ensure Product Availability*, GAO-14-194 (Washington, D.C.: Feb. 10, 2014); and *Drug Shortages: Threat to Public Health Persists, Despite Actions to Help Maintain Product Availability*, GAO-14-339T (Washington, D.C.: Feb. 10, 2014).

[7]The five largest national GPOs by purchasing volume are Premier, Novation, MedAssets, HealthTrust Purchasing Group, and Amerinet. See *GPO Facts & Figures; Largest Group Purchasing Organizations* (Healthcare Purchasing News, October 2012).

related to the GPO safe harbor. We interviewed FTC, DOJ, and HHS officials about their oversight of GPOs. To obtain contextual information about their experiences with GPOs, we interviewed representatives from five hospitals and eight vendors of medical products. We selected hospitals based on variation in the number of hospital beds, the extent to which the hospital had an ownership interest in a GPO, and which GPOs they used. We selected vendors based on variation in the types of products manufactured. To determine the reported effects of the GPO funding structure, we interviewed 13 experts in economics, the healthcare market, and purchasing cooperatives. We identified these experts through our search of the relevant literature on GPOs, healthcare markets, purchasing cooperatives, and economics. We also interviewed trade associations representing GPOs and vendors of medical products. Information obtained from interviews is not generalizable. A more extensive discussion of our scope and methodology appears in appendix 1.

We conducted this performance audit from June 2013 through October 2014 in accordance with generally accepted government auditing standards. Those standards require that we plan and perform the audit to obtain sufficient, appropriate evidence to provide a reasonable basis for our findings and conclusions based on our audit objectives. We believe that the evidence obtained provides a reasonable basis for our findings and conclusions based on our audit objectives.

Background

GPOs are organizations that act as purchasing intermediaries that negotiate contracts between health care providers and vendors of medical products and services, including manufacturers, distributors, and other suppliers. The intent of GPOs is to save their customers money by pooling their purchases in order to obtain lower prices and by taking on the administrative burden of negotiating contracts with vendors. Through GPO-negotiated contracts, health care providers can purchase products from vendors, including medical devices, commodities, branded drugs, and generic drugs, as well as services, such as laundry and food services. The Healthcare Supply Chain Association (HSCA)—a trade association representing 14 healthcare GPOs—estimates that U.S. hospitals use, on average, 2 to 4 GPOs per facility, and nearly every hospital in the United States—approximately 96 percent to 98 percent—purchases through GPO contracts.

According to HSCA, the first GPO was established in 1910 by the Hospital Bureau of New York, and by the 1980s, there were more than

100 GPOs. While over 600 GPOs in various markets are currently active in the United States, a relatively small number of GPOs dominate the healthcare market for products and services sold through GPO contracts. According to HSCA, GPOs vary in size, type of ownership, and the contracting services they offer their customers. For example, some GPOs

- are owned by hospitals, while others are not.
- operate nationally, while others operate regionally to negotiate contracts with local vendors.
- serve not-for-profit hospitals, others serve for-profit hospitals, and some serve both.
- offer a broad portfolio of products and services, while others focus on specific product categories or certain types of health care, such as long-term care.

In recent years, the GPO market has become more consolidated as some large GPOs have merged. The five largest national GPOs have reported contracting for a similar, broad portfolio of products, including, for example, commodities such as cotton balls and bandages, devices such as pacemakers and stents, and branded and generic drugs. During fiscal year 2012, the 5 largest GPOs by purchasing volume reported a total purchasing volume of $130.7 billion.

Administrative Fees

During the contracting process for products and services, GPOs negotiate the payment of administrative fees by the vendor to the GPO. In addition to using these administrative fees to cover operating expenses, GPOs may distribute a portion of the fees to their health care provider customers or use them to finance other ventures, such as investing in other companies. GPOs may also use administrative fees to fund additional services outside of group purchasing for their customers, which can include custom contracting; services related to product evaluation, such as clinical evaluation and standardization of products; assessments of new technology; benchmarking data services; and marketing and insurance services.[8] (See fig. 1.)

[8]For additional information on services GPOs provide to their customers, see GAO-10-738.

EXHIBIT 92

THIS DOCUMENT HAS

BEEN REDACTED IN ITS

ENTIRETY

EXHIBIT 93

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EXHIBIT 94

340B Drug Pricing Program

Guidance to 340B providers in California/Florida/Georgia/North Carolina/South Carolina/Virginia/Commonwealth of the North Mariana Islands/US Virgin Islands: Public Health Emergency Declaration by the Secretary

HRSA recognizes that circumstances surrounding disaster relief efforts warrant flexibility for entities eligible for participation in the 340B Program.

Therefore, eligible entities in California/Florida/Georgia/North Carolina/South Carolina/Virginia/Commonwealth of the North Mariana Islands/US Virgin Islands may immediately enroll for the 340B Program during the Public Health Emergency Declaration by the Secretary, rather than having to wait for the normal quarterly registration period.

We believe this will enable these entities to meet the needs of the residents affected by this disaster. If you are in the listed states/territories and would like to enroll, email the 340B Prime Vendor Program or call 1-888-340-2787.

HRSA/OPA conducted a 340B Recertification webinar for hospitals. Recertification began August 15, 2018 and ended September 12, 2018.

The 340B Program enables covered entities to stretch scarce federal resources as far as possible, reaching more eligible patients and providing more comprehensive services.

Manufacturers participating in Medicaid, agree to provide outpatient drugs to covered entities at significantly reduced prices.

Eligible health care organizations/covered entities are defined in statute and include HRSA-supported health centers and look-alikes, Ryan White clinics and State AIDS Drug Assistance programs, Medicare/Medicaid Disproportionate Share Hospitals, children's hospitals, and other safety net providers. See the full list of eligible organizations/covered entities.

To participate in the 340B Program, eligible organizations/covered entities must register and be enrolled with the 340B program and comply with all 340B Program requirements. Once enrolled, covered entities are assigned a 340B identification number that vendors verify before allowing an organization to purchase 340B discounted drugs.

Date Last Reviewed: November 2018

News

OPA Program Update – August 2018

OPA Program Update - 340B OPAIS, July 2018 (PDF - 28 KB)

OPA Program Update – July 2018

340B Drug Pricing Program

Contact OPA

Office of Pharmacy Affairs
Health Resources and Services Administration
5600 Fishers Lane, 08W05A
Rockville, MD 20857

Contact the 340B Prime Vendor Program

340B Prime Vendor Program website
1-888-340-2787 (Monday – Friday, 9 a.m. – 6 p.m. ET)
apexusanswers@340bpvp.com

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EXHIBIT 95

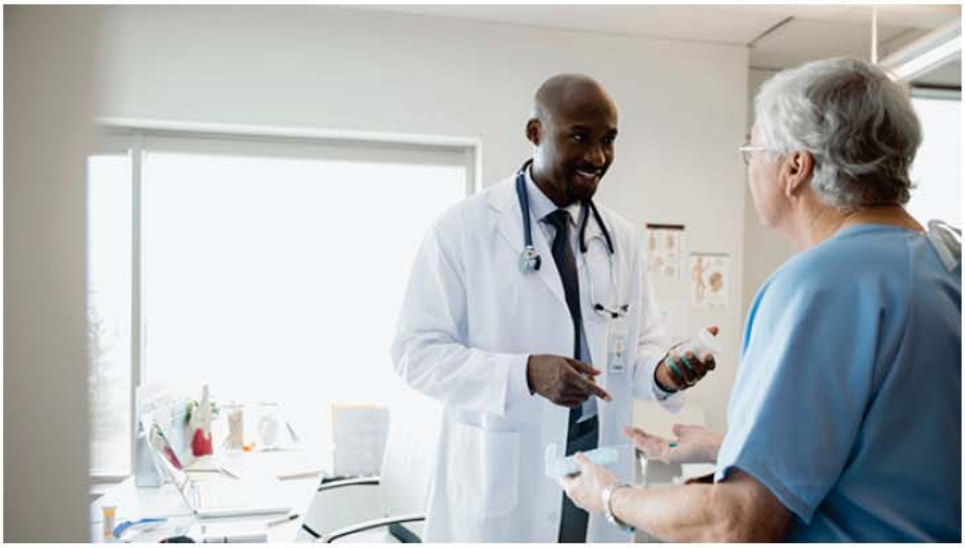
Health Affairs

HEALTH AFFAIRS BLOG HEALTH EQUITY

Does A 'One-Size-Fits-All' Formulary Policy Make Sense?

Adrienne Chung, Joanna MacEwan, Dana P. Goldman

JUNE 2, 2016 10.1377/hblog20160602.055116



Over the last decade, insurers have increasingly used step therapy, or "fail-first," po icies as a strategy to contain pharmaceutical costs. Step therapy requires patients to begin treatment for a medical condition on a typically less expensive drug, and only progress to more costly second-line drugs when the first- ine therapy becomes ineffective or inappropriate. Step therapy shifts clinical decision-making away from physicians and toward centralized policies that define treatment steps for patient populations based on the potential for more cost-effective care.

The rapid growth in the use of step therapy po icies in recent years—from 27 percent in 2005 to 73 percent in 2013 among employers—indicates a misunderstanding about the direct and indirect harms of this "one-size-fits-all" approach.

Step therapy can delay access to the most efficacious therapies

This can increase the duration of illness and raise the total cost of health care in the long-run. Delays in receiving health care, whether caused by step therapy edits or other factors, have been shown to be significantly detrimental to patient health outcomes.

For example, breast cancer patients with a treatment delay of three months or more had a 12 percent lower five-year survival rate compared with breast cancer patients with only a zero to three month delay. Similarly, patients with rheumatoid arthritis who delayed disease-modifying treatment for approximately four months experienced significantly more radiologic joint damage after two years compared with patients who began treatment within two weeks of diagnosis.

Delaying effective treatment can lead to disease progression, increased symptom severity, poorer patient outcomes, or even death. For example, a four-week delay in receiving adjuvant chemotherapy has been associated with a significant decrease in disease-free survival and overall survival in colorectal cancer patients. Similarly, patients with multiple sclerosis (MS) who initiated interferon beta-1b treatment at the time of diagnosis had a 41 percent lower risk of developing clinically definite MS compared with MS patients who started treatment two years after diagnosis.

Alzheimer's research also indicates that patients treated early and persistently show less behavioral, functional, and cognitive deterioration over time than those treated later – early detection and treatment can delay Alzheimer's progression by at least 2.8 years in some cases. Thus, the available evidence clearly demonstrates that delays in health care, including those potentially caused by waiting for step therapy edits, can result in significant undue harm to patients.

In the case of chronic illness, medication switching due to blunt formulary policy can also have negative health consequences. For example, approximately 100 million Americans suffer from chronic pain. Acute and chronic pain management is unique to each patient and must be approached as such – what relieves pain for one patient may not work for another.

Related

CONTENT

TOPICS

- Pharmaceuticals
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- Costs And Spending
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- Patient Care
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- Access Primary Care
- Diseases
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- Decision Making

Cite As

"Does A 'One-Size-Fits-All' Formulary Policy Make Sense?," Health Affairs Blog, June 2, 2016.
DOI: 10.1377/hblog20160602.055116

Furthermore, efficacy, adherence, compliance, and should be considered. Side effects and other factors must also be taken into account. For example, psoriasis medications are well known for side effects (e.g., renal problems and bone marrow suppression), which requires doctors to monitor patients and rotate therapies as needed based on changes in symptoms resulting from accumulated toxicities. Similarly, although COX-2 painkillers are typically $50 to $70 more than traditional NSAIDS, COX-2 painkillers can reduce the risk of serious gastrointestinal adverse events. Although Blue Cross Blue Shield states that they would allow exemptions for "members at high risk for adverse events from NSAID therapy" (i.e., those with ulcer history), is it ethical to require a patient to experience severe gastrointestinal side effects before approving a COX-2?

Step therapy trades prescription spending for time and hospital costs to patients and providers

One study reported that 28 percent of patients who had encountered a step therapy edit spent three or more hours trying to obtain second-line drugs from their physicians' offices. Increased rates of discontinuation, along with delays in accessing treatment, can contribute to less efficient use of health care resources and increased costs over time. For example, the introduction of step therapy for schizophrenia medications initially saved Georgia's Medicaid program $20 per member per month, but the state subsequently spent $32 per member per month on outpatient services because patients utilized ineffective medications.

Overall, the combination of prior authorization and step therapy is associated with higher inpatient spending, while formulary restrictions have been positively correlated with higher drug costs, more office visits, and higher likelihood of hospitalization among patients with certain diseases. Furthermore, drugs that require laboratory tests and monitoring can increase non-pharmacy costs that may have been avoidable with alternative therapies.

Step therapy also increases the administrative burden on medical providers. Staff must spend time contacting insurance companies to determine if a drug will be covered, in addition to appealing denied treatments, which leaves less time for patient-centered health care. By some estimates, this increased administrative burden takes approximately two hours per patient.

From a financial perspective, maintaining insurer preferred drug ists, spending time requesting authorization for second-line therapies, and imposing on physicians' ability to prescribe their first choice drug is estimated to cost $1,569 per physician per year for statins and anti-hypertensives alone. Thus, it is no surprise that an American Medical Association survey of 2,400 physicians revealed that 78 percent of doctors rated "e iminating hassles caused by prior authorization requirements" as very important to address.

Complicated step therapy rules create barriers to health care

The time and administrative burden associated with step therapy is an obstacle to access that can lead to unnecessary breaks in treatment. Indeed, depending on therapeutic class, 7 percent to 22 percent of patients did not submit any prescription claim to their insurance provider following a step edit, instead forgoing treatment.

This lack of follow-up may be due to insufficient levels of effective pharmacist involvement in the resolution of rejections, or due to the reality that more than 77 million U.S. adults have basic or below basic health iteracy skills. This widespread low level of health iteracy makes it challenging for patients to decipher complex policies and take appropriate action. Ultimately, the hassle patients face attempting to obtain coverage in restrictive health plans may result in lower medication utilization and adherence, with a related increase in total health care spending.

'Fail-first' policies, as their name suggests, increase the risk of dangerous side effects

For certain patients-- ike those who need immunologic and biologic agents—these concerns are particularly salient. Researchers found that 18 insurance plans— representing approximately 97 million insured ives—required 45 percent of beneficiaries to "step through" one or two drugs bearing an FDA "black box warning" of serious adverse events before progressing to a drug without such warning. As a result, patients may needlessly face severe health risks in disease areas that have benefited from recent advances in immunologic and biologic therapy, such as cancer and inflammatory diseases.

Legislative and regulatory options

State legislatures are clearly concerned about these issues. Most recently, Indiana and West Virginia joined seven other states, including Connecticut, California, and Louisiana, in passing laws providing step therapy protections for patients. Other state legislatures, such as New York, Ohio, Illinois, and Florida, are in the process of attempting to limit the reach of step therapy protocols. Proposed bills about step therapy echo similar concerns – they typically recommend regulating the number of times a patient can be forced to fail on a sub-optimal medication and defining what constitutes "failure" before a patient can be exempt from the step therapy protocol.

Unfortunately, insurers in most states are still not required to justify formulary policies with evidence, have transparency in their policies, or address exemption requests in a timely manner. Thus, there is a clear need for legislation that protects patient access by, for example, imiting the length of time that patients must fail on an inadequate treatment before ifting a restriction.

One size does not fit all

In an ideal world, insurers would be able to provide limitless coverage of care while charging low premiums, allowing providers to make patient-by-patient decisions and leveraging the best treatments that medical innovation has to offer. However, in reality, insurers must balance the cost of covering care against the need to increase premiums (and potentially lose customers). Similarly, public payers are faced with resource constraints that require attempts to contain

costs. Resulting efforts to contain coverage costs have led to centralized medical decision-making with a "one size fits all" approach.

But one size does not fit all. Each patient has unique symptoms and side effects, making them respond differently to mandated choices. This problem is not exclusive to step therapy, but encompasses all health plan restrictions, including differential copays and cost sharing, pre-authorization rules, and quantity imits on prescriptions.

Centralized decision-making assumes that what works for one patient will work for another. However, doctors typically understand the nuances of their patients' health issues best. Thus, the goal of a plan's po icies should be to promote optimal matching of patients to existing therapies rather than to declare, without medical expertise, that one therapy is better than another for everyone. Health plan restrictions designed to control costs should be implemented with great caution. Otherwise, over time, uncontrolled restrictions on access will lead to worse health outcomes and more health care spending down the road.

Authors' Note

Adrienne Chung and Joanna MacEwan are employees at Precision Health Economics and Dana Goldman is a founder, member of the Value and Evidence Advisory Board, and Executive Economist at Precision Health Economics, a consulting firm to the health care industry.

Mo - 2 years ago

Step therapy IS problematic because it forces all individual members of that health plan to follow the same treatment algorithm. We all know that no two patients are the same. I understand the need to reign in high pharmaceutical costs but that cannot be done to the detriment of the patient. If they said "first line therapy" but didn't really include all of the current medically available first line agents in that formulary, a patient that truly did fail a first line treatment agent albeit not formulary for that company could appear as if they didn't and therefore not have appropriate access to escalation of treatment.

Example, I am a patient living with MS still working and have commercial insurance. I was on first line therapy for over a year, failed it due to aggressive disease activity effecting my brainstem. Disease activity in the brainstem and spinal cord carry a high risk for permanent and rapid disability. In all clinical guidelines and by expert accounts the next appropriate step for managing my disease is to escalate therapy to second line treatment. However, because the first line therapy I failed (which is generally more affective then what insurance recommends) was not yet defined by my insurance company as being first line (they haven't defined it as anything at all, out of simple omission) to them I hadn't failed it and they wanted me to start on another first line agent generally considered less effective than the one I failed. So, someone like me has to either spend months fighting them (all while not being treated) or just play along and take the less effective drug, fail that by getting worse clinically before I get what I really need. Either way they have control over my fate.

So, for those that have said this is all driven by big pharma, put yourselves in my position. If your brainstem were under attack and couldn't get appropriate treatment what would you say? They are playing Russian roulette with patient's lives.

Treatment MUST be individualized for each patient as no two are the same and by depriving people access to the full arsenal of available treatments for their condition at any given time, insurance agencies are putting people at risk, PERIOD!

^ | v • Reply • Share ›

P Oberg - 3 years ago

Well said! With the new guidelines published by AACE for Obesity and DM, we are still in the dark ages as far as formulary selections. No one in their right mind can look at the overwhelming evidence in favor of liraglitude which appears in both guidelines and tell me that Byetta is a better selection. I have patient's with BMIs over 50 with multiple co-morbidities that I can't get appropriate treatment for. Orthopedic problems inhibit the exercise component and poverty and the nearest grocery store 40 miles away impacts diet choices. Can you seriously tell me that national policy would prefer bariatric surgery to addressing the barriers to logical progression of treatment we see in our own public health arena? What happened to the outrage about "cook-book" medicine. You can't use a cookie cutter! You also can't tell me I'll be paid by outcome and deny me the tools I need to accomplish the job!!! A single prevented IP admit resulting from the lowered risk would pay for the medication. Lets get common sense back into healthcare.

^ | v • Reply • Share ›

Dorothy - 3 years ago

The authors are absolutely correct. Step therapy approaches to treatment often creates barriers to patients getting optimal treatment in a timely fashion. The step therapy approach is akin to the old adage penny wise pound foolish.

^ | v • Reply • Share ›

Jeff Mason - 3 years ago

Doctors are not all knowing seers and their recommendation are often based on experience, rather than science, and sometimes influenced by detailing. t is true that formulary considerations and step therapy are informed by cost but they are also rooted in science. I think step therapy improves outcomes much more frequently then it causes harm.

^ | v • Reply • Share ›

T Culhane - 3 years ago

So what pharmaceutical lobby funded this article? Most the references quoted are studies of poor quality and not at all connected to step therapy interventions. I believe funding disclosures are in order.

^ | v • Reply • Share ›

Mike Barrett 3 years ago

If the dollars where infinite or the cost of the Rx was identical then I would agree The compromise is and epidemiology of the topic begs what care would NOT be available because the unnecessary expensive solution was used and the lower cost solution was never pursued?

The solution is simple. Pharma needs to charge the same amount for each therapeutic class. Regardless of cost of man'f if they can't man'f at the truly therapeutic alternative cost levels then don't bring the product to market. Advancements in therapy have to REPLACE not be simple me too options Pre therapy selectivity and sensitivity have to be substantive before any new therapy or dx process is deployed.

Reply • Share ›

HealthAffairs

7500 Old Georgetown Road, Suite 600
Bethesda, Maryland 20814
T 301 656 7401
F 301 654 2845
customerservice@healthaffairs.org

EXHIBIT 96

Prescription Drug Prices: Why Do Some Pay More Than Others Do?

An accurate understanding of price differences is essential to the crafting of sound prescription drug policies.

by Richard G. Frank

ABSTRACT: The fact that sick elderly people without prescription drug coverage pay far more for drugs than do people with private health insurance has created a call for state and federal governments to take action. Antitrust cases have been launched, state price control legislation has been enacted, and proposals for expansion of Medicare have been offered in response to price and spending levels for prescription drugs. This paper offers an analysis aimed at understanding pricing patterns of brand-name prescription drugs. I focus on the basic economic forces that enable differential pricing of products to exist and show how features of the prescription drug market promote such phenomena. The analysis directs policy attention toward how purchasing practices can be changed to better represent groups that pay the most and are most disadvantaged.

THE PRICING OF PRESCRIPTION DRUGS in the United States has become a political "hot button" issue. Strong claims are made in Congress and before state legislatures about the motives of drug manufacturers and about the workings of the market. Growth in spending and the fact that people without drug coverage pay higher prices than do those with such coverage have ignited passions on this issue.

Participants in this policy debate sometimes draw conclusions about drug prices as if the "law of one price" prevails. For instance, U.S./international comparisons of drug prices typically rely on choosing a retail price in the United States and comparing it with one in Canada or Western Europe. Thus, the comparison and the resulting conclusions—typically, that prices are higher in the United States—commonly rely on the implicit assumption that there is a single price charged to all buyers.

Legislatures, insurers, and advocates for the elderly, among others, are alarmed by the fact that the law of one price does not seem to

Richard Frank is the Margaret T. Morris Professor of Health Economics at Harvard University.

the potential for arbitrage. The existence of market power simply means that a seller can profitably raise its price above that charged by rivals in the market. In the case of brand-name prescription drugs, market power is conveyed upon their manufacturers by patents. A patent gives a manufacturer the exclusive right to sell a particular product for a defined period of time. Hence, as a matter of law, there is no perfect substitute available for that product as long as a patent is valid.

The second condition is that a market be made up of distinct segments that respond differently to changes in the price of a product. This means that a seller will face a number of distinct demand curves for a given product. The seller of the product will maximize profits by selling the product at a different price to each segment according to its responsiveness to price. In fact, profit-maximizing firms will charge the most to market segments that are the least responsive to price, or, in the language of economics, price will be highest to market segments with the lowest price elasticity of demand. This explains why movie theaters offer discounts to the elderly. The elderly typically have lower incomes than adults under age sixty-five and as a result tend to be more responsive to the price of a movie ticket. They display a higher elasticity of demand.

Offering different prices to different market segments can be sustained only if it is difficult (high-cost) to resell the product in question. That is, if a low-price buyer can easily resell the product to a high-price buyer, a differential pricing scheme will collapse. This is known as arbitrage. Markets where differential pricing persists are characterized by features that make arbitrage either impossible or very costly. For example, take a physician service such as psychotherapy. Psychiatrists have been known to charge lower-income patients less than they charge more affluent clients. The fact that there is no physical exchange of a commodity makes reselling the service nearly impossible. Therefore, differential pricing of psychotherapy services might be expected to persist.

In considering the differential pricing of brand-name prescription drugs, I examine the institutions that underpin the formation of market segments with differing responses to the prices of prescription drugs and those that render arbitrage difficult or costly.

■ **Institutional change in the health sector.** Market segmentation among buyers of prescription drugs has come as a consequence of institutional change in health care generally and in the market for prescription drugs specifically. One indication of the change in the manner in which drugs are bought and paid for is reflected in the changing responsibility for final payments for drugs. In 1990 private third-party payers plus Medicaid accounted for about 31 percent of

payments for prescription drugs in the United States; in 1999 they accounted for an estimated 69.8 percent.[9] These figures reflect an expansion not only in the share of the population with insurance coverage for prescription drugs but also in the level of coverage.

Over the past fifteen years insured persons have poured into managed care plans. In 1985 approximately 25 percent of the insured population was enrolled in a managed care plan; today that share exceeds 75 percent.[10] The corresponding figure for the population under age sixty-five was 91 percent in 1998. Prescription drug spending has grown at rates in excess of 15 percent in recent years. This has meant that the impulse to control drug costs has been even more pronounced and has resulted in the application of managed care techniques to prescription drugs even when they have been associated with a fee-for-service (FFS) indemnity health plan (via prescription drug carve-out programs). Pharmacy benefit managers (PBMs), private firms that specialize in insuring and managing prescription drug use and spending, have become increasingly important forces. They contract directly with employers or enter into subcontracts with health plans. Some HMOs own their own PBM companies. It has been estimated that in 1999, 70 percent of private health plan prescriptions were managed by a PBM.[11]

PBMs and health plans that administer their own drug benefit use formularies to steer prescribing toward cost-effective products. Formularies (lists of drugs that identify preferred drugs for treatment of specific illnesses) often contain summaries of scientific information about specific drugs that inform clinicians about their use. About three-fourths of employers report contracting with health plans and PBMs that use formularies.[12] Formularies are typically tied to a set of administrative processes and financial incentives aimed at encouraging adherence to the formulary by clinicians. Formularies have long been part of the management of care in hospitals but are relatively new features of health insurance.

The most direct method for encouraging use of formulary drugs is to "close" the formulary, which means that use of drugs not listed will not be covered unless prior approval is obtained from the health plan or PBM. It is estimated that about 10 percent of all health plans and 27 percent of HMOs use closed formularies.[13] However, payers are often reluctant to use closed formularies, and, as a result, a number of other mechanisms are used to steer patients toward formulary drugs. Copayments are increasingly being used to encourage adherence to a formulary. One popular approach is to create three tiers of copayments. In the first tier generic drugs carry a copayment of say, $5. A second tier might consist of "on-formulary" brand-name drugs with a copayment of $15. The third tier is for "off-formulary"

"Price differentials represent unequal bargaining power across different classes of purchasers."

drugs with a $30 copayment.

Therapeutic substitution programs involve utilization review and physician contacts to increase and maintain use of formulary products. About half of health plans use such methods.[14] Physician education programs (sometimes known as academic detailing) represent another method of encouraging use of formulary drugs. Finally, designing physician payment systems that have physicians bear some risk for prescription drug costs serves to encourage use of lower-price, on-formulary products.

■ **Market segments and price response.** As noted above, congressional investigators long ago recognized the role of institutional structure, buying power, and market forces in explaining the price structure for prescription drugs. Formularies enhance a buyer's bargaining power, enabling a purchaser such as a health plan or PBM to be more aggressive in negotiating prices with manufacturers. By being able to redirect the flow of drug sales within a therapeutic category such as proton pump inhibitors or selective serotonin reuptake inhibitor (SSRI) antidepressants, a buyer presents a seller—in this case, drug manufacturers—with more price-elastic demand. In drug classes with multiple products that are therapeutically equivalent for most patients, a buyer can use the threat of redirecting sales to a competing product to stimulate price competition. Manufacturers wish to have their products be a preferred drug listed on the formulary. As a result, buyers can negotiate a lower price. The implication is that buyers that can present profit-maximizing manufacturers with the greatest price-sensitivity in sales through strong management and high adherence to their formulary will realize the largest price concessions. Thus, the price concessions are responses by profit-maximizing manufacturers to demands by price-sensitive buyers. Hence, price differentials are not related to recouping losses by shifting costs. Rather, they represent unequal bargaining power across different classes of purchasers reflected by their ability to shift purchases in response to price.

The recent implementation of a national formulary by the VA illustrates the buying power of formularies. Under the national formulary, several drug classes were closed. In each closed class, only a subset of available drugs were considered to be eligible for reimbursement without resorting to an exceptions process. Using off-formulary drugs obtained at a higher price would exert extra pres-

EXHIBIT 97

Inside The Secret World Of Drug Company Rebates

Matthew Herper Forbes Staff
Pharma & Healthcare
I covered science and medicine, and believe this is biology's century.

The free market is alive and well when it comes to drug prices – if you're an insurance company or a government program. But not if you're a consumer.

Top-selling pharmaceuticals, protected by patents, often seem priced in a manner that has little to do with the laws of supply and demand. Want that new cholesterol medicine ($2,000 per year), that cancer treatment ($60,000 per year) , or the medicine for your child's rare disease ($300,000 per year)? No negotiation. It's your money or your life.

But in fact drug companies are constantly negotiating, not with individuals but with payers – Medicare, Medicaid, insurers such as United Health Care and Aetna AET +0%

and pharmacy benefit plans such as Express Scripts ESRX +0% . They don't reduce the price of their medicines. Instead, the drug firms pay rebates after the fact. For Medicaid, the price decreases are mandated by law, but everywhere else, free market forces are very much in effect. Me too drugs and those facing patent expiration have to deal with bigger rebates. Drug firms annual price increases are partly a way to deal with all this rebating. Of course, if you're a person without health insurance buying medicines at the counter of Walgreen WAG +0% 's, you're stuck with the list price.

Rebates cut about $40 billion out of the drug industry's sales every year, says Pratap Khedkar, a principal at pharma marketing consultancy ZS Associates. We know that because the drug industry reports both its gross sales (before the rebates) and net sales (after the rebates are taken out). The size of the rebate

average about 30% of a medicines sales, Khedkar says, and can be as low as single digits or as higher than 50% of gross sales.

"These may not be visible to the consumer," says Khedkar. "But between the insurance company and the pharma company, it is a very efficient free market."

What Drug Companies Give Back

Drug	IMS estimated U.S. sales ($Bil)	Company reported U.S. Sales ($Bil)	Estimated rebates (%)
Lipitor	$7.7	$5.0	35%
Plavix	$6.8	$6.6	3%
Nexium	$6.2	$2.4	61%
Abilify	$5.2	$4.0	24%
Advair	$4.6	$4.0	13%
Seroquel	$4.6	$3.3	27%
Singulair	$4.6	$3.5	23%
Crestor	$4.4	$3.1	30%
Cymbalta	$3.7	$3.2	14%
Humira	$3.5	$3.4	2%

Sources: IMS Health, company statements, analyst reports

No company reports how much of the gross sales of an individual drug are being given back to the payers. But there is a way to peer into the hidden world of pharma rebates. Every year, IMS Health, the prescription data tracking service, publishes its own lists of the most prescribed and the top-selling medicines in the country. But IMS' data capture gross sales at pharmacies, before the rebates happen. By comparing the gross sales reported by IMS to the sales the companies report to the Securities and Exchange Commission, it's possible to get an idea of how much of a medicine's gross sales are being given back in the form of rebates.

Caveats: there are other factors that could be affecting the difference, including if drug wholesalers are buying up extra inventory of a medicine, temporarily boosting sales. But generally speaking, I think we can assume that the bulk of these differences are from the rebates.

In the table in this story, I've calculated the difference between the IMS numbers and the numbers reported to the S.E.C. If U.S. sales were not immediately available, I took them from reports from sell-side analysts. The resulting figures show how greatly the numbers vary and give some hints as to why.

In the face of sudden generic discounts, Pfizer PFE +0%

seems to have given a lot of rebates to keep Lipitor on insurance company formularies, giving up 35% of gross sales, up from 26% last year. (This matches up with reporting I did here; promotion of Lipitor is finally grinding to a halt.) By contrast, Bristol-Myers Squibb and Sanofi-Aventis, the makers of Plavix, only gave 2.6% of sales in rebates; Plavix was until now the only medicine of its kind, and competitors from Eli Lilly and AstraZeneca have been unable to unseat it.

The most stunning discount is for Nexium, the purple pill for heartburn sold by AstraZeneca and derided by many as the perfect example of a me-too drug. Astra is giving back 60% of gross sales, most likely in the form of rebates. IMS lists Nexium as the third-best-selling drug in the country based on gross sales of $6.2 billion. But AstraZeneca reports U.S. Nexium sales of just $2.4 billion, putting it more on a par with Eli Lilly's cancer drug Alimta than behemoths like Lipitor and Plavix.

Why? As much as people rail against me-too drugs, being a me-too med is actually bad for the company, too. Insurers may be using the fact that they could direct consumers to generic Protonix or over-the-counter Prilosec or Prevacid as a bargaining stick, forcing Astra to cede ground.

Medicines in the same category seem to have the same level of discount. Astra's Crestor, a cholesterol drug that competes with Lipitor, seems to be giving 30% in rebates. The antipsychotics Seroquel (sold by AstraZeneca) and Abilify (from Otsuka & Bristol) give rebates of 27% and 24%, respectively.

AstraZeneca spokeswoman Stephanie Andrzejewski wrote via email that the company would not "discuss or disclose specifics around rebates" for Nexium. She added: "What I can tell you is that AstraZeneca is committed to helping people get the medicines they need and we understand our medicines won't do patients any good if they can't access them." She said it would be "inaccurate" to say AstraZeneca gave a 60% discount "across the board" – which is true. That appears to be the average discount.

The good news here is that, in the world of health insurers and drug giants, the free market is having an effect on drug prices. The bad news is that you have to be participating in this market by being insured in order to get those reduced rates. People who walk in off the street pay full price.

Matthew Herper Forbes Staff

From June 5, 2000, until December 21, 2018, I covered science and medicine for Forbes. That took me from the Human Genome Project through Vioxx to the blossoming DNA te

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EXHIBIT 98

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EXHIBIT 99

Yale Journal of Health Policy, Law, and Ethics

Volume 5
Issue 2 *Yale Journal of Health Policy, Law, and Ethics*

Article 8

2005

The Effects and Role of Direct-to-Physician Marketing in the Pharmaceutical Industry: An Integrative Review

Puneet Manchanda

Elisabeth Honka

(detailing);[6] sampling (provision of drugs at no cost); physician meetings and events; and advertisements in medical journals.[7] Since 1997, a change in the legal environment that allowed direct-to-consumer advertising (DTCA) has resulted in a 350% increase in expenditures for such advertising between 1996 and 2001.[8] However, the biggest chunk of marketing expenditure is directed toward detailing.[9] Historically, detailing has been the pharmaceutical industry's primary promotional instrument.[10] Our aim in this Article is to provide an integrative review of the academic research on the effect and role of detailing. We highlight the main findings that arise from the medical, legal, economics, and marketing literature. Finally, we propose an explanation of the pervasiveness of detailing over a drug's life. We conclude by proposing how an increase in the efficiency and effectiveness of this expenditure can benefit firms, physicians, and patients.

As noted above, we attempt to provide an integrative review of the literature on detailing. As a result, we need to provide organizational criteria in order to deal with the large number of studies on the subject. We use two such criteria to organize this review: the outcome variable and the nature of the data collected by the researcher. The outcome variable is the variable that is affected by detailing, which can range from "softer" variables, such as physician attitudes, to "harder" variables, such as drug sales. The nature of data collected can be survey data or actual behavioral (market) data. While we believe that these two criteria are important, we also describe the extant literature using all relevant criteria in the form of tables in the Appendix.[11] We first examine physician attitudes toward

6. For an excellent overview of the evolution of modern detailing in the United States, see Jeremy E. Greene, *Attention To 'Details': Etiquette and the Pharmaceutical Salesman in Postwar America*, 34 SOC. STUD. SCI. 271 (2004).

7. STEPHEN P. BRADLEY & JAMES WEBER, THE PHARMACEUTICAL INDUSTRY: CHALLENGES IN THE NEW CENTURY 7 (Harvard Bus. Sch., Working Paper No. 9-703-489, 2004).

8. *Id.*

9. WITTINK, *supra* note 5, at 6-7.

10. BRADLEY & WEBER, *supra* note 7, at 8-9.

11. There have been other such integrative articles. *See, e.g.*, Dale B. Christensen & Patricia J. Bush, *Drug Prescribing: Patterns, Problems and Proposals*, 15a SOC. SCI. & MED. 343 (1981); Richard J. Plumridge, *A Review of Factors Influencing Drug Prescribing* (pt. 1), 13 AUSTL. J. HOSP. PHARMACY 16 (1983). But not all include detailing as an independent variable, *see, e.g.*, Dennis W. Raisch, *A Model of Methods for Influencing Prescribing* (pts. 1 & 2), 24 DICP, ANNALS PHARMACOTHERAPY 417, 537 (1990), even the ones that do not differentiate between detailing as a general source of information, detailing's function in new product introductions, and its influence on physician prescribing, *see, e.g.*, James R. Williams & Paul J. Hensel, *Changes in Physicians' Sources of Pharmaceutical Information: A Review and Analysis*, 11 J. HEALTH CARE MARKETING 46 (1991). Most other literature reviews cover a very broad set of variables that affect physician prescribing. *See, e.g.*, T.S. Caudill & Nicole Lurie, *The Influence of Pharmaceutical Industry Advertising on Physician Prescribing*, 22 J. DRUG ISSUES 331 (1992); Elina Hemminki, *Review of*

detailing using studies from the medical literature. As the purported reason for the existence of detailing is that it provides information to physicians, we then examine whether the medical community indeed perceives it as such and if these perceptions have changed over time. We then look at whether detailing affects stated and actual prescription behavior. Finally, we examine the role of detailing over the life cycle of a drug with a special emphasis on its effects in the early, awareness-building stage. We conclude by integrating the main findings into a coherent explanation of the role of detailing.

Based on our analysis we draw the following major conclusions. First, it seems that physicians have negative (at one extreme) to neutral (at the other) attitudes toward pharmaceutical sales representatives. The variance in this attitude is explained by a variety of factors. Some of the important factors are the quality of informational and educational support provided via detailing, detailer style, and the physician's practicing environment. However, detailing exists and flourishes in spite of this attitude as it provides an inexpensive and convenient source of information. Interestingly, the importance of detailing as a source of information has declined over the past five decades, as it is no longer the most important source of information.

Second, not only is detailing an important source of information, it affects physician prescription behavior in a positive and significant manner. More important, this seems to occur over the length of the drug's life cycle. This is puzzling considering that over a drug's life cycle, most information about the drug is likely to be disseminated early on—a fact confirmed by physician surveys. Thus, detailing's effect should diminish over the life cycle of a drug. There is no obvious explanation for the fact that detailing has a positive and significant effect late in the drug life cycle. Based on our analysis and industry observations, our explanation is that in addition to providing a "reminder effect," constant interaction builds a stock of goodwill between a detailer (or the firm) and the physician, translating into positive physician prescription behavior. This goodwill is not based on purely objective and rational factors but on social and cultural norms. Its character changes from informative to more persuasive in the

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Literature on the Factors Affecting Drug Prescribing, 9 SOC. SCI. & MED. 111 (1975); Russell R. Miller, *Prescribing Habits of Physicians: A Review of Studies on Prescribing of Drugs* (pts. 1-8), 7 DRUG INTELLIGENCE & CLINICAL PHARMACY 492, 557 (1973), 8 DRUG INTELLIGENCE & CLINICAL PHARMACY 81 (1974); J.P. Rovers, *The Doctor's, the Druggist's, and the Detail Rep's Dance: Who Leads, Who Follows*, 37 CAN. FAM. PHYSICIAN 100 (1991); Dennis B. Worthen, *Prescribing Influences: An Overview*, 7 BRIT. J. MED. EDUC. 109 (1973). In other words, reviews concentrating on detailing as a factor influencing physician attitudes and prescribing behavior are relatively rare. Also noteworthy is Joel Lexchin, *Doctors and Detailers: Therapeutic Education or Pharmaceutical Promotion?*, 19 INT'L J. HEALTH SERVS. 663 (1989), which critically discusses doctors, detailers, and their relationships.

later stages of the drug life cycle. The evolution of goodwill in this manner reflects the deepening relationship between the physician and the pharmaceutical sales representative.

Finally, detailing is clearly here to stay. Although physicians claim to tolerate it as a necessary evil, detailing evidently has an impact on prescription behavior via both a subjective and an objective path. From the industry perspective, pharmaceutical firms continue to invest heavily in this mode of promotion—they have more than doubled their 1997 sales force to about 90,000 in 2002.[12] Thus, one possible approach that could be beneficial to all concerned parties—patients, physicians, firms, and policy makers—would be to ensure that this large expenditure on detailing is carried out in the most efficient manner possible. We conclude the Article by providing suggestions on how this could be carried out.

I. REVIEW OF PAST STUDIES

A. Physician Attitudes Toward Detailing

In this Section, we focus our attention on physician attitudes as documented (mostly) in the medical literature. We focus on general attitudes toward detailing and detailers and attitudes toward gifts. We then look at studies that provide an explanation for the formation of these attitudes. (Tables 1a-1c provide a more detailed overview of the studies discussed.)

1. Physician Attitudes Toward Detailers

A series of studies document that physician attitudes toward detailing and pharmaceutical sales representatives are mostly negative. First, Poirier et al. surveyed physicians on their attitudes toward pharmaceutical marketing practices.[13] They found that only 24% of the physicians were satisfied with detailing and 48% were dissatisfied.[14] These skeptical attitudes were confirmed by the finding that only 20% of the physicians believed in the accuracy and objectivity of presented information, while 44% did not.[15] Nevertheless, 56% admitted that representatives could influence formulary decisions if efficacy,

12. *Pushing Pills*, THE ECONOMIST, Feb. 15, 2003, at 61.

13. Therese I. Poirier et al., *Pharmacists' and Physicians' Attitudes Toward Pharmaceutical Marketing Practices*, 51 AM. J. HOSP. PHARMACY 378 (1994).

14. *Id.* at 379.

15. *Id.*

EXHIBIT 100

Session 2

Addressing the trust issue: From share of voice to share of care

Received (in revised form): 31st May, 2007

Marc Pesse
is a manager at Executive Insight, a professional services firm focusing exclusively on the healthcare industry. Over the last seven years, Marc has completed a number of projects across Europe, focusing on the areas of customer-centric strategy and business transformation.

Keywords *networked healthcare, sustainable value creation, trust, corporate social responsibility, share of voice, share of care, physician access*

Abstract The pharmaceutical industry is looking for answers to the trust and public image issues it is facing. Public relations and corporate social responsibility initiatives fail to address the root causes of those issues. Using networks as a framework to understand the changing nature of the healthcare environment, the paper proposes a shift from the traditional marketing metric of share of voice to a more balanced approach to measure the value the industry is creating: share of care. The paper outlines the high-level organisational implications of implementing this change.
Journal of Medical Marketing (2007) **7,** 303–307. doi:10.1057/palgrave.jmm.5050110

A GROWING DISCONNECT

While a couple of decades ago, pharmaceutical representatives were often the primary source of information on medical and pharmacological developments for physicians, the value added of those interactions has significantly deteriorated as representatives focus on maximising their coverage and frequency. The erosion of the physician–representative relationship is symptomatic of a wider disconnect between the pharmaceutical industry and the healthcare system as a whole. Decreased levels of trust and a deteriorating public image are empowering governments, themselves struggling to sustainably fund the delivery of health, to increase the pressure on the industry's margins.

Short-term corporate initiatives to address the trust issue are only 'skin-deep'. They are often driven by noncore functions such as corporate communications or corporate social responsibility departments or in some cases are even outsourced. These projects will change the discourse, but not the behaviour of the customer-facing staff. At best, the impact on the long-term perception of the environment will be limited. At worst, these initiatives are seen to further widen the gap between the industry's communication and the perception the consumer environment has of its business behaviour.

Looking at the market as a network of stakeholders, this paper proposes a shift in the way companies measure the value they create as a first step for long-lasting change.

AN OVERUSED METRIC?

A traditional metric for pharmaceutical sales and marketing organisations has

Marc Pesse
Metallstrasse 9
CH-6034 Zug, Switzerland
Tel: +41 78 639 52 43
Fax: +41 41 711 52 51
e-mail: m.pesse@executiveinsight.ch
Web: www.executiveinsight.ch

been that of 'share of voice', that is the exposure physicians get to the representatives detailing a certain product, relative to the total exposure they are getting to the all representatives detailing products in the same therapeutic class. Meant as a leading indicator of sales, the use of the share of voice metric drove a relentless focus on prescribers. Pharmaceutical representatives are incentivised to maximise the quantity of product-centred, transactional interactions with physicians. Measured on their ability to convey a standardised marketing message, representatives have little incentive to identify and respond to customer needs beyond that specific product, reducing the value of the sales call.

The management attention given to that metric has provided the rationale for the surge in sales force numbers observed in the last two decades. Predictably, the growth in the number of representatives led to access problems. Physicians, overwhelmed by the number of representatives in their waiting rooms (sometimes for the same product), disappointed by the short tenure of these representatives and in some cases, by their lack of experience, started to limit the time they spent with each representative. An increasing number of prescribers now simply refuse to see representatives. More worryingly, some medical institutions and even some governments have taken steps to limit industry access to medical staff. While the pharmaceutical representative was seen as a trusted, respected knowledge provider, they increasingly seem to become part of the trust problems the industry is facing.

Ultimately, there are signs that the correlation between share of voice and sales is fading. Some companies have seen their sales stagnate while they have increased their share of voice. Partly in response to these diminishing returns, partly as a result of external cost pressures, key players in the pharmaceutical industry have recently taken steps to reduce the size of their sales forces.

The question facing sales and marketing executives is whether to continue to do the same with fewer people. One answer is to improve targeting models, focus on the 'high-value' prescribers and continue to maximise the number of product-focused interactions. What should be examined, however, is whether the share of voice concept, with such a successful track record, is in fact the right model for the future. To address this question, it is necessary to consider how the healthcare environment has evolved.

THE NETWORK IS THE CUSTOMER

The healthcare environment has always been a network. In its simplest expression, the network consisted of doctors diagnosing and prescribing, a pharmacist dispensing, a payer footing the bill and a patient complying. Direct interactions between these players were limited in number and intensity. The environment is however becoming more networked in two key ways. First, the number of stakeholder types involved in the network is diversifying. Secondly, the frequency and speed of interactions between stakeholders is increasing. This change is in part driven by the following factors:

- *Economic pressure*: As payers face growing difficulties in footing the healthcare bill, reforms of the healthcare system are being implemented. While patterns differ, European governments are taking steps towards partial deregulation of healthcare systems in the hope of achieving a degree of market-driven efficiency. A side effect of these changes is to increase the interaction level between network stakeholders as they are forced into collaboration. Examples of this are the German Diagnosis-Related Groups (DRG) or the English practice-based commissioning,

which are both resulting in more frequent interaction between primary and secondary care players. Another result of these reforms is that nonprescribing stakeholders are gaining influence in terms of the prescription of drugs. Institutions such as the UK NICE or the German IQWiK have now established themselves as major influencers in their respective healthcare systems. Lower down the decision-making process, administrators in regional health authorities and insurances are also increasingly impacting the prescription process, or at least restricting physician freedom to prescribe.

- *Technological evolution*: Technology is enabling more frequent direct interactions between peers (eg physician online forums) at practically no cost. Whereas the role of connecting physicians with common interests was in the past in part played by the pharmaceutical representative, doctors can now more easily connect and interact online. In addition, their ease of access to independent medical information has improved drastically as platforms such as the Cochrane Collaboration for Evidence-based information have multiplied.
- *Social changes*: In conjunction with the access to information enabled by technology, there are changes in the relationship of society to healthcare. More informed patients are taking a more involved role in the decisions concerning their own health. Patient advocacy groups have become an increasingly important stakeholder group in the healthcare network. They have learnt how to effectively influence decisions such as treatment guidelines and reimbursement.

These are just some examples of how the complexity of the network is growing. The key consequence is that the single, centrally important decision maker, the target of share of voice-driven activities is actually less important, giving way to a network of tightly interrelated professionals, advisors, informants, budget holders and policy makers. These stakeholders influence the prescription of pharmaceutical products, but they have different motivations for doing so. In addition to treatment decisions for individual patients, they are responsible for improving the overall health of a given population and containing the costs of healthcare provision. For both these new stakeholders and the prescribers, the industry is looking for new ways to create value by bundling products with services, going beyond the product alone and addressing the needs of the healthcare network.

BALANCED VALUE CREATION

At the core of the discussion lies the question of the value pharmaceutical comapanies are providing to the healthcare network. The industry focuses much of its communication on its track record of bringing to market innovative products. If, however, sales and marketing executives have a clear understanding of their market share and share of voice, they are less able to articulate what impact their products are having on the healthcare environment, in terms of improvement of patient population outcomes and cost. To address these diverse needs of the network, it is proposed to adopt a more complete model to capture the full value the industry is creating, a 'share of care' set of metrics:

- *Health effectiveness*: The improvement of health outcomes is part of every pharmaceutical mission statement. Beyond the somewhat serendipitous process of bringing to market the best drugs, there is a real need for pharmaceutical companies to create transparency around the health outcomes of their products. The collection and communication of evidence has to extend beyond the data required for the approval and reimbursement process.
- *Health efficiency*: One way or another, the cost of providing healthcare will come under control. So far, most stakeholders have been working on how to shift these costs onto other players, in essence playing a zero-sum game. Pharmaceutical companies usually defend this position putting forward their

high R&D spending, their driving role as innovators, the relatively short period of patent protection and their commitment to shareholders. If companies do however want to be seen as partners by the healthcare system, and as truly integrated into the healthcare network, there is a need for them to develop solutions that can control the cost of care for the network as whole. These solutions will need to go beyond the provision of products and address the full cycle of care, from prevention to diagnosis and compliance.

- *Profitability*: Pharmaceutical companies, like any other company, are valued on their ability to generate profits. Logically, most internal metrics are geared to incentivise staff accordingly. This will continue to be the case, but to draw a parallel from corporate social responsibility field, the point is that profitability, transparency around health outcomes and evidence of the ability to keep costs under control are not mutually exclusive components of the value pharmaceutical companies are creating in the long run.

It is argued that companies that can actively balance and measure their efforts across all three proposed dimensions of value creation will be more successful in the long run than those which focus their efforts on one or the other dimension. Companies that strive for this balance internally will be more responsive to customer needs, enabling them to develop superior value propositions and laying the foundation for more trust-based relationship. In turn, this will allow for a more grounded communication of the value the industry is creating. Shifting this focus in practice does however require some fundamental organisational changes.

ORGANISATIONAL IMPLICATIONS

First of all, there is a need to develop new organisational capabilities. For example, developing the ability to understand and map existing and emerging healthcare networks is not something that is systematically done within pharmaceutical companies. Given the adequate tools, it can be achieved internally through the sales force, thus generating proprietary knowledge for a true competitive advantage. That will however require a change in the way the field force interacts with customers. From purely transactional, the interaction needs to become more consultative. From pushing a product message, representatives will need to learn how to listen to customer needs. From product-centred solutions for prescribers, representatives will need to co-develop solutions with a range of stakeholders within a given network or account. These changes in capabilities require a significant amount of re-training and in some cases the recruitment of a different type of representative.

Secondly, there is a need to redesign the organisational structure. Healthcare networks are by definition local in nature. Identifying and addressing their needs will require higher degrees of autonomy and regional focus. While most organisations subscribe to the concept of empowerment, field forces are still very much centralised, operating in national brand teams across entire markets. A network-centric model would have one central point of contact or owner of a healthcare network, owning a portfolio of products and supported by a multi-capability team, including marketing and medical.

Finally, there is a need to rethink the metrics that drive organisational behaviour. The focus on quantity, such as the coverage and frequency metrics, has in part created the trust and access problems the field force is facing. Ultimately, there is a need to align the internal performance indicators with the value objectives the company has defined. Following the 'share of care' approach for example, would result in including metrics on the evolution of

health outcomes for a given population and the cost of providing those outcomes. Including such metrics at all levels of the organisation will help align organisational behaviours with the needs of the company's customer base.

FROM SHARE OF VOICE TO SHARE OF CARE?

Many pharmaceutical executives are searching for solutions that address their access, cost, trust and public image issues. Quick-fix solutions such as corporate social responsibility initiatives, plain headcount reductions and more targeted call drives are unlikely to help as they do not address the diverse needs of an increasingly networked customer base. For long-term change, companies need to re-think the way they measure, drive and communicate the value they create. Shifting away from quantitative metrics such as 'Share of Voice' to a more balanced measure of the value created, such as the proposed 'Share of Care', is a concrete step in this direction.

EXHIBIT 101

ABOUT US

Considered the founder of the industry, Genentech, now a member of the Roche Group, has been delivering on the promise of biotechnology for over 40 years.

Genentech is a leading biotechnology company that discovers, develops, manufactures and commercializes medicines to treat patients with serious or life-threatening medical conditions. We are among the world's leading biotech companies, with multiple products on the market and a promising development pipeline.

Our Purpose: Doing now what patients need next

We believe it's urgent to deliver medical solutions right now – even as we develop innovations for the future. We are passionate about transforming patients' lives. We are courageous in both decision and action. And we believe that good business means a better world.

That is why we come to work each day. We commit ourselves to scientific rigor, unassailable ethics, and access to medical innovations for all. We do this today to build a better tomorrow.

We are proud of who we are, what we do, and how we do it. We are many, working as one across functions, across companies, and across the world.

We are Roche.

Our Values

The three Roche values—Integrity, Courage, and Passion—are core to how we want to behave, as individuals and collectively as an organization.

- **Passion** means we use our drive and commitment to energize, engage and inspire others.
- **Courage** means we are entrepreneurial and thus take risks, reach beyond boundaries and experiment.
- **Integrity** means we are consistently open, honest, ethical and genuine.

These values define fundamental attributes for guiding decisions and actions leading to increased innovation and business performance.

A Member of the Roche Group

Genentech became a member of the Roche Group in March of 2009. As part of their merger agreement, Roche and Genentech combined their pharmaceutical operations in the United States. Genentech's South San Francisco campus now serves as the headquarters for Roche pharmaceutical operations in the United States. Genentech Research and Early Development operates as an independent center within Roche.

EXHIBIT 102

Thursday, Mar 26, 2009

Roche Completes Acquisition of Genentech

Basel, Switzerland and South San Francisco, California -- March 26, 2009 --

Roche (SWX: ROG.VX; RO.S, OTCQX: RHHBY) and Genentech (NYSE: DNA) announced today that Roche has completed its acquisition of Genentech pursuant to a short-form merger in which Genentech became a wholly-owned member of the Roche Group. Roche had announced earlier in the day the successful completion of its tender offer, which expired on Wednesday, March 25. In connection with the merger, all remaining public shareholders will, subject to appraisal rights, receive $95.00 per share for their shares.

Genentech's common stock will no longer be traded on the New York Stock Exchange after Thursday, March 26.

About Roche

Headquartered in Basel, Switzerland, Roche is one of the world's leading research-focused healthcare groups in the fields of pharmaceuticals and diagnostics. As the world's biggest biotech company and an innovator of products and services for the early detection, prevention, diagnosis and treatment of diseases, the Group contributes on a broad range of fronts to improving people's health and quality of life. Roche is the world leader in in-vitro diagnostics and drugs for cancer and transplantation, and is a market leader in virology. It is also active in other major therapeutic areas such as autoimmune diseases, inflammatory and metabolic disorders and diseases of the central nervous system. In 2008 sales by the Pharmaceuticals Division totaled 36.0 billion Swiss francs, and the Diagnostics Division posted sales of 9.7 billion francs. Roche has R&D agreements and strategic alliances with numerous partners, including majority ownership interest in Chugai, and invested nearly 9 billion Swiss francs in R&D in 2008. Worldwide, the Group employs about 80,000 people. Additional information is available on the Internet at www.roche.com.

About Genentech

Founded more than 30 years ago, Genentech is a leading biotechnology company that discovers, develops, manufactures and commercializes medicines to treat patients with significant unmet

medical needs. The company has headquarters in South San Francisco, California and is listed on the New York Stock Exchange under the symbol DNA.. For additional information about the company, please visit www.gene.com.

EXHIBIT 103

Annual Report 2018

PATIENTS
In cancer, modern care helps where no effective treatments were available previously. Innovative therapies allow this woman on the cover picture to carry on with her life. See back cover for more.

INNOVATION
Advanced analytics enable us to create a wealth of new data insights and opportunities across the entire product lifecycle and R&D value chain to ultimately improve outcomes for patients.

PARTNERS
Roche is expanding its collaborations, combining its own strengths with the unique tools of its partners to elevate personalised healthcare to a new level for many more patients.

Highlights on medicines launched since 2012

Perjeta. For HER2-positive breast cancer. Sales (CHF 2.8 billion, +27%) grew in all regions. As of December 2018, Perjeta was registered in 73 countries for adjuvant treatment. This indication strongly supports its continued growth, which is also driven by increased demand in the adjuvant eBC (US) and the neoadjuvant metastatic settings in Europe.

Ocrevus (CHF 2.4 billion, +172%). For the treatment of relapsing (RMS) and primary progressive (PPMS) forms of MS. Growth was driven by new patients and patients requesting follow-up therapy alike.

Esbriet (CHF 1.0 billion, +19%). For idiopathic pulmonary fibrosis (IPF). Sales continued to expand, driven by growth in the US (+19%).

Tecentriq (CHF 772 million, +59%). For advanced bladder cancer, advanced lung cancer and initial therapy of non-squamous NSCLC. Growth was driven by post-launch uptake in Europe and launch in Japan.

Alecensa (CHF 637 million, +76%). For ALK-positive NSCLC. Alecensa showed continued strong sales growth across all regions.

Gazyva/Gazyvaro (CHF 390 million, +40%). For chronic lymphocytic leukaemia (CLL), rituximab-refractory follicular lymphoma and previously untreated advanced follicular lymphoma. Sales expanded, especially in Europe and in the US.

Hemlibra (CHF 224 million). Hemlibra is approved for people with haemophilia A with inhibitors to factor VIII in more than 50 countries, including the US, the EU, Australia and Japan. Hemlibra is also approved for people with haemophilia A without factor VIII inhibitors in the US and other countries.

Key growth-drivers in 2018 (CHF millions)

6,982 +1%
Herceptin
Oncology

6,849 +3%
Avastin
Oncology

2,773 +27%
Perjeta
Oncology

2,353 +172%
Ocrevus
Neuroscience

2,160 +12%
Actemra/RoActemra
Immunology

1,912 +11%
Xolair
Immunology

1,031 +19%
Esbriet
Immunology

979 +8%
Kadcyla
Oncology

772 +59%
Tecentriq
Oncology

637 +76%
Alecensa
Oncology

* All growth rates in this report are at constant exchange rates (CER; average 2017).

Rejuvenating our portfolio

New options for patients

Our new medicines, including Ocrevus, Perjeta, Tecentriq, Alecensa and Hemlibra, saw continued and very strong uptake in multiple markets.

With sales of CHF 2.4 billion in its first full year on key markets, **Ocrevus** has been the most successful new product launch in Roche's history. In addition to it having been met with extremely positive responses in new markets during 2018, the vast majority of patients with both forms also returned for follow-up treatment with this twice-a-year medication. Strong demand in both indications has continued. Five-year data showed that the efficacy of Ocrevus is maintained on key measures of disease activity, and that people with MS treated earlier with Ocrevus had superior disability progression outcomes compared with RMS patients who switched from interferon beta-1a or PPMS patients who switched from placebo.[1] Longer-term safety data continue to show a favourable risk-benefit profile.

Ocrevus has now been approved in 74 countries, with more than 80,000 people treated globally as of December 2018.

Perjeta, representing a major advance for the treatment of patients with breast cancer, generated total sales of CHF 2.8 billion. Launched in 2012, its usage continues to broaden as study results confirm its medical benefits in additional indications, including results of the phase III Aphinity study for adjuvant treatment of HER2-positive early breast cancer in patients who are at high risk of recurrence.

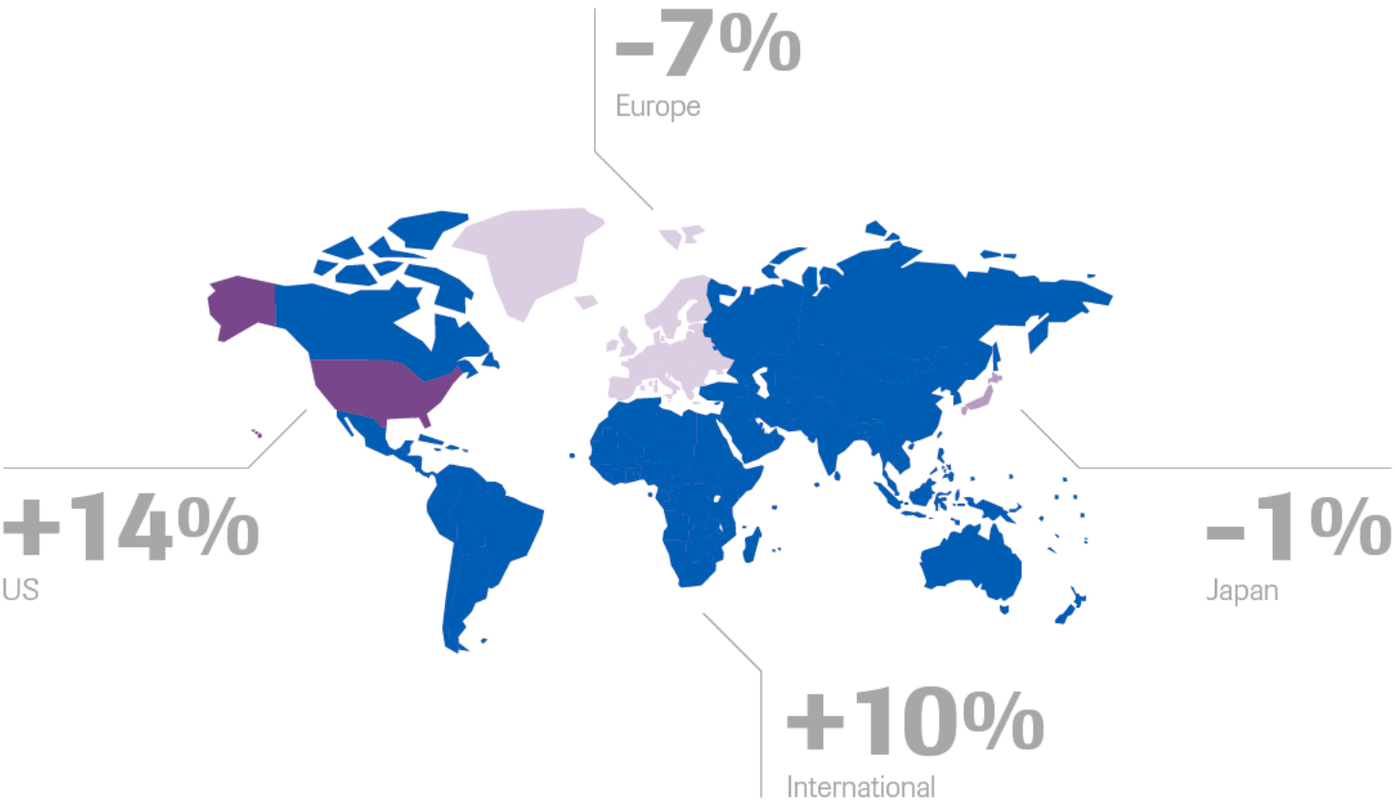
Results from the phase III Alex and J-Alex studies on **Alecensa** added to a wealth of evidence that supported the first-line use of Alecensa in multiple patient populations within ALK-positive NSCLC. This was followed by rapid worldwide regulatory approvals. Recently announced results of the third head-to-head phase III Alesia study of Alecensa versus crizotinib in an Asian patient population with ALK-positive advanced or metastatic NSCLC reinforce the findings of the Alex and J-Alex studies, showing a reduction in the risk of disease worsening or death by 78%. Alecensa lowered the risk of tumour spread or growth in the brain or central nervous system by 86%.[2]

In 2018, Alecensa was approved in China for ALK-positive advanced NSCLC, just eight months after approval in Europe.

In 2018, strong data were announced from **Tecentriq** studies in triple-negative breast cancer (TNBC) and extensive-stage small cell lung cancer.

Positive results were announced from the phase III IMpassion130 study of Tecentriq plus chemotherapy (*nab*-paclitaxel) for the initial (first-line) treatment of unresectable locally advanced or metastatic TNBC—the first positive phase III immunotherapy study in TNBC, an aggressive disease with limited treatment options. The Tecentriq and chemotherapy combination significantly reduced the risk of disease worsening or death (progression-free survival; PFS) compared with chemotherapy alone in the intention-to-treat and the PD-L1-positive population, a subgroup determined

1 Phase III open-label extension studies of Opera I, Opera II and Oratorio | 2 Zhou C et al. Primary results of Alesia, Presented at ESMO Congress 2018; Munich, Germany. Abstract #LBA10



● Eastern Europe, Middle East and Africa, Latin America, Asia-Pacific and Canada form the 'International' region.

by PD-L1 biomarker testing, and showed an encouraging overall survival benefit in the PD-L1-positive population at interim analysis.

Positive results from the phase III IMpower133 study of Tecentriq plus carboplatin and etoposide (chemotherapy) for the initial (first-line) treatment of people with previously untreated extensive-stage small cell lung cancer showed that Tecentriq and chemotherapy helped people live significantly longer compared with chemotherapy alone in the intention-to-treat population. The combination based on Tecentriq also significantly reduced the risk of disease worsening or death compared with chemotherapy alone.

Hemlibra is approved for people with haemophilia A with inhibitors to factor VIII in more than 50 countries. These approvals have transformed medical practice in the treatment of haemophilia. In 2018, Hemlibra also gained US FDA approval for people with haemophilia A without factor VIII inhibitors. Together with previous approvals, this new medicine is now indicated for most haemophilia patients in the US, along with three dosing regimens for subcutaneous treatment: once weekly, every two weeks or every four weeks. Data from the Haven 3 and Haven 4 studies, which supported this approval, are under review by the European Medicines Agency.

Results from the **Kadcyla** phase III Katherine study for patients with HER2-positive early breast cancer (eBC) showed that treatment with Kadcyla as a single agent led to a significant reduction in the risk of disease recurrence or death, compared to Herceptin as an adjuvant (after surgery) treatment in people with HER2-positive eBC who have residual disease present following neoadjuvant (before surgery) treatment.

Approvals and expedited reviews

In December, the FDA approved **Tecentriq** in combination with Avastin, paclitaxel and carboplatin (chemotherapy) for the initial (first-line) treatment of people with metastatic non-squamous non-small cell lung cancer (NSCLC) with no EGFR or ALK genomic tumour aberrations.

In October 2018, the FDA approved **Xofluza** for the treatment of influenza infection. Xofluza is a first-in-class, single-dose oral medicine with a novel proposed mechanism of action. It is approved for the treatment of acute, uncomplicated influenza in people aged 12 years and older. It has demonstrated efficacy against a wide range of influenza viruses, including oseltamivir-resistant strains and avian strains (H7N9, H5N1) in non-clinical studies.

The FDA also granted approval for **MabThera/ Rituxan** for the treatment of adults with moderate to severe pemphigus vulgaris, a rare, serious, life-threatening condition characterised by progressive, painful blistering of the skin and mucous membranes. This is the first biologic therapy approved by the FDA for pemphigus vulgaris and the first major advancement in the treatment of the disease in more than 60 years.

Additionally, approvals were granted by the FDA for the subcutaneous formulation of **Actemra/ RoActemra** for a form of juvenile idiopathic arthritis and **Avastin** for a form of ovarian cancer.

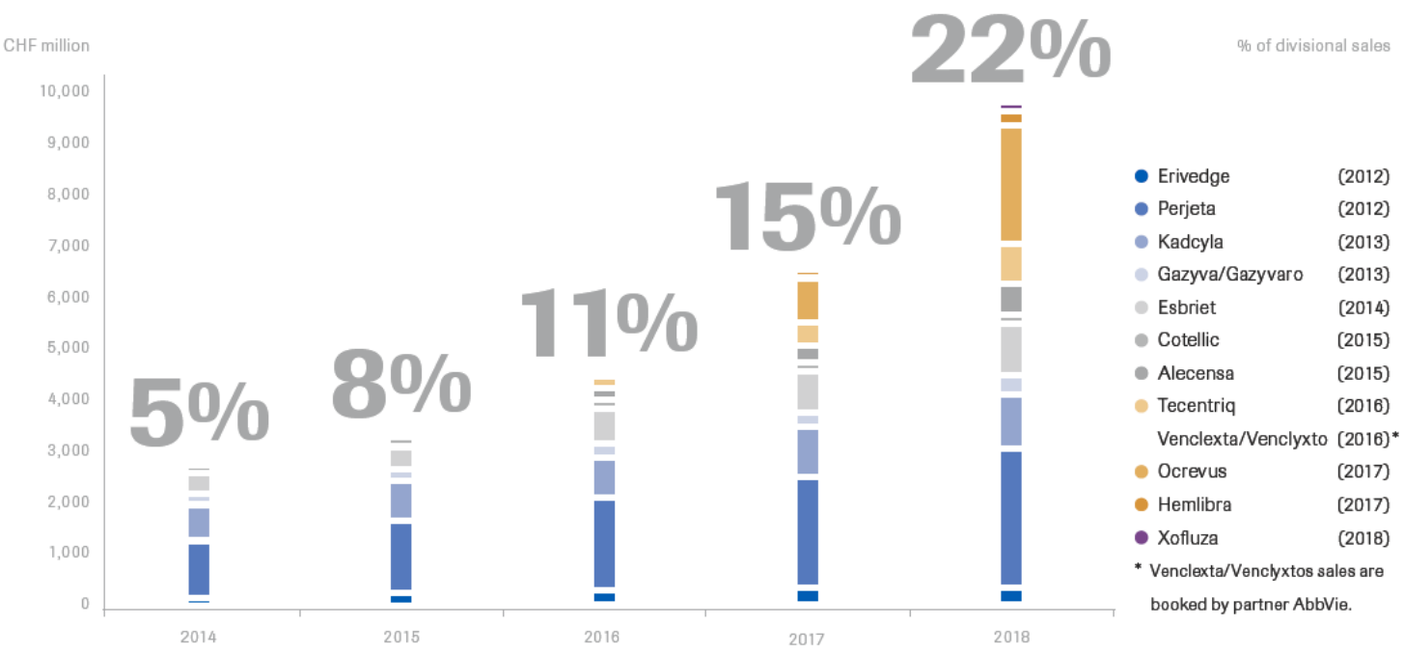
Almost all

of the division's growth is driven by new products.

Expedited review status

The FDA granted priority review status for **Tecentriq** plus chemotherapy (*nab*-paclitaxel) for the initial (first-line) treatment of unresectable, locally advanced or metastatic TNBC in people whose disease expresses the PD-L1 protein, as determined by PD-L1 biomarker testing. In July, the FDA granted breakthrough therapy designation for Tecentriq in combination with Avastin as a first-line treatment for people with advanced or metastatic hepatocellular carcinoma based on an ongoing phase Ib study. IMbrave150, a phase III study, is ongoing.

The European Medicines Agency (EMA) has granted PRIME (PRIority MEdicines) designation for the company's investigational medicine **RG6042** (formerly known as IONIS-HTTRx) for the treatment of people with Huntington's disease and for the investigational oral medicine **risdiplam** (RG7916) for the treatment of people with spinal muscular atrophy.



The percentage of sales contribution of medicines launched since 2012 increased steadily.

Entrectinib has been granted expedited review status by the three major regulators: the US (FDA breakthrough therapy designation), the EU (EMA PRIME designation) and Japan (Japanese Ministry of Health, Labour and Welfare Sakigake and orphan drug designations). Entrectinib is in development for the treatment of NTRK fusion-positive, locally advanced or metastatic solid tumours in adult and paediatric patients whose cancer has progressed following prior therapies or have no acceptable standard therapies.

Advancing personalised healthcare

In April 2018, Roche completed the acquisition of Flatiron Health. This acquisition will help combine the efforts of two companies committed to improving the lives of cancer patients by making optimal use of healthcare data and analytics. The partnership will leverage this combined expertise to advance the use of real-world evidence and set new industry standards for oncology research and development.

In late July 2018, Roche completed the transaction to take 100% ownership of Foundation Medicine, Inc. (FMI), US. This transaction will accelerate comprehensive genomic profiling in oncology by making FMI's high-quality, comprehensive genomic profiling testing and innovative data services more commonly available. Together, the companies will leverage their expertise in genomics and molecular information to enhance the development of personalised medicines and care for patients with cancer.

EXHIBIT 104

Finance Report *2018*

PATIENTS
In cancer, modern care helps where no effective treatments were available previously. Innovative therapies allow this woman on the cover picture to carry on with her life. See back cover for more.

INNOVATION
Advanced analytics enable us to create a wealth of new data insights and opportunities across the entire product lifecycle and R&D value chain to ultimately improve outcomes for patients.

PARTNERS
Roche is expanding its collaborations, combining its own strengths with the unique tools of its partners to elevate personalised healthcare to a new level for many more patients.

Sales in the Pharmaceuticals Division were CHF 44.0 billion (2017: 41.2 billion). New products were the major growth driver, with Ocrevus, Perjeta, Tecentriq, Alecensa and Hemlibra together contributing an additional CHF 2.9 billion (CER) of new sales. Ocrevus in particular continued its strong performance with total sales now reaching CHF 2.4 billion due to continuing growth in the US and launches in most major European markets in 2018. Perjeta sales were CHF 2.8 billion, an increase of 27%, with higher demand in early-stage adjuvant settings in the US. New product sales more than compensated for the initial impacts of biosimilar entry in Europe and Japan, where sales of MabThera/Rituxan and Herceptin fell by CHF 1.3 billion (CER) during 2018. The first biosimilar versions of MabThera/Rituxan were anticipated to come to market in the US in mid- to end-2018. The first biosimilar versions of MabThera/Rituxan, Herceptin and Avastin are now anticipated to come to market in the US in the second half of 2019. Avastin sales were 3% higher mainly due to growth in China. Sales growth in immunology was 8%, with sales of Actemra/RoActemra, Xolair and Esbriet all increasing by over 10%. Lucentis sales grew 18% in the US with increased market share across all indications. Competitive pressure in the US led to a 36% fall in Tarceva sales.

The Diagnostics Division reported sales of CHF 12.9 billion, an increase of 7% at CER. The major growth area was Centralised and Point of Care Solutions, which represented more than half of the division's sales and which grew by 8%, led by the immunodiagnostics business. Molecular Diagnostics sales increased by 5%, with growth from the cobas Liat system, blood screening and virology businesses, while Diabetes Care sales increased by 2%.

IFRS operating profit increased by 13% in the Pharmaceuticals Division and by 115% in the Diagnostics Division, with the results of both divisions impacted by impairments of goodwill and intangible assets in both the current year and the comparative period. The 2018 results include CHF 3.3 billion for the impairment of goodwill and intangible assets, with the largest items being CHF 1.8 billion relating to the InterMune acquisition. Impairments of goodwill and intangible assets in 2017 were CHF 3.5 billion. Amortisation of intangible assets was CHF 1.3 billion and there were CHF 0.9 billion of expenses from global restructuring plans.

The Pharmaceuticals Division's core operating profit increased by 8% at CER, which was above the 7% sales increase. Cost of sales increased by 10%, due to volume-driven growth in manufacturing costs and increased royalty expenses, notably for Ocrevus. Marketing and distribution grew by 4% due to product launches including Ocrevus and Tecentriq. Research and development costs grew by 6%, especially in the oncology, neuroscience and immunology therapeutic areas. Operating profitability benefited from various productivity initiatives. IFRS operating profit grew ahead of the core operating profit due to lower restructuring charges and also due to lower amortisation charges for intangible assets. Operating free cash flow grew with the underlying business partly offset by higher capital expenditure, notably at Chugai.

In the Diagnostics Division core operating profit increased by 9% at CER, which was also above the increase in sales of 7%. Cost of sales grew by 6% due to increased sales volumes partially offset by favourable instrument and reagent mixes. Research and development increased by 7% due to higher spending on high/mid-volume systems in Centralised and Point of Care Solutions and development of digital clinical decision support products. IFRS operating profit grew by more than core operating profit as a result of lower amortisation charges for intangible assets. Operating free cash flow was 11% of sales, but decreased due to the higher net working capital.

The Group's operating free cash flow was CHF 18.7 billion, an increase of 5% at CER, due to the high cash generation of the business, partly offset by higher capital expenditure. The free cash flow was CHF 14.8 billion, an increase of CHF 1.4 billion, due to the higher operating free cash flow and lower income tax payments.

Financing costs were 8% lower on an IFRS basis at CHF 0.8 billion due to the base impact of the losses on debt redemption in the prior year. Income tax expenses were lower, with the Group's effective core tax rate at 19.7% compared to 26.6% in 2017. This was largely due to the impact from the US tax reform which decreased the effective core tax rate by more than 7 percentage points.

Net income increased by 24% at CER on an IFRS basis and by 20% on a core basis, driven in both cases by the operating results and the impact of the US tax reform. Excluding the impact of the US tax reform Core EPS increased by 8%.

The results expressed in Swiss francs were negatively impacted by the appreciation of the Swiss franc against the US dollar and the Brazilian real, partly offset by the depreciation of the Swiss franc against the euro. The net impact on the results expressed in Swiss francs compared to constant exchange rates was negligible on sales and a 1 percentage point impact on core operating profit and on Core EPS.

Income statement

	2018 (CHF m)	2017 (CHF m)	% change (CHF)	% change (CER)
IFRS results				
Sales	56,846	53,299	+7	+7
Royalties and other operating income	2,651	2,447	+8	+9
Revenue	**59,497**	**55,746**	**+7**	**+7**
Cost of sales	(17,269)	(18,179)	–5	–5
Marketing and distribution	(10,109)	(9,847)	+3	+3
Research and development	(12,092)	(11,292)	+7	+7
General and administration	(5,258)	(3,425)	+54	+54
Operating profit	**14,769**	**13,003**	**+14**	**+15**
Financing costs	(770)	(839)	–8	–8
Other financial income (expense)	149	84	+77	+73
Profit before taxes	**14,148**	**12,248**	**+16**	**+17**
Income taxes	(3,283)	(3,423)	–4	–3
Net income	**10,865**	**8,825**	**+23**	**+24**
Attributable to				
– Roche shareholders	10,500	8,633	+22	+23
– Non-controlling interests	365	192	+90	+88
EPS – Basic (CHF)	12.29	10.12	+21	+23
EPS – Diluted (CHF)	12.21	10.04	+22	+23
Core results[1]				
Sales	56,846	53,299	+7	+7
Royalties and other operating income	2,635	2,447	+8	+8
Revenue	**59,481**	**55,746**	**+7**	**+7**
Cost of sales	(15,464)	(14,366)	+8	+8
Marketing and distribution	(9,905)	(9,512)	+4	+4
Research and development	(11,047)	(10,392)	+6	+6
General and administration	(2,560)	(2,464)	+4	+4
Operating profit	**20,505**	**19,012**	**+8**	**+9**
Financing costs	(744)	(819)	–9	–9
Other financial income (expense)	149	75	+99	+94
Profit before taxes	**19,910**	**18,268**	**+9**	**+10**
Income taxes	(3,929)	(4,864)	–19	–18
Net income	**15,981**	**13,404**	**+19**	**+20**
Attributable to				
– Roche shareholders	15,593	13,192	+18	+19
– Non-controlling interests	388	212	+83	+82
Core EPS – Basic (CHF)	18.25	15.47	+18	+19
Core EPS – Diluted (CHF)	18.14	15.34	+18	+19

1) See pages 155–158 for the definition of core results and Core EPS.

Mergers and acquisitions

The Group has implemented the amendments to IFRS 3 'Business Combinations' issued in October 2018. The amendments further clarify the definition of a business. The effect of the amendments is particularly applicable for many of the acquisitions carried out by the Roche Group, since the value in the acquired companies often consists of the rights to a single product or technology. From 2018 such transactions will be accounted for as asset acquisitions rather than as business combinations. As a result the acquisition of Ignyta has been reassessed and accounted for as an asset acquisition in the 2018 Annual Financial Statements rather than as a business combination as disclosed in the 2018 Interim Financial Statements. Further details are given in Note 6 to the Annual Financial Statements.

Business combinations. On 5 April 2018 the Pharmaceuticals Division acquired a 100% controlling interest in Flatiron Health, Inc. ('Flatiron Health') for CHF 1.6 billion. Flatiron Health is a market leader in the curation and development of real-world evidence for cancer research as well as oncology-specific electronic health record software.

Asset acquisitions. On 8 February 2018 the Pharmaceuticals Division acquired a 100% controlling interest in Ignyta, Inc. ('Ignyta') for CHF 1.8 billion. With the acquisition, the Group obtained rights to Ignyta's lead product candidate, entrectinib, an orally bioavailable, CNS-active tyrosine kinase inhibitor for patients who have tumours that harbour ROS1 or NTRK fusions. The Pharmaceuticals Division also completed the acquisitions of Tusk Therapeutics Ltd and Jecure Therapeutics, Inc. for a total cash consideration of CHF 0.2 billion.

Other transactions. On 18 June 2018 the Group entered into a merger agreement with Foundation Medicine, Inc. ('FMI') to acquire the outstanding shares of FMI's common stock not already owned by the Group at a price of USD 137.00 per share in cash. FMI has been a fully consolidated subsidiary of the Group since 2015. On 31 July 2018 the transaction closed and FMI became a 100% owned subsidiary of the Group. The cash consideration for the purchase of all public shares, including shares issuable on FMI's outstanding stock incentive plans and payment of related fees and expenses, amounted to CHF 2.3 billion. These amounts have been recorded to equity as a change in ownership interest in subsidiaries.

Further details are given in Notes 6 and 30 to the Annual Financial Statements.

Global restructuring plans

During 2018 the Group continued with the implementation of various resourcing flexibility plans in its Pharmaceuticals Division to address various future challenges including biosimilar competition. The focus areas of the plans include biologics manufacturing, commercial operations and product development/strategy. The Group also continued with the implementation of several major global restructuring plans initiated in prior years, notably the strategic realignment of the Pharmaceuticals Division's manufacturing network, and programmes to address long-term strategy in the Diagnostics Division.

Global restructuring plans: costs incurred in 2018 in millions of CHF

	Diagnostics[1]	Site consolidation[2]	Other plans[3]	Total
Global restructuring costs				
– Employee-related costs	105	153	202	460
– Site closure costs	49	173	5	227
– Divestment of products and businesses	8	0	0	8
– Other reorganisation expenses	73	1	138	212
Total global restructuring costs	**235**	**327**	**345**	**907**
Additional costs				
– Impairment of goodwill	0	0	0	0
– Impairment of intangible assets	0	0	0	0
– Legal and environmental cases	7	12	0	19
Total costs	**242**	**339**	**345**	**926**

1) Includes strategy plans in the Diagnostics Division.
2) Includes the Pharmaceuticals Division's strategic realignment of its manufacturing network and resourcing flexibility in biologics manufacturing network.
3) Includes plans for outsourcing of IT and other functions to shared service centres and external providers and for resourcing flexibility in the Pharmaceuticals Division's commercial operations and global product development/strategy organisations.

Sales in the Pharmaceuticals Division were CHF 44.0 billion (2017: 41.2 billion). New products were the major growth driver, with Ocrevus, Perjeta, Tecentriq, Alecensa and Hemlibra together contributing an additional CHF 2.9 billion (CER) of new sales. Ocrevus in particular continued its strong performance with total sales now reaching CHF 2.4 billion due to continuing growth in the US and launches in most major European markets in 2018. Perjeta sales were CHF 2.8 billion, an increase of 27%, with higher demand in early-stage adjuvant settings in the US. New product sales more than compensated for the initial impacts of biosimilar entry in Europe and Japan, where sales of MabThera/Rituxan and Herceptin fell by CHF 1.3 billion (CER) during 2018. The first biosimilar versions of MabThera/Rituxan were anticipated to come to market in the US in mid- to end-2018. The first biosimilar versions of MabThera/Rituxan, Herceptin and Avastin are now anticipated to come to market in the US in the second half of 2019. Avastin sales were 3% higher mainly due to growth in China. Sales growth in immunology was 8%, with sales of Actemra/RoActemra, Xolair and Esbriet all increasing by over 10%. Lucentis sales grew 18% in the US with increased market share across all indications. Competitive pressure in the US led to a 36% fall in Tarceva sales.

The Diagnostics Division reported sales of CHF 12.9 billion, an increase of 7% at CER. The major growth area was Centralised and Point of Care Solutions, which represented more than half of the division's sales and which grew by 8%, led by the immunodiagnostics business. Molecular Diagnostics sales increased by 5%, with growth from the cobas Liat system, blood screening and virology businesses, while Diabetes Care sales increased by 2%.

IFRS operating profit increased by 13% in the Pharmaceuticals Division and by 115% in the Diagnostics Division, with the results of both divisions impacted by impairments of goodwill and intangible assets in both the current year and the comparative period. The 2018 results include CHF 3.3 billion for the impairment of goodwill and intangible assets, with the largest items being CHF 1.8 billion relating to the InterMune acquisition. Impairments of goodwill and intangible assets in 2017 were CHF 3.5 billion. Amortisation of intangible assets was CHF 1.3 billion and there were CHF 0.9 billion of expenses from global restructuring plans.

The Pharmaceuticals Division's core operating profit increased by 8% at CER, which was above the 7% sales increase. Cost of sales increased by 10%, due to volume-driven growth in manufacturing costs and increased royalty expenses, notably for Ocrevus. Marketing and distribution grew by 4% due to product launches including Ocrevus and Tecentriq. Research and development costs grew by 6%, especially in the oncology, neuroscience and immunology therapeutic areas. Operating profitability benefited from various productivity initiatives. IFRS operating profit grew ahead of the core operating profit due to lower restructuring charges and also due to lower amortisation charges for intangible assets. Operating free cash flow grew with the underlying business partly offset by higher capital expenditure, notably at Chugai.

In the Diagnostics Division core operating profit increased by 9% at CER, which was also above the increase in sales of 7%. Cost of sales grew by 6% due to increased sales volumes partially offset by favourable instrument and reagent mixes. Research and development increased by 7% due to higher spending on high/mid-volume systems in Centralised and Point of Care Solutions and development of digital clinical decision support products. IFRS operating profit grew by more than core operating profit as a result of lower amortisation charges for intangible assets. Operating free cash flow was 11% of sales, but decreased due to the higher net working capital.

The Group's operating free cash flow was CHF 18.7 billion, an increase of 5% at CER, due to the high cash generation of the business, partly offset by higher capital expenditure. The free cash flow was CHF 14.8 billion, an increase of CHF 1.4 billion, due to the higher operating free cash flow and lower income tax payments.

Financing costs were 8% lower on an IFRS basis at CHF 0.8 billion due to the base impact of the losses on debt redemption in the prior year. Income tax expenses were lower, with the Group's effective core tax rate at 19.7% compared to 26.6% in 2017. This was largely due to the impact from the US tax reform which decreased the effective core tax rate by more than 7 percentage points.

Net income increased by 24% at CER on an IFRS basis and by 20% on a core basis, driven in both cases by the operating results and the impact of the US tax reform. Excluding the impact of the US tax reform Core EPS increased by 8%.

The results expressed in Swiss francs were negatively impacted by the appreciation of the Swiss franc against the US dollar and the Brazilian real, partly offset by the depreciation of the Swiss franc against the euro. The net impact on the results expressed in Swiss francs compared to constant exchange rates was negligible on sales and a 1 percentage point impact on core operating profit and on Core EPS.

Income statement

	2018 (CHF m)	2017 (CHF m)	% change (CHF)	% change (CER)
IFRS results				
Sales	56,846	53,299	+7	+7
Royalties and other operating income	2,651	2,447	+8	+9
Revenue	**59,497**	**55,746**	**+7**	**+7**
Cost of sales	(17,269)	(18,179)	–5	–5
Marketing and distribution	(10,109)	(9,847)	+3	+3
Research and development	(12,092)	(11,292)	+7	+7
General and administration	(5,258)	(3,425)	+54	+54
Operating profit	**14,769**	**13,003**	**+14**	**+15**
Financing costs	(770)	(839)	–8	–8
Other financial income (expense)	149	84	+77	+73
Profit before taxes	**14,148**	**12,248**	**+16**	**+17**
Income taxes	(3,283)	(3,423)	–4	–3
Net income	**10,865**	**8,825**	**+23**	**+24**
Attributable to				
– Roche shareholders	10,500	8,633	+22	+23
– Non-controlling interests	365	192	+90	+88
EPS – Basic (CHF)	12.29	10.12	+21	+23
EPS – Diluted (CHF)	12.21	10.04	+22	+23
Core results[1)]				
Sales	56,846	53,299	+7	+7
Royalties and other operating income	2,635	2,447	+8	+8
Revenue	**59,481**	**55,746**	**+7**	**+7**
Cost of sales	(15,464)	(14,366)	+8	+8
Marketing and distribution	(9,905)	(9,512)	+4	+4
Research and development	(11,047)	(10,392)	+6	+6
General and administration	(2,560)	(2,464)	+4	+4
Operating profit	**20,505**	**19,012**	**+8**	**+9**
Financing costs	(744)	(819)	–9	–9
Other financial income (expense)	149	75	+99	+94
Profit before taxes	**19,910**	**18,268**	**+9**	**+10**
Income taxes	(3,929)	(4,864)	–19	–18
Net income	**15,981**	**13,404**	**+19**	**+20**
Attributable to				
– Roche shareholders	15,593	13,192	+18	+19
– Non-controlling interests	388	212	+83	+82
Core EPS – Basic (CHF)	18.25	15.47	+18	+19
Core EPS – Diluted (CHF)	18.14	15.34	+18	+19

1) See pages 155–158 for the definition of core results and Core EPS.

Mergers and acquisitions

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Sales overview

Pharmaceuticals Division – Sales by therapeutic area

	2018 (CHF m)	2017 (CHF m)	% change (CER)	% of sales (2018)	% of sales (2017)
Oncology	26,183	25,743	+2	59.6	62.5
Immunology	8,160	7,611	+8	18.6	18.5
Neuroscience	3,005	1,542	+96	6.8	3.7
Ophthalmology	1,659	1,414	+18	3.8	3.4
Infectious diseases	1,084	1,357	–20	2.5	3.3
Other therapeutic areas	3,876	3,553	+9	8.7	8.6
Total sales	**43,967**	**41,220**	**+7**	**100**	**100**

Sales in the Pharmaceuticals Division were CHF 44.0 billion, an increase of 7% at CER. New product sales more than compensated for the growing impacts of biosimilar competition for MabThera/Rituxan and Herceptin in Europe.

The sales growth was driven by the continuing rollout of the new products Ocrevus, Perjeta, Tecentriq, Alecensa and Hemlibra, which together contributed an additional CHF 2.9 billion (CER) of new sales. Ocrevus in particular continued its strong performance with total sales now reaching CHF 2.4 billion (2017: 0.9 billion) due to continuing growth in the US and strong initial uptake in other markets, notably in Germany. Perjeta sales were up by 27% to CHF 2.8 billion due to increased demand in early-stage adjuvant settings in the US and continued growth in neoadjuvant and metastatic settings in Europe.

Biosimilar competition had a negative impact, with continuing erosion for MabThera/Rituxan in Europe and the first biosimilar launches of Herceptin in Europe and MabThera/Rituxan and Herceptin in Japan. Sales of these two products fell by CHF 1.3 billion (CER) in Europe and Japan in 2018. The first biosimilar versions of MabThera/Rituxan had been expected to come to market in the US in mid- to end-2018. The first biosimilar versions of MabThera/Rituxan, Herceptin and Avastin are now anticipated to come to market in the US in the second half of 2019. In total, MabThera/Rituxan, Herceptin and Avastin sales in 2018 were CHF 20.6 billion, a decrease of 2%.

Oncology remains the Division's largest therapeutic area with total growth of 2% with the new products Perjeta, Tecentriq and Alecensa being major contributors. Avastin sales increased by 3%, mainly due to growth in China. Herceptin sales were 1% higher, with growth in the US offsetting the initial impact from the biosimilar competition in Europe. MabThera/Rituxan sales fell following biosimilar launches in Europe. In Japan, the recent biosimilar launches had a limited impact on MabThera/Rituxan and Herceptin sales, with the main factor of the sales decline being government price cuts. Tecentriq (increase of 59%) and Alecensa (increase of 76%) both reported continuing post-launch uptake. Sales of Tarceva fell by 36% due to competitive pressure in the US.

Sales in immunology grew, with Actemra/RoActemra, Xolair and Esbriet all increasing by over 10%. Lucentis sales grew 18% in the US driven by increased market share across all indications. Infectious diseases sales were 20% lower due mainly to the patent expiry of Tamiflu in the US and other major markets in 2016. The new influenza medicine Xofluza was launched in the US in late 2018 and initial sales were CHF 13 million. In other therapeutic areas, sales of Activase/TNKase were 6% higher in the US. The launch and rollout of Hemlibra, a medicine for haemophilia A, continued and sales in 2018 were CHF 224 million, mostly in the US, major EU markets and Japan.

Product sales

Pharmaceuticals Division – Sales

	2018 (CHF m)	2017 (CHF m)	% change (CER)	% of sales (2018)	% of sales (2017)
Oncology					
Herceptin	6,982	7,014	+1	15.9	17.0
Avastin	6,849	6,688	+3	15.6	16.2
MabThera/Rituxan [1]	5,191	5,832	–10	11.8	14.1
Perjeta	2,773	2,196	+27	6.3	5.3
Kadcyla	979	914	+8	2.2	2.2
Tecentriq	772	487	+59	1.8	1.2
Alecensa	637	362	+76	1.4	0.9
Tarceva	538	843	–36	1.2	2.0
Xeloda	427	453	–6	1.0	1.1
Gazyva/Gazyvaro	390	278	+40	0.9	0.7
Others	645	676	–2	1.5	1.8
Total Oncology	**26,183**	**25,743**	**+2**	**59.6**	**62.5**
Immunology					
Actemra/RoActemra	2,160	1,926	+12	4.9	4.7
Xolair	1,912	1,742	+11	4.3	4.2
MabThera/Rituxan [1]	1,561	1,556	+1	3.6	3.8
Esbriet	1,031	869	+19	2.3	2.1
Pulmozyme	739	730	+2	1.7	1.8
CellCept	669	697	–4	1.5	1.7
Others	88	91	–13	0.3	0.2
Total Immunology	**8,160**	**7,611**	**+8**	**18.6**	**18.5**
Neuroscience					
Ocrevus	2,353	869	+172	5.3	2.1
Madopar	341	334	+3	0.8	0.8
Others	311	339	–7	0.7	0.8
Total Neuroscience	**3,005**	**1,542**	**+96**	**6.8**	**3.7**
Ophthalmology					
Lucentis	1,659	1,414	+18	3.8	3.4
Total Ophthalmology	**1,659**	**1,414**	**+18**	**3.8**	**3.4**
Infectious diseases					
Tamiflu	378	535	–29	0.9	1.3
Rocephin	305	299	+1	0.7	0.7
Others	401	523	–23	0.9	1.3
Total Infectious diseases	**1,084**	**1,357**	**–20**	**2.5**	**3.3**
Other therapeutic areas					
Activase/TNKase	1,284	1,219	+6	2.9	3.0
Mircera	532	505	+5	1.2	1.2
NeoRecormon/Epogin	288	312	–9	0.7	0.8
Others	1,772	1,517	+17	3.9	3.6
Total other therapeutic areas	**3,876**	**3,553**	**+9**	**8.7**	**8.6**
Total sales	**43,967**	**41,220**	**+7**	**100**	**100**

1) Total MabThera/Rituxan sales of CHF 6,752 million (2017: CHF 7,388 million) split between oncology and immunology therapeutic areas.

MabThera/Rituxan. For non-Hodgkin lymphoma (NHL), chronic lymphocytic leukaemia (CLL), follicular lymphoma (FL) and rheumatoid arthritis (RA) as well as certain types of antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis.

MabThera/Rituxan regional sales

	2018 (CHF m)	2017 (CHF m)	% change (CER)	% of sales (2018)	% of sales (2017)
United States	4,290	4,133	+4	63.5	55.9
Europe	916	1,690	–47	13.6	22.9
Japan	188	293	–36	2.8	4.0
International	1,358	1,272	+11	20.1	17.2
Total sales	**6,752**	**7,388**	**–8**	**100**	**100**

Sales were 8% lower, driven by Europe where sales fell by 47% due to the launch of biosimilars in most EU markets. In the US, where MabThera/Rituxan is widely used across nearly all approved indications, sales increased by 4%. There was growth in both the immunology and oncology segments, also driven by the subcutaneous formulation. The first biosimilar launches had been expected in the US in mid- to end-2018, but now could come to market in the second half of 2019. Sales were also higher in the International region, particularly in China (+40%) due to broader market penetration. In Japan sales were adversely affected by government price cuts and, to a limited extent, by the first biosimilar versions which were launched in 2018.

HER2 franchise (Herceptin, Perjeta and Kadcyla). For HER2-positive breast cancer and HER2-positive metastatic (advanced) gastric cancer (Herceptin only).

Herceptin regional sales

	2018 (CHF m)	2017 (CHF m)	% change (CER)	% of sales (2018)	% of sales (2017)
United States	2,908	2,697	+9	41.6	38.5
Europe	1,849	2,123	–16	26.5	30.3
Japan	249	295	–16	3.6	4.2
International	1,976	1,899	+10	28.3	27.0
Total sales	**6,982**	**7,014**	**+1**	**100**	**100**

Perjeta regional sales

	2018 (CHF m)	2017 (CHF m)	% change (CER)	% of sales (2018)	% of sales (2017)
United States	1,325	1,013	+32	47.8	46.1
Europe	915	767	+15	33.0	34.9
Japan	143	120	+18	5.2	5.5
International	390	296	+45	14.0	13.5
Total sales	**2,773**	**2,196**	**+27**	**100**	**100**

Kadcyla regional sales

	2018 (CHF m)	2017 (CHF m)	% change (CER)	% of sales (2018)	% of sales (2017)
United States	359	343	+5	36.7	37.5
Europe	376	347	+5	38.4	38.0
Japan	75	70	+6	7.7	7.7
International	169	154	+22	17.2	16.8
Total sales	**979**	**914**	**+8**	**100**	**100**

Sales in the HER2 franchise grew by 7% to CHF 10.7 billion of sales. Herceptin sales were 1% higher overall, driven by growth in the US and in the International region largely offset by falls in Europe and Japan. Factors in the US growth of 9% include the rollout of the new formulation launched in 2017 and longer duration of treatment in combination with Perjeta. In the International region, growth of 10% was driven by China due to broader market penetration. Herceptin sales in Europe were 16% lower due to the first biosimilar launches from mid-2018. Biosimilar launches also had an impact on Herceptin sales in Japan. Sales of Perjeta grew by 27% with increased demand in all regions, notably in the early breast cancer adjuvant setting in the US, Europe, Japan and Brazil. Kadcyla sales increased in particular in the International region (+22%).

Avastin. For advanced colorectal, breast, lung, kidney, cervical and ovarian cancer, and relapsed glioblastoma (a type of brain tumour).

Avastin regional sales

	2018 (CHF m)	2017 (CHF m)	% change (CER)	% of sales (2018)	% of sales (2017)
United States	2,904	2,894	+1	42.4	43.3
Europe	1,820	1,776	–1	26.6	26.6
Japan	847	817	+3	12.4	12.2
International	1,278	1,201	+12	18.6	17.9
Total sales	**6,849**	**6,688**	**+3**	**100**	**100**

Overall sales increased by 3% compared to prior year. In the International region, sales grew by 12%, in particular with broader market penetration in China. US sales increased by 1% due to growth in front-line ovarian cancer (following FDA approval in June 2018) and colorectal cancer. In Japan sales increased by 3% due to steady growth for ovarian cancer. In Europe sales declined by 1%, with France being the largest factor.

Actemra/RoActemra. For rheumatoid arthritis (RA), systemic juvenile idiopathic arthritis, polyarticular juvenile idiopathic arthritis and giant cell arteritis.

Actemra/RoActemra regional sales

	2018 (CHF m)	2017 (CHF m)	% change (CER)	% of sales (2018)	% of sales (2017)
United States	857	756	+14	39.7	39.3
Europe	701	631	+7	32.5	32.8
Japan	354	304	+15	16.4	15.8
International	248	235	+15	11.4	12.1
Total sales	**2,160**	**1,926**	**+12**	**100**	**100**

Sales increased by 12%, with growth in all regions, driven by continued uptake of the subcutaneous formulation, notably in the recently approved giant cell arteritis indication. The US and Japan were the major contributors to the sales increase, along with major EU markets, Brazil and Australia.

Xolair. For moderate to severe persistent allergic asthma (AA) and chronic idiopathic urticaria (CIU).

Xolair regional sales

	2018 (CHF m)	2017 (CHF m)	% change (CER)	% of sales (2018)	% of sales (2017)
United States	1,912	1,742	+11	100	100
Total sales	**1,912**	**1,742**	**+11**	**100**	**100**

Sales grew by 11%, driven by demand growth in chronic idiopathic urticaria and expansion of the overall asthma market. Xolair remains the market leader in the larger allergic asthma indication.

Ocrevus. For relapsing forms of multiple sclerosis (RMS) and primary progressive multiple sclerosis (PPMS).

Ocrevus regional sales

	2018 (CHF m)	2017 (CHF m)	% change (CER)	% of sales (2018)	% of sales (2017)
United States	2,080	860	+144	88.4	99.0
Europe	206	4	Over +500	8.8	0.5
International	67	5	Over +500	2.8	0.5
Total sales	**2,353**	**869**	**+172**	**100**	**100**

There was continuously growing demand in both indications in the US in 2018, with growth driven both by new patients and by returning patients. Ocrevus was launched in the US in April 2017 so the comparative period includes only 9 months of sales during the initial launch phase. Elsewhere Ocrevus is showing strong initial uptake where launched, notably in Germany.

Lucentis. For wet age-related macular degeneration (wet AMD), macular oedema following retinal vein occlusion (RVO), diabetic macular oedema (DME) and diabetic retinopathy (DR).

Lucentis regional sales

	2018 (CHF m)	2017 (CHF m)	% change (CER)	% of sales (2018)	% of sales (2017)
United States	1,659	1,414	+18	100	100
Total sales	**1,659**	**1,414**	**+18**	**100**	**100**

US sales grew 18% driven by increased market share across all indications and the ongoing rollout of prefilled syringes.

Activase/TNKase. For acute ischaemic stroke (AIS) and acute myocardial infarction (AMI).

Activase/TNKase regional sales

	2018 (CHF m)	2017 (CHF m)	% change (CER)	% of sales (2018)	% of sales (2017)
United States	1,231	1,168	+6	96.0	95.8
International	53	51	+5	4.0	4.2
Total sales	**1,284**	**1,219**	**+6**	**100**	**100**

Sales were 6% higher, led by the US, and mainly driven by broader use in hospitals and a higher number of patients being treated.

Esbriet. For idiopathic pulmonary fibrosis (IPF).

Esbriet regional sales

	2018 (CHF m)	2017 (CHF m)	% change (CER)	% of sales (2018)	% of sales (2017)
United States	754	640	+19	73.1	73.6
Europe	230	190	+17	22.3	21.9
International	47	39	+29	4.6	4.5
Total sales	**1,031**	**869**	**+19**	**100**	**100**

Sales grew by 19%, with growth in both the US and Europe, in part driven by the launch of a new tablet formulation.

Tecentriq. For advanced bladder cancer, advanced lung cancer and initial therapy of non-squamous non-small cell lung cancer (NSCLC). Sales grew by 59% to CHF 772 million due to the post-launch uptake in Europe, notably in Germany, and also due to the launch in Japan in 2018.

Alecensa. For ALK-positive non-small cell lung cancer. The global uptake continued with a 76% increase in sales to CHF 637 million, with growth across all regions, notably in the US which reported a 65% sales growth.

Pharmaceuticals Division – Sales by region

	2018 (CHF m)	2017 (CHF m)	% change (CER)	% of sales (2018)	% of sales (2017)
United States	23,233	20,496	+14	52.8	49.7
Europe	8,693	9,051	–7	19.8	22.0
Japan	3,701	3,713	–1	8.4	9.0
International	8,340	7,960	+10	19.0	19.3
– EEMEA[1)]	*1,416*	*1,524*	*–1*	*3.2*	*3.7*
– Latin America	*2,004*	*2,121*	*+9*	*4.6*	*5.1*
– Asia-Pacific	*3,931*	*3,397*	*+15*	*8.9*	*8.2*
– Other regions	*989*	*918*	*+9*	*2.3*	*2.3*
Total sales	**43,967**	**41,220**	**+7**	**100**	**100**

1) Eastern Europe, Middle East and Africa.

United States. Sales grew by 14% led by the continued uptake of Ocrevus, which was launched in April 2017. The HER2 franchise grew 14%, with sales increase of Perjeta in particular in the early breast cancer adjuvant setting as well as sales growth for Herceptin. Lucentis sales increased by 18% due to the ongoing rollout of prefilled syringes, with increased market share in all approved indications. Hemlibra and Alecensa sales showed a strong initial uptake. Sales of Tarceva fell 49% due to competitive pressure. Mandatory discounts to hospitals under the 340B Drug Discount Program increased due to higher sales, notably for Ocrevus and oncology products.

Europe. Sales declined 7% due to increasing biosimilar penetration of MabThera/Rituxan in most EU markets, notably in Germany, France and the UK. Herceptin sales declined by 16% due to biosimilar launches in major EU markets from mid-2018. This negative impact on sales was partly offset by the launches of Ocrevus, Tecentriq, Perjeta as well as Alecensa and Gazyva/Gazyvaro, in particular in Germany. Actemra/RoActemra sales increased due to continued uptake of the subcutaneous formulation.

Japan. Sales decreased by 1% due to the 2018 government price cuts which had an annualised negative effect on sales of approximately 5.9%. In particular, MabThera/Rituxan (–36%) and Herceptin (–16%) sales were both negatively affected. Tamiflu (–37%) sales decreased due to lower government stockpiles. This was partially offset by higher sales of Tecentriq, which was launched in 2018, Actemra/RoActemra (+15%) and Alecensa (+27%).

International. Sales increased by 10% driven by the Asia-Pacific and Latin America subregions. Sales in China grew due to broader market penetration for Avastin, MabThera/Rituxan and Herceptin. Sales in Brazil increased mainly due to higher sales of Perjeta, MabThera/Rituxan and Actemra/RoActemra. In Turkey the main drivers of growth were Avastin and MabThera/Rituxan, while in Russia sales growth was driven by higher sales across the HER2 franchise.

Pharmaceuticals Division – Sales for E7 leading emerging markets

	2018 (CHF m)	2017 (CHF m)	% change (CER)	% of sales (2018)	% of sales (2017)
Brazil	909	958	+9	2.1	2.3
China	2,307	1,799	+27	5.2	4.3
India	62	63	+4	0.1	0.2
Mexico	260	280	–5	0.6	0.7
Russia	127	98	+37	0.3	0.2
South Korea	340	319	+4	0.8	0.8
Turkey	257	286	+19	0.6	0.7
Total sales	**4,262**	**3,803**	**+18**	**9.7**	**9.2**

Competition from generic medicines and biosimilars

The Group's pharmaceutical products are generally protected by patent rights which are intended to provide the Group with exclusive marketing rights in various countries. However, patent rights are of varying scope and duration, and the Group may be required to enter into costly litigation to enforce its patent and other intellectual property rights. Loss of market exclusivity for one or more major products – either due to patent expiration, challenges from generic medicines, biosimilars and non-comparable biologics or other reasons – could have a material adverse effect on the Group's business, results of operations or financial condition. The introduction of a generic, biosimilar or non-comparable biologic version of the same or a similar medicine typically results in a significant reduction in net sales for the relevant product, as other manufacturers typically offer their versions at lower prices.

Patents and their expiry are, and always have been, an integral part of the Group's business model and future growth will remain driven by innovation. The latest information from clinical studies is included in the Annual Report on pages 40 to 55 and details of the Group's Product Development Portfolio are available for download at:
http://www.roche.com/research_and_development/who_we_are_how_we_work/pipeline.htm

2018 product sales affected by recent patent expiry

	2018 (CHF m)	2017 (CHF m)	% change (CER)	Comment
Tamiflu	378	535	–29	Patent expiry in US and other major markets in 2016

The intellectual property for biologics can involve multiple patents and patent timelines for each individual product and therefore it is more difficult to give an exact date for patent expiry for biologic medicines. The Group currently estimates that some basic, primary patents for its major biologic medicines will begin to expire as follows:

- MabThera/Rituxan: from around mid-2018 in the US.
- Herceptin: from mid-2019 in the US.
- Avastin: from mid-2019 in the US and from around 2020 in the EU.
- Subcutaneous formulations of MabThera/Rituxan and Herceptin: beyond 2025 (secondary patent rights).

Product sales

Pharmaceuticals Division – Sales

	2018 (CHF m)	2017 (CHF m)	% change (CER)	% of sales (2018)	% of sales (2017)
Oncology					
Herceptin	6,982	7,014	+1	15.9	17.0
Avastin	6,849	6,688	+3	15.6	16.2
MabThera/Rituxan [1]	5,191	5,832	–10	11.8	14.1
Perjeta	2,773	2,196	+27	6.3	5.3
Kadcyla	979	914	+8	2.2	2.2
Tecentriq	772	487	+59	1.8	1.2
Alecensa	637	362	+76	1.4	0.9
Tarceva	538	843	–36	1.2	2.0
Xeloda	427	453	–6	1.0	1.1
Gazyva/Gazyvaro	390	278	+40	0.9	0.7
Others	645	676	–2	1.5	1.8
Total Oncology	**26,183**	**25,743**	**+2**	**59.6**	**62.5**
Immunology					
Actemra/RoActemra	2,160	1,926	+12	4.9	4.7
Xolair	1,912	1,742	+11	4.3	4.2
MabThera/Rituxan [1]	1,561	1,556	+1	3.6	3.8
Esbriet	1,031	869	+19	2.3	2.1
Pulmozyme	739	730	+2	1.7	1.8
CellCept	669	697	–4	1.5	1.7
Others	88	91	–13	0.3	0.2
Total Immunology	**8,160**	**7,611**	**+8**	**18.6**	**18.5**
Neuroscience					
Ocrevus	2,353	869	+172	5.3	2.1
Madopar	341	334	+3	0.8	0.8
Others	311	339	–7	0.7	0.8
Total Neuroscience	**3,005**	**1,542**	**+96**	**6.8**	**3.7**
Ophthalmology					
Lucentis	1,659	1,414	+18	3.8	3.4
Total Ophthalmology	**1,659**	**1,414**	**+18**	**3.8**	**3.4**
Infectious diseases					
Tamiflu	378	535	–29	0.9	1.3
Rocephin	305	299	+1	0.7	0.7
Others	401	523	–23	0.9	1.3
Total Infectious diseases	**1,084**	**1,357**	**–20**	**2.5**	**3.3**
Other therapeutic areas					
Activase/TNKase	1,284	1,219	+6	2.9	3.0
Mircera	532	505	+5	1.2	1.2
NeoRecormon/Epogin	288	312	–9	0.7	0.8
Others	1,772	1,517	+17	3.9	3.6
Total other therapeutic areas	**3,876**	**3,553**	**+9**	**8.7**	**8.6**
Total sales	**43,967**	**41,220**	**+7**	**100**	**100**

1) Total MabThera/Rituxan sales of CHF 6,752 million (2017: CHF 7,388 million) split between oncology and immunology therapeutic areas.

MabThera/Rituxan. For non-Hodgkin lymphoma (NHL), chronic lymphocytic leukaemia (CLL), follicular lymphoma (FL) and rheumatoid arthritis (RA) as well as certain types of antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis.

MabThera/Rituxan regional sales

	2018 (CHF m)	2017 (CHF m)	% change (CER)	% of sales (2018)	% of sales (2017)
United States	4,290	4,133	+4	63.5	55.9
Europe	916	1,690	–47	13.6	22.9
Japan	188	293	–36	2.8	4.0
International	1,358	1,272	+11	20.1	17.2
Total sales	**6,752**	**7,388**	**–8**	**100**	**100**

Sales were 8% lower, driven by Europe where sales fell by 47% due to the launch of biosimilars in most EU markets. In the US, where MabThera/Rituxan is widely used across nearly all approved indications, sales increased by 4%. There was growth in both the immunology and oncology segments, also driven by the subcutaneous formulation. The first biosimilar launches had been expected in the US in mid- to end-2018, but now could come to market in the second half of 2019. Sales were also higher in the International region, particularly in China (+40%) due to broader market penetration. In Japan sales were adversely affected by government price cuts and, to a limited extent, by the first biosimilar versions which were launched in 2018.

HER2 franchise (Herceptin, Perjeta and Kadcyla). For HER2-positive breast cancer and HER2-positive metastatic (advanced) gastric cancer (Herceptin only).

Herceptin regional sales

	2018 (CHF m)	2017 (CHF m)	% change (CER)	% of sales (2018)	% of sales (2017)
United States	2,908	2,697	+9	41.6	38.5
Europe	1,849	2,123	–16	26.5	30.3
Japan	249	295	–16	3.6	4.2
International	1,976	1,899	+10	28.3	27.0
Total sales	**6,982**	**7,014**	**+1**	**100**	**100**

Perjeta regional sales

	2018 (CHF m)	2017 (CHF m)	% change (CER)	% of sales (2018)	% of sales (2017)
United States	1,325	1,013	+32	47.8	46.1
Europe	915	767	+15	33.0	34.9
Japan	143	120	+18	5.2	5.5
International	390	296	+45	14.0	13.5
Total sales	**2,773**	**2,196**	**+27**	**100**	**100**

Kadcyla regional sales

	2018 (CHF m)	2017 (CHF m)	% change (CER)	% of sales (2018)	% of sales (2017)
United States	359	343	+5	36.7	37.5
Europe	376	347	+5	38.4	38.0
Japan	75	70	+6	7.7	7.7
International	169	154	+22	17.2	16.8
Total sales	**979**	**914**	**+8**	**100**	**100**

Sales in the HER2 franchise grew by 7% to CHF 10.7 billion of sales. Herceptin sales were 1% higher overall, driven by growth in the US and in the International region largely offset by falls in Europe and Japan. Factors in the US growth of 9% include the rollout of the new formulation launched in 2017 and longer duration of treatment in combination with Perjeta. In the International region, growth of 10% was driven by China due to broader market penetration. Herceptin sales in Europe were 16% lower due to the first biosimilar launches from mid-2018. Biosimilar launches also had an impact on Herceptin sales in Japan. Sales of Perjeta grew by 27% with increased demand in all regions, notably in the early breast cancer adjuvant setting in the US, Europe, Japan and Brazil. Kadcyla sales increased in particular in the International region (+22%).

Avastin. For advanced colorectal, breast, lung, kidney, cervical and ovarian cancer, and relapsed glioblastoma (a type of brain tumour).

Avastin regional sales

	2018 (CHF m)	2017 (CHF m)	% change (CER)	% of sales (2018)	% of sales (2017)
United States	2,904	2,894	+1	42.4	43.3
Europe	1,820	1,776	–1	26.6	26.6
Japan	847	817	+3	12.4	12.2
International	1,278	1,201	+12	18.6	17.9
Total sales	**6,849**	**6,688**	**+3**	**100**	**100**

Overall sales increased by 3% compared to prior year. In the International region, sales grew by 12%, in particular with broader market penetration in China. US sales increased by 1% due to growth in front-line ovarian cancer (following FDA approval in June 2018) and colorectal cancer. In Japan sales increased by 3% due to steady growth for ovarian cancer. In Europe sales declined by 1%, with France being the largest factor.

Actemra/RoActemra. For rheumatoid arthritis (RA), systemic juvenile idiopathic arthritis, polyarticular juvenile idiopathic arthritis and giant cell arteritis.

Actemra/RoActemra regional sales

	2018 (CHF m)	2017 (CHF m)	% change (CER)	% of sales (2018)	% of sales (2017)
United States	857	756	+14	39.7	39.3
Europe	701	631	+7	32.5	32.8
Japan	354	304	+15	16.4	15.8
International	248	235	+15	11.4	12.1
Total sales	**2,160**	**1,926**	**+12**	**100**	**100**

Sales increased by 12%, with growth in all regions, driven by continued uptake of the subcutaneous formulation, notably in the recently approved giant cell arteritis indication. The US and Japan were the major contributors to the sales increase, along with major EU markets, Brazil and Australia.

Xolair. For moderate to severe persistent allergic asthma (AA) and chronic idiopathic urticaria (CIU).

Xolair regional sales

	2018 (CHF m)	2017 (CHF m)	% change (CER)	% of sales (2018)	% of sales (2017)
United States	1,912	1,742	+11	100	100
Total sales	**1,912**	**1,742**	**+11**	**100**	**100**

Sales grew by 11%, driven by demand growth in chronic idiopathic urticaria and expansion of the overall asthma market. Xolair remains the market leader in the larger allergic asthma indication.

Ocrevus. For relapsing forms of multiple sclerosis (RMS) and primary progressive multiple sclerosis (PPMS).

Ocrevus regional sales

	2018 (CHF m)	2017 (CHF m)	% change (CER)	% of sales (2018)	% of sales (2017)
United States	2,080	860	+144	88.4	99.0
Europe	206	4	Over +500	8.8	0.5
International	67	5	Over +500	2.8	0.5
Total sales	**2,353**	**869**	**+172**	**100**	**100**

There was continuously growing demand in both indications in the US in 2018, with growth driven both by new patients and by returning patients. Ocrevus was launched in the US in April 2017 so the comparative period includes only 9 months of sales during the initial launch phase. Elsewhere Ocrevus is showing strong initial uptake where launched, notably in Germany.

Lucentis. For wet age-related macular degeneration (wet AMD), macular oedema following retinal vein occlusion (RVO), diabetic macular oedema (DME) and diabetic retinopathy (DR).

Lucentis regional sales

	2018 (CHF m)	2017 (CHF m)	% change (CER)	% of sales (2018)	% of sales (2017)
United States	1,659	1,414	+18	100	100
Total sales	**1,659**	**1,414**	**+18**	**100**	**100**

US sales grew 18% driven by increased market share across all indications and the ongoing rollout of prefilled syringes.

Activase/TNKase. For acute ischaemic stroke (AIS) and acute myocardial infarction (AMI).

Activase/TNKase regional sales

	2018 (CHF m)	2017 (CHF m)	% change (CER)	% of sales (2018)	% of sales (2017)
United States	1,231	1,168	+6	96.0	95.8
International	53	51	+5	4.0	4.2
Total sales	**1,284**	**1,219**	**+6**	**100**	**100**

Sales were 6% higher, led by the US, and mainly driven by broader use in hospitals and a higher number of patients being treated.

Esbriet. For idiopathic pulmonary fibrosis (IPF).

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Total sales	**1,031**	**869**	**+19**	**100**	**100**

Sales grew by 19%, with growth in both the US and Europe, in part driven by the launch of a new tablet formulation.

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Alecensa. For ALK-positive non-small cell lung cancer. The global uptake continued with a 76% increase in sales to CHF 637 million, with growth across all regions, notably in the US which reported a 65% sales growth.

Pharmaceuticals Division – Sales by region

	2018 (CHF m)	2017 (CHF m)	% change (CER)	% of sales (2018)	% of sales (2017)
United States	23,233	20,496	+14	52.8	49.7
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India	62	63	+4	0.1	0.2
Mexico	260	280	–5	0.6	0.7
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1) Total MabThera/Rituxan sales of CHF 6,752 million (2017: CHF 7,388 million) split between oncology and immunology therapeutic areas.

MabThera/Rituxan. For non-Hodgkin lymphoma (NHL), chronic lymphocytic leukaemia (CLL), follicular lymphoma (FL) and rheumatoid arthritis (RA) as well as certain types of antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis.

MabThera/Rituxan regional sales

	2018 (CHF m)	2017 (CHF m)	% change (CER)	% of sales (2018)	% of sales (2017)
United States	4,290	4,133	+4	63.5	55.9
Europe	916	1,690	–47	13.6	22.9
Japan	188	293	–36	2.8	4.0
International	1,358	1,272	+11	20.1	17.2
Total sales	**6,752**	**7,388**	**–8**	**100**	**100**

Sales were 8% lower, driven by Europe where sales fell by 47% due to the launch of biosimilars in most EU markets. In the US, where MabThera/Rituxan is widely used across nearly all approved indications, sales increased by 4%. There was growth in both the immunology and oncology segments, also driven by the subcutaneous formulation. The first biosimilar launches had been expected in the US in mid- to end-2018, but now could come to market in the second half of 2019. Sales were also higher in the International region, particularly in China (+40%) due to broader market penetration. In Japan sales were adversely affected by government price cuts and, to a limited extent, by the first biosimilar versions which were launched in 2018.

HER2 franchise (Herceptin, Perjeta and Kadcyla). For HER2-positive breast cancer and HER2-positive metastatic (advanced) gastric cancer (Herceptin only).

Herceptin regional sales

	2018 (CHF m)	2017 (CHF m)	% change (CER)	% of sales (2018)	% of sales (2017)
United States	2,908	2,697	+9	41.6	38.5
Europe	1,849	2,123	–16	26.5	30.3
Japan	249	295	–16	3.6	4.2
International	1,976	1,899	+10	28.3	27.0
Total sales	**6,982**	**7,014**	**+1**	**100**	**100**

Perjeta regional sales

	2018 (CHF m)	2017 (CHF m)	% change (CER)	% of sales (2018)	% of sales (2017)
United States	1,325	1,013	+32	47.8	46.1
Europe	915	767	+15	33.0	34.9
Japan	143	120	+18	5.2	5.5
International	390	296	+45	14.0	13.5
Total sales	**2,773**	**2,196**	**+27**	**100**	**100**

Kadcyla regional sales

	2018 (CHF m)	2017 (CHF m)	% change (CER)	% of sales (2018)	% of sales (2017)
United States	359	343	+5	36.7	37.5
Europe	376	347	+5	38.4	38.0
Japan	75	70	+6	7.7	7.7
International	169	154	+22	17.2	16.8
Total sales	**979**	**914**	**+8**	**100**	**100**

Sales in the HER2 franchise grew by 7% to CHF 10.7 billion of sales. Herceptin sales were 1% higher overall, driven by growth in the US and in the International region largely offset by falls in Europe and Japan. Factors in the US growth of 9% include the rollout of the new formulation launched in 2017 and longer duration of treatment in combination with Perjeta. In the International region, growth of 10% was driven by China due to broader market penetration. Herceptin sales in Europe were 16% lower due to the first biosimilar launches from mid-2018. Biosimilar launches also had an impact on Herceptin sales in Japan. Sales of Perjeta grew by 27% with increased demand in all regions, notably in the early breast cancer adjuvant setting in the US, Europe, Japan and Brazil. Kadcyla sales increased in particular in the International region (+22%).

Avastin. For advanced colorectal, breast, lung, kidney, cervical and ovarian cancer, and relapsed glioblastoma (a type of brain tumour).

Avastin regional sales

	2018 (CHF m)	2017 (CHF m)	% change (CER)	% of sales (2018)	% of sales (2017)
United States	2,904	2,894	+1	42.4	43.3
Europe	1,820	1,776	–1	26.6	26.6
Japan	847	817	+3	12.4	12.2
International	1,278	1,201	+12	18.6	17.9
Total sales	**6,849**	**6,688**	**+3**	**100**	**100**

Overall sales increased by 3% compared to prior year. In the International region, sales grew by 12%, in particular with broader market penetration in China. US sales increased by 1% due to growth in front-line ovarian cancer (following FDA approval in June 2018) and colorectal cancer. In Japan sales increased by 3% due to steady growth for ovarian cancer. In Europe sales declined by 1%, with France being the largest factor.

Actemra/RoActemra. For rheumatoid arthritis (RA), systemic juvenile idiopathic arthritis, polyarticular juvenile idiopathic arthritis and giant cell arteritis.

Actemra/RoActemra regional sales

	2018 (CHF m)	2017 (CHF m)	% change (CER)	% of sales (2018)	% of sales (2017)
United States	857	756	+14	39.7	39.3
Europe	701	631	+7	32.5	32.8
Japan	354	304	+15	16.4	15.8
International	248	235	+15	11.4	12.1
Total sales	**2,160**	**1,926**	**+12**	**100**	**100**

Sales increased by 12%, with growth in all regions, driven by continued uptake of the subcutaneous formulation, notably in the recently approved giant cell arteritis indication. The US and Japan were the major contributors to the sales increase, along with major EU markets, Brazil and Australia.

Xolair. For moderate to severe persistent allergic asthma (AA) and chronic idiopathic urticaria (CIU).

Xolair regional sales

	2018 (CHF m)	2017 (CHF m)	% change (CER)	% of sales (2018)	% of sales (2017)
United States	1,912	1,742	+11	100	100
Total sales	**1,912**	**1,742**	**+11**	**100**	**100**

Sales grew by 11%, driven by demand growth in chronic idiopathic urticaria and expansion of the overall asthma market. Xolair remains the market leader in the larger allergic asthma indication.

Ocrevus. For relapsing forms of multiple sclerosis (RMS) and primary progressive multiple sclerosis (PPMS).

Ocrevus regional sales

	2018 (CHF m)	2017 (CHF m)	% change (CER)	% of sales (2018)	% of sales (2017)
United States	2,080	860	+144	88.4	99.0
Europe	206	4	Over +500	8.8	0.5
International	67	5	Over +500	2.8	0.5
Total sales	**2,353**	**869**	**+172**	**100**	**100**

There was continuously growing demand in both indications in the US in 2018, with growth driven both by new patients and by returning patients. Ocrevus was launched in the US in April 2017 so the comparative period includes only 9 months of sales during the initial launch phase. Elsewhere Ocrevus is showing strong initial uptake where launched, notably in Germany.

Lucentis. For wet age-related macular degeneration (wet AMD), macular oedema following retinal vein occlusion (RVO), diabetic macular oedema (DME) and diabetic retinopathy (DR).

Lucentis regional sales

	2018 (CHF m)	2017 (CHF m)	% change (CER)	% of sales (2018)	% of sales (2017)
United States	1,659	1,414	+18	100	100
Total sales	**1,659**	**1,414**	**+18**	**100**	**100**

US sales grew 18% driven by increased market share across all indications and the ongoing rollout of prefilled syringes.

Activase/TNKase. For acute ischaemic stroke (AIS) and acute myocardial infarction (AMI).

Activase/TNKase regional sales

	2018 (CHF m)	2017 (CHF m)	% change (CER)	% of sales (2018)	% of sales (2017)
United States	1,231	1,168	+6	96.0	95.8
International	53	51	+5	4.0	4.2
Total sales	**1,284**	**1,219**	**+6**	**100**	**100**

Sales were 6% higher, led by the US, and mainly driven by broader use in hospitals and a higher number of patients being treated.

Esbriet. For idiopathic pulmonary fibrosis (IPF).

Esbriet regional sales

	2018 (CHF m)	2017 (CHF m)	% change (CER)	% of sales (2018)	% of sales (2017)
United States	754	640	+19	73.1	73.6
Europe	230	190	+17	22.3	21.9
International	47	39	+29	4.6	4.5
Total sales	**1,031**	**869**	**+19**	**100**	**100**

Sales grew by 19%, with growth in both the US and Europe, in part driven by the launch of a new tablet formulation.

Tecentriq. For advanced bladder cancer, advanced lung cancer and initial therapy of non-squamous non-small cell lung cancer (NSCLC). Sales grew by 59% to CHF 772 million due to the post-launch uptake in Europe, notably in Germany, and also due to the launch in Japan in 2018.

Alecensa. For ALK-positive non-small cell lung cancer. The global uptake continued with a 76% increase in sales to CHF 637 million, with growth across all regions, notably in the US which reported a 65% sales growth.

Pharmaceuticals Division – Sales by region

	2018 (CHF m)	2017 (CHF m)	% change (CER)	% of sales (2018)	% of sales (2017)
United States	23,233	20,496	+14	52.8	49.7
Europe	8,693	9,051	–7	19.8	22.0
Japan	3,701	3,713	–1	8.4	9.0
International	8,340	7,960	+10	19.0	19.3
– EEMEA[1)]	*1,416*	*1,524*	*–1*	*3.2*	*3.7*
– Latin America	*2,004*	*2,121*	*+9*	*4.6*	*5.1*
– Asia-Pacific	*3,931*	*3,397*	*+15*	*8.9*	*8.2*
– Other regions	*989*	*918*	*+9*	*2.3*	*2.3*
Total sales	**43,967**	**41,220**	**+7**	**100**	**100**

1) Eastern Europe, Middle East and Africa.

United States. Sales grew by 14% led by the continued uptake of Ocrevus, which was launched in April 2017. The HER2 franchise grew 14%, with sales increase of Perjeta in particular in the early breast cancer adjuvant setting as well as sales growth for Herceptin. Lucentis sales increased by 18% due to the ongoing rollout of prefilled syringes, with increased market share in all approved indications. Hemlibra and Alecensa sales showed a strong initial uptake. Sales of Tarceva fell 49% due to competitive pressure. Mandatory discounts to hospitals under the 340B Drug Discount Program increased due to higher sales, notably for Ocrevus and oncology products.

Europe. Sales declined 7% due to increasing biosimilar penetration of MabThera/Rituxan in most EU markets, notably in Germany, France and the UK. Herceptin sales declined by 16% due to biosimilar launches in major EU markets from mid-2018. This negative impact on sales was partly offset by the launches of Ocrevus, Tecentriq, Perjeta as well as Alecensa and Gazyva/Gazyvaro, in particular in Germany. Actemra/RoActemra sales increased due to continued uptake of the subcutaneous formulation.

Japan. Sales decreased by 1% due to the 2018 government price cuts which had an annualised negative effect on sales of approximately 5.9%. In particular, MabThera/Rituxan (–36%) and Herceptin (–16%) sales were both negatively affected. Tamiflu (–37%) sales decreased due to lower government stockpiles. This was partially offset by higher sales of Tecentriq, which was launched in 2018, Actemra/RoActemra (+15%) and Alecensa (+27%).

International. Sales increased by 10% driven by the Asia-Pacific and Latin America subregions. Sales in China grew due to broader market penetration for Avastin, MabThera/Rituxan and Herceptin. Sales in Brazil increased mainly due to higher sales of Perjeta, MabThera/Rituxan and Actemra/RoActemra. In Turkey the main drivers of growth were Avastin and MabThera/Rituxan, while in Russia sales growth was driven by higher sales across the HER2 franchise.

Pharmaceuticals Division – Sales for E7 leading emerging markets

	2018 (CHF m)	2017 (CHF m)	% change (CER)	% of sales (2018)	% of sales (2017)
Brazil	909	958	+9	2.1	2.3
China	2,307	1,799	+27	5.2	4.3
India	62	63	+4	0.1	0.2
Mexico	260	280	–5	0.6	0.7
Russia	127	98	+37	0.3	0.2
South Korea	340	319	+4	0.8	0.8
Turkey	257	286	+19	0.6	0.7
Total sales	**4,262**	**3,803**	**+18**	**9.7**	**9.2**

Competition from generic medicines and biosimilars

The Group's pharmaceutical products are generally protected by patent rights which are intended to provide the Group with exclusive marketing rights in various countries. However, patent rights are of varying scope and duration, and the Group may be required to enter into costly litigation to enforce its patent and other intellectual property rights. Loss of market exclusivity for one or more major products – either due to patent expiration, challenges from generic medicines, biosimilars and non-comparable biologics or other reasons – could have a material adverse effect on the Group's business, results of operations or financial condition. The introduction of a generic, biosimilar or non-comparable biologic version of the same or a similar medicine typically results in a significant reduction in net sales for the relevant product, as other manufacturers typically offer their versions at lower prices.

Patents and their expiry are, and always have been, an integral part of the Group's business model and future growth will remain driven by innovation. The latest information from clinical studies is included in the Annual Report on pages 40 to 55 and details of the Group's Product Development Portfolio are available for download at:
http://www.roche.com/research_and_development/who_we_are_how_we_work/pipeline.htm

2018 product sales affected by recent patent expiry

	2018 (CHF m)	2017 (CHF m)	% change (CER)	Comment
Tamiflu	378	535	–29	Patent expiry in US and other major markets in 2016

The intellectual property for biologics can involve multiple patents and patent timelines for each individual product and therefore it is more difficult to give an exact date for patent expiry for biologic medicines. The Group currently estimates that some basic, primary patents for its major biologic medicines will begin to expire as follows:

- MabThera/Rituxan: from around mid-2018 in the US.
- Herceptin: from mid-2019 in the US.
- Avastin: from mid-2019 in the US and from around 2020 in the EU.
- Subcutaneous formulations of MabThera/Rituxan and Herceptin: beyond 2025 (secondary patent rights).

EXHIBIT 105

Foreign Exchange Rates - H.10

RSS DDP

Effective on February 4, 2019, the Federal Reserve Board staff has made major changes to the methodology used to construct the trade-weighted dollar indexes in the H.10, G.5, and G.5A releases. These changes affect the calculation of index weights and country composition. The new dollar indexes go back to (and are indexed to) January 2006. For more information, see "Revisions to the Federal Reserve Dollar Indexes" and "Technical Q&As".

Release Date: Monday, May 13, 2019

Historical Rates for the Swiss Franc

(Rates in currency units per U.S. dollar except as noted by an asterisk)

Date	Rate
3-Jan-00	1.5808
4-Jan-00	1.5565
5-Jan-00	1.5526
6-Jan-00	1.5540
7-Jan-00	1.5623
10-Jan-00	1.5704
11-Jan-00	1.5605
12-Jan-00	1.5660
13-Jan-00	1.5707
14-Jan-00	1.5945
17-Jan-00	ND
18-Jan-00	1.5942
19-Jan-00	1.5965
20-Jan-00	1.5915
21-Jan-00	1.5973
24-Jan-00	1.6090
25-Jan-00	1.6085
26-Jan-00	1.6102
27-Jan-00	1.6317

The Fed - Foreign Exchange Rates - H.10 - May 12, 2019

Date	Rate
11-Nov-09	ND
12-Nov-09	1.0164
13-Nov-09	1.0141
16-Nov-09	1.0075
17-Nov-09	1.0192
18-Nov-09	1.0080
19-Nov-09	1.0149
20-Nov-09	1.0177
23-Nov-09	1.0097
24-Nov-09	1.0116
25-Nov-09	1.0004
26-Nov-09	ND
27-Nov-09	1.0063
30-Nov-09	1.0050
1-Dec-09	0.9984
2-Dec-09	1.0006
3-Dec-09	0.9995
4-Dec-09	1.0136
7-Dec-09	1.0199
8-Dec-09	1.0245
9-Dec-09	1.0262
10-Dec-09	1.0270
11-Dec-09	1.0356
14-Dec-09	1.0321
15-Dec-09	1.0421
16-Dec-09	1.0355
17-Dec-09	1.0491
18-Dec-09	1.0452
21-Dec-09	1.0441
22-Dec-09	1.0486
23-Dec-09	1.0380
24-Dec-09	1.0369
25-Dec-09	ND
28-Dec-09	1.0341
29-Dec-09	1.0365
30-Dec-09	1.0391
31-Dec-09	1.0358

Date	Rate
30-Dec-10	0.9369
31-Dec-10	ND
3-Jan-11	0.9329
4-Jan-11	0.9478
5-Jan-11	0.9644
6-Jan-11	0.9630
7-Jan-11	0.9650
10-Jan-11	0.9686
11-Jan-11	0.9755
12-Jan-11	0.9717
13-Jan-11	0.9624
14-Jan-11	0.9657
17-Jan-11	ND
18-Jan-11	0.9633
19-Jan-11	0.9585
20-Jan-11	0.9656
21-Jan-11	0.9590
24-Jan-11	0.9488
25-Jan-11	0.9451
26-Jan-11	0.9436
27-Jan-11	0.9464
28-Jan-11	0.9429
31-Jan-11	0.9402
1-Feb-11	0.9388
2-Feb-11	0.9406
3-Feb-11	0.9435
4-Feb-11	0.9557
7-Feb-11	0.9569
8-Feb-11	0.9570
9-Feb-11	0.9611
10-Feb-11	0.9659
11-Feb-11	0.9755
14-Feb-11	0.9708
15-Feb-11	0.9677
16-Feb-11	0.9616
17-Feb-11	0.9508
18-Feb-11	0.9483

Date	Rate
28-Dec-11	0.9430
29-Dec-11	0.9412
30-Dec-11	0.9374
2-Jan-12	ND
3-Jan-12	0.9319
4-Jan-12	0.9417
5-Jan-12	0.9528
6-Jan-12	0.9555
9-Jan-12	0.9520
10-Jan-12	0.9486
11-Jan-12	0.9554
12-Jan-12	0.9444
13-Jan-12	0.9534
16-Jan-12	ND
17-Jan-12	0.9492
18-Jan-12	0.9427
19-Jan-12	0.9335
20-Jan-12	0.9327
23-Jan-12	0.9268
24-Jan-12	0.9290
25-Jan-12	0.9310
26-Jan-12	0.9174
27-Jan-12	0.9142
30-Jan-12	0.9178
31-Jan-12	0.9220
1-Feb-12	0.9141
2-Feb-12	0.9144
3-Feb-12	0.9208
6-Feb-12	0.9188
7-Feb-12	0.9129
8-Feb-12	0.9126
9-Feb-12	0.9103
10-Feb-12	0.9176
13-Feb-12	0.9149
14-Feb-12	0.9185
15-Feb-12	0.9223
16-Feb-12	0.9209

Date	Rate
25-Dec-12	ND
26-Dec-12	0.9128
27-Dec-12	0.9138
28-Dec-12	0.9130
31-Dec-12	0.9155
1-Jan-13	ND
2-Jan-13	0.9166
3-Jan-13	0.9222
4-Jan-13	0.9262
7-Jan-13	0.9227
8-Jan-13	0.9250
9-Jan-13	0.9244
10-Jan-13	0.9162
11-Jan-13	0.9120
14-Jan-13	0.9174
15-Jan-13	0.9275
16-Jan-13	0.9313
17-Jan-13	0.9331
18-Jan-13	0.9346
21-Jan-13	ND
22-Jan-13	0.9278
23-Jan-13	0.9295
24-Jan-13	0.9288
25-Jan-13	0.9252
28-Jan-13	0.9272
29-Jan-13	0.9216
30-Jan-13	0.9124
31-Jan-13	0.9093
1-Feb-13	0.9030
4-Feb-13	0.9087
5-Feb-13	0.9084
6-Feb-13	0.9100
7-Feb-13	0.9176
8-Feb-13	0.9183
11-Feb-13	0.9186
12-Feb-13	0.9172
13-Feb-13	0.9182

Date	Rate
23-Dec-13	0.8942
24-Dec-13	0.8961
25-Dec-13	ND
26-Dec-13	0.8963
27-Dec-13	0.8893
30-Dec-13	0.8866
31-Dec-13	0.8904
1-Jan-14	ND
2-Jan-14	0.8998
3-Jan-14	0.9044
6-Jan-14	0.9036
7-Jan-14	0.9086
8-Jan-14	0.9102
9-Jan-14	0.9085
10-Jan-14	0.9032
13-Jan-14	0.9026
14-Jan-14	0.9009
15-Jan-14	0.9084
16-Jan-14	0.9064
17-Jan-14	0.9100
20-Jan-14	ND
21-Jan-14	0.9092
22-Jan-14	0.9116
23-Jan-14	0.9002
24-Jan-14	0.8949
27-Jan-14	0.8956
28-Jan-14	0.8984
29-Jan-14	0.8948
30-Jan-14	0.9042
31-Jan-14	0.9052
3-Feb-14	0.9014
4-Feb-14	0.9050
5-Feb-14	0.9042
6-Feb-14	0.8992
7-Feb-14	0.8992
10-Feb-14	0.8967
11-Feb-14	0.8969

Date	Rate
19-Dec-14	0.9832
22-Dec-14	0.9820
23-Dec-14	0.9872
24-Dec-14	0.9865
25-Dec-14	ND
26-Dec-14	ND
29-Dec-14	0.9878
30-Dec-14	0.9880
31-Dec-14	0.9934
1-Jan-15	ND
2-Jan-15	1.0004
5-Jan-15	1.0079
6-Jan-15	1.0062
7-Jan-15	1.0160
8-Jan-15	1.0169
9-Jan-15	1.0151
12-Jan-15	1.0150
13-Jan-15	1.0195
14-Jan-15	1.0172
15-Jan-15	0.8930
16-Jan-15	0.8488
19-Jan-15	ND
20-Jan-15	0.8751
21-Jan-15	0.8596
22-Jan-15	0.8678
23-Jan-15	0.8760
26-Jan-15	0.8988
27-Jan-15	0.9042
28-Jan-15	0.9055
29-Jan-15	0.9226
30-Jan-15	0.9210
2-Feb-15	0.9262
3-Feb-15	0.9234
4-Feb-15	0.9238
5-Feb-15	0.9248
6-Feb-15	0.9228
9-Feb-15	0.9258

Date	Rate
17-Dec-15	0.9987
18-Dec-15	0.9940
21-Dec-15	0.9912
22-Dec-15	0.9866
23-Dec-15	0.9938
24-Dec-15	0.9872
25-Dec-15	ND
28-Dec-15	0.9878
29-Dec-15	0.9924
30-Dec-15	0.9890
31-Dec-15	1.0017
1-Jan-16	ND
4-Jan-16	1.0042
5-Jan-16	1.0096
6-Jan-16	1.0084
7-Jan-16	1.0018
8-Jan-16	0.9972
11-Jan-16	1.0000
12-Jan-16	1.0030
13-Jan-16	1.0064
14-Jan-16	1.0072
15-Jan-16	0.9984
18-Jan-16	ND
19-Jan-16	1.0032
20-Jan-16	1.0032
21-Jan-16	1.0112
22-Jan-16	1.0148
25-Jan-16	1.0148
26-Jan-16	1.0189
27-Jan-16	1.0176
28-Jan-16	1.0134
29-Jan-16	1.0226
1-Feb-16	1.0202
2-Feb-16	1.0181
3-Feb-16	1.0070
4-Feb-16	0.9926
5-Feb-16	0.9938

Date	Rate
14-Dec-16	1.0099
15-Dec-16	1.0334
16-Dec-16	1.0258
19-Dec-16	1.0226
20-Dec-16	1.0282
21-Dec-16	1.0262
22-Dec-16	1.0246
23-Dec-16	1.0268
26-Dec-16	ND
27-Dec-16	1.0284
28-Dec-16	1.0313
29-Dec-16	1.0230
30-Dec-16	1.0160
2-Jan-17	ND
3-Jan-17	1.0266
4-Jan-17	1.0228
5-Jan-17	1.0107
6-Jan-17	1.0150
9-Jan-17	1.0148
10-Jan-17	1.0158
11-Jan-17	1.0203
12-Jan-17	1.0066
13-Jan-17	1.0098
16-Jan-17	ND
17-Jan-17	1.0028
18-Jan-17	1.0028
19-Jan-17	1.0094
20-Jan-17	ND
23-Jan-17	0.9990
24-Jan-17	0.9998
25-Jan-17	0.9996
26-Jan-17	1.0011
27-Jan-17	0.9992
30-Jan-17	0.9976
31-Jan-17	0.9888
1-Feb-17	0.9930
2-Feb-17	0.9894

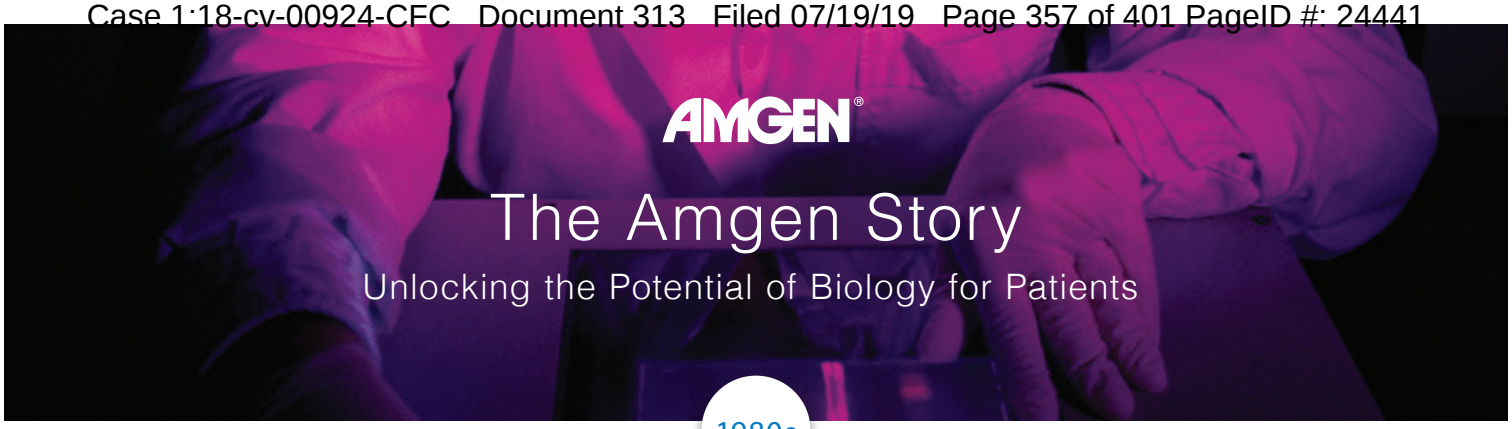
Date	Rate
12-Dec-17	0.9926
13-Dec-17	0.9894
14-Dec-17	0.9900
15-Dec-17	0.9903
18-Dec-17	0.9856
19-Dec-17	0.9857
20-Dec-17	0.9859
21-Dec-17	0.9890
22-Dec-17	0.9898
25-Dec-17	ND
26-Dec-17	0.9891
27-Dec-17	0.9870
28-Dec-17	0.9774
29-Dec-17	0.9738
1-Jan-18	ND
2-Jan-18	0.9718
3-Jan-18	0.9762
4-Jan-18	0.9753
5-Jan-18	0.9752
8-Jan-18	0.9762
9-Jan-18	0.9832
10-Jan-18	0.9780
11-Jan-18	0.9748
12-Jan-18	0.9713
15-Jan-18	ND
16-Jan-18	0.9618
17-Jan-18	0.9616
18-Jan-18	0.9586
19-Jan-18	0.9612
22-Jan-18	0.9636
23-Jan-18	0.9598
24-Jan-18	0.9452
25-Jan-18	0.9357
26-Jan-18	0.9342
29-Jan-18	0.9380
30-Jan-18	0.9355
31-Jan-18	0.9321

Date	Rate
10-Dec-18	0.9896
11-Dec-18	0.9931
12-Dec-18	0.9920
13-Dec-18	0.9938
14-Dec-18	0.9970
17-Dec-18	0.9934
18-Dec-18	0.9930
19-Dec-18	0.9918
20-Dec-18	0.9918
21-Dec-18	0.9914
24-Dec-18	ND
25-Dec-18	ND
26-Dec-18	0.9908
27-Dec-18	0.9902
28-Dec-18	0.9838
31-Dec-18	0.9832
1-Jan-19	ND
2-Jan-19	0.9884
3-Jan-19	0.9889
4-Jan-19	0.9859
7-Jan-19	0.9810
8-Jan-19	0.9810
9-Jan-19	0.9767
10-Jan-19	0.9817
11-Jan-19	0.9829
14-Jan-19	ND
15-Jan-19	0.9885
16-Jan-19	0.9899
17-Jan-19	0.9944
18-Jan-19	0.9954
21-Jan-19	ND
22-Jan-19	0.9972
23-Jan-19	0.9946
24-Jan-19	0.9965
25-Jan-19	0.9930
28-Jan-19	0.9910
29-Jan-19	0.9950

EXHIBIT 106

THIS DOCUMENT HAS BEEN REDACTED IN ITS ENTIRETY

EXHIBIT 107



AMGEN®

The Amgen Story

Unlocking the Potential of Biology for Patients

1980s

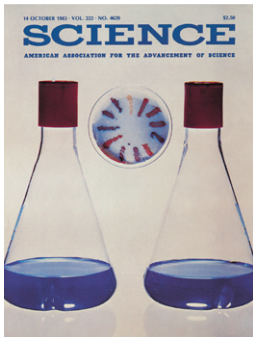
Left: Farmers herd sheep near the Ventura Highway in this 1967 archival image. The Security Bank building would become the future site of Building 29 on Amgen's Thousand Oaks campus. Photo courtesy of Ed Lawrence.

Right: Amgen has had three logos in its history. This is the first logo.

1980

AMGen incorporates.

AMGen (Applied Molecular Genetics Inc.) is established in Thousand Oaks, California, on April 8, 1980, as the brainchild of venture capitalists William K. (Bill) Bowes and associates. With a staff of three, the Company occupies a shared building, now called "Building 1."



Amgen's research in cloning genes led to the Company's production of indigo in E coli *in the early 1980s. The discovery and subsequent patent made the cover of* Science *magazine in 1983.*

1980

Early experiments.

In the first three years, AMGen scientists attempt many things: creating organisms to extract oil from shale, growing chickens faster, making specialty chemicals, cloning luciferase (the light source for fireflies) and creating a process for producing indigo dye in *E coli*—an achievement that garners the prestigious cover of *Science* magazine. The final direction for the Company would be treating and curing disease.

Fu-Kuen Lin examines x-ray film to identify gene coding for erythropoietin. The black areas show bacterial colonies containing the gene.

1983

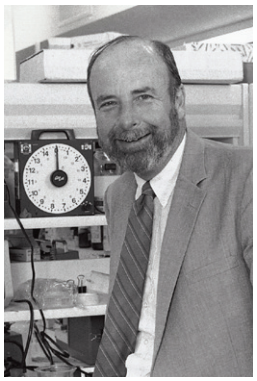
The clone that launched a company.

A team led by a young researcher from Taiwan named Fu-Kuen Lin is tasked with finding and cloning the erythropoietin gene. Their job is staggering: finding a gene on a single fragment of DNA among 1.5 million fragments of the human genome. After working tirelessly for two years, they did it. This groundbreaking achievement enables the creation of one of the most successful drugs in biotech history, EPOGEN® (epoetin alfa).

1980

George B. Rathmann is named first CEO.

AMGen names its first CEO, scientist and businessman George B. Rathmann. Dubbed "Mr. Biotech" by *Red Herring* magazine, Rathmann has been called one of the great geniuses of high-tech entrepreneurialism. Working from a small trailer to free up space for scientists, Rathmann quickly establishes scientific goals and secures funding to conduct grand experiments in technology.



George Rathmann in one of the Building 2 laboratory bays in 1982.

1983

Led by CFO Gordon Binder, Amgen's IPO on June 17, 1983, raises nearly $40 million.

The Company officially changes its name to Amgen.

Amgen Files Initial Offering Of 2 Million Common Shares

THOUSAND OAKS, Calif.—Amgen, a biological-engineering concern, said it filed with the Securities and Exchange Commission for a proposed initial public offering of two million common shares for $16 to $19 each.

The company said it expects to offer the shares in mid-June through underwriters managed by Smith Barney, Harris Upham & Co., Dean Witter Reynolds Inc. and Montgomery Securities.

Proceeds will be used for research, product development, clinical testing and expansion of facilities.

* * *

A May 1983 article of The Wall Street Journal *announces Amgen's IPO.*

1984

Kirin and Amgen form a joint venture, Kirin-Amgen, for the worldwide commercialization of erythropoietin.

KIRIN

Research head Larry Souza led the team in the creation of NEUPOGEN®, Amgen's second blockbuster drug.

1985

A second discovery.

While Lin was working on erythropoietin, researcher Larry Souza and his team are able to clone granulocyte colony-stimulating factor (G-CSF). This discovery would lead to the development of Amgen's second blockbuster drug NEUPOGEN® (filgrastim).

1988

Gordon Binder is appointed CEO.

Amgen had just received the first U.S. patent for recombinant erythropoietin, completed a 20,000-page filing to the FDA for approval of EPOGEN® and completed building a new 24,000 square foot manufacturing facility. At this height, Rathmann announces that he is ready to retire, explaining "I figured that would be a great thing if they got a running start by launching EPOGEN® as the new management team." Gordon Binder is promoted from CFO to CEO and ushers in a new and promising era.

Gordon Binder and Harry Hixson during the Company's transition following George Rathmann's retirement.

1989

On June 1, 1989, the FDA approves EPOGEN® (epoetin alfa).

EPOGEN® named Product of the Year by *Fortune* magazine.

1989

Amgen goes international.

Amgen establishes its European headquarters in Lucerne, Switzerland. Later, the European headquarters will relocate to Zug, also in Switzerland. Over the next several years, Amgen would quickly establish offices across Europe, including a key manufacturing and distribution center in Breda, the Netherlands.

Aart Brouwer was the first head of Amgen's European office from 1989 to 2001.

1990s

1991

On February 21, 1991, NEUPOGEN® (filgrastim) is approved by the FDA.

NEUPOGEN® is named Product of the Year by *Fortune* magazine.

1991

Giving back for good: the Amgen Foundation is formed.

Amgen establishes the Amgen Foundation as a way to coordinate the various groups and individuals who were already giving back to the community. Today, the Amgen Foundation focuses on excellence in science education to inspire the next generation of innovators, and invest in strengthening communities where Amgen staff members live and work. By the end of 2014, the Foundation had donated more than $200 million in grants to local, regional and international nonprofit organizations that reflect Amgen's core values and impact lives in inspiring and innovative ways.

Manufacturing staffers oversee a filling machine to dispense final, formulated product into vials ready for distribution.

1992

A billion-dollar company.

Amgen hits $1 billion in product sales for EPOGEN® and NEUPOGEN® combined. On January 2, 1992, Amgen is added to the S&P 500 and months later, the Company debuts on the *Fortune* 500 list.

Research director Frank Martin is just one of the many Amgen staffers who take their love of science to the classroom. In this 1995 photo, Martin guides students in an experiment at Walnut Elementary School in Thousand Oaks.

Since 1993, Amgen has relied heavily on its facility in Puerto Rico.

1993

Amgen opens its Puerto Rico facility, which would become Amgen's flagship manufacturing site with over 1.7 million square feet of space.

MID 1990s

Two important discoveries.

Amgen researcher Steve Elliott and his team add two sugar chains to erythropoietin, causing the protein to remain in the body longer. From this discovery, Aranesp® (darbepoetin alfa) is created.

Around the same time, Amgen researcher Olaf Kinstler and his team are experimenting with a longer-lasting form of NEUPOGEN® (filgrastim). Amgen attaches the waxy, water-soluble polymer polyethylene glycol (PEG) to G-CSF, which expands the molecule and greatly slows down excretion. From this discovery, Neulasta® (pegfilgrastim) is created.

The top page of scientist Steve Elliott's lab notebook contains early data from cells transformed with pDEC321, the plasmid used to construct the cell line that produces Aranesp®. With this data, he knew he'd found what he was seeking.

1996

The Amgen Values launch.

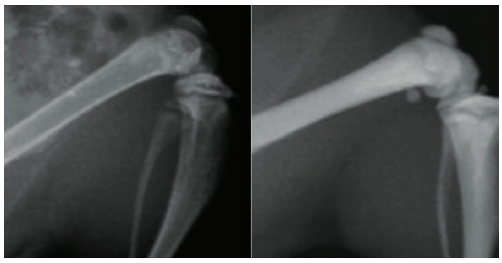
The Amgen Values were first launched in 1996. Amgen could not have accomplished what it did if not for its commitment to building a culture and social architecture that embraces science and innovation—a culture that continues to shape what Amgen is today.

Staffers help develop the principles that guide the way Amgen conducts business. This early mission statement has evolved into the current mission, aspiration, values and leadership attributes.

MID TO LATE 1990s

Key discoveries.

Scientists at Amgen identify and clone osteoprotegerin (OPG). Subsequent research showed that OPG functioned as a decoy receptor for RANK ligand. These insights form the scientific basis for denosumab.



An original x-ray from 1995.

2001

Amgen's Cambridge, Mass., research center opens.

Amgen becomes one of the early pioneers in what would become a biotechnology hotbed in Kendall Square, opening a 285,000-square-foot facility.

2000s

1994

A time of scale and growth.

Staff numbers reach 3,396 globally, up from only 344 when Binder was named CEO in 1988. The Thousand Oaks headquarters had grown, too—from half a building in 1980 to a sprawling campus with well over a million square feet of space by 1992. Local newspapers describe the area as "perpetually under construction."

In 1995, the Los Angeles Times *writes a glowing article about Amgen's relationship with the city of Thousand Oaks, calling it "a Match Made in Heaven."*

1994

Amgen wins the National Medal of Technology.

Amgen becomes the first biotech company to receive the U.S. Department of Commerce National Medal of Technology. This award is considered by the U.S. government to be on par with the Nobel Prize. Given that year by Vice President Al Gore and Commerce Secretary Ron Brown, the award recognizes Amgen for "its leadership in developing innovative and important cost-effective therapeutics based on advances in the cellular and molecular biology for delivery to critically ill patients throughout the world."

Vice President Al Gore presents the 1994 National Medal of Technology to CEO Gordon Binder. The award is the highest honor awarded by the President of the United States to America's leading innovators.

1998

On November 2, 1998, the FDA approves Enbrel® (etanercept).

Enbrel® etanercept

2000

A new CEO for a new century.

Kevin W. Sharer becomes Amgen's third CEO, following the retirement of Gordon Binder. When Binder stepped down, Amgen had grown to become the fourteenth largest drug company in the world, having outstripped its early biotech rivals years before. As Amgen's former President and COO, Sharer had split many responsibilities with Binder. Binder explained, "Like an athlete, there comes a time for the CEO to leave. We were about to launch preparations for several new products, and Kevin was ready to take command."

Kevin Sharer and Amgen's executive management team are featured in the July 2001 Pharmaceutical Executive *magazine—the top trade journal in the industry.*

NASA guest badges identified spectators at the liftoff.

2001

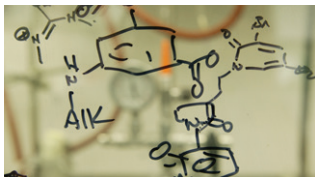
Amgen in space.

Amgen and NASA team up to study Amgen's investigational treatment, osteoprotegerin (OPG), on the space shuttle *Endeavour*. The experiment mimics the effects of the rapid bone loss that astronauts experience due to microgravity.

2002

Neulasta® (pegfilgrastim)

On January 31, 2002, Neulasta® (pegfilgrastim) is approved by the FDA.



Writing on a hood in one of Amgen's small molecule labs.

2004

Amgen acquires Tularik, adding five candidates to Amgen's pipeline and establishing a strong presence in South San Francisco.

2005

Breakaway from Cancer®

Amgen founds *Breakaway from Cancer*, a national initiative to increase awareness of important resources available to people affected by cancer—from prevention through survivorship. *Breakaway from Cancer* represents a partnership between Amgen and four nonprofit organizations dedicated to empowering patients with education, resources and hope, wherever they may be in the cancer care continuum. Today, *Breakaway from Cancer* has reached hundreds of thousands of people touched by cancer with information about resources and services available to people affected by cancer, and more than $4 million has been donated to the *Breakaway from Cancer* nonprofit partners.

Actor and cancer patient advocate Patrick Dempsey participates in a Breakaway from Cancer® *"Breakaway Mile" through Thousand Oaks honoring cancer survivors and their supporters during the 2011 Amgen Tour of California. Photo by Andy Tao.*

2007

Providing cutting-edge research experiences.

The Amgen Foundation, in collaboration with Massachusetts Institute of Technology (MIT), launches the Amgen Scholars program to provide undergraduates with access to research experiences and exposure to biotechnology and drug discovery at top institutions globally.

As an Amgen Scholar in 2013, Maithreyi Raman has the opportunity to conduct research on Huntington's disease in Professor Franz-Ulrich Hartl's laboratory at Ludwig-Maximilians-Universität in Germany.

2001

On September 17, 2001, Aranesp® (darbepoetin alfa) is approved by the FDA.

Aranesp® (darbepoetin alfa)

2002

Every patient, every time.

Amgen acquires Immunex, the developer of Enbrel® (etanercept), along with a manufacturing plant in Rhode Island that had not been used since being built 10 years earlier. Within a matter of months, Amgen teams secure FDA approval, start production and are now able to manufacture enough ENBREL to meet demand.

The Amgen Rhode Island manufacturing facility starts production with the creed: "We make ENBREL so that no patient goes without."

2004

On March 8, 2004, Sensipar® (cinacalcet) is approved by the FDA.

Sensipar® (cinacalcet) Tablets 30mg · 60mg · 90mg

MID 2000s

Elucidating the biology of PCSK9.

Scientists in Amgen's labs in South San Francisco play a critical role in elucidating the function of PCSK9, which lays the groundwork for evolocumab.

A desktop in an Amgen lab in South San Francisco.

2006

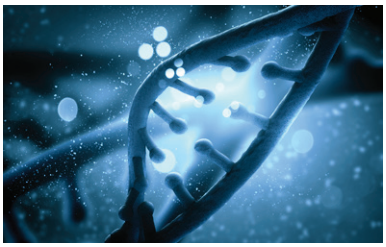
On September 27, 2006, Vectibix® (panitumumab) is approved by the FDA.

Vectibix® (panitumumab) Injection for IV Infusion

2006

Women's Genome Health Study begins.

Amgen collaborates with Brigham and Women's Hospital and NIH's National Heart, Lung, and Blood Institute on the Women's Genome Health Study (WGHS). The purpose: to identify genetic variations that may underlie a range of serious illnesses including heart disease, stroke, diabetes, breast cancer and osteoporosis.



A strand of DNA. The initiative combs the DNA of 28,000 women, who donated their DNA to the groundbreaking study, for differences between those who have developed serious illness and those who have remained healthy.

2008

On August 22, 2008, Nplate® (romiplostim) is approved by the FDA.

Nplate® romiplostim

2009

Nplate® (romiplostim) is awarded "Best Biotechnology Product" by Prix Galien.

Prix Galien is an international award that recognizes outstanding achievements in improving the human condition through the development of innovative therapies.

2011

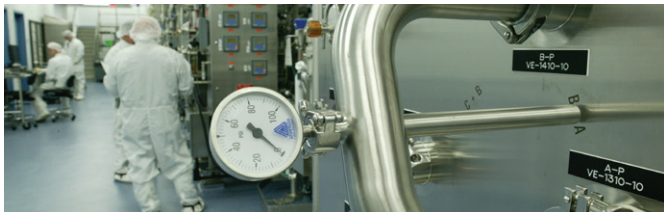
Prolia® (denosumab) and XGEVA® (denosumab) are awarded "Best Biotechnology Product" by Prix Galien.

Prix Galien is an international award that recognizes outstanding achievements in improving the human condition through the development of innovative therapies.

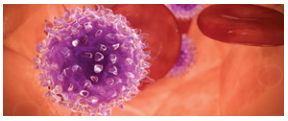
2011

Tapping Amgen's biomanufacturing expertise to create biosimilars.

Amgen and Actavis, Inc. announce that they will collaborate to develop and commercialize, on a worldwide basis, several oncology antibody biosimilar medicines. This collaboration reflects the shared belief that the development and commercialization of biosimilar products will not follow a pure brand or generic model, and will require significant expertise, infrastructure and investment to ensure safe, reliably supplied therapies for patients. Learn more about Amgen's biomanufacturing expertise at BiotechnologybyAmgen.com.



Manufacturing equipment in Rhode Island.



A T cell.

2011

Amgen acquires BioVex, developers of talimogene laherparepvec.

Robert A. Bradway

2012

Robert A. Bradway is appointed as Amgen's fourth CEO.

After more than a decade of leading Amgen as the world's largest biotechnology company, Sharer announces his retirement and that the reins will be handed over to Bradway, Amgen's president and COO. Vance Coffman, chairman of the board's governance and nominating committee at that time, explains, "During [Kevin's tenure], Amgen grew significantly in every dimension and is well positioned for the future."

2010s

2010

Prolia® (denosumab) and XGEVA® (denosumab) are approved by the FDA on June 1, 2010, and November 18, 2010, respectively.

Prolia® wins Best New Drug from *Scrip*, one of the industry's highest global accolades.

2011

Amgen, CDC and CDC Foundation partner to improve infection control for cancer patients.

Preventing Infections in Cancer Patients is a comprehensive public health collaboration between the CDC, the CDC Foundation and Amgen to help reduce infections by raising awareness among patients, caregivers and healthcare providers about steps they can take to protect themselves during chemotherapy treatment. Program resources include a Basic Infection Control and Prevention Plan for outpatient oncology clinics and an online patient risk assessment tool, in addition to posters, fact sheets and postcards. As of 2015, nearly 650,000 pieces of initiative materials have been disseminated to the public.

3 STEPS TOWARD
Preventing Infections During Cancer Treatment
PREPARE • PREVENT • PROTECT
www.preventcancerinfections.org

2011

Amgen acquires a manufacturing facility near Dublin, Ireland.

2011

Amgen expands in Brazil, including the acquisition of Bergamo, a privately held Brazilian pharmaceutical company.

Bergamo
A wholly owned subsidiary of Amgen

2012

Strategic partners and acquisitions.

Amgen acquires deCODE Genetics, a global leader in human genetics. The acquisition reflects a core tenet of Amgen's current R&D strategy: finding and pursuing drug targets that are validated by human genetics.

That same year, Amgen and AstraZeneca agree to jointly develop and commercialize five monoclonal antibodies from Amgen's inflammation portfolio. Amgen also acquires Micromet Inc., developers of what would later be approved by the FDA as BLINCYTO® (blinatumomab); KAI Pharmaceuticals, developers of AMG 416; and Mustafa Nevzat, a leading privately held Turkish pharmaceutical company.

2013

Amgen acquires Onyx Pharmaceuticals, developers of Kyprolis® (carfilzomib) for Injection.

Kyprolis™ (carfilzomib) for Injection

2014

On December 3, 2014, BLINCYTO® (blinatumomab) is approved by the FDA.

BLINCYTO® (blinatumomab) for injection 35 mcg single-use vial

2014

The next generation of biomanufacturing.

Construction is completed on a state-of-the-art facility in Singapore. The plant has the same capacity as a conventional plant, but in a smaller space, using less water and less energy while producing fewer solid wastes and fewer emissions.

The groundbreaking ceremony on June 3, 2013, for the Singapore manufacturing facility.

2015

Amgen turns 35.

AMGEN® 35 YEARS

Today, Amgen remains committed to unlocking the potential of biology for patients suffering from serious illnesses by discovering, developing, manufacturing and delivering innovative human therapeutics. The first 35 years were just the beginning. In biotechnology and at Amgen—**the best is yet to come**.

2012

Amgen Teach launches in Europe.

Amgen Teach launches in Europe to provide hundreds of science educators with free training sessions that emphasize hands-on, inquiry-based experiential learning for their students.

Science teacher Kirstie McAdoo of Ireland shares that participating in Amgen Teach "has given me a huge amount of confidence to use inquiry-based learning in the classroom."

2013

Amgen Astellas BioPharma K.K. alliance forms in Japan and Amgen-Betta Pharmaceuticals joint venture is established in China.

astellas AMGEN BioPharma

AMGEN BETTA 贝达 安进

2013

Through a collaboration with Servier, Amgen obtains the U.S. commercial rights to ivabradine.

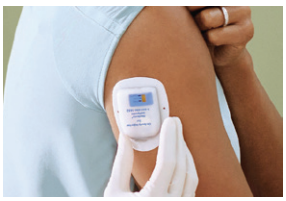
2014

Amgen's Asia Research and Development Center opens at ShanghaiTech University in China.

The R&D Center's opening ceremony.

2015

On March 2, 2015, the Neulasta® (pegfilgrastim) Delivery Kit, including the On-body Injector, launches.



2015

On April 15, 2015, Corlanor® (ivabradine) is approved by the FDA.

Corlanor® (ivabradine) 5 mg 7.5 mg tablets

2015

On August 27, 2015, Repatha® (evolocumab) is approved by the FDA.

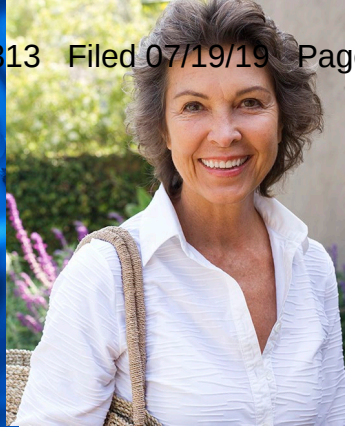
Repatha® (evolocumab) injection 140 mg/mL

2015

On October 27, 2015, IMLYGIC™ (talimogene laherparepvec) is approved by the FDA.

IMLYGIC™ (talimogene laherparepvec) SUSPENSION FOR INJECTION 10^6 PFU/mL and 10^8 PFU/mL single-use vials

EXHIBIT 108



ABOUT AMGEN

Amgen is committed to unlocking the potential of biology for patients suffering from serious illnesses by discovering, developing, manufacturing and delivering innovative human therapeutics. This approach begins by using tools like advanced human genetics to unravel the complexities of disease and understand the fundamentals of human biology.

Our belief—and the core of our strategy—is that innovative, highly differentiated medicines that provide large clinical benefits in addressing serious diseases are medicines that will not only help patients, but also will help reduce the social and economic burden of disease in society today.

Amgen focuses on areas of high unmet medical need and leverages its expertise to strive for solutions that improve health outcomes and dramatically improve people's lives. A biotechnology innovator since 1980, Amgen has grown to be one of the world's leading independent biotechnology companies, has reached millions of patients around the world and is developing a pipeline of medicines with breakaway potential.

INNOVATIVE MEDICINES

We have a presence in approximately 100 countries and regions worldwide and our innovative medicines have reached millions of people in the fight against serious illnesses. We focus on six therapeutic areas: cardiovascular disease, oncology, bone health, neuroscience, nephrology and inflammation. Our medicines typically address diseases for which there are limited treatment options, or they are medicines that provide a viable option to what is otherwise available.

TRANSFORMATIVE RESEARCH

Understanding the fundamental biological mechanisms of disease is a defining feature of Amgen's discovery research efforts—and a major contributor to the development of Amgen's deep and broad pipeline of potential new medicines. Amgen's "biology first" approach permits its scientists to first explore the complex molecular pathways of disease before determining what type of medicine, or modality, is most likely to deliver optimal efficacy and safety. With the advances in human genetics, Amgen continues to shed new light on the molecular roots of disease. Amgen subsidiary deCODE Genetics, a global leader in human genetics, is a powerful differentiator, greatly improving how we identify and validate human disease targets.

WORLD-CLASS BIOMANUFACTURING

The treatment of millions of seriously ill patients worldwide depends on the safe and reliable production of biologic medicines, which are administered by injection or intravenously. A worldwide leader in biologics manufacturing, Amgen has an outstanding track record of reliably delivering high-quality medicines to patients who need them. Significant skill, experience, vigilance and commitment are critical to help ensure the quality of a biologic medicine each time a new batch is made. At Amgen, robust quality control and a reliable supply of medicines for patients are every bit as important as scientific innovation.

AMGEN MISSION

To serve patients

AMGEN QUICK FACTS

Headquarters
Thousand Oaks, California

Staff
Approximately 21,000 worldwide

Stock Listing
NASDAQ: AMGN

Chairman and CEO
Robert A. Bradway

2018 Financial Highlights
Total revenue: $23.7 billion
Product sales: $22.5 billion
R&D expense: $3.7 billion

Address/Phone
One Amgen Center Drive
Thousand Oaks, CA 91320-1799
Main: (805) 447-1000
Investors: (805) 447-1060

PRODUCTS

Aimovig® (erenumab-aooe)
Aranesp® (darbepoetin alfa)
BLINCYTO® (blinatumomab)
Corlanor® (ivabradine)
Enbrel® (etanercept)
EPOGEN® (epoetin alfa)
EVENITY™ (romosozumab-aqqg)
IMLYGIC® (talimogene laherparepvec)
KYPROLIS® (carfilzomib)
Neulasta® (pegfilgrastim)
NEUPOGEN® (filgrastim)
Nplate® (romiplostim)
Parsabiv® (etelcalcetide)
Prolia® (denosumab)
Repatha® (evolocumab)
Sensipar®/Mimpara® (cinacalcet)
Vectibix® (panitumumab)
XGEVA® (denosumab)

Aimovig® is developed in collaboration with Novartis

For information about our pipeline and therapies, visit **www.amgen.com**.

SENIOR MANAGEMENT

Robert A. Bradway
Chairman and Chief Executive Officer

Victoria H. Blatter
SVP, U.S. Government Affairs

Judy Gawlik Brown
SVP, Corporate Affairs

Tia Bush
SVP, Quality

Raymond Deshaies
SVP, Global Research

Steven K. Galson
SVP, Global Regulatory Affairs and Safety

Murdo Gordon
EVP, Global Commercial Operations

Jonathan Graham
SVP, General Counsel and Secretary

Anthony C. Hooper
EVP

Lori Johnston
SVP, Human Resources

Raymond C. Jordan
SVP

Corinne M. Le Goff
SVP, General Manager U.S. General Medicine

Elliott M. Levy
SVP, Global Development

Robert Maroney
SVP

Gilles Marrache
SVP, Regional General Manager

David W. Meline
EVP and Chief Financial Officer

Liam Murphy
SVP

Jerry Murry
SVP, Process Development

Mike Nohaile
SVP, Strategy, Commercialization & Innovation

Joshua J. Ofman
SVP, Global Health Policy

Cynthia M. Patton
SVP and Chief Compliance Officer

Arleen Paulino
SVP, Manufacturing

Joe Peter
SVP, Finance

David A. Piacquad
SVP, Business Development

Annalisa Pizzarello
SVP, Results Delivery Office

David M. Reese
EVP, Research and Development

Esteban Santos
EVP, Operations

Darryl Sleep
SVP, Global Medical and Chief Medical Officer

Ian Thompson
SVP, Regional General Manager

Michael Zahigian
SVP, Chief Information Officer

OUR HERITAGE

Building on advances in recombinant DNA and molecular biology, Amgen is counted among the early pioneers of biotechnology. Since 1980, Amgen scientists have been at work developing novel therapies for patients with serious illnesses. Our scientists have characterized key biologic processes that have led to the development of innovative, first-in-class therapies. We have helped shape the scientific world's understanding of certain disease processes, and we have engineered new types of therapeutic platforms. As a company, we could not have accomplished what we have were it not for our deep commitment to building a culture that embraces science and innovation—a culture that continues to shape who we are today.

THE AMGEN FOUNDATION

The Amgen Foundation seeks to advance excellence in science education to inspire the next generation of innovators, and invest in strengthening communities where Amgen staff members live and work. To date, the Foundation has donated nearly $300 million in grants to local, regional and international nonprofit organizations that impact society in inspiring and innovative ways. The Amgen Foundation brings the excitement of discovery to the scientists of tomorrow through several signature programs, including Amgen Scholars, Amgen Biotech Experience and Amgen Teach. For more information, visit **www.AmgenInspires.com**.

REACHING PATIENTS WORLDWIDE

Amgen medicines help patients worldwide with facilities or subsidiaries in the following locations:

In the United States

California (South San Francisco, Thousand Oaks)
Florida (Tampa)
Kentucky (Louisville)
Massachusetts (Cambridge, Woburn)
Puerto Rico (Juncos)
Rhode Island (West Greenwich)
Washington, D.C.

Outside the United States

Algeria
Argentina
Australia
Austria
Belgium
Brazil
Bulgaria
Canada
China
Colombia
Croatia
Czech Republic
Denmark
Egypt
Estonia
Finland
France
Germany
Greece
Hong Kong
Hungary
Iceland
India
Ireland
Italy
Israel
Japan
Jordan
Korea
Latvia
Lebanon
Lithuania
Luxemburg
Mexico
Morocco
Netherlands
New Zealand
Norway
Poland
Portugal
Romania
Russia
Saudi Arabia
Singapore
Slovakia
Slovenia
South Africa
Spain
Sweden
Switzerland
Taiwan
Thailand
Turkey
United Arab Emirates
United Kingdom

Investor Information

This fact sheet is a summary of more detailed disclosure that can be found in Amgen's filings with the U.S. Securities and Exchange Commission and its press releases. This fact sheet contains forward-looking statements that involve significant risks and uncertainties, discussion of which can be found in Amgen's most recent Forms 10-K, 10-Q, and 8-K and on **http://investors.amgen.com**. The information in this fact sheet is given as of the date below, and Amgen does not undertake any obligation to update any information in this document.

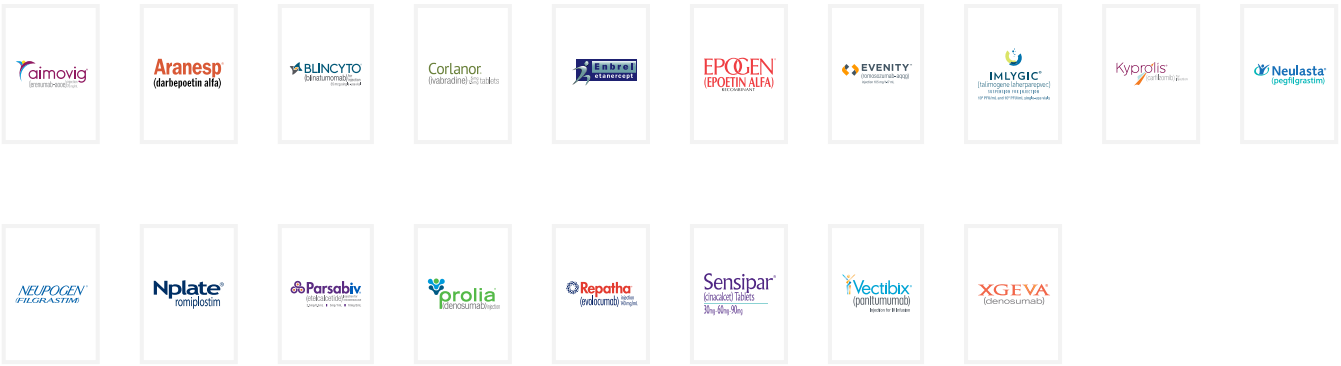
AMGEN®

EXHIBIT 109

PRODUCTS

Amgen's medicines treat serious illnesses and typically address diseases with a limited number of treatment options. With a presence in approximately 100 countries, we are proud to have reached millions of people with our products.

The product information provided below is intended for residents of the U.S. only. For information in other countries, please select your country from the "Amgen Worldwide" menu above.



PRODUCTS (/PRODUCTS/)

Overview (/products/)

Medical Information (http://www.amgenmedinfo.com)

Global Patient Safety (/products/global-patient-safety/)

Counterfeit Drug Statement (/products/counterfeit-drug-statement/)

Safety Data Sheets (/products/safety-data-sheets/)

In This Section

Medical Information

Intended for U.S. healthcare professionals, this application provides information on submitting inquiries, prescribing information and speaking directly to a medical information healthcare professional.

(https://www.amgenmedinfo.com/)

Global Patient Safety

Amgen is committed to patient Safety and the Global Patient Safety Department is responsible for oversight of Pharmacovigilance activity. Patient safety is our highest priority. To fulfill our commitment to patient safety, Amgen's Global Patient Safety Team applies a comprehensive, continuous and rigorous approach to pharmacovigilance.

(/products/global-patient-safety/)

Counterfeit Drug Statement

Amgen takes the issue of counterfeit drugs very seriously and is committed to the highest standards of drug quality and patient safety.

(/products/counterfeit-drug-statement/)

Safety Data Sheets

Safety data sheets provide information for healthcare professionals and others seeking information on implications of the exposure to our products in the workplace.

(/products/safety-data-sheets/)

Related Links

(/responsibility/access-to-medicine/) Access to Medicine

(http://www.amgenpipeline.com/) Pipeline

(/science/clinical-trials) Clinical Trials

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The Amgen Difference (http://www.theamgendifference.com/)

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Mission and Values (/about/mission-and-values/)

Leadership (/about/leadership/)

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Amgen History (http://www.amgenhistory.com/)

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Research and Development Strategy (/science/research-and-development-strategy/)

Pipeline (http://www.amgenpipeline.com)

Scientific Advisory Boards (/science/scientific-advisory-board/)

Amgen Science (https://www.amgenscience.com/)

Clinical Trials (/science/clinical-trials/)

Manufacturing (/science/manufacturing/)

Biosimilars (http://www.amgenbiosimilars.com)

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Amgen's Commitment to Patients (/responsibility/amgens-commitment-to-patients/)

2017 Responsibility Highlights Report (/responsibility/responsibility-highlights-report/)

Amgen Foundation (/responsibility/amgen-foundation/)

Our Approach to Pricing, Access and Affordability (/responsibility/amgen-approach-to-pricing--access-and-affordability-of-our-medicines/)

Access to Medicine (/responsibility/access-to-medicine/)

Diversity and Inclusion (/responsibility/diversity-and-inclusion/)

Environment (/responsibility/environmental-sustainability/)

Supplier Sustainability (/responsibility/supplier-sustainability/)

Grants and Giving (/responsibility/grants-and-giving/)

Safety and Wellness (/responsibility/safety-and-wellness/)

Reporting and Metrics (/responsibility/reporting-and-metrics/)

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Careers (http://careers.amgen.com)

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(https://www.linkedin.com/company/amgen

(http://investors.amgen.com/corporate.rss?c=61656&Rule=Cat~news~subcat~ALL)

Privacy Statement (/privacy-statement/)

Terms of Use (/terms-of-use/)

EXHIBIT 110

FDA-Approved Biosimilar Products

Please click the links below to download PDF versions of the following documents:

AMJEVITA™ Prescribing Information (https://pi.amgen.com/~/media/amgen/repositorysites/pi-amgen-com/amjevita/amjevita_pi_hcp_english.pdf)

AMJEVITA™ Medication Guide (https://pi.amgen.com/~/media/amgen/repositorysites/pi-amgen-com/amjevita/amjevita_mg.pdf)

AMJEVITA™ Patient Instructions for Use (https://pi.amgen.com/~/media/amgen/repositorysites/pi-amgen-com/amjevita/amjevita_ppi_pt_english.pdf)

This is not an offer for sale. AMJEVITA™ is currently not available commercially in the United States.

MVASI™ Prescribing Information (https://pi.amgen.com/~/media/amgen/repositorysites/pi-amgen-com/mvasi/mvasi_pi_hcp_english.pdf)

This is not an offer for sale. MVASI™ is currently not available commercially in the United States.

(../../SUPPORT/VALUE/) (../OUR-PIPELINE/)

PREVIOUS:
VALUE

NEXT:
OUR PIPELINE

Privacy and Terms (http://www.amgen.com/privacy-statement/) | **Contact Us (/contact-us/)** | **Site Map (/site-map/)**

(https://twitter.com/AmgenBiosim) (https://www.youtube.com/user/Amgen)
(http://www.amgen.com/)

EXHIBIT 111

NEWS RELEASES

FDA Approves Amgen And Allergan's KANJINTI™ (trastuzumab-anns), A Biosimilar To Herceptin® (trastuzumab)

Approval Based on Totality of Evidence Demonstrating KANJINTI is Biosimilar to Herceptin

Third FDA Approval From Amgen's Biosimilars Portfolio

THOUSAND OAKS, Calif., June 13, 2019 /PRNewswire/ -- Amgen (NASDAQ:AMGN) and Allergan plc (NYSE:AGN) today announced that the U.S. Food and Drug Administration (FDA) has approved KANJINTI™ (trastuzumab-anns) for all approved indications of the reference product, Herceptin® (trastuzumab): for the treatment of HER2-overexpressing adjuvant and metastatic breast cancer and HER2-overexpressing metastatic gastric or gastroesophageal junction adenocarcinoma.

"The FDA approval of KANJINTI is an important milestone for our biosimilars portfolio, providing an additional treatment option for patients across three types of cancer," said David M. Reese, M.D., executive vice president of Research and Development at Amgen. "KANJINTI is the third biosimilar from our portfolio to receive FDA approval, highlighting our long-term commitment to providing patients with serious illnesses access to high-quality biological therapies."

KANJINTI was proven to be highly similar to, and to have no clinically meaningful differences from, Herceptin based on a comprehensive totality of evidence which included extensive comparative analytical, pharmacokinetic and clinical data. At the time of approval, KANJINTI is the only trastuzumab biosimilar to incorporate the evaluation of a single transition in the clinical study, demonstrating similar safety and immunogenicity in patients who were previously on Herceptin.

"KANJINTI is the second of four biosimilars from Amgen and Allergan's collaboration to be approved by the FDA," said David Nicholson, chief research and development officer at Allergan. "We are proud of the progress being made as we continuously strive to develop and deliver high-quality cancer therapies in collaboration with Amgen."

Amgen has a total of 10 biosimilars in its portfolio, three of which have been approved in the U.S. and three that are approved in the European Union (EU).

About KANJINTI™ (trastuzumab-anns) in the U.S.
KANJINTI is a biosimilar to trastuzumab, a recombinant DNA-derived humanized monoclonal immunoglobulin G1 kappa antibody. The active ingredient of KANJINTI is a humanized monoclonal antibody that has the same amino acid sequence, structure and function as trastuzumab. KANJINTI has the same pharmaceutical dosage form and same strength after reconstitution as trastuzumab.

KANJINTI is currently not available commercially. This is not an offer for sale. The following information is derived from the approved label in the U.S.

In the U.S., KANJINTI is approved for:

Adjuvant Breast Cancer
KANJINTI is indicated for adjuvant treatment of HER2-overexpressing node-positive or node-negative (ER/PR-negative or with one high-risk feature*) breast cancer:

- As part of a treatment regimen containing doxorubicin, cyclophosphamide and either paclitaxel or docetaxel

- With docetaxel and carboplatin
- As a single agent following multi-modality anthracycline-based therapy

Select patients for therapy based on an FDA-approved companion diagnostic for a trastuzumab product.

* High-risk is defined as ER/PR positive with one of the following features: tumor size >2 cm, age <35 years, or tumor grade 2 or 3.

Metastatic Breast Cancer
KANJINTI is indicated:

- In combination with paclitaxel for the first line treatment of HER2-overexpressing metastatic breast cancer
- As a single agent for treatment of HER2-overexpressing breast cancer in patients who have received one or more chemotherapy regimens for metastatic disease

Select patients for therapy based on an FDA-approved companion diagnostic for a trastuzumab product.

Metastatic Gastric Cancer
KANJINTI is indicated, in combination with cisplatin and capecitabine or 5-fluorouracil, for the treatment of patients with HER2-overexpressing metastatic gastric or gastroesophageal junction adenocarcinoma, who have not received prior treatment for metastatic disease.

Select patients for therapy based on an FDA-approved companion diagnostic for a trastuzumab product.

KANJINTI U.S. Boxed WARNINGS and Important Safety Information

Boxed WARNINGS and Additional Important Safety Information
Cardiomyopathy

- **Administration of trastuzumab products can result in sub-clinical and clinical cardiac failure. The incidence and severity was highest in patients receiving trastuzumab with anthracycline-containing chemotherapy regimens**

- **Evaluate left ventricular function in all patients prior to and during treatment with KANJINTI™. Discontinue KANJINTI™ treatment in patients receiving adjuvant therapy and withhold KANJINTI™ in patients with metastatic disease for clinically significant decrease in left ventricular function**

Infusion Reactions; Pulmonary Toxicity

- **Administration of trastuzumab products can result in serious and fatal infusion reactions and pulmonary toxicity. Symptoms usually occur during or within 24 hours of administration. Interrupt KANJINTI™ infusion for dyspnea or clinically significant hypotension. Monitor patients until symptoms completely resolve. Discontinue KANJINTI™ for anaphylaxis, angioedema, interstitial pneumonitis, or acute respiratory distress syndrome**

Embryo-Fetal Toxicity

- **Exposure to trastuzumab products during pregnancy can result in oligohydramnios and oligohydramnios sequence manifesting as pulmonary hypoplasia, skeletal abnormalities, and neonatal death. Advise patients of these risks and the need for effective contraception**

Cardiomyopathy

- **Administration of trastuzumab products can result in sub-clinical and clinical cardiac failure. The incidence and severity was highest in patients receiving trastuzumab with anthracycline-containing chemotherapy regimens. In a pivotal adjuvant breast cancer trial, one patient who developed CHF died of cardiomyopathy**
- Trastuzumab can cause left ventricular cardiac dysfunction, arrhythmias, hypertension, disabling cardiac failure, cardiomyopathy, and cardiac death
- Trastuzumab can also cause asymptomatic decline in LVEF
- Discontinue KANJINTI™ treatment in patients receiving adjuvant breast cancer therapy and withhold KANJINTI™ in patients with metastatic disease for clinically significant decrease in left ventricular function

Cardiac Monitoring

- **Evaluate cardiac function prior to and during treatment. For adjuvant breast cancer therapy, also evaluate cardiac function after completion of KANJINTI™**
- Conduct thorough cardiac assessment, including history, physical examination, and determination of LVEF by echocardiogram or MUGA scan
- Monitor frequently for decreased left ventricular function during and after KANJINTI™ treatment
- Monitor more frequently if KANJINTI™ is withheld for significant left ventricular cardiac dysfunction

Infusion Reactions

- **KANJINTI™ administration can result in serious and fatal infusion reactions**
- **Symptoms usually occur during or within 24 hours of KANJINTI™ administration**
- **Interrupt KANJINTI™ infusion for dyspnea or clinically significant hypotension**
- **Monitor patients until symptoms completely resolve**
- **Discontinue KANJINTI™ for infusion reactions manifesting as anaphylaxis, angioedema, interstitial pneumonitis, or acute respiratory distress syndrome. Strongly consider permanent discontinuation in all patients with severe infusion reactions**
- Infusion reactions consist of a symptom complex characterized by fever and chills, and on occasion include nausea, vomiting, pain (in some cases at tumor sites), headache, dizziness, dyspnea, hypotension, rash, and asthenia

Embryo-Fetal Toxicity

- **Exposure to trastuzumab products during pregnancy can result in oligohydramnios and oligohydramnios sequence manifesting as pulmonary hypoplasia, skeletal abnormalities, and neonatal death. Advise patients of these risks and the need for effective contraception**
- Verify the pregnancy status of females of reproductive potential prior to the initiation of KANJINTI™
- Advise pregnant women and females of reproductive potential that exposure to KANJINTI™ during pregnancy or within 7 months prior to conception can result in fetal harm

- Advise females of reproductive potential to use effective contraception during treatment and for at least 7 months following the last dose of KANJINTI™. Advise female patients to contact their healthcare provider with a known or suspected pregnancy
- Consider the developmental and health benefits of breastfeeding along with the mother's clinical need for KANJINTI™ treatment and any potential adverse effects on the breastfed child from KANJINTI™ or from the underlying maternal condition

Pulmonary Toxicity

- **Trastuzumab products can result in serious and fatal pulmonary toxicity,** which includes dyspnea, interstitial pneumonitis, pulmonary infiltrates, pleural effusions, noncardiogenic pulmonary edema, pulmonary insufficiency and hypoxia, acute respiratory distress syndrome, and pulmonary fibrosis. Such events can occur as sequelae of infusion reactions
- Patients with symptomatic intrinsic lung disease or with extensive tumor involvement of the lungs, resulting in dyspnea at rest, appear to have more severe toxicity
- Discontinue KANJINTI™ in patients experiencing pulmonary toxicity

Exacerbation of Chemotherapy-Induced Neutropenia

- In randomized, controlled clinical trials, the per-patient incidences of NCI-CTC Grade 3-4 neutropenia and of febrile neutropenia were higher in patients receiving trastuzumab in combination with myelosuppressive chemotherapy as compared to those who received chemotherapy alone. The incidence of septic death was similar among patients who received trastuzumab and those who did not

Most Common Adverse Reactions

- The most common adverse reactions associated with trastuzumab products in breast cancer were fever, nausea, vomiting, infusion reactions, diarrhea, infections, increased cough, headache, fatigue, dyspnea, rash, neutropenia, anemia, and myalgia
- The most common adverse reactions associated with trastuzumab products in metastatic gastric cancer were neutropenia, diarrhea, fatigue, anemia, stomatitis, weight loss, upper respiratory tract infections, fever, thrombocytopenia, mucosal inflammation, nasopharyngitis, and dysgeusia

You may report side effects to the FDA at (800) FDA-1088 or **www.fda.gov/medwatch (https://c212.net/c/link/?t=0&l=en&o=2496399-1&h=3295474688&u=http%3A%2F%2Fwww.fda.gov%2Fmedwatch&a=www.fda.gov%2Fmedwatch)**. You may also report side effects to Amgen at 1-800-772-6436.

Please see additional select Important Safety Information throughout, and the accompanying **full Prescribing Information (https://c212.net/c/link/?t=0&l=en&o=2496399-1&h=2578339727&u=http%3A%2F%2Fwww.gene.com%2Fdownload%2Fpdf%2Fherceptin_prescribing.pdf&a=full+Prescribing+Infor** including **Boxed WARNINGS**.

Please see the accompanying full Prescribing Information (https://c212.net/c/link/?t=0&l=en&o=2496399-1&h=2578339727&u=http%3A%2F%2Fwww.gene.com%2Fdownload%2Fpdf%2Fherceptin_prescribing.pdf&a=full+Prescribing+Information), including **Boxed WARNINGS**.

About the Amgen and Allergan Collaboration

In December 2011, Amgen and Allergan plc. (then Watson Pharmaceuticals, Inc.) formed a collaboration to develop and commercialize, on a worldwide basis, four oncology antibody biosimilar medicines. This collaboration reflects the shared belief that the development and commercialization of biosimilar products will not follow a pure brand or generic model and will require significant expertise, infrastructure, and investment to ensure safe, reliably supplied therapies for patients. Under the terms of the agreement, Amgen will assume primary responsibility for developing, manufacturing and initially commercializing the oncology antibody products.

About Amgen Biosimilars

Amgen is committed to building upon Amgen's experience in the development and manufacturing of innovative human therapeutics to expand Amgen's reach to patients with serious illnesses. Biosimilars will help to maintain Amgen's commitment to connect patients with vital medicines, and Amgen is well positioned to leverage its nearly four decades of experience in biotechnology to create high-quality biosimilars and reliably supply them to patients worldwide.

For more information, visit www.amgenbiosimilars.com (https://c212.net/c/link/?t=0&l=en&o=2496399-1&h=2410409827&u=http%3A%2F%2Fwww.amgenbiosimilars.com%2F&a=www.amgenbiosimilars.com) and follow us on www.twitter.com/amgenbiosim (https://c212.net/c/link/?t=0&l=en&o=2496399-1&h=1424277939&u=http%3A%2F%2Fwww.twitter.com%2Famgenbiosim&a=www.twitter.com%2Famgenbiosim).

About Amgen Oncology

Amgen Oncology is searching for and finding answers to incredibly complex questions that will advance care and improve lives for cancer patients and their families. Our research drives us to understand the disease in the context of the patient's life – not just their cancer journey – so they can take control of their lives.

For the last four decades, we have been dedicated to discovering the firsts that matter in oncology and to finding ways to reduce the burden of cancer. Building on our heritage, Amgen continues to advance the largest pipeline in the Company's history, moving with great speed to advance those innovations for the patients who need them.

At Amgen, we are driven by our commitment to transform the lives of cancer patients and keep them at the center of everything we do.

For more information, follow us on www.twitter.com/amgenoncology (https://c212.net/c/link/?t=0&l=en&o=2496399-1&h=1415995369&u=https%3A%2F%2Fc212.net%2Fc%2Flink%2F%3Ft%3D0%26l%3Den%26o%3D2484513-1%26h%3D3077978101%26u%3Dhttp%253A%252F%252Fwww.twitter.com%252Famgenoncology%26a%3Dwww.twitter.com%252Famgen

About Amgen

Amgen is committed to unlocking the potential of biology for patients suffering from serious illnesses by discovering, developing, manufacturing and delivering innovative human therapeutics. This approach begins by using tools like advanced human genetics to unravel the complexities of disease and understand the fundamentals of human biology.

Amgen focuses on areas of high unmet medical need and leverages its expertise to strive for solutions that improve health outcomes and dramatically improve people's lives. A biotechnology pioneer since 1980, Amgen has grown to be one of the world's leading independent biotechnology companies, has reached millions of patients around the world and is developing a pipeline of medicines with breakaway potential.

For more information, visit www.amgen.com (https://c212.net/c/link/?t=0&l=en&o=2496399-1&h=2076865164&u=http%3A%2F%2Fwww.amgen.com%2F&a=www.amgen.com) and follow us on www.twitter.com/amgen (https://c212.net/c/link/?t=0&l=en&o=2496399-1&h=554521011&u=http%3A%2F%2Fwww.twitter.com%2Famgen&a=www.twitter.com%2Famgen).

About Allergan plc

Allergan plc (NYSE: AGN), headquartered in Dublin, Ireland, is a bold, global pharmaceutical leader. Allergan is focused on developing, manufacturing and commercializing branded pharmaceutical, device, biologic, surgical and regenerative medicine products for patients around the world.

Allergan markets a portfolio of leading brands and best-in-class products primarily focused on four key therapeutic areas including central nervous system, eye care, medical aesthetics and gastroenterology.

Allergan is an industry leader in Open Science, a model of research and development, which defines our approach to identifying and developing game-changing ideas and innovation for better patient care. With this approach, Allergan has built one of the broadest development pipelines in the pharmaceutical industry.

Allergan's success is powered by our global colleagues' commitment to being Bold for Life. Together, we build bridges, power ideas, act fast and drive results for our customers and patients around the world by always doing what is right.

With commercial operations in approximately 100 countries, Allergan is committed to working with physicians, healthcare providers and patients to deliver innovative and meaningful treatments that help people around the world live longer, healthier lives every day.

For more information, visit Allergan's website at www.Allergan.com (https://c212.net/c/link/?t=0&l=en&o=2496399-1&h=2038676929&u=https%3A%2F%2Furldefense.proofpoint.com%2Fv2%2Furl%3Fu%3Dhttp-3A__www.Allergan.com%26d%3DDwMGaQ%26c%3DSexio4usKrYWFsrnxgjbcQ%26r%3D18nQDdemERmeQu0LHLPOYmA00jmh72Lm59

Amgen Forward-Looking Statements

This news release contains forward-looking statements that are based on the current expectations and beliefs of Amgen. All statements, other than statements of historical fact, are statements that could be deemed forward-looking statements, including estimates of revenues, operating margins, capital expenditures, cash, other financial metrics, expected legal, arbitration, political, regulatory or clinical results or practices, customer and prescriber patterns or practices, reimbursement activities and outcomes and other such estimates and results. Forward-looking statements involve significant risks and uncertainties, including those discussed below and more fully described in the Securities and Exchange Commission reports filed by Amgen, including its most recent annual report on Form 10-K and any subsequent periodic reports on Form 10-Q and current reports on Form 8-K. Unless otherwise noted, Amgen is providing this information as of the date of this news release and does not undertake any obligation to update any forward-looking statements contained in this document as a result of new information, future events or otherwise.

No forward-looking statement can be guaranteed and actual results may differ materially from those Amgen projects. Discovery or identification of new product candidates or development of new indications for existing products cannot be guaranteed and movement from concept to product is uncertain; consequently, there can be no guarantee that any particular product candidate or development of a new indication for an existing product will be successful and become a commercial product. Further, preclinical results do not guarantee safe and effective performance of product candidates in humans. The complexity of the human body cannot be perfectly, or sometimes, even adequately modeled by computer or cell culture systems or animal models. The length of time that it takes for Amgen to complete clinical trials and obtain regulatory approval for product marketing has in the past varied and Amgen expects similar variability in the future. Even when clinical trials are successful, regulatory authorities may question the sufficiency for approval of the trial endpoints Amgen has selected. Amgen develops product candidates internally and through licensing collaborations, partnerships and joint ventures. Product candidates that are derived from relationships may be subject to disputes between the parties or may prove to be not as effective or as safe as Amgen may have believed at the time of entering into such relationship. Also, Amgen or others could identify safety, side effects or manufacturing problems with its products, including its devices, after they are on the market.

Amgen's results may be affected by its ability to successfully market both new and existing products domestically and internationally, clinical and regulatory developments involving current and future products, sales growth of recently launched products, competition from other products including biosimilars, difficulties or delays in manufacturing its products and global economic conditions. In addition, sales of Amgen's products are affected by pricing pressure, political and public scrutiny and reimbursement policies imposed by third-party payers, including governments, private insurance plans and managed care providers and may be affected by regulatory, clinical and guideline developments and domestic and international trends toward managed care and healthcare cost containment. Furthermore, Amgen's research, testing, pricing, marketing and other operations are subject to extensive regulation by domestic and foreign government regulatory authorities. Amgen's business may be impacted by government investigations, litigation and product liability claims. In addition, Amgen's business may be impacted by the adoption of new tax legislation or exposure to additional tax liabilities. If Amgen fails to meet the compliance obligations in the corporate integrity agreement between Amgen and the U.S. government, Amgen could become subject to significant sanctions. Further, while Amgen routinely obtains patents for its products and technology, the protection offered by its patents and patent applications may be challenged, invalidated or circumvented by its competitors, or Amgen may fail to prevail in present and future intellectual property litigation. Amgen performs a substantial amount of its commercial manufacturing activities at a few key facilities, including in Puerto Rico, and also depends on third parties for a portion of its manufacturing activities, and limits on supply may constrain sales of certain of its current products and product candidate development. Amgen relies on collaborations with third parties for the development of some of its product candidates and for the commercialization and sales of some of its commercial products. In addition, Amgen competes with other companies with respect to many of its marketed products as well as for the discovery and development of new products. Further, some raw materials, medical devices and component

parts for Amgen's products are supplied by sole third-party suppliers. Certain of Amgen's distributors, customers and payers have substantial purchasing leverage in their dealings with Amgen. The discovery of significant problems with a product similar to one of Amgen's products that implicate an entire class of products could have a material adverse effect on sales of the affected products and on its business and results of operations. Amgen's efforts to acquire other companies or products and to integrate the operations of companies Amgen has acquired may not be successful. A breakdown, cyberattack or information security breach could compromise the confidentiality, integrity and availability of Amgen's systems and Amgen's data. Amgen's stock price may be volatile and may be affected by a number of events. Amgen's business performance could affect or limit the ability of the Amgen Board of Directors to declare a dividend or its ability to pay a dividend or repurchase its common stock. Amgen may not be able to access the capital and credit markets on terms that are favorable to it, or at all.

Allergan plc Forward-Looking Statement

Statements contained in this press release that refer to future events or other non-historical facts are forward-looking statements that reflect Allergan's current perspective on existing trends and information as of the date of this release. Actual results may differ materially from Allergan's current expectations depending upon a number of factors affecting Allergan's business. These factors include, among others, the difficulty of predicting the timing or outcome of FDA approvals or actions, if any; the impact of competitive products and pricing; market acceptance of and continued demand for Allergan's products; the impact of uncertainty around timing of generic entry related to key products, including RESTASIS®, on our financial results; risks associated with divestitures, acquisitions, mergers and joint ventures; risks related to impairments; uncertainty associated with financial projections, projected cost reductions, projected debt reduction, projected synergies, restructurings, increased costs, and adverse tax consequences; difficulties or delays in manufacturing; and other risks and uncertainties detailed in Allergan's periodic public filings with the Securities and Exchange Commission, including but not limited to Allergan's Annual Report on Form 10-K for the year ended December 31, 2018 and Allergan's Quarterly Report on Form 10-Q for the period ended March 31, 2019. Except as expressly required by law, Allergan disclaims any intent or obligation to update these forward-looking statements.

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CONTACT: Amgen, Thousand Oaks
Kelley Davenport, 202-585-9637 (media)
Kristen Davis, 805-447-3008 (media)
Arvind Sood, 805-447-1060 (investors)

CONTACT: Allergan plc:
Daphne Karydas, 862-261-8006 (investor relations)
Amy Rose, 862-261-7001 (media relations)

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EXHIBIT 112

Our Pipeline

Inflammation

Oncology

Hematology

ABP 798 (biosimilar rituximab)

ABP 710 (biosimilar infliximab)

ABP 494 (biosimilar cetuximab)

ABP 959 (biosimilar eculizumab)

ABP 980 (biosimilar trastuzumab)

(/PRODUCTS/APPROVED-PRODUCTS/) (../CLINICAL-TRIALS/)

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FDA-APPROVED PRODUCTS

NEXT:
CLINICAL TRIALS

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(http://www.amgen.com/)

EXHIBIT 113

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CERTIFICATE OF SERVICE

The undersigned counsel hereby certifies that true and correct copies of the foregoing document were caused to be served on July 10, 2019 on the following counsel in the manner indicated:

VIA EMAIL:

Neal C. Belgam
Eve H. Ormerod
Jennifer M. Rutter
SMITH, KATZENSTEIN & JENKINS, LLP
1000 West Street, Suite 1501
Wilmington, DE 19801
(302) 652-8400
nbelgam@skjlaw.com
eormerod@skjlaw.com
jrutter@skjlaw.com

Orion Armon
COOLEY, LLP
380 Interlocken Crescent, Suite 900
Broomfield, CO 80021-8023
(720) 566-4119
oarmon@cooley.com

Eamonn Gardner
COOLEY, LLP
4401 Eastgate Mall
San Diego, CA 92121-1909
(858) 550-6086
egardner@cooley.com

Michelle Rhyu
Susan Krumplitsch
Daniel Knauss
Philip H. Mao
Alexandra Leeper
Lauren Krickl
Benjamin S. Lin
Alissa M. Wood
COOLEY, LLP
3175 Hanover Street
Palo Alto, CA 94304-1130
(650) 843-5287
rhyums@cooley.com
skrumplitsch@cooley.com
dknauss@cooley.com
pmao@cooley.com
aleeper@cooley.com
lkrickl@cooley.com
blin@cooley.com
amwood@cooley.com

Nancy Gettel
AMGEN, INC.
One Amgen Center Drive
Thousand Oaks, CA 91320-1799
(805) 447-1000
ngettel@amgen.com

Xiaoxiao Xue
1299 Pennsylvania Avenue, NW, Suite 700
Washington, DC 20004-2400
(202) 842-7809
xxue@cooley.com

Attorneys for Defendant Amgen Inc.

Dated: July 10, 2019

/s/ Michael P. Kelly
Michael P. Kelly (#2295)