FDA and EMA Biosimilar Approvals

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INTRODUCTION

In 2010, Congress streamlined Food and Drug Administration (FDA) approval of versions of biologic drugs made by other manufacturers ("biosimilars") after market exclusivity expiration. This pathway, codified in section 351(k) of the Public Health Service Act, was intended to leverage existing knowledge about originator biologics to require fewer trials. By reducing cost of entry, policymakers incentivized competition and lower drug prices.

Biosimilar market growth, however, has been slow.[1] The FDA approved its first biosimilar in 2015.[2] As of February 2019, 17 biosimilars of 9 originator biologics had received regulatory approval, but only 7 had been marketed with limited price reductions.[3] Concern has arisen whether biosimilar testing requirements have hindered market entrants, leading some to doubt that the US biosimilar marketplace will eventually flourish.[4]

Europe has had more experience with biosimilars than the USA. The European Medicines Agency (EMA) approved its first biosimilar in 2006, and 60 biosimilars have since been approved and marketed to patients in Europe, leading to substantially lower prices.[5] To look at how the US and European biosimilar approval processes have evolved over time, we compared the clinical testing required for FDA- and EMA-approved biosimilars.

METHODS

Sixteen biosimilars of 9 originator biologics had been approved by both the FDA and the EMA by February 2019 (the infliximab biosimilar Ifixi was FDA- but not EMA-approved). Using FDA medical reviews, labeling, and advisory committee meeting materials, EMA public assessment reports, and ClinicalTrials.gov, we extracted dates of biosimilar regulatory approval and submitted clinical trials. We also recorded overlap among the clinical trials submitted to FDA and EMA.

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RESULTS

Ten biosimilars received EMA approval first, with a median time of 18 months to FDA approval (interquartile range (IQR), 6–63 months). Five of these biosimilars received FDA approval based on the same clinical trials supporting EMA approval (Table 1). Among the other 5 biosimilars for which different clinical trials were submitted, 4 were approved by the EMA before the FDA had approved its first biosimilar. In total, 36 trials were submitted to the EMA to support the 10 biosimilars, compared to 44 to the FDA (Table 2). About two-thirds of the trials (EMA, 69%; FDA, 73%) were phase I trials. The median number of patients enrolled in phase I trials submitted to the EMA and FDA was 153 (IQR, 116–353) and 352 (IQR, 145–515), respectively. A median of 537 patients (IQR, 304–601) and 573 patients (IQR, 437–773) were enrolled in phase II or III trials, which had a median duration of 24 weeks (EMA) (IQR, 16–30) and 28 weeks (FDA) (IQR, 22–30).

Six newer biosimilars received earlier approval from the FDA, with a median time of 6 months to EMA approval (IQR, 5–9). Of those biosimilars, five were EMA- and FDA-approved based on the same clinical trials. FDA and EMA approvals were based on 20 and 22 clinical trials, respectively, about two-thirds of which (FDA, 65%; EMA, 64%) were phase I trials. A median of 587 patients [IQR, 508–644 (FDA); 508–702 (EMA)] were enrolled in the phase II or III trials submitted to both regulators. The median duration of these trials was 15 weeks [IQR, 12–20 (FDA); 10–20 (EMA)].

Five biosimilars were second-to-market, meaning another biosimilar linked to the same originator biologic had already been approved by FDA or EMA. Two were approved without a phase II or III trial: the filgrastim biosimilar Nivestym (FDA) and the pegfilgrastim biosimilar Udenyca (FDA/EMA).

DISCUSSION

Although the level of biosimilar testing needed for FDA approval exceeded the EMA soon after the 351(k) process

Table 1 FDA- and EMA-Approved Biosimilar Products

Biosimilar product (FDA/EMA)	Approval date	Months between FDA and EMA approvals	Clinical trials	FDA and EMA equivalent trials	Total patients enrolled	Phase I trials	Total patients in phase I trials	Phase II or III trials	Total patients in phase II orIII trials
Zarxio/Zarzio (filgrastim)	FDA: 03/06/15 EMA: 02/06/09	+ 73	12 5	5	792 316	10 4	364 146	2 1	428 170
Inflectra (infliximab)	FDA: 04/05/16 EMA: 09/10/13	+ 31	6 3	3	1248 875	4 2	627 269	2 1	621 606
Erelzi (etanercept)	FDA: 08/30/16 EMA: 06/23/17	− 10	5 5	5	747	4	216	1	531
Amjevita/ Amgevita (adalimumab)	FDA: 09/23/16 EMA: 03/22/17	− 6	3 3	3	1079	1	203	2	876
Renflexis/Flixabi (infliximab)	FDA: 04/21/17 EMA: 05/26/16	+ 11	2 2	2	743	1	159	1	584
Cyltezo (adalimumab)	FDA: 08/25/17 EMA: 11/10/17	− 3	3 5	3	1162 1305	2 3	517 583	1 2	645 722
Mvasi (bevacizumab)	FDA: 09/14/17 EMA: 01/15/18	− 4	2 2	2	844	1	202	1	642
Ogivri (trastuzumab)	FDA: 12/01/17 EMA: 12/12/18	− 12	4 4	4	789	3	289	1	500
Retacrit (epoetin alfa)	FDA: 05/15/18 EMA: 12/17/07	+ 125	4 5	0	1142 1299	2 2	932 72	2 3*	210 1227
Fulphila (pegfilgrastim)	FDA: 06/04/18 EMA: 11/20/18	− 6	3 3	3	460	2	266	1	194
Nivestym/Nivestim (filgrastim)	FDA: 07/20/18 EMA: 06/07/10	+ 99	3 3	0	340 342	3 2	340 92	0 1	0 250
Hyrimoz (adalimumab)	FDA: 10/30/18 EMA: 07/26/18	+ 3	5 5	5	1286	4	821	1	465
Udenyca (pegfilgrastim)	FDA: 11/02/18 EMA: 09/20/18	+ 2	4 4	4	509	4	509	0	0
Truxima (rituximab)	FDA: 11/28/18 EMA: 02/17/17	+ 22	3 4§	2	770†‡ 753†‡	1 3	140 381	3 2	770 512
Herzuma (trastuzumab)	FDA: 12/14/18 EMA: 08/02/18	+ 4	3 3	3	702	2	140	1	562
Ontruzant (trastuzumab)	FDA: 01/18/19 EMA: 11/15/17	+ 14	2 2	2	983	1	108	1	875

Plus sign (+), EMA approval preceded FDA approval; minus sign (−), FDA approval preceded EMA approval

** Phase information for one clinical trial was not noted. We concluded that this trial's characteristics were suggestive of a phase II or III trial*

†Trial CT-P10 1.3 was an extension of CT-P10 1.1 enrolling 83 patients from CT-P10 1.1 and 4 new patients. The total number of patients enrolled reflects the number of distinct patients (i.e., we did not double-count the patients in both trials

‡Trial CT-P10 3.3 was a phase I and III trial, consisting of two parts. The "total patients enrolled" reflects the number of distinct patients (i.e., we did not double-count the patients in both parts). However, these patients were accounted for in both the "total patients enrolled in phase I trials" and the "total patients enrolled in phase II or III trials"

§The EMA public assessment report mentioned a fifth trial (CT-P10 1.2) enrolling 1 patient, but it was terminated

Table 2 Clinical Trial Characteristics of FDA- and EMA-Approved Biosimilars

	EMA pre-dating FDA approval (*N* = 10)		FDA pre-dating EMA approval (*N* = 6)	
	EMA	**FDA**	**FDA**	**EMA**
Clinical trials	36	44	20	22
Double-blinded (%)	27 (75%)	35 (80%)	16 (80%)	16 (73%)
Randomized (%)	31 (86%)	43 (92%)	20 (100%)	21 (95%)
Use of regulator-licensed comparators (%)	12 (33%)	23 (52%)	15 (75%)	7 (32%)
Phase I trials (%)	25 (69%)	32 (73%)	13 (65%)	14 (64%)
Median patients enrolled* (IQR)	153 (116–353)	275 (145-473)	241 (206–283)	241 (206–283)
Median ITT* (IQR)	83 (71–207)	162 (70-245)	153 (84–206)	174 (84–235)
Phase II or III trials (%)	12† (33%)	13 (30%)	9 (45%)	10 (45%)
Median patients enrolled* (IQR)	537 (304–601)	573 (437-733)	587 (508–644)	587 (508–702)
Median ITT* (IQR)	255 (196–292)	295 (243–354)	294 (251–327)	296 (251–383)
Median trial duration (weeks) (IQR)	24 (16–30)	28 (22–30)	15 (12–20)	15 (10–20)

EMA European Medicines Agency, FDA Food and Drug Administration, IQR interquartile ratio, ITT intention to treat
**Median number of total patients enrolled per biosimilar*
†Phase information for one clinical trial for EMA-approved epoetin alfa (Retacrit) was not noted. We concluded that this trial's characteristics were suggestive of a phase II or III trial

was established, that is no longer the case. For 10 of the 12 biosimilars not approved for marketing in the EU prior to 2015, the same clinical trials supported EMA and FDA approval. More recently, the agency has approved some second-to-market biosimilar products without phase II or III trials. The USA was late to establish a biosimilar pathway, but the FDA has streamlined its approval process; it now approves many new biosimilars several months before the EMA. As more biosimilars are approved in the USA, policymakers must now grapple with other barriers to ensure that biosimilars reach the market, are priced at competitive levels, and are utilized by physicians and patients.

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