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Extrapolation: Experience gained from original biologics

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Biologicals undergo modifications throughout their commercial lifecycle. Major changes can unintentionally magnify their inherent physicochemical variability. Although trials comparing the pre- and the post-change versions have been requested occasionally, analytical comparison is the most sensitive approach to anticipating clinical equivalence. Therefore, it may be concluded, by means of 'extrapolation', that non-identical versions of a given biologic will behave equally in all indications. Despite the lessons learned with original biologics, there are still controversies around the approval of biosimilars through extrapolation. Here, a comprehensive analysis of scattered information allows for an account of cases of original biologic versions approved in some indications with no patient trials involved. Healthcare professionals can be reassured that inasmuch as extrapolation has proven valid for new versions of original biologics, the same holds for biosimilars.

Keywords: Adalimumab; Biologic; Biosimilar; Canakinumab; Darbepoetin; Extrapolation; Manufacturing change; Omalizumab; Trastuzumab

Marketing authorization of new versions of biological medicines

Throughout their commercial lifecycle, biologics may be subject to changes in their manufacturing process and/or composition that are neither intended to modify the active substance nor to create a new product.[1,2] Such changes are meant either to transform the production process (for example, to optimize manufacturing efficiency) or to add therapeutic value (for example, to allow a different route of administration).[3] In those scenarios, no changes in the medicine's biological activity are expected. However, besides the intended consequences, modifications might induce unwanted alterations that can have an unintentional clinical impact, as documented for a number of original biologics.[3–8] Indeed, in light of their origin and their protein nature, most biologics have an inherent structural variability that can be inadvertently magnified through those changes.[9,10] Moreover, unwanted variations of other attributes (such as the amount of impurities) might occur as a result of environmental fluctuations.[7] When a change has the potential to alter the identity, strength, quality, purity, or potency of the product, it is considered a major change.[11] European Medicines Agency (EMA) experts coined the expression 'new version' for biomedicines that shift structurally in certain attributes as a result of such modifications.[12]

In order to ensure that the expected outcome of a major modification is not accompanied by an unacceptable threat to the risk-to-benefit balance, authorities often require customized comparability studies before granting marketing authorization.[13–15] The nature and extension of the comparability program is

Abbreviations: AUC, Area under curve; CHO, Chinese Hamster Ovary; CRF, chronic renal failure; EBC, early breast cancer; EC, European Commission; EMA, European Medicine's Agency; EPO, erythropoietin; EU, European Union; FDA, US Food & Drug Administration; HCP, health care professionals; HER2, human epidermal growth factor receptor 2; IV, Intravenous; mAB, Monoclonal Antiibody; MAH, marketing authorization holder; MBC, metastatic breast cancer; MCB, Master cell bank; PD, pharmacodynamic; PK, pharmacokinetic; RA, rheumatoid arthritis; rHuEPO, recombinant human EPO; rHuP20, recombinant human hyaluronidase; SC, subcutaneous; TNF-α, Tumor Necrosis Factor-α; tpCR, total pathologic complete response.

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1359-6446/
https://doi.org/10.1016/j.drudis.2021.05.006

established on a case-by-case basis, considering the extent of the modification, the product's features and its intended clinical use. Specifically, when a major change is implemented, it is often necessary to carry out a comprehensive physicochemical and functional comparability exercise, which may occasionally be supported by non-clinical and/or clinical data.[13] Even when a modified original biologic exhibits physicochemical or pharmacological changes, approval for some indications or patient populations may be awarded by means of 'extrapolation', with no specific comparative trials involved. Although approval based on extrapolation is scientifically justified and has been practiced for decades with original biologics, debate among healthcare professionals (HCP) over the risks of this practice started when biosimilars, products that are similar to an approved 'original' reference biologic, (i.e. versions of original biologics), reached the market. To reassure HCP, cases in which the US Food and Drug Administration (FDA) and/or the EMA supported the marketing authorization of modified original biologics with no comparative patient studies in all indications, despite evidence of unintended alterations, are thoroughly reviewed below.

Extrapolation of original biologics

The work over many years of the FDA, EMA, and other reference regulatory agencies in assessing original biotechnology-derived medicines has helped to shape stringent regulatory guidance for the authorization of major changes. Three real-world cases of such modifications to original products containing darbepoetin, adalimumab, and trastuzumab are analyzed below. The main features of the products under scrutiny are listed in Table 1. Although details of the changes implemented and their regulatory assessment are not publicly available, there are some reliable relevant data in scattered FDA and EMA documents and in research papers, including some from marketing authorization holders (MAH).

Aranesp® (darbepoetin)

Modifications may be applied to a manufacturing process with no primary intent to change the product's therapeutic performance or usage, but rather to meet regulatory requirements in certain jurisdictions, scale up production, improve consistency, change or upgrade technology, move to a new manufacturing site, or optimize production efficiency.[14] Some changes may be considered 'major' in light of their potential unintended collateral impact on the product's pharmacological behavior. Despite that risk, regulatory agencies may authorize the use of the modified product on the basis of comparability data (with no clinical trials) in all the targeted indications. Aranesp® is a paradigmatic example (summarized in Table 2).

Darbepoetin alfa (darbepoetin) is the active substance of Aranesp®, an original biotechnology-derived medicine. Darbepoetin is a heavily glycosylated recombinant human erythropoietin (EPO) analog that functions as a regulator of erythropoiesis.[16,17] The European Commission (EC) approved darbepoetin on the basis of safety and efficacy trials for the treatment of anemia resulting from chronic renal failure (CRF) in adults and children, and for the treatment of chemotherapy-induced anemia in adults with non-myeloid malignancies.[18–20] In 2008, the manufacturer of Aranesp® implemented a major change in the production process[16,21]: a more scalable and efficient high-throughput system, based on serum-free bioreactor technology, was introduced probably to reduce contamination.[22] This necessitated the reestablishment of the master cell bank (MCB). As explained by the FDA[13] and others,[23,24] changing the culture medium and reestablishing the MCB are both major modifications of the production process.

This change produced a structurally distinct version of darbepoetin, which had a reduced sialylation rate, as reported by the MAH and others.[9,25] As the number of sialic acid units may have a significant impact on the behavior of any protein,[26] sialylation may be considered a critical quality attribute.[27,28] Indeed, recombinant human EPO (rHuEPO) isoforms that have quantitative differences in sialic acid contents exhibit different efficacies as a result of differences in serum half-life.[29] In addition, glycopattern modifications can alter the immunogenicity of rHuEPO.[30] In view of the potential clinical impact of the altered glycopattern in the new darbepoetin version, additional studies to compare the functions of the pre- and the post-change versions of Aranesp®, as well as a bioequivalence trial in healthy individuals,[16] were undertaken. Neither significant functional differences, nor differences in the pharmacokinetic (PK) profile were revealed. A

TABLE 1

FDA, and/or EMA approved indications, and active substance, of the three original biologics extrapolation case-studies.

Original biological product	Active substance	Approved population or indication
Aranesp®	Darbepoetin alfa	– Pediatric and adult patients with symptomatic anemia associated with chronic renal failure – Chemotherapy-induced anemia in adult cancer patients with non-myeloid malignancies
Humira®	Adalimumab	– Adult patients with rheumatoid arthritis – Juvenile polyarticular idiopathic arthritis – Psoriatic arthritis – Ankylosing spondylitis – Adult and pediatric Crohn's disease – Ulcerative colitis – Adult and pediatric plaque psoriasis – Axial spondylarthritis without radiographic evidence of ankylosing spondylitis – Enthesitis-related arthritis – Hidradenitis suppurativa
Herceptin®	Trastuzumab	– HER2-positive metastatic breast cancer – HER2-positive early breast cancer

TABLE 2

Aranesp® case-study. The table highlights a major modification associated with the shift in Aranesp® manufacturing (to serum-free bioreactor technology), the purpose of this change, and the unintended physicochemical consequence that affects the glycopattern in the post-change version of this original biological product. It also summarizes the comparability exercise carried out to unravel essential sameness (post-modification studies). A single safety and efficacy trial was conducted to confirm comparability in adult patients who had symptomatic anemia associated with chronic renal failure (CRF). Approval was also granted by means of extrapolation to two additional patient populations/indications: pediatric patients with symptomatic anemia associated with chronic renal failure, and chemotherapy-induced anemia in adult cancer patients with non-myeloid malignancies.

		Reference (s)
Modification implemented	Major modification: production process change to serum-free bioreactor technology Objective: reduce contamination of the active substance, remove a potential source of infectious agents, and decrease costs	18,24,25
Unwanted impact of the modification	Glycopattern variation: modification of the sialylation rate. The amount of the more highly sialylated isoform decreased by an average of 10%, whereas the less sialylated isoforms increased by 3% and 5%	11,28
Post-modification studies	a) Physicochemical comparability studies. b) Non-clinical studies: – Single-dose pharmacokinetics study in male beagle dogs – A 4-week toxicity study in beagle dogs (PK and immunological) – *In vitro* binding study on frozen sections of human tissues. c) Clinical studies: – Comparative pharmacokinetic study in healthy subjects (n = 48) – Comparative clinical efficacy study in adult patients with symptomatic anemia associated with CRF (n = 446). – Open-label, single-arm clinical safety study in patients with anemia associated with CRF (n = 1127)	18,24,34
Approval involving a trial in patients	– Adult patients with symptomatic anemia associated with CRF	18
Approval through extrapolation (No patient trials conducted)	– Pediatric patients with symptomatic anemia associated with CRF – Chemotherapy-induced anemia in adult cancer patients with non-myeloid malignancies	18

comparative and a non-comparative safety trial in adult patients with CRF confirmed that neither the efficacy nor the safety (including the immunogenicity) of the drug were significantly altered as a result of the new production process.[16,21,31] In spite of the undesired physicochemical divergence in the active substance, the European authorities estimated that the comparability assessment in adult CRF patients was sufficient to also claim high similarity in pediatric patients with anemia associated with CRF and in adult patients with non-myeloid malignancies undergoing chemotherapy, based on the totality of the evidence. The new, non-identical version of Aranesp® was therefore approved by means of extrapolation.

Humira® (adalimumab)

Some major modifications are aimed primarily at changing the way in which a given product is administered in order to increase adherence (for example, by reducing the frequency of administration), reduce the incidence of local adverse reactions, facilitate preparation, or extend the marketing authorization to new indications or populations. Such modifications may involve changes to the excipients, the strength of the product (i.e. the concentration of the active substance), the formulation and/or the delivery device. Even when those modifications unintentionally alter other properties, approval does not necessarily require trials in all the targeted patient populations. Modification of the original biologic Humira® is one such example (summarized in Table 3).

Adalimumab, the active substance in Humira®, is a monoclonal antibody that binds to tumor necrosis factor (TNF)-α and effectively mitigates the inflammatory cascade.[32] Humira® was initially approved in the US and in the EU to treat rheumatoid arthritis (RA) in adult patients.[33–35] Subsequent approvals in adults included use in psoriatic arthritis, ankylosing spondylitis, Crohn's disease, ulcerative colitis, plaque psoriasis, hidradenitis suppurativa, and axial spondylarthritis without radiographic evidence of ankylosing spondylitis (the latter only in the EU). In pediatric patients, adalimumab was approved for the treatment of polyarticular juvenile idiopathic arthritis, Crohn's disease, and, only in the EU, plaque psoriasis and active enthesitis-related arthritis.[36–38] All of those approvals were based on clinical trials in each target population.

In 2015, the manufacturer of Humira® presented a supplemental application for a new formulation, intended to reduce pain associated with injection, that contained a doubled concentration of adalimumab (100 mg/ml) and only two of the eight original excipients.[33,38,39] Notwithstanding the expected benefits, the modifications were considered major. The FDA warned that the new formulation might produce different plasma concentrations of adalimumab, which might change the benefit-to-risk balance.[33] Likewise, an increased strength might foster aggregate formation, as highlighted by Humira®'s MAH itself.[40] Aggregates can alter the delivery of the medicine, modify the PK profile, change the medicine's efficacy and/or safety, and potentiate immunogenicity.[41–43] In light of the warnings, a PK comparison in healthy individuals between the original and the new formulation was considered necessary.[33] The area under the curve (AUC) showed that the new formulation produced a moderate increase overall in exposure to adalimumab.[33,40] Pharmacodynamic (PD) differences between the old and new

TABLE 3

Humira® case study. The table highlights the major modification of the composition of Humira® (formulation and strength), the purpose of this change, and the unintended consequence for the pharmacokinetic profile of the post-change version of this original biological product. It also summarizes the comparability exercise carried out to unravel essential sameness (post-modification studies). A single safety and efficacy trial was conducted in adult patients with rheumatoid arthritis to confirm comparability. Approval was also granted by means of extrapolation to 11 additional patient populations/indications.

		References
Modification implemented	Major modification: formulation/concentration change/device needle Objective: increasing patient comfort through less injection-related pain on the basis of reduced injection volume and removal of some of the excipients in the currently marketed formulation that may contribute to pain sensation.	36,41,42
Unwanted impact of the modification	Pharmacokinetic (PK) variation	36,43
Post-modification studies	a) Chemistry, manufacturing and control comparability data. b) Device functional testing (needle) c) Clinical studies [56,62]: – SD comparative PK study in healthy subjects (n = 200). – SD comparative PK study in healthy subjects (n = 296). – 24-week, randomized, double-blind, PK, pharmacodynamic, safety and immunogenicity comparative study in adult patients with rheumatoid arthritis (n = 100). – 24-week, open-label study in adult patients with rheumatoid arthritis (n = 88). – Two phase 2, randomized, single-blind, crossover studies in adult patients with rheumatoid arthritis (n = 122).	36,42,43
Approval involving a trial in patients	– Adult patients with rheumatoid arthritis	36,42,43
Approval through extrapolation (No patient trials conducted)	– Juvenile polyarticular idiopathic arthritis – Psoriatic arthritis – Ankylosing spondylitis – Adult and pediatric Crohn's disease – Ulcerative colitis – Adult and pediatric plaque psoriasis – Axial spondylarthritis without radiographic evidence of ankylosing spondylitis – Enthesitis-related arthritis – Hidradenitis suppurativa	36,40,41

Humira® versions were also reported.[33] Therefore, a comparative efficacy and safety trial, as well as an open label extension study with the new formulation, were performed in adult patients with RA. Those studies did not reveal any clinical difference between the two product formulations in RA.[33,44,45] Furthermore, no differences in aggregate formation were found.[40] The FDA and the EMA[33,37] determined that the results of the analytical studies and the clinical assessment in RA were sufficient to anticipate equivalence between both versions in indications that had not been specifically tested, even though the development of the original formulation of Humira® had revealed differences in PK and safety across indications.[46] Hence, the observed PK and PD differences upon reformulation did not prevent agencies from approving the new non-identical Humira® version in nine indications on the basis of extrapolation.

Herceptin® (trastuzumab)

Modifications that are broader than those described above may be applied to a biologic with the primary aim of producing an incremental therapeutic gain. A change in the delivery route, for instance, accompanied by dosage adjustments, might be paralleled by unwanted changes. In spite of the magnitude of the variation, authorization may be awarded for indications for which there has been no pre-approval comparative testing in patients; that is, through extrapolation. Herceptin® is a well-documented example (summarized in Table 4).

Trastuzumab, the active substance of Herceptin®, is a humanized monoclonal antibody that binds to human epidermal growth factor receptor 2 (HER2). This receptor is overexpressed on certain tumor cells and trastuzumab inhibits their proliferation.[47] Herceptin® powder formulation was approved for intravenous (IV) infusion to treat HER2-positive metastatic breast cancer (MBC) as monotherapy or in combination with paclitaxel.[48–50] Subsequent extensions of marketing authorizations included adjuvant treatment of HER2-positive early breast cancer (EBC) as a monotherapy or in combination with cytotoxic agents, treatment of HER2-positive MBC in combination with aromatase inhibitor or docetaxel (only in the EU), treatment of HER2-positive metastatic gastric cancer or gastroesophageal junction adenocarcinoma in combination with chemotherapy, and neoadjuvant-adjuvant combination treatment of HER2-positive EBC (only in the EU).[51–53] Each of these approvals relied on a specific clinical efficacy and safety trials.

In 2012, the MAH of Herceptin® applied for approval of a subcutaneous (SC) formulation to be administered as monotherapy or in combination to treat MBC and EBC patients.[51] The SC route has the advantage of being less invasive and requiring a shorter time for administration. In addition, as claimed by the MAH,[54,55] SC administration causes fewer infusion-related reactions, requires less hospital resources, and costs less than IV administration, and therefore was expected to improve patient convenience and compliance. However, as per the relevant guidance,[56,57] a change in the administration route can alter the

TABLE 4

Herceptin® case study. The table highlights the major modification of the manufacturing and composition of Herceptin® resulting from the development of the subcutaneous formulation, the purpose of such development, and the unintended pharmacological consequences uncovered in the subcutaneous (SC) variant of this original biological product. It also summarizes the comparability exercise carried out to unravel essential sameness (post-modification studies). A single safety and efficacy trial comparing the intravenous (IV) and the SC formulation was conducted in HER2-positive early breast cancer (EBC) patients to confirm comparability. Approval was also granted by means of extrapolation to HER2-positive metastatic breast cancer (MBC) and combination therapy in EBC.

		Reference (s)
Modification implemented	Major modification: route of administration change (from IV to SC)/formulation/pharmaceutical form/concentration change Objective: reduce infusion-related reactions, improve the use of hospital resources, and reduce the costs associated with IV administration. All in all, this route was meant to improve patient convenience and compliance.	54,57
Unwanted impact of the modification	– Pharmacokinetic (PK) variation – Adverse events variation – Immunogenicity variation	54,64–66
Post-modification studies	a) Physicochemical comparability studies for active substance and finished medicinal product. b) Physicochemical assays for recombinant human EPO (rHuPH20). c) Non-clinical studies: – Toxicity profile of rHuPH20 in mice and in cynomolgus monkeys. – Kinetics of rHuPH20 in mice. – Repeated dose PK study of rHuPh20 in cynomolgus monkeys. – PK study of subcutaneously administered trastuzumab with rHuPH20 in mice, Göttingen minipigs and cynomolgus monkeys. – SC local tolerance study with trastuzumab formulated with rHuPH20 in rabbits.	54,64,65
Approval involving a trial in patients	– HER2-positive early breast cancer.	58
Approval through extrapolation (No patient trials conducted)	– HER2-positive metastatic breast cancer – HER2-positive early breast cancer (additional combined therapy)	54

benefit-to-risk balance. Indeed, SC administration of biologics has been associated with degradation at the injection site, increased incidence of local adverse reactions, greater inter-individual variability in dosing, and decreased bioavailability, and it is generally considered to be more immunogenic than the IV formulation.[57–59] In addition to the increased concentration of trastuzumab, SC Herceptin®, which was formulated as a solution for injection rather than as a powder, contained L-methionine as a stabilizer and a novel biological excipient, recombinant human hyaluronidase (rHuP20).[47,51,60] The new formulation required a shift from a body-weight-adjusted IV regimen to a fixed-dose SC regimen, with no loading dose required.[47,51] These are substantial changes that may have an impact on the benefit-to-risk balance of any biologic.[11]

In the USA, the subcutaneous variant was not considered to be the same product and was re-named Hylecta®, because according to the FDA, this product contains two active ingredients, trastuzumab and hyaluronidase-oysk.[61] In Europe, the brand name was preserved. In light of the anticipated risks, the MAH supported the application with a comprehensive comparability data package. Analytical, non-clinical, and clinical studies comparing the SC and IV formulations were conducted. In addition, non-clinical studies with the new excipient rHuP20 were performed to supplement the existing knowledge, given that the addition of rHuP20 was considered a major in-product innovation.[51,62,63] The clinical comparability program consisted of one PK study in healthy male volunteers and female patients with HER2-positive EBC to determine the dose of SC trastuzumab that resulted in an exposure comparable to that achieved through IV administration,[54] and one pivotal comparative study (HannaH) in which trastuzumab was administered as a neoadjuvant treatment (in combination with chemotherapy) and as an adjuvant treatment (monotherapy) in patients with HER2-positive EBC.[55] Although the efficacies of the SC and IV formulations were found to be comparable, there were differences at other levels. The SC regimen (a fixed dose every three weeks) resulted in increased systemic exposure to trastuzumab, especially in patients with lower body weight.[51,61–63] Furthermore, immunogenicity and the incidence of serious adverse events were higher in patients that received the SC regimen,[51,61,62] although it was not possible to unequivocally associate these events to the increased exposure. Despite the remaining uncertainty, SC Herceptin® was approved on the basis of the totality of the evidence for all the combination therapies for which IV Herceptin® had been approved. Including adjuvant settings, and patients with MBC. Hence, the conclusion of equivalence between the two formulations of Herceptin® was extrapolated to untested indications on the basis of a consistent scientific rationale.

Lessons learned from extrapolating original biologics

Modifications of the manufacturing or composition of original biologics have had unintended clinical consequences. A well-known example is the unique but dramatic shift in the immunogenicity of epoetin alfa as a result of the replacement of a single excipient.[8] Also, the relocation of manufacturing processes for Erbitux® (cetuximab) resulted in significant PK changes, as noti-

fied in the US prescribing information,[6,7] although it did not result in meaningful differences in efficacy or safety.[64] The potential for the development of thrombotic microangiopathy in a cluster of patients treated with Rebif® (interferon β-1a) after removing albumin from the formulation[4,6] was added to the prescribing information,[65] although it was not possible to unambiguously establish a cause–effect relationship. Likewise, a drift in the glycan expression in some Herceptin® batches was found to affect the antibody-dependent cell-mediated cytotoxicity (ADCC),[3] which in turn impacted the complete response rate.[5,66] In light of the clinical risk associated with major changes, regulators often request comparative studies to inform the approval of the novel biologic versions.[13,15] Although the FDA and EMA have learned lessons from monitoring original biologics, they usually do not provide detailed information about the studies presented to support the approval of post-modified versions. Therefore, a comprehensive integrative bibliographic analysis, primarily looking at information from regulatory sources but also examining information and scientific papers from manufacturers, has allowed the reciprocal connection of data, leading to the construction of a rigorous account of the regulatory decisions and studies behind authorization. One lesson learned is the low sensitivity, and therefore the limited value, of efficacy and/or safety trials in identifying minor differences between versions of a given biologic. Indeed, two versions of a given biomolecule must behave the same way clinically if they share the critical quality attributes shown analytically. The three case studies described here (Aranesp®, Humira®, and Herceptin®) reflect the regulatory thinking, and hence the scientific evidence, behind approvals based on extrapolation.

The FDA, EMA, and other regulatory bodies have provided extensive explanations of the science behind extrapolation.[12,67,68] A study in patients to support a claim of comparability may sometimes be requested by regulators. In these cases, the trial selection and design should be suitable to unravel version-to-version, rather than patient- or disease-related, differences.[69] Further comparative studies in additional indications or populations may not be needed in light of the totality of the comparability evidence. The requirement for studies to determine the comparability of pre- and post-change versions needs to be established on a case-by-case basis.

In the Aranesp® situation, where the modifications were not intended to change the product composition, the new version of the active substance exhibited unwanted physicochemical differences of potential clinical significance. Despite those structural differences, a PK study in healthy volunteers, a comparative efficacy trial in a single indication, and a non-comparative safety trial were sufficient to justify authorization of the non-identical Aranesp® version in unstudied indications. Interestingly, approval through extrapolation was granted despite evidence that the benefit-to-risk balance and/or the PK profile might differ among patient populations or indications.[20,70] The remaining uncertainty was considered insignificant, a decision that has been justified by the performance of the product after the new version reached the market. Likewise, Enbrel®, an original biologic that contains the active substance etanercept was subjected to a change involving a shift to a serum-free bioreactor[71] (Table 5). A significant variation of the glycan profile was observed around the time of the implementation of the new production process,[9] although available information does not allow an unequivocal connection between these two events. According to Enbrel®'s MAH registry of clinical trials, the new version was probably authorized for various indications on the basis of analytical studies and just one non-comparative clinical trial in adult patients with RA.[72–74]

The comparative PK assessment of the two formulations/strengths of Humira® revealed differences that triggered the requirement for a safety and efficacy trial in RA. Subsequent to the trial outcome, in spite of PK differences, the new Humira® version was approved in nine indications by means of extrapolation. Noticeably, in the development of original Humira®, some patients were exposed to higher doses without any consequences for the overall safety profile, which probably contributed to the post-change approval decision. Interestingly, by contrast, a comparative PK study of Erbitux®, another product undergoing a strength modification, raised no concerns, and marketing authorization was granted without the need for an efficacy trial. [75] Similarly, major modifications were made to two original biologics, Xolair® (omalizumab) and Ilaris® (canakinumab), to ease the preparation or the administration of the product, or to reduce the volume injected.[76–81] During the post-modification comparability studies, unintended variations of potential clinical concern were detected (Table 5). However, preclinical and clinical data packages provided reassuring comparability, which formed the basis for the approval of the modified versions of both drugs without the requirement to extend the comparative assessment to all targeted patient populations and indications.

The development of a new route of administration for a biologic is a considerable endeavor, entailing substantial modifications for which some health authorities would require a new marketing authorization.[82] In the case of Herceptin®, those modifications were implemented to shift from IV to SC administration. Notwithstanding the expected benefits, the risks associated with this shift justified the need for an extensive comparative assessment. To gain approval, the MAH of Herceptin® presented a comprehensive, analytical, nonclinical and clinical comparability data package. EMA and Herceptin®'s MAH[51,83] agreed that EBC was the most sensitive population for a comparative trial, given the relatively high homogeneity of inter-patient responses resulting from the drug-free phase following adjuvant treatment. Despite revealing comparable efficacy, the two formulations exhibited differences in their PK and safety profiles, which were possibly attributable to either physicochemical differences or differences in the dosage regimens. Noticeably, the new excipient, rHuP20, was shown to generate anti-hyaluronidase antibodies in patients with EBC.[51,55] In addition, the production of anti-protein antibodies, as per EMA guidance, may vary among indications.[57] Furthermore, during the clinical development of the original IV formulation, the drug displayed differences in safety[51,84] and PK[85] between patients with EBC and with MBC. In spite of those uncertainties, in light of the totality of the evidence, the remaining residual risk was considered acceptable for approval of the SC Herceptin® in MBC with no patient trials involved. Recommended post-authorization studies confirmed the anticipated conclusions.[51,53,86,87] Interestingly, when the same MAH developed an SC variant of the orig-

TABLE 5

Additional cases of the approval through extrapolation of non-identical versions of biological medicines resulting from major changes. The table highlights the patient trials undertaken for the approval of post-manufacturing-change versions of three original biological medicines containing etanercept, omalizumab and canakinumab, all of which had undergone major modifications. It also lists the unintended variations detected as a result of the modification, and the authorized indications for the new modified non-identical version. On average, most of the approved indications were not tested during the comparability assessment of the pre- and post-change products. Approval has been mostly granted through extrapolation. The table also notes the actual unintended impact of the modifications on the quality attributes of the product and on its clinical behavior. The studies required for approval are not extensively made public, so some relevant facts may be missing. In any case, the information provided to the evaluators allowed them to justify approval through extrapolation on the basis of a solid scientific rationale. FMF, familial Mediterranean fever; HIDS/MKD, hyperimmunoglobulin D syndrome/mevalonate kinase deficiency; TRAPS, tumor necrosis factor receptor-associated periodic syndrome. [1]From indirect sources. [2]Variations observed in the initial studies, but not in the definitive studies presented. [3]Cause not reliably identified.

Original biological product	Unwanted impact of modification	Approval involving a trial in patients	Approval through extrapolation (No patient trials conducted)
Enbrel (etanercept)	Change to a serum-free manufacturing process Impact: – Glycan profile variation[1]	– Adult rheumatoid arthritis (no comparability study)	– Polyarticular juvenile idiopathic arthritis in children aged 4 to 17 years – Psoriatic arthritis – Ankylosing spondylitis – Plaque psoriasis in adults
Xolair (omalizumab)	Formulation/pharmaceutical form/concentration/device change Impact: – new Fab fragment identified (initially[2]) – PK variation (initially[2]) – PD variation (initially[2])	- Adult patients with asthma, and/or allergic or perennial rhinitis with elevated serum immunoglobulin E (IgE) levels – Patients (≥12 years) with moderate to severe persistent allergic asthma	– Severe persistent asthma in children from 6 years age – Chronic idiopathic urticaria in adults and adolescents 12 years of age and older
Ilaris (canakinumab)	Formulation/pharmaceutical form change Impact: – Immunogenicity variation[3]	– Adult and pediatric TRAPS – Adult and pediatric HIDS/MKD – Adult and pediatric FMF	– Adult and pediatric (≥2 years) Cryopyrin-associated periodic syndromes – Still's disease (≥2 years) – Systemic juvenile idiopatic arthritis (≥2 years) – Gouty arthritis in adults

inal biologic Mabthera®/Rituxan® (rituximab), regulators determined that the evidence did not support extrapolation, and did not grant authorization for use in the three requested indications.[88] Therefore, extrapolation is not always granted, and needs a thorough scientific justification. In the study cases and examples mentioned in this paper (Aranesp®, Humira®, Herceptin®, Enbrel®, Ilaris® and Xolair®), the post-modification versions were granted a marketing authorization by means of data extrapolation in an average of 68% of the approved indications (Fig. 1). Extrapolation is therefore not a new concept but a well-established scientific principle.

Extrapolation for biosimilars: Building on lessons learned from original biologics

A biosimilar is a biological medicine that is essentially the same as an original reference product as assessed by stringent regulatory standards,[13,69,89] to the extent that they may be considered interchangeable.[90–92] The scientific principles for establishing biosimilarity are the same as those for demonstrating comparability after a change in the manufacturing process or in the composition of an already licensed biological.[93] On the basis of such principles, relying on the totality of the evidence, a conclusion of biosimilarity may be extended to the full range of indications granted to the original reference medicine with no comparative patient trials, given that such trials have intrinsically limited resolution when compared to modern analytics.[13,69,92,94] Indeed, because structure and function are integrally related, extrapolation is between molecules and not between indications.[13]

Although understanding of the science of biosimilarity has increased among HCP, the approval of biosimilars by extrapolation is still subject to an ongoing controversial debate.[95,96] As for pre- and post-change versions of original biologics, studies of essential molecular overlap and equivalent biological activity are the most sensitive approach to detect minute (even clinically meaningless) differences between a biosimilar candidate and the original reference biologic.[89,90] Although analytical comparability may be fairly reassuring on its own, regulatory bodies require additional pre-authorization evidence of similarity. The most sensitive clinical studies for comparing two products include PK equivalence (bioequivalence) preferably in healthy volunteers, PD data when there is an appropriate surrogate marker, and immunogenicity assessment.[97–99] A regulatory filing should contain the data necessary to make a regulatory decision, but not be overbuilt for reasons beyond science. Accordingly, on the basis of experience gained from the monitoring of original biologics, it appears that comparative efficacy and safety trials in patients are generally much less sensitive than analytical comparability in substantiating a claim of high similarity,[100] although

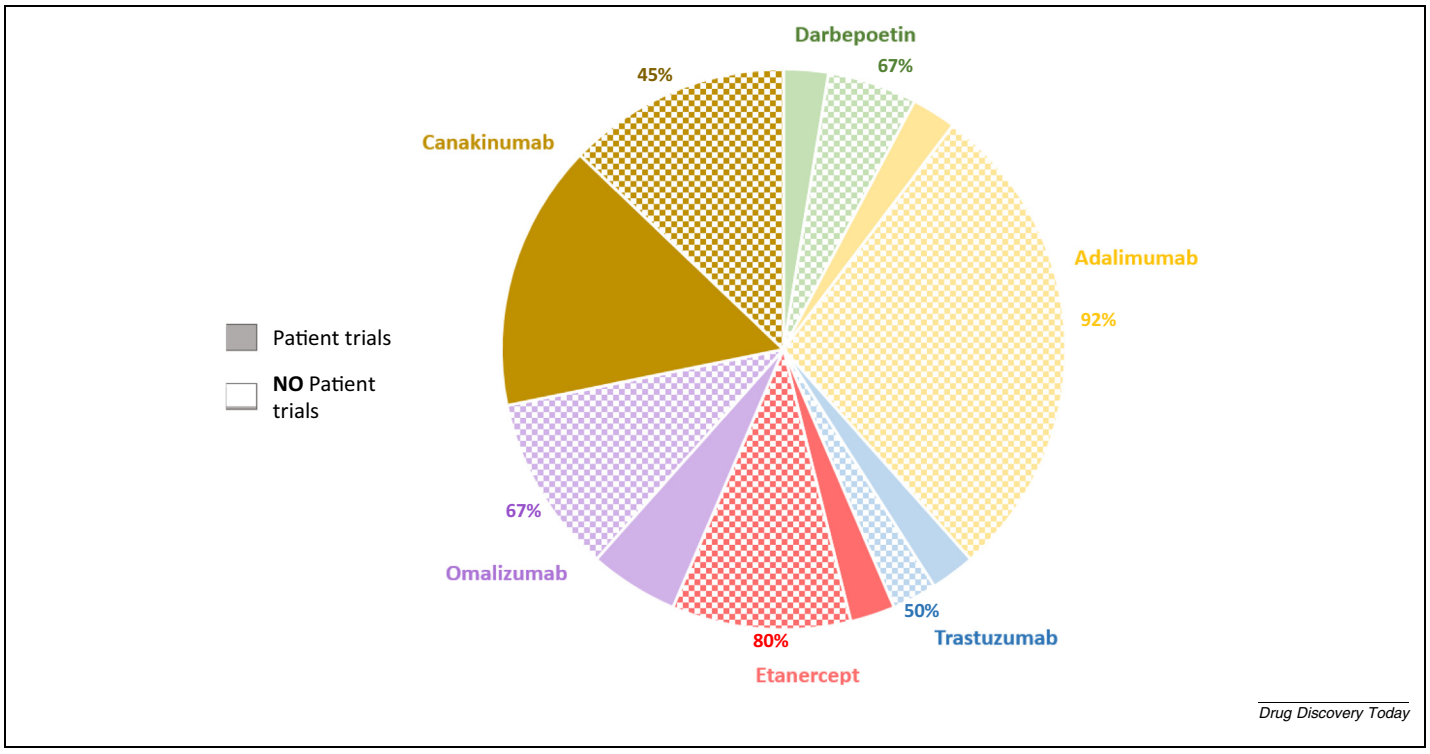

FIGURE 1

Percentage of patient populations in which post-change versions of original biologics were approved with no trials involved. Each color in the chart symbolizes one of six original biological medicines that have been the subject of a manufacturing or composition change. For each medicine/color, the solidly colored area represents the number of patient populations in which a trial was conducted for post-change approval, and the dotted area represents the patient populations in which approval of the post-change version did not involve a patient trial (the relative ratio is stated). The sum of both areas per color represents the overall number of patient populations/indications for which the post-change product was approved. In the six reported cases, approval was granted by means of extrapolation in an average of 67% of the patient populations/indications.

in some cases such confirmatory studies have been requested by authorities on the grounds that they can mitigate a residual risk.[69,91,97,101,102] On those same grounds, in most cases it would be scientifically meaningless, and also ethically questionable, to extend patient comparability studies to all indications.[103] Recently, biosimilar industry representatives and the UK regulatory authority have bluntly questioned the need for patient trials at all, unless exceptionally justified.[96,104] Notwithstanding this current debate, biosimilar products bearing infliximab,[105] rituximab,[106] adalimumab,[107] trastuzumab,[108] bevacizumab,[109] rFSH[110] and others, have been approved in most patient populations through extrapolation. The European model has proven successful,[111,112] and such practice has contributed to add value to biosimilars.[113] Hence, to patients.

In conclusion, approval through extrapolation has been practiced by regulators in the original medicines arena for decades. Despite that, a debate over the risks of extrapolation was created with the arrival of biosimilars. The approval of non-identical versions of original biologics for indications or populations that are not specifically studied during development has been fully justified scientifically, and extensively explained. Real world evidence from post-marketing surveillance has further supported such practice. Likewise, more than fourteen years of experience with biosimilars in the European market supports their efficacy and safety in all approved indications, whether tested during development or authorized on the basis of extrapolation.[13,112,113] This supports the affirmation that biosimilars are at least as safe as any original biologic that has undergone a manufacturing or a composition change. Hence, extrapolation of a conclusion of equivalence among non-identical versions of biological products, whether post-manufacturing batches or biosimilar candidates, reflects the ever-increasing experience of biopharmaceutical companies and regulatory bodies in comparing versions of original biologics. HCP should trust that a modified version of a given biologic is only approved if the active substance, as well as the quality, efficacy, and safety of the pre-change version, are preserved. Noticeably, referring to the original SC Herceptin® case, EMA experts stated that[12] "a formulation difference of this magnitude would not be acceptable for a biosimilar compared with the reference product". Approval of biosimilars by extrapolation should therefore not trigger discomfort among HCP, as it has not caused concerns in the original biologics scenario.

Declaration of Competing Interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: FdeM has worked as speaker or consultant for both companies that develop and/or market biosimilars (Amgen, Biogen, Boehringer, Celltrion, Kern Pharma, Lilly, Novartis, Pfizer, Samsung Bioepis, Sandoz, and Stada) and companies that develop and/or market original biologics (Amgen, Biogen, Boehringer, Lilly, Pfizer, Roche). LFRC declares no competing financial interests or other relationships with other people or organizations that could have appeared to influence the work reported in this paper.

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