Annex 1
Summary of the characteristics and findings of the reviews identified

AUTHOR, YEAR	FUNDING AND CONFLICTS OF INTEREST (COI)	No. AND DESIGN OF STUDIES	DRUGS EVALUATED	CLINICAL AREAS OR INDICATIONS EVALUATED	EFFICACY/EFFECTIVENESS, SAFETY, IMMUNOGENICITY, COSTS	INTERPRETATION AND CONCLUSIONS
DIFFERENT DRUGS, DIFFERENT THERAPEUTIC AREAS						
Barbier et al., 2020[32]	KU Leuven (MABEL Fund). Authors with CoI with pharmaceutical companies	178 studies (n=140 non-randomised real-life studies, n=38 open extension studies of RCTs). n=6 multiple switching, n=0 switching between biosimilars	Somatropin, epoetin, filgrastim, insulin, anti-TNFs (adalimumab, etanercept, infliximab), follitropin, mAbs oncology (rituximab, trastuzumab).	Immune-mediated inflammatory diseases	Simple switching was not associated with any major efficacy, safety or immunogenicity issues. Some studies identified an increased discontinuation rate after switching, which was mainly attributed to a nocebo effect.	
Cohen et al., 2018[33]	No funding. Authors with CoI with pharmaceutical companies	90	Multiple drugs	Immune-mediated inflammatory diseases, CKD, growth alterations, neutropenia, cancer, healthy volunteers	No significant differences in ADAs after switching in comparison with patients who did not switch. No increase in AEs or loss of efficacy related to switching. Multiple switching did not result in significant differences in efficacy or safety. Two studies reported a loss of efficacy or increase in droput rates.	The risk of immunogenicity-related safety concerns or diminished efficacy is unchanged after switching from the reference medicineto the biosimilar.
Inotai et al., 2017[34]	Funded by Egis Pharmaceuticals PLC. Authors linked to Syreon Research Institute, which is funded by Egis Pharmaceuticals PLC	58 (n=12 empirical papers, n=5 systematic reviews, n=41 non-empirical papers)	Multiple drugs	Multiple indications	No additional risk or negative clinical outcomes in patients switching to biosimilars.	Preventing the switch to biosimilars due to anticipated risks seems to be disproportional compared to the expected cost savings and/or improved patients access.
Liu et al., 2019[35]	Funded by AbbVie. Authors with CoI with AbbVie	54 (n=23 budget impact models, simulations, cost studies, n=26 cohort studies, n=3 national database analyses, n=1 interview, n=1 policy review)	Multiple drugs	Multiple indications	Increased healthcare resource utilization in patients with biosimilar non-medical switching	The overall economic impact of biosimilar medicines remains uncertain.
McKinnon et al., 2018[36]	Funded by Medicines Australia and pharmaceutical companies. Authors with CoI with pharmaceutical companies	57 (n=22 RCT, 1 non-RCT, n=34 observational)	Multiple drugs	Multiple indications	The majority of studies did not find statistically significant differences in efficacy. The majority of studies reported a similar safety profile.	There are evidence gaps around safety of switching.
Hillhouse et al., 2022[37]	Funded by AbbVie. Authors with CoI with pharmaceutical companies	49 (n=41 cohort studies, n=2 interviews, n=2 simulations, n=1 post-marketing study, n=3 database studies)	Multiple drugs	Multiple indications	An increased healthcare resource utilization and costs associated with non-medical switching was found when compared with the period prior to switching or with non-switched patients.	It is suggested that the expected overall saving due to the lower price of biosimilars may be reduced due to an increase in healthcare resource utilization and associated costs. The overall economic impact of these medicines in renal clinical practice is uncertain as the majority of studies only consider the cost of these medicines without taking into account other healthcare costs.
SPECIFIC DRUGS OR DRUG GROUPS, DIFFERENT THERAPEUTIC AREAS						
Bakalos, et al., 2019[38]	Medical writing support by F. Hoffmann-La Roche Ltd. The author is employed by F. Hoffmann-La Roche Ltd	14 observational	Infliximab (biosimilar: CT-P13)	Immune-mediated inflammatory diseases	78.6% of the studies reported a biosimilar discontinuation rate >10% (range: 12.2–28.2%). A lack of effect and AEs accounted for biosimilar discontinuation rates ranging from 1.4–28.1% of all patients. Nocebo-related reactions and ADAs were infrequent, and no increase was identified upon switching.	The discontinuation rate after switching, which was higher than expected, may be attributed, in part, to a subjective disease worsening or subjective AEs, which may be indicative of a potential nocebo effect in switching studies.
Ebbers et al., 2019[39]	Funded by Biogen International GmbH. Authors with CoI with Biogen	31 (n=6 journal articles, n=2 journal letters, n=23 congress abstracts). *Naïve* patients and patients with switching	Etanercept (biosimilar: SB4)	Immune-mediated inflammatory diseases	The switch acceptance rate was 51.6–99%. Patient-support programs had a positive effect on acceptance. Disease activity was similar before and after switching (over a 3-month period). A retention rate of at least 75% was identified (up to 12 months of follow-up). The differences in discontinuation rate were attributed to possible differences in treatment practices, lack of clinician confidence and the nocebo effect. No new safety signals were identified.	In general, the experience with switching to the biosimilar was positive, with no loss of efficacy or detriment to safety or tolerability. The results with the biosimilar were similar to those for the reference medicine in naive patients. The evidence shows that the biosimilar etanercept is as effective and safe as the reference medicine in both switched and naive patients.
Feagan et al., 2019[39]	Funded by Janssen Pharmaceuticals. Authors with CoI with pharmaceutical companies	70 (n=13 RCT, n= 53 observational, n=4 case series/reports)	Infliximab (biosimilar: SB2, CT-P13, BOW015)	Immune-mediated inflammatory diseases	No significant risks associated with single switch identified.	The limitations include the fact that the studies available only report simple switching and the majority are observational studies with no control group. The evidence supports the efficacy and safety of simple switching between the reference medicine and biosimilar.
SPECIFIC DRUGS OR GROUPS OF DRUGS, DIFFERENT THERAPEUTIC AREAS						
García-Beloso et al., 2022[40]	No funding. Author with CoI with pharmaceutical company	21 (n=12 RCT/RCT extension studies, 9 observational) No *naive* patients	Adalimumab (biosimilar: ABP501, SB5, FKB327, MSB11022, GP2017, PF-061410293, CTP17)	Chronic immune-mediated inflammatory diseases	The efficacy results in the switching groups were comparable to those obtained in the arms of continuous biosimilar and continuous reference adalimumab. No significant differences in treatment emergent AEs or ADAs or neutralising antibodies were observed among the three groups. Higher incidence of injection site pain in thee switching group.	Switching between reference adalimumab and biosimilars has no impact on efficacy, safety and immunogenicity in patients with rheumatoid arthritis, psoriasis or IBD. This finding is consistent for the different adalimumab biosimilars analysed. The higher incidence of injection pain observed upon switching groups in non-randomised studies may be due to a nocebo effect.
Lauret et al., 2020[41]	No funding or CoI	16 (n=1 RCT, n=5 observational) in patients switching from reference medicine to biosimilar 12 (n=9 RCT, n=3 observational) in patients *naïve* to the biosimilar	Infliximab (biosimilar: CTP-13)	Chronic immune-mediated inflammatory diseases	Frequency of ADAs in switched patients: 4.7%, 95% CI: 3.5–6.1% (no heterogeneity). Frequency of ADAs in patients naive to the biosimilar: observational studies: 21.1%, 95% CI: 13.1–30.3% (heterogeneity); RCT: 30.7%, 95% CI: 18.2–44.9% (heterogeneity).	Immunogenicity was not favoured by non-medical switching to the biosimilar, but was associated with treatment discontinuation.
Liu et al., 2022[17,32]	Funded by AbbVie. Authors with CoI with AbbVie.	66 real-world studies (n=29 full-text articles, n=35 abstracts, n=2 letters to the editor).	Anti-TNF (infliximab, etanercept)	Gastroenterology, rheumatology	The annualized biosimilar discontinuation was 21% (95% CI: 18–25%). The annual switch back rate among switching participants was 14% (95% CI: 10–17%), and 62% (95% CI: 44–80%) among biosimilar discontinuers. The annualized incremental biosimilar discontinuation rate was 18% (95% CI: 4–31%).	Biosimilar discontinuation was found to be prevalent among patients who underwent non-medical switching from the reference medicine to the biosimilar. Switchback to the reference medicine was common following biosimilar discontinuation.
Mezones-Holguin et al., 2019[42]	Authors with CoI with pharmaceutical companies	5 (n=2 RCT, n=3 RCT open-label extension studies)	Infliximab (biosimilar: CTP-13, SB2)	Gastroenterology, rheumatology, dermatology	The two double-blind RCTs did not find differences in efficacy or safety between the group maintained with the reference medicine (IFX ref/IFX ref) (maintenance group) and the group of switching patients (IFX ref/CTP-13) (interchangeability group). The three open-label extension studies did not find differences in efficacy or safety between the maintenance and interchangeability groups. The inclusion of biosimilars implied a saving of S/7.642.780 (1USD=S/3.30).	
Numan et al., 2018[20]	Funded by AbbVie. Authors with CoI with AbbVie.	91 (n=17 RCT, n= 74 real-world evidence studies)	Anti-TNF: Infliximab (biosimilar: CT-P13, SB2, BOW015) Adalimumab (biosimilar: ABP 501, SB5, BI 695501, GP2017, FKB327, CHS-1420) Etanercept (biosimilar: SB4, GP2015)	Immune-mediated inflammatory diseases	Discontinuation rates in RCT: 5–33% switching group vs 4–18% comparison group Discontinuation rate in real-world evidence studies with comparator group: Infliximab: 0–87% Etanercept: 8–17%	The evidence shows heterogeneity and inconclusiveness as regards the efficacy, safety and immunogenicity of switching. The safety and efficacy of switching from the reference anti-TNF medicine to the biosimilar has not yet been fully demonstrated. The decision to switch in patients with a good response should be taken with care and evaluated on a case-by-case basis.
INFLAMMATORY BOWEL DISEASE (IBD)						
Bernard et al., 2020[43]	Funded by Janssen Inc. Authors with CoI with pharmaceutical companies	49 studies (n=40 observational studies, n=3 RCT, n=1 case series)	Infliximab (biosimilar: CT-P13)	IBD	RCTs: -Efficacy: in general, no significant differences. -Safety: no significant differences. -Discontinuation at 52 weeks: 4% in group with reference medicine vs 4% in the switching group (n=1 study). -Immunogenicity: 1 study: 7% new ADAs in group with reference medicine vs 8% in the switching group. Remainder: no significant differences in ADAs.	It was concluded that non-medical switch is safe and effective.
Dipasquale et al., 2022[44]	No funding information. No CoI	9 (n=8 retrospective, n=1 prospective)	Infliximab (biosimilar: CT-P13)	IBD Paediatrics.	No significant differences in clinical response or remission rate were identified after induction or during maintenance with the biosimilar in comparison with the reference medicine (clinical response 86–90%, remission rate 67–68% with biosimilar). AEs with the biosimilar were mild, with upper respiratory tract infections being the most common. Switching to the biosimilar did not have a significant impact on immunogenicity.	
Gisbert et al. 2018[30]	No funding information. Authors with CoI with pharmaceutical companies	25 (n=9 retrospective, 16 prospective)	Infliximab (biosimilar: CT-P13)	IBD	Disease control (no worsening after switching) with the biosimilar was confirmed in the majority of patients (weighted mean 88%; 95% CI: 86–89%) No unexpected AEs were reported in any of the studies. Switching was not associated with immunogenicity concerns.	The risk of switching seems to be purely theoretical and are not supported by the (still) limited) real-world clinical practice experience. Switching may be considered acceptable. In any case, switching should only be considered once the disease is well controlled with the reference medicineduring a sufficient time.
INFLAMMATORY BOWEL DISEASE (IBD)						
Milassin et al., 2019[45]	Public funding. No CoI	29	Infliximab (biosimilar: CT-P13)	IBD	The biosimilar was found to be safe and equally efficient as the reference medicine for both induction and maintenance therapy, with no loss of response being found. Switching from the reference medicine to the biosimilar was noninferior to continuous biosimilar use. Switching from the reference medicine to the biosimilar did not affect the efficacy, safety or immunogenicity in comparison with continuous biosimilar use.	Switching is acceptable, although scientific and clinical evidence is lacking regarding reverse switching, multiple switching and cross-switching among biosimilars.
Solitano et al., 2020[8]	No funding. Authors with CoI with pharmaceutical companies	15 (n=2 retrospective, n=5 retrospective)	Infliximab (biosimilars: CT-P13, SB2) Adalimumab (biosimilars: BI 695501, Exemptia, SB5, ABP 501)	IBD	A high similarity between the reference medicines and biosimilars was found, with the efficacy, safety and immunogenicity of reference infliximab medicine and its biosimilar being comparable. The evidence regarding adalimumab biosimilars in IBD is limited.	Adoption of biosimilars in clinical practice represents a great opportunity from an economic point of view, reducing healthcare costs and increasing patients' access to effective biologic treatments.
Queiroz et al., 2020[18]	No funding. Authors with CoI with pharmaceutical companies	30 observational	Infliximab (biosimilars: CT-P13, SB2)	IBD	The discontinuation rates were 8%, 14% and 21% at 6, 12 and 24 months, respectively. The main reasons for discontinuation were worsening of the disease (2%), remission (4%), loss of adherence (4%), AE (5%), loss of response (7%). The subjective symptoms that led to discontinuation of the biosimilar were infrequent.	The discontinuation rates following a switch to a biosimilar increased with time. It was not possible to confirm the nocebo effect as a reason for discontinuation.
RHEUMATOID ARTHRITIS (RA)						
Yoo et al., 2018[21]	No funding. Authors with CoI with pharmaceutical companies	35 (n=17 RCT extension studies, n=1 RCT, n=17 real-word observational studies)	Infliximab (biosimilars: CT-P13, SB2) Etanercept (biosimilar: GP2015, SB4) Adalimumab (biosimilar: ABP 501, BI 695501, SB5, FKB327, GP2017, CHS-1420) Rituximab (biosimilar: CT-P10, GP2013, BCD-020)	RA	Switching was safe and effective in the majority of studies. Real-world data showed a slightly lower retention rate for switched biosimilars. Most discontinued patients have shown no objective clinical or biological evidence supporting inefficacy, therefore this small difference in discontinuation might be associated with a possible nocebo effect or other confounding factors.	A fear of biosimilars or their immunogenicity is often exaggerated and is based on small studies and theoretical worries rather than on solid evidence.
ONCOLOGY						
Declerck et al., 2018[46]	No funding information. Authors with CoI with pharmaceutical companies	8 (n=5 randomised, n=3 non-randomised)	Rituximab (biosimilar: CT-P10, GP2013, PF- 05280586, BCD-020) trastuzumab (biosimilar: ABP 980)	Cancer, RA		The consequences of switching between the reference medicine and the biosimilar in the oncology setting are yet unknown.
SWITCHING BETWEEN BIOSIMILARS						
Allocati et al., 2022[22]	No funding information. No CoI	19 observational (n=10 cohort studies; n=8 single-arm studies; n=1 studies with historical control)	Switching between anti-TNF biosimilars (infliximab, adalimumab, etanercept)	Immune-mediated inflammatory diseases	Switching between one biosimilar and another and multiple switching is safe and effective in terms of disease activity, remission rate, loss of response, AEs and immunogenicity. Switching did not result in a change in immune response, exhibiting similar ADA levels.	
Cohen et al., 2022[23]	Funded by Novartis Pharma AG. Authors with CoI with pharmaceutical companies	23 Observational studies. Switching between biosimilars	Anti-TNF, rituximab	Immune-mediated inflammatory diseases, cancer	No reduction in effectiveness or increase in AEs was detected in biosimilar-to-biosimilar switching.	Biosimilar-to-biosimilar switching is considered to be safe and effective.
REVERSE SWITCHING						
Meijboom et al., 2022[24]	No funding. No CoI	37 (n=36 cohort studies, n=1 case series)	Anti-TNFα (etanercept, infliximab, adalimumab), multiple drugs	Gastroenterology, rheumatology, multiple indications	The weighted median cumulative incidence of retransitioning was 7.6% (95% CI: 6.8–17.2%). The incidence of retransitioning was lower when extra laboratory monitoring was performed (1.6% vs 6.1%).	Retransitioning was lower in studies including only patients with stable disease, in studies that did not offer the option of retransitioning at the introduction of the biosimilar, and in studies that implemented extra laboratory monitoring as part of the biosimilar-implementation strategy.
NOCEBO EFFECT						
Odinet et al., 2018[26]	No funding. No CoI	31 studies (n=4 double-blind RCT, n=27 open-label observational)	Infliximab, etanercept	Gastroenterology, rheumatology, dermatology, multiple diseases	The median discontinuation rate for any reason was 14.3% (range: 0–33.3%) in open-label studies vs 6.95% (range: 5.2–11.0%) in double-blinded studies. The discontinuation rate for AEs was 5.6% (range: 0–24.2%) in open-label studies vs 3.1% (range: 2.0–5.2%) in double-blinded studies, suggesting a nocebo effect. Subgroup analyses of ADA development and infusion reactions were similar in open-label and double-blinded studies. Infliximab: the discontinuation rates for any reason, for AEs and for lack of efficacy of the biosimilar were higher in open-label studies than in double-blinded studies. Etanercept: the discontinuation rate for any reason for the biosimilar was similar in open-label and double-blinded studies. The incidence of injection site reactions and discontinuation rate for AEs were higher in the double-blinded than in the open-label studies.	Current evidence is insufficient to confirm a biosimilar nocebo effect, although higher discontinuation rates in open-label studies support this theory.

ADA Anti-drug antibody
AE Adverse event
anti-TNF Anti-tumour necrosis factor
CoI Conflicts of interest
CI Confidence interval
CKD Chronic kidney disease
IBD Inflammatory bowel disease
IFX Infliximab
mAbs Monoclonal antibodies
RA Rheumatoid arthritis
RCT Randomised controlled trial