

TCH-012 DIFFERENCES IN PURITY BETWEEN BIOSIMILAR FILGRASTIMS AND COPY BIOLOGICAL FILGRASTIMS

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Background Biosimilars are follow-on versions of peptide biological drugs, and differences in manufacturing and formulation can result in variations in physicochemical and clinical profiles. The European Medicines Agency (EMA) has set stringent standards (Ph Eur) that must be met for the approval of a biosimilar.

Purpose Standards of manufacture may differ between biosimilars approved via EMA pathways, and copy biologicals that lack approval pathways. Therefore, we undertook comparative characterisation tests of a range of biosimilar products from different global regions to determine if variations exist. This study is the first of its kind.

Materials and Methods Samples of Nivestim (Ni), Neupogen (Ne), Tevagrastim (T), Ratiograstim and Zarzio (Z) were obtained from the EU region; and Leucostim (L), GeSysin (G), Filgen (F) and Neukine (Nk) were obtained from the Middle East and Africa (MENA) region. All samples were within the expiry date. Samples were analysed for impurities using iso-electric focussing (IEF) to identify differences in charge, size-exclusion high-performance liquid chromatography (SEC-HPLC) to identify differences in higher molecular weight impurities, reverse phase HPLC (RP-HPLC) to identify differences in total and individual related impurities, and ion chromatography (IC) to detect differences in f-met filgrastim and related, more acidic, impurities.

Results All biosimilars met EMA standards for IEF and SEC-HPLC analysis. Total impurities (RP-HPLC) for the EU products were in the range 1.8–2.6% and within EMA requirements ($\leq 3.5\%$); however, the MENA samples contained impurities in the range 5.9% (G) – 8.2% (L), which is beyond the Ph Eur range. IC analysis revealed f-met and acidic impurities to be $<0.20\%$ for most EU products (threshold 1.0%) and 0.4% for Ne. However, for MENA compounds, these impurities comprised 0.4% (Nk) – 1.7% (G) of the samples.

Conclusions Copy biologicals from MENA have higher levels of impurities than biosimilars from the EU and do not meet EMA standards for approval.

No conflict of interest.

TCH-013 DISINFECTANT EFFICACY OF ULTRAVIOLET LIGHT IRRADIATION IN AN AUTOMATED SYSTEMS FOR THE ASEPTIC COMPOUNDING.

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Background Ultraviolet (UV) light irradiation is used in a variety of applications, such as food, air and water purification. The mechanism of UV disinfection differs considerably from chemical disinfectants: UV is mutagenic to bacteria, viruses and other microorganisms by damaging nucleic acids and preventing replication. However, the effectiveness of UV disinfection depends on a number of factors: time of UV exposure; power of the UV source; presence of UV barriers like airborne particles; microorganism resistance.

Purpose To study the effectiveness of UV disinfection inside APOTECACHemo, the robot for preparing antitumour drugs in use at the University Hospital of Ancona. The Killing Rate (KR) and optimal exposure time were determined.

Materials and Methods 5 different microorganisms were chosen for the study in order to cover all the most common families of microbes: *Candida albicans*; *Escherichia coli*; *Bacillus subtilis*; *Staphylococcus aureus*; *Pseudomonas aeruginosa*. Different concentrations of each organism (from 107 CFU/ml to 0.5 CFU/ml) were subjected to UV radiation for different exposure times. The plates were located inside the APOTECACHemo compounding room, using the robot's UV equipment. The KR (logarithmic ratio of the concentration of microorganisms after and before irradiation) was plotted against the exposure time in order to chart the inactivation curves.

Results With a four-hour exposure, the UV irradiation kills all microorganisms at the highest concentrations. The location of the plates inside the system showed only a slight effect on the killing rate, probably thanks to the mirror effect of the stainless steel surfaces. *Bacillus subtilis* confirmed the strongest UV resistance, indeed 4-hour exposure was necessary to kill 107 CFU/ml. The least resistant microorganism was *Escherichia coli*, which required 2 hours of UV irradiation.

Conclusions UV radiation is a fundamental step in the sterilisation of workplaces. In fact, 4-hour exposure showed an effective sterilisation (KR < 7) outcome, even for very resistant microorganisms (*Bacillus subtilis*).

No conflict of interest.

TCH-014 EVALUATION OF LONG-TERM BIOLOGICAL ACTIVITY OF INFLIXIMAB 10 MG/ML AND 5 MG/ML IN NaCl 0.9% BY ELISA

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Background Tumour necrosis factor alpha (TNF- α) is a pro-inflammatory cytokine, the main mediator in inflammatory and autoimmune diseases, as well as during various attacks on cells such infections. It is therefore involved in the course of a large number of pathologies such as rheumatoid arthritis, Crohn's disease, psoriatic arthritis, ankylosing spondylitis, plaque psoriasis and ulcerative colitis. Infliximab (Remicade) is a chimeric monoclonal antibody (75% human, 25% murine) which acts by binding to TNF- α and blocking its effect. The cost of treatment with infliximab is quite high and the stability indicated by the manufacturer once the vial is opened is 24 hours.

Purpose The purpose of this research has been to evaluate the biological activity of infliximab when reconstituted and diluted to 10.0 mg/ml and 5.0 mg/ml in NaCl 0.9% in a long term stability study up to 15 days. A study of the drug degradation has been also tackled to cheque any remaining activity.

Materials and Methods An indirect non-competitive ELISA immunoassay was developed based on the use of ELISA plates sensitised with TNF- α . The plates were incubated 'overnight' at 4°C using recombinant TNF- α from *E. Coli* at a concentration of 1 μ g/ml. The immunoassay was validated in terms of calibration function (from 0.2 to 50.0 μ g/ml), detection limit (0.06 μ g/ml), precision as within-day reproducibility (relative standard deviation lesser than 10%), and accuracy as percentage of recovery (higher than 90%). The infliximab solutions of 10.0 mg/ml and 5.0 mg/ml in NaCl 0.9% were stored refrigerated at 4°C protected from daylight. The biological activity of these solutions was tested periodically up to 15 days by the ELISA method developed. The ELISA was also used to study the drug degradation in a stress study involving the exposure of samples of infliximab (50.0 mg/ml) for 24 hours to different stress conditions: basicity (NaOH 0.1M), acidity