Large-scale manufacturing of GMP-compliant anti-EGFR targeted nanocarriers: Production of doxorubicin-loaded anti-EGFR-immunoliposomes for a first-in-man clinical trial

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Abstract

We describe the large-scale, GMP-compliant production process of doxorubicin-loaded and anti-EGFR-coated immunoliposomes (anti-EGFR-ILs-dox) used in a first-in-man, dose escalation clinical trial. 10 batches of this nanoparticle have been produced in clean room facilities. Stability data from the pre-GMP and the GMP batch indicate that the anti-EGFR-ILs-dox nanoparticle was stable for at least 18 months after release. Release criteria included visual inspection, sterility testing, as well as measurements of pH (pH 5.0–7.0), doxorubicin HCl concentration (0.45–0.55 mg/ml), endotoxin concentration (<1.21 IU/ml), leakage (<10%), particle size (Z-average of Caelyx 20 nm), and particle uptake (uptake absolute: >0.50 ng doxorubicin/mg protein; uptake relatively to PLD: >5 fold). All batches fulfilled the defined release criteria, indicating a high reproducibility as well as batch-to-batch uniformity of the main physico-chemical features of the nanoparticles in the setting of the large-scale GMP process. In the clinical trial, 29 patients were treated with this nanoparticle between 2007 and 2010. Pharmacokinetic data of anti-EGFR-ILs-dox collected during the clinical study revealed stability of the nanocarrier in vivo. Thus, reliable and GMP-compliant production of anti-EGFR-targeted nanoparticles for clinical application is feasible.

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