ON THE “FATE OF LEACHABLES” IN BIOPHARMACEUTICAL UP-STREAM AND DOWN-STREAM PROCESSES

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Single use systems (SUS), based on polymeric materials, are widely used in the biopharmaceutical manufacturing. Compounds potentially migrating from the polymeric materials into the production process at various stages as leachables can either negatively influence the production process performance (e.g. inhibit cell growth) or can contribute to process related drug impurities, which may potentially have an effect on product quality and/or patient safety.

Today, the concept of investigating leachables is mainly focused on the measurement of extractables under worst case- or simulation-conditions plus their assessment including an interpolation towards potential leachables. In particular, in the frame of this assessment of leachables, substance specific properties and the effective process conditions are not taken into account.

To better understand the range, the load and the concentration of leachables within a dynamic process and finally in a drug product a paradigm change towards the “Fate of Leachables” concept is required. This “Fate of Leachables” concept is based on underlying physical-chemical principles rather than a sequence of worst-case experiments and conservatively adding up concentrations. Relevant levels of leachables can be quantitatively modeled and predicted based on the knowledge of potential extractables in the materials, their phys.-chem. properties and the effective process conditions (medium composition, volume, flow, surfaces, temperature), i.e. Leachables may reach equilibrium concentration in certain static process steps, whereas in dynamic process steps diffusion controlled leachables levels have to be anticipated and appropriately modeled. Adsorption and desorption processes significantly influence the levels of leachables in any biopharmaceutical manufacturing, e.g. in down-stream filtration, separation and purification steps. Ultrafiltration and diafiltration steps can influence the leachables load by diluting or removing them completely. For all these process steps illustrative examples from SSB research studies and based on existing published data will be discussed together with a quantitative description of the underlying physical-chemical processes to demonstrate the capability of the “Fate of Leachables” concept. To motivate the use of the “Fate of Leachables” concept, for a generic process stream, the level of leachables estimated via a worst case evaluation will be compared with the results based on the “Fate of Leachables” concept.