expander tube is reported in EP 0 204 836. A combination of at least two membrane filter units of different membrane material and different filter pore size and filter pore geometries is reported in DE 3 818 860.

Aldington et al. (J. Chrom. B 848 (2007) 64-78) report a scale-up of monoclonal antibody purification processes. In CS 247484 a method of preparing immunoglobulin against human lymphocytes is reported.

Summary ~~of the Invention~~

It has been found that a combination of two filters each comprising a pre-filter and a main-filter and each with a specifically selected pore size can be used to filter highly concentrated immunoglobulin solutions during the final packaging step without the risk of pore blocking and the need to replace the filter during the filtration process.

There is provided ~~One aspect as reported herein is~~ a method for the preparation of an immunoglobulin solution comprising the following steps

a) providing an immunoglobulin solution with a protein concentration of at least 100 g/l,

b) filtering the immunoglobulin solution through a combination of a first and second filter, whereby the first filter comprises a pre-filter with a pore size of 3.0 µm and a main-filter with a pore size of 0.8 µm and the second filter comprises a pre-filter with a pore size of 0.45 µm and a main-filter with a pore size of 0.22 µm, and thereby preparing an immunoglobulin solution.

In a first aspect, there is provided a method for producing an immunoglobulin solution comprising a) providing an immunoglobulin solution with a concentration of at least 100 g/l, b) applying the immunoglobulin solution to a combination of a first and second filter unit, whereby the first filter unit comprises a pre-filter with a pore size of 3.0 µm and a main-filter with a pore size of 0.8 µm and the second filter unit comprises a pre-filter with a pore size of 0.45 µm and a main-filter with a pore size of 0.22 µm with a pressure of from 0.1 to 4.0 bar, and thereby producing an immunoglobulin solution.

There is also provided~~Another aspect as reported herein is~~ the use of a filter combination as reported herein of a combination of a first and second filter, whereby the first filter comprises a pre-filter with a pore size of 3.0 µm and a main-filter with a pore size of 0.8 µm and the second filter comprises a pre-filter with a pore size of 0.45 µm and a main-filter with a pore size of 0.22 µm, for the final filtration of an immunoglobulin solution prior to active pharmaceutical ingredient preparation.

There is also provided~~Another aspect as reported herein is~~ a method for producing an immunoglobulin comprising the following steps

a) providing a cell comprising a nucleic acid encoding the immunoglobulin,

b) cultivating the cell,

c) recovering the immunoglobulin from the cell or the cultivation medium,

d) purifying the immunoglobulin with one or more chromatography steps and providing an immunoglobulin solution, and

e) filtrating the immunoglobulin solution of step d) through a combination of a first and second filter, whereby the first filter comprises a pre-filter with a pore size of 3.0 µm and a main-filter with a pore size of 0.8 µm and the second filter comprises a pre-filter with a pore size of 0.45 µm and a main-filter with a pore size of 0.22 µm, and thereby producing an immunoglobulin.

In a second aspect, there is provided a method for producing an immunoglobulin comprising the following steps a) cultivating a cell, comprising a nucleic acid encoding the immunoglobulin b) recovering the immunoglobulin from the cell or the cultivation medium, c) purifying the immunoglobulin with one or more chromatography steps, and providing an immunoglobulin solution, d) optionally adding a sugar, an amino acid and/or a detergent to the solution, e) concentrating the immunoglobulin solution to a concentration of 100 g/l or more with a method selected from diafiltration or tangential-flow filtration, and f) applying the immunoglobulin solution of the previous step to a combination of a first and second filter unit, whereby the first filter unit comprises a pre-filter with a pore size of 3.0 µm and a main-filter with a pore size of 0.8 µm and the second filter unit comprises a pre-filter with a pore size of 0.45 µm and a main-filer with a pore size of 0.22 µm with a pressure of from 0.1 to 4.0 bar, and thereby producing an immunoglobulin.

There is also provided~~A further aspect as reported herein is~~ a kit comprising a first filter comprising a pre-filter with a pore size of 3.0 µm and a main-filter with a pore size of 0.8 µm and the second filter comprising a pre-filter with a pore size of 0.45 µm and a main-filter with a pore size of 0.22 µm. In a third aspect, there is provided a kit comprising a first filter with a pore size of from 3.0 µm to 0.8 µm and a second filter with a pore size of from 0.45 µm to 0.22 µm.

In one embodiment the first filter has an area that is at most twice the area of the second filter. In another embodiment the first and second filter have about the same total filter area. In an embodiment the immunoglobulin solution comprises a sugar, and/or an amino acid, and/or a surfactant, and/or a salt. In a further embodiment the immunoglobulin solution has a concentration of from 100 g/l to 300 g/l. In still another embodiment the immunoglobulin solution has a volume of from 3 liter to 100 liter. In a further embodiment the filtrating is with an applied pressure of from 0.1 bar to 4.0 bar. In one embodiment the immunoglobulin solution has a concentration of 160 g/l or more and the filtrating is with an applied pressure of 1.45 bar or more. In a further embodiment of 1.50 bar or more. In another embodiment the immunoglobulin solution comprises a sugar and a surfactant and has a concentration of 125 mg/ml or more and the filtrating is with an applied pressure of 0.75 bar or less. In a further embodiment of 0.7 bar or less.

In one embodiment the immunoglobulin is an anti-IL13 receptor alpha antibody or an anti-HER2 antibody. In a further embodiment the purifying is with a protein A affinity chromatography step and at least one step selected from cation exchange chromatography, anion exchange chromatography, and hydrophobic interaction chromatography.

Detailed Description of the Invention

It has been found that a combination of two filters or filter units each comprising a pre-filter and a main-filter and each with a specifically selected pore size can be used to filter highly concentrated and viscous, as well as formulated