

significantly from batch to batch. At the same time one or more excipients need to be present in certain concentrations in the final composition to form a stable formulation. Said excipients may or may not be present at all in the initial liquid drug substance (LDS) or may or may not be present in the final concentration in the initial liquid drug substance (LDS). Such excipients are considered as adjustable excipients. Final pharmaceutical compositions according to this disclosure are initially liquid but may subsequently be dried, e.g. by lyophilization.

[0005] Thus manufacturing the final liquid pharmaceutical composition (LPC) from the initial liquid drug substance (LDS) requires adjusting several concentrations and in particular requires adjusting the concentration of the active agent based on significantly varying source concentrations. This leads to a highly variable batch mixing process. There is thus a need for an effective batch mixing process that minimizes process variables (batch to batch variables) despite batch to batch variable active agent starting materials.

15 OBJECTS AND SUMMARY

[0006] It is an object of the present disclosure to provide a batch mixing process for preparing a liquid pharmaceutical composition (LPC) with a target concentration of at least one biological active agent and a target concentration of at least one adjustable excipient, wherein the LPC is prepared from one or more liquid drug substances (LDS) with a concentration of one biological active agent that may vary from batch to batch.

[0007] The present disclosure also relates to pharmaceutical compositions obtained or obtainable by said process and to the use of such pharmaceutical compositions, in a method of treatment or prevention.

25 [0008] The above objects are achieved by examples of the present disclosure as described and claimed herein.

[0009] In one aspect, the present disclosure is, therefore, directed to a batch mixing process for preparing a liquid pharmaceutical composition (LPC) comprising at least one biological active agent and at least one adjustable excipient, wherein the at least one biological active agent has a target concentration in the LPC ($T[A_i]_{LPC}$) and the at

least one adjustable excipient has a target concentration in the LPC ($^T[E_x]_{LPC}$), the process comprising at least two steps:

step 1: providing

5 a variable excipient liquid (VEL) comprising the at least one adjustable excipient at a predefined concentration ($^P[E_x]_{VEL}$),

one or more liquid drug substances (LDS) comprising one biological active agent at a variable concentration ($^V[A_i]_{LDS}$) and the at least one adjustable excipient at a predefined concentration ($^P[E_x]_{LDS}$), and

10 a fixed excipient liquid (FEL) comprising the at least one adjustable excipient at a predefined concentration ($^P[E_x]_{FEL}$), wherein the predefined concentration of each of the adjustable excipients is defined in accordance with equation 1:

$$^P[E_x]_{VEL} = ^P[E_x]_{LDS} \neq ^P[E_x]_{FEL}, \quad (1)$$

wherein $^P[E_x]_{LDS}$ is predefined by the process of manufacture of LDS and $^P[E_x]_{FEL}$ is further defined by the conditions of step 2

step 2: combining

15 all of the LDSs each at a variable volume ($^V V_{LDS(i)}$),

the VEL at a variable volume ($^V V_{VEL}$), and

the FEL at a predefined volume ($^P V_{FEL}$),

to form the LPC with a target volume ($^T V_{LPC}$) and with a target concentration of all of the biological active agents and all of the adjustable excipients, wherein

20 the variable volume of each LDS is defined according to equation 2:

$$^V V_{LDS(i)} = \frac{^T[A_i]_{LPC}}{^V[A_i]_{LDS}} \times ^T V_{LPC}, \quad (2)$$

the combined total volume of all LDSs ($^V V_{LDS(total)} = \sum_{i=1}^{\infty} V_{LDS(i)}$) and the VEL is predefined ($^P V_{(VEL+LDS)}$), and the variable volume of the VEL is defined according to equation 3:

$$v_{VEL} = p_{V_{(VEL+LDS)}} - v_{LDS(total)}, \quad (3)$$

and the predefined volume of the FEL ($p_{V_{FEL}}$) is defined according to equation 4:

$$p_{V_{FEL}} = T_{V_{LPC}} - p_{V_{(VEL+LDS)}}, \quad (4)$$

and the pre-defined concentration of each of the adjustable excipients in the FEL is defined according to equation 5:

$$p_{[E_x]_{FEL}} = \frac{T_{[E_x]_{LPC}} \times T_{V_{LPC}} - p_{V_{(VEL+LDS)}} \times p_{[E_x]_{VEL}}}{p_{V_{FEL}}} \quad (5)$$

[0009a] In another aspect, the present disclosure provides a batch mixing process for preparing a liquid pharmaceutical composition (LPC) with a predefined target volume ($T_{V_{LPC}}$), comprising (a) at least one adjustable excipient, wherein the at least one adjustable excipient has a target concentration in the LPC ($T_{[E_x]_{LPC}}$), and (b) four biological active agents A_1 , A_2 , A_3 and A_4 , wherein said four biological active agents are

- dengue serotype 1 (dengue-1)
- dengue serotype 2 (dengue-2)
- dengue serotype 3 (dengue-3)
- dengue serotype 4 (dengue-4)

and wherein each biological active agent has a target concentration in the LPC ($T_{[A_1]_{LPC}}$, $T_{[A_2]_{LPC}}$, $T_{[A_3]_{LPC}}$, $T_{[A_4]_{LPC}}$), wherein said batch mixing process comprises the following steps: (i) providing four liquid drug substances (LDS), each LDS comprising a biological active agent at variable concentration ($v_{[A_1]_{LDS1}}$, $v_{[A_2]_{LDS2}}$, $v_{[A_3]_{LDS3}}$, $v_{[A_4]_{LDS4}}$) (ii) combining variable volumes ($v_{V_{LDS(i)}}$) of the four LDSs together making a combined total volume of all LDSs according to equation 6:

$$v_{V_{LDS(total)}} = v_{V_{LDS(1)}} + v_{V_{LDS(2)}} + v_{V_{LDS(3)}} + v_{V_{LDS(4)}} \quad (6)$$

and either subsequently to step (ii) or simultaneously with step (ii); (iii) combining an intermediate liquid (IL) at a variable volume ${}^vV_{IL}$, with said combined total volume of all LDSs ${}^vV_{LDS(total)}$ to generate the LPC; wherein said batch-mixing process is characterised in that

- 5 • the variable volume (${}^vV_{LDS(i)}$) of each of the four LDSs is defined in accordance to equation 2:

$${}^vV_{LDS(i)} = \frac{{}^T[Ai]_{LPC} \times {}^T V_{LPC}}{{}^v[Ai]_{LDS(i)}} \quad (2)$$

- the variable volume of intermediate liquid (IL) ${}^vV_{IL}$ is calculated by subtracting the calculated combined total volume of all LDSs to be combined in step (ii) from the predefined target volume of the LPC according to the equation 3:

$${}^vV_{IL} = {}^T V_{LPC} - {}^vV_{LDS(total)} \quad (3)$$

- 10 • the IL is made by mixing a predefined volume of a fixed excipient liquid (FEL) ${}^pV_{FEL}$ with a variable volume of variable excipient liquid (VEL) ${}^vV_{VEL}$, said variable volume of VEL being calculated by subtracting the predefined volume of the FEL from the calculated variable volume of IL ${}^vV_{IL}$ according to the equation 4:

$${}^vV_{VEL} = {}^vV_{IL} - {}^pV_{FEL} \quad (4)$$

- 15 wherein the adjustable excipient(s) in the VEL are at the same concentration(s) as the adjustable excipient(s) in the combined total volume of all LDSs.

[0010] In one example, the target concentration of the at least one biological active agent in the LPC (${}^T[Ai]_{LPC}$) and the target concentration of the at least one adjustable excipient in the LPC (${}^T[E_x]_{LPC}$) are predefined. The (${}^T[Ai]_{LPC}$) and (${}^T[E_x]_{LPC}$) of the LPC
20 do not change from batch to batch, i.e. they are constant. They are chosen at appropriate target values for the desired LPC.

[0011] It is in the nature of the disclosure that the concentration of the at least one adjustable excipient in the VEL (${}^p[E_x]_{VEL}$), LDS (${}^p[E_x]_{VEL}$) and FEL (${}^p[E_x]_{FEL}$) are predefined and are in accordance with equation 1 above.

[0012] The concentration of the at least one adjustable excipient in the FEL ($^P[E_x]_{FEL}$) is predefined in accordance with the predefined concentrations of the at least one adjustable excipient in the VEL/LDS and the target concentration of the at least one adjustable excipient in the LPC ($^T[E_x]_{LPC}$). Once the concentrations have been
5 determined for the particular example, they are constant and do not change from batch to batch.

[0013] The target volume of the LPC ($^TV_{LPC}$) is chosen according to the appropriate target volume for the desired LPC. It may be for example chosen based on the maximum volume of a vessel used in the batch mixing process. Furthermore, the
10 predefined volume of the FEL ($^PV_{FEL}$) is chosen in accordance with the chosen target volume of the LPC. In one example, $^PV_{FEL}$ is smaller than $^TV_{LPC}$. In a preferred example, $^PV_{FEL}$ is at least 10% of $^TV_{LPC}$.

[0014] In a preferred example, the target volume of the LPC according to the disclosure can also be expressed as:

$${}^TV_{LPC} = {}^PV_{FEL} + {}^vV_{VEL} + {}^vV_{LDS(total)}, \text{ wherein } {}^vV_{LDS(total)} = \sum_{i=1}^{\infty} V_{LDS(i)}.$$

[0015] Accordingly, the volume of the sum of ${}^vV_{VEL} + {}^vV_{LDS(total)}$ is also predefined. Furthermore, the predefined volume of the sum of ${}^vV_{VEL} + {}^vV_{LDS(total)}$ is chosen in accordance with the chosen target volume of the LPC. In one example, the sum of ${}^vV_{VEL} + {}^vV_{LDS(total)}$ is smaller than ${}^TV_{LPC}$. In a preferred example, the sum of ${}^vV_{VEL} + {}^vV_{LDS(total)}$ is up to 90% of ${}^TV_{LPC}$.

[0016] Hence, the variable volume parameters ${}^vV_{LDS(total)}$ and ${}^vV_{VEL}$ are calculated for each batch of LPC according to the variable concentrations of biological active ingredient in each of the at least one LDS. It is preferred that all other parameters are predefined according to the desired target values of the LPC.

[0017] Thus, one preferred example of the method of the disclosure provides a batch mixing process for preparing a liquid pharmaceutical composition (LPC) wherein only the variable volume of the ${}^vV_{LDS(total)}$ and ${}^vV_{VEL}$ that need to be added to each batch of LPC need to be calculated. Hence, the method provides an efficient and streamlined process that is applicable to any LPC of choice and can be used for the large-scale manufacture of liquid pharmaceutical compositions, such as tetravalent dengue vaccines, in particular live attenuated tetravalent dengue vaccines.

In a preferred example, the tetravalent dengue vaccine includes all four live, attenuated dengue serotypes including dengue serotype 1 such as dengue 2/1 chimera or TDV-1 represented by SEQ ID NO: 1 and/or SEQ ID NO:2, dengue serotype 2 or TDV-2 represented by SEQ ID NO: 3 and/or SEQ ID NO:4, dengue serotype 3 such as dengue serotype 2/3 or TDV-3 represented by SEQ ID NO: 5 and/or SEQ ID NO:6, dengue serotype 4 such as dengue serotype 2/4 or TDV-4 represented by SEQ ID NO: 7 and/or SEQ ID NO:8.

[0018] The present disclosure further relates to a product or pharmaceutical composition obtainable or obtained by the process described above and the use of said product or pharmaceutical composition in a method of treating or preventing a disease, in particular in a method of preventing dengue disease.

- [0018a]** In another aspect, the disclosure provides a pharmaceutical composition (PC) obtainable by the batch mixing process as described herein. In yet another aspect, the disclosure provides the pharmaceutical composition (PC) as described herein for use in therapy. In yet another aspect, the disclosure provides a use of the
- 5 pharmaceutical composition (PC) as described herein, in the manufacture of a medicament for treatment or prevention, in particular prevention of dengue disease, in a subject or subject population.

CLAIMS

1. A batch mixing process for preparing a liquid pharmaceutical composition (LPC) comprising at least one biological active agent and at least one adjustable excipient, wherein the at least one biological active agent has a target concentration in the LPC ($^T[A_i]_{LPC}$) and the at least one adjustable excipient has a target concentration in the LPC ($^T[E_x]_{LPC}$), the process comprising at least two steps:

step 1: providing

- a variable excipient liquid (VEL) comprising the at least one adjustable excipient at a predefined concentration ($^P[E_x]_{VEL}$),
- one or more liquid drug substances (LDS) comprising one biological active agent at a variable concentration ($^V[A_i]_{LDS}$) and the at least one adjustable excipient at a predefined concentration ($^P[E_x]_{LDS}$), and
- a fixed excipient liquid (FEL) comprising the at least one adjustable excipient at a predefined concentration ($^P[E_x]_{FEL}$), wherein the predefined concentration of each of the adjustable excipients is defined in accordance with equation 1:

$$^P[E_x]_{VEL} = ^P[E_x]_{LDS} \neq ^P[E_x]_{FEL} \quad (1)$$

wherein $^P[E_x]_{LDS}$ is predefined by the process of manufacture of LDS and $^P[E_x]_{FEL}$ is further defined by the conditions of step 2

step 2: combining

- all of the LDSs each at a variable volume ($^V V_{LDS(i)}$),
- the VEL at a variable volume ($^V V_{VEL}$), and
- the FEL at a predefined volume ($^P V_{FEL}$),

to form the LPC with a target volume ($^T V_{LPC}$) and with a target concentration of all of the biological active agents and all of the adjustable excipients, wherein

the variable volume of each LDS is defined according to equation 2:

$$v_{V_{LDS(i)}} = \frac{T_{[A_i]_{LPC}}}{V_{[A_i]_{LDS}}} \times T_{V_{LPC}}, \quad (2)$$

the combined total volume (${}^pV_{(VEL+LDS)}$) of all LDSs (${}^vV_{LDS(total)} = \sum_{i=1}^{\infty} V_{LDS(i)}$) and the VEL is predefined, and the variable volume of the VEL is defined according to equation 3:

$$v_{V_{VEL}} = {}^pV_{(VEL+LDS)} - v_{V_{LDS(total)}}, \quad (3)$$

and the predefined volume of the FEL (${}^pV_{FEL}$) is defined according to equation 4:

$${}^pV_{FEL} = T_{V_{LPC}} - {}^pV_{(VEL+LDS)}, \quad (4)$$

and the pre-defined concentration of each of the adjustable excipients in the FEL is defined according to equation 5:

$${}^p[E_x]_{FEL} = \frac{T_{[E_x]_{LPC}} \times T_{V_{LPC}} - {}^pV_{(VEL+LDS)} \times {}^p[E_x]_{VEL}}{{}^pV_{FEL}} \quad (5)$$

2. The batch mixing process of claim 1, comprising in step 1

- providing one LDS comprising one biological active agent at a variable concentration of ${}^v[A_1]_{LDS}$, and in step 2 mixing the one LDS at a variable volume of ${}^vV_{LDS(1)}$ to provide a LPC with a target concentration of one biological active agent of ${}^T[A_1]_{LPC}$;
- or providing two LDSs each comprising one biological active agent at a variable concentration of ${}^v[A_1]_{LDS}$ and ${}^v[A_2]_{LDS}$, and in step 2 mixing the two LDSs each at a variable volume of ${}^vV_{LDS(1)}$ and ${}^vV_{LDS(2)}$ to provide a LPC with a target concentration of the two biological active agents of ${}^T[A_1]_{LPC}$ and ${}^T[A_2]_{LPC}$; or
- providing three LDSs each comprising one biological active agent at a variable concentration of ${}^v[A_1]_{LDS}$, ${}^v[A_2]_{LDS}$ and ${}^v[A_3]_{LDS}$ and in step 2 mixing the three LDSs each at a variable volume of ${}^vV_{LDS(1)}$, ${}^vV_{LDS(2)}$ and ${}^vV_{LDS(3)}$ to provide a LPC with a target concentration of the three biological active agents of ${}^T[A_1]_{LPC}$, ${}^T[A_2]_{LPC}$ and ${}^T[A_3]_{LPC}$; or
- providing four LDSs each comprising one biological active agent at a variable concentration of ${}^v[A_1]_{LDS}$, ${}^v[A_2]_{LDS}$, ${}^v[A_3]_{LDS}$ and ${}^v[A_4]_{LDS}$ and in step 2 mixing the four LDSs each at a variable volume of ${}^vV_{LDS(1)}$, ${}^vV_{LDS(2)}$, ${}^vV_{LDS(3)}$ and ${}^vV_{LDS(4)}$ to provide a LPC with a target concentration of the four biological active agents of ${}^T[A_1]_{LPC}$, ${}^T[A_2]_{LPC}$, ${}^T[A_3]_{LPC}$ and ${}^T[A_4]_{LPC}$.

3. The batch mixing process according to any one of the preceding claims, wherein in step 2 the component liquids are combined in the following order:

- a. the FEL and the VEL are first combined to provide an intermediate liquid (IL),
- b. the IL and the at least one LDS are then subsequently combined to provide the LPC.

4. The batch mixing process of any one of the preceding claims for preparing a LPC, wherein

the VEL, LDS(s), and FEL each comprise a predefined concentration of one adjustable excipient

- $P[E_a]_{VEL}$ in the VEL,
- $P[E_a]_{LDS}$ in the LDS and
- $P[E_a]_{FEL}$ in the FEL,

providing a LPC with a target concentration of the one adjustable excipient

$T[E_a]_{LPC}$; or wherein

the VEL, LDS(s), and FEL each comprise a predefined concentration of two adjustable excipients

- $P[E_a]_{VEL}$ and $P[E_b]_{VEL}$ in the VEL,
- $P[E_a]_{LDS}$ and $P[E_b]_{LDS}$ in the LDS and
- $P[E_a]_{FEL}$ and $P[E_b]_{FEL}$ in the FEL,

providing a LPC with a target concentration of the two adjustable excipients

$T[E_a]_{LPC}$ and $T[E_b]_{LPC}$; or wherein

the VEL, LDS(s), and FEL each comprise a predefined concentration of three adjustable excipients

- $P[E_a]_{VEL}$, $P[E_b]_{VEL}$ and $P[E_c]_{VEL}$ in the VEL,
- $P[E_a]_{LDS}$, $P[E_b]_{LDS}$ and $P[E_c]_{LDS}$ in the LDS and
- $P[E_a]_{FEL}$, $P[E_b]_{FEL}$ and $P[E_c]_{FEL}$ in the FEL;

providing a LPC with a target concentration of the three adjustable excipients $T[E_a]_{LPC}$, $T[E_b]_{LPC}$ and $T[E_c]_{LPC}$; or wherein

the VEL, LDS(s), and FEL each comprise a predefined concentration of four adjustable excipients

- 5
- $P[E_a]_{VEL}$, $P[E_b]_{VEL}$, $P[E_c]_{VEL}$ and $P[E_d]_{VEL}$ in the VEL,
 - $P[E_a]_{LDS}$, $P[E_b]_{LDS}$, $P[E_c]_{LDS}$ and $P[E_d]_{LDS}$ in the LDS and
 - $P[E_a]_{FEL}$, $P[E_b]_{FEL}$, $P[E_c]_{FEL}$ and $P[E_d]_{FEL}$ in the FEL;

providing a LPC with a target concentration of the four adjustable excipients $T[E_a]_{LPC}$, $T[E_b]_{LPC}$, $T[E_c]_{LPC}$ and $T[E_d]_{LPC}$.

10 5. The batch mixing process of any one of the preceding claims, wherein the VEL, LDS(s), and FEL further comprise at least one set excipient; wherein optionally the at least one set excipient is selected from the group of non-ionic surfactants and albumins.

6. The batch mixing process of claim 5, wherein the VEL, LDS(s), FEL each comprise a predefined concentration of four adjustable excipients

- 15
- $P[E_a]_{VEL}$, $P[E_b]_{VEL}$, $P[E_c]_{VEL}$ and $P[E_d]_{VEL}$ in the VEL,
 - $P[E_a]_{LDS}$, $P[E_b]_{LDS}$, $P[E_c]_{LDS}$ and $P[E_d]_{LDS}$ in the LDS and
 - $P[E_a]_{FEL}$, $P[E_b]_{FEL}$, $P[E_c]_{FEL}$ and $P[E_d]_{FEL}$ in the FEL; and

a predefined concentration of two set excipients,

providing a LPC with a target concentration of four adjustable excipients

20 $T[E_a]_{LPC}$, $T[E_b]_{LPC}$, $T[E_c]_{LPC}$ and $T[E_d]_{LPC}$; and

two set excipients.

7. The batch mixing process of any one of the previous claims, wherein the one biological active agent is a virus, such as a live attenuated virus.

8. The batch mixing process of claim 7, wherein the virus is a flavivirus, such as a dengue virus.

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9. The batch mixing process of claim 8, comprising in step 1 providing four LDSs each comprising one of the four serotypes of dengue virus D_1 , D_2 , D_3 and D_4 at a variable concentration of $^V[D_1]_{LDS}$, $^V[D_2]_{LDS}$, $^V[D_3]_{LDS}$, and $^V[D_4]_{LDS}$ and in step 2 mixing the four LDSs each at a variable volume of $^V V_{LDS(1)}$, $^V V_{LDS(2)}$, $^V V_{LDS(3)}$ and $^V V_{LDS(4)}$ to provide a LPC with a target concentration of all four serotypes of dengue virus of $^T[D_1]_{LPC}$, $^T[D_2]_{LPC}$, $^T[D_3]_{LPC}$, $^T[D_4]_{LPC}$.
10. The batch mixing process of any one of the preceding claims, wherein the process further comprises:
step 3:
 - drying the liquid pharmaceutical composition (LPC) obtained from step 2, such as by lyophilization, to obtain a dry pharmaceutical composition (DPC).
11. A batch mixing process for preparing a liquid pharmaceutical composition (LPC) with a predefined target volume ($^T V_{LPC}$), comprising
 - (a) at least one adjustable excipient, wherein the at least one adjustable excipient has a target concentration in the LPC ($^T[E_x]_{LPC}$), and
 - (b) four biological active agents A_1 , A_2 , A_3 and A_4 ,
wherein said four biological active agents are
 - dengue serotype 1 (dengue-1)
 - dengue serotype 2 (dengue-2)
 - dengue serotype 3 (dengue-3)
 - dengue serotype 4 (dengue-4)
 and wherein each biological active agent has a target concentration in the LPC ($^T[A_1]_{LPC}$, $^T[A_2]_{LPC}$, $^T[A_3]_{LPC}$, $^T[A_4]_{LPC}$),
wherein said batch mixing process comprises the following steps:
 - (i) providing four liquid drug substances (LDS), each LDS comprising a biological active agent at variable concentration ($^V[A_1]_{LDS1}$, $^V[A_2]_{LDS2}$, $^V[A_3]_{LDS3}$, $^V[A_4]_{LDS4}$)
 - (ii) combining variable volumes ($^V V_{LDS(i)}$) of the four LDSs together making a combined total volume of all LDSs according to equation 6:

$${}^vV_{LDS(total)} = {}^vV_{LDS(1)} + {}^vV_{LDS(2)} + {}^vV_{LDS(3)} + {}^vV_{LDS(4)} \quad (6)$$

and either subsequently to step (ii) or simultaneously with step (ii);

- (iii) combining an intermediate liquid (IL) at a variable volume ${}^vV_{IL}$, with said combined total volume of all LDSs ${}^vV_{LDS(total)}$ to generate the LPC;

wherein said batch-mixing process is characterised in that:

- 5 • the variable volume (${}^vV_{LDS(i)}$) of each of the four LDSs is defined in accordance to equation 2:

$${}^vV_{LDS(i)} = \frac{{}^T[Ai]_{LPC} \times {}^T V_{LPC}}{{}^v[Ai]_{LDS(i)}} \quad (2)$$

- the variable volume of intermediate liquid (IL) ${}^vV_{IL}$ is calculated by subtracting the calculated combined total volume of all LDSs to be combined in step (ii) from the predefined target volume of the LPC according to the equation 3:

$${}^vV_{IL} = {}^T V_{LPC} - {}^vV_{LDS(total)} \quad (3)$$

- 10 • the IL is made by mixing a predefined volume of a fixed excipient liquid (FEL) ${}^pV_{FEL}$ with a variable volume of variable excipient liquid (VEL) ${}^vV_{VEL}$, said variable volume of VEL being calculated by subtracting the predefined volume of the FEL from the calculated variable volume of IL ${}^vV_{IL}$ according to the equation 4:

$${}^vV_{VEL} = {}^vV_{IL} - {}^pV_{FEL} \quad (4)$$

- 15 wherein the adjustable excipient(s) in the VEL are at the same concentration(s) as the adjustable excipient(s) in the combined total volume of all LDSs.

12. The batch mixing process of claim 11, wherein the process further comprises:

step 3:

- drying the liquid pharmaceutical composition (LPC), such as by lyophilization, to obtain a dry pharmaceutical composition (DPC).

- 20 13. The batch mixing process of any one of the preceding claims, wherein the batch mixing process is a large-scale batch process.

14. A pharmaceutical composition (PC) obtainable by the batch mixing process according to any of the claims above.
 15. The pharmaceutical composition (PC) of claim 14 for use in therapy.
 16. Use of the pharmaceutical composition (PC) of claim 14, in the manufacture of a medicament for treatment or prevention, in particular prevention of dengue disease, in a subject or subject population.
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