Implementation of an anticipated reconstitution circuit, and reconstitution modalities of cyclophosphamide vials using a PharmashakerV3©

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Introduction

In our sterile production unit (SPU) approximately 26 vials of cyclophosphamide (CYP) 1000mg are reconstituted per week

❑ **Occuring issues :**
- Long dissolution of CYP
- Contributes to the development of musculoskeletal disorders
- Impact on production flow and preparation quality

Objectives

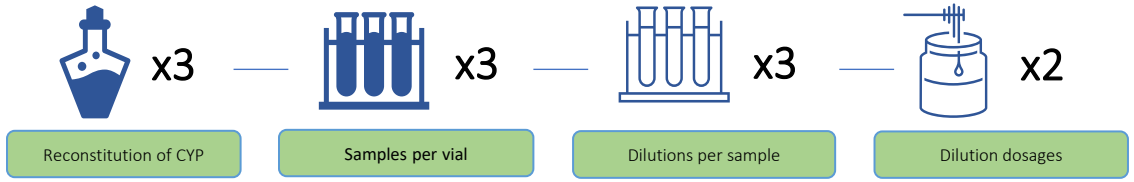
✓ Study the feasibility of an early reconstitution of CYP vials using a PharmashakerV3© (PS)
✓ Study the reconstitution modalities in order to fluidify the circuit while guaranteeing the handler's comfort and the patient's safety

Material and methods

❑ **Feasibility :**
- List the possible scenarios based on the UPS organization
- Rate the advantages and disadvantages at a multidisciplinary meeting
  - -2 = major negative impact on activity
  - +2 = major positive impact on activity

❑ **Reconstitution and shaking of the CYP vials:**
- Manually or via the PS for 2, 4 and 6 minutes (3 vials per method)
- Visual check at the end of shaking → repeat the procedure in the event of incomplete dissolution

❑ **Assessed by High Performance Liquid Chromatography method (HPLC-UV) (1) (C18 RP; H20/ACN 50/50; 50mmx4mmx3µm; 200nm).**



Total :
Assay of 216 samples

Controls 3 parameters :
✓ Average conformity
✓ Standard deviation
✓ Coefficient of variation

Results

		Description	Advantages	Disadvantages	Average rating
Scenario n°1	URC1	PS in isolator	- ↓ risk of microbiological contamination and handling accidents - Optimization of production time - No need for additional formation - One sterilisation	- PS sterilisation - cluttered isolator	+ 5
Scenario n°2	URC1 Reconstitution in isolator → Agitation → URC2 PS in sterile hood		- Uncluttered isolator - Agitation programmable by non-handling personnel - Staff training in sterile dressing	- Additional precautions (cross-contamination) - Sterile dressing - cluttered isolator - Moving between two different rooms - Several sterilisations	- 5,5
Scenario n°3	URC2	Reconstitution and agitation in sterile hood	- Uncluttered isolator - Sterile hood handling training - Staff training in sterile dressing - One sterilisation	- Additional precautions (cross-contamination) - Staff unavailable during handling - cluttered isolator - Strerile dressing - Double visual control	-9,25

Vials conservation : 4°C

	Manual	2x2min	4min	6min
Average conformity	96,13%	97,83%	96,359%	96,545
Standard deviation	1,121	0,294	5,067	3,941
Coefficient of variation	0,012	0,003	0,053	0,041

A better result was obtained with 2x2min method :
✓ higher average compliance
✓ lower standard deviation
✓ lower coefficient of variation

To note :
✓ Only the 2 minutes method required repetition to be successful

Discussion

- This project enabled us to set up an early reconstitution of CYP in our UPS **according to the procedure in scenario 1 :**
  - Reconstitution in an isolator, shaking on PS in an isolator then kept vials at 4°C.
  - After **multidisciplinary evaluation**, scenario 1 appears to be the most suitable in terms of **organization and staff protection**.
- A similar quality of dissolution to manual shaking was noted (**average in our SPU : 3min40**), **with the 2 minutes repeated method.**
- This method allows us :
  - ✓ To **observe the progress** of the dissolution
  - ✓ **Turn the bottle** upside down between each procedure to **homogenise the contents**
  - ✓ Limit the **aggregates' formation**
- The introduction of **PS in our SPU limited TMS** and associated with **a human action**, optimizes the **dissolution** and fluidify the **production**.

→ It remains to be seen if this process can be applied **to other products** in the future**, in SPU or other services.**