Opinion Paper

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Methods for the Study of Physical and Chemical Stability and Container-Content Interactions: Report of a GERPAC Workshop

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Abstract: This opinion paper describes the discussions of the attendees of the last GERPAC European conference workshop on the question of chemical stability and container-content interactions. Pharmacists discussed the steps to implement to carry out those studies that are particularly important to assess the quality of the compounded preparations in hospital pharmacies.

Keywords: stability, container, sorption, leachables

The 21st European conference of the Group of Evaluation and Research for Protection in Areas under Control (GERPAC) has devoted a breakout session on methods for the study of physico-chemical stability and container-content interactions concerning hospital preparations on 3 October 2018. This workshop brought together about thirty participants whose experience of stability studies was quite different. Most of the participants were familiar with the Methodological guidelines [1] for stability studies of hospital pharmaceutical preparations edited in 2013 by GERPAC and the French society for clinical pharmacy (SFPC) and has used it for the implementation of a stability study. Part of the group did not have any particular experience in the field but wanted to respond to their practical problematic and give expiry dates to their hospital preparations. Thus, their expectations of the workshop were to understand the main issues of pharmaceutical-preparation stability in order to develop their own studies or to better understand the literature on the subject and may be able to extrapolate the results.

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The objective of this workshop was therefore to take up the methodological basis described in the guide, to discuss the different aspects and the potential evolutions in order to conclude on the stability of a preparation with a good level of security.

The first part of the session took place in 5 phases:

- Phase 1: identification of the different types of physicochemical instabilities that may occur in a pharmaceutical preparation. The instability is mainly due to chemical reactions occurring spontaneously or delayed, involving essentially hydrolysis and oxidation phenomena. In the case of liquid forms, the instability can also result in physical phenomena such as the appearance of haze, particles, change in viscosity, coloring or phase separation for dispersed systems. Interactions may also occur between the primary packaging and the preparation, which may lead to a loss of active ingredient by sorption or a release of chemical compounds from the material.
- Phase 2: identification of factors influencing these instabilities. These may be related to the preparation itself (nature of the active ingredient and its concentration, nature of the excipients), to the packaging (type, nature of the materials, container capacity, sterilization mode) and to the environment in which the preparation will be stored (temperature, light, humidity).
- Phase 3: steps to implement to develop a stability study. It is first necessary to identify the different parameters that may influence the stability of the preparation. Thus, the origin of the active ingredient will have to be clearly identified. If the preparation is made from a commercialized drug, the excipients thereof may have an impact on the stability of the final preparation. Thus, after a change of market, it is important to check that the composition of the new drug (generic for example) does not differ from the initial one. Otherwise a reassessment of the stability of the preparation may be necessary. For example, the stability of ciclosporin eye drops can vary according to the drug used to carry the

active ingredient (Sandimmun® or Neoral®). A particular attention will be paid to the drugs containing surfactants, their dilution being likely to modify the stability of the preparation. Furthermore, dilution solvents may have different pH that may influence the stability of the preparation. The knowledge of the materials constituting the primary packaging is also an important piece of information, in particular their air permeability making possible the oxidation of the contents, their mode of sterilization (a sterilization by the radiation can cause the migration of acid impurities likely to modify the pH of the preparation ...).

In a stability study, the storage and use conditions of the preparation should also be clearly defined. The study is conducted under conditions of temperature, humidity, exposure to light corresponding to the storage of the preparation. When the preparation is kept in the freezer, a particular attention must be paid on the thawing phase because it is particularly subject to instability of the preparation. Use tests in real-life situations will have to be carried out. For example in the case of eye drops, it is necessary to study the stability after the opening of the eye-drop and to simulate the administration of drops. Indeed the entry of air, the contact of the solution with the materials of the delivery device can change the stability of a preparation.

The sampling method is a subject of discussion in a stability study. It seems better, as far as possible, to make a minimum of 3 independent samples taken from 3 different batches for each analysis time.

- Phase 4: analytical techniques to be used to achieve stability studies? How to equip? The analytical method must be specific to the active ingredient in order to identify it with a high level of security and to prove that there is no interference with its possible degradation products. Thus, separative methods are preferred, such as liquid chromatography or capillary electrophoresis. A diode array detector coupled to liquid chromatography provides a good view of the main active ingredients and their degradation products due to the possible scanning of wavelengths in the UV-visible. A mass spectrometer will provide better information on degradation products from the point of view of their identification and quantification at low levels. However the cost of the equipment limits its access to some hospital pharmacies. The workshop moderators insist on the risks of conducting stability studies with non-separative methods with simple UV-visible spectrometers often available in pharmacies for the quality control of preparations.

An example presented in session shows that a cis-atracurium preparation is considered stable via a UV-spectrometric method at 280 nm whereas a separative method with UV-detection shows a degradation of 75 % of the active ingredient in some days.

Another point is also highlighted: the need to carry out assays to verify the integrity of the dosage form. These analyzes are specific to each pharmaceutical form. For example, a stability study of an injectable form must include the monitoring of sub-visible particles. It should also be noted that pH and osmolality are easy to measure and are relevant indicators of the stability of a liquid preparation.

The determination of extractables and leachables from packaging will have to be implemented given the impact of compounds from the material on the stability of the preparations. However this evaluation can only be done in some laboratories with a high performance technical platform. In fact, this determination requires the joint use of LC-MS, GC-MS and ICP-MS for the analysis of non-volatile, semi-volatile, volatile and non-organic compounds.

The problem of preparations based on active ingredient of protein nature is mentioned. It is recalled that the stability of these preparations requires a physico-chemical analysis involving complementary techniques. These must be combined to increase the level of evidence and specially to verify that the tertiary and quaternary structure of the protein compounds is not modified. Furthermore, it is better to add enzyme immunoassays in order to check that the biological activity of the protein is maintained.

- Phase 5: interpretation of the data. The session invite the participants to consult the decision support flow chart presented in the GERPAC guide. When a variation of a parameter is observed, the interpretation must include a clinical component. The concept of a narrow therapeutic margin of an active ingredient, the toxic risk of degradation products or impurities from the container will be determining factors in the decision concerning the methods of preserving a preparation and also on the choice between the acceptance threshold i. e. 90 % or 95 % of the initial concentration. The reference to princeps publications is also very important in designing the analytical protocol as well as final decision making [2–4].

The second part of the workshop was a discussion about the evolution of the methodological guidelines for stability studies managed by GERPAC/SFPC. During these exchanges it

was suggested to expand the chapter on the dosage of active ingredients by integrating other analytical techniques and readjusting the selection criteria. A qualitative approach via the levels of evidence provided by the different techniques was suggested. A chapter on extractable and leachables analysis could also be integrated with a risk analysis approach.

It was proposed to the users of the methodological guide to allow a feed-back of their remarks and proposals for the next evolution of the guide via the forum of GERPAC. An evaluation questionnaire will also be sent to the members of the association. Following the collection of user comments, a new working group will be formed to develop the guide.

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