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STABILITY ASPECTS OF CLINICAL SUPPLIES AND SCALE-UP STUDIES

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10.1 Introduction

When one glances at the stability aspects of scale-up experiments and the preparation of clinical supplies, even though one may have considerable experience in research and development and/or pilot and commercial production, it is difficult to comprehend the scope of the subject. This is particularly true for attempts to inter-relate stability and scale-up work. If one works in the area of scale-up and/or the production of clinical supplies, many things are taken for granted, because they constitute procedures that are carried out as standard operating procedures. However, if one steps back and takes a careful look in perspective at the number of stability considerations that must be dealt with, and that take on significant meaning, the importance of stability studies become evident.

Before the latest "Good Manufacturing Practices" regulations were issued, and the initiation of "Good Laboratory Practices", limited consideration was given to the stability of a clinical batch of a new drug entity, as to the stability of a scale-up batch of a new drug. In many instances, the clinical batch is the scale-up pilot lot. This limited consideration was particularly

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true if no stability problems had surfaced during the formulation and product development work. Preformulation stability work may catch many potential problems during development, but may escape detection if the stability problem is the result of a number of ingredient interactions, all possibilities of which cannot be tested.

This lack of consideration for the importance of stability studies, may be attributed in part to the feverish pace that has been set because of ambitious time talbes to get the new formula into the clinic for testing. In the industry, "as soon as possible", often means yesterday, and in all cases, stability is synonymous with time, and the stability time may often be sacrificed. This primarily adds up to the lack of insight into the importance of stability follow-up so necessary in both clinical batch work and scale-up work.

During the preparation of clinical batches of new drug formulas, and the scale-up from development through pilot and into commercial production, stability work is an integral part of each of these steps leading to the marketing of a pharmaceutical product.

10.2 Examination of Reason for Stability Work

10.2.1 Forms New Drugs Take

In order to examine the reasons for this stability work it is instructive to take a look at the forms a new drug formula may take:

10.2.1.1 New Drug Substances

The formula may contain an entirely new active ingredient or drug substance. The need for stability work is obvious. Even though pre-formulation work indicated no incompatibilities, stability of the finished new formula must be fully defined.

10.2.1.2. Addition of a Second Active Ingredient

Although not as common today as back in the 1960's, a new drug formula may take the form of a second active ingredient addition. The second drug

entity may act in conjunction with the existing active ingredient to provide another pharmacological activity, or perhaps a synergistic affect such as a narcotic antagonist to prevent narcotic drug abuse.

10.2.1.3 Excipient Change

A change in excipients and/or colorants, flavors, etc. also constitute a formula change. Over the last decade, changes in colorants has been running rampant through the pharmaceutical industry. Decertification of many of the old dependable colors has created a considerable amount of reformulating work, and has lead to near chaos in the scramble to match existing colors. In many cases, color matches cannot be made and some problems come about as a result of creating new appearances with the available light stable dyes and lakes. This reformulation work has lead to untold stability studies which last for years for expiration dating.

10.2.1.4 Change of Dosage Form

A new dosage form may be exactly what it says: whether it is a new injectable form of a compound which has been marketed only as a tablet, or the switch from a tablet to a capsule, or an emulsion to a solubilized clear liquid. All are changes or new drug dosage forms of new or existing drugs.

Summarizing the four examples of new drug formulas that are of concern during clinical batch preparation and the scale-up to pilot and production, they include: an entirely new active ingredient, the addition of another active ingredient, the change of excipients or non-active ingredients, and a change in dosage form.

10.2.2 Scale-up of New Active Ingredients

During the preparation of a clinical batch, which must be prepared according to Current Good Manufacturing Practices, stability must be initiated for a number of reasons, including the following:

The new active ingredient may well be prepared by a new scale-up process, and may present slight differences in physical characteristics from that used in earlier laboratory development. Take for example the clinical batch

preparation of a formula containing a new drug entity. This new drug compound has just been prepared by a scaled-up synthesis or an extraction, perhaps 100-1000 times the bench scale size. This will depend on the amount required for clinical testing and the planned stability work.

Although the compound may meet specifications chemically, including potency, some differences may possibly exist physically such as bulk density, surface area, porosity or crystal habit to name a few. A good example of this is one from this author's personal experience with two operators who had never made a direct compression formula newly transferred to commercial production. All weights of ingredients had been weighed and checked, and the raw materials were screened into a mixer and dry mixed. The mixer was emptied into drums and sent to compression. This lot would not compress. Four previous lots had compressed without difficulty. Records indicated a new lot of active ingredient had been used in this current uncompressable lot. Inquiry revealed that the operators had used almost twice the volume of the active ingredient; 4 drums vs. 2 drums. The active ingredient constituted the majority of the tablet so its presence had a considerable affect on compressability.

The number of drums to be compressed verified the larger volume. A bulk density determination of the new lot of material compared to the bulk density of the active ingredient used in previous lots, indicated the volume was almost double for the same weight of active material. It had not been picked up in quality control because no bulk density specification had been set. This was immediately corrected, and the remainder of the bulky lot of raw material was used in the liquid dosage form of the product.

10.2.3 Different Design and Size Equipment

Pilot size batches usually require different design and/or size equipment than that used during smaller scale development work. This usually leads to slight modifications in the formula. A formula with either a single active ingredient or a number of active ingredients may present a problem which may not be evident on a small scale such as slight color changes due to oxidation during dry or wet mixing, or the milling of solids, or the handling of liquids

on a large scale. During scale-up, the formula may be subjected to higher shear and longer exposure to the atmosphere during longer preparation times. This problem may not show up until scale-up, because small problems usually scale-up as the product scales-up.

Murphy's Law always comes into play when a new formula is assembled in a scaled-up version, be it pilot or commercial scale. It should be noted that in order to illustrate the weights of materials involved, pilot and commercial scale lots or batches mean different sizes to each of us. For example, the pilot lot scale may range from 10 kg to 300 kg or more, and the commercial scale may range from 50 kg to 5,000 kg or more. This is dependent on the size manufacturing plant, the equipment capacity, and product volume each company works with. Clinical batch sizes have even wider ranges in weight or volume depending on dosage form, dose level, the extent of the study being conducted, and the duration of the study. In any case, Murphy's Law creates liquids should appear, powder masses that will not flow, capsule and tablet weights that show unsatisfactory weight variation, not to mention granulation sticking to tableting punches, and some granulation that will not even compress. People working in the scale-up area have traveled this road more times than they would like to count. As a result, ranges within the Investigational New Drug Application (IND) must be made available in the formula to allow for these problems. Many of these scale-up problems may be anticipated from experiences with equipment size and design.

10.2.4 Clinical Package

Another reason for initiating stability studies with clinical batches of drug formulas is related to packaging. In many situations, the package used to supply the clinical material under study may be different than was originally used during the development stability work. This encompasses flint as compared to amber glass, plastic rather than metal caps, child-proof rather than non-child proof caps, glass instead of plastic bottles, ampuls instead of vials, etc. The list as illustrated is only several of the choices that can be made when one considers choices of cap liners or

dropper bottles, etc. The clinical package is also selected because of convenience, label space, and dosage size. If several packages are selected, all should be set on stability at normal and exaggerated conditions.

10.2.5 Expiration Dating

It is essential that information for expiration dating start as soon as possible, and perchance the proper package follows through to production, this dating may be started with clinical testing.

10.2.6 Alternate Formulas

It is also suggested that an alternative formula be considered should problems occur during clinical testing of the formula of choice. The rationale behind this follows that it is much cheaper to run formulas "X" and "Y" side by side in the clinic rather than have to set up an entirely new study.

It is obvious from the above why stability is so important in clinical and scale-up work. Wherever a change in formula or process takes place, stability work must establish and confirm the quality of the product.

10.3 The Stability Study

10.3.1 Conditions and Initial Observations

The stability study itself should be carried out at normal and exaggerated conditions as well as cycling temperatures where temperatures are changed daily from freezing to room temperature (R.T.) (25°C). Each company usually has their own stability exaggerated temperatures such as -10°C, 0°C, 30°C, 40°C, 50°C and sometimes 60°C. Relative humidity (R.H.) may also be varied from 10% R.H. at R.T. to 80% R.H. Again this is dependent upon the program set up by each company or institution. Humidity conditions are particularly important when dry products such as powders, tablets and capsules are the object of the study.

It must be stressed that initial stability of clinical material must be followed closely. The initial observations in addition to zero time,

should be made once-a-week for the first four (4) weeks, including chemical, as well as physical testing. Any changes in the product(s) should be noted and tagged immediately so their significance can be evaluated. Significant changes in the product may require the termination of the clinical study and the stability work. If one has the luxury of stability testing the new formula before it goes to the clinic, a recall of clinical material would not have to be initiated, and considerable monies could be saved. At this point, it would mean starting at ground zero again. This might be avoided, as mentioned earlier, if an alternate formula showing satisfactory stability were available.

10.3.2 Length of Time

If all stability testing appears normal for the first month or two, testing may be carried out on a monthly basis for three (3) to six (6) months for at least two (2) years and usually five (5) years in order to follow through on the expiration dating mentioned earlier.

10.4 Clinical Batch Preparation

During the planning stages of preparing a clinical batch of material, two obvious but very important items should be remembered:

10.4.1 Quantity

Make certain the batch of clinical material is large enough to back-up any clinical supplies in the field should anything go wrong during testing, e.g., broken packages during shipment, mishandling during the test, damaged seals, etc.

10.4.2 Stability Quantity

Make certain that enough clinical material has also been prepared to allow each lot being clinically tested to also be subjected to an extensive stability test. The reason being that the batch will be checked closely, and will require a considerable number of samples for the study and back-up samples.

The clinical batch is likely to need a much greater percentage of units for stability testing than is a regular production batch.

10.5 Consideration of Additional Problems During Scale-up

Some of the stability aspects of scale-up were mentioned briefly earlier in the clinical batch stability follow-up. These are related to process equipment changes such as the milling of raw materials where heat may be generated that was not anticipated during the scale-up of a milling operation. This in turn may produce polymorphic changes or create auto-degradation products not detectable or not present during the milling of small quantities of active ingredients. The same is true for mixing equipment. This is particularly true if one chooses to go to the high intensity bowl type chopper blade, or even the high intensity agitator bar in the large tumbling mixers. Additional blending time and exposure to moisture and the atmosphere for these extended periods during mixing may require stability follow-up. Switching a granulation from a sigma blade mixer to a fluid bed granulation, or any other different granulating method, requires a stability follow-up because the formula is being subjected to different forces, changes in surface area may take place, and the method and rate of applying the granulating solution may be different.

The same type of consideration must be given to solutions which may become aerated during rapid mixing, or the differences in shear applied to a polymer determines its structure and resulting viscosity.

It becomes evident from examples mentioned above that validation of old and new processes will require stability work to complete the validation of products subjected to these processes.

10.6 Conclusion

In conclusion, stability is a vital part of the preparation of clinical material for testing and for the upgrading of pilot and commercial scale-up manufacturing processes. It is not to be neglected, but carefully planned, and followed up.