Ongoing Stability Testing: Requirements, Solutions and Potential Pitfalls

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EU GMP Guidelines require ongoing stability testing for the market-life of all medicinal products – but with sensible and skilled planning of the test protocol, it is possible for expenditure, and hence production costs, to be kept to a minimum.

All medicinal products on the market must be monitored in a continuous programme in order to demonstrate stability and quality over their entire market life. Laboratory analysis is a cost factor that still offers room for manoeuvre in many companies, and with improved study design, the burden of ongoing stability tests can be reduced. In the realisation of more efficient stability testing, however, it is important to be aware of the potential pitfalls.

BACKGROUND

The revised version of Chapter 1 of the EU GMP Guidelines (1) came into force in 2006; item 1.5 makes the annual Product Quality Review (PQR) compulsory for all licensed products. This continuous revision of the consistency and validity of the entire manufacturing process also includes a stability-monitoring programme as listed under sub-item vii. These ongoing stability tests are specified in Chapter 6 of the EU GMP Guidelines, which were updated in the same year.

Areas of quality control which previously formed only part of R&D are now included in official GMP inspections. This is the case, for example, with the qualification of special equipment for stability testing, such as controlled storage cabinets. Standard operating procedures (SOPs) for dealing with out-of-specification results, not only for batch release but also during stability testing, and for evaluating out-of-trend results have to be implemented.

External laboratories contracted to carry out ongoing stability testing must be included in the manufacturing licence. Technical Agreements for third-party analysis (which define responsibilities on both sides) must be thoroughly revised under theses premises or must take account of it when they are first drawn up. The Qualified Person employed by the manufacturing or contracting company must ensure that the tests are carried out in accordance with GMP requirements by means of an audit.

It should be kept in mind that ongoing stability testing differs from other stability tests in its regulatory and legal background (see Table 1) (2,3). However, these requirements only apply to licensed medicinal products which are currently on the market.

REQUIREMENTS FOR ONGOING STABILITY TESTING

The categorical requirements of the GMP Guidelines for ongoing stability testing are that:

- All medicinal products/formulations have to be tested, with no exception, in principle, for homeopathic products, herbals, and so on
- All finished products and, where appropriate, bulk products have to be tested (for example, when stored or transported for prolonged periods). Excipients and active substances are not taken into account here
- Requirements apply in principle to every product in every dosage and pack size or (primary) packaging type/package
- Tests have to be carried out continuously, usually one batch a year
- Studies have to be carried out under long-term conditions (for example, 25°C and 60 per cent relative humidity) continuously over the period of the labelled shelf life

Tests following storage under intermediate and accelerated conditions should only be carried out if supplementary information is required at an early stage. In principle, all decisions which affect the test protocol, the frequency of testing and the choice of test samples should be product-based, targeted and founded on a risk analysis (see Table 2).

Table 1: Summary of the different types of stability testing (exemplarily for a new registration of a human medicinal product)

Study type	R&D study	Follow-up (commitment) study	**On-going study**
Time point	Before registration	After submission of the dossier	After registration and marketing
Aim of the study	Setting shelf-life, storage conditions and specifications	Verify registration data	Proof that conditions are still valid
Background	Registration procedures, guidelines for stability testing (for example, ICH)	Registration procedures, guidelines for stability testing (for example, ICH)	**EU-GMP guideline**
Extent	Two pilot- or production-scale batches of the finished project. If 'critical', for example when known as unstable, three batches	Production-scale, three batches of the finished product	Continuous; one batch – per year – each product – each strength – each package
Competent authority	Regulatory agency (for example, BfArM and MHRA)	Regulatory agency (for example, BfArM and MHRA)	**National GMP surveillance – regulatory agency or health authority**

Ongoing studies are intended to prove that, over the period of its labelled shelf life and under 'real life conditions', the product remains of the quality defined in the authorisation/registration documents. Stability studies done for registration solely provide a 'snap-shot'. Adverse effects such as changes in manufacture and the supply chain (even those not on a variation level) should be identified by ongoing studies. However, this procedure also implies that the test protocol can be adjusted at any time to the current situation. The stability protocol does not necessarily have to comply with the ICH stability testing guidelines.

POTENTIAL SAVINGS – REALISATION AND PITFALLS

Item 6.28 of the EU GMP Guidelines specifically states that the protocol for the ongoing stability programme may differ from that of the initial long-term stability protocol (3), giving a reduction in the frequency of testing as an example. If it has been shown that a test parameter is not critical, for example during the course of commitment (follow-up) studies or later in ongoing studies that have already been performed, the frequency of testing may be reduced.

A given example shows that, overall, there is a possible reduction in the required frequency of testing of about 50 per cent or even more (see Table 3). It should be noted that at the end of the shelf life, all the test parameters should be checked again (in this case t60), in order to prove stability over the entire storage life.

If the product is manufactured in different strengths (same API with similar matrix) and pack sizes, the 'bracketing' recommendations can be applied (4). If there are more than two sizes for any parameter, this provides for only the extremes to be tested (see Table 4). This example shows the requirements in the guidance. Assuming an identical bulk product, then if the exemplary product above is packed in blister packs of 10 tablets, each with identical primary packaging material, the effect of secondary packaging – for example, different secondary packaging for different foreign markets – does not have to be taken into account. Testing of only one pack size would therefore be sufficient. The same applies to multi-dose containers, where only the most sensitive size of container would have to be tested on a 'worst case scenario' basis.

In the latter (ideal) example, the number of tests could be reduced from nine to two, with corresponding cost-savings. However, consideration of the individual case is always important. It may be necessary, for example, for the first batches to be tested in accordance with the full protocol in order to provide sufficient data for trend analyses.

The combination of ongoing studies with follow-up (commitment) studies is often discussed. It should be emphasised here that, in principle, the data that are generated in follow-up studies can also be used for review, as mentioned in sub-item vii in the PQR. Conversely, however, this means that tests must cover the full protocol in the dossier. Savings, such as those discussed above, are hardly possible in this case.

If it was agreed in the post-marketing commitment that, after launch, one batch per year would be tested for three years for the follow-up study, then the additional (ongoing) tests could be saved for three years. As usual, analyses for the release of a product batch can also be used as starting values for ongoing studies, but possible differences in the specifications have to be observed. Thus, further ongoing testing does not start until a year after the start of storage.

It is also recommended that production and hence starting dates should, if possible, be in the same period of the calendar year. As a result, in subsequent years there will be further synergies as a result of parallel testing.

STEPS AFTER TESTING

Suitable data analysis procedures that allow not only retrospective but also prospective evaluation have to be established. The EU GMP Guidelines require that, at the individual test times, it must be stated whether it can be assumed that, for example, the active substance content

Table 2: Selection of stability-limiting parameters. Decision should be made on the basis of existing data

	Less critical parameters	More critical and essential parameters
Capsules and tablets	Organoleptic and physical tests, uniformity of mass and content, disintegration and dissolution, microbiological quality	Assay and impurities
Liquids (for oral use)	Organoleptic tests, uniformity of dosage, density, pH-value, preservation, microbiological quality	Assay and impurities
Sterile solutions (*Ophthalmica*, *Parenteralia*)	Organoleptic tests, uniformity of dosage, density, pH-value, preservation	Assay, impurities, sterility and particles

Table 3: Protocol with reduced frequency of testing for an ongoing study (solid formulation): T = Test, (T) = Test optional, o = designated testing, dossier (2), (3) omitted

Test	t0	t3	t6	t9	t12	t18	t24	t36	t48	t60
Organoleptic	T	(T)	(T)	(T)	(T)	(T)	(T)	(T)	(T)	T
Mass uniformity	T	o	o	o	o	o	o	o	o	T
Resistance to crushing	T	o	o	o	(T)	o	(T)	(T)	(T)	T
Dissolution test	T	o	o	o	T	o	T	T	T	T
Identity	T	-	-	-	-	-	-	-	-	-
Assay	T	o	o	o	T	o	T	T	T	T
Purity	T	o	o	o	T	o	T	T	T	T
Microbiological quality	T	-	-	-	T	-	o	o	o	T
25°C/60% rh	T	(T)	(T)	(T)	T	(T)	T	T	T	T
30°C/65% rh	-	-	o	o	o	-	-	-	-	-
40°C/75% rh	-	o	o	-	-	-	-	-	-	-

Table 4: Example of bracketing, (T = Test; o = Test omitted), solid formulation

	Strength		
	50mg	**75mg**	**100mg**
20 tablets	**T**	**o**	**T**
50 tablets	**o**	**o**	**o**
100 tablets	**T**	**o**	**T**

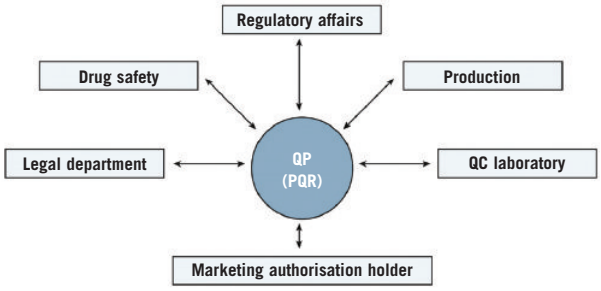

Figure 1: Interactions between specialist departments and external service providers

is likely to remain within the specified limits as testing continues. Here, statistical methods of regression and confidence interval analysis can be useful, although they should be used with caution.

The results of ongoing stability testing have to be summarised in a report. All current results have to be compared with data from previous tests, for example from follow-up studies, and trend analyses have to be carried out (if applicable). The results have to be incorporated and discussed in the relevant PQR.

It must also be noted that the manufacturing department (internal or contract manufacturer) and the Qualified Person responsible for market release have to be notified of the results of the ongoing stability studies.

An appropriate SOP should specify what should be done in the case of out-of-specification (OOS) results and significant negative trends. If verified, they must be reported to the supervisory authorities. Further considerations should also be taken into account here, for example:

- A review of sensitive or relevant areas in production should be undertaken to try to identify the cause and possible transmission to other batches/products
- A critical review of the labelled stability and, if necessary a recall of the affected product batch must be considered
- Measures to avoid errors should be discussed and implemented (corrective and protective actions, (CAPA)). In justified cases, other specialist personnel such as the Qualified Person for Pharmacovigilance will need to be involved

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After the implementation of corrective actions, the subsequent production batch should be reviewed by an ongoing study in addition to the normal yearly round of testing. The test parameters must be agreed on the basis of the individual situation.

TEAMWORK

As with PQR in general, ongoing stability testing requires the intensive exchange of information between the responsible persons and relevant specialist departments (see Figure 1). Responsibilities must be clearly laid down, and if external service providers are involved, appropriate technical agreements must be drawn up which define these responsibilities.

The involvement of an external service provider may be beneficial to the marketing authorisation holder; expensive implementation of an in-house system can be avoided by employing the existing system of the service company. Investments and fixed costs are not increased, and the marketing authorisation holder can concentrate on its core competences such as marketing. Outsourcing all other functions is, in principle, possible (5).

CONCLUSION

The message to take away from this review is that expenditure, and hence production costs, can be minimised by sensible and skilled planning of the test protocol for ongoing stability testing.

Note

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References

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