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Case study

Spotlight on stability: API and drug product testing

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Stability studies are key to drug development. An integral part of any New Drug Application (NDA) is a requirement to perform stability studies on active pharmaceutical ingredients (APIs) and drug products to assess degradation and inform shelf-life prior to market release. For some programmes, further investigation is required to demonstrate stability of key raw materials, intermediates or excipients used in the manufacturing process. Anna Cousens, Business Development Manager at Almac Sciences, describes what studies need to be performed, and how, to ensure best product performance.

Article: Spotlight on stability - API and drug product

Developing a drug is a long and complex process, and the stability requirements change depending on the phase of development. At the early stage, little is known about the API and formulation, so this work is required to inform on the degradation profile of the compound. It is critical to know how the API degrades over time; if it is particularly sensitive to light, heat or humidity,and how best to store it to ensure that when it finally reaches a patient it is of the required quality and purity.

When formulating a drug, studies must be conducted to demonstrate interactions between the API and any excipients used, and to confirm that these do not accelerate the degradation of the active ingredient. Once the final product is packaged, stability studies must also be undertaken to confirm that the finished product remains intact, and that the packaging selected is fit for purpose.

During the early stages of clinical development, every new batch of API or drug product should be placed on stability, and each new packaging presentation will also require supporting stability data. Once stability data has been generated it may not be necessary to place every new manufacture on stability provided that there is reasonable coverage from existing studies.

When performing stability studies there is much to consider:

- Analytical methods
- Batches required to be set down
- Conditions
- Analysis required at each timepoint
- Transport studies
- In-use stability
- Reference standards

Analytical methods

When conducting stability testing it is imperative that the analytical methods used are fit for purpose. Without a good understanding of the analytical testing, stability studies would be pointless as the methods need to be able to detect any degradation in the product. For GMP stability programs, validated analytical methods are required. As an example, Almac were provided with some client methods but were required to perform full ICH validation of the HPLC method. This was required for both the API and drug product, and because the methods were similar for both, we found efficiencies in the project by conducting these two validations in parallel. Many outsourcing partners routinely perform ICH validations for methods developed in their own labs, or at client or third-party labs.

When releasing a batch of API or drug product, a specification describing the full scope of testing is required. Often when setting down batches on stability, this release testing will be leveraged by the stability group. In some circumstances it is possible to leverage the release testing results for the T = 0 timepoint.
This can save time and money by not duplicating these results.

However, using release data for T = 0 is not always practical, and repeating this testing can add value to a project. In some instances, the stability partner will be setting down stability on products that are not manufactured on site and will have no previous experience of the analytical methods. For a GMP stability study, these methods will require validation prior to use. The inclusion of T = 0 testing of these batches can be used to perform a limited validation of the required methods by comparison of data with the releasing lab. This is a convenient and efficient way of bringing fully validated methods into the partnering company.

Batches to be set down
As the drug proceeds through early clinical trials and moves towards commercialisation, there may be multiple presentations to consider.

A typical example of such presentations includes:

- Active ingredient (API)
- Drug product formulation (capsules)
- Drug packaging (capsules in blister)
- Drug packaging (capsules in bottle)

It is imperative that the stability team fully understands when samples need to be pulled. The project can be made more efficient by pulling stability timepoints together thus reducing the time required to set up analytical equipment. However, there are standard requirements around the window for testing to be performed at each timepoint, so the length of the testing runs must be considered and samples pulled in line with the testing regimen. A dedicated stability team with sufficient equipment to prevent bottlenecks when large studies require significant sample numbers at a specific timepoint is hugely beneficial.

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Test conditions

Table 1 highlights standard ICH conditions within stability chambers. Whilst there is often commonality, the conditions required are informed by the nature of the compound.

For example, it is more likely that peptides, proteins and biologics will be stored at cold or frozen conditions due to their instability, and early-phase small-molecule studies typically follow a standard approach (Table 2). Results from this early data will inform later-phase studies.

Table 1: ICH stability conditions.

-20˚C	**2-8˚C**
30˚C/65%RH	**25˚C/60%RH**
30˚C/75%RH	**40˚C/75%RH**
Photo stability (lightbox)	

Table 2: A typical stability schedule for small molecules.

Condition	Time point (months)										
	0	1	3	6	9	12	18	24	36	48	60
2°C – 8°C	X	O	O	O	O	O	O	O	O	O	O
25°C/60% RH		X	X	X	X	X	X	X	X	X	X
40°C/75% RH		X	X	X							

X = Scheduled testing, O = Optional testing on request

Analysis at each timepoint

A typical study runs between 3 and 5 years, and whilst these studies are used to obtain long-term shelf-life data, at early stages products will be exposed to harsher conditions – higher temperature, increased relative humidity – to stress them and increase the rate of degradation. This is important as it provides an overall idea of the degradation profile of the compound and potentially highlights issues with analytical methods or the rise in level of certain impurities.

Accelerated conditions are important when considering the infrastructure of the end user market. They can also be used to predict the shelf life of API or drug product in line with ICH guidelines.

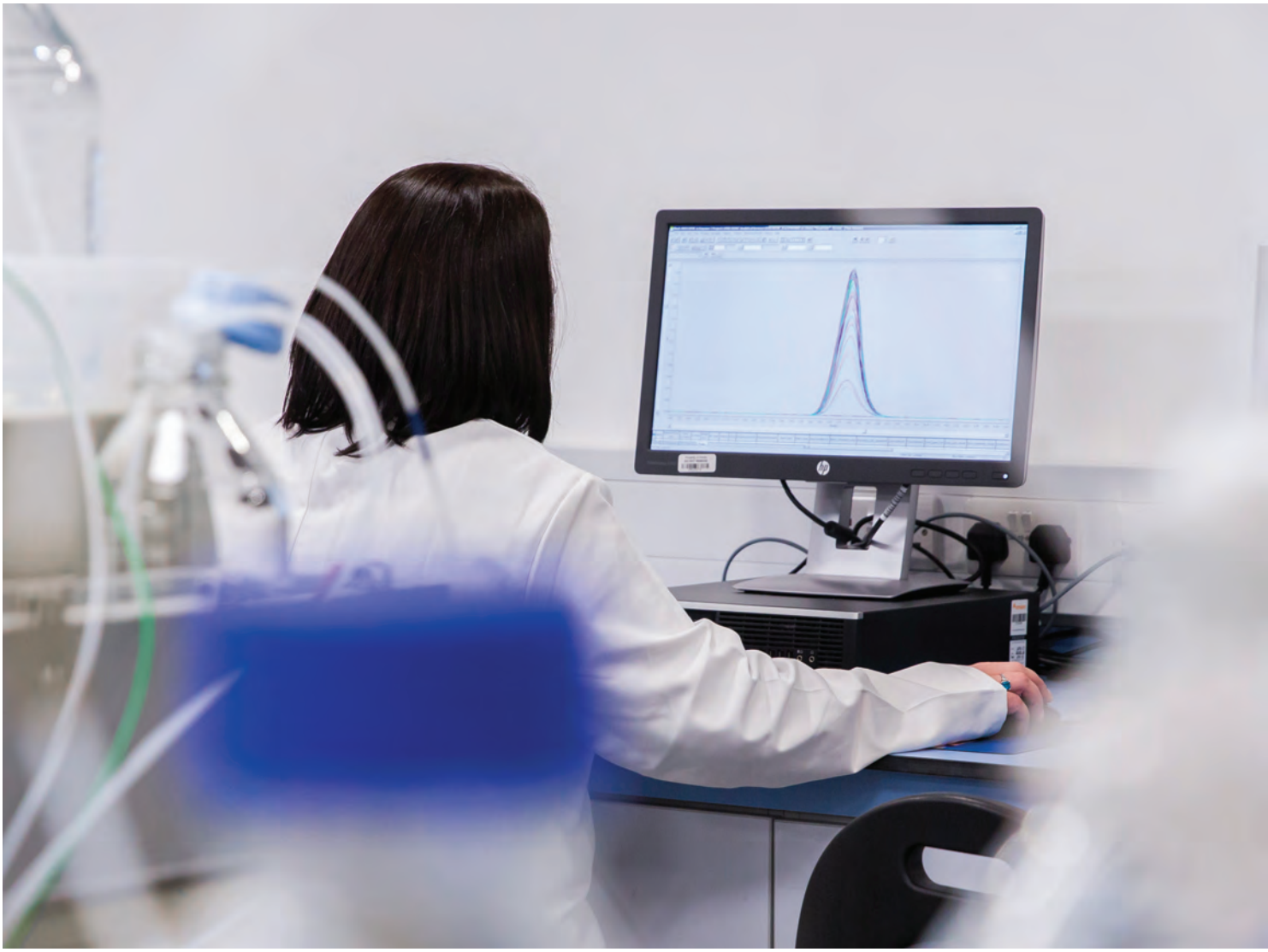
A limited testing schedule is performed at each timepoint, and typical testing requires a purity method (likely by HPLC) that has been proven to be stability indicating. XRPD analysis can be included to demonstrate there has been no change in physical form, and a Karl Fisher technique is included to show the presence of moisture and indicate if the drug is hygroscopic.

Microbiological testing can be included at some (but not necessarily all) timepoints to prove the absence of microbial contamination. For finished products, dissolution testing will be included to simulate the effectiveness of the drug in vivo.

In-use stability

Stability studies indicate degradation of products under fixed conditions, but in the real world it can be difficult to maintain these conditions when distributing worldwide. Logistically, planes can be delayed, trucks can be stopped at customs, or stuck in a long tailback on the motorway.

To ensure that temperature excursions do not lead to wasted product, a transport study can be conducted. This is where the drug is exposed to temperature cycling to mimic freezing and thawing. Typically, a drug will be exposed in its final packaged form to 3 cycles ranging from -20 °C to 40 °C/75% RH over 2 weeks, then set down onto a formal stability study for 36 months. This temperature cycling is performed prior to the set down of the main stability study, allowing the increase of efficiency by pulling these time points in parallel.



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Reference standards

Most stability studies include purity/assay by HPLC as part of their testing regime. These methods require the use of a reference standard – a highly purified and fully characterised sample of the API or impurity. These standards are typically small quantities stored in vials with a need for recertification, most likely on an annual basis.

Over a 5 year stability study it is probable that standards will need recertification multiple times. Over a prolonged period of time it is possible that reference standards can become depleted and an in-house strong synthetic chemistry group that can assist with remanufacture of reference standards is beneficial. This could be performed via chromatographic purification of API samples, extraction of/by degradation products from manufacturing mother liquors, or total synthesis.

In conclusion

There is much to consider when addressing stability studies. Typical conversations include capacity and the conditions available, but as discussed, there are a wider number of factors to consider. It is therefore critical when partnering to consider lab footprint, experience and supporting capabilities to ensure your product is in the safest hands.

Case study:
Spotlight on stability

In this case study we take an in-depth look at a specific project that ran at Almac for 5 years. As demonstrated in our article, when performing stability studies there is much to consider, but what makes this case study so interesting is that whilst most projects cover a subset of the main activities described, this one study encompassed them all, and was the biggest study ever run at Almac.

This project was conducted on behalf of a multi-national Big Pharma company, generating data for a small molecule therapeutic going into Phase II development. The study encompassed API, bulk drug product and packaged drug product which came to Almac from multiple vendors.

Case Study: Spotlight on stability

Analytical methods

It is imperative that the analytical methods used are fit for purpose. Without a good understanding of the analytical testing, stability studies would be pointless.

Several of the analytical methods used - XRPD, KF and dissolution - were transferred to Almac via comparative testing of a single batch. This analysis was carried out by 2 analysts at Almac and results were compared to those generated at the clients' lab.

We were provided with the clients' HPLC methods but were required to perform full ICH validation of these for both the API and drug product. Since the methods were similar, we found efficiencies in the project by conducting these two validations in parallel. Almac routinely perform ICH validations for methods developed in our own labs, or at client or third-party labs.

Batches to be set down

For this project a significant number of test articles were set down on stability **(Fig 1.):**

Figure 1: Test articles supplied to Almac for stability work

	Batch 1	Batch 2	Batch 3	Total
API	1kg	1kg	1kg	3kg
Drug product (capsules)	~95,000	~75,000	~75,000	245,0000 capsules
Drug packaging (capsules in blister)	2300	2300	2300	6,900 Blisters
Drug packaging (capsules in bottle)	350	350	350	1050 bottles

As well as receiving these samples to our GMP facility, they required preparation prior to set down. The API was aliquoted into ~25g bags to ensure adequate material for each testing point. The bags were sourced by the client to be representative of the bulk API storage material. The bulk capsules were portioned into 500 count bags, again into materials sourced to mimic the bulk storage conditions. Bulk capsules were also portioned into 60 count bottles for the in-use stability programme. The efficiency of the team at this point was paramount, as some of the release testing data was included in the T=0 timepoint certificate of analysis, and in order for this to be valid, there was a limited time period to set down. Typically, the study must be set down within 30 days of the release testing for the data to be accepted.

Both the size of the team and the efficiency of practices were key to process the significant volume of materials on time. The consequences of not meeting this timeline would mean repeating T=0 testing which would cost time, money, and material. The size and flexibility of Almac's wider team encompassing stability, QA, project management and material store personnel, was key in meeting the set-down timeline.

Conditions

The stability data generated at the scheduled timepoints provided sufficient coverage for the drug. However, at project set down it was imperative to include sufficient material to allow for testing at all optional points.

This stability study ran for 5 years at Almac, and whilst these studies are used to obtain long term shelf-life data, at the early stages products are exposed to harsher conditions (e.g. higher temperature, increased relative humidity) to stress them and increase the rate of degradation.

This is important as it provides an overall idea of the degradation profile of the compound (and potentially highlights issues with analytical methods or the rise in level of certain impurities). Accelerated conditions can also be important when considering the infrastructure of the end user market. Whilst 25°C/60% RH would be considered room temperature in the UK/US, for some African and Asian countries this would be impossible to achieve without control. Accelerated conditions can also be used to predict the shelf life of API or Drug Product in line with ICH guidelines.

Testing is used to mitigate issues with stability of the compound. If the article shows good stability at 25°C/60% RH then this will allow the product to be stored long term at room temperature but if results returned are Out Of Scope (OOS) or Out Of Trend (OOT) and do not adhere to the set specification, then further work will need to be done. On occasion these OOS and OOT results can be attributed to errors in the analysis, e.g. Issues with sample preparation or calibration of instrument, and investigations are performed for each OOS/OOT result obtained. If these results are shown to be valid, then these optional timepoints can be initiated, this will give data on the stability of the product in cooler conditions. The refrigeration of the compound will slow the degradation and will still allow shelf life data to be set for the drug, but it may be a requirement that the drug is stored and shipped under cold conditions.

A study has also gone the other way with this. Pfizer had performed stability studies on their COVID vaccine and were happy with the data under frozen conditions, so they stored and shipped at –70°C. This caused logistical problems but enabled the vaccine to be put to use as soon as possible. Whilst the rollout of the vaccine was ongoing the stability studies rolled on in the background. The new data obtained showed sufficient stability in the range –25°C -15°C, these freezers are more widespread and made a big difference to the logistics of the programme, allowing the vaccine to reach a wider audience more quickly.

Case Study: Spotlight on stability

Analysis at each timepoint

For this project, the full T=0 release testing was performed by the client as part of their in-house manufacturing process. Almac performed a subset of the full release at each timepoint in line with the stability protocol covering:

- Assay / Impurities (HPLC)
- Physical form (XRPD)
- Water content (KF Stromboli)

Microbiological testing was included at some (but not all) timepoints to prove the absence of microbial contamination. For finished products, dissolution testing is also included to simulate the effectiveness of the drug in vivo.

Transport / Temperature cycling studies

To ensure that temperature excursions did not lead to wasted product, a transport study was conducted. This is where the drug is exposed to temperature cycling to mimic freezing and thawing of the drug.

We exposed the drug product in its final packaged form to 3 cycles ranging from –20°C to 40°C /75%RH over 2 weeks, then set down onto a formal stability study for 36 months. This temperature cycling was performed prior to the set down, allowing the increase of efficiency by pulling these time points in parallel with the main stability study.

In-use stability

Due to the dose regimen, in-use stability was required. We conducted an in-use stability trial where bottles of the drug product capsules were exposed to 25°C/60% RH conditions for 20 minutes each day, and 2 capsules were removed from bottles. This study was conducted over 2 weeks and was used to mimic the actions of a patient's dosage regime. In this instance the testing was not performed daily, but the timepoints required were tested alongside the main study, thus increasing the efficiency of the project.

Reference standards

Most stability studies include purity/assay by HPLC as part of their testing regime and these methods require the use of a reference standard - a highly purified and fully characterised sample of the API (or impurity). Over this 5-year stability study, the reference standards required recertification multiple times, and we found efficiencies performing the recertification of reference standards alongside stability timepoints.

Project outcome

At the end of the project the client had sufficient stability data to inform their choices for the Phase III study and was very happy with the quality of data provided.

Due to the large volume of work associated with longer and larger stability studies it is also important to make the process as efficient as possible and through this article we have highlighted where efficiencies have been found in this case study.

Often finding opportunities to increase efficiency will come with experience.

In this instance the client benefited hugely from running all the samples in the same lab. For some analytical methods it can take a full day to set up the apparatus and by grouping samples we minimised the number of set ups required. From Figure 2. below it is clear that nearly 3 weeks of lab time was saved at each time point where analysis of all batches was required. When all of the time points are taking into consideration this saving is over 7 months of resource.

Figure 2: Project time saving

	Batches	Set ups / timepoint	Timepoints	Total potential saving
API Stability	3	3	11	33
Drug product bulk	3	3	11	33
Drug product blisters	3	3	11	33
Drug product bottles	3	3	11	33
Temperature cycling study	1	1	11	11
In use stability	1	1	2	2
Total		14		145

Of course it is usual to set down batches in parallel where possible, and all labs will look for efficiencies but due to the sheer volume of samples the client needed to select a vendor with the capability to manage and run multiple samples within the short window allowed for stability testing.

The client was pleased with the delivery of this study and continues to work with Almac for analytical testing.

Conclusion

This specific case study exemplifies the breadth of Almac's expertise when it comes to stability studies. Conversations involving capacity, conditions, etc, are typical and whilst these are important, there are also a wider number of factors to consider. It is therefore critical when partnering, to understand lab footprint, experience and supporting capabilities to ensure your product is in the safest hands.

Almac have significant expertise in stability studies; our team have over 20 years' experience, with 350 studies currently active. Across our global laboratories, we set down 60-70 studies each year covering small molecule, peptides, biologics, active ingredients, tablets, capsules, vials, blisters, bottles and devices. Each month Almac's dedicated team process 30 pull points, each of which includes sampling, analysis, QA review and reporting. Our capacity, capability and experience make us a world-leading partner for stability studies.


ALMAC
STORAGE CONDITION
25°C/60%RH
APPROVED BY:
Myra Duane – Quality Assurance Bioclin
DATE:
MMM
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Biography:

Anna Cousens - Business Development Manager

A degree in Chemistry with Medicinal Chemistry from Warwick University assists Anna with her role at Almac. Anna joined our API and Chemical services Business Development team in 2012 and works with a number of clients on API and Biocatalysis manufacturing projects. More recently Anna made the transition to our Analytical BD team where she looks after our global analytical services clients across our global laboratories.

Prior to joining Almac Anna worked for University of Wales, developing relationships between academia and industry through government funded initiatives. Anna has a particular interest in working with academic institutions, both for integrated projects and analytical support. During her time at University of Wales she completed an MPhil with a thesis on “Rheological properties of Acacia gums” which included characterisation of complex protein-polysaccharide products by GPC-MALLS, providing useful insight supporting her analytical role.

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