

outsourcing Q&A

BEFORE YOU TAKE THE PLUNGE: TIPS ON DISSOLUTION TESTING

Sharing their expertise



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Lancaster, PA. Lancaster Laboratories is an analytical contract laboratory founded in 1961. It offers dissolution services for tablets, capsules, comparator products, devices, and transdermal patches. It also handles method development and validation, stability studies for new drug development, and release testing of marketed products.



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development, method transfer, and instrument training. It relies on its employees as well as a network of external consultants and universities to provide customer support.



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Courtesy of Lancaster Laboratories, Lancaster, PA

Dissolution testing helps monitor the quality of tablets, capsules, and novel dosage forms by showing how the drug dissolves in solution. Even in the environment of Process Analytical Technology and Quality by Design, the dissolution test will likely continue to play a significant role in drug development and quality control. Conducting the test, however, requires a good deal of time, space, and expertise, so some companies prefer to outsource it. In this article, people with first-hand knowledge of dissolution testing discuss the topics related to outsourcing it.

Q What are the key issues a company must address before it decides to outsource dissolution testing?

A Lehman: We'd like the company to let us know if they have a preference for the type of dissolution that is conducted, whether it's baskets, paddles, flow-through, or reci-

procating. It's helpful if the company has some starting points available for us. Analytical finish approach would also be useful. They may not have dissolution conditions but they may have an assay method to use as a starting point.

Mayock: If they do have an analytical procedure already in place for an assay, that helps us to develop a dissolution method on the analytical side. If you look at dissolution, there are really two sides to it: There is the dissolution of the dosage form—also called the sample preparation—where you look at the release of the drug over a time course, and the analytical finish, which is typically HPLC or, in some cases, UV-visible spectroscopy. When a company comes to us, they should have an idea of what they want. When we get started with a contract, one of the first things is a quoting process. The more information they have on what they're looking for, the more accurately we can provide a quote.

Riley: The phase of development is another key consideration. In early development, you might need dissolution results almost immediately. In a later phase of development where dissolution is being used more as a QC tool, you can probably tolerate a little bit of delay in getting those results back from the contract lab. You also want to consider what the technical capability of the contract lab is and what their experience has been in developing products, whether it be immediate release or controlled release. In addition to a technical audit, you should also conduct a quality audit if you are intending to use the contract lab for clinical work or work that might go into a regulatory submission.

Q What are some reasons companies decide to outsource their dissolution testing?

A **Riley:** In my experience, when we've outsourced dissolution we've typically outsourced it as part of a complete project. I don't recall outsourcing dissolution as a stand-alone activity. If, say, we were outsourcing a stability study, then the dissolution testing would be part of the overall testing protocol. Similarly, if you were outsourcing formulation development, then dissolution testing would be included as part of the overall project plan.

Magnier: It can be a "time-to-market" pressure. The company might not have the specific instrument. But dissolution instruments can't be purchased on a guess or a feeling, and there's always a transition phase to add on to it. Other times, the company might not have any expertise, and with short deadlines and side projects appearing, they decide to outsource. Our know-how is dissolution. Their know-how is somewhere else. Outsourcing can also be proactive: Feasibility studies, training on theory and application, and method development are all logical ways to approach and prepare a new instrument or implement a new technique. They save time and money without losing any control of their main research.

Emig: From a development and validation perspective, we can support their entire program—we can write all

the development plans, the validation protocols, and the final reports. From a production perspective, it's really about capacity and resources. If they don't have the capacity in their current dissolution lab to sustain a large stability program, or if it's a company that's ramping up production without the equipment in the lab to keep up, they'll look to us to fill that capacity. There is also the comparator side of the novel dosage form, where companies are getting into clinical studies and might not have the expertise in the laboratory. Those companies are looking for not only the laboratory service but also the regulatory consulting.

Mayock: People come to us for different reasons. A lot of times the virtual companies don't have anything—they're looking for us to provide them with the entire gamut of analytical services, whereas Big Pharma companies may already have certain methodologies developed, and they're coming to us to relieve their R&D or QC folks to work on other projects. Also, instead of using a typical dissolution bath they may want an alternative apparatus—the specialized, less frequently used equipment they'd have to invest in and we already own: apparatuses 3, 4, 5, 6, 7, Franz cell, and those for non-compendial dissolution. Additionally, sometimes companies, especially smaller companies, don't have the technical expertise. They want to use our technical expertise to help develop the science behind the dissolution so that they have a better package to present to the FDA.

Q How does your company ensure that the outsourcing progresses as planned?

A **Lehman:** Client interaction is the key to progressing the project. We have, at a minimum, weekly meetings where we provide the client with a summary of all the work that has been conducted during the past week. They see what situations need to be addressed, make decisions, and have discussions about the past and the future of the project. It's been very successful, and we highly encourage every client that comes in to establish that type of communication with us.

Emig: On the production side, we try to understand the client's deliverable needs, as far as their turnaround time requirements for whatever type of program they're running. We're always trying to plan ahead to make sure that we're going to have the staffing and the equipment to handle the volume once we get to that point. So on the project-based side, where we're doing development and validation work, it's really about collaboration. A client needs to feel involved and see the progress rather than wait for 6 weeks to see if they get a product at the end. And on the production end, it's about delivery.

Mayock: The other thing is that if you hit any snags, it's important to communicate those. There are critical quality attributes that control the release of the drug and, ideally, you want the dissolution method to be able to detect when that drug is not releasing properly. You want

to be able to detect a failing batch—that's really the goal of a dissolution method. For example, a drug-to-polymer ratio is often a critical parameter. If I have a higher polymer-to-drug, it will release slower, and if there is a lower polymer-to-drug, it should release faster. When the product is at those different extremes, does the dissolution method detect that? Now if it doesn't detect it, or it has difficulty detecting it, then you have to go back to your method and ask, "How can I modify it so that it will?"

Riley: We particularly wanted to be informed by the contract lab if there was a problem because dissolution is one of the key indicators of a problem with the formulation. So if you've got, say, a registration stability study ongoing or clinical stability study ongoing, and a contract lab notices a systematic dissolution or, even more seriously, out-of-specification results, you'd want to know about that right away. We always made sure that somebody was trending the data very carefully to keep track of changes, whether it was the contract lab that was providing us with regular reports, or whether they provided us with raw data and we did the analysis ourselves. In other words, it was important to clearly define roles and responsibilities. The other factor to consider is proximity. It's much easier to just hop in the car and drive over to find out what's going on than to try to resolve the issue by teleconference, especially if multiple time zones are involved.

Q What types of products pose the biggest dissolution challenges?

A Riley: Controlled release and special drug delivery systems often required specialized equipment. Most contract labs have type 1 or type 2, but not some of the other USP apparatuses. If you have to use some of the other dissolution apparatuses you would have to transfer that capability to the contract lab and set them up.

Mayock: The longer the release profile is extended, the more challenging it is, both in terms of analytical resources and potential method challenges. The other thing about extended release is the FDA is expecting to see an in vivo-in vitro correlation, if not a relationship. Essentially what you're doing is you're slowing down the dissolution. You're taking a fairly soluble drug, you're slowing it down with the formulation so that it releases over a period of time, and dissolution is the rate-limiting step in the delivery of the drug to the blood. You should see the drug release profile correlate with your blood drug levels. An important part of developing an extended-release profile is that you have a relationship or correlation present.

Lehman: With extended release, you usually have to conduct sample pools over a prolonged period of time, so unless your system is validated for automation, you have to ensure that staffing is available to make those pools. It's

a capacity issue at that point because you are taking up an instrument for a considerably longer period of time, both the dissolution bath and the equipment used for the finish, whether it be UV or HPLC.

Magnier: New dosage forms will probably be more and more difficult to design, manufacture, and copy. So it makes sense that they will also be more and more difficult to characterize. Dissolution testing has to follow the evolution of the drug delivery system. One of the most challenging parts is to manufacture innovative instruments that are able to follow that dosage form evolution.

Q Has the issue of calibrator tablets versus mechanical calibration affected your outsourcing relationships?

A Riley: Not really. I was somewhat removed from the issue to get very involved. However, it is certainly important to ensure that a CRO follows the proper calibration procedures and keeps good documentation. I am fairly convinced that problems with the calibration tablets are mostly related to instrument setup or metrology issues.

Magnier: I don't think it's an issue. Like our customers, we see any new information as a benefit. It's obviously important for us to stay tuned into USP and FDA points of view for new instruments and new developments. A better understanding of dissolution mechanisms can bring instrument validation to the next level.

Mayock: Our company's philosophy is that we use whatever instrument calibration procedure our customer wants. Mechanical calibration hasn't been completely accepted yet. First, the FDA needs

"Before we institute mechanical calibration, the FDA, the USP, and our customers need to buy into it."

to make it official, then the USP needs to buy into it, and then our customers need to buy into it. I've personally endorsed more of a modified version, sort of a hybrid, where you would still use the calibrator tablets, but not as frequently.

You would probably use them on an annual basis. Certainly every time you set up a piece of equipment for a run there are certain mechanical checks that you do. As far as the overall mechanical calibration, that would be done on a semi-annual basis. Typically in the contract lab we don't make significant changes until we get the buy-in from our customers.

Emig: It really doesn't affect the outsourcing relationship at all. Currently, we use a traditional calibrator tablet approach semi-annually for apparatuses 1 and 2. On the other hand, we also do what would be considered very close to a mechanical calibration at the time of every dissolution. We have some standard mechanical checks, which have been proposed as part of a mechanical calibration, that we do prior to every dissolution. We don't use it as our mechanical calibration program; we use it more as a check of the performance of the piece of equipment. So if the decision were to be made down the road by all the forums and groups discussing this that they

would want to go to a more mechanical calibration agenda, we would have no problems in adjusting our operation to do that since we do the majority of it now. It's good to have that data, too, because if there ever was a problem during an investigation we could go back and say, "Mechanically, everything was operating properly at the time of the dissolution."

Q What are the most promising innovations in dissolution testing?

A **Riley:** Well, there haven't been many new apparatuses since the introduction of type 7, and that's been around for a long time. Dissolution is often where the bottleneck occurs in the lab, so any time it can be automated is very useful. Automation can help reduce variability in results as well as increase sample throughput. Often it's the analytical testing of the samples after dissolution that takes the time. So any time you can accelerate the testing or gather real-time data, it's always very useful, particularly during product development. The other thing I hear people talking about a lot is space because dissolution equipment, as well as the associated testing apparatus, take up a lot of lab space. Thus, innovation in equipment consolidation is especially warranted. I've also seen issues related to the interface between the dissolution testing system and LIMS and people having to customize their LIMS to accommodate dissolution results. That's another reason why online measurements using technology like fiber optics to get the data in real time can be helpful. On the more scientific side, there's a lot of interest in tying together the biopharmaceutical classification system (BCS) with dissolution experiments to optimize formulations, particularly for water-insoluble drugs.

Emig: There are some new apparatuses out there that are being discussed as official in the USP as apparatus 8 that would use a Franz cell or modified basket type of approach.

Magnier: UV fiber optic is still an interesting tool as long as it is correctly designed for dissolution, considering hydrodynamics, not only multiplying it by six to fit in a dissolution bath. Fast in-situ measurements can really open some doors. Because of the API market shift to low-cost suppliers, another interesting subject is working earlier on API characterization with apparent and intrinsic dissolution. Fully automated dissolution is still underestimated in some R&D departments, even though R&D needs high productivity levels, too. USP 4 is a big part of our expertise. It solves a lot of problems and has a great technical potential for novel dosage forms, pH changes, poorly soluble compounds, and small-volumes testing.

Mayock: I think what we'll probably see are some small, incremental changes. For example, I get problems thrown at me all the time with dosage forms that are unique. And that's where we step in and provide solutions. For one company, I came up with a novel approach of

conducting dissolution. Then, about 3 years after that solution occurred to us, I actually saw someone present a poster at AAPS on the method, and I said, "That's what we did!" When I think about innovation in the contract realm, we see more innovations for unique dosage forms than for solid oral dosage.

Q Do you think the outsourcing provider or the client will spearhead these innovations?

A **Mayock:** For me, as a contractor, to go out and spend a lot of time developing or working with specialized equipment and specialized automation, there would have to be a return on investment for both the CRO and the customer.

Emig: I think actually it starts with the manufacturing companies, then it goes back to the client to adopt that as an approach for their product. The contract lab needs to be aware of what's out there and be prepared to purchase and put that piece of equipment in place when we get a request. It's not strategic enough for us to be the leader, put that technology in, and then hope that we get return on investments by having somebody ask for it out of the blue. However, we do attend trade shows and dissolution conferences to stay familiar with what's going on with the vendors of dissolution equipment. So if we're in a conference call and there's a new project, we'll be able to say, "What did you think about this? We don't have it right now, but as a consulting tool, that might be an approach we want to look at for this particular product."

Q What is the future of dissolution testing?

A **Emig:** Though there'll always be a need, I'd say there will be fewer new solid dosage drug products launched. Specialized analysis for novel dosage forms will be the key to future analytical services.

Lehman: Especially for the generic side, comparator products for clinical trial support will continue to be in demand.

Riley: That's an interesting question. With the new FDA initiatives and the new ICH initiatives around pharmaceutical development, QbD, and so forth, I think that you could make an argument that dissolution testing, for certain types of products, doesn't provide any useful information and isn't a critical quality attribute. This is particularly for highly soluble drugs, or low-dose drugs, where the rate of dissolution is not rate-determining for absorption into the body. That would certainly be very helpful because dissolution is expensive, time-consuming, takes up a lot of space, and requires a lot of resources. If you didn't need to use dissolution as a quality control tool, or if you could find a better alterna-

Will PAT and QbD
reduce the need for
dissolution testing?

tive, that would be quite attractive in certain cases.

Magnier: I would love to know the future! I can see a few trends, and I think that dissolution will simply renew itself like it already has with novel dosage forms. A good understanding of dissolution testing can also bring it closer to manufacturing. I think that dissolution testing can easily be a part of both PAT and QC. It's an important test that belongs equally in small project-based R&D structures and Big Pharma QC labs.

Mayock: With PAT and QbD, people are coming up with methods to help them say, "We know that we can predict the dissolution rate by monitoring these critical quality attributes." That's fantastic for the process and for release testing of the finished dosage form. But can this fancy technique, whether it be near-IR or Raman, tell you what's going to happen to the finished dosage form after it sits on the shelf? Is it going to still dissolve and release the same way 12, 24, 36 months from now? You're still going to have a dissolution method for stability because it's the only test we have that tells you how the dosage performs within the human body. With drug products that are highly soluble, highly permeable, BCS Class I, you might be able to get away with simpler testing like disintegration. But there's a fair amount of development work you've got to do, even for that. And let's face it, we're only talking about immediate-release products. For any kind of extended-release or sustained-release products, I think you will always have to do dissolution because many variables can control the release of the drug. Certainly there might be people out there who might disagree, but I can't see how PAT and QbD can eliminate the need for dissolution testing. T&C

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