

VALUE OF DISSOLUTION THROUGHOUT DEVELOPMENT - PHASE 1

Phase 1 is the time to choose bio-relevant media based on the API characteristics. API characterization done relatively early. Need to know structure, pKa as well as particle size range and distribution.

API selection strategy: select form or salt that is most stable, with low probability of polymorph formation, even though it may be a more insoluble form.

Amorphous drug form: another strategy to avoid polymorphism.

Use of uDISS to evaluate dissolution of API different forms and salts.

Does anyone see intrinsic dissolution as a relevant test? **Limited affirmative response.**

If so, is it performed at 37C? **All those performing intrinsic disso are using 37C.**

Issues with drug crashing out upon dilution. Compression of API powder for intrinsic disso may change properties of the powder and result in artifactual effects.

Use of uDISS in place of intrinsic disso.

Fiber optics has been found to be useful for API disso. Use of App. 4 at GSK and Schering Plough.

Two activities could occur:

- 1) Develop method for formulation development
- 2) develop method for QC or regulatory filing work.

Perfect case would be to have one method to screen formulations and one for QC.

We are now doing more development for formulation screening. Need to keep this in mind.

We should focus up front on getting the info needed to develop the best formulation. Dissolution as a performance test only can still give us manufacturing consistency, stability, etc. Present methods typically do only this. Need to change to consider IVIVR/C. As long as formulation changes are small the test should continue to be relevant. But what change will make the test invalid? How would we determine this?

Would we run disso on a suspension? **If goal is to estimate disso of API then yes. When we run disso on API with different particle sizes then we run suspensions in order to get better variability. We have run disso on Powder in Bottle samples.**

Does anyone run disso on Tox formulations? **Sometimes**

Dissolution value to tox studies: to evaluate tox formulation that may be soluble in low pH (gastric) but insoluble at high pH (precipitates out in upper intestinal tract)

Phase I objective of dissolution testing: study dissolution of API and/or drug product at different pHs.

Trouble with mechanics of decision tree. Need to make decision on API and then give next steps. BCS classification is the key element. Determine before PK data what is the BCS classification?

Need to have this knowledge at very early phase. If we know when we move from dogs to humans we will know what are likely to be the critical factors.

Considering 3 decision trees, one for each phase of development.

Separate trees for IR versus MR formulations?

Need to have decision tree based on BCS. For example, if BCS class 1 how can I develop IVIVC?

For class 2 particle size may be very important. Then go to dosage form, what is controlling disso?

Is disso even meaningful for Class 1 drugs? **Only if formulation is rate limiting. With class1 couldn't we have relevance with just PK data?**

Is relevance even necessary with class 1 drug? Not really. With class 1 correlation is not an issue. The assumption is that it will have IVIVC unless efficacy is affected in the digestive system. Such as 1st pass metabolism or degradation in vivo. Reason for many pro-drug. pH could impact availability and drive to a MR formulation.

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Always do 0.1N HCl and phosphate buffer to test stability of drug? Not really can just make judgment call. Although not really disso still important for developing method. Can we use disintegration instead? Need to determine if stability affects release.

Need to use computer modeling early on when we get early tox or PK data. **We often don't have enough in-vivo data to make a relevant comparison early on.**

For BCS class 1 pK data and computer models can definitely obtain IVIVC.

For BCS Class 2 drugs there is debate as to when IVIVC is definite, possible or impossible. **Where does dose come in, could change the BCS class in some cases?** If you actually have the target dose determined it won't be an issue. All is a grey area you must make certain assumptions. Usually dose will only change by small amount.

Might want to think of Class 1 & 3 together. Rapidly dissolving API might be a starting place for the Decision Tree branches.

Not comfortable that you cannot get IVIVR/C for class 3 IR products.

Can you get IVIVC for Class 4? **We have obtained IVIVR. Rank order. At least then you know the disso is somewhat predictive.**

Back to Class 2- there is debate if looking at PK profile and physical properties when can I get IVIVR and when is it not possible? Based on 1/2 life can I get IVIVR?

IVIVC is related to in-vivo dissolution not in-vivo absorption. So how can I get correlation? If absorption is limiting cannot apply correlation. You can if FDA allows mathematical model with in-vivo model of absorption for drug included.

Boundary is not clear between BCS classes. BCS 2 but not soluble at higher pH-just out of luck.

If absorption is rate limiting then can use disso to determine how much needs to be available to get desired effect. Set a spec for a certain level at early timepoint, then absorption alone will control.

Maybe we shouldn't be so tied to BCS. Could just look at highly soluble in base or acid and use that to separate. Then disso would almost be competing with stomach emptying. For most Class 1 & 3 dissolution is almost never going to be rate limiting. **BCS is nice but can modify based on the formulation.**

Although many say all soluble drugs have been discovered already, we still need to address in the decision tree.

There is no reason to force IVIVR/C on BCS Class 1 compounds. HAS anyone has success with IVIVR in Phase 1? **We develop IVIVR then change for QC. Have had many issues with animal data used to develop relationship not having human relevance. So why can't we get human data sooner. In vitro still in vitro even animal data at least gives some in-vivo aspects. Animal data can be very useful for gastric pH variability issues. What is the purpose of doing a lot of animal studies to develop IVIVR wouldn't human data be more useful? Animal data not generated for IVIVR it is just what is available. Can perhaps at least look at rank order.**

Can we get relevance for class 1? **No it is just a performance test. But we can look at formulation differences. It can be useful for Class 1 if you have a limited absorption window. We had an experiment where at low pH we got no dissolution, we raised the pH and got dissolution. When we lowered the pH again the drug stayed in solution. Perhaps could get an even better fit with App 4.**

Very soluble in low pH but low solubility in high pH-then you can also use disso to predict.

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We tend to over discriminate in-vitro. What are we trying to discriminate? We need to know what the key quality attributes are. If we see changes on stability and are asked what is the meaning of these changes? How are they relevant? We need to be able to answer. So we need to have a discriminating test and one that is relevant. Generally these will be 2 different methods. Many large pharma companies are working towards that.

Do you see 2 different methods being developed? **Yes, at least trying to talk about that.**

For a phase 1 method it may make more sense to use a method that only gives 50% release but the correct hierarchy of profiles. **Some feel that Phase 1 QC testing is an oxymoron.**

Can use relevant media at the very least. Disso w/out IVIVR or disso as a risk management test. What is the risk if you have 20% less release. If you have IVIVR it is possible to go with that method, if not possible you can use the traditional QC test for risk management.

Where do we get value? If we have 50% release and that is known to be relevant then it is useful. But what if the capsule hardens on stability? Will the test show that? Formulation change would not have any impact in-vivo. But you may need to be able to demonstrate both. We have formulations that change significantly on stability but not relevant in-vivo. So the performance test that shows the changes is over discriminating.

Back to Science. Should we have a performance method if we don't have any IVIVR? 2 gaps:

- 1) How useful is my animal data? (for Phase 1 that is what's available) Think about how to design animal studies to be useful.
- 2) Without any IVIVR what is the value of the dissolution test

Dissolution technologies utilized during Phase I: Apparatus 1, 2, 4; intrinsic dissolution; μ Diss system for API powder solubility studies; GastroPlus and DDDPlus software programs; UV fiber-optic detection.

MECHANICAL VS CHEMICAL CALIBRATION OF DISSOLUTION APPARATUS

ASTM drafted new procedures. Procedures approved in March 2007 but not unanimous opinion. FDA endorsed but nothing official. FDA labs are using new procedure.

How many people have heard of the ASTM mechanical calibration? **Everyone.**

How many people in company? **Key players.**

Is anyone using it? **My company waiting for FDA endorsement. We are considering it.**

Key issue is vibration. How are we going to address this? **Equipment, trains etc. can influence.**

Question is where do we go from here? If officially established what will we do?

Develop in house calibrator tablets, keep using USP, or what? **Internal decision lab to lab.**

The real question is 'Are the systems being adequately evaluated?'

Our company did an evaluation of calibration failures correlated to system issues, did not find 1 instance for 42 systems.

We had drafted procedure to change but didn't know anyone else that had done so, so back off.

FDA has started using mechanical calibration only. **They determined analyst issues most likely source of failures, so now use prednisone tabs as training tool for analysts.**

Use separate bath for training so any failures are not going to reflect on suitability of bath.

We work in a regulated industry. The ASTM procedure is an alternate procedure. We must validate if we want to start using it. **Must be a well thought out decision, evaluated side by side. Holes in procedure, vibration, vessel condition, vessel shape, etc. not included.**

Must have means of performance verification.

The USP test is a holistic check of the system. Calibrator tablets can be considered a system suitability test. **FDA wants to know how a tablet can be used as a std on an instrument meant to test tablets.**

Need orthogonal method.

Still need vibration, vessel concentricity and vessel smoothness. No orthogonal way to verify these parameters now.

Goal would be to go the mechanical only calibration.

Last issue of Disso Tech talks about vibration. Next issue will have summary of industry comments on mechanical calibration. Good way to get feeling for how industry is viewing this topic.

Any info on manufacturers of vessels, etc.

Overall assumption that disso systems are nice, not the case. Horrendous conditions out there. These systems could never pass any calibration. Must have a sound process for evaluating suitability.

If you followed ASTM procedure and passed it, what is the chance of failing the calibrator test? This info has not been provided. **Didn't they do an MSA on the systems and determine that most of the mechanical criteria were as tight or tighter.**

FDA did not test it. For labs with issues I think the calibrator tablets keep in line.

But tablets only a US requirement. Not required in other countries. Why would other countries not use new process. They have never used anyway.

If you ran mechanical would calibrators fail? There are parameters that are captured with the new process. Until a spec is determined for vibration Pharma is planning to hold off. Need to measure the vibration in the vessel filled with media and in use. Vibration is only going to really cover everything if it is at time of use and on-going. Vibration can be dependant on specific instrument or even analyst using. Very complicated could take years to accurately evaluate.

Should industry or reg. agencies or manuf. be responsible for this evaluation?

Recent work gets back to why ranges so wide for calibrators 30% variability allowed. In 30 labs there is variance between labs is high but intra lab variance is very low.

5 analysts, 6 testers-residual variance outside of tablets less than 4% feel that 2% actual variance. Issue is method, no quantitative number for O2 content, tablets are terrible. One manufacturer is much better of variability. Vessels also make a huge difference. Must take a meter and measure gas content, re-measure at 30 minutes due to re-aeration. If moved tester get different results, if use different vessels manufacture get different results. There is no state of the art now. Sampling zone matters, filter process matters. We are going to re-run and tighten ranges on calibrator tablets. Different testers respond differently to insults. Some are sensitive to vibration some to

wobble. Want to tighten spec to make valuable not too tight. Should we test for dissolved O₂ or total gasses. Need to keep below 2 micrograms/L.

Estimates can get as high as 4K for calibrations.

What to do in event of failure? What do people do now when they get a tablet failure?

Need to have an SOP. What about when there is no spec but you know intuitively that the parameter could have an impact i.e. basket wobble or mesh size. May or may not pass at this stage. What about Teflon paddles that are just starting to peel. Are either of these addressed in mechanical calibration? Yes, it states to inspect. But what is the spec. How often are you going to do it. Checklist, every 3 months? Need to have a well thought out process.

Are there issues with system problems resulting in high calibrator tablet variability? Probably some built into ranges, Pharm. Forum May/June article will talk about proposed changes that may add more value.

There is no way at present to evaluate critical aspects of the test. USP is in process of changing that and deliver something that is more useful to industry. As response to this dialogue.

E25-03 is the ASTM method proposed. If you implement please let Alger, Brian Crist or Vivian Gray know what the outcome is. **We should know whether our systems are working properly based on our stability data. Also need well trained staff to perform calibration.**

QBD, if Toyota can use 6 sigma, why can't we expect our suppliers to use same standards. The manuf should be able to communicate what the quality critical aspects that we should focus our efforts on. But once system is delivered it is up to the owner to maintain the system. Toyota provides guidance on how to maintain. It is important for manufacturers to put quality into systems but some don't. Toyota also drives each car.

QBD is fantastic idea, we know what some critical attributes are but not how to measure. Manuf. is black box for formulators, formulations is black box for manuf. Who is working to make these connections. In past we tested with tablets. Maybe we need to start pushing for better control before we get the systems. Mechanical calibration may not be stringent enough to test all quality critical attributes.

The moment we say how you drop the tablet affects the test, where the system is sitting affects the test, etc. This is very disturbing, still discussing same issues as 20-30 years ago. We are stuck with certain hydrodynamics cannot deviate without becoming unharmonized. We have to think about a dissolution test that is not so significantly affected by these tiny differences, that we can have confidence in.

How can we use this test as surrogate for in vivo data with out confidence in the test?

We just repeat test if fails, we routinely have 2-3 vessels fail but pass on retest, we never see any product as sensitive as prednisone. Also degassing critical in calibration, but not that critical for most formulations. We have to get past these issues for calibrations with prednisone.

VALUE OF DISSOLUTION THROUGHOUT DEVELOPMENT - PHASE 2

At this stage want to evaluate IVIVR but now want to move on the IVIVC. First use decision tree to help determine if IVIVC is likely, unlikely, not possible.

If IVIVC can be established how does it add value?

One thing that can affect formulation in disso but also affect formulation i.e. pH stability issues that can then be addressed in the formulation.

In early studies where you don't have good availability it can help you to guide formulation dev if you have a relevant method.

Case Study-Glyburide formulations

Disso in bio-relevant media did not show difference but clinical saw difference. Ran Gastroplus using disso data

Used API characteristics got good predictive model.

Reran in disso media but simulation totally off using disso data.

Decided pH gradient was what was missing in disso test. When used bio-relevant media drug stayed in solution rather than crashed out. New model looked good.

Case Study mean particle size

Used PK data model way off. Tested in bio-relevant media reran model better then used this data and varied what we considered to be the critical parameter. Based on absorption limited drug.

Turned out the critical parameter was particle size and particle size distribution. Gave different profiles.

Can use this info to try and choose formulation direction. So particle size distribution and size specification are what we need to control to affect formulation.

Older software to estimate physicochemical parameters were way off. You must make sure that you have all components meshed.

2 batches with basically identical surface area, intrinsic disso different, so still have some parameter that we have not captured with other physicochemical test.

Goes back to investigating API solubility in different pH conditions. If you don't have IVIVC/R does the dissolution test still have value?

Can we still use it for formulation development? **May be of value for optimization of formulation/process and to support DOE testing.**

It is possible that there may be some IVIVR/C just not possible to prove it by making formulation with different profiles.

Should we be promoting greater use and dissemination of IVIVR/C data with level B/C correlations.

It doesn't necessarily need to be level B/C just what we as scientists think is important.

If we have correlation then we should find a simple buffer test that can evaluate the formulation.

Need to change the test to be relevant. How far would you go, would you use alcoholic media for a poorly soluble drug?

Why not. Also can use App 4 to change not only pH but also flow rate. **Danger is if you change formulation again does the model hold.** For any DOE must find data that is meaningful or else not

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useful. Sometimes you just can't get IVIVC too many variables. That doesn't mean the dissolution test is not useful. You just move on using the test to measure attributes that you feel are significant but may not be able to prove that.

Why does dissolution need to have a larger context of meaning, assay doesn't.

If we don't have correlation do we have a rank order for what we would want to be able to determine?

What parameters are more important? Can investigate in DOE and get very valuable information. You can change numerous parameters and see what the impacts are. But not necessarily able to correlate that to what will happens in the clinic. **But with relevant method cannot change as many parameters. So perhaps should do DOE first then go for relevance.**

DOE serves 2 purposes for process robustness and product quality. Even if cannot predict in-vivo performance. Human performance DOE can only be for 1 parameter. Would add value from process perspective because it is a performance test. Do not have another performance test at this point. But this still won't tell you if the process variability is relevant. To predict clinical performance the disso test has no value unless based on in-vivo data, either animal or human. Also stability of formulation needs to be evaluated. Dissolution needs to provide that information as well. The perfect test is a test that gives biopharmaceutical quality and in-vivo performance. But if you cannot get that then move on to test that will give that.

How do formulators make the 3 formulations in the first place. What do they base those formulations on. Is the science completely worked out? Why don't they use the DOE? Can we help them with that, using DOE information to make decisions.

This is why we are probably more successful with MR release formulations. We have minute control over when the drug is released. For IR products we do not have as much control.

Would be better off looking at what we think the few critical manuf. attributes and put it into a human study then that data is what we can base our in-vitro correlation on.

As group we are at mercy of clinicians because you can only develop this when you look at multiple formulations in humans. And this only happens when the clinicians are not happy with the initial studies. Even if the clinicians are happy with initial formulation should we still advocate for a DOE in-vivo for quality by design?

Yes, we should push for that. There should be enough information to promote using this plan. This group is only putting out a position paper to promote this type of testing. Then it is up to the individuals to make the decisions about whether to adopt it.

This is where we can use the software to help make a more scientific based decision rather than an empirical decision based on what worked last time. This would at least move us to a more scientific decision. DOE is not a single thing, selection of parameters and ranges are critical for success. Also there are numerous different statistical models for DOE many of which are not valid for these types of study. Each design has an equation associated with it and that equation determines the methodology that can be used with it.

If have relevant test it would be ideal to use for design studies. Evaluate if a better test than dissolution. Test can still be of value to help understand process and control process even if not relevant.

We have a product with extended release, 8hrs. For NDA filing we proposed use of weight variation to replace dissolution but it was not successful. Agency stated not mature enough. Had very strong level IVIVC established. Polymer is majority of tablet weight. We had data to support that polymer content was critical attribute for release.

It is our job to say there are other ways to evaluate batch quality. This is a great case study should be able to study weight variability to determine drug product quality.

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Merck has also used disintegration as surrogate for dissolution test. **There is still some hesitancy from the agency to use disintegration. We have continued to provide information to support use and are introducing plan to use to agency earlier to get them used to the idea. Used for Class 1 compounds in IR formulations. Resistance is based on whether disintegration can be used for stability we argue that we have other tests to help evaluate that. Is there perhaps resistance due to concern that undissolved excipients could potentially be undissolved API?**

FDA member of subteam putting position paper together. Are many people using bio-relevant tests to evaluate your design space studies? **Likely just using method available (non-relevant) for this testing.**

Phase 2 is critical point where you want to look at IVIVC. Phase 3 is a little late to be looking at this. This is where you want to use for bioequivalence, SUPAC requirements, etc. If we do not have correlation that is where we have debates? Quality of DOE. Should we put DOE study in humans? From scientific perspective perhaps human study is the way to go rather than using dissolution because we don't know the in vivo performance.

So what can we use instead of dissolution if we don't have any relevance or correlation to in vivo?

If we have fast disso >95% in 30 minutes-tablet rupture is representative of the disso test-use disintegration as performance test.

If don't have fast disso-then we need to characterize what is controlling disso. Could be granule or formulation properties-if erosion controls release then again can use disintegration.

If granule or particle size controls disso then disso test can add value.

Low solubility API

API solubilized in formulation (liquid filled capsules) if API stays in solution-capsule rupture or disintegration test.

API not solubilized then need to characterize disso rate mechanism-look at API properties by disso.

Challenges with oil filled capsule to using disintegration test? How would you know if API stays in solution.

2 different cases if have oil that just floats then rupture would be good test. If contents go into solution then you would want a dissolution test.

Can use surfactants or pH ranges beyond physiologically relevant range and you almost saponified the oil and API.

You can have other means of technologies to evaluate whether the API stays in solution. Want to clarify decision tree. Yes, to if API stays in solution-use disintegration.

Have comparison of cross-linking correlating with disintegration time. Still use dissolution to evaluate long term stability of formulation, very good test.

If not liquid dosage form-is it API solubility controlled?

Yes, critical attributes, particle size and surface area. Can we evaluate particle size with disso? Can we change formulation to make more soluble? Is disintegration or capsule rupture controlling disso rate? If not then multiple parameters controlling dissolution so then would want disso testing.

Do we account for the fact that we could have API characterization prior to manufacture and that in the manufacturing process these attributes could be impacted? Concerned about anything that could affect properties and are the proposed methods appropriate to evaluate this.

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This process is dependant on a well characterized process. You would have to prove this prior to going forward with surrogate tests.

Anyone looked at disintegration in-vitro compared to disintegration in vivo? How do you measure disintegration in vivo? **They looked at radio labeled dosage forms in vivo, sig. different than in vitro.**

Can we be sure that disintegration in vivo would be same? Well same question can be asked about dissolution. Disintegration is a part of the dissolution process prior to going into solution.

Disso on Oral solution, put on minimum requirements that the drug goes into solution by certain time, then just use solution criteria for dissolution.

For extended release we need correlation, so have drug release profile match disso profile.

If I understand my disso profile and can use it to monitor my process parameters then we can use the disso test to monitor quality. Need to understand release mechanism, how do you know you understand. Are the mechanisms so transparent or do you just guess, is there a bar you have to reach to demonstrate understanding? Should we have criteria for understanding.

If you have determined a correlation between polymer coat level and disso rate changes, then they have demonstrated that the critical release mechanism is polymer level.

You assume the release mechanism and then perform tests to confirm that assumption. Formulator should be able to design formulation that gives desired release. 2 expectations release spec and shelf life spec. Because of the formulation the changing rate may be different from initial but you specify what is acceptable change, what change has no in vivo impact.

If the release rate changes on stability do you understand the release mech enough to project if this happens on stability how it will impact the disso rate.

Not sure what my view is, when you talk about IVIVC then use in vitro for surrogate for in vivo. But in development I think it is naïve TO SAY WE ARE GOING FORWARD WITH BIOSTUDY WITH NO DISSO. For IVIVR/C we are looking for mathematical correlation this is not always what is needed. If the disso is reasonable then still provides useful information, is it going to be predictive perhaps not but if performed in bio-relevant media it is still quite useful. What if we have another surrogate test that we feel provides critical data is that acceptable. It could be, as in your soft gel example but don't have enough data to give definitive answer. I

If have no correlation to in vivo then disso is nice but has very limited useful for designing meaningful product and process.

We have to very careful we need to use at least 25 subjects to have a valid clinical study so if you demonstrate equivalence then may not be valid. If bioequivalence study shows differences then disso should be able to show this as well.

Frequently, dissolution has a lot of value prior to IVIVC by giving insight into interactions of different parameters. Allows us to see the synergistic effects that other surrogate tests will not pick up. Especially over time for stability testing, this is at present the best test to evaluate formulation changes on stability.

Not sure if disso is any good for IVIVC what one test would you want to try and determine what went wrong. **Dissolution test is best indicator of a problem. Won't tell you what problem is but quick and effective test.**

But does the difference we see in dissolution have any meaning. We can spend a year chasing a ghost, the difference has no in vivo impact.

At some point you have a ton of disso data then can you argue that there is no value added to collecting more dissolution data.

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I don't think you can assume you have covered all your bases. It is always possible that something new will come up.

Unless you can say we know everything, everything, everything. I don't think we are ever going to be there.

But when you have a thorough understanding of your design space you can suspend disso testing unless you need to investigate something.

Perhaps another test is more useful for monitoring and if you see issue with that test then you can use disso to help investigate.

When we talk about IVIVC we are really only mimicking ½ of the in-vivo process, the dissolution half, we are never evaluating the absorption half. Should we be trying to look at the whole picture?

Academics doing it and rather well. But we have our hands full with just looking at the portion we are trying to use now. So not advisable to take on more now.

How to drive IVIVC is a discussion for another day. **Dissolution testing can test the interactions of the multiple variables that the individual tests cannot get to. We have tablets that change and when we test moisture, hardness, particle size or distribution we don't see changes but dissolution was affected.**

Host of issues with using organic to mimic absorption. Found in several studies.

If we can prove it is not needed to use dissolution then we have demonstrate that to the reg agency. To rule out dissolution as a value test then you would have to demonstrate that there is no IVIVC/R. We never try to demonstrate IVIVC/R.

Is there IVIVC/R? Make a good attempt. If not then you can state that there is no biorelevance.

You must start with two hypotheses:

1. Disso is a useful test
2. Disso is not a useful test

Then you must go about proving both hypotheses.

Until you have knowledge of what is relevant in vivo then how can you determine if you have a relevant test. For poorly soluble drugs disso test can not see relevant differences but in vivo you see them. This doesn't mean that the disso is not relevant it just means we haven't developed the test right.

If we develop a test that is meaningful then we can try to establish a relevant correlation. You can't just state there is no IVIVC you have to make a diligent effort to develop a relevant rest.

In reality you are going to have to try to develop a disso method that is relevant for almost all drugs.

We are all promoting a culture where we say lets do our best to develop a test that is relevant. But if at end of day science tells us that there is no way to correlate what are we going to do then?

How do we define if disso is meaningful then? If based on your knowledge of API, dosage form, clinical data there is no chance of developing IVIVC.

At that point you need to be able to point to your in vivo data to support your decision that IVIVC is not possible. Due to bizarre disso profile, first pass metabolism, insufficient in-vivo data, or in-vivo data too variable.

No study designed to help establish correlation. In future should we involve clinical in design of formulation. Think about of future state.

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Future state or dream state.

In-vivo is complicated study is not designed to get in-vivo disso data. To get that you need to dose oral solution with IR oral dosage form. So this makes it very difficult to establish correlation. Can analyze in-vivo data to try and understand in-vivo dissolution.

If we had better studies then we would have good shot at establishing correlation. If we have this decision tree then it will help us to perform due diligence in evaluating our tests.

How can we use dissolution to study drug release mechanisms?

The disso test should be able to discriminate CQP and CPP but if no relevance established then what is the value of this test?

We need to add to decision tree what are actual tests that would need to be performed in order to demonstrate that correlation cannot or can be established.

If we can not develop relevance do we still care about using this test to evaluate CPP and CQP? **Don't you still need to develop a high quality product?**

But how do you know what is quality without relevance? **But what about manufacturing quality in the absence of in-vivo relevance?**

But how do you set what is acceptable? All those limits are set based on what might impact efficacy or safety. All this is based on in vivo relevance.

You can test against what you obtained for the pivotal clinical batch? If there is a change then that should set off alarms. And you may need to re-evaluate if the changes are relevant. Why are you not making the same clinical batch you put into the pivotal study.

Looking at the future state in the case where no IVIVC/R is readily obtainable then perhaps extensive in-vivo study should be designed to allow understanding of relevant attributes. Dissolution could be used for manufacturing surrogate test to monitor process consistency. But of very limited value. Perhaps better to use alternative tests that apply to critical attributes determined by analytical process DOE. Best to use relevant method for DOE testing.

There is a drive to move away from in vivo studies in the future. So should we be moving in this direction to add a study? How are we going to get support for adding an additional study?

A properly designed study would avoid later stage failed studies with many more patients. If you could obtain useful data from a small well designed study early on then you could establish a relevant predictive method and avoid later failures.

You can pick 3 formulations and put them in but with no way to predict, you are only going to get useful data if lucky. How are you going to pick the 3 formulations? You predict which formulation based on use of dissolution with likely bio-relevant media.

VALUE OF DISSOLUTION THROUGHOUT DEVELOPMENT - PHASE 3

We do little work in early stage so have very little data and poorly designed studies so little chance of IVIVC. If we do thorough job early then we will have good chance of obtaining IVIVR.

Very confident of future. Now we have an approach for 5% of cases where we have no hope of IVIVR. With well designed study to allow understanding of bio-relevant attributes of formulations.

Bio-waivers? What kind of data do we need? Dissolution should help us get waiver. BCS classification system should really help us to get waiver. BCS 1 easy to obtain waiver with disso correlation. Also can be obtained with BCS 2 compounds.

Have seen cases where F2 criteria eliminated possibility for waiver for a higher strength vs lower strength product. May not meet the F2 criteria but highly likely that they are equivalent. Can you suggest any arguments or alternatives to these arbitrary F2 criteria? Any alternative similarity tests?

Now have 2 approaches. 1 regulatory approach. 2 scientific approach. **Any method that gives relevance is appropriate? Can we then obtain bio-waiver? If we have a bio-relevant method. If we have very strong correlation, level A.**

Have seen multimedia methods accepted to demonstrate equivalence. And obtain waiver.

Have to evaluate the level of change that you are trying to get waiver for. If have study where we design space and have relevance or correlation. Any changes included in the design space should be able to use the dissolution method developed to obtain waiver.

If you cannot demonstrate that the method is predictive how can you base a waiver on that?

Why not? If you can say if my formulation will be within this relationship why can you not be given a bio-waiver?

Correlation is mathematical for relationship it is not mathematical. You still have a relationship just not 1 to 1 relationship. You can say the slow formulation was equally slow in vivo. Not exactly the same profile.

Everything within the window of the study it would all be considered equivalent. As long as included in space should be automatically equivalent.

What data can you use to support that equivalence? Will have in-vivo data from well designed study early.

If you have a level B correlation or even level C if you have covered it in your design space then why shouldn't you get the waiver?

What else can dissolution be correlated with? **Particle size - near IR/Disso - Disintegration**

It will tell you the connective process, current industry practice. Discriminates against CQA & CPP.

Future state-define QC? QC test should be correlated with disso test that is relevant.

If we are saying it is good on stability then you have to generate data to demonstrate that. The relevant test may not be able to see those small changes.

Do we agree that at phase 3 we are doing QC testing whether we have a method with correlation or not?
Yes

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How do we use the QBD initiative to minimize QC testing? In future if use QBD then you will have a space for adjustment in parameters that should not be considered a change.

If you use another test such as near IR to demonstrate blend homogeneity for example then you should be able to use that test to evaluate the impact of using a different blender.

When would you have more than one method? **When you have a complex relevant method.**

Example: pH 6.8 QC method. But had pH 4.5 had rank order correlation but only 65% release so could not be used for QC but used anytime we wanted more relevant data.

Future state would allow use of relevant method despite low release. But especially for more complex dosage forms we would also like a simpler test.

Challenges to having 2 methods. Could have a QC test that is over discriminating. **Would FDA allow test with relevant test to demonstrate that difference is not relevant?**

Why would we want to do that? We would want the QC test to have specifications that would be reflective of what really has in-vivo relevance.

If move out of design space then would have to have a way to evaluate those changes. If QC test fails then you have a problem.

My control space is a subset of my design space so if I fail my QC test I can still have a batch that is acceptable in vivo performance.

Not a new paradigm we always work within this type of environment.

Set specs so that QC test would cover the relevant design space determined for IVIVR test.

How do we perform disso in phase 3?

App 1, 2 & 4. If we want to introduce another apparatus can we? As long as you demonstrate that the change is needed. **Why do we need to demonstrate that? We don't justify going to app 2 without trying app1 first. That is true. Perhaps you don't need to demonstrate but possible question would be asked.** For media as well we can go with what works best. We can use my grandma's chicken soup if it works.

During Phase 3, perhaps more opportunities to try new or alternate technologies because of increased knowledge base about the process and product.

Would only use bio-relevant media when trying to investigate other wise would likely use QC media. We need to define what we mean by bio-relevant media by defining as media that has demonstrated relevance to in-vivo results. Are we talking about bio-relevant or bio-mimicking?

IVIVR will be a continuous effort throughout development.

What is your experience with Gastroplus in phase 3? **Used for product line extensions predominately with combination products. To allow development of method for prediction for minor formulation changes to try and demonstrate equivalence to original formulation.**

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DISSOLUTION WORKSHOP 2008

Follow up on progress from 2006 workshop.

Difference in 2 workshops. First workshop very confusing. In second workshop much more focused. Should not have extensive debate and what debate occurs should be focused. Do not throw out open-ended questions such as "should we even do dissolution". We want to provide useful information. Continue to influence policies and practices.

Any preferred dates? AAPS in November, but they are not excited about workshops. They proposed holding prior to meeting or get FDA to cosponsor. We can approach FDA. The AAPS meeting is planned for the DC area. We must submit proposal soon. 2 day conference is better but may need to propose 2 ½ day to avoid everyone leaving early on second day. Vivian will propose time of 2 days; if issue let everyone know. Try Thurs/Friday maybe will help with travel issues?

FDA representative, ask about co-sponsor. Tahseen Mirza chair. Need USP, brand name and generic volunteers. Tahseen to contact FDA. Develop proposal before contacting FDA. Vivian will contact AAPS to determine how to get FDA to sponsor.

Title Proposals:

- Dissolution Testing for 21st Century
- Role of Dissolution in 21st Century Product Development
- Role of Dissolution in Drug Product Development

We are going to include extended release in this session. Could have special topic session on hydrodynamics? Thought we were going to put into a workshop? Yes.

Topics replicate this F2F agenda.

Phase-based dissolution - utility of disso, science of disso and future practices.

Day 1: Phases 1 & 2

Day 2: Phases 3 & 4, QbD, Special topics