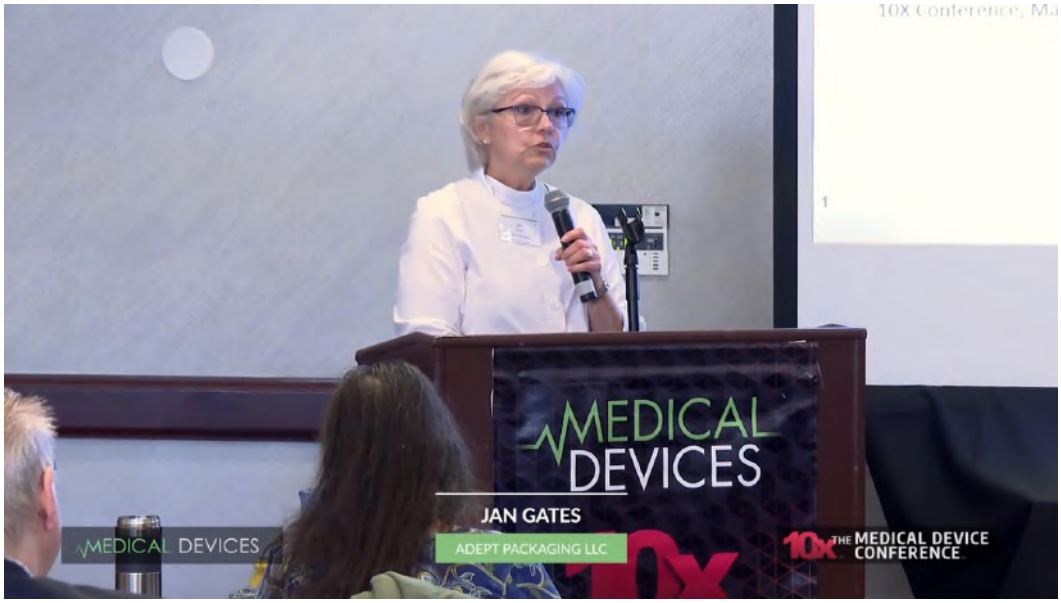

Are you prepared for ISO 11607 Packaging Changes?

presented by Jan Gates, Principal Packaging Engineer, Adept Packaging
at the 10x Medical Device Conference – San Diego 2019

Jan Gates: I'm gonna be talking about ISO 11607-1 and -2. If you are making terminally sterilized medical devices, you should be compliant with this standard. The FDA and the EU and Japan really like this standard.

A little bit about me. I say 35+ years cause I'm not gonna tell you how long I've been in the business. I've worked on a whole bunch of different aspects of packaging with various types of companies. I was very glad I got high-speed production with detergents, even though I was allergic to the perfumes. Which is why I had to get into a business that didn't have any scent to it.

How I ended up in medical devices. I also worked with a lot of different standards, ASTM and ISO BEAM. Fun ones to be working on. That's what this tag is.

I actually have a group of standards that I try and get other packaging experts around the United States to give me their opinion on so we can vote on them as a U.S. representative for whether we like those standards or not. And we've got some new ones coming up that I really enjoy.

These are some of my old products, just so you know. My only claim to fame is inventing microwave popcorn. I was pregnant with my first kid with that one.

Anyway, I've worked on some of these other products and then I started getting into in-vitro diagnostics here. Which was quite interesting putting these kits together, and they had to be controlled temperature shipped. My thesis work for my master's was actually on brick packs with tomato sauce.

Now, the products I work on, I say, if you know what they are, I'm sorry. Cause that usually means you're sick or have some problems. But I've worked on active and non-active devices, making sure the packaging works, some of the programmers that go with them.

Blisters, prefilled syringes, so it's a wide variety of packaging. This is what a Packaging Engineer can do for you. And I'll let you read that later.

We do help you save money in the long run. And we try to make sure we do it right the first time, because if you have to go back and change, that's resubmissions for a lot of different countries you have to worry about.

So these are the Standard Titles. The dash one is actually about design and development. And the dash two is talking about equipment and process validations.

They're actually the first standards that were ever developed for packaging, putting it on the same level as product. Because you do not have a product going out, if you can't package it right.

This is the history of it. It took about ten years for this to be published. There was a lot of FDA inputs, as well as other people around the world.

I don't know if you know ISO documents give you an idea that you should be doing something, but they never tell you how to do it, so we developed a standard with AAMI, which is a group that does sterilization stuff in the US, and came up with this TIR 22.

That's a technical information report on how you can actually comply with that standard. And I was lucky I got to work as a task group leader on that standard. They had taken the TIR and made it into an ISO document. Took 'em a little while to decide to do it, but it's there.

Unfortunately, this is a little hard to read because they also have it applied to hospitals, and it's a little bit hard to pull out manufacturing stuff from the hospital. They're rewriting that and it should be out in another year or two.

Now, at the end of February they just revised the 11607. And they put in human factors and use pieces into it.

> **They changed critical process parameters. They've taken that out because they found too many people were looking at one point in the process instead of the whole thing. So they wanted to make sure that people look at the whole process.**

As I said before, if you don't have acceptable packaging that you've validated, qualified, you don't have a product going out, because it's gotta survive distribution, warehouse and aging. If you're sterilizing, you gotta make sure your material doesn't fall apart too.

So these are new terminologies that were introduced. There is no primary packaging for medical devices any more. It's all called sterile barrier system, and these terms should be used in all submissions and on your reports.

And I know I usually have to work with the regulatory people and make sure the language is done properly. We do work with terminal sterilized medical devices. We don't do sterilization validation, but what we do have to do is make sure that the packaging system you have never gets a hole in it until you open it.

So we have to know a lot about the different types of sterilizations and how they affect the materials. Shall statements.

> **When you are working with ISO documents and they say shall, you must comply with that. Well, there's over 115 'shalls' in the ISO documents.**

There's a few that you can actually say, "Well that isn't applicable to my product," but almost everything else has to have the shalls done with it. I put a few up there. These are ones I found in my role as a consultant, a lot of companies have problems with. I don't want to read 'em to you all. I do have a few more slides saying what those things are.

Joe Hage: Jan, do you have a favorite 'shall?'

Jan Gates: A favorite shall. The newest, the hardest one to do? I'm not saying it's my favorite, but.

Joe Hage: It's your favorite.

Jan Gates: No, my favorite is actually sampling plan. Statistical sampling.

Because I'm finding most people don't know how to do that very well. But this one is actually been reinforced with the new standard that's come out saying that you have to show and document that you can have aseptic presentation, and you have to have documentation that the people actually know how to open your package correctly. So that's been a fun one to go through.

Test method validations always kills people off. I'll talk to it a little bit.

So this is my first one, why it says statistics.

We've got to have statistical justification. To do that, we have to make sure we have our risk assessments known.

From that, we can develop the confidence in reliability around defects. Once you get your confidence and reliability set up, which is individualized by company, then we can come up with a way of having a statistical sampling.

A lot of people are trying to use AQL, it's a AZ one point four by the quality group, American Society for Quality, but it says right in the scope it's not for individual lots, so you can't use that, you have to have a different way of doing your statistics.

So I always try and work with the company and get a policy set up so that the engineers don't have to know all their statistics too, they can just point to that standard and get the sample sizes they need.

We've got test method validations. This is a very key thing to know about. They say just because test method is published, that does not mean that it's validated for your lab.

You have to validate that test method.

So we've been lucky in packaging. There is a new ASTM test method that we've put out on how to validate packaging test methods, so that's been a help for people so they can actually figure out how to do it.

Test method sensitivity for whole package integrity is very important to do, and some people don't know how to do that, but it's a fairly easy one.

You have to have Design and Development Documents too for your packaging. Just like you do with your product, you're supposed to be doing it with the packaging too. Some companies will put that into their

design reviews when they're doing their product stuff. Other times companies will keep that as a separate type of design review.

Equipment EIOQ. This one has been an interesting thing; the clause talks about requiring it for your equipment.

What I have found is a lot of people will do the installation qualification, and then they mix up a material OQ with the equipment OQ, and then they get a new material in that has to be sealed at different conditions, and it doesn't work because they have to redo their EIOQ. And then you want to make sure.

Hopefully you know what all that is, EIOQ's and know Q's and PQ's. A lot of people don't realize there's production drift with your PQ, which is supposed to be your nominal center point on how you're producing your stuff.

Well, you've got to make sure that that drift is within your OQ, your extreme parameters for your production qualification.

Joe Hage: Jan, to be safe, I'm confident someone watching this video does not know those acronyms. What do they mean please?

Jan Gates: Okay, a **DQ** is a design qualification.

You're required to find out what the extra worse case conditions are that your product will ever be in and test them.

An **EIOQ** would be equipment installation and qualification. Making sure that it actually works the way that you think it's gonna work with all of your information pulled in there. And that includes parts for consumable parts, and the electrical work, and everything works right.

And then you have the **OQ**, which is an operation qualification for how you think your production will actually be set for a high and a low.

And then you have your **PQ**, which is where your supposed to be operating all the time as a nominal.

Okay, so we get through all that. I'm just giving you little highlights on this.

Here's your PQ, it says you must have a minimum of three lots for medical devices. And please note it says minimum, that means you can have more. And a lot of people don't realize that sometimes three isn't enough, especially if you're only doing maybe a hundred units a day.

If you're doing that as a lot, you might want to do more than one or three lots of a hundred units.

There are best practices.

One thing that's fun is statistical equivalents. Sometimes you will find out that your statistically equivalent stuff really practically doesn't make any sense, which you need to put into your protocols and what you're working on to show that it's okay, even if they're statistically nonequivalent that might mean that it's still okay practically, and that's where you might get something that has...

Like I'm doing case compressions, you might have a 25-pound difference, and statistically that's significant from another one on this 25-pound plus or minus difference, but when you're looking at the test method and cases themselves, 50 pounds really doesn't make any difference between cases.

Well, I can just say that's no practical difference where I'm trying to use logic with my statistics, and a lot of people don't do that.

Well of course with production qualifications, you should have consecutive lots, and you're supposed to have all of your production stoppages and material changes and stuff. But sometimes you can't do material changes.

You should have three lots of material you're trying to test. I had a case where three lots of a foil pouch would give me ten years' worth of production.

That wasn't practical, so I had to come up with a new way of testing the material so that if they changed the master lots somewhere along the line, I could actually see it, and incoming receiving, and decide if we needed to re-qualify.

Stability testing. Everything has to be stability tested. I know people are doing it with their products, but you have to do it with materials too of the packaging. You've got to make sure it's actually gonna last the same length of time as your product. And believe it or not, that's difficult for some people to understand.

Luckily, there is a ASTM test method we've developed that helps with that. And usually they look at just the sterile barrier system, but you also want to make sure any cartons or cases and other things you might be using, labels, don't have any problems and fall off, or discolor, or fall apart.

Oh, the other note, what's nice, once you do qualify a material with aging, you never really have to do it again if you change the design, because the aging is separate from performance, which is a different kind of test.

Anyway, I talked about humidity not being part of the aging considerations. Well, we're having a lot of problems with people not understanding humidity, and so that's something we go through, making sure people understand that what you're really worried about is the actual water vapor density in the air at a particular temperature and humidity. Not, excuse me, at a particular temperature and with a saturation of water in there.

You're not really looking at relative humidity when you're doing your tests.

So in that case, like if I'm doing something that's two to eight degrees, and I bring it into a room that's 20 degrees, it's gonna be sweating, okay?

You don't want to test at an accelerated temperature and aging with something that if you actually took that 20-degree thing and put it in to your eight degree that it would start having problems there too.

So those are things that we work through as a packaging engineer to make sure that we do the tests properly. Because if you don't you get labels bubbling up or something falling apart that shouldn't be.

Aging and Performance Tests are two separate things.

Performance test is the vibration and the handling that's out in the field and what's happening to it. Where aging is just having the material and seeing if it's gonna fall apart on you.

The best analogy I could figure out how to do was rubber rot on tires. You know after tires get about five or six years old they start cracking? And it doesn't really matter if you've driven on them or not. Well that's aging. Your tire has hit its stability, and you shouldn't be using it anymore.

And be careful, 'cause the US is the only country in the world that I have found that actually allows tires that are over five years old and not been on a car to be sold as new, and they shouldn't be. That's why we're seeing a lot of the tires falling apart out on the road.

This is just to show a performance test that was done with D4169 in ASTM, and it simulates what's happening out on the road with a truck. And I had fun trying to get a drop test and a compression test on vibration.

And we've been using this particular test method for something like 35 years and refining it and making sure that it follows what's actually happening out on the field.

This is always fun, trying to figure out what altitude you want to test a non-permeable package to. Because if you can go over the continental divide, and you go over 14,000 feet, guess what's going to happen to your package?

I had a problem with a bunch of sterile medical devices being shipped to China, and we had 'em on a plane, and they went up to 18,000 feet, and I had only tested to 16,000 feet.

I thought if you're gonna get up to 18,000 feet the pilot should have an oxygen mask or something, but they didn't. So that was pretty interesting, that was 25,000 dollars' worth of product that we were sending there for testing that could not be used.

These are the normal performance tests that are done. There is ASTM and there is ISTA, International Safe Transit Association, but they are not as broad as a consensus standard as the ASTM, and they're a little more restrictive on what can be done.

This is not being used in medical devices too much right now because there's one part of the test seems to be overdone and it destroys the packages when it doesn't really happen in the field, we've got to fix it. These test methods are used for environmental conditioning of cases, just to see if they're gonna fall apart and have problems.

It's best when someone can develop their own standards for testing. They can take all the different test methods and string 'em together in a way that makes sense for them, but most companies don't know how to do that at this point in time which is why the other test methods are there.

I was talking about performance testing and aging test, if you are going to work on it, you have to make sure that you don't get those defects confused. So this was a performance problem because this IFU actually punctured a hole in the pouch when it was doing vibration.

This is a design problem from a performance test. If you were doing aging with it, it would still be a performance problem. If it were an aging problem, you would have a crack going up the foil pouch. And its hard to keep those different types of defects separated, but that's what packaging engineers work on.

These are just talking about the 'shalls' on how to do it.

The biggest thing that I have found too, or one of the big things I should say, is packaging engineer or product development has to test the product after distribution testing and conditioning to make sure the product is still good.

In pharmaceuticals we do it a lot because some of the liquid products, if they get vibrated at the right vibration level, they actually precipitate out the active ingredient and have problems.

Here we can have something break in a medical device that wasn't set up properly for shipping, and we need to make sure if it's still functional or not.

I always find it easier to try and have the product testing done separately from the package testing so we don't overlap each other. As long as we do the same tests.

So you got to know your distribution system. I don't have time to go into this but I always put the bicycle in because I had problems with that once. This is a general distribution mapping, just to show people what it looks like when you're shipping things.

Where you're handling it, where you're gonna stack it, where you're gonna put it on a plane. I went and did a detailed analysis for a multiple shipping issue that we had at one point in time. Trying to show how many times when we had round trips going on with a product we were getting different handling plane transits, those things.

My ASTM test I can probably justify up to one or two round trips. Beyond that we've got to do other kinds of tests, cause those ASTM and ISTA was not set up for multiple testing.

Update. Here's update on my opinion, not a lot of changes. These are the reds, are the ones that are big and new. And there is a new labeling requirement that's gonna take a lot more room for sterile barrier systems.

This was the O2-2, and you can read that. Human factors we have to do a lot of testing on. Doctor Laura Bix at Michigan State is about the only person I know that's working on that and actually developing numbers that we can use and test to. I want to show this really bad.

Joe Hage: Okay.

Jan Gates: This is design. Do you think the FDA would like the way this product was being used? So this is where I'm just trying to say you've got to design...

You've got to design your product properly so it can be used properly. This is just to show you some examples of how they think the sterile barriers should be labeled so you can inspect the sterile barrier before use by the customer.

Unfortunately, even though it's in the standard, these have not been checked. You have to validate it yourself that they're actually gonna work. And we do have some new challenges, and then off just two slides and then I will be done.

Jan Gates: Well, what I will say is, having had the luxury of a little extra time to review your presentation there's a lot in there.

Jan Gates: Yes, it's an awful lot but I wanted to make sure you had some technical information to ask questions to whoever you're working with.

Joe Hage: The point I would make is that packaging is a lot harder that I thought.

Jan Gates: And I'm only skimming the top for ya.

Joe Hage: So with a half hour skimming the top, and not having enough time for even that, my advice to anyone watching this video is, there's a lot, and you need a packaging engineer.

Jan Gates: Yeah, well we're also looking at this third-party distributors are doing really weird things with the packages that we haven't validated, and they are. And that's scaring us. And then with the new stuff where they're actually handling and putting product into UV cabinets for 24 hours a day.

I don't have UV inhibitors in my packaging materials, and I don't know if it's in the product either. Spraying... hydrogen peroxide.

Joe Hage: Jan, you'd be more familiar certainly than I. What percentage of companies that need a packaging engineer have one on staff?

Jan Gates: Big companies tend to have at least one.

Joe Hage: Okay. big companies have one.

Jan Gates: Yeah, smaller companies, well really big companies will have 25, 30, so that you can do a lot of development on packaging materials and get things done before it has to actually be used anywhere.

Smaller companies I'm finding... I know I worked with Dexcom when they were first starting up and helped them with a product and they kept calling me and calling me, and I finally said, "You need a full time packaging engineer."

So they got a full-time engineer, they now have 12. So there's a lot more than what most people realize can be done and helped with the packaging engineers, so.

Joe Hage: Well.

Jan Gates: And I think it's fun because it's always changing, and it's always new.

Joe Hage: I'm grateful for this presentation, and that you're making it available online for later. It sounds to me as though, at a minimum, folks should be getting a consultation from you or the folks at Adept, talk to a packaging engineer sooner rather than later.

Jan Gates: Yeah, the sooner, because we can give you little ideas that will help with shipping, sterilization, what kind of materials to use, then we can disappear for a while until you get everything done and then...

Joe Hage: I recently worked with a manufacturer who had his entire clinical trial pushed back like a month or two because packaging was an afterthought, and the bottle that they had didn't survive the drop test, and then they had to go, and then they needed another carton, and it was a mess, so if they had only asked Jan first.

Jan Gates: And there's other ones too but...

Joe Hage: Ladies and gentlemen, Jan Gates. Thank you Jan.

[applause]