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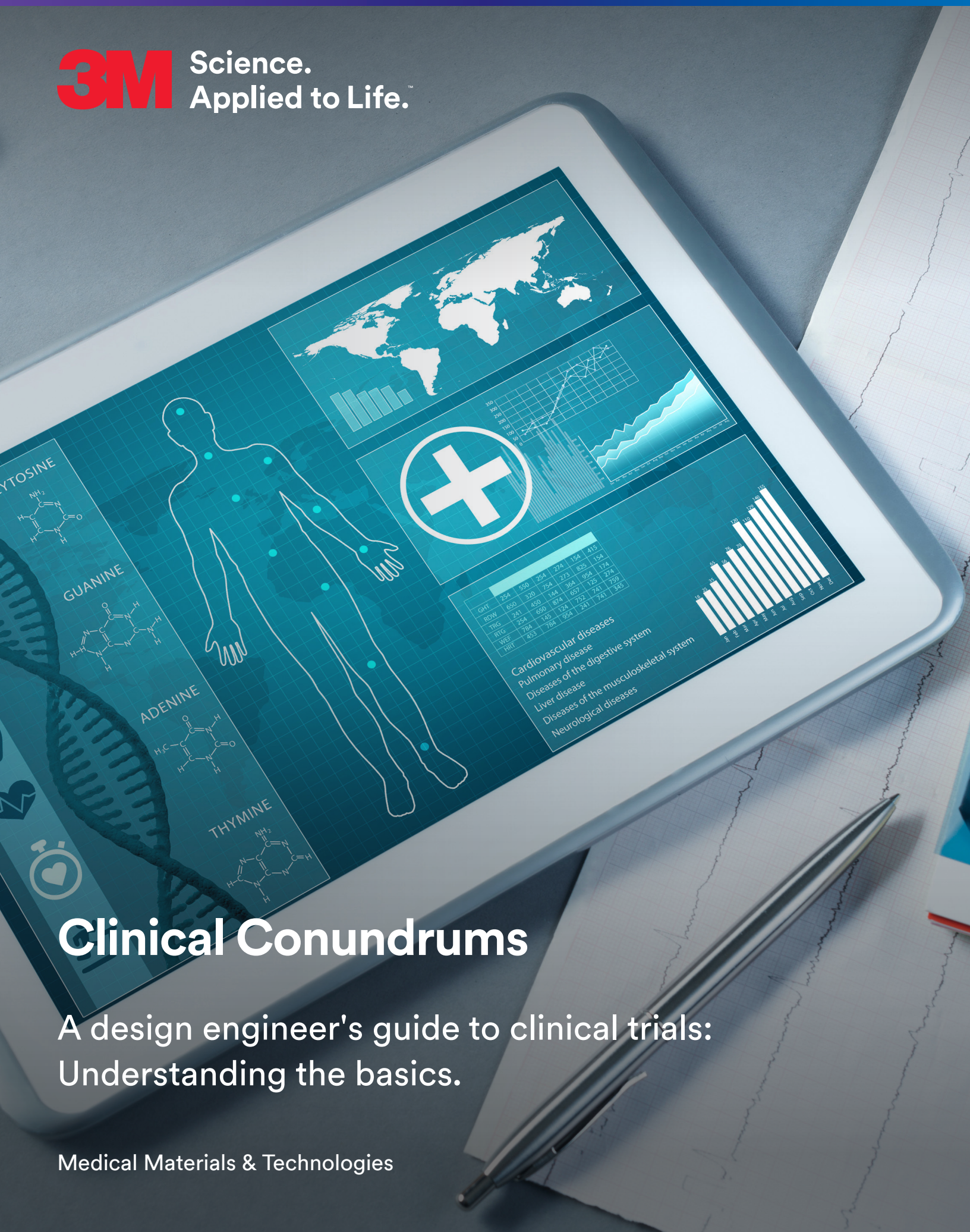

Clinical Conundrums

A design engineer's guide to clinical trials: Understanding the basics.

Medical Materials & Technologies

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The importance of clinical trials

Clinical trials, while only one step in the journey of bringing a medical device to market, are crucial. They allow the opportunity to move your device from research to reality by verifying if the device and its components will perform as intended for the application. They can teach you something new, decrease the potential of device errors, and improve or verify the safety of the device before it goes to market.

Mapping out your clinical trials early on can help yield the best results. With some studies lasting up to 90 days, they require foresight, planning and persistence. It can also mean that at some point, the question will get asked if the testing was conducted using good laboratory practices (GLP). With many moving parts at play, significant investment, and pivotal questions that can change the course of your project, approaching clinical trials can be a challenge.

By conducting testing under good laboratory practice (GLP) standards, you establish validity and integrity in your results. GLP challenges clinical trial design to consider the processes that will provide key data points in the device development and approval application. Product development groups partner with an in-house IRB (institutional review board) to ensure your clinical design and trials meet stringent criteria for safeguarding human subjects and other biomedical considerations before starting a trial. The board reviews documents such as the clinical investigative protocol, consent and inclusionary/exclusionary criteria that will be considered during the trial. An IRB's responsibility is to ensure that the proposed trial design has met biomedical and ethical safeguards to protect human (or Veterinary) volunteers during a study. These practices make sure that the quality of the clinical trial is reproducible and sufficient for regulatory review.

To deliver the results you need to move your project forward, design engineers play a critical role—from working with a cross-functional team to design the study to ensuring the device gets applied and removed accurately during the clinical trials. We put together this guide as a starting point based on our experience. We hope it helps design engineers like you understand the clinical trial fundamentals and continue innovating throughout the entire development process.

Kickoff clinical trial design on the right foot

Clinical trials are a pivotal stage in the device development process, involving many people and moving parts, but breaking it down into smaller steps can make it feel more manageable. Preparation is key for a successful study. The saying “measure twice, cut once” might border on a cliché, but in this case – it is true.

Map out your path forward

When designing your clinical trial, an important first step is understanding the different phases that your device and/or its materials may go through and the role each stage should play.

Bench testing

Bench testing will help you decide which products to pull forward into screening for the preclinical testing. It is not in itself a clinical trial, but bench testing can help determine which prototypes are most likely to meet device performance requirements.

This phase can help build confidence that the selections made for the clinical trial will be worthy of further consideration. For example if you are developing a wearable device, bench tests can investigate the tensile strength of the tape, sheer adhesion, tear strength or adhesive modulus (the flexibility of an adhesive when dry).

Bench testing can be an iterative process. If the products used in the clinical trials do not perform in the way you would like them to, this could mean more bench tests are needed, possibly delaying the project and eating into your budget.

Preclinical trials

This phase determines if the material or device at hand is safe for humans. Testing on substrates using *in vivo* and *in vitro* methods can provide initial safety and efficacy data, as well as point to potential risks that should be addressed in future testing.

Screening clinical trials

These will help determine which of your material options perform best. At this point, you have likely narrowed down your options but may still need to decide which are the most qualified to move forward into the next stage. The goal is often to select two to three constructions to be tested along with a control.

Product development clinical trials

These trials determine which device or materials perform with an optimized construction. This phase focuses on understanding overall performance and is often a continuous process as you develop the product. If you add new components or substances to the device, some earlier tests might have to be repeated.

Assemble your team

We recommend working with a cross-functional team to help you define and execute the clinical trials. Think about the different factors of the project—everything from engineering, to lab work, to legal and clinical review—to help you build out your team accordingly.

Building a cross-functional team can be important in identifying potential roadblocks or when more funding and resources are needed. Clearly outline the process to help your team members take ownership of the parts of the trial in their area of expertise. When you have team meetings, be sure to take detailed notes—and document what steps are taken, revised or omitted in a consistent and timely manner. The outline also serves to track key events and deadlines.

Consider this, the clinician on your team can be one of the primary interfaces between you, your design team and the participants via the clinical trial. They can help ensure the trial's design fulfills clinical requirements, keeping in mind whether education and credentialing in clinical research and biomedical ethics is expected or required.

Biostatisticians are another crucial team member. They ensure your results will be statistically relevant and can help identify the sub-population requirements for your trial. Producing product descriptors to design a process for a specific claim or indication for use is another area where biostatisticians make key contributions.

The CITI program is one resource for education and credentialing. This program has a detailed training suite on everything from GLP to biosafety and biosecurity. Many organizations and credentialing services require education from CITI in order to be involved in the process.

Pick your priorities

As you plan for your clinical trials, and throughout them as well, always keep top-of-mind what you want the device to accomplish. Identify the target location—both on the body and in the type of environment it will be used—wear time and the safety requirements.

To achieve this goal, consider setting priority levels for each characteristic your device needs to possess. This step is an opportunity to think about the tactile nature of the device. For example, does the device's adhesive need to be gentle on the skin, be able to stick for up to 14 days, or be somewhere in the middle? Does the device need to be repositionable, or does it need to remain fixed in place? Consider these priorities in light of the device's "early claims." You may have to make tradeoffs when bringing the product to life.

During the planning stage, also try to narrow down the prototypes for testing. While not always an enjoyable or straightforward process, most clinical trials have time and budget limitations, with finite room for variables. You can work with your team to figure out which prototypes should be tested, and which should be set aside. Data from bench testing can be valuable in making this decision.

On top of device design considerations, regulatory submission plans can also impact the planning process. Will your device need pre-market approvals or can you file for 510(k) to the U.S. FDA? Your regulatory expert can help make sure this process will meet regulatory expectations for approval.

Keep in mind that it can be normal to redesign clinical trials several times before actually starting them. Repeat trials are also possible.

Remember if outside resources are brought in, consider the need for them to sign the appropriate non-disclosure agreements.

Curate accurate conditions

Replicating end-use conditions as closely as possible within the clinical trial can be pivotal for gathering reliable data. When recruiting for trial participants, it can be challenging to find people representative of your target end-user. Even for a relatively broad study, recruitment can be a challenge. Offering compensation to your participants to increase interest, whether that is a gift card or other item of monetary value, can be an option. But if you go this route, check corporate or other policies to understand what is acceptable and allowed, ethically and otherwise.

Do your best to find participants who will meet the needs of the end device—and the end-user. When it comes to adhesives, this can mean a wide variety of skin types. Since skin is a living, breathing organ, it can change with age, health conditions, and the environment. It also varies from person to person, particularly in terms of hairiness, oiliness or moisture.

Should participants be asked to have multiple devices on a single part of their body, body size can impact their ability to wear them all. For example, if you need to stick multiple devices on the back of an arm as a continuous glucose monitor (CGM) mock-up, requesting participants of a particular height can aid in ensuring their arms have enough surface area.

Relevant environmental requirements are also essential to simulate. If the end product should not be submerged in water, it should be clear to participants they should keep out of the lake, swimming pools, or taking long baths. Or, if the end-user will not actively lift things while wearing the device, but the participants may face difficulties adhering to this, these inconsistencies could influence the success or failure of your samples. Again, focus on the end-use when determining stipulations and controls.

Lastly, in the age of COVID-19, your regular interactions with participants could be altered—as they could have safety concerns themselves. To address this, you might rely more heavily on video meetings and less on face-to-face contact whenever possible. And you may have to be even more deliberate and careful in your preparation: thinking through potential challenges and keeping everyone safe.

Moreover, the thinking and planning around the safety of testing may be even more stringent in a limited-contact environment, which could increase restrictions on which studies move forward in the first place.

However you move forward with your study, thoughtful planning can increase your chance for a successful clinical trial. This determination will not only help keep everyone safe but will help yield the most impactful results for your study.

Pre-clinical trial testing

Biocompatibility

This method measures the interactions, or compatibility, between a medical device and the end user's tissue. Any device involving human use or application to humans requires biocompatibility testing for submissions, such as FDA and CE filing.

Biocompatibility primarily consists of three parts: cytotoxicity, sensitization and irritation.

Cytotoxicity testing measures whether a substance can be harmful to living cells. Keep in mind that adverse results are not necessarily bad. If the desired outcome is to "destroy" living cells, like with chemotherapy agents, the test could be considered successful.

Sensitization testing mimics a repeated product application to the point where there could be an exaggerated response to the substance. This is commonly known as an allergic response.

Primary skin irritation testing determines whether the material, device, or an extract of either will cause irritation and present a skin reaction. This test is performed in vivo and should be conducted on tissue similar to the device's planned skin site.

For those looking to file in the United States, consider visiting the FDA site on good clinical practice to help get a lay of the land. For those looking to file in the EU, consider visiting the European Medicines Agency's website for medical devices.

To help guide the way, consider referring to ISO-10993, which provides broad guidance and benchmarks on cytotoxicity, skin irritation and the ability to cause a fever. Refer to other guidelines, standards and requirements, as well, that are relevant to where you will run your clinical trials and sell the final product.

Clinical toxicology

Toxicology studies are ongoing tests to verify if the device and its components are safe for skin. Resulting reports are completed early on in the medical device's testing to assess the degree of potential risks.

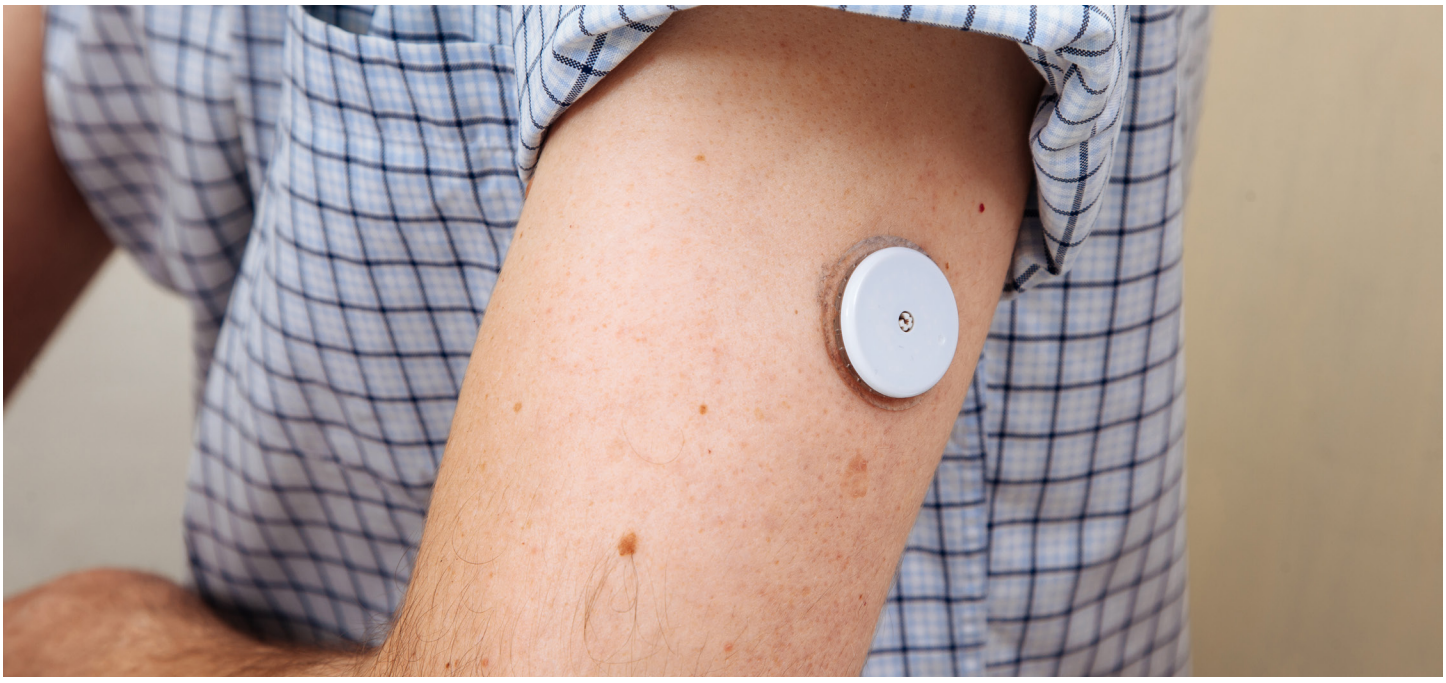
Moisture vapor transmission rate (MVTR)

Generally speaking, the MVTR is the measure of the amount of moisture vapor that will pass through a material in a given time. However, its definition can change depending on when it is used in the clinical trial process and what it is intended to measure. For example:

During bench testing, MVTR could measure how fast moisture can move through the tape in a set amount of time. Like most other bench tests, this can provide clues to the tape's potential performance on skin. However, it is not a definitive predictor of performance.

In other phases, if you are looking to understand why a tape will not stick, MVTR can refer to how skin produces moisture due to being covered by an adhesive or other material. This test can help you understand the amount of moisture an adhesive, material, or component can handle before it fails.

MVTR can help determine which adhesive may be best particularly if your end device may come into contact with moisture.



Possible tests to run during clinical trials

Clinical trials take time to plan, schedule and source the appropriate funding. They also can be an important stage where you listen to the "voice of the customer" about potential concerns. Although this is not an exhaustive list, knowing the different methodologies at play during clinical trials can help streamline the process and understand how to gain the most value out of each study's results.

Adhesive performance in clinical studies

Wear time: The durability and performance of a device can be a great concern to you and the end user – particularly if the device is not able to stay on the skin as intended. Wear time studies can be conducted both in screening clinical trials and product development clinical trials.

In screening trials, wear time studies can include situations in which you test a new family of adhesives, or other materials, seeking the one that performs the best based on what you need the adhesive to do. The same backing should be used with each adhesive to keep additional variables at a minimum.

The product development version of a wear time study can look at variations in product design, such as the size and shape of the tape patch, as well as the backing used and the wearable device's dimensions. The ultimate goal would be to generate data to support product claims.

In both study settings, adhesive performance is typically measured at specified intervals, such as 24 or 48 hours, based on the expected use and requirements of the product. At each time, the following can be measured to inform adhesive selection:

Skin condition: Is there noticeable redness, injuries or rash? Did the adhesive leave residue when removed?

Adhesive lift: How much of the adhesive has started lifting from the skin?

Peel adhesion: What is the average force needed to remove the tape?

What you can do when tests go wrong or fail

Medical devices often require an iterative development process. Even if you prepared for any possibility as much as you could, there can still be surprises. Unforeseen results can be riddled with ambiguity. Data can fall into a gray area, where results are neither clearly positive or negative. Marginal or inconclusive results can signal a need for more testing and design refinement. With no simple, straightforward answer for clinical testing when things do not go as planned, the solution can depend on how you designed each test and what your ideal outcome is.

If there are unexpected results during preliminary testing, you might want to consider the following:

Contaminants

Are you aware of any potential contaminants that could have compromised the testing settings? Were the test panels used during bench testing to screen adhesive performance cleaned before the first use and reliably cleaned between uses? Have you taken into account the possible diffusion of small-molecule additives (tackifiers, plasticizers, stabilizers, etc.) between various layers of your construction? Did study participants follow protocol guidelines against the use of lotions and sunscreen near the samples? When the testing environment is jeopardized, rerunning testing may be the only solution.

Cytotoxicity

Did the cells die, or did they survive? If the former, note how long it took for cellular death. Did the cells change in structure? Which result indicates success for your test? Reflecting on your original goal will clarify whether getting a “negative” result is actually a positive for the overall test.

Irritations and sensitizations

There are many variables here because every person's skin varies. Even if you take this into account early on, factors can change in ways that are out of your control.

Sometimes responses to irritations and sensitivity can be unintentionally exaggerated by the participants. For instance, the device might have been used in an unexpected way. While unplanned, it can provide valuable usability feedback. During preliminary testing, it can help to address human factors when dealing with adhesives. This is the time for making changes at less expense.

When it comes to product development testing, if you have an unexpected result, you might have to look back to the original design intent. Compare your assumptions about how you envision the device working to how it did work. If you need more insights into your data, your team's biostatistician can help develop recommendations based on what happened with the testing.

Working with your cross-functional team when you encounter unintended results can help problem-solve and determine a new path forward. Your materials supplier, and other external partners, may be able to help as well, especially when it comes to their expertise.

Overcoming clinical conundrums

As the saying goes, necessity is the mother of invention. It's a saying that can feel particularly relevant when designing and developing medical devices and especially so in conducting clinical trials. No matter what stage of testing you might be in, surprises can happen. Validated, rigorous protocols and known test methods are a reliable starting point, but being open to new possibilities that arise during testing can help innovate even further. Your team is an invaluable sounding board to help synthesize these insights into what these surprises may mean—both for the approval process and for the end-user—and help ensure you can meet end requirements.

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