The Premarket Notification a.k.a. 510k:

Using substantial equivalence to your advantage!

presented by: ***Michael Drues, Ph.D.***

The premarket notification, better known as the 510K, is the most common regulatory pathway medical device manufacturers use to bring new medical devices to market. But because of a few highly publicized problems with some medical devices, 510k submissions are experiencing greater regulatory scrutiny prior to clearance. Although most submissions are eventually cleared, nearly 75% of first-time 510k applications are rejected leading to review times of 114 days in 2014. This creates costly delays for medical device manufactures – many of which could be minimized if not avoided completely!

One of the areas receiving the greatest regulatory scrutiny is the substantial equivalence argument. Simply put without a strong substantial equivalence argument, your 510k submission may not be successful. But what does substantial equivalence really mean and how do I show it? How do I use not just what the regulation says but also what it does not say to my advantage? Using the case study approach, these questions and others will be presented in an interactive fashion. Following this presentation, participants will:

- understand the regulatory requirements of substantial equivalence and how to use them to your advantage
- learn to design a substantial equivalence regulatory strategy using regulatory logic and how to defend it
- appreciate the split- and multi-predicate strategies and how and when to use each
- be aware of several new FDA guidance documents and how to use them to your advantage
- discuss the proposed changes currently under debate and what the future may hold for the 510K program

Bottom line: knowing what the regulation says, although it's a good start, is not enough – you must know how to use it to your advantage!

What to know more? See:
Substantial Equivalence in plain English (MedDeviceOnline, Sept., 2014) Part 1 & Part 2. Listen to the podcast here.

Speaker Biography



Michael Drues, Ph.D., is President of Vascular Sciences, an education, training, & consulting company offering a broad range of services to medical device, pharmaceutical & biotechnology companies including (but not limited to): stimulating & innovative educational programing, brain-storming sessions, prototype design, product development, benchtop & animal testing, innovative regulatory strategy & completive regulatory intelligence, clinical trial design, FDA presentation preparation & defense, reimbursement, clinical acceptance, business development & technology assessment.

Dr. Drues received his B.S., M.S., and Ph.D. degrees in Biomedical Engineering from Iowa State University in Ames, Iowa. He has worked for and consulted with leading medical device, pharmaceutical and biotechnology companies ranging in size from start-ups to Fortune 100 companies. He also works on a regular basis for the U.S. Food and Drug Administration (FDA), Health Canada, the US and European Patent Offices, the Centers for Medicare and Medicaid Services (CMS) and other regulatory and governmental agencies around the world.

Dr. Drues is an internationally recognized expert and featured keynote speaker on cutting-edge medical technologies and regulatory affairs. He conducts seminars and short-courses for medical device, pharmaceutical and biotechnology companies, the U.S. Food and Drug Administration (FDA), Health Canada, the US and European Patent Offices, the US Centers for Medicare and Medicare Services (CMS) and other regulatory and governmental agencies around the world.

Finally, as an Adjunct Professor of Medicine, Biomedical Engineering & Biotechnology, Dr. Drues teaches graduate courses in Regulatory Affairs & Clinical Trials, Clinical Trial Design, Medical Device Regulatory Affairs & Product Development, Combination Products, Pathophysiology, Medical Technology & Biotechnology at several universities & medical schools on-ground & on-line.

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Listen to the free podcast at
www.meddeviceonline.com/doc/simplifying-substantial-equivalence-in-fda-premarket-notifications-0001

Guest Column | September 12, 2014

510(k) Substantial Equivalence In Plain English — Part 1

By Michael Drues, Ph.D., President, Vascular Sciences



The 510(k), or premarket notification, process has been around since 1976, when it was introduced as part of the Medical Device Amendments to the Federal Food, Drug, and Cosmetic Act. In the nearly 40 years that have passed since its implementation, the 510(k) has become the most commonly used regulatory pathway for bringing new medical devices and diagnostic products to market in the United States.

Although it is a well-worn path, the 510(k) is poorly understood, in my opinion. This is evidenced by the fact that almost 75 percent of first-time 510(k) applications are initially rejected by the FDA — a major reason why the 510(k) review process is taking 114 days to complete, on average, in 2014.

The two most important components of a successful 510(k) submission are the substantial equivalence argument and the risk mitigation strategy. You can fill out all of the forms — you can dot all your i's and cross all your t's — but if you don't have a very strong substantial equivalent argument and a bulletproof risk mitigation strategy, you probably are not going to be successful in getting your submission cleared, and certainly not in the first review cycle!

This two-part article will focus specifically on the substantial equivalence component of 510(k) submissions, explaining what it is and how to establish it. It will also explore two recently issued FDA guidances related to substantial equivalence, and how they should influence your regulatory strategy.

What Exactly Is Substantial Equivalence?

Substantial equivalence is the crux of the medical device industry, because we all rely on it so heavily to bring our products onto the market under the 510(k). But how many really understand what it means? Before getting into the regulatory gobbledygook, I'd like to share a couple metaphors to help explain the concept of substantial equivalence.

Is a car substantially equivalent to a truck? If you want to bring a truck onto the market under the 510k, you could compare it to a car (i.e., predicate device), and the regulatory logic is quite simple. You want to emphasize the similarities and at the same time de-emphasize — or at least not draw attention to — the differences. So, you would emphasize that both cars and trucks are vehicles for transportation, both have wheels, both have internal combustion engines, both consume fuel, both travel on roads, and so on.

At the same time, we have to downplay the differences. Cars usually have four wheels, while trucks may have as many as 18 wheels. Cars usually burn gasoline or perhaps electricity; trucks often burn diesel fuel. Cars are usually designed to carry people and maybe a small amount of cargo, and trucks, on the other hand, carry much more cargo.

We need to acknowledge the differences if they are to our advantage and show that, although they exist, they will not impact the safety, efficacy, or performance of the device. If the differences are not to our advantage, however, we should not bring them up prophylactically but be prepared to respond to them if and when we are asked. This gets into much more sophisticated regulatory strategy, but to use another metaphor this is a poker game, and just because you know the rules does not make you a good poker player!

Another very simple metaphor that everybody can relate to: apples and oranges. Is an apple substantially equivalent to an orange? Well, once again, you want to underscore the similarities: They are both fruits, they both grow on trees, they both deliver calories and nutrients, they both have skin, they both have seeds, etc. But you also want to minimize the differences: they are different colors, they have different nutritional content, they grow on different trees, and so on.

Why use simple metaphors like these? Because Einstein said if we can't explain something simply, we don't understand it well enough. The same principle applies to establishing substantial equivalence for more complicated medical devices, like a vena cava filter or a hip implant. Emphasize the similarities; de-emphasize the differences. I know this sounds like a very basic concept, but I am consistently surprised by how many companies fail to utilize it.

The regulation says that in order to use the 510(k) pathway, there must be a predicate device. But the regulation does *not* say how close the predicate device must be to the new device — nor should it! That is up to the manufacturer and the FDA to negotiate by working together. Is a car close enough to a truck? How about comparing a Honda CR-V to a Toyota RAV4? That is closer yet, but is it close enough? How about instead of comparing an apple to an orange, we compare a red apple to a green apple? In general, the closer the comparison, the easier it is to make the substantial equivalence argument. But where do you draw the line, and who decides?

Recent FDA Guidance And Its Impact On Substantial Equivalence

In order to provide industry with some much-needed clarity regarding the premarket notification process, the FDA's Center for Devices and Radiological Health (CDRH) has issued several 510(k)-related guidances over the past several months. In the next section — and Part 2 of this article — we will look at two specific draft guidances that could have implications in formulating substantial equivalence arguments.

Benefit-Risk Factors to Consider When Determining Substantial Equivalence in Premarket Notifications [510(k)] with Different Technological Characteristics

Issued in mid-July, this guidance emphasizes — and this is right out of the original Court of Federal Regulations — that in order for a device to be shown substantially equivalent to its predicate, it has to have either:

1. The same intended use as the predicate and the same technological characteristics, or
2. The same intended use and different technological characteristics.

What does this mean? I have no idea, but I use such regulatory ambiguities to my advantage all the time! I don't think anybody really understands it completely. It seems to suggest that as long as you get to where you want to go (intended use), it doesn't matter how you get there — whether you use the same technological characteristics in your device or different technological characteristics.

Once again, let me use a very simple metaphor. Say you wanted to get from Boston to Los Angeles. You could drive a car there, though it would take you a couple of days to do it. You could also fly an airplane from Boston to Los Angeles, which would be much quicker and more efficient. In the end, either method of transportation will get you to Los Angeles. So by that regulatory logic, a car is substantially equivalent to an airplane, because although we use different technologies, we end up in the same place (i.e., the intended use).

That's exactly the regulatory logic behind the substantial equivalence argument in the 510(k). But where do you draw the line? You could also fly a helicopter from Boston to Los Angeles. You could ride your bicycle. You could take a cruise ship through the Panama Canal. You could even take a UFO from Boston to Los Angeles. Does that mean all of these modes of transportation are substantially equivalent? As long as you get to Los Angeles, it's the same intended use, so can the technology can be the same or different?

This ambiguity is one of the reasons why the 510(k) has become so controversial in the eyes of some people. As a matter of fact, the Institute of Medicine (IoM) came out with a report in 2011 recommending that the 510(k) should be totally thrown out. I strongly disagree with IoM's position —that would be throwing the baby out with the bathwater. I think the 510(k), and more specifically the substantial equivalence regulatory logic, is a valid path to bring medical devices onto the market when used properly. But like any tool, it can be misused. The key to making this or any regulation work is not to focus on the regulation, but rather the negotiation between the manufacturer and the FDA — that is what will ultimately determine how long a submission will take and whether it will be successful.

We'll delve into the use/misuse of regulation further in Part 2 of this article, as we look at a second draft guidance and discuss potential CDRH changes to so-called split-predicate approach to establishing substantial equivalence.

Dr. Drues will be teaching an online course called The Premarket Notification/510(k) Submission: Using Substantial Equivalence to your Advantage *on October 16, 2014, at 1:00 pm. The course will go into much more detail on the topic of substantial equivalence, using actual medical device case studies to illustrate these concepts.*

510(k) Substantial Equivalence In Plain English — Part 2

By Michael Drues, Ph.D., President, Vascular Sciences

Part 1 of this article sought to provide a better understanding of the concept of substantial equivalence in premarket notifications, more commonly known as 510(k)'s, using easy-to-understand metaphors. We also looked at recently issued CDRH draft guidance concerning different technological characteristics of a 510(k) submission. In Part 2, we move on to another piece of recent CDRH guidance, this one dealing with the controversial topic of split predicates.



The 510(k) Program: Evaluating Substantial Equivalence in Premarket Notifications [510(k)]

Since this guidance was issued on July 28, it has generated a lot of discussion in the medical device industry — not all of it positive. The controversy centers on the guidance's interpretation of split predicates. What is the split predicate strategy? Once again, let me use a metaphor that everybody can understand.

Let's think of ketchup. If ketchup was a new medical device — there was no other ketchup on the market — how could we get it onto the market under the 510(k) using the split-predicate logic? One way would be to deconstruct the ketchup. In other words, what are the components we find within the ketchup? We find tomatoes; tomatoes are on the market. We find vinegar; vinegar is also on the market. We find sugar, which is on the market. We find a variety of spices that are already on the market. If each of these components of ketchup has been previously cleared, then the combination of those components in ketchup should also be cleared. This is how the split predicate strategy works.

I'm dating myself here, but I was one of the first to successfully argue the split-predicate rationale at CDRH about 20 years ago. At the time, I was seeking clearance for a multifunction patient monitor. This was a single monitor, within one box, that could be used to measure blood pressure, respiratory rate, electrical activity of the heart, and a variety of other things. Of course, today such monitors are ubiquitous, but at the time, they did not exist.

What we did was deconstruct the multifunction monitor into its constituent capabilities using the split predicate strategy. We said there are already blood pressure monitors, electrocardiograms (EKG), and other monitors on the market. If you add those together, you get this multifunction monitor. We were able to get the new monitor onto the market using the split-predicate strategy.

Unfortunately, some companies have been permitted to bring products onto the market using the split-predicate strategy that, in hindsight, probably should not have been allowed. As a result, these products have caused problems and, in some cases, harm to patients.

In response to these incidents, some folks at CDRH are now against the split-predicate strategy. Until recently, I have always advised companies to consider the split predicate strategy and to use it, if it makes sense. But I also told them to be aware — this is part of what I call regulatory risk — that the split predicate will be a red flag to some folks on the other side of the table, and that they were opening themselves up to the possibility of getting questioned further.

This new guidance seeks to take matters a step further, proposing a ban on the split-predicate approach. In my opinion, that does not make sense. The split predicate strategy is a tool, and like any other tool, including medical devices, it can be very effective when used properly. When it's not used properly, of course, problems can develop.

One interesting question to consider: How can you tell people not to do something within a guidance document that is itself nonbinding? In all of the debate that's going on around this guidance and the split predicate strategy — and all of it is important debate — I have not seen many people asking, "Is this even possible to do within the context of a guidance document?" Now, if a ban on split predicates were added to the Code of Federal Regulations or the Federal Register, that would be a different matter altogether. I truly hope that does not happen, because it would really hamstring the industry and prevent us from bringing a lot of important products onto the market.

So what's a device maker to do? Today, I still advise companies to consider the split-predict approach when it makes sense, but at the same time they should recognize that taking this route will have a greater regulatory risk than it did just a few months ago. I will make this same recommendation until the split-predicate approach is definitively prohibited and there is case law to support it — something I hope never happens!

It's a balance. I understand FDA has a very important job to do. As I like to say, while a physician can kill patients one at a time, an FDA reviewer can kill patients thousands at a time. So we can't lose track of the importance of the job the FDA has to do.

On the other hand, we also have to be aware that the more regulatory hoops that we create, the more difficult it is for companies to bring products onto the market. It's one thing to measure how many people are harmed or killed because they use a medical device that is not safe enough, whatever that means. But how do we measure the number of people who will be harmed or killed because they don't have access to a particular medical device — because we made the regulatory burden so great that the device maker decides simply not to develop it?

So it's a fine line. We want to have enough regulation to ensure that safe and effective medical devices get to market. On the other hand, we don't want to have so much regulation that it stifles innovation. There is a definitely a fulcrum, a pivot point, in there somewhere. I have no idea where it should be, but this is a topic that is very important to us as an industry and, indeed, to all of us as a society, and we need more people talking about such issues.

Split Predicates Vs. Multipredicates

I'd like to talk for a moment about the multipredicate strategy, and how it differs from a split predicate. While these are similar terms, they're not exactly the same.

Hopefully this will help you keep the two approaches straight. When you think of the split predicate strategy, think of the ketchup example we discussed previously. In short, this approach involves deconstructing your product into its individual components.

When you think of the multipredicate strategy, think about the legs of a stool. The stability of the stool is a function of how many legs it has. If a stool only has one or two legs, it will be unstable. If you have three or four or five or seven legs, then the stability of the overall stool becomes greater and greater.

Each of those legs under the stool can be thought of as a different predicate. And you can bring medical devices onto the market under the 510(k) using this strategy, where you identify not necessarily one predicate or several different aspects of other predicates (split-predicate) but multiple predicates of the similar type. (What does "similar" mean again?)

To take the stool metaphor even one step further, it's not simply the number of legs under the stool that's important. It's the relative strength or the relative length of each one. In other words, you might have, say, seven legs under your stool. But if one of those legs is much longer or much shorter than all of the rest, once again, the stability of the entire stool becomes compromised. Bottom line: There is a lot more to designing a successful regulatory strategy than meets the eye!

How To Approach Future 510(k) Submissions

The 510(k) pathway is in a state of flux, and that's a good thing! Regulatory science, if there is such a thing, should be an evolutionary science. Just like in design controls, where your outputs become your inputs in order to make better products and ultimately make the world a better place. However, you will be able to weather the storm if you put into practice the recommendation of Steven Covey, author of the bestselling book *The Seven Habits of Highly Effective People*: Begin with the end in mind.

If you have a medical device that you hope to bring to market under the 510(k), before you start writing your submission — very early in your design process — begin with the end in mind. Figure out what it is exactly that you want to accomplish. One of the best places to start is with the label claims, with the intended use. It will be a very effective strategy for you in developing your regulatory strategy.

One other recommendation I would make is to think about your regulatory submission as a design process, rather than a writing process. There are a lot of folks out there that write regulatory submissions, whether they're for a 510(k), a premarket approval (PMA), or other pathway. Instead, I would suggest you design your submission. Just like an engineer would sit down and design a medical device, you should design your regulatory submission.

Lastly, consider the most radical approach: Forget FDA, forget regulatory requirements. If a family member, close friend, or perhaps even you were need of you medical device, what would you need to see in terms of safety, efficacy, performance, etc. to recommend it? That's the ultimate test. If you pass that test, everything else should be a walk in the park!

If you employ these techniques, they will take you a long way toward developing a 510(k) submission that will be among the 25 percent that are accepted by FDA upon first submission, first time out of the box. That would be a great place to start.

For more on the 510(k) process, substantial equivalence, split predicates, and more check out Dr. Drues' upcoming online course The Premarket Notification/510(k) Submission: Using Substantial Equivalence to your Advantage, *which will take place on November 5, 2014, at 1:00 pm. It will go into further detail on these and other topics, using actual medical device case studies to illustrate important concepts.*

Medical Device Regulatory Affairs:

The PreMarket Notification (PMN a.k.a. 510k) and Substantial Equivalence



Here's what we'll talk about…

- ✓ What is the PreMarket Notification (PMN) a.k.a. 510k?
- ✓ How can we use it to our advantage?
- ✓ What does substantial equivalence ***really*** mean?
- ✓ Examples to understand the regulatory logic
- ✓ Why is the 510k so controversial?
- ✓ What is predicate creep?
- ✓ What is the future of the 510k?

Remember:

Knowing what the regulation says…

although it's a good start, is not enough!

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What are the pathways to bring medical devices to market



There are many of them!

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Medical Device Regulatory Affairs:

The PreMarket Notification (PMN a.k.a. 510k) and Substantial Equivalence

How many ways (i.e., pathways) are there to get medical devices on to the market in the United States?



Remember,



You do not need to take the path <u>most</u> travelled…

unless it's to your advantage!

Short answer:

There are many of them…

and there are advantages and disadvantages of each!

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A Three Step Process

1. Not PMA, 510k, de Novo, HDE or CDE but…

   Is it a <u>regulated</u> medical device?

2. What classification?
   - Class I, Class II, Class III
   - Depends on level of "risk"
3. Select appropriate marketing application, i.e., regulatory pathway

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Medical Device Regulatory Affairs:

The PreMarket Notification (PMN a.k.a. 510k) and Substantial Equivalence

Bring Medical Devices to Market in the US

Two *common* choices:

1. Premarket Notification (PMN)

based on "Substantial Equivalence" (510K)

– or –

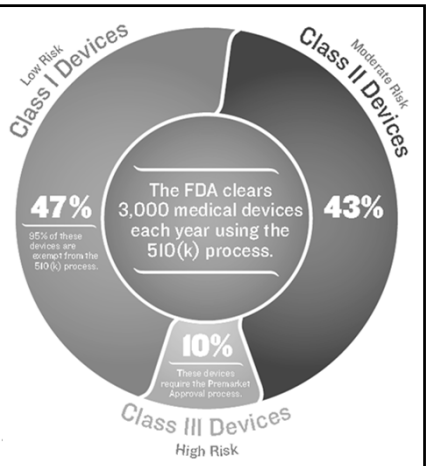
2. Investigational Device Exemption (IDE)

⇓

Premarket Approval (PMA)

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The Costs of Doing Business



510(k) Reform and the Resulting Impact on Medical Device Developers (Novella Clinical, A Quintiles Company, 2013)

Industry reports estimate that it ***costs $31 million on average to bring a 510(k) product to market and $94 million to bring a PMA device to market. Further, more than 75% of those costs are directly related to clearing regulatory requirements.***

Single Sourcing: The Cure for the Common Supply Chain (MDDI Magazine, September 9, 2013)

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Additional Pathways to Market

Product Development Protocol (PDP)

– and –

de Novo pathway

– and –

Humanitarian Use Device (HUD) ⇒ Humanitarian Device Exemption (HDE)

– and –

Custom Device Exemption (CDE)

– and –

Emergency / compassionate use situations

Bottom line: Although seldomly used,

Unless you understand <u>all</u> possible pathways <u>and</u> the advantages and disadvantages of each, how can you know when to use (or not use) each one? i.e., how can you do your job?

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There are many pathways to market…

Many more than drugs!

And it can be confusing…





But…

Must we take the path most taken?

Must we choose only one?

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Medical Device Regulatory Affairs:

The PreMarket Notification (PMN a.k.a. 510k) and Substantial Equivalence

What is and is not a 'regulated' medical device



Not a simple question!

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What is and is not a 'regulated' medical device?

- ✓ Certain class I & II devices for which 510(k) review is not necessary to assure safety and effectiveness before these devices enter the market place ***because they are sufficiently well understood and do not present risks that require premarket notification (510(k)) review***
- ✓ Categories of devices include: Anesthesiology, Cardiovascular, Dental, ENT, GI/Urology, General & Plastic Surgery, General Hospital and Personal Use, Neurological Devices, OB/GYN, Ophthalmic and Physical Medicine Devices
- ✓ Regulatory 'logic' analogous to OTC drugs

Intent to Exempt Certain Class II and Class I Reserved Medical Devices from Premarket Notification Requirements (CDRH, August, 2014) available here

Intent to Exempt Certain Class II and Class I Reserved Medical Devices from Premarket Notification Requirements

Draft Guidance for Industry and Food and Drug Administration Staff

DRAFT GUIDANCE

This guidance document is being distributed for comment purposes only.
Document issued on: August 1, 2014

You should submit comments and suggestions regarding this draft document within 60 days of publication in the *Federal Register* of the notice announcing the availability of the draft guidance. Submit written comments to the Division of Dockets Management (HFA-305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852. Submit electronic comments to http://www.regulations.gov. Identify all comments with the docket number listed in the notice of availability that publishes in the *Federal Register*.

For questions regarding this document, contact Abiy Desta at 301-796-0293 or by email at Abiy.Desta@fda.hhs.gov.

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Devices and Radiological Health
Office of Device Evaluation

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Medical Device Regulatory Affairs:

The PreMarket Notification (PMN a.k.a. 510k) and Substantial Equivalence

510k Statistics

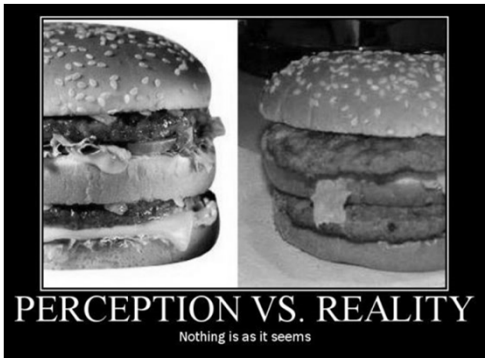


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510k Timeline of Communication

This is the theory…

i.e., what the CFR or FR says but…



what is the reality?

Day 1: FDA receives 510(k) application.

By 7 Days

FDA sends **Acknowledgement Letter**.
OR
FDA sends **Hold Letter** if unresolved issues with User Fee and/or eCopy.

By Day 15

FDA conducts **Acceptance Review**.

FDA informs applicant if 510(k) is accepted for **Substantive Review** or placed on **RTA Hold**.

By Day 60

FDA conducts **Substantive Review** (usually by Day 60).

FDA communicates **Substantive Interaction** with applicant that indicates FDA will proceed with **Interactive Review** or ask for **Additional Information**.

By Day 90

FDA sends final **MDUFA Decision** on 510(k) (usually by Day 90).

By Day 100

If MDUFA Decision is not reached by Day 100, FDA provides **Missed MDUFA Decision Communication** that identifies outstanding review issues.

Important Notes:

- Days are Calendar Days.
- The timeline is based on the performance goals set by Medical Device User Fee Amendments of 2012 (MDUFA III).
- This timeline has been simplified

January 9, 2014

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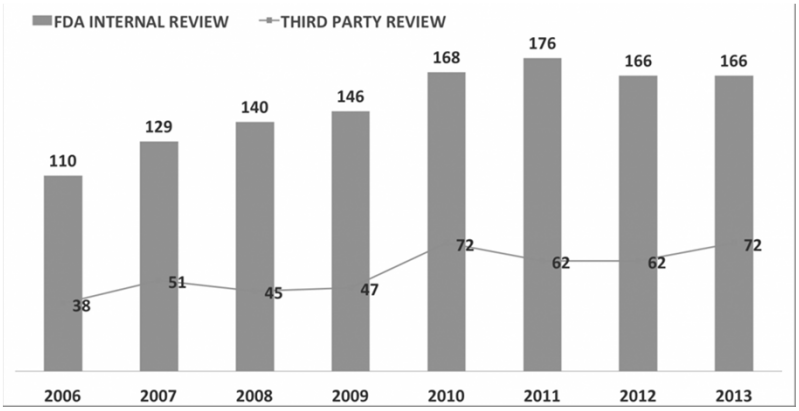
Medical Device Regulatory Affairs:

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Traditional 510k Review Times: *FDA vs. Third Party*

Seems faster using third party but is this a fair comparison?

Average number of calendar days to clear traditional 510k



[Based on 24K submissions cleared between 2006–2013]

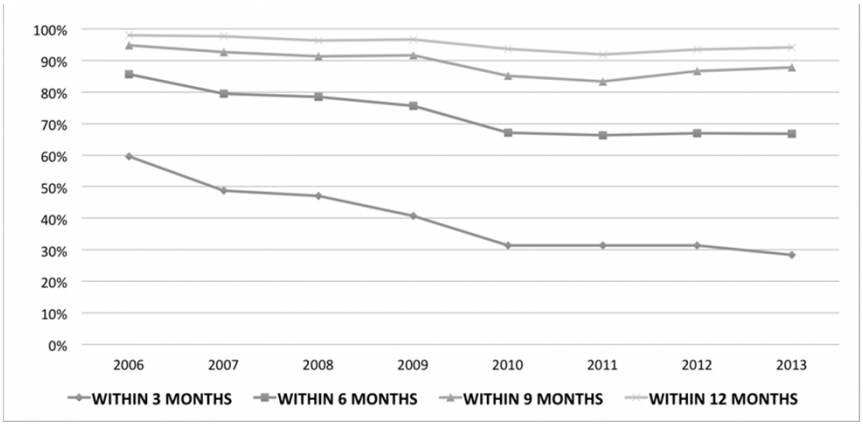
Hint: *Only the 'least risky' devices are eligible for third party review!*

Also keep in mind third party review fees so do the math!

Emergo Group, March, 2014

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What are odds FDA will clear your 510k within a specific time?



Emergo Group, March, 2014

FDA clears >3K devices per year of which:

~ 75% are "Traditional" 510(k)

~ 22% are "Special" 510(k) [based on modifications to device with existing 510(k)]

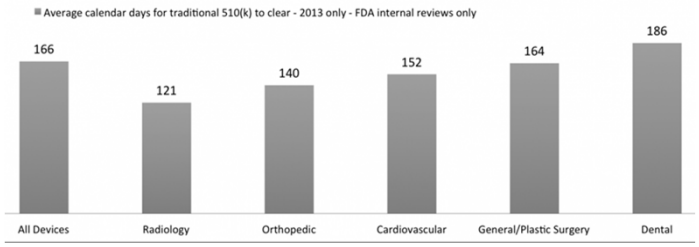
< 4% are "Abbreviated" [based on guidance, special controls or recognized standards]

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Medical Device Regulatory Affairs:

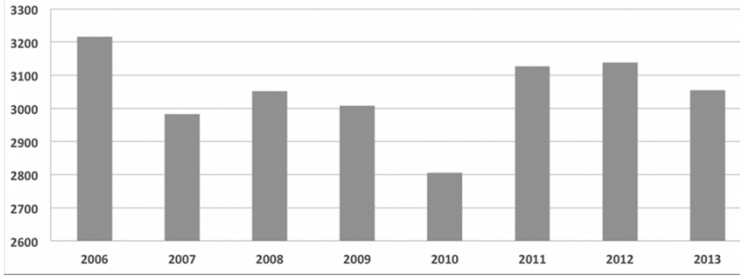
The PreMarket Notification (PMN a.k.a. 510k) and Substantial Equivalence

510k Clearance Times for Common Device Categories



510k by Time and Number

510k Submissions Cleared for All Types of Devices

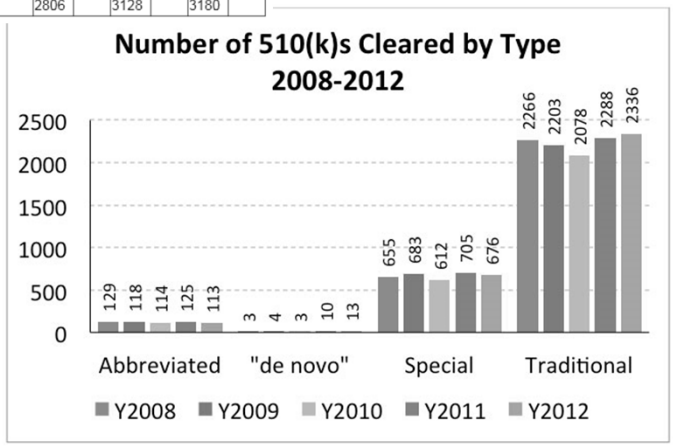


Emergo Group, March, 2014

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Statistics by Submission Type

Submission Type	2008		2009		2010		2011		2012	
	No.	%	No.	%	No.	%	No.	%	No.	%
Abbreviated	129	4.2	118	3.9	114	4.1	125	4.0	113	3.6
De Novo	3	0.11	4	0.1	3	0.1	10	0.3	13	0.4
Special	655	21.5	683	22.7	612	21.8	705	22.5	676	21.5
Traditional	2266	74.2	2203	73.2	2078	74.0	2288	73.2	2336	74.4
Total	3053		3008		2806		3128		3180	



510(k) Statistical Patterns
MDDI, December 2, 2014
available here.

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Average Review Times

Average Review Days by Submission Type

	2008	2009	2010	2011	2012
Abbreviated	148	150	160	153	173
De Novo	507	676	751	693	687
Special	54	62	73	73	73
Traditional	128	135	160	168	160
All 510(k)s	114	120	142	147	144

Abbreviated 510k ≈ Traditional 510k

a510k: ↓ time & ↓ cost to prepare

Special 510k << Traditional 510k

De Novo statistics very deceptive – don't use them!

Primary IVD Review Areas:

Clinical Chemistry, Hematology, Immunology, Microbiology, Pathology and Clinical Toxicology

Bottom line:

"In the end, the single most important variable is the 510k itself. A well-written, well-supported 510k is the *sine qua non* [indispensable and essential]. Yet, even well-written, well-supported 510k's are subject to other forces and trends that can influence the speed with which a 510k is cleared."

510(k) Statistical Patterns
MDDI, December 2, 2014 available here.

Average Review Days by Review Committee

Reviewing Committee	Average Review Days
Anesthesiology	156
Clinical Chemistry	176
Cardiovascular	108
Dental	134
Ear, Nose, and Throat	138
Gastroenterology and Urology	142
Hematology	215
General Hospital	132
Immunology	221
Microbiology	151
Neurology	148
Obstetrics/Gynecology	188
Ophthalmic	171
Orthopedic	121
Pathology	273
Physical Medicine	256
Radiology	92
General and Plastic Surgery	135
Clinical Toxicology	214

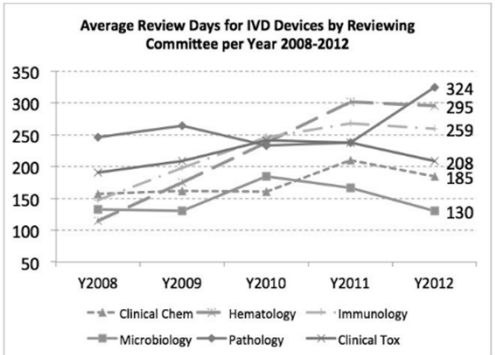
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Average Review Times for IVDs

Table 4. Average Number of Review Days per 510(k) per Year for IVD Medical Specialties

Medical Special	2008	2009	2010	2011	2012	Overall
Clinical Chemistry	157	161	160	210	185	176
Hematology	114	175	237	301	295	215
Immunology	147	198	246	268	259	221
Microbiology	133	130	185	166	130	151
Pathology	246	264	233	237	324	273
Clinical Toxicology	190	209	241	237	208	214
Overall IVD	151	164	194	215	189	183
All Non-IVD	111	116	137	140	140	127

Figure 2. Average Number of Review Days per 510(k) per Year for IVD Medical Specialties



510(k) Statistical Patterns
MDDI, December 2, 2014 available here.

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Medical Device Regulatory Affairs:

The PreMarket Notification (PMN a.k.a. 510k) and Substantial Equivalence

Common Reasons for Unsuccessful 510k Submissions



Regulatory Outlook

The Top 10 Pitfalls of a 510(k) Submission

The 510(k) submission process can be challenging, but learning to overcome these common problems can ease the process.

TIM M. LOHNES
Orchid Design

While the U.S. regulatory system can be credited with ensuring high standards of patient safety and device effectiveness, the process of submitting a 510(k) can pose many challenges for medical device manufacturers both inside and outside of the United States.

Each 510(k) submission is nuanced and dynamic, with any number of variations depending on the type of device, the risk level, its history, etc. Therefore, it is essential to have a strong understanding of the most up-to-date 510(k) submission requirements and how they relate to your device. The following 10 pitfalls should be understood and successfully navigated.

1. Having Misconceptions About 510(k)'s Goals

For a device to receive 510(k) clearance, it must be shown to be 'substantially equivalent' to a previously cleared (predicate) device. Any technical differences, must be shown to not affect safety or efficacy when compared with the predicate. In the 510(k) review process, devices that meet eligibility requirements are 'cleared' as opposed to 'approved' by FDA. But completing a compliant 510(k) can be confusing, time-consuming, expensive, and frustrating. The 510(k) process is no longer about filling out numerous forms and sending them to FDA along with a user fee payment. The requirements and expectations have evolved alongside medical technology.

2. Not Knowing the Regulatory History of Your Product in the United States

It is imperative for a medical device company to know, and to be able to explain, the regulatory history of its device in the United States. For instances, the last metal-on-metal hip implant was cleared in October 2012. On January 13, 2013, FDA issued an order proposing that future metal-on-metal hips be required to meet certain elements of the PMA program.

3. Choosing the Wrong Comparison (Predicate) Device

Predicates should be carefully selected based on design, materials, sizes, sterility, indications for use, and packaging, among other considerations. For example, a company may consider its suture anchor to be just like every other one on the market, but if the device is sterilized by the user before use and the predicate is supplied already sterile (or vice versa), it is likely that FDA will ask for additional data or clarification, which slows the review process.

4. Choosing a Predicate That is Not Available to Test

Testing data is often a crucial part of a complete 510(k) submission. Note that for some testing data there are cases in which the comparison may be based on published literature on the predicate and performance standards recognized by FDA.

To adequately test the two devices side-by-side, samples of the predicate device must be acquired. This process can be challenging. There are devices with 510(k) clearance that have never been brought to market, have limited production, have controlled distribution, or are considered antiquated. And, more often than not, a predicate is a competitor's product, which can make obtaining samples a difficult and often expensive proposition.

5. Choosing a Predicate That is Not Available in the United States

Just because a predicate is available in another jurisdiction does not mean it's available in the United States. Many devices have line extensions of sizes, product features, or materials that may not be covered by a 510(k) clearance. For example, a device may have seven sizes available outside the United States, but only four of them have been cleared in the United States. To complicate matters, it is not always possible to determine this from the available marketing materials or 510(k) information. Therefore, it is crucial for medical device companies to have in-depth knowledge of the history and regulatory status of their predicate in the United States.

6. Not Understanding (or Being Able to Find) Appropriate Guidance

FDA publishes guidance documents on various topics from general procedural recommendations to specific device testing. While using FDA's guidance is not required, it is highly recommended by the agency, and it is expected that any deviation from a guidance document be justified. The way FDA handles guidance has been a point of contention for many in the medical device industry for some time. Guidance documents can be difficult to find, and may even be obsolete, outdated, or withdrawn. Without experience with FDA, locating the appropriate guidance documents can be complicated, time-consuming, and frustrating.

7. Not Starting Validation Testing

In some cases, it may be appropriate to submit a 510(k) while validation testing is still in process. It's important to make absolutely sure that the testing is actually in process. If the 510(k) states that a 60-day sterility validation is "in process" on the day it's submitted and the reviewer asks for them on day 84, that information must be readily available.

8. Errors and Inconsistencies

When you have been working on a 510(k) submission for weeks, it is easy to develop blind spots to mistakes and discrepancies. It is valuable to have a knowledgeable individual proofread the entire document before submitting. Enlisting a second (or third) set of eyes helps prevent minor errors or typos that could hold up the review of your submission.

9. Inattention to FDA's Instructions

FDA has clear instructions for how a 510(k) should be formatted and submitted. For example, the entire document must be paginated, and page numbers must match the table of contents. Last year the agency published two useful guidance documents. The first is the *Refuse to Accept Policy for 510(k)s*, which is a clear and comprehensive checklist for a properly formatted submission. The second is the *eCopy Program for Medical Device Submissions*. Both documents provide detailed and thorough descriptions of the agency's requirements and expectations with regard to 510(k) submission structure and format.

10. Missing and Incomplete Forms

With 510(k) submissions, every form is influential. Read each and every form carefully and fill them out completely. Every form is there for a reason and should be considered equally significant.

Stay Focused on the Purpose

For many small medical device companies and those outside the United States in particular, the 510(k) process can be confusing and frustrating. It also requires substantial investments in patience, time, and resources. It's important to remember that the purpose of a 510(k) is to improve public health and well being. As a result, it deserves the same level of attention, expertise, and commitment that was applied to the design and development of the device.

Tim M. Lohnes is the senior regulatory consultant at Orchid Design. He is an experienced medical device regulatory professional with more than 25 years in quality and regulatory affairs.



Top 10 Pitfalls of a 510(k) Submission and How to Avoid Them (MDDI, Oct, 2013)

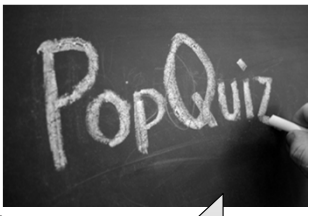
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How does the 510k compare to the PMA?



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510k vs. PMA



What is the average total review time for 510(k)'s?

144 days in 2012 → 114 days in 2014

What is the average total review time for PMA's?

419 days in 2010 → 297 days in 2012

Is there a relationship?

What percent of 510(k)s are ***eventually*** found substantially equivalent? i.e. successful?

79% in 2012 → 84% in 2014

What percent of PMAs are approved?

70% in 2012 → 85% in 2013 → 73% in 2014

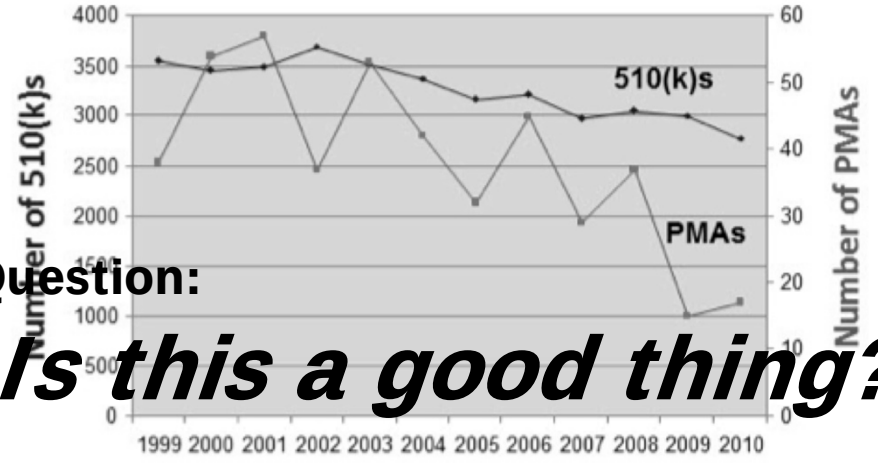
What percent of PMAs receive a major deficiency letter? [Note: Not necessarily unsuccessful but → delay!]

86% in 2010 → 70-71% in 2011/12 → 78% in 2013

MDDI, July, 2014 available here

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Number of Successful 510k vs. PMA Submissions



Question:

Is this a good thing?

Note the two different scales

Number of 510k submissions outnumber PMA submissions by ~200X – ***Why?***

Reinventing Life Science Startups – Medical Devices and Digital Health (August, 2013) available here

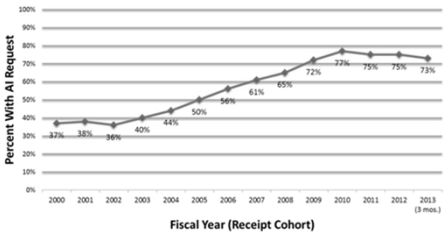
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Medical Device Regulatory Affairs:

The PreMarket Notification (PMN a.k.a. 510k) and Substantial Equivalence

What percent of submissions are kicked back upon first review?

Percent of 510(k)s With Additional Information (AI) Request on 1st FDA Review Cycle



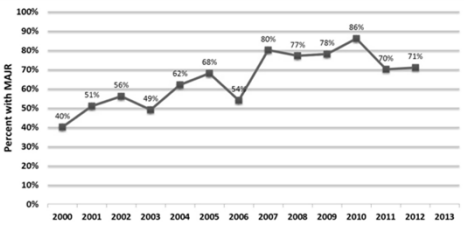
Bottom line:

>70% 510k & PMA submissions are rejected upon first review!

My goal:

Not simply acceptance… anyone can to that!

Percent of PMAs With Major Deficiency Letter (MAJR) on 1st FDA Review Cycle*



*Includes all filed original PMAs (1st cycle completed for all cohorts)

My goal:

Acceptance upon first review…

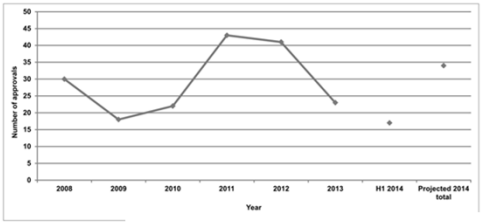
or with the few number of questions/kickbacks as possible!

How do you achieve this?

Reinventing Life Science Startups – Medical Devices and Digital Health (August, 2013) available here

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Number of PMAs and HDEs granted, 2008-2014



PMA Statistics

First-time PMAs granted by the FDA in the first half of 2014

Device Name	EvaluateMedTech Device Classification - L1	EvaluateMedTech Device Classification - L3	Company	Number	Decision Date	Review Time (Months)
ReSure	Ophthalmics	Other Ophthalmic Surgical Devices	Ocular Therapeutix	P130004	January 8, 2014	11.0
CoreValve	Cardiology	Transcatheter Heart Valves	Medtronic	P130021	January 17, 2014	5.8
Monovisc	Orthopedics	Viscosupplementation	Anika Therapeutics	P090031	February 25, 2014	49.9
Elecsys HBeAg Immunoassay and Elecsys PreciControl HBeAg	In Vitro Diagnostics	Viral Immunoassays	Roche	P130015	March 14, 2014	9.3
Nucleus Hybrid L24	Ear, Nose & Throat	Hearing Implants	Cochlear	P130016	March 20, 2014	9.5
Supera	Cardiology	Peripheral Vascular Devices	Abbott Laboratories	P120020	March 28, 2014	16.3
Inspire II upper airway stimulator	Anesthesia & Respiratory	Other Anesthesia & Respiratory Therapeutic Devices	Inspire Medical Systems	P130008	April 30, 2014	12.0
Sinovial	Orthopedics	Viscosupplementation	IBSA Institut Biochimique	P110005	May 9, 2014	38.9
Advia Centaur HBsAgII	In Vitro Diagnostics	Viral Immunoassays	Siemens	P110041	May 16, 2014	28.8
PreciseType	In Vitro Diagnostics	Hematology Molecular Diagnostics	Immucor	BP130026	May 21, 2014	11.3
Therascreen KRAS RGQ PCR kit	In Vitro Diagnostics	Oncology Molecular Diagnostics	Qiagen	P110027	May 23, 2014	34.0
CardioMEMS HF	Cardiology	ECG Monitoring	St. Jude Medical	P100045	May 28, 2014	41.4
Artus CMV RGQ MDx kit	In Vitro Diagnostics	Infectious Disease Molecular Diagnostics	Qiagen	P130027	June 2, 2014	5.9
Sapien XT	Cardiology	Transcatheter Heart Valves	Edwards Lifesciences	P130009	June 16, 2014	13.5
FluencY Plus	Cardiology	Graft Prosthesis	C. R. Bard	P130029	June 17, 2014	5.9
Freedom SOLO	Cardiology	Tissue Heart Valves	Sorin	P130011	June 24, 2014	13.3
Rebel	Cardiology	Non-Drug-Eluting Coronary Stents	Boston Scientific	P130030	June 27, 2014	5.9

Data sourced to EvaluateMedTech. Copyright © 2014 Evaluate Ltd. and EP Vantage. All rights reserved.

Average PMA review time 18.4 months in 2014 compared to 35.9 months in 2013 – ***why?***

MDDI, August, 2014 available here.

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What is the PreMarket Notification (PMN) a.k.a. 510k and how can we use it to our advantage



Consider this:

Many use it but most do not use it well!

Remember,

70-75% of 510k and PMA submissions are rejected upon first review!

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Premarket Notification (PMN) a.k.a. 510k

- ✓ Submission made to FDA to demonstrate that the device is "substantially equivalent" (SE) to a legally marketed device (so-called predicate device), i.e.,
  - ➢ Must compare device to one or more similar (predicate) devices currently on the U.S. market
- ✓ If the FDA agrees that the new device is SE, it can be marketed but… *the 510K is <u>not</u> an FDA approval*
- ✓ Clinical data is usually not required!

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There is much confusion on this point!



Sometimes road signs can be confusing…

and regulation can be confusing as well.

Remember,

Premarket Notification (PMN) a.k.a. 510(k)
is NOT an approval!
510(k) applications are "cleared" not approved

Don't think so? Look up Riegel v. Medtronic

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What are the two most important components of a <u>successful</u> 510k



Substantial Equivalence Argument
and Risk Mitigation Strategy

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Medical Device Regulatory Affairs:

The PreMarket Notification (PMN a.k.a. 510k) and Substantial Equivalence

How to avoid unnecessary delays?



Most delays are avoidable!

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How to avoid unnecessary delays?

Most delays are avoidable!

What's the review process?

Administrative Review

↓

Scientific Review

Remember,

Never OMIT a section!

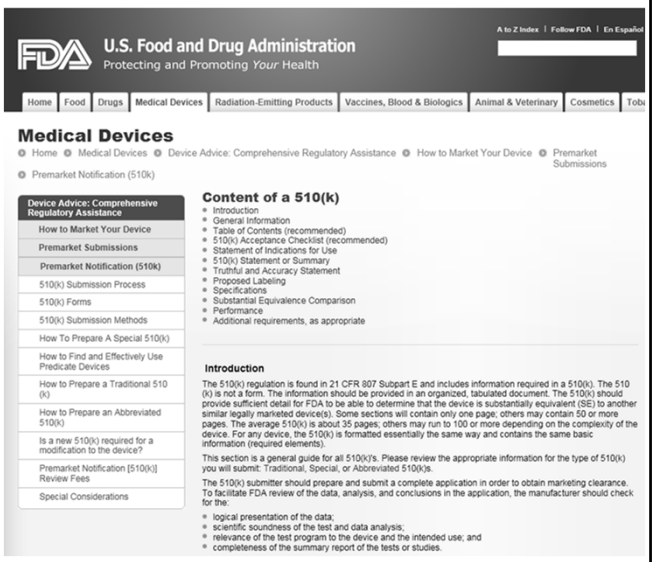
and

Always use the current forms!

Keeps the bureaucrats happy! ☺

Call DSMICA?

Sept, 2014



www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/HowtoMarketYourDevice/PremarketSubmissions/PremarketNotification510k/ucm142651.htm

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Medical Device Regulatory Affairs:

The PreMarket Notification (PMN a.k.a. 510k) and Substantial Equivalence

What happens when you get substantial equivalence wrong



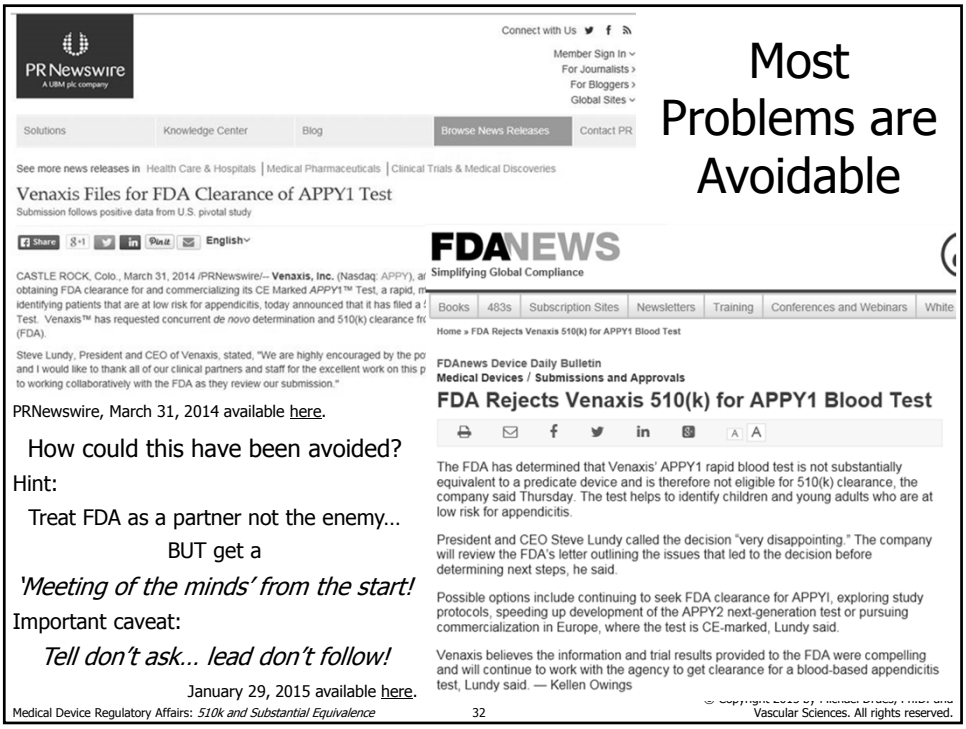
Usually nothing good… i.e.,

more time, more money, more rigorous pathway to market

How about an example…

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Most Problems are Avoidable



PR Newswire
A UBM plc company

Connect with Us
Member Sign In
For Journalists
For Bloggers
Global Sites

Solutions | Knowledge Center | Blog | Browse News Releases | Contact PR

See more news releases in Health Care & Hospitals | Medical Pharmaceuticals | Clinical Trials & Medical Discoveries

Venaxis Files for FDA Clearance of APPY1 Test

Submission follows positive data from U.S. pivotal study

CASTLE ROCK, Colo., March 31, 2014 /PRNewswire/-- **Venaxis, Inc.** (Nasdaq: APPY), a
obtaining FDA clearance for and commercializing its CE Marked *APPY1*™ Test, a rapid, m
identifying patients that are at low risk for appendicitis, today announced that it has filed a
Test. Venaxis™ has requested concurrent *de novo* determination and 510(k) clearance fr
(FDA).

Steve Lundy, President and CEO of Venaxis, stated, "We are highly encouraged by the po
and I would like to thank all of our clinical partners and staff for the excellent work on this p
to working collaboratively with the FDA as they review our submission."

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Home » FDA Rejects Venaxis 510(k) for APPY1 Blood Test

FDAnews Device Daily Bulletin
Medical Devices / Submissions and Approvals

FDA Rejects Venaxis 510(k) for APPY1 Blood Test

The FDA has determined that Venaxis' APPY1 rapid blood test is not substantially equivalent to a predicate device and is therefore not eligible for 510(k) clearance, the company said Thursday. The test helps to identify children and young adults who are at low risk for appendicitis.

President and CEO Steve Lundy called the decision "very disappointing." The company will review the FDA's letter outlining the issues that led to the decision before determining next steps, he said.

Possible options include continuing to seek FDA clearance for APPYI, exploring study protocols, speeding up development of the APPY2 next-generation test or pursuing commercialization in Europe, where the test is CE-marked, Lundy said.

Venaxis believes the information and trial results provided to the FDA were compelling and will continue to work with the agency to get clearance for a blood-based appendicitis test, Lundy said. — Kellen Owings

PRNewswire, March 31, 2014 available here.

How could this have been avoided?

Hint:

Treat FDA as a partner not the enemy…

BUT get a

'Meeting of the minds' from the start!

Important caveat:

Tell don't ask… lead don't follow!

January 29, 2015 available here.

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Medical Device Regulatory Affairs:

The PreMarket Notification (PMN a.k.a. 510k) and Substantial Equivalence

Can your 510k be rejected



Short answer – *Absolutely, in fact… most are!*

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Checklist vs. Refuse to Accept

Use this to avoid this!

But do we really need this?

Organizational Elements *Failure to include these items alone generally should not result in an RTA designation*	Yes	No
a. Submission contains Table of Contents	☐	☐
b. Each section is labeled (e.g., headings or tabs designating Device Description section, Labeling section, etc.)	☐	☐
c. All pages of the submission are numbered *All pages should be numbered in such a manner that information can be referenced by page number. This may be done either by consecutively numbering the entire submission, or numbering the pages within a section (e.g., 12-1, 12-2…).*	☐	☐
d. Type of 510(k) is identified– traditional, abbreviated, or special *If type of 510(k) is not designated, review as a traditional*	☐	☐
Comments:		

Apparently so…

"As of September 2013, ~60% of all newly filed 510(k)s were refused under the RTA."

FDA News, Falls Church, VA Sept. 30, 2013

Refuse to Accept Policy for 510(k)s (December 31, 2012) available here.

Contains Nonbinding Recommendations

Refuse to Accept Policy for 510(k)s

Guidance for Industry and Food and Drug Administration Staff

Document issued on: December 31, 2012

This document supersedes Center for Devices and Radiological Health's Premarket Notification (510(k)) Refuse to Accept Policy, dated June 30, 1993, and 510(k) Refuse to Accept Procedures (K94-1) blue book memo, dated May 20, 1994.

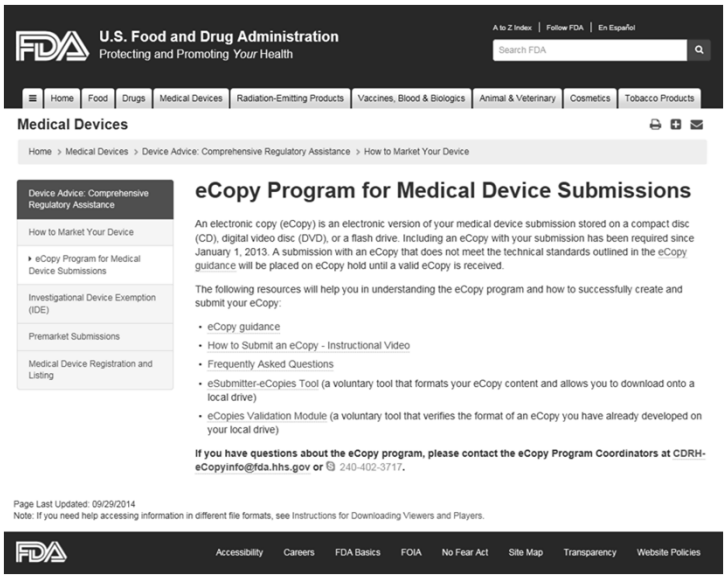
The draft of this document was issued on: August 13, 2012

For questions regarding this document, contact the 510(k) Staff at 301-796-5640. For questions regarding submissions to the Center for Biologics Evaluation and Research (CBER), contact CBER's Office of Communication, Outreach and Development at 1-800-835-4709 or 301-827-1800.

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Devices and Radiological Health
Center for Biologics Evaluation and Research

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Requirements of e-Submissions



Available here.

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Where can I find additional information



There are many places!

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Medical Device Regulatory Affairs:

The PreMarket Notification (PMN a.k.a. 510k) and Substantial Equivalence

510K Database

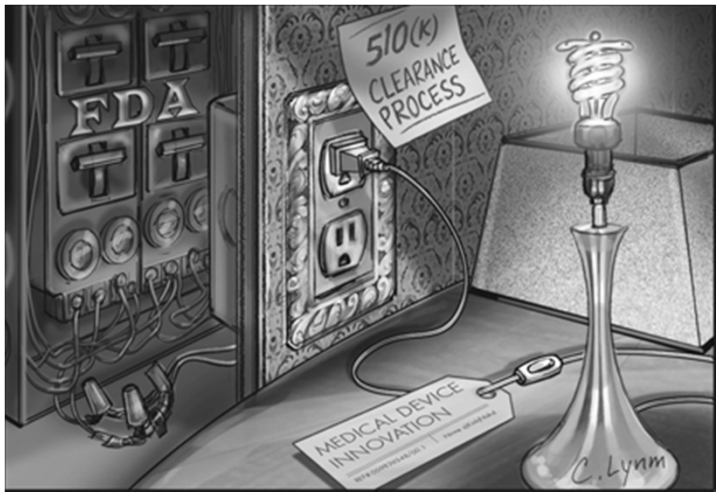


But what if there is no precedent, no predicate device?

http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfPMN/pmn.cfm

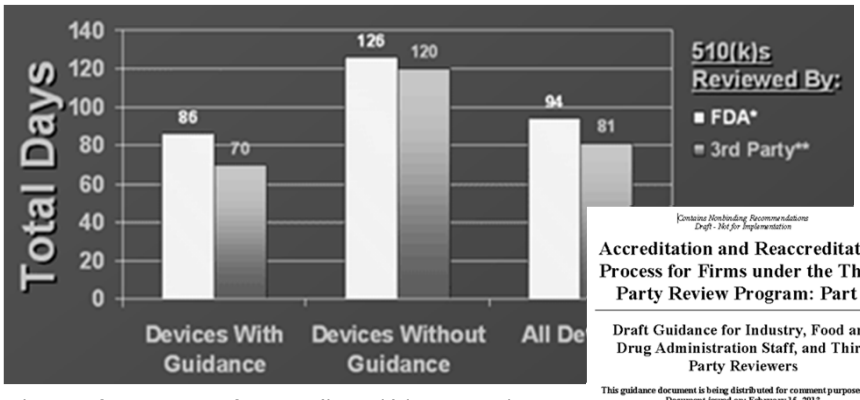
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Here's another twist on the 510k…



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Third Party Review Program




Contains Nonbinding Recommendations
Draft - Not for Implementation

Accreditation and Reaccreditation Process for Firms under the Third Party Review Program: Part I

Draft Guidance for Industry, Food and Drug Administration Staff, and Third Party Reviewers

This guidance document is being distributed for comment purposes only.
Document issued on: February 15, 2013

You should submit comments and suggestions regarding this draft document within 60 days of publication in the *Federal Register* of the notice announcing the availability of the draft guidance. Submit written comments to the Division of Dockets Management (HFA-305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852. Submit electronic comments to http://www.regulations.gov. Identify all comments with the docket number listed in the notice of availability that publishes in the *Federal Register*.

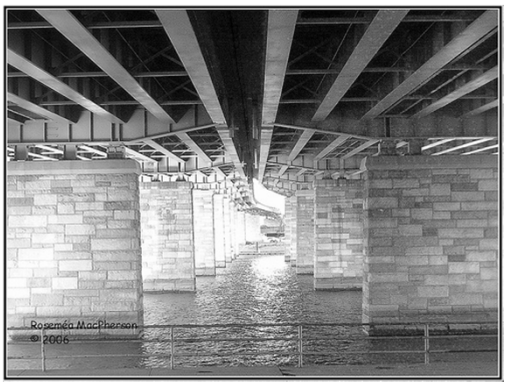
For questions regarding this document, contact Scott McFarland at 301-796-6217 or Scott.McFarland@fda.hhs.gov

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Devices and Radiological Health

- provides manufacturers option for certain 'low-risk' devices to submit 510k to private party rather than directly to CDRH… *sound familiar?*
- similar to Notified Body system in EU & commercial IRB in clinical trials… *does that create bias?*
- not common [~300 in FY 2008 or 8% of all 510k submissions] but… *60% of all 510(k) submissions are eligible! …so why not used more?* [small time savings *vs.* risk of taking less common path]
- may offer advantages in certain situations… *when?*

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Putting things in perspective…



510(k) vs. PMA Devices

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What percentage of medical devices (by volume) have been tested in humans?



Source: US FDA CDRH 2005 Strategic Plan

> 95% (nearly all) 54.2% (about half) < 5% (very few)

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Consider this…

Greater than 95% by volume of the medical devices used in the US each year have never been "tested" in a human being.

Why?

Either they are 510K non-significant risk (NSE) risk devices

or

they were on the market and grandfathered in by the "Safe Medical Devices Act of 1976"

Either way, no clinical data was required!

or put another way…

98-99% of 'new' medical devices are cleared thru 510k process

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Medical Device Regulatory Affairs:

The PreMarket Notification (PMN a.k.a. 510k) and Substantial Equivalence



An interesting observation…

Few regulatory affairs professionals are experienced in or even knowledgeable of medical device clinical trials?

Why?

There are two reasons:

First, there are not many medical device trials done

And here is the second reason…

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Medical device firms do many clinical studies offshore. Here's why:

Many, if not most, medical device companies perform pilot clinical studies outside of the U.S. Cost reductions, avoiding a protracted FDA Investigational Device Exemption (IDE) approval process, and the ability to make design changes during the study without continual IDE amendments are the leading reasons to perform early studies outside the U.S.

MedCity News, April, 2011

Here's more…

Device Trials Driven Overseas By Cost, Ease of Patient Recruitment

"Moving a 510k product to market typically took half the time in Europe that it did in the U.S. — nine months versus 18 months. The difference is even larger for premarket approval applications, which average 54 months in the U.S., compared with just 11 months in the EU."

Clinical Trials Advisor (June, 2012)

But is expediency necessarily a good thing?

More reasons why so few are experienced in or even knowledgeable of medical device clinical trials?

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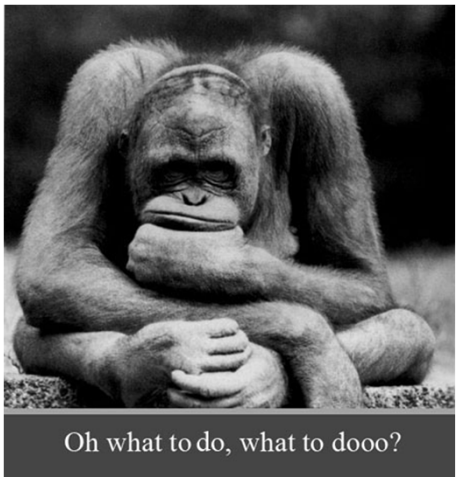
What does substantial equivalence really mean



Does anyone really know?

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So the 510(k) is based on the concept of "Substantial Equivalence"



but what does "substantial equivalence" really mean?

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Medical Device Regulatory Affairs:

The PreMarket Notification (PMN a.k.a. 510k) and Substantial Equivalence

Step 1:

Read the Guidance

Step 2:

But lets dig deeper…



The 510(k) Program: Evaluating Substantial Equivalence in Premarket Notifications (Dec. 27, 2011)

Draft Guidance for Industry and Food and Drug Administration Staff

The 510(k) Program: Evaluating Substantial Equivalence in Premarket Notifications [510(k)]

DRAFT GUIDANCE

This guidance document is being distributed for comment purposes only.
Document issued on: December 27, 2011

You should submit comments and suggestions regarding this draft document within 120 days of publication in the *Federal Register* of the notice announcing the availability of the draft guidance. Submit written comments to the Division of Dockets Management (HFA-305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852. Submit electronic comments to http://www.regulations.gov. Identify all comments with the docket number listed in the notice of availability that publishes in the *Federal Register*.

For questions for the Center for Devices and Radiological Health regarding this document contact the Premarket Notification (510(k)) Section at 301-796-5640.

For questions for the Center for Biologics Evaluation and Research regarding this document, contact the Office of Communication, Outreach and Development at 1-800-335-4709 or 301-827-1800.

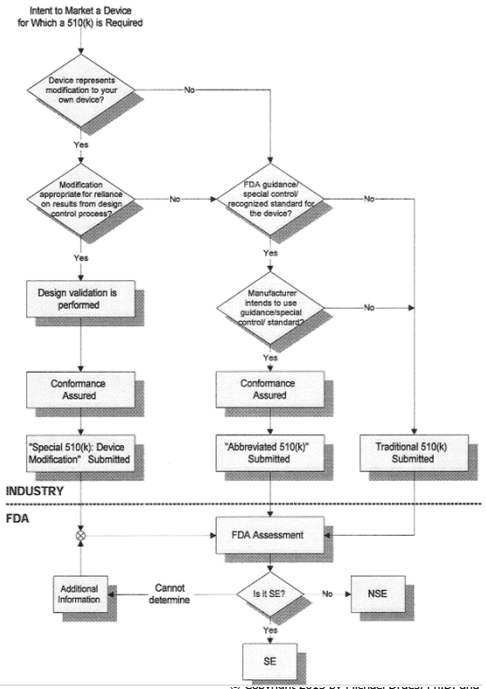
When final, this document will supersede, Guidance on the CDRH Premarket Notification Review Program, 510(k) Memorandum K86-3, dated June 30, 1986 and The New 510(k) Paradigm - Alternate Approaches to Demonstrating Substantial Equivalence in Premarket Notifications, dated March 20, 1998.

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Devices and Radiological Health

Center for Biologics Evaluation and Research

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510K and Substantial Equivalence Flowchart



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Medical Device Regulatory Affairs:

The PreMarket Notification (PMN a.k.a. 510k) and Substantial Equivalence

What is Substantial Equivalence?

A 510(k) requires demonstration of "substantial equivalence" to another legally U.S. marketed device (i.e., a predicate device). ***Substantial equivalence means that the new device is at least as safe and effective as the predicate.***

A device is substantially equivalent if, in comparison to a predicate it:

- has the ***same intended use*** as the predicate; and
- has the ***same technological characteristics*** as the predicate;

or

- has the ***same intended use*** as the predicate; and
- has ***different technological characteristics*** and the information submitted to FDA;
- does not raise new questions of safety and effectiveness; and
- demonstrates that the device is at least as safe and effective as the legally marketed device.

A claim of substantial equivalence does not mean the new and predicate devices must be identical. Substantial equivalence is established with respect to intended use, design, energy used or delivered, materials, chemical composition, manufacturing process, performance, safety, effectiveness, labeling, biocompatibility, standards, and other characteristics, as applicable.

Easy to understand in theory but reality is far more complex!

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What is Substantial Equivalence?

The 510(k) Program: Evaluating Substantial Equivalence in Premarket Notifications [510(k)]

Guidance for Industry and Food and Drug Administration Staff

Document issued on: July 28, 2014

The draft of this document issued on December 27, 2011.

This document supersedes FDA's Guidance on the CDRH Premarket Notification Review Program, 510(k) Memorandum K86-3, dated June 30, 1986.

For questions regarding this document, contact the Center for Devices and Radiological Health regarding this document, contact the Premarket Notification (510(k)) Section at 301-796-5640.

For questions for the Center for Biologics Evaluation and Research regarding this document, contact the Office of Communication, Outreach and Development at 301-827-1800, 800-835-4709 or 240-402-8010.

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Devices and Radiological Health
Center for Biologics Evaluation and Research

Not nearly as simple as so many think… or is it?

The 510(k) Program: Evaluating Substantial Equivalence in Premarket Notifications [510(k)] (CDRH, July, 2014) available here

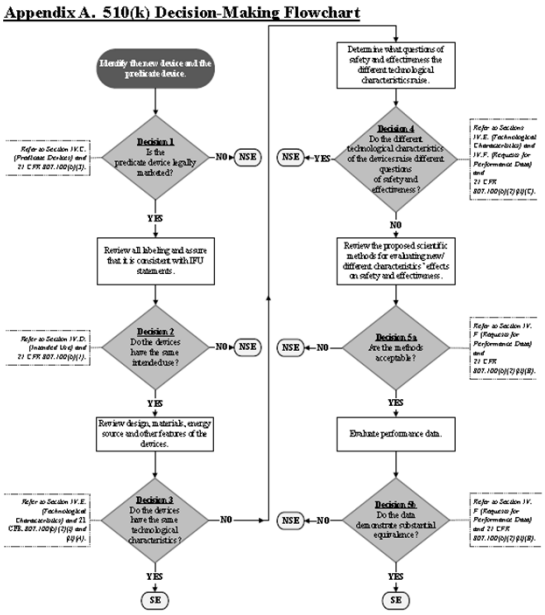
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Medical Device Regulatory Affairs:

The PreMarket Notification (PMN a.k.a. 510k) and Substantial Equivalence

What is Substantial Equivalence?

Has anything changed since 1976?



The 510(k) Program: Evaluating Substantial Equivalence in Premarket Notifications [510(k)] (CDRH, July, 2014) available here

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What does *different technological characteristics* really mean



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Medical Device Regulatory Affairs:

The PreMarket Notification (PMN a.k.a. 510k) and Substantial Equivalence

Crux of the 510k

A device is substantially equivalent if, in comparison to a predicate it:

- has the ***same intended use*** as the predicate; and
- has the ***same technological characteristics*** as the predicate;

or

- has the ***same intended use*** as the predicate; and
- has ***different technological characteristics*** and the information submitted to FDA

Easy to understand in theory but reality is far more complex!

Benefit-Risk Factors to Consider When Determining Substantial Equivalence in Premarket Notifications [510(k)] with Different Technological Characteristics (CDRH, July, 2014) available here

Benefit-Risk Factors to Consider When Determining Substantial Equivalence in Premarket Notifications [510(k)] with Different Technological Characteristics

Draft Guidance for Industry and Food and Drug Administration Staff

DRAFT GUIDANCE

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For questions about this document regarding CDRH-regulated devices, contact the Office of the Center Director at 301-796-5900.

For questions about this document regarding CBER-regulated devices, contact the Office of Communication, Outreach and Development (OCOD) by calling 1-800-835-4709 or 240-402-7800.

Department of Health and Human Services
Food and Drug Administration

Center for Devices and Radiological Health

Center for Biologics Evaluation and Research

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Where do you draw the line?

Is a car "substantially equivalent" to a truck?

What is the 'regulatory logic'?

What kind of truck?



Car vs. 18-Wheeler



compared to

Car vs. Pick-Up



And who draws the line?

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My on-going challenge…

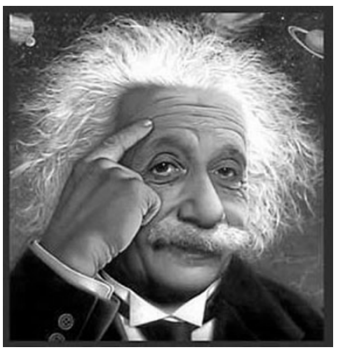
To simplify so that you can understand…

While at the same time, not oversimplifying to the point of introducing error.

Or put another way…

If you can't explain something simply…

you don't understand it well enough.



Albert Einstein (1879-1955) German born American Physicist who developed the special and general theories of relativity and earned the Nobel Prize for Physics in 1921.

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Are they substantially equivalent?



Are they bioequivalent?

We must always look for similarities…

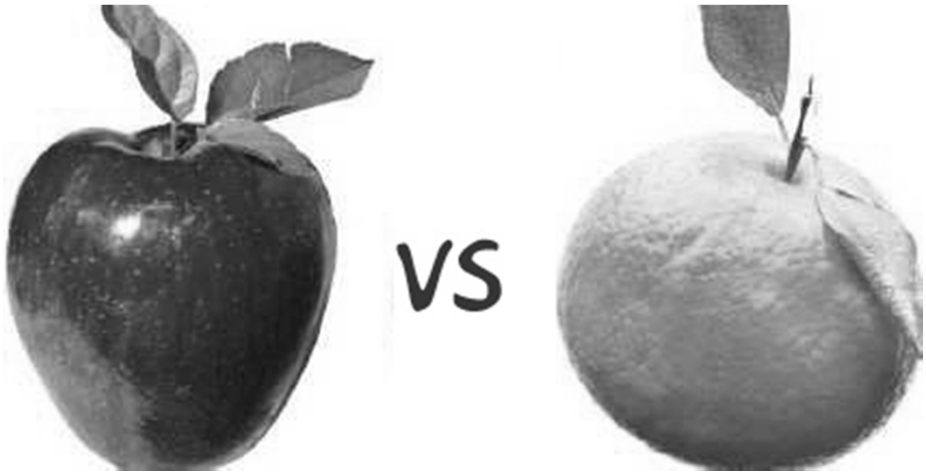
even when no similarities appear to exist!

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Medical Device Regulatory Affairs:

The PreMarket Notification (PMN a.k.a. 510k) and Substantial Equivalence

Is an apple "substantially equivalent" to an orange?



Let's take this even further…

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Can we use apples to explain substantial equivalence?

Question:

Is  *"substantially equivalent" to*  *?*

And what if we combine them? 

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Combination Fruit?



What happens when we can grow one of these?

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The Psychology and Neurobiology of Substantial Equivalence

Are these two images similar?



"If two images are similar, the brain assumes they are identical."

Scientific American Mind (2008) available here.

How does this apply to substantial equivalence?

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Can we use ketchup and mustard explain substantial equivalence?

Question:

Is 

"substantially equivalent" to 

?

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How about some more sophisticated substantial equivalence strategies



Split vs. Multiple Predicate Strategy

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Split-Predicate Strategy

What's another way to get  on to the market (if it were new)?

First question:

What other products have similar *individual* functions?

In this case, what's in ketchup?

 +  +  +  → 

So what's the *regulatory logic* to make this argument*?*

The split-predicate strategy is a form of *indirect precedent.*

Has become very controversial but when used properly, very effective!

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Split vs. Multiple Predicate Strategy

Split predicate strategy – think catchup

Multiple predicate strategy – think legs of a stool



 *vs.*  *vs.* 

vs. 



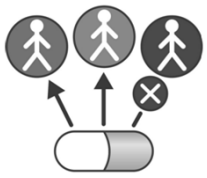
But it's not so simple!

Both are 'safe and effective' regulatory tools when used properly but…

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How about a quick example?

Personalized Medicine



- ✓ Guidelines for approval/clearance of certain molecular diagnostic (IVD) devices
- ✓ Guidance clarifies molecular diagnostic tools that combine both approved and unapproved functions in single label will not be allowed ***– DUH!***
- ✓ Companies may market devices that contain both approved/cleared uses and other functions for which approval or clearance is not required provided certain controls are established.

"FDA Provides Some Clarity to Complex Regulatory Environment for Molecular Diagnostics" (RAPS Focus, Nov. 10, 2014) available here.

Molecular Diagnostic Instruments with Combined Functions (CDRH Guidance, November, 2014) available here.

Molecular Diagnostic Instruments with Combined Functions

Guidance for Industry and Food and Drug Administration Staff

Document issued on November 12, 2014.
The draft of this document was issued on April 9, 2013.

For questions about this document, contact the Division of Microbiological Devices in CDRH's OIR and Andrew Grove, PhD, 301-796-6198, Andrew.grove@fda.hhs.gov. For questions for CBER, contact the Office of Communication, Outreach and Development (OCOD) by calling 1-800-835-4709 or 240-402-7800.

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Devices and Radiological Health
Office of *In Vitro* Diagnostic Device Evaluation and Safety
Division of Microbiology Devices

Center for Biologics Evaluation and Research

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Direct vs. Indirect Precedent

If we want to bring 

to market, could we use 

?

Must we?

Absolutely not!

We could use any of these:



How?

Bottom line: *what we use is not so important… the logic we use is!*

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Let's take this a step further…



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Simple Metaphors: *Cars vs. Airplanes*

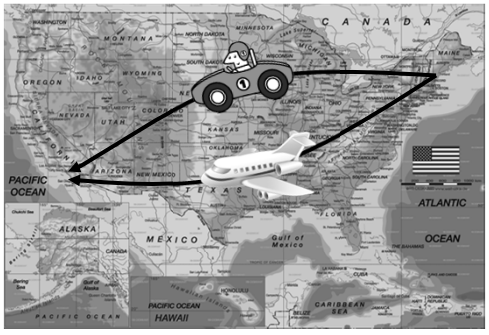
Question: Is a car "substantially equivalent" to an airplane?

I can drive a car from Boston to Los Angeles…

I can fly a plane from Boston to Los Angeles.

In both cases, I end up in Los Angeles.

Therefore…



a car is "substantially equivalent" to an airplane, i.e. the "intended use" is the same!

So how about…



Where do we draw the line and most importantly… who decides?

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We should always look for similarities where no similarities seem to exist…

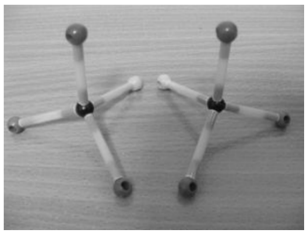
Substantial Equivalence vs. Bioequivalence

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Substantial Equivalence vs. Bioequivalence

Are these two medical devices *substantially equivalent?*

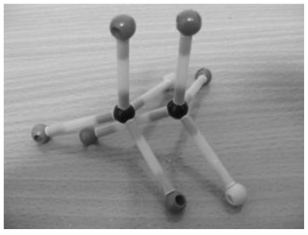
They're made of the same materials, same components, same shape… in fact, they are mirror images of one another but are they *substantially equivalent?*



What if these are not medical devices but drugs…

are they *bioequivalent?*

They are made of the same materials, same components (atoms), same shape… in fact, they are mirror images of one another (stereoisomers) which cannot be super-imposed. So…



Are they *bioequivalent?*

Are they *substantially equivalent?*

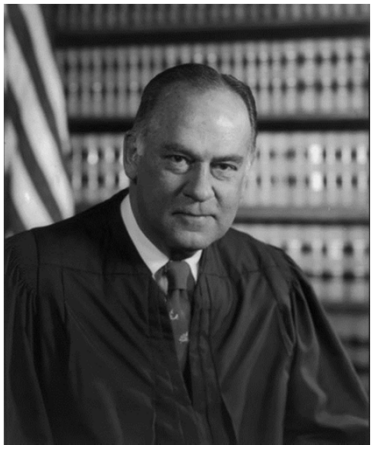
The paradox is stunning… or at least it should be!

So do we really understand this stuff or just think we do?

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We use these terms all the time but what do they mean?

Substantial Equivalence vs. Bioequivalence

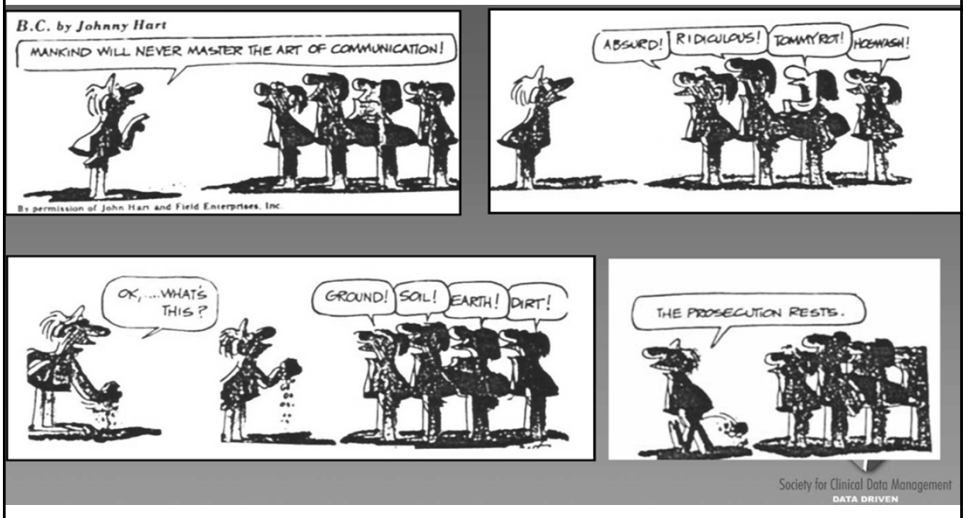


To the lay public, Stewart may be best known for a quotation, or a fragment thereof, from his opinion in the obscenity case of Jacobellis v. Ohio (1964). Stewart wrote in his short concurrence that **"hard-core pornography" was hard to define, but that "I know it when I see it."**

Potter Stewart
Associate Justice of the United States Supreme Court
1958 – 1981

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Why is terminology important?



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It's often about perception…



So what do some people think…

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Where are we now?



And where are we going?

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Medical Device Regulatory Affairs:

The PreMarket Notification (PMN a.k.a. 510k) and Substantial Equivalence

Science & Politics



Is this science or politics?

FDA Clearing Fewer 510(k)s to Meet User Fee Goals

The percent of 510(k) applications that FDA finds "not substantially equivalent" (NSE) has doubled in the past year — from 4% 2009 to 8% 2010 — and device makers say the agency is using its "discretion" in issuing NSEs in an attempt to meet user fee review goals.

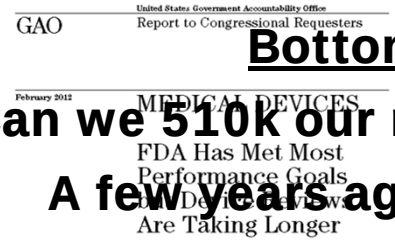
An internal FDA inquiry found the substantial equivalence (SE) rate has been on the decline for the past four years, the agency told industry representatives during a March 7 meeting to negotiate the next reauthorization of the Medical Device User Fee Modernization Act (MDUFMA).

FDANews Devices & Diagnostics Letter, April 4, 2011

Lets look further…

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Substantial Equivalence Today


United States Government Accountability Office

GAO

Report to Congressional Requesters

February 2012

MEDICAL DEVICES

FDA Has Met Most Performance Goals for Device Reviews, but Reviews Are Taking Longer

GAO-12-418

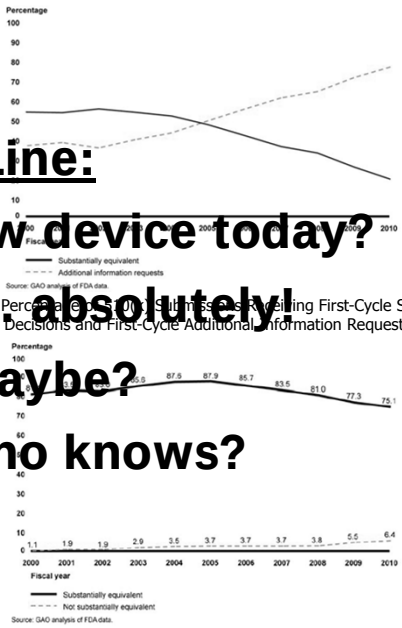
Bottom Line:

Can we 510k our new device today?

A few years ago… absolutely!

Today… maybe?

Tomorrow… who knows?



Percentage of First-Cycle Substantial Equivalence Rescinding First-Cycle SE Decisions and First-Cycle Additional Information Requests

GAO Report "Medical Devices: FDA Has Met Most Performance Goals but Device Reviews Are Taking Longer" (GAO-12-418, Feb., 2012)

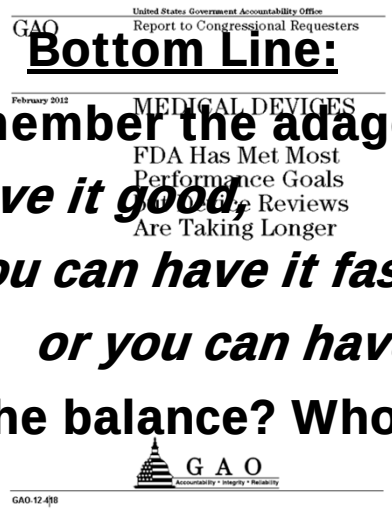
Percentage of FDA Final Decisions That Devices Were either SE or NSE for 510(k) Submissions

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Medical Device Regulatory Affairs:

The PreMarket Notification (PMN a.k.a. 510k) and Substantial Equivalence

Review Times


United States Government Accountability Office
Report to Congressional Requesters
February 2012
MEDICAL DEVICES
FDA Has Met Most
Performance Goals
Are Taking Longer
GAO
GAO-12-418

Bottom Line:

Remember the adage…

You can have it good,

you can have it fast

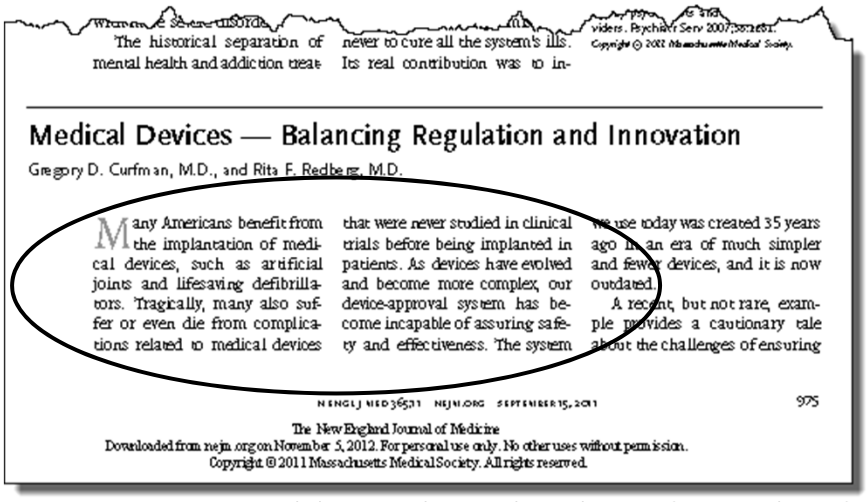
or you can have it cheap!

Where is the balance? Who decides?

GAO Report "Medical Devices: FDA Has Met Most Performance Goals but Device Reviews Are Taking Longer" (GAO-12-418, Feb., 2012)

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Regulation vs. Innovation


The historical separation of mental health and addiction treat… never to cure all the system's ills. Its real contribution was to in…

Medical Devices — Balancing Regulation and Innovation

Gregory D. Curfman, M.D., and Rita F. Redberg, M.D.

Many Americans benefit from the implantation of medical devices, such as artificial joints and lifesaving defibrillators. Tragically, many also suffer or even die from complications related to medical devices that were never studied in clinical trials before being implanted in patients. As devices have evolved and become more complex, our device-approval system has become incapable of assuring safety and effectiveness. The system we use today was created 35 years ago in an era of much simpler and fewer devices, and it is now outdated.

A recent, but not rare, example provides a cautionary tale about the challenges of ensuring

N ENGL J MED 365;11 NEJM.ORG SEPTEMBER 15, 2011 975

The New England Journal of Medicine
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Medical Devices — Balancing Regulation and Innovation (NEJM, September, 2011)

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Medical Device Regulatory Affairs:

The PreMarket Notification (PMN a.k.a. 510k) and Substantial Equivalence

What do people think about the 510k program



Depends on who you ask!

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Why should 2014 be any different?

The 'tumult' continues…

"Regulatory science"

(if there is such a thing!)

is an evolutionary science…

or at least it should be!

Think Design Controls…

outputs become the inputs

Think feedback…

nervous, endocrine, etc.

It's all about balance…

regulation vs. innovation

What do you think?

MDDI, December, 2014 (p28) available here.



Washington Wrap-Up

The Year of 510(k) Tumult

Complaints that FDA's busiest pathway to market for medical devices is anything but straight piled up in 2014.

JIM DICKINSON

Looking back, 2014 will be remembered as the year when FDA's busiest medical device route to market, the 510(k) "substantially equivalent" process, came under unprecedented challenge amid calls for structural change and even general abandonment.

There is dissatisfaction with the 510(k) status quo both within FDA (if unexpressed) and throughout industry and patient activist communities.

Industry Complaints

Kicking off the argument in January was a petition from the Minneapolis-based DuVal & Associates law firm on behalf of the Minnesota Medical Device Alliance and the medical device industry generally asking FDA to stop the administrative practices and definitional interpretations it has put into practice since 2009 in reviewing 510(k)s.

The petition charged that these have "dramatically changed the manner in which the 510(k) program operates. These disparate administrative practices have (a) the practical effect of changing the 510(k) program without statutory authorization; (b) ignored statutory and regulatory parameters; and (c) have made such changes without conducting notice-and-comment rulemaking to effectuate such changes."

This would become a recurring theme over the course of 2014—not only in other DuVal filings focused on FDA 510(k) policies, but also those from other constituencies.

Shifting Process, Unclear Instruction

The Washington Legal Foundation (WLF) promptly chimed in with a [illegible] of guidance documents and regulatory actions, FDA had transformed the 510(k) process from one that encouraged development of new and innovative medical devices that are as safe as existing devices, into one that evaluates whether the device meets some absolute level of safety.

"A significant part of the blame is attributable to inadequate supervision of FDA [illegible]," WLF commented, adding that "they are not receiving clear instructions that absolute assurance of safety is rarely attainable and that clearance is warranted under federal law whenever a new device is shown to be as safe as the predicate device."

Recissions Ruled Illegal

The degree of FDA's tinkering with the 510(k) was highlighted in April in a federal District of Columbia Court of Appeals case involving 510(K) recission letters. In this, it was revealed that the agency had for years been avoiding device reclassification requirements of the FD&C Act by simply writing letters to companies rescinding their product clearances administratively.

In September, the court ruled against FDA, declaring the practice illegal.

There is dissatisfaction with the 510(k) status quo both within FDA (if unexpressed) and throughout industry and patient activist communities.

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Medical Device Regulatory Affairs:

The PreMarket Notification (PMN a.k.a. 510k) and Substantial Equivalence

Change is in the air… or is it?

Here's a quote I gave a national reporter on the morning the IOM report was released commenting on recent developments and today's news:

"On the surface, many would argue the 510k process is changing even as we speak. On a much deeper and more important level however, here's my concern: *the more things change, the more they remain the same!"*

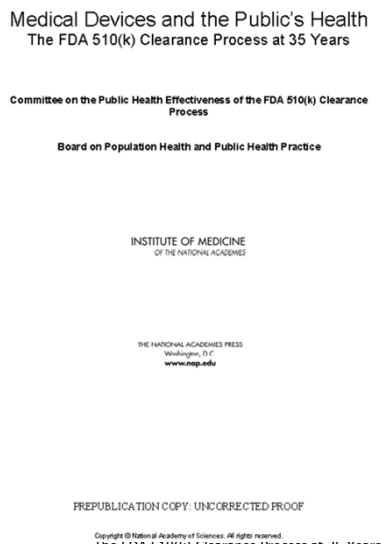
Michael Drues, Ph.D. July 29, 2011

So is this good or bad?

It depends on who you ask! How so?

And remember…

FDA has no obligation to follow any of the IOM recommendations!


Medical Devices and the Public's Health
The FDA 510(k) Clearance Process at 35 Years

Committee on the Public Health Effectiveness of the FDA 510(k) Clearance Process

Board on Population Health and Public Health Practice

INSTITUTE OF MEDICINE
OF THE NATIONAL ACADEMIES

THE NATIONAL ACADEMIES PRESS
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The FDA 510(K) Clearance Process at 35 Years
(IOM Report, July, 2011)

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These concerns are nothing new!


United States Government Accountability Office

GAO

Testimony
Before the Subcommittee on Health, Committee on Energy and Commerce, House of Representatives

For Release on Delivery
Expected at 9:30 a.m. EDT
Thursday, June 18, 2009

MEDICAL DEVICES

Shortcomings in FDA's Premarket Review, Postmarket Surveillance, and Inspections of Device Manufacturing Establishments

Statement of Marcia Crosse
Director, Health Care

GAO
Accountability • Integrity • Reliability

GAO-09-370T

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Let's give credit where credit is due!



Jean-Baptiste Alphonse Karr (1808–1890), a French critic, journalist, and novelist, said

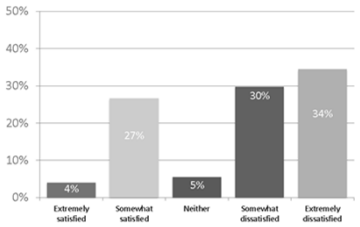
"Plus ça change, plus c'est la même chose."

Usually translated as

"The more things change, the more they stay the same.".

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How satisfied are companies with FDA's *management* of the 510k pathway?



510(k) Pathway Med-tech Industry Survey (August, 2012)

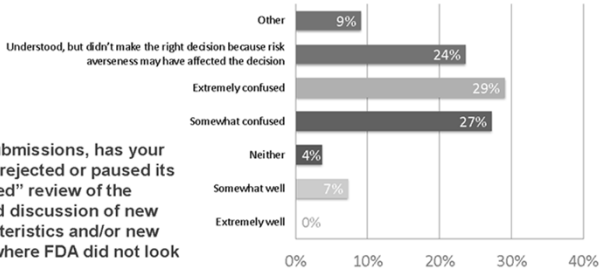
- ✓small study of device makers found that most companies are dissatisfied with the 510k process
- ✓out of 128 survey respondents, 64% said they were either "extremely dissatisfied" or "somewhat dissatisfied"
- ✓groups that report the highest dissatisfaction are ophthalmic, neurological and ENT device companies, while those with the highest satisfaction make cardiovascular devices, infection-control and dental devices as well as devices for anesthesiology and hospitals
- ✓primary reason for dissatisfaction appears to be a delay in communication, especially if the FDA ultimately ruled that the product could not be cleared because it wasn't substantially equivalent to a product currently available in the market
- ✓43% agreed that the FDA paused its review after doing a quick evaluation without reviewing performance data and issued a "not substantially equivalent" ruling or indicated that it will
- ✓another source of discontent: "lack of scientific expertise" at FDA. Only 7% said that in issuing NSE, FDA demonstrated "sound scientific issues" that device posed. Nearly 30% said FDA staff was "extremely confused," while another 27% said it was "somewhat confused."

MedCity News, November 12, 2012

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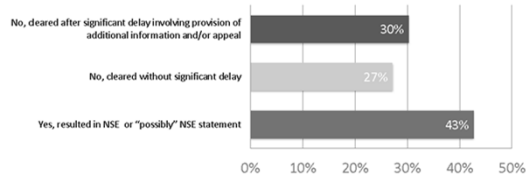
More perceptions about FDA and 510k

How well did you think FDA's review staff (reviewer, review team and Branch Chief) understood the *scientific issues surrounding your device in the NSE decision?*



7% of FDA's Staff understand scientific issues

In your experience with recent 510(k) submissions, has your company been notified that the Agency rejected or paused its review of your device after a "stage-gated" review of the legal/regulatory issues (i.e. that involved discussion of new intended use, new technological characteristics and/or new questions of safety and effectiveness) where FDA did not look at your performance data?



Are the criticisms justified?

Do you agree?

What do you think?

510(k) Pathway Med-tech Industry Survey (August, 2012)

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Is the 510k program perfect



Short answer – No!

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FDA Device Chief Says Loophole Needs to Be Closed

Question:

Can we use a predicate device that has been recalled?

Answer:

Until recently, yes!

The FDA's top medical-device regulator said **the agency needs more power to block unsafe products and prevent repeats of faulty hip implants and vaginal mesh that sparked thousands of patient lawsuits.**

…if there's a problem, it can get replicated through future generations of devices.

[FDA] approved vaginal mesh implants even though some traced their designs to a product that was recalled. The devices, used by 300,000 women to treat weakened pelvic muscles, have sparked hundreds of lawsuits from patients who say they lead to internal injuries, incontinence and painful sex.

[AdvaMed] criticized the proposal saying the bill would add regulatory burdens for manufacturers who already struggle with long FDA reviews. The agency already has "abundant authority to carry out its mandate'" and the legislation "will not contribute to patient safety."

A device is five times as likely to be recalled with a design flaw if it was based on a predicate that was itself pulled for safety problems, Shuren said.

Bloomberg, Feb. 28, 2012

Bottom line:

Predicates to recalled devices are no longer allowed – DUH!

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But it's not so simple:

Why did the recall occur?

Design problem? – if so, don't use it!

Manufacturing problem? – if so, why not use it!

Regulation does not address this!

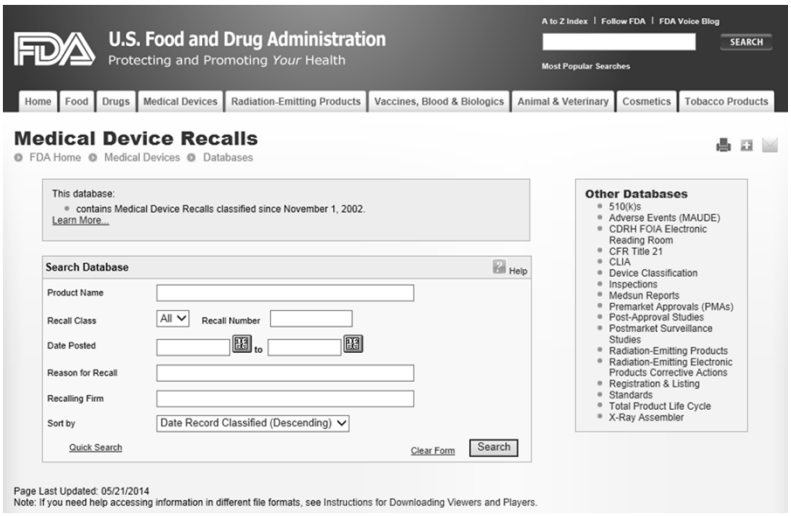
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Medical Device Recall Database

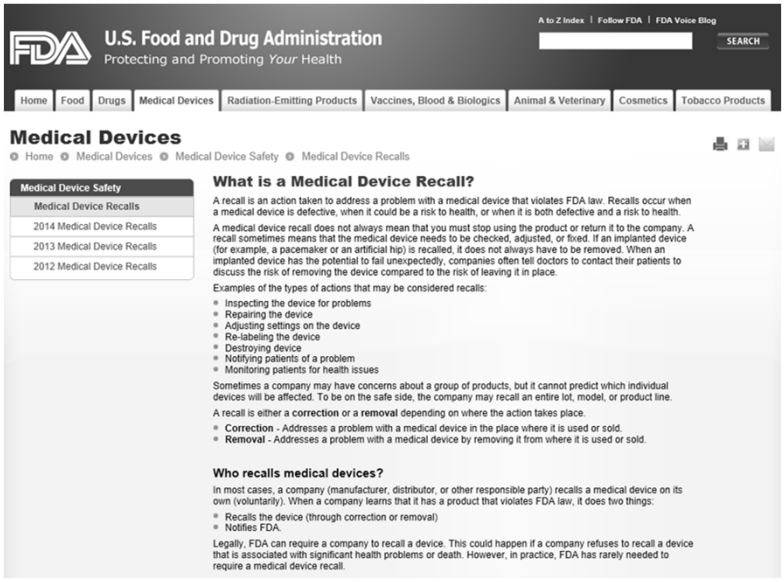
Always check for recalls before finalizing your predicate strategy!



www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfRES/res.cfm May, 2014

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Medical Device Recalls

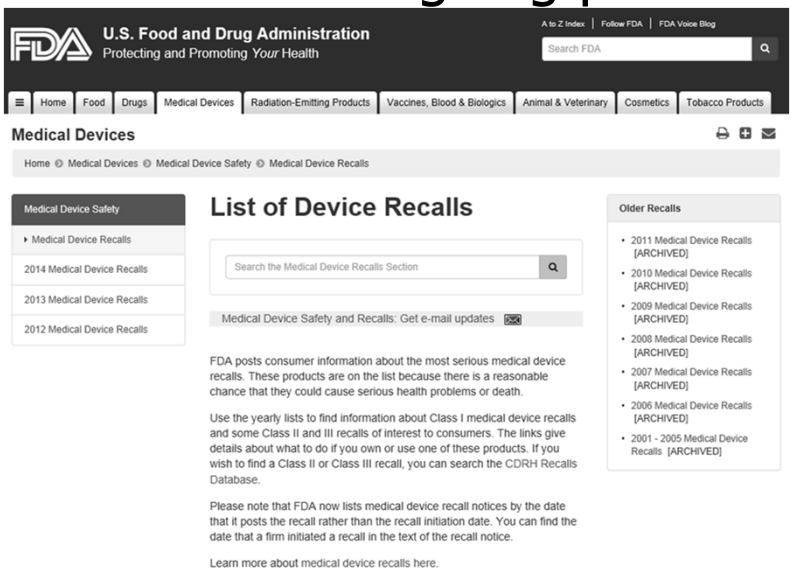


May, 2014

http://www.fda.gov/MedicalDevices/Safety/ListofRecalls/ucm329946.htm

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Recalls are a on-going problem…



May, 2014

www.fda.gov/MedicalDevices/Safety/ListofRecalls/default.htm

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What is predicate creep



Any guesses?

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What is predicate creep?

What is engineering creep?

- in materials science, creep (or deformation) is the tendency of a solid material to slowly deform permanently under the influence of stress (i.e., pulling)
- occurs as a result of long term exposure to high levels of stress and at higher temperatures and/or prolonged periods of time.

What is predicate creep?

- incremental device changes that seem innocuous individually in one 510(k) submission, may accumulate over time to create a device that is significantly different from the original device leading to 'predicate creep'

Do you see any similarities?

Similar to 'non-inferiority creep'

- when a series of non-inferiority studies is conducted over time
- for example, device B is non-inferior to A, device C is non-inferior to B, and device D is non-inferior to C), but the difference in effectiveness between device A and D may approach clinical significance

Similar to 'endpoint creep'

- adding additional clinical endpoints to study design (usually added as an amendment, i.e., after the fact… very expensive!)

So is there a test for predicate creep? or non-inferiority creep?

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Can your 510k be 'uncleared'?

Yep… it's called a rescission letter!



How many 510k's have been rescinded?

~100

Average ~3 per year (1976-2012)

Where Have All the 510(k) Rescission Letters Gone? (MDDI, August 7, 2014) available here.

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Why do some feel this way?



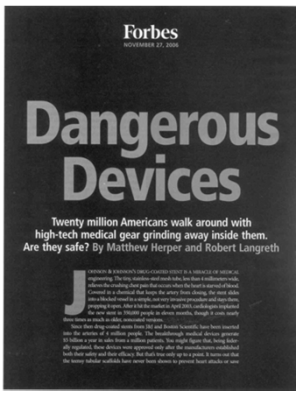
Let's look at some examples…

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Case Study: *Dangerous Devices*



"Dangerous Medical Devices:
Most medical implants have never been tested for safety"
(Consumer Reports, May, 2012)



Dangerous Devices
(Forbes, Nov. 27, 2006)

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What is the future of the 510k



Any guesses?

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What is the future of the 510k?

Some say it will look like this…



http://www.fda.gov/medicaldevices/deviceregulationandguidance/howtomarketyourdevice/premarketsubmissions/premarketapprovalpma/default.htm

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Will the 510(k) go away completely?

Maybe… though I certainly hope not!



Let's not throw the baby out with the bath water!

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The debate continues…


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NEWS

Regulatory 'Loophole' Allowing Unsafe Devices to be Marketed, Say Researchers

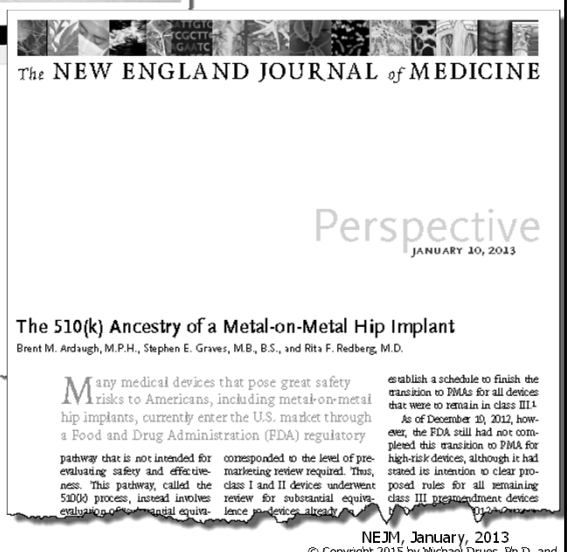
By Alexander Gaffney, RF News Editor

A "loophole" in the way in which some medical devices are regulated is allowing unsafe devices to reach—and harm—patients, argues a new editorial published in the *New England Journal of Medicine*.

The loophole stems from the 1976 *Medical Device Amendments*, which established for the first time in the US a system for the regulation of medical devices. The system classified medical devices into three general categories: Class I for low-risk devices, class II for moderate risk devices and class III for high-risk devices such as implantable devices.

Because many medical devices had already been on the market, Congress proposed—and the US Food and Drug Administration (FDA) implemented—a compromise: Some class III devices could be reviewed under the 510(k) substantial equivalence pathway, avoiding the more rigorous premarket approval (PMA) pathway that would require data from clinical trials to support an application.

Regulatory Focus, January, 2013


The NEW ENGLAND JOURNAL of MEDICINE

Perspective
JANUARY 10, 2013

The 510(k) Ancestry of a Metal-on-Metal Hip Implant

Brent M. Ardaugh, M.P.H., Stephen E. Graves, M.B., B.S., and Rita F. Redberg, M.D.

Many medical devices that pose great safety risks to Americans, including metal-on-metal hip implants, currently enter the U.S. market through a Food and Drug Administration (FDA) regulatory pathway that is not intended for evaluating safety and effectiveness. This pathway, called the 510(k) process, instead involves evaluation of substantial equivalence to devices already on the market. Devices that corresponded to the level of premarketing review required. Thus, class I and II devices underwent review for substantial equivalence to devices already on the market. Devices that establish a schedule to finish the transition to PMAs for all devices that were to remain in class III.[1]

As of December 10, 2012, however, the FDA still had not completed this transition to PMA for high-risk devices, although it had stated its intention to clear proposed rules for all remaining class III premendment devices

NEJM, January, 2013

Remember,

It's all about balance!

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Regulatory Impact on Biomaterials

Regulatory Considerations for Selecting Materials for Medical Devices
Dr. Linda Braddon, President, Secure BioMed Evaluations, USA

"All too often in the design of a new medical device, regulatory considerations do not come to the forefront until after the device is designed. By performing a regulatory impact review of your material choices very early in the design process, a new medical device company can expedite their time to market and reduce the regulatory burden."

Agree 100%

"By performing simple activities early in the process, such as identification of **FDA friendly materials**, manufacturers can reduce the burden of proving safety of their medical devices and decrease the time to product launch."

Agree but… at what cost?

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Does it make sense to 510k any permanent implant?

It happens all the time…

Breast Implants?

Orthopaedic Implants?

Vena Cava Filters? Pacing Leads?

Not just devices… what about materials?

It's all about balance…

What is safety? How safe is safe? How much testing is enough?

How many patients are harmed by *existing* devices

vs. how many patients are harmed by not having access to *new* devices?

These are not easy questions to answer!

But ***that doesn't mean we shouldn't ask anyway!***

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