

SIGNIFICANT RISK VS. NONSIGNIFICANT RISK DEVICES:

WHAT'S THE DIFFERENCE & WHY DOES IT MATTER?

presented by:

Michael Drues, Ph.D.

President, Vascular Sciences
Carlsbad, California

and

Adjunct Professor of Regulatory Science, Medicine
and Biomedical Engineering

Cornell University Graduate Dept. of Biomedical Engineering

GreenLight.Guru (February 15, 2024)

<https://www.greenlight.guru/webinar/significant-vs-nonsignificant-risk-devices>

For questions or more information, call
(508) 887 – 9486 or e-mail mdrues@vascularsci.com

SIGNIFICANT RISK VS. NON-SIGNIFICANT RISK DEVICES:

What's the difference and why does it matter?

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

In the US, there are three *independent* but also *interdependent* systems to categorize the risk a medical device poses. Perhaps the best known is the classification system, i.e., Class I, Class II and Class III. A second system is the Software Documentation Level, i.e., basic or enhanced system (formerly known as the Software Level of Concern, i.e., Class A, Class B or Class C system). Finally, the third important but seldom talked about risk system is the [Significant Risk](#) (SR) vs. [Non-Significant Risk](#) (NSR) system.

There is plenty of information available on the classification and software risk systems as well as SR devices, e.g., their regulatory requirements and the IDE process. However, there is much less available on how to handle an NSR device. Given that the vast majority of devices are NSR, what is a manufacturer of a NSR device to do?

Using his unique signature style, Dr. Drues will use the case study approach to take a detailed look at the various risk systems focusing on the SR vs. NSR system including:

- What is a significant risk (SR) vs. non-significant risk (NSR) device?
- How does the SR vs. NSR system compare to the other systems of risk?
- Who determines if my device is SR or NSR and how is the determination made?
- Why does SR vs. NSR matter? What are the requirements of each?
- If my device is SR, what do I do? If my device is NSR, what do I do?
- When and how should you take my SR vs. NSR determination to the IRB(s) and/or FDA?
- Does my device need a clinical trial? How are clinical trials different for SR vs. NSR devices?
- How should I select clinical trial sites and IRB's?
- Is there a template for the SR vs. NSR determination?
- Should I do a pre-submission meeting with FDA for an NSR device even though it's *not* required?
- What are the challenges for the future?

Using the case study approach, participants will learn best practices to avoid timely and costly mistakes as well as creative ways to use the SR vs. NSR system to their advantage!

Additional Resources

- Podcast: *3 systems of Risk* (Mike on Medtech, Sept, 2021) [here](#).
- Podcast: *3 Systems of Risk for Medical Devices from FDA* (April, 2021) [here](#)
- Presentation: *Risks that No One Wants to Talk About* [here](#)
- Webinar: *The Many Connotations of Risk and the Consequences of Getting Them Wrong* (Mar, 2017) [here](#).
- Podcast: *Significant Risk vs. Non-Significant Risk Devices – What's the Difference?* (Feb, 2017) [here](#)
- Podcast: *Using the Bucket Method for Medical Device Risk Management* (Dec, 2016) [here](#).
- Column: *The Many Connotations Of Risk and the Consequences of Getting Them Wrong* (Aug, 2015) [here](#).

Additional columns, articles, podcasts and webinars can be found: Global Medical Device Podcast (GreenLight.Guru) [here](#), Mike on MedTech (Medical Product Outsourcing) [here](#), Medical Design and Outsourcing [here](#), Guerilla Regulatory Strategy (MED Device Online) [here](#) and Healthcare Packaging [here](#) or LinkedIn [here](#).

Presenter Bio



[Michael Drues](#), Ph.D., is a regulatory strategy consultant specializing in designing novel regulatory strategies to bring new and innovative medical products to market and in developing effective communication strategies between companies and regulatory agencies to minimize time to market and avoid delays.

Dr. Drues received his B.S., M.S., and Ph.D. degrees in Biomedical Engineering from Iowa State University. He works 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, Health Canada, the US and European Patent Offices, the Centers for Medicare and Medicaid Services 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 FDA, Health Canada, the US and European Patent Offices, CMS and other regulatory and governmental agencies around the world.

Finally, Dr. Drues is an Adjunct Professor of Regulatory Affairs, Medicine and Biomedical Engineering at several universities and medical schools. He regularly teaches graduate courses in Regulatory Affairs and Clinical Trials, Medical Device Regulatory Affairs and Product Development, Combination Products and Pathophysiology.

Significant Risk vs. Nonsignificant Risk Devices: *What's the Difference & Why Does It Matter?*

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(508) 887 – 9486 or mdrues@vascularsci.com
Join me on LinkedIn at www.linkedin.com

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Significant Risk vs. Nonsignificant Risk Devices:

What's the Difference & Why Does It Matter?

Introductions



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Not bragging but...



The image shows a screenshot of the MDDI Qmed website. The header includes the MDDI Qmed logo, a search bar, and a 'SIGN UP TODAY' button. The navigation menu lists: Sectors, Product Development, Manufacturing, Regulatory & Quality, Digital Health, Business, and Qmed Directory. The main content area features the article '24 Medtech Voices to Follow in 2024' with a subtext: 'Looking to expand your online network in the new year? Check out these industry experts for inspiring and unique content concerning all things medtech.' Overlaid on the right is a LinkedIn post from Michael Drues, President of Vascular Sciences, dated December 3, 2023. The post includes a photo of Michael Drues and text: 'Product Development', 'Why We Follow Them', 'If you're looking to learn from someone with a deep level of knowledge about prototype design, product development, benchtop and animal testing, regulatory strategy and clinical trial design, presentation preparation and defense, reimbursement, clinical acceptance, or business development and technology assessment, you would be hard pressed to find someone better than Mike Drues.', 'You'll Find Them Talking About: #BiomedicalEngineering #FDA #ProductDevelopment #DeviceDesign', and '6K' likes. The bottom of the slide contains a footer with the text 'from 24 Medtech Voices to Follow in 2024 (MDDI, Dec 5, 2023) [here](#)', the GreenLight Guru logo, 'Vascular Sciences', and a copyright notice: '© Copyright by Michael Drues, Ph.D. and Vascular Sciences. All rights reserved.'

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First, an important disclaimer...



The image shows a hand holding a magnifying glass over a document. The magnifying glass is focused on the words 'READ THE SMALL PRINT' which are printed in a large, bold font. The background of the slide is blue with a white diagonal stripe.

I can't make you an expert in a few minutes!
I'm not even going to try but...

Remember my philosophy of education:

To teach you how to think not what to think!

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What's the Difference & Why Does It Matter?

Is it possible to think regulatory?

"Science is a way of thinking much more than it is a body of knowledge."

Carl Sagan (1934–1996)
American astronomer, author and science journalist

So how about this?

**Guerilla Regulatory Strategy:
Tips And Tactics**

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

"Regulatory affairs is a way of thinking much more than it is a body of rules and regulations – or at least it should be!"

Michael Drues (1964–)
Regulatory Strategist and Amateur Philosopher ©
www.meddeviceonline.com/author/michael-drues

Maybe Carl Sagan would be proud!

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Before we begin...

Polling Questions

Are you working on a significant risk (SR) device? (y/n)

Are you working on a non-significant risk (NSR) device? (y/n)

Do you know the difference? (y/n)

Are you sure? ☺ (y/n)

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What's the Difference & Why Does It Matter?



Here's what we'll talk about...

- ✓ What is a significant risk (SR) vs. nonsignificant risk (NSR) device?
- ✓ How does the SR vs. NSR system compare to the other systems of risk?
- ✓ Who determines if my device is SR or NSR and how is the determination made?
- ✓ Why does SR vs. NSR matter? What are the requirements of each?
- ✓ If my device is SR, what do I do? If my device is NSR, what do I do?
- ✓ When and how should you take my SR vs. NSR determination to the IRB(s) and/or FDA?
- ✓ Does my device need a clinical trial? How are clinical trials different for SR vs. NSR devices?
- ✓ How should I select clinical trial sites and IRB's?
- ✓ Should I do a pre-submission meeting with FDA for an NSR device even though it's not required?
- ✓ What are the challenges for the future?
- ✓ Bonus: Is there a template for the SR vs. NSR determination?
- ✓ Lots more tips and tricks... time permitting!
- ✓ Final thoughts...


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What's the Difference & Why Does It Matter?

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What is a significant risk (SR) vs. nonsignificant risk (NSR) device



Here's what FDA thinks but...

Is it what you think?

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Significant Risk vs. Nonsignificant Risk Devices:

What's the Difference & Why Does It Matter?

What is a Significant Risk (SR) Device?

Under [21 CFR 812.3\(m\)](#), an SR device means an investigational device that:

- ✓ Is **intended as an implant** and **presents a potential for serious risk to the health, safety, or welfare** of a subject;
Hmmm... what is an implant? Note does not specify permanent implant.
- ✓ Is purported or represented [i.e., intended] **to be for use supporting or sustaining human life** and **presents a potential for serious risk to the health, safety, or welfare** of a subject;
Hmmm... what does "supporting or sustaining human life" mean?
- ✓ Is **for a use of** [i.e., intended for] **substantial importance in diagnosing, curing, mitigating, or treating disease, or otherwise preventing impairment of human health** and **presents a potential for serious risk to the health, safety, or welfare of a subject**; or
Hmmm... what does "substantial importance" mean? what does "impairment of human health" mean?
- ✓ Otherwise **presents a potential for serious risk to the health, safety, or welfare of a subject**.
Note redundancy... why limit to "subject" i.e., patient?

Examples of SR Devices

Surgical Lasers, Tissue Adhesives, Cardiac Bypass Devices, Intravascular Stents, etc.

Note: SR not limited to Class III devices!

Guidance: *Significant Risk and Nonsignificant Risk Medical Device Studies: Guidance For IRBs, Clinical Investigators, and Sponsors* (Jan, 2006) [here](#).

FDA Website SR Devices [here](#).

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What is a Non-Significant Risk (NSR) Device?

Under [21 CFR 812.3\(m\)](#), an NSR device means an investigational device that:

"...does not meet the definition for an SR device." – *nothing else said!*

Does this help?

Examples of NSR Devices

Contact Lens Solutions, Dental Filling Materials, Digital Mammography, Ureteral Stents, etc.

Mike's Recommendation:

Start by assuming your device is SR... then prove its not!

Guidance: *Significant Risk and Nonsignificant Risk Medical Device Studies: Guidance For IRBs, Clinical Investigators, and Sponsors* (Jan, 2006) [here](#).

FDA Website NSR Devices [here](#).

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How does the SR vs. NSR system compare to the other systems of risk



Short answer:

They do NOT compare!

...other than by categorizing risk of course.

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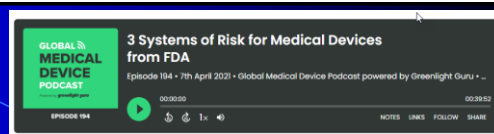
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Podcast: Three Systems of Risk



Podcast [here](#).

Highlights:

- Three systems for risk: classification, SR vs. NSR, Basic/Enhanced Documentation (formerly sLOC)
- Classification system stratifies risk in layers (i.e., classes), e.g., Class I, II, or III
 - The higher the class, the higher the risk. The lower the class, the lower the risk
 - Gross oversimplification *and* there are a ton of exceptions
- Classification in US does not translate linearly to class in EU and elsewhere
 - Similar systems but are philosophically different, i.e., NSE (pun intended!)
- SR vs. NSR system important in clinical trials
 - Does device require an investigational device exemption (IDE) or is it IDE Exempt?
 - Determination of SR vs. NSR is not made by FDA or IRB but the medical device company.
 - Is this the fox in charge of the henhouse? Absolutely... but that's what the reg says!
- Basic/Enhanced Documentation (formerly sLOC, i.e., class a, b, and c) determines level of documentation required for software
- Reminder: Default classification for any new medical device is Class III.
- Reminder: When it comes to labeling, say anything you want... so long as you can support it. However, if same technology but different labeling, risk also changes (usually).

Three systems are independent and interdependent!

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Webinar

UNDERSTANDING THE MANY CONNOTATIONS OF RISK IN MEDICAL DEVICE DEVELOPMENT AND THE CONSEQUENCES OF GETTING THEM WRONG

The Many Connotations of Risk and the Consequences of Getting Them Wrong™

presented by:


Michael Drues, Ph.D.
President, Vascular Sciences, Grafton, Massachusetts
Adjunct Professor of Regulatory Science, Medicine, and Biomedical Engineering
GreenLight.Guru Webinar (March 23, 2017)
<http://blog.greenlight.guru/topic/mike-drues>
For questions or more information, contact me at or (508) 887 - 9486 or mdrues@vascularsci.com
Join me on LinkedIn at www.linkedin.com/in/michaeldrues

March, 2017 [here](#).

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Who determines if my device is SR or NSR and how is the determination made



Hint:

It's not the FDA... Its not the IRB...

It's you!

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What's the Difference & Why Does It Matter?

Why does SR vs. NSR matter? What are the requirements of each

For SR Devices:

- ✓ submit IDE to FDA and obtain FDA approval (§812.20) AND
- ✓ submit investigational plan including prior investigations (§812.25 and §812.27) to each IRB

For NSR Devices:




- ✓ submit investigational plan including prior investigations (§812.25 and §812.27) to each IRB
- ✓ No IDE required (i.e. IDE Exempt)


...but take your NSR device to FDA anyway even though its not required! Why?

Reminders:

- FDA considers a NSR device to have an "approved IDE" when IRB agrees with NSR determination and approves study – *how do you show this?*
- If IRB disagrees with NSR determination, sponsor must notify FDA within five working days [§812.150(b)(9)] – *this is to be avoided! Why?*

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 17   IDE Approval Process [here](#)
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If my device is SR, what do I do? If my device is NSR, what do I do

In a nutshell...

- ✓ If device is SR, notify FDA (via IDE) and all IRB's
- ✓ If device is NSR, not required to notify FDA (IDE Exempt) but still notify all IRB's

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What's the Difference & Why Does It Matter?

When and how should
you take my SR vs. NSR
determination to the
IRB(s) and/or FDA



Just like pre-sub...

It's never to early but no earlier than when you are ready!

At the very least...

Identify clinical trial site(s), traditional vs. commercial IRB options, etc.
i.e., get your ducks in a row!

More specifically...

Anticipated Start Date – Average IRB Approval Time X Safety Factor

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Does my device
need a clinical trial



Unlike many believe...

This is not a regulatory decision... at least not completely!

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Substantial Equivalence and Regulatory Burden

Question: When is clinical data required?

Clinical data is never required!

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;

↓ regulatory burden → ↓ reliant on clinical data

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 the device **is at least as safe and effective** as legally marketed device.

↑ regulatory burden → ↑ reliant on clinical data

In other words,

The more similar you are, the less you have to do... but is this a good thing?

Question: *do you want to swing for a single or swing for a home run?*

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How are clinical trials different for SR vs. NSR devices



Regardless of SR/NSR determination...

- ✓ Labeling - device must be labeled in accordance with IDE regulations (§812.5) and must bear the statement "CAUTION - Investigational Device. Limited by Federal (or United States) law to investigational use."
- ✓ Distribution - Investigational devices can only be distributed to qualified investigators §812.43(b).
- ✓ Informed Consent - Each subject must be provided with and sign an informed consent form before being enrolled in the study (21 CFR 50, Protection of Human Subjects)
- ✓ Monitoring - All investigations must be properly monitored to protect the human subjects and assure compliance with approved protocols (§812.46)
- ✓ Prohibitions - Commercialization, promotion, and misrepresentation of an investigational device and prolongation of the study are prohibited (§812.7).
- ✓ Records and Reports - Sponsors and investigators are required to maintain specified records and make reports to investigators, IRBs, and FDA (§812.140 and §812.150).

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How should I select clinical trial sites and IRB's



That's really the subject of another webinar but here's a start... consider:

- ✓ Investigator/site experience with same/similar devices
- ✓ Patient enrollment
- ✓ Average IRB approval time for your clinical area
- ✓ How often does IRB meet? How responsive (i.e., cooperative) are they?
- ✓ Traditional vs. Commercial IRB options?
- ✓ Economics, i.e., "indirect" costs
- ✓ PR Value of investigator and/or site and/or key opinion leaders
- ✓ Many other factors to consider...

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Should I do a pre-submission meeting with FDA for an NSR device even though it's not required



Short answer:

Almost **ALWAYS!**

Why? Mitigate/eliminate two common problems:

- ✓ Confirm FDA agreement on SR vs. NSR determination
- ✓ Confirm FDA agreement on clinical trial design

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What are the challenges for the future



Can you say...

Personalized medicine, i.e., 3DP, etc.?

Question:

Could changing the manufacturing method(s) flip the SR/NSR determination?

Short answer: absolutely YES!

Reminder: current CFR SR criteria from <2006!

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Bare Metal Stents



Stent Grafts



Drug-Eluting Stents

Can we print a stent?



What kind of stent?

Better...

Can we print a customized bioabsorbable stent?

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Can we 3DP a 'customized' vascular stent?

Video: 3DP Vascular Stent (1 min) 

Absolutely! Watch this...



Method:
micro continuous liquid interface production (microCLIP)
↓
liquid photo-curable resin to print objects with light
↓
fabricate stent precisely matching patient anatomy

Advantages:

- Extremely high res (print features small as 7µm)
- Print up to 100 stents at a time → faster/cheaper than traditional manufacturing
- Speed: print 4-cm stent in minutes


What's next?
How about a personalized (i.e., 3-D printed) *DES*? – *wicked cool!* ☺
Advantages: choose drug (drugs), dosage, release rates, location, etc.
Should FDA regulate this? If so, how?

Northwestern Engineering News (Oct, 2016) available [here](#).

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If Time Permits...



BONUS QUESTIONS

AND ANSWERS BELOW

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Significant Risk vs. Nonsignificant Risk Devices:

What's the Difference & Why Does It Matter?

Is there a template for
the SR vs. NSR
determination



There are many...

Google "significant risk vs. non-significant risk template" [here](#)

But would you sue any of these? I would not!

Significant Risk vs. Nonsignificant Risk Devices:
What's the Difference & Why Does It Matter?



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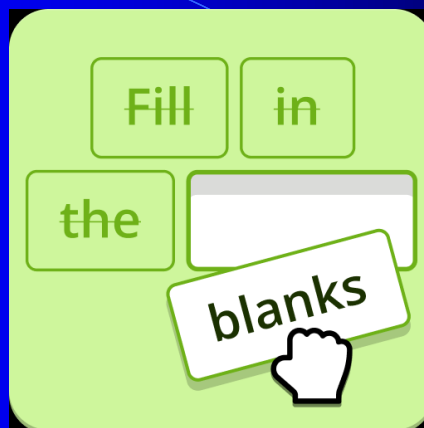
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For those who like templates...



Can you say *thinking inside the box?* No *creativity?* No *imagination?*

But if you really want one, I have one...

NSR Justification Example Template [here](#) (not publicly available...sorry)

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IF YOU CAN THINK IT, WE CAN DO IT.

"Imagination is more important than knowledge, for while knowledge points to all there is, imagination points to all that can be."
Albert Einstein

A Logic B
Imagination A B

"Logic will get you from A to B. Imagination will take you anywhere."
Albert Einstein

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IMAGINATION

"PERHAPS IMAGINATION IS ONLY INTELLIGENCE HAVING FUN."
- GEORGE SCIALABBA

George Scialabba is a book critic living in Cambridge, Massachusetts. His reviews have appeared in the Boston Globe, Dissent, the Virginia Quarterly Review, The Nation, The American Prospect, and many others.

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Want more?

Have you seen the musical Oliver?

Oliver Video [here](#) (20 sec).




PLEASE, SIR, I WANT SOME MORE.


Additional Resources

- Podcast: *3 systems of Risk* (Mike on Medtech, Sept, 2021) [here](#).
- Podcast: *3 Systems of Risk for Medical Devices from FDA* (April, 2021) [here](#)
- Presentation: *Risks that No One Wants to Talk About* [here](#)
- Webinar: *The Many Connotations of Risk and the Consequences of Getting Them Wrong* (Mar, 2017) [here](#).
- Podcast: *Significant Risk vs. Non-Significant Risk Devices – What's the Difference?* (Feb, 2017) [here](#)
- Podcast: *Using the Bucket Method for Medical Device Risk Management* (Dec, 2016) [here](#).
- Column: *The Many Connotations Of Risk and the Consequences of Getting Them Wrong* (Aug, 2015) [here](#).

Additional columns, articles, podcasts and webinars can be found: Global Medical Device Podcast (GreenLight.Guru) [here](#), Mike on MedTech (Medical Product Outsourcing) [here](#), Medical Design and Outsourcing [here](#), Guerilla Regulatory Strategy (MED Device Online) [here](#) and Healthcare Packaging [here](#) or LinkedIn [here](#).

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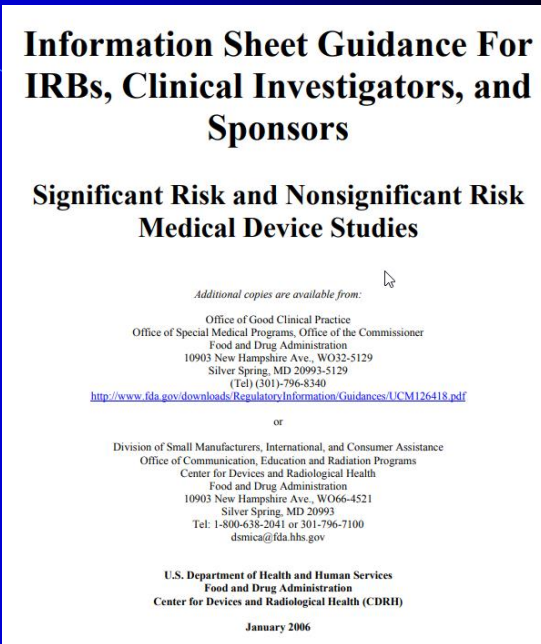
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"Current" Guidance



Significant Risk and Nonsignificant Risk Medical Device Studies:
Guidance For IRBs, Clinical Investigators, and Sponsors
(Jan, 2006) [here](#).

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Have you had enough?



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What's the



- ✓ SR/NSR determination is not up to FDA or IRB's... its up to you!
- ✓ IDE required for SR devices
- ✓ For NSR devices, strongly consider taking it to FDA before beginning your clinical trial(s)... even though its not required!
- ✓ Begin cite/IRB selection process early... its likely to take longer than you think!
- ✓ Whatever else is important to you!

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Significant Risk vs. Nonsignificant Risk Devices:




What's the Difference & Why Does It Matter?



Here's what we just talked about...

- ✓ What is a significant risk (SR) vs. nonsignificant risk (NSR) device?
- ✓ How does the SR vs. NSR system compare to the other systems of risk?
- ✓ Who determines if my device is SR or NSR and how is the determination made?
- ✓ Why does SR vs. NSR matter? What are the requirements of each?
- ✓ If my device is SR, what do I do? If my device is NSR, what do I do?
- ✓ When and how should you take my SR vs. NSR determination to the IRB(s) and/or FDA?
- ✓ Does my device need a clinical trial? How are clinical trials different for SR vs. NSR devices?
- ✓ How should I select clinical trial sites and IRB's?
- ✓ Should I do a pre-submission meeting with FDA for an NSR device even though it's not required?
- ✓ What are the challenges for the future?
- ✓ Bonus: Is there a template for the SR vs. NSR determination?
- ✓ Lots more tips and tricks... time permitting!
- ✓ Final thoughts...


Significant Risk vs. Nonsignificant Risk Devices:
What's the Difference & Why Does It Matter?

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What is the "right" amount of regulation?



There's nothing magic about regulations, too much is bad, too little is bad.

— Hillary Clinton —

Mike's Mantra (one of many):

If the regulation makes sense... we shouldn't need it!



If the regulation doesn't make sense... we shouldn't have it!

Remember...

The surgery went perfectly but the patient died anyway!

We followed the regulations perfectly but the patient died anyway!

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Significant Risk vs. Nonsignificant Risk Devices:

What's the Difference & Why Does It Matter?

There are many regulatory consultants out there...
but there are surprisingly few good ones!
So how do you become a good one?

**Learn when to follow and
more importantly...
when to lead!**

**A MAN WHO WANTS TO LEAD THE ORCHESTRA
MUST TURN HIS BACK ON THE CROWD.**

MAX LUCADO

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Logic

Imagination

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Taking inspiration from one of best...




"Here's to the crazy ones. The misfits. The rebels. The troublemakers. The round pegs in the square holes. The ones who see things differently. They're not fond of rules. And they have no respect for the status quo. You can quote them, disagree with them, glorify or vilify them. About the only thing you can't do is ignore them. Because they change things. They push the human race forward. And while some may see them as the crazy ones, we see genius. Because the people who are crazy enough to think they can change the world, are the ones who do."




Steve Jobs (1955 – 2011), entrepreneur, marketer and inventor, the co-founder of Apple Inc. and widely recognized as a pioneer of the personal computer revolution.

More importantly...

"Imagine where we could be if discontent for the status quo was the norm rather than the exception."

Can you guess who said this?



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Questions?

Comments?

Suggestions?

Criticisms?

Complaints?



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