Post-Market Surveillance for Medical Device and Combination Products:

If a device is FDA cleared or approved, can we assume it's safe and effective?

Presented by:

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GreenLight.Guru Webinar (October 30, 2019)

http://blog.greenlight.guru/topic/mike-drues

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Product Post-Market Surveillance for Medical Device and Combination Products:

Can we assume if a device is FDA cleared or approved, that it's safe and effective?

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

When a medical device or combination product is clearance or approval by FDA, can we assume it's safe and effective? In a word… NO! Only 3-5% of adverse events are reported to manufactures or FDA. Spun in reverse… *95-97% of adverse events are never reported!* If problems are not reported, can we conclude our devices are working perfectly? *Is the absence of evidence, evidence of absence?*

Post-market surveillance (PMS) is the process of watching our devices perform while on the market. PMS is a vital component of the medical device and combination product lifecycle. Yet historically, the med-tech industry has had a poor record when it comes to PMS. As a result, PMS requirements have been increasing in the US, the EU and around the globe. But having an effective PMS system means more than simply meeting the regulatory and quality requirements. A strong PMS system cannot simply find problems that may have been missed as part of the pre-market development or quality assurance process. A strong PMS system can be used to add additional indications, a.k.a. label expansions, which translates to greater revenues for the manufacturer!

Having an effective PMS system is important from both a regulatory and quality perspective. But can you assume if your PMS system meets the regulatory and quality requirements, that its effective? that its working? Absolutely not! And when companies make such assumptions, they often find themselves in trouble… not just with the FDA but with product liability attorneys as well! This presentation will use the case study approach to take a broad look at medical device and combination product post-market surveillance in an interactive fashion including:

- What are the key elements of an effective PMS system?
- With increasing pre-market regulatory requirements, do we still need PMS?
- Is passive PMS enough? What about active PMS?
- What is the role of risk management in PMS?
- How do we integrate usability into PMS?
- What about PMS for combination products? How does device PMS compare to drugs?
- How can PMS be used for label expansions? Either via RCT and/or real-world evidence?
- How do we meet PMS regulatory requirements without increasing product liability risk?
- How is PMS similar and different in the US vs. EU?
- What are the PMS challenges for the future, i.e., PMS for personalized devices including 3D printing?

In this presentation, participants will learn best practices to avoid timely and costly mistakes as well as creative ways to use post-market surveillance to their advantage!

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.

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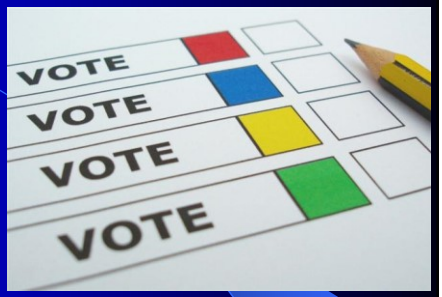
Before we begin…

Polling Questions



Are you currently conducting *any* post-market surveillance?

Are you currently conducting *passive* post-market surveillance?

Are you currently conducting *active* post-market surveillance?

Are you doing a good job conducting post-market surveillance?

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Here's what we'll talk about…

- ✓ What are the key elements of an effective PMS system?
- ✓ With increasing pre-market regulatory requirements, do we still need PMS?
- ✓ Is passive PMS enough? What about active PMS?
- ✓ What is the role of risk management in PMS?
- ✓ How do we integrate usability into PMS?
- ✓ What about PMS for combination products? Device PMS compare to drugs?
- ✓ How can PMS be used for label expansions? RCT vs. RWE?
- ✓ How do we meet regulatory requirements without increasing product liability?
- ✓ How is PMS similar and different in the US vs. EU?
- ✓ What are the PMS challenges for the future, i.e., personalized devices including 3DP?
- ✓ Anything else important?

In other words…

There is no better way to avoid finding a problem than not to look for one!

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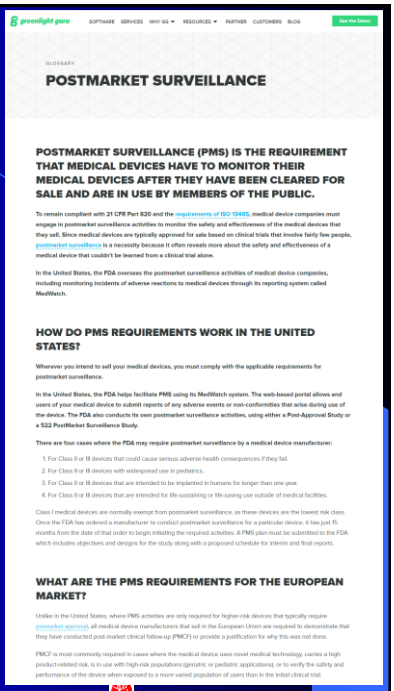
Where to go for additional information?

FDA Postmarket Requirements (Devices) here



We will go beyond the basics…

and don't forget the drug world!

GreenLight.Guru here

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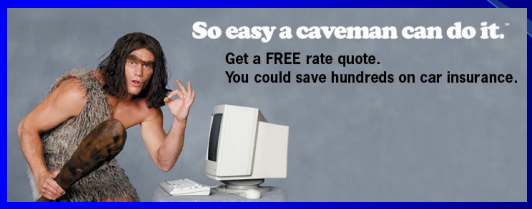
What is post-market surveillance (PMS)



Textbook:

"Monitoring the *safety* of a product (i.e., medical device) after it's been released and is the market."

Is it really so simple?

Where?

How long?

Safety only? What about efficacy?

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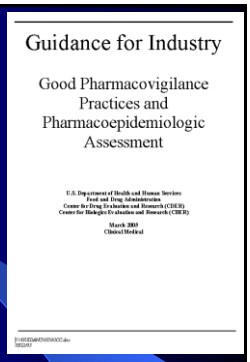
What is pharmacovigilance?

the detection, understanding and prevention of both acute and chronic *adverse effects* of *regulated* medical products, i.e., pharmaceuticals, but also includes (or should include) nutraceuticals, biologics, medical devices, combination products, etc.

The much more important question to ask is…

Does pharmacovigilance work?



FDA Guidance (March 2005)

Consider this:

Only an estimated 10% of all drug related adverse events are actually reported to manufacturers or regulators.

Applied Clinical Trials (April, 2019)

For medical devices, its even worse!

What do you think?

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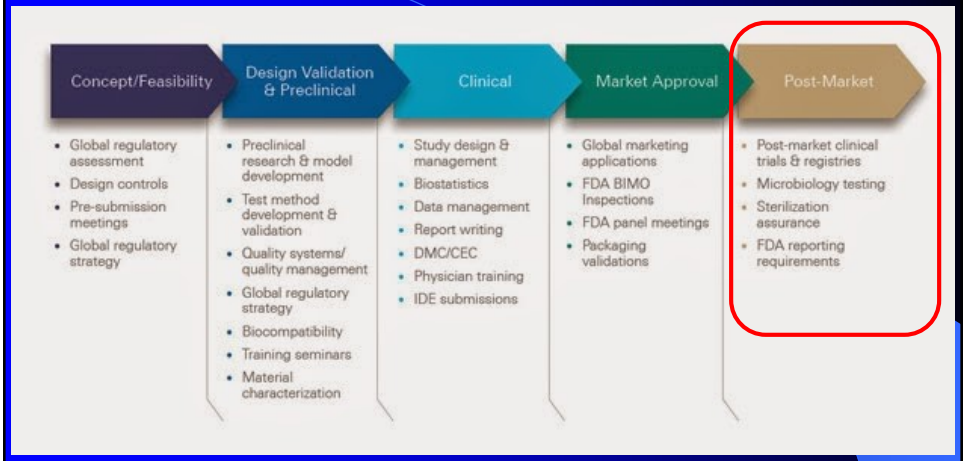
Medical Device Development Process



Where does PMS fit?

Is it this simple? Nope!

What about "pre-market" post-market surveillance?

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Why do PMS

For most people…

Because its required? Not a good reason to do anything!

Better reasons…

Safety… looking for problems

Efficacy… looking for opportunities (i.e., label expansion)

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When we get "permission to market" isn't that enough

Nope! Why not?

Hint: remember the adage…

Wait one year before prescribing a new drug…

and if its for a family member, wait 5 years!

Any different for devices?

Question:

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

What is the "philosophical basis" of post-market surveillance?

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If a device is FDA cleared or approved, can we assume it's safe and effective?

Is passive PMS enough

What about active PMS

What are the product liability implications

Passive PMS: Waiting for problems to come to you *vs.* Active PMS: proactively looking for them

In most circumstances (i.e., low-to-moderate risk),

Passive PMS is required… but is it enough?

What do you look at?

Your device, predicate device, other similar devices, beyond that, etc.

When and where do you look?

Weekly, monthly, quarterly, yearly… ?

What's directly reported to you? (passive) *vs.*

What about databases, literature (medical, popular press), etc. (active)

All of this is up to you!

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Why has there been a significant increase in PMS requirements worldwide

Could it be we have not been doing our jobs?

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If we are doing a good job, why an OMG review?


FEDERAL REGISTER
The Daily Journal of the United States Government

Notice

Agency Information Collection Activities; Submission for Office of Management and Budget Review; Comment Request; Postmarket Surveillance of Medical Devices

A Notice by the Food and Drug Administration on 10/24/2019

This document has a comment period that ends in 32 days. (11/25/2019)

SUBMIT A FORMAL COMMENT

PUBLISHED DOCUMENT

AGENCY:

Food and Drug Administration, HHS.

DOCUMENT DETAILS

Printed version:
PDF

Publication Date:
10/24/2019

Submission for Office of Management and Budget Review; Comment Request; Postmarket Surveillance of Medical Devices (Oct 24, 2019) Announcement here / PDF here.

Maybe we can do better?

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Why is OIG doing this?

One reason:

We are not doing our jobs!

OIG Report on FDA's PMS of Devices Coming in 2020 (RAPS, Oct. 18, 2019) here.

Assessment of the U.S. FDA's PMS of Medical Devices here.


Office of Inspector General

An Assessment of the U.S. Food and Drug Administration's Postmarket Surveillance of Medical Devices

Talking Points:

- OIG will "assess and describe" how FDA's "established *passive* postmarket surveillance system" identifies and tracks safety concerns and responds to them.
- "We will also describe how elements of FDA's newer surveillance system initiatives, such as the Unique Device Identification system, are being integrated into the passive postmarket surveillance system. In addition, we will describe how FDA plans to integrate these initiatives into the National Evaluation System for health Technology [NEST], its in-development active postmarket surveillance system," OIG said.
- UDI compliance dates were pushed back by FDA for several different classes of devices over the past several years, but ***compliance dates for Class III and implantable devices took effect in 2016 and 2015***, respectively.
- revised draft guidance on postmarket surveillance is coming in 2020
- follows FDA's decision (May) to end an alternative summary reporting program after a investigation showed how FDA had collected 1.1 million reports through the program since 2016
- in 2018, OIG found flaws in FDA's postmarket cybersecurity procedures.

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And now this?

"An investigative report claims FDA is hiding millions of adverse event reports from the public under the guise of an alternative summary reporting program."

FDA Slammed for 'Hiding' Device-Related Injury Reports (MDDI, March 7, 2019) here.

Factually correct but inherently biased statement!

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Want to know more?

Listen to the podcast here

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Why hasn't our industry (specifically us!) been very good at PMS in the past

Many reasons including…

Lack of enforcement

Here's another…

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Challenges of Post-Market Surveillance

Simple fact:

Many if not most PMS studies are simply not done. Why?

Here is one possible explanation:

"Nothing ruins good results better than long-term follow-up!"

Dr. Anthony Schepsis, Director of Sports Medicine at Boston University School of Medicine

In other words…

"There is no better way to avoid finding a problem…
than to not look for one!"

Dr. Michael Drues

Further,

It is not sufficient to look only at the products that are on the market, in clinical trials or under development. We must also ask *what products are we not developing and why are we not developing them?*

Similar for clinical trials:

It is not sufficient to look only at the clinical trials we have done in the past or the clinical trials we are currently doing. We must also ask *what clinical trials are we not doing and why are we do doing them?*

This is a very powerful and interesting way to look at the world.

Cannot the clinical trials we don't do be more important than the clinical trials we do?

Can we regulate trials that are not done? So how does this apply here?

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What have we really learned?

Stent grafts for abdominal aortic aneurysms (AAA) have been around for decades yet they continue to have problems… and not new problems, the same problems!

FDA U.S. FOOD & DRUG ADMINISTRATION

Home / Medical Devices / Medical Device Safety / Safety Communications / Update on Risk of Type III Endoleaks with Use of Endologix AFX Endovascular AAA Graft Systems: FDA Safety Communication

Update on Risk of Type III Endoleaks with Use of Endologix AFX Endovascular AAA Graft Systems: FDA Safety Communication

Safety Communications
2019 Safety Communications
2018 Safety Communications
2017 Safety Communications

Date Issued: October 28, 2019

The FDA is evaluating new information about the risk of blood continuing to leak into the aneurysm (Type III endoleak) when Endologix AFX endovascular grafts (AFX with Strata, AFX with Duraply, or AFX2) are used for the treatment of abdominal aortic aneurysms (AAA). We've previously communicated about the greater risk of Type III endoleaks occurring with the Endologix AFX with Strata device compared to other endovascular graft systems, which can result in serious injury. It is important for patients and health care providers to be aware that data from an integrated healthcare system, published in a recent conference abstract, suggest there also may be a higher than expected risk of Type III endoleaks occurring with the use of AFX with Duraply and AFX2 endovascular grafts. We recommend lifelong follow-up for patients treated with any endovascular graft. However, while we continue our evaluation, we are emphasizing the importance of at least yearly, lifelong follow-up for all patients who have any type of Endologix AFX endovascular graft in order to monitor for Type III endoleaks.

Content current as of: 10/28/2019

FDA Safety Communication (Oct 28, 2019) here.

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Case Study: Breast Implants

WARNING:

- **Breast implants are not considered lifetime devices. The longer people have them, the greater the chances are that they will develop complications, some of which will require more surgery.**
- **Breast implants have been associated with the development of a cancer of the immune system called breast implant-associated anaplastic large cell lymphoma (BIA-ALCL). This cancer occurs more commonly in patients with textured breast implants than smooth implants, although rates are not well defined. Some patients have died from BIA-ALCL.**
- **Patients receiving breast implants have reported a variety of systemic symptoms such as joint paint, muscle aches, confusion, chronic fatigue, autoimmune diseases and others. Individual patient risk for developing these symptoms has not been well established. Some patients report complete resolution of symptoms when the implants are removed without replacement.**

FDA Calls for New Warning on Breast Implants (RAPS, Oct 23, 2019) here.

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Can you say Paclitaxel?

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What's the relationship between human factors and post-market surveillance

Pre-Market:

Formative HF (forms/shapes design during development)

+

Summative HF (issues/problems/benefits of existing/prototype design)

+

What's missing?

Post-Market:

Human Factors PMS

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Talk is cheap…

Is this theory or reality?

Human Factors and Postmarket Surveillance here

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Case Study: *da Vinci surgical robot*

At the end of the day…

Questions for Discussion:

1. What is the *root cause* of this problem? Hint: is lack of training the *real* root cause? How much training is enough?
2. Were these problems *unforeseeable*, i.e., *anticipated risks?* Were these problems new?
3. How does human factors / usability fit into this equation?
4. Who's to blame? FDA: "does not have jurisdiction" / Manufacturer: "cannot require training" Is this a copout?
5. Speaking of blame… what happens when we get it wrong?
6. Does it make sense to separate the efficacy of the device from the skill level of the user?
7. How is this similar to Enteryx?
8. What are the lessons to be learned? What else is important?

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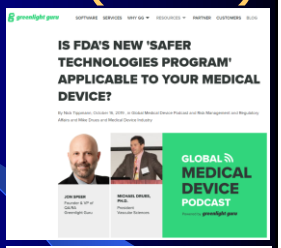
Safer Technologies Program (STeP)

Podcast here.

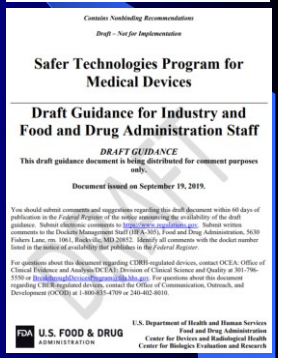


Safer Technologies Program (STeP):

- STeP similar (SE) to BDP ☺
- Focus on safety not efficacy, i.e.,

  device should be reasonably expected to significantly improve the benefit-risk profile of a treatment or diagnostic through substantial safety innovations that provide for one or more of the following:

  - ✓ a reduction in the occurrence of a **known serious adverse event,**
  - ✓ a reduction in the occurrence of a **known device failure mode,**
  - ✓ a reduction in the occurrence of a **known use-related hazard or use error**, or
  - ✓ an improvement in the safety of **another device or intervention**.



Guidance here.

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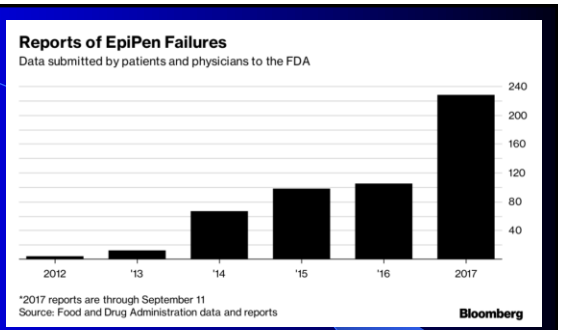
Case Study: *EpiPen*



EpiPen Failures Cited in Seven Deaths This Year (Bloomberg, Nov. 2, 2017) here.

Why is this happening?

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Post-Market Surveillance for Medical Device and Combination Products:

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How does US PMS compare to EU

In a nutshell…

EU $_{PMS}$ >> US $_{PMS}$ …at least for now!

Why?

Implant Files to name just one reason!

Is this justified?

Partially but not completely

PMS should be based on technology and risk… not regulatory requirements which sometimes may not be enough, other times may be to much i.e., overly burdensome.

Recommendation:

Do what makes sense in your situation and then document your justification…

not just what you are doing but what you are not doing and why you're not doing it!

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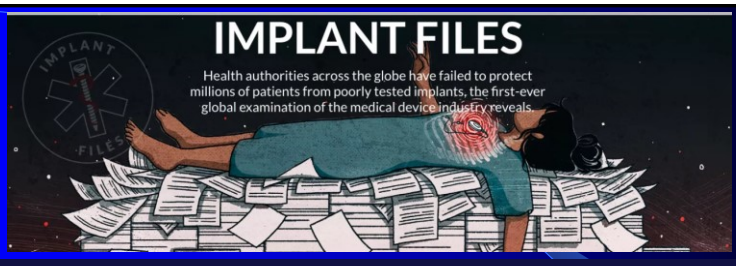

The Implant Files: A Global Communications Crisis

GLOBAL HEALTHPR

In November 2018, the International Consortium of Investigative Journalists published the results of the largest-ever investigation into medical device safety. The Implant Files investigation, from the same organization that released the infamous Panama Papers in 2016, involved more than 250 journalists across 36 countries coordinating to look into the behaviors of the medical device industry around the world.

The findings were grim, among them:

Globally, **as many as 83,000 people have died** in the last decade as a result of faulty medical devices and **as many as 1.7 million injuries** could have occurred

A rare type of **cancer** has been linked to a widely used model of breast implants

Some devices in question were approved in the UK after being tested on **as few as 30 people**

Yet, absent from the conversation was the medical device industry itself. While the investigation's findings were hitting headlines from Australia to New York, mum was the word—with no major manufacturers commenting, they became the elephant in the room.

Implant Files Video: here Home Page here.

The regulatory ancestral network of surgical meshes here.

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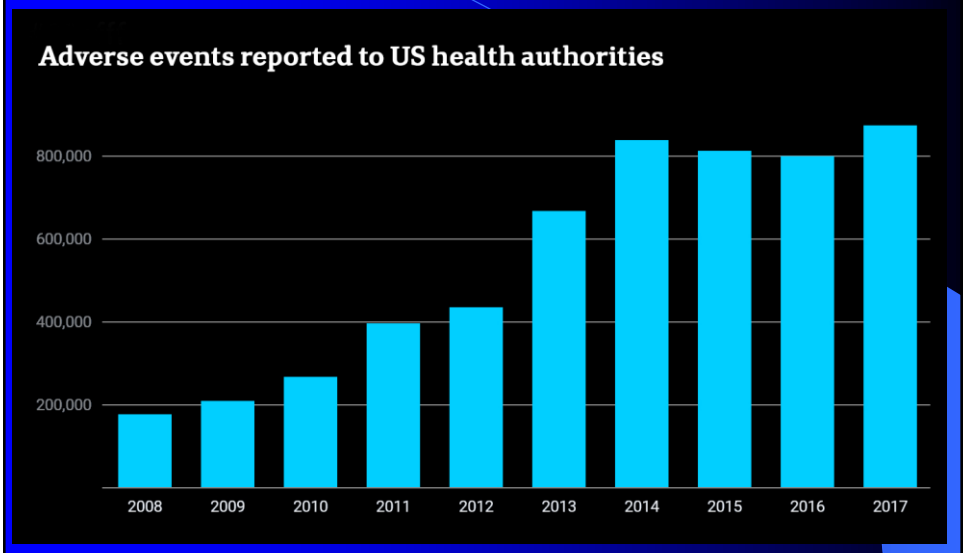
Is this concerning?



Implant Files (Nov, 2018) here

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www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/PostmarketRequirements/QualitySystemsRegulations/default.htm

Good regulation is neither specific nor rigid… *nor should it be!*

Flexibility of the QS Regulation (Preamble)

"The QS regulation embraces the same "umbrella" approach to the CGMP regulation that was the underpinning of the original CGMP regulation. Because the ***regulation must apply to so many different types of devices, the regulation does not prescribe in detail how a manufacturer must produce a specific device. Rather, the regulation provides the framework that all manufacturers must follow by requiring that manufacturers develop and follow procedures and fill in the details that are appropriate to a given device*** according to the current state-of-the-art manufacturing for that specific device.

Manufacturers should use good judgment when developing their quality system and apply those sections of the QS regulation that are applicable to their specific products and operations, 21 CFR 820.5 of the QS regulation. Operating within this flexibility, ***it is the responsibility of each manufacturer to establish requirements for each type or family of devices that will result in devices that are safe and effective,*** and to establish methods and procedures to design, produce, distribute, etc. devices that meet the quality system requirements. ***The responsibility for meeting these requirements and for having objective evidence of meeting these requirements may not be delegated even though the actual work may be delegated.***

FDA has identified in the QS regulation ***the essential elements that a quality system shall embody, without prescribing specific ways to establish these elements. Because the QS regulation covers a broad spectrum of devices, production processes, etc., it allows some leeway in the details of quality system elements. It is left to manufacturers to determine the necessity for, or extent of, some quality elements and to develop and implement specific procedures tailored to their particular processes and devices."***

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Don't just follow the rules… think!

Rules are mostly made to be broken
and are too often for the lazy to hide behind.

General Douglas MacArthur (1880 –1964) was an American general in the US Army during the 1930s and played a prominent role in the Pacific theater during World War II. He was one of only five men ever to rise to the rank of General of the Army in the U.S.

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What about post-market surveillance for combination products?

That's a topic for a different discussion… or is it?

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Combination Product PMS

What's in the guidance?

- comply with 2016 final rule (RAPS) that established new requirements for submitting safety reports based on ***all the constituent parts of the product*** in addition to application-type reporting.
- ***makers of constituent parts must share certain postmarket safety information with one another.***

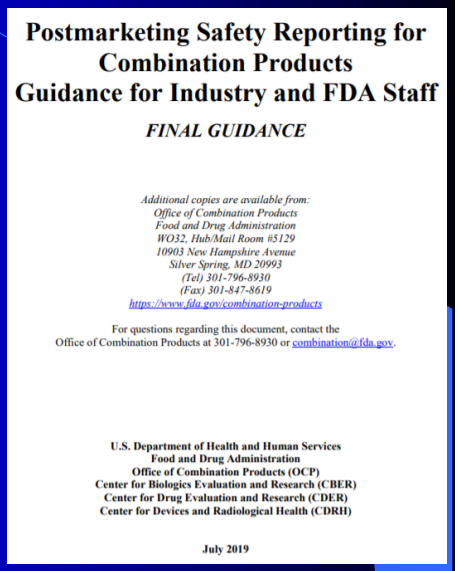
Statement of the obvious?

- includes two "hypothetical" examples of PMS reporting for combo products:
  1. PMOA $_{Drug}$: Pre-Filled Syringe (NDA)
  2. PMOA $_{Device}$: Drug-Eluting Stent (PMA)

Note:

Administratively complicated but logic is simple!

FDA Finalizes Combo Product Post-market Safety Reporting Guidance (RAPS, July, 2019) here / FDA Guidance here



Postmarketing Safety Reporting for Combination Products
Guidance for Industry and FDA Staff

FINAL GUIDANCE

Additional copies are available from:
Office of Combination Products
Food and Drug Administration
WO32, Hub/Mail Room #5129
10903 New Hampshire Avenue
Silver Spring, MD 20993
(Tel) 301-796-8930
(Fax) 301-847-8619
https://www.fda.gov/combination-products

For questions regarding this document, contact the Office of Combination Products at 301-796-8930 or combination@fda.gov.

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Food and Drug Administration
Office of Combination Products (OCP)
Center for Biologics Evaluation and Research (CBER)
Center for Drug Evaluation and Research (CDER)
Center for Devices and Radiological Health (CDRH)

July 2019

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Why should Medical Device Companies care about Drug PMS?

FDA can require PMS and /or clinical trials for drugs and biologics *either at time of approval OR thereafter* if and/or when *new safety information* becomes available, i.e.,

- assess known serious risk related to drug
- identify unexpected serious risk when indicated

Q: *What about efficacy?*

Q: *Why wait for FDA to "require" this?* [prod liability implications!]

What is the regulatory logic / justification for this?

Is this any different for devices? i.e., ~~drug~~ → device ?

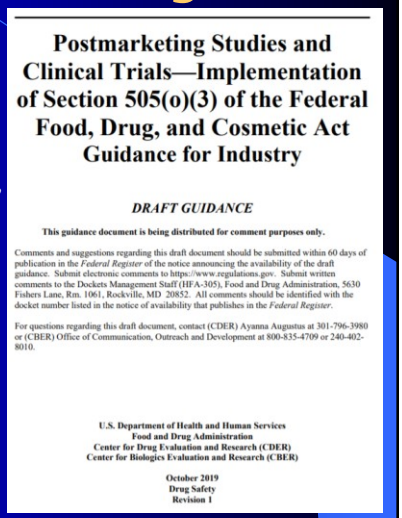
Why is this important for device manuf? Many reasons…

- ✓ Often CDER leads CDRH
- ✓ Combination Products
- ✓ *Being a professional = understanding entire universe!*

Looking for similarities… here.

Postmarketing Studies and Clinical Trials—Implementation of Section 505(o)(3) of the Federal Food, Drug, and Cosmetic Act (October, 2019) here.

FDA Revises Guidance on Postmarketing Studies (RAPS, Oct 24, 2019) here.



Postmarketing Studies and Clinical Trials—Implementation of Section 505(o)(3) of the Federal Food, Drug, and Cosmetic Act
Guidance for Industry

DRAFT GUIDANCE

This guidance document is being distributed for comment purposes only.

Comments and suggestions regarding this draft document should be submitted within 60 days of publication in the *Federal Register* of the notice announcing the availability of the draft guidance. Submit electronic comments to https://www.regulations.gov. Submit written comments to the Dockets Management Staff (HFA-305), Food and Drug Administration, 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852. All comments should be identified with the docket number listed in the notice of availability that publishes in the *Federal Register*.

For questions regarding this draft document, contact (CDER) Ayanna Augustus at 301-796-3980 or (CBER) Office of Communication, Outreach and Development at 800-835-4709 or 240-402-8010.

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)

October 2019
Drug Safety
Revision 1

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GreenLight.Guru Webinar (October 30, 2019)

www.greenlight.guru/webinar/post-market-surveillance-medical-devices-combination-products

Post-Market Surveillance for Medical Device and Combination Products:

If a device is FDA cleared or approved, can we assume it's safe and effective?

How can PMS be used for label expansions?

Randomized Clinical Trial (RCT) vs. Real World Evidence (RWE)

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What are the PMS challenges for the future, i.e., personalized devices including 3DP

Current regulation is totally inadequate…

personalized devices require personalized PMS!

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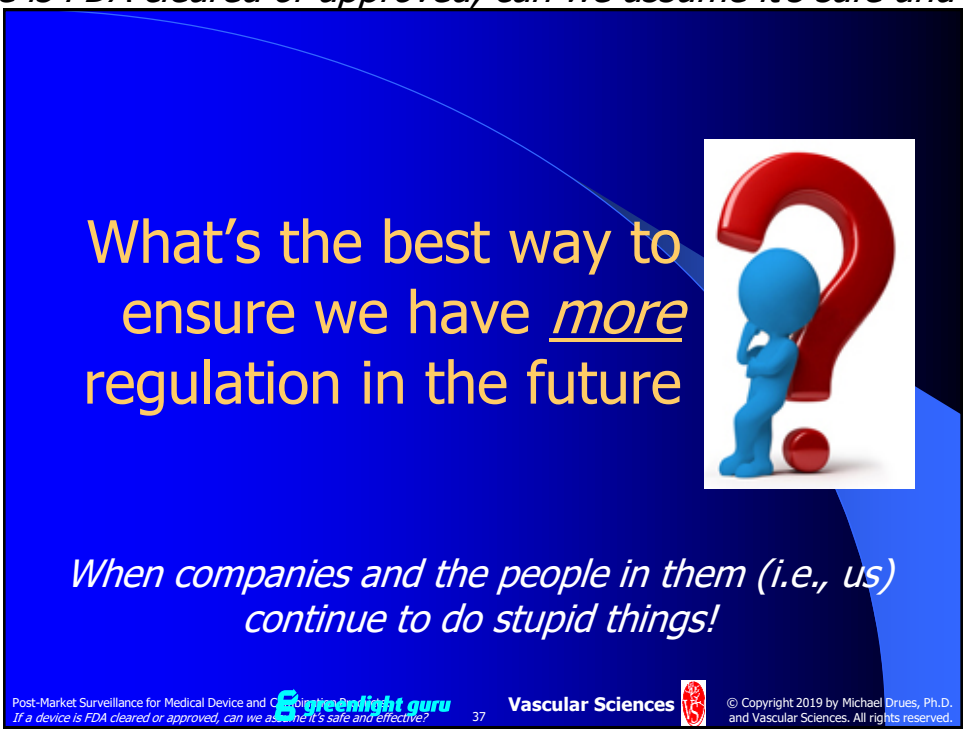

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