Combination Products:

What are they, why are they important & why should medical device companies care?

presented by:

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and

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GreenLight.Guru (June 17, 2021)
https://www.greenlight.guru/webinar/combination-products

For questions or more information, call
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What is a Combination Product and Why are they Really Important?

Why should medical device professionals care?

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

Before you stop reading because you think this topic is a no-brainer, think again! Like most things regulatory, this topic is not nearly as simple or straight forward as so many seem to think. Consider this: more than 30% of all new healthcare products under development are combination products and the global market for combination products is >$115B! But are combination products important simply because of the money?

During this webinar, participants will be exposed to a wide range of combination products on the market, under development and on the drawing board. Examples include drug-eluting stents and balloons, pre-loaded syringes and transdermal patches, drug-biologic combinations a.k.a. antibody-drug conjugates and companion diagnostics to name just a few! More complex examples of a combination product will also be presented including 3-D printing, personalized medicine, tissue engineering (a.k.a. regenerative medicine) and biomedical nanotechnology.

In this webinar, we will explore the seemly simple question: *what is a combination product and why are they important?* In other words, what can combination product due that medical devices, drugs and biologics alone cannot? Why should medical device professionals care? Using the case study approach, these questions and others will be presented in an interactive fashion including:

- What is and is not a combination product? Is it as simple as reading the CFR or is the CFR holding us back?
- Why are combination products important? Is it just about the money or is there a more important reason?
- How are combination products regulated? Is it simply a matter of PMOA?
- What does the future hold? How will tissue engineering, nanotechnology and other "advanced" technologies impact the medical device industry as we know it today?

And this is just the tip of the iceberg! Bottom line: current combination products, i.e., drug-eluting stents, transdermal patches, pre-filled syringes, etc., although a good start – are boring! There are multiple examples of combination products and what the CFR currently recognizes is only a small fraction of the possibilities!

Who Should Attend: Geared for both experienced medical technology professionals as well as those new to the industry, this webinar is designed for those who need a better understanding of the current regulatory requirements surrounding combination products. This unique seminar demonstrates important regulatory requirements and concepts using case study discussions of real products from a variety of clinical specialties. Scientists, engineers and technicians working in product and business development, regulatory affairs and quality professionals and marketing and investment specialists will all benefit from this webinar.

What to know more? See:

Article: *Combination products: The future of medicine* here
Article: *Combination Products 101: A Primer for Medical Device Makers* here
Podcast: *Medicinal Combination Products* here
Podcast: *Combination Products: Exploring The Opportunities And Challenges For Medical Device Makers* here
Article: *Combination Products: Engineering and Biologics Make Good Bedfellows* here
Column: *Companion Diagnostics: Why Medical Device Manufacturers Should Care* here

For a comprehensive list of columns, webinar, podcasts, etc., visit 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, LinkedIn here.

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 stimulating & innovative educational programing, creative regulatory strategy & completive regulatory intelligence, regulatory submission design, FDA presentation preparation & defense, brain-storming sessions, prototype design, product development, benchtop & animal testing, , clinical trial design, 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 Regulatory Science, 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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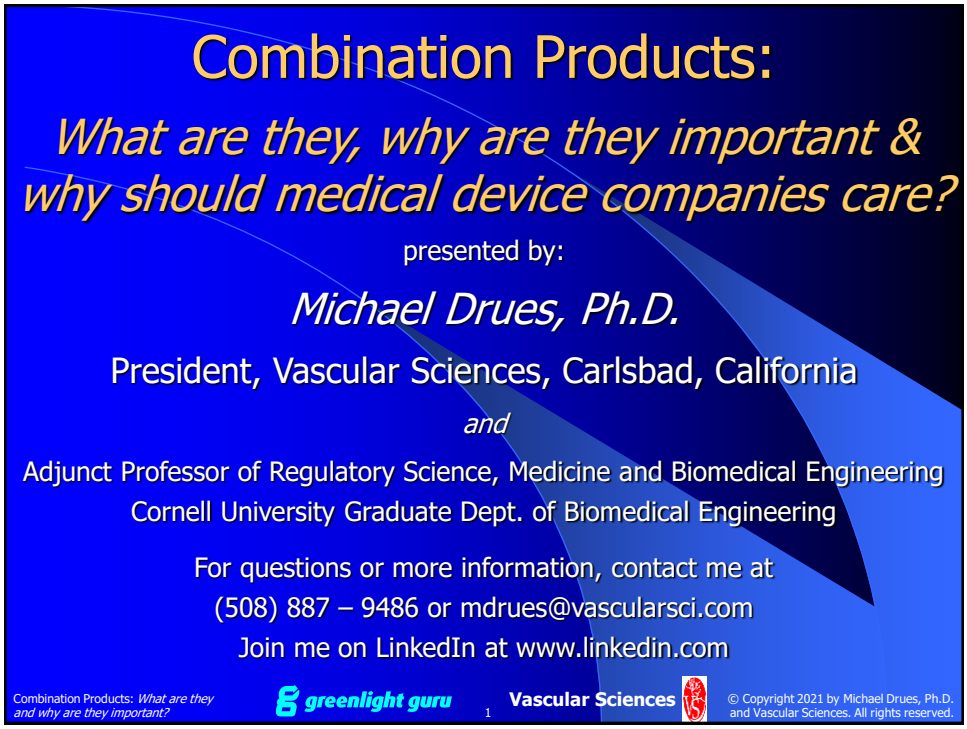

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First, an important disclaimer...

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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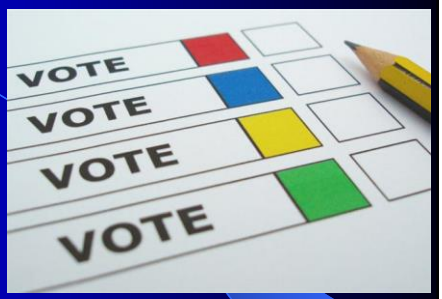
Before we begin…

Polling Question



Are you working on combination product now? (now/future)

What is the primary mode of action (PMOA)?

Device? Drug? Biologic? Something else? Don't know what PMOA is?

Must a combination product involve a medical device? (y/n)

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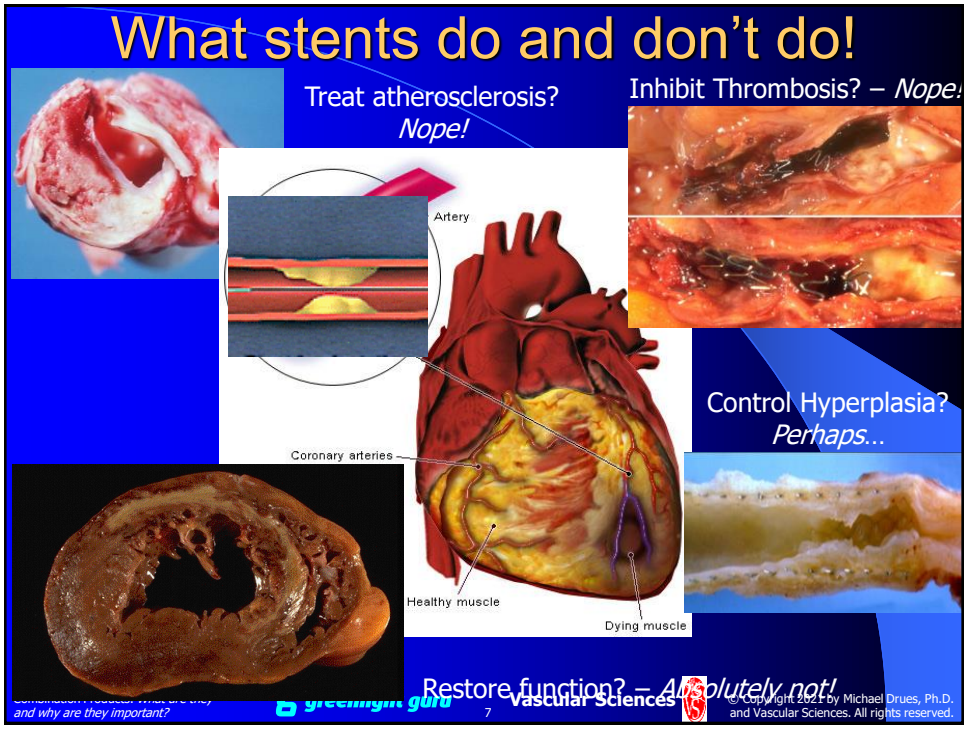

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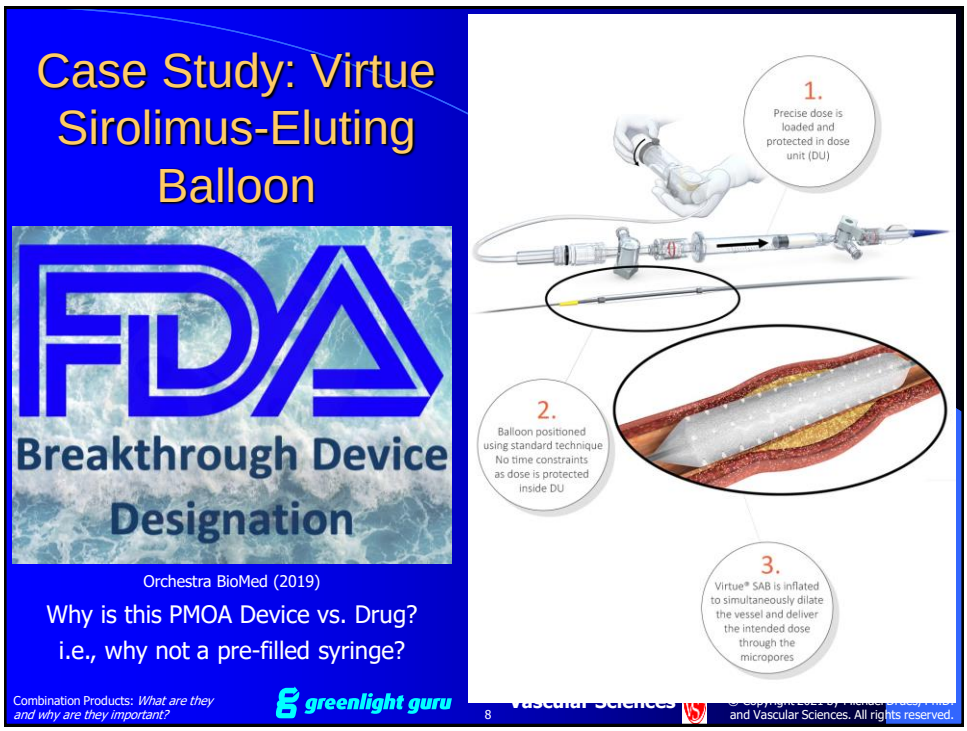

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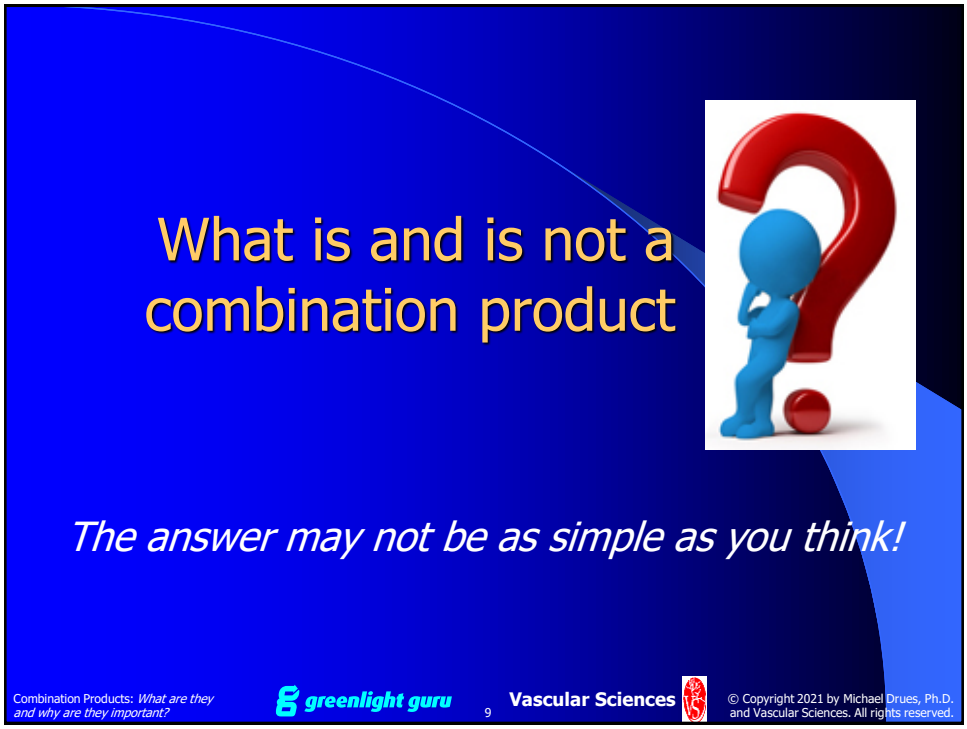

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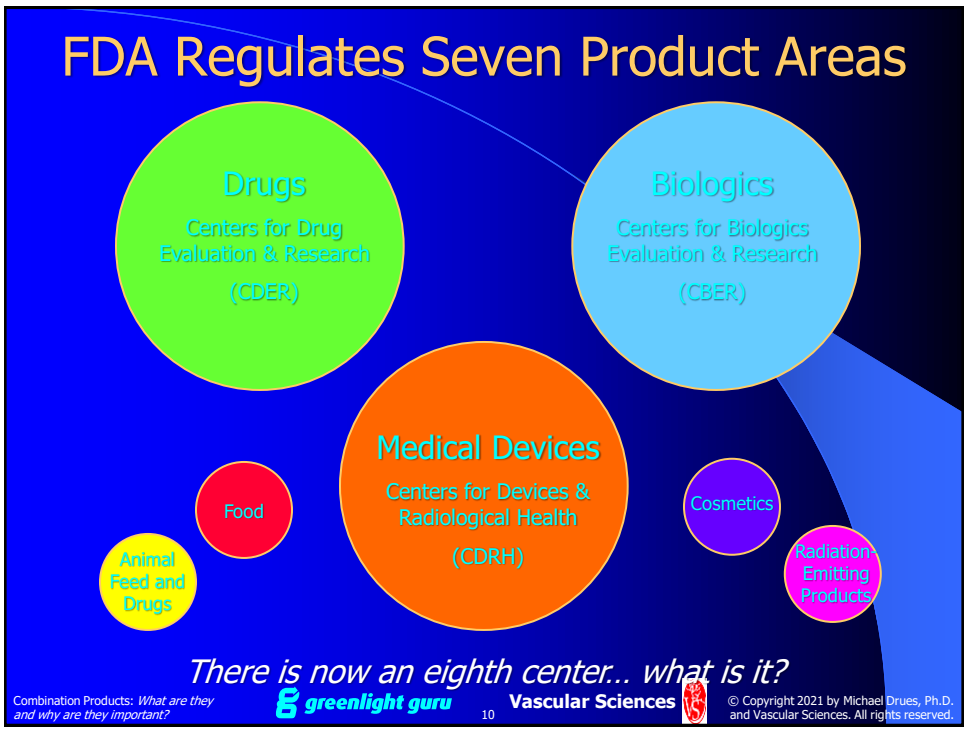

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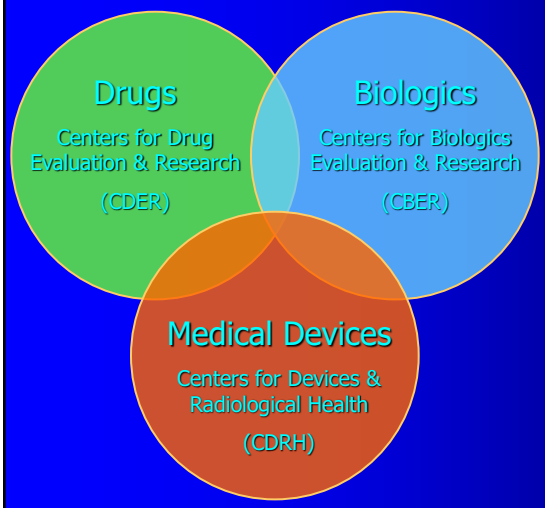
Combination Products



Not just a drug…

Not just a medical device…

Not just a biologic.

but a

Combination of

two or even three areas

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How about some regulatory

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A bit or regulatory mumbo-jumbo…

What is a Combination Product?

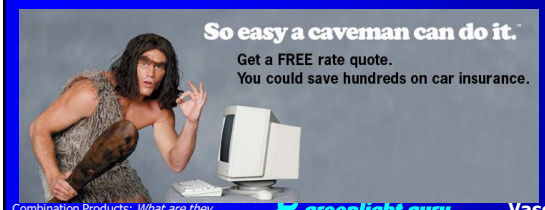
Categories of combination products include:

Co-Integrated: ***a product comprised of two or more regulated components***, i.e., drug/device, biologic/device, drug/biologic, or drug/device/biologic, ***that are physically, chemically or otherwise combined or mixed and produced as a single entity.*** [Most common ~75%]

Co-Packaged: ***two or more separate products packaged together*** in a single package or as a unit and comprised of drug and device products, device and biological products, or biological and drug products.

Cross-Labeled: ***any drug/device/biologic packaged separately that according to its labeling is for use only with another individually specified drug/device/biologic where both are required to achieve the intended use, indication, or effect.***

Adopted from combination product definition in 21 CFR 3.2(e)



But is it really so easy?

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Examples of Combination Products

Co-integrated:

- a.k.a. 'physically combined' [21 CFR 3.2(e)(1)] so-called '(e)(1)' combination products
- Examples include
  - Drug-eluting stents & Antimicrobial-coated catheters
  - Chemotherapeutic drug-monoclonal antibody conjugates
  - Prefilled syringes & other drug delivery devices
- Most common type of combination product (~75% in FY10)

Co-packaged:

- [21 CFR 3.2(e)(2)] so-called '(e)(2)' combination products
- Examples include
  - Drug or biological product packaged with injector pen or other delivery device
  - Surgical kit with catheter, gloves and antimicrobial wipes [Case Study: *First Aid Kits*]
  - Orthopedic cage with bone morphogenetic protein

Cross-Labeled:

- [21 CFR 3.2(e)(3)] so-called '(e)(3)' combination products
- Whether this type of concomitant use creates a combination product hinges on the labeling
- Examples include
  - Photodynamic therapy drug and light source
  - Drug and dedicated auto-injector [What about an auto-injecting prefilled syringe?]
  - Drug and pharmacogenomic test (companion diagnostics a subset of *in vitro* diagnostics)

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Is a pill a combination product

YES and NO!

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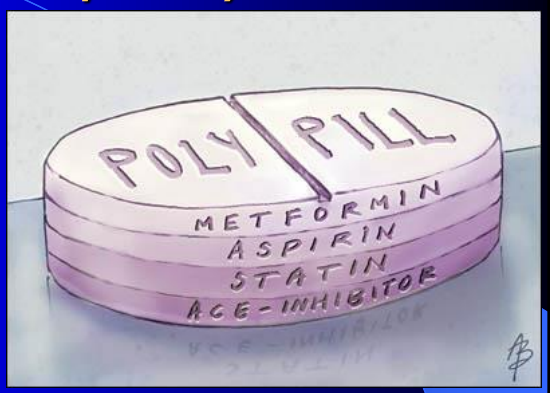
Case Study: *PolyPill*



Questions to consider:

- ✓ Is this a combination product?
- ✓ Regulatory implications, i.e.,

if a patient swallows 5 pills separately, is FDA involved?

vs.

if a patient swallows 1 "polypill" containing the same 5 meds, is FDA involved?

Thinking beyond regulation… is there really a difference?

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Examples of "Combination Drugs"

But remember…

		Company	Dosage form (route)	Indication
Amturnide	aliskiren hemifumarate, amlodipine besylate, hydrochlorothiazi	Novartis	Tablet (oral)	Hypertension
Beyaz	drospirenone, eth			Contraceptive
Complera	emtricitabine, rilpi disoproxil fumarat			HIV infection
Edarbyclor	azilsartan medoxo			Hypertension
Jalyn	dutasteride, tams			Hypertension
Janumet XR	sitagliptin phosph			Type II diabetes
Jentadueto	linagliptin, metfor			Type II diabetes
Juvisync	simvastatin, sitagl			High cholesterol Type II diabetes
Kombiglyze XR	saxagliptin HCl, m			Type II diabetes
Natazia	estradiol valerate,			Contraceptive
Nuedexta	dextromethorphar			Pseudobulbar effect
Qsymia	phentermine HCl,			Obesity/weight management
Safyral	drospirenone, eth calcium			Contraceptive
Stribild	elvitegravir, cobici			HIV infection
Suboxone	buprenorphine HC			Opioid dependence
Tekamlo	aliskiren hemifumarate, amlodipine besylate	Novartis	Tablet (oral)	Hypertension
Tribenzor	olmesartan medoxomil, amlodipine besylate, hydrochlorothiazi	Daiichi Sankyo	Tablet (oral)	Hypertension
Truvada	emtricitabine, tenofovir disoproxil fumarate	Gilead Sciences	Tablet (oral)	HIV infection

Combination Drug ≠ Combination Product!

or can they…?

"Combination Drugs: Adding Up the Opportunities" (Pharmaceutical Tech, Oct, 2012)

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How about this?

In the conventional (i.e., CFR) sense… *no!*

Combination Product *vs.* Combination Therapy

Any different than the *PolyPill?*

But is it really so simple?

If we package it this way…

But if we package it this way…

Is this a

distinction without a real difference?

EC cleared Sanofi's 6-in-1 pediatric vaccine for infants six weeks and older (April, 2013)

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What is a "digital pill"

What is a "smart pill"

Very broad and confusing topic!

Hint: Must a pill contain a drug?

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Is a "smart pill" a combination product

First,

What is a combination product?

Short answer:

It depends!

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What does Proteus and a syringe have in common

Hint: think empty syringe vs. pre-filled syringe

Device vs. Combination Product

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How do we view the world?

Discovery is seeing what everyone else has seen and thinking what no one else has thought.

– Albert Szent-Gyorgi, 1937 Nobel Prize in Physiology and Medicine

Or put another way…

It's not what you look at that matters, it's what you see.

– Henry David Thoreau (1817–1862), American author, poet and philosopher

So what do you see?

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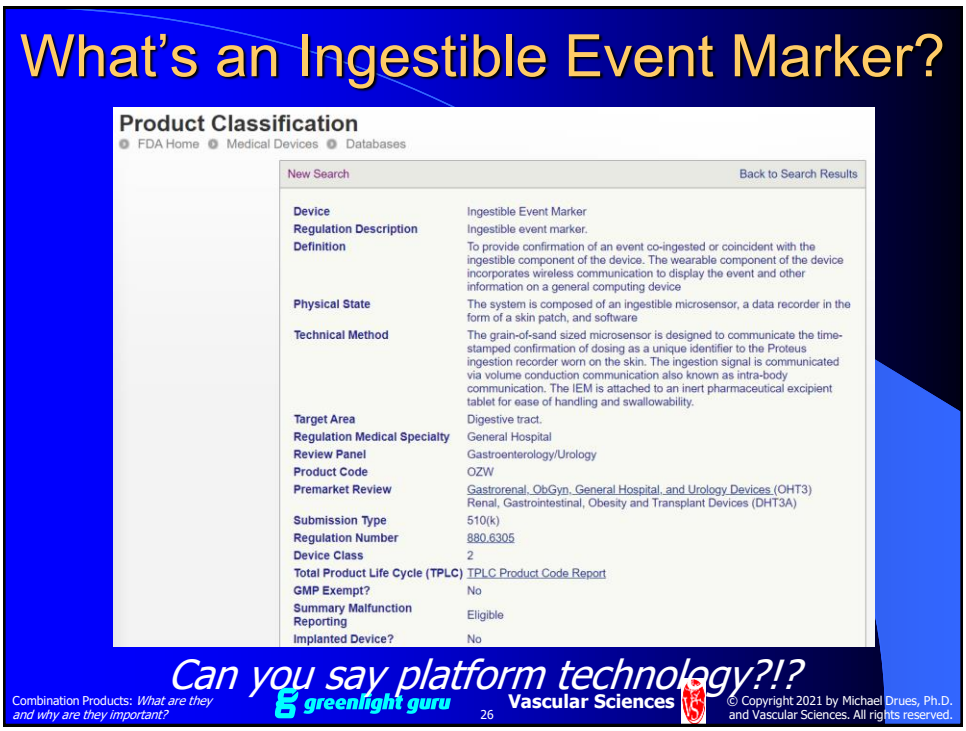

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What is NOT a combination product?

Be careful… this is not a simple question!

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What is *not* a Combination Product?

A combination product is NOT a:

- ✓ drug-drug combination,
- ✓ device-device combination, or
- ✓ biologic-biologic combination

Also,

Be careful using the term combination device!

And what about combination therapies?

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Is this a combination product?

Nope… it's a medical device!

Absolutely… at least by definition, but it's not regulated that way!

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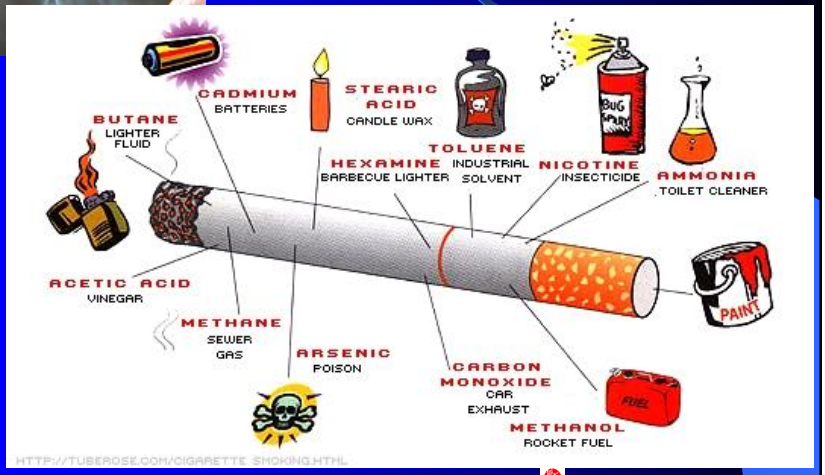
Is a cigarette a combination product?



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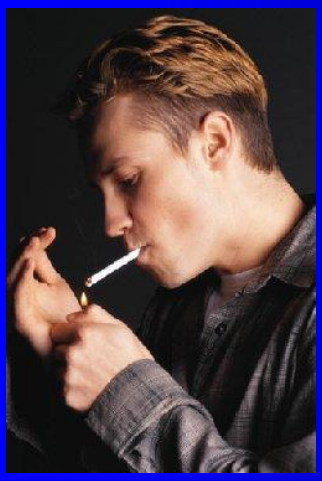
What's the difference?



Other than politics?

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What about vaping?

Depends on what you're vaping…

Vaping Nicotine → e-Cigarette → FDA Regulated (2016)

[note: not all e-cigarettes contain nicotine]

Vaping Vitamins → 'VitaCig' → FDA ???

What about 'vaping' caffeine?

Is this a device, combination product, something else?

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What about a leech?

Or maybe leaches should be considered combination products?

Why?

Hint: Primary action is mechanical

Secondary action is secretion of anticoagulant-like proteins

Sound familiar…

can you say Drug-Eluting Stent?

It's a medical device… not a biologic!

Why… what is the regulatory justification?

Hint: How is primary task accomplished… biological or mechanical?

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How do we view the world?

"Discovery is seeing what everyone else has seen and thinking what no one else has thought."

Albert Szent-Gyorgi,
1937 Nobel Prize in Physiology and Medicine

Or put another way…

Average regulatory professionals see a leech and think a leech…

better regulatory professionals see a leech and think a syringe…

the best regulatory professionals see a leech and think a pre-loaded syringe!

So what do you see?

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How are combination products regulated

Do you have several days… several weeks?!?

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History of Combination Product Regulation

Prior to 1990, FDA regulated combination products on a case-by-case basis. For example,

- ✓ condoms with nonoxynol–9
- ✓ biliary lithotriptors used with ursodeoxycholic acid
- ✓ transdermal patches for drug delivery
- ✓ antimicrobial coated catheters

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Safe Medical Devices Act of 1990

- ✓ Congress sought to add some structure to combination product regulation in 1990
- ✓ FDA promulgated procedures pursuant to the SMDA directive
- ✓ A lead center within FDA to be designated for review authority based on "primary mode of action" of product

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What does primary mode of action mean (PMOA)?

Why is PMOA important?

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Primary Mode of Action

- ✓Is the primary mode of action of the product a medical device, drug or biologic?
- ✓Answer determines which center (CDRH, CBER or CDER) has *primary regulatory responsibility*
- ✓As products become increasingly complex, rapidly becoming an outdated concept!

PMOA Definition (Federal Register, August, 2005)

Why do we have a PMOA concept

It's not enough to understand <u>what</u> the regulation says…
we must also understand <u>why</u> it's there to use it to our advantage!

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Knowing what the regulation *says* or even knowing *how* to use it is not enough… we must always ask *why does the regulation exist?*

Why do we have PMOA?

Maybe it allows us to put a square peg into a round hole?

Or better… think of farm silos!

Maybe a "new silo" for combination products?

Will new regulations be needed or will the current regs suffice?

What do you think?

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What is the Silo Effect?

What we have…

What we need…

The Silo Effect refers to a lack of information flowing between groups or parts of an organization. On a farm, silos prevent different grains from mixing. In an organization, *the Silo Effect limits the interactions between members of different branches of the company, thus leading to reduced productivity.*

How to eliminate the 'Silo Effect' in LTC organizations (March 26, 2012)

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Is PMOA holding us back

Short answer: ***Absolutely!***

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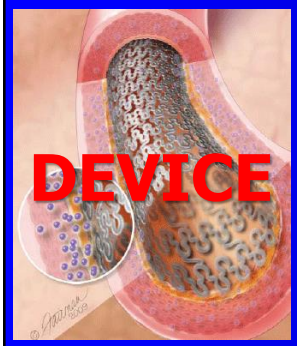
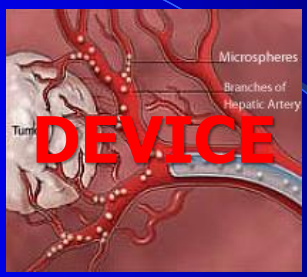
Trying to understand the world in which we live…



Drug-eluting stents (DES) used for coronary artery atherosclerosis



Drug-eluting beads (transcatheter arterial chemoembolization) used for liver cancer (Hepatocellular Carcinoma)

Drug-eluting disks used for brain cancer

What is the PMOA?

And this is just the beginning of these technologies but…

does the regulation make any sense?

What will the next one be? Is there really any difference?

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Once PMOA is established, must it remain the same

Not necessarily… much to many people's chagrin!

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Think about this not so hypothetical scenario…

Many assume once the PMOA has been established, it will remain the same.

Not necessarily!

What if we deploy a DES in an artery with no atherosclerotic disease?

Why would we do this?

What if down-stream of the DES lives a tumor?

What is a tumor?

And what if the drug coming off the stent is a chemotherapeutic?

Now we don't really have a DES anymore…

Rather we have something more akin to a *implantable preloaded syringe!*

And how are preloaded syringes regulated? As drugs!

So we have changed the indication…

Atherosclerosis → Oncology

What does that do to the PMOA?

$PMOA_{Device} \rightarrow PMOA_{Drug}$???

Bottom line:

If the indication changes, all bets are off! And… this is really holding of back!

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Must a combination product include a medical device

Absolutely NOT!

Case Study: *Drug-Biologic Combination Products (a.k.a. ADC's)*

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Not all combination products include medical devices!

Case Study: *Drug-Biologic Combination Products*

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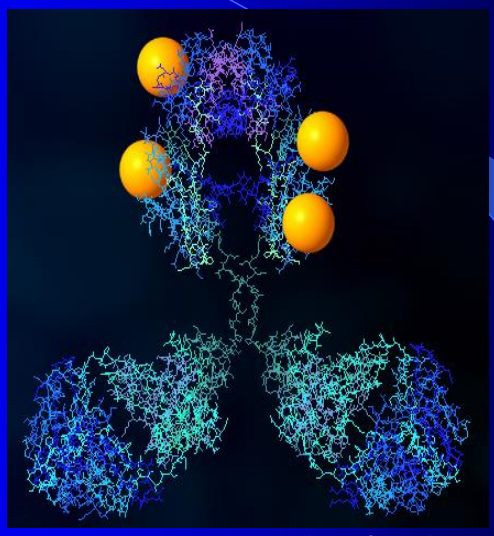
Case Study: *Drug-Biologic Combination*



Courtesy of ImmunoGen, Inc.

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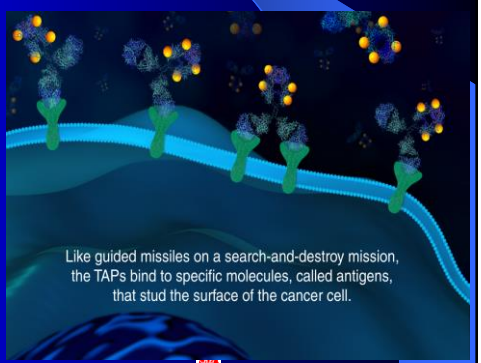
Case Study: *Drug-Biologic Combination*



Courtesy of ImmunoGen, Inc.

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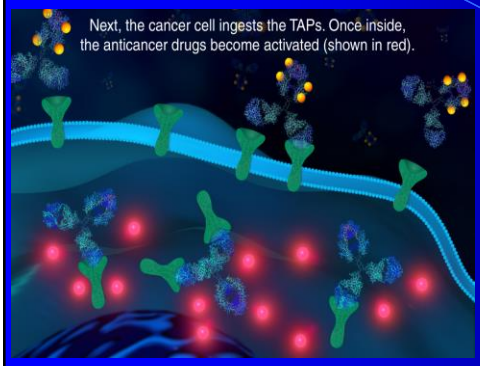
GreenLight.Guru Webinar (June 17, 2021)
https://www.greenlight.guru/webinar/combination-products

Combination Products: *What are they, why are they important & why should medical device companies care?*

Case Study: *Drug-Biologic Combination*



Courtesy of ImmunoGen, Inc.

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What does the future hold

Just the tip of the iceberg!

Case Study: *SkinGun*

Case Study: *BioLife4D*

Case Study: *3DP Tatoo/Patch*

Case Study: *Future of PMOA*

Case Study: *Possimpible*

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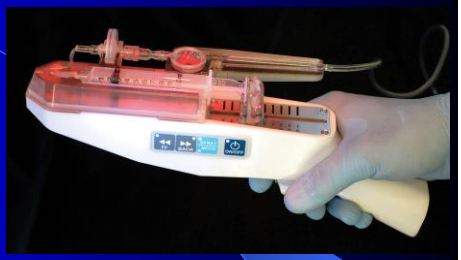
Combination Products: *What are they, why are they important & why should medical device companies care?*

Case Study: *Spray-On Stem Cells*

How would you bring this to market?
Hint: think empty syringe
Discovery is… here.



Spray-On Stem Cells Can Step Up Healing (Gen Engr News, April, 2017) here.

SkinGun™ is the world's most advanced, novel medical-grade sprayer with a liquid-into-air stream system.

RenovaCare products are under development and not approved for sale in the United States.

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Can we print a combination product

Absolutely!

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Combination Products: *What are they, why are they important & why should medical device companies care?*

Can we print a combination product?

We're doing it already!

It's easy if we approach it the right way!

Hint: think syringe!

Design objective:

Pre-loaded

vs.

Empty delivery system

There are advantages and disadvantages to both!

Todays Medical Developments (Sept. 4, 2014) available here.

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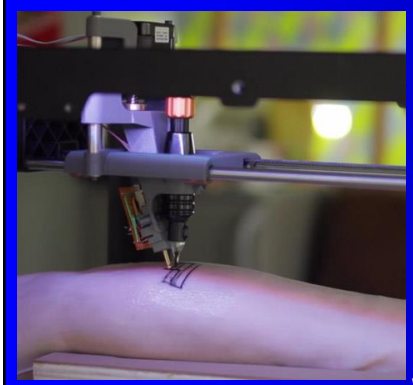
Can a 3-D printer replace your tattoo artist?



Absolutely! Watch this…

Should FDA regulate this?

Does FDA regulate tattoo parlors? Why/why not?

What's next?

How about a personalized (i.e., 3-D printed) *transdermal patch?*

How about printing a *subdermal patch in situ? – wicked cool!* ☺

Advantages: choose drug (drugs), dosage, release rates, location, etc.

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What is the future of PMOA

Is PMOA an antiquated concept?

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Looking towards the future…

Something to think about…

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Combination Products: *What are they, why are they important & why should medical device companies care?*

What is this?

A DNA Repair Nanobot or a mechanical ribosome?

How should this be regulated? By whom?
i.e., what is the PMOA of a DNA Repair Nanorobot?
What is the PMOA of a ribosome? i.e., is it mechanical, pharmacological or biological?
Does asking these questions make sense? Or is it 'silo' thinking?
To some, the DNA robot appears to act mechanically (fixing damaged DNA). If so, it could be regulated as a medical device, but…
At the molecular scale, cannot ALL drugs and biologics be viewed as mechanical devices? i.e., at the quantum level, there is NO difference between physics and chemistry… it's called physical chemistry or better, quantum mechanics. Similarly, at that scale, mechanical devices become chemical, and biologics become meaningless… drawing such lines, which PMOA forces us to do, becomes futile! What does that say about PMOA for nanotech???

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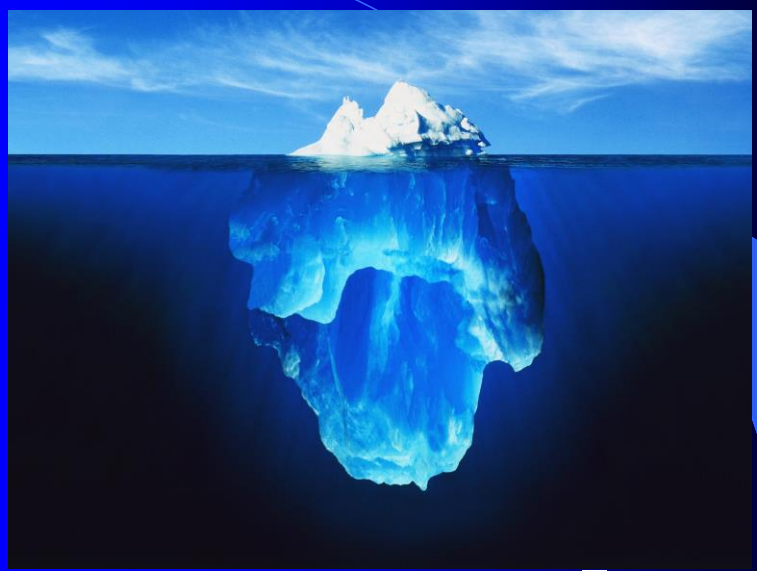
Just the tip of the iceberg!



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What's *Possimpible?*

The Possimpible (How I Met Your Mother, February 2, 2009)

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Here's what we talked about…

- ✓ What is and is not a combination product?
- ✓ Why are combination products important?
- ✓ How are combination products regulated?
- ✓ What does the future hold?
- ✓ Lots more tips and tricks… time permitting!
- ✓ Final thoughts…

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Combination Products: *What are they, why are they important & why should medical device companies care?*

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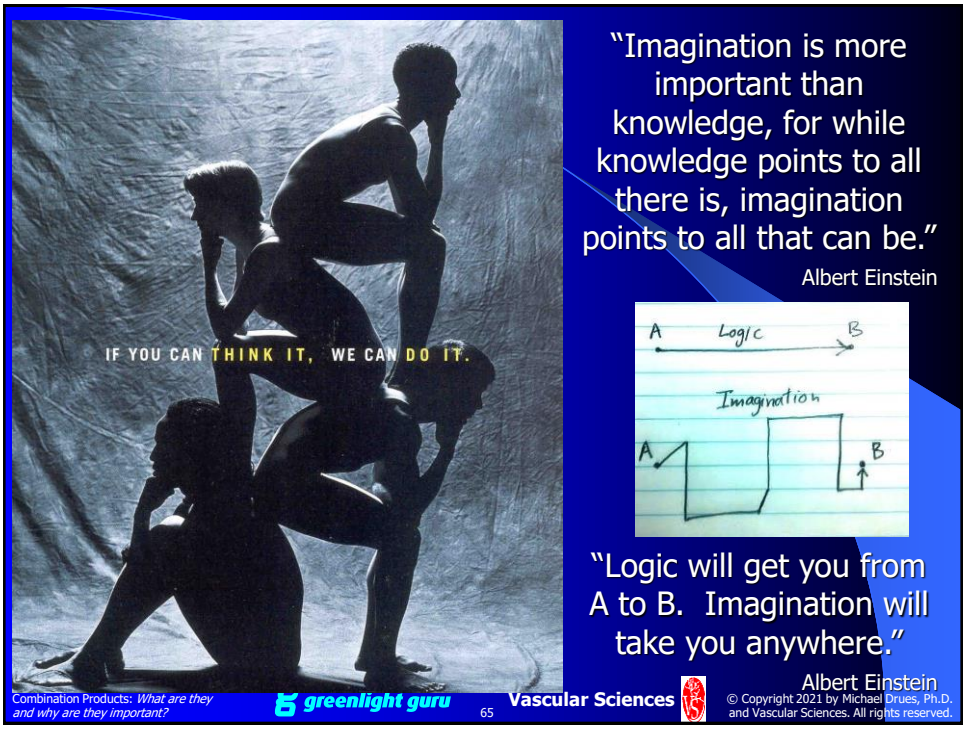
Combination Products: *What are they, why are they important & why should medical device companies care?*



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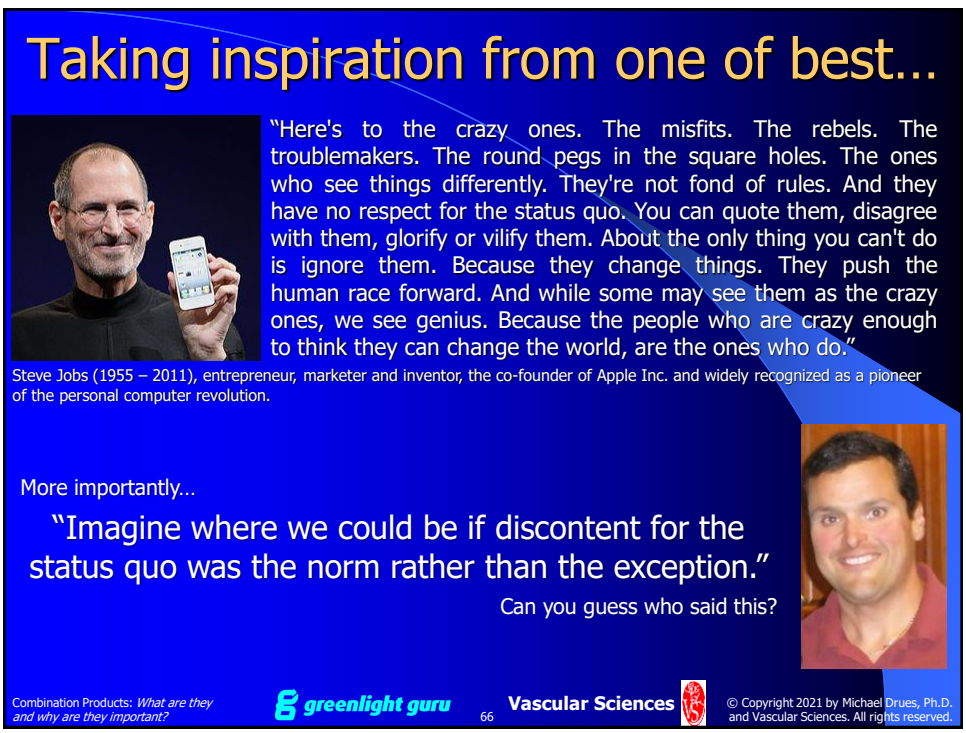

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Combination Products: *The future of medicine*

Want to know more?

Follow ***Michael Drues*** on **LinkedIn!**

Combination Products: *The future of medicine*

Combination Products: *The future of medicine*

EDITOR *Jim Butschli*

HEALTHCARE PACKAGING PERSPECTIVE

FORWARD-THINKING STATEMENTS

A 'fantastic voyage' into the future

Dr. Michael Drues recently e-mailed me a story idea about nanoparticles in food—to which I responded, thanks but no thanks, if it's not in the healthcare sector and it's not packaging-centric. His much-wiser answer included the following quote by Hippocrates, referred to by some as the father of western medicine: "Let your food be your medicine and your medicine be your food."

With healthcare increasingly focused on preventive care, companies are developing more functional foods and beverages packed with vitamins, minerals, and other nutritional ingredients. Expect to see more frequent reports on the packaging of these health-focused products in future print and Web editorial coverage from *Healthcare Packaging (HCP)*.

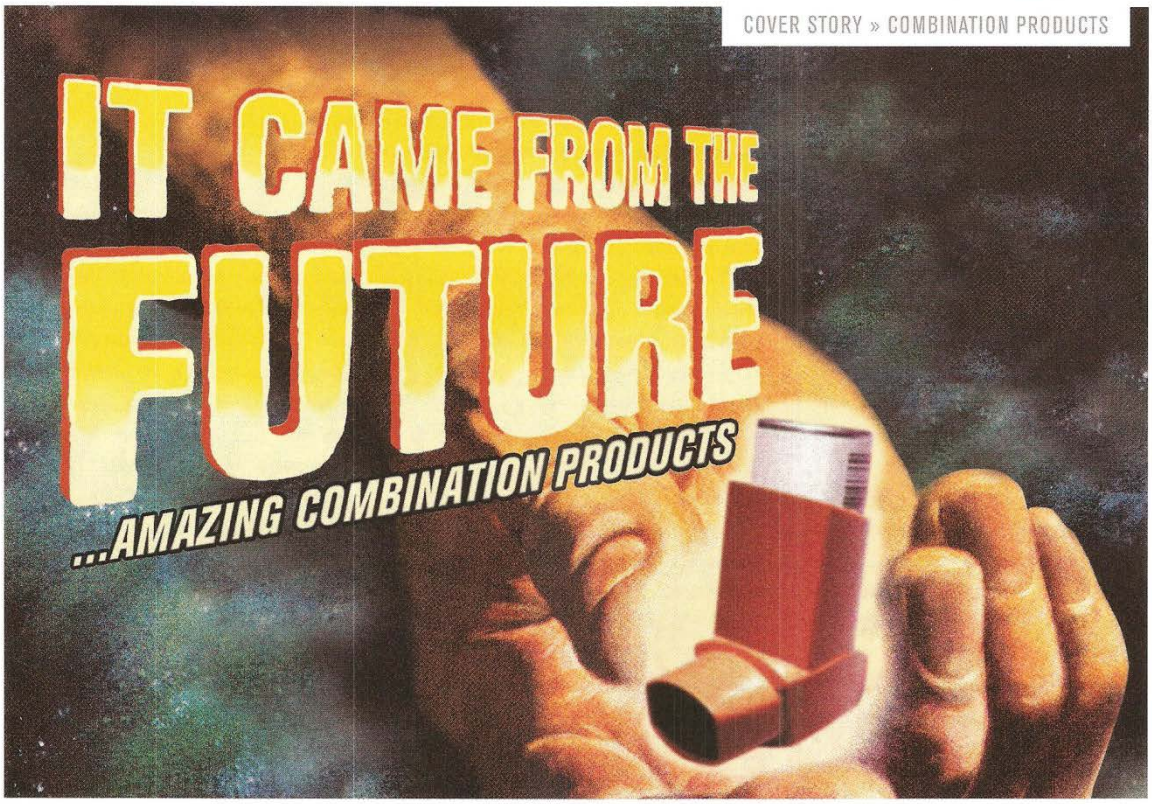
HCP readers may recognize Drues' name from previous articles, where his expertise—based on years of consulting with the U.S. Food and Drug Administration and other regulatory agencies, as well as with biopharmaceutical, pharmaceutical, and medical device firms, combined with his dynamic presentations and teaching experience—give him a unique perspective and vision.

With this issue, HCP is proud to introduce Drues as a regulator contributor. This issue's cover story taps into one of Drues' primary areas of expertise: combination products, which he believes are "clearly the future of medicine."

Drues would be the first to admit he's no packaging expert, but his acumen related to the future of medicine will benefit HCP readers seeking success in that future, whether your business provides a medicinal/therapeutic product, or the packaging materials, machinery, and/or services to bring such advanced treatments to patients.

In coming issues, HCP will take a "fantastic voyage" into forward-thinking topics such as nanotechnology, pharmacogenomics/personalized medicine, regenerative tissue, and to coin a Drues phrase, "multiple combination products." The journey begins on page 18. **[HCP]**

Combination Products: *The future of medicine*



COMBINATION PRODUCTS: THE FUTURE OF MEDICINE

The advancement of medical treatments depends in part on education and communication.

EDITOR | *Jim Butschli*

Editor's note: *With this Q&A, Healthcare Packaging welcomes Dr. Michael Drues in discussing issues pertaining to the future of medicine, beginning with this issue's focus on combination products.*

HEALTHCARE PACKAGING (HCP): The U.S. Food and Drug Administration's Office of Combination Products (www.fda.gov/CombinationProducts) was formed in late 2002. Since then there have been many developments and new treatments in this area. Can you walk us through what's been going on and what OCP's role is in getting products to market?

DR. MICHAEL DRUES: From a regulatory perspective, when it comes to combination products, the first question that one needs to ask is, "What is the product's primary mode of action, or PMOA? PMOA essentially means, when you put your product into a patient, how does it work? Is it mechanical or electrical? If so, then the product is acting primarily as a medical device. Is it pharmacological or biochemical? If so, then the product is acting primarily as a pharmaceutical (i.e., a drug). Is it biological? If so, then the product is acting primarily as a biologic.

PMOA determines the lead center at the FDA—either CDER (drugs), CBER (biologics) or CDRH (medical devices). The lead center will ultimately have "control" over the approval process of the product. For many reasons, it is ideal to have CDRH designated as the lead center. Here's how you can do it: From a strategy perspective, you want to argue the PMOA is mechanical or electrical so CDRH is designated the lead center, even if you have a drug-biologic combination, i.e., what some now call an Antibody-Drug Conjugate (or ADC), and there is no "obvious" medical device component as CDRH tends to have fewer regulatory challenges. But there are no guarantees. It's wise to have backup or contingency plans.

On the surface, the PMOA seems like

Combination Products: *The future of medicine*

a straightforward concept. However, reality is far less simple. For simple products like the drug-eluting stent, one can easily argue (as was done in the past) that the PMOA of the DES is mechanical, in that the primary action is the stent mechanically "holding open" the artery while the action of the drug on the stent is secondary in that it keeps the artery open over time. Whether you agree with the logic of this argument is now largely a moot point as the precedent has already been set.

However, in the future we will be using far more complex combination products, the quintessential example being tissue engineering. For example, what is the primary mode of action of a tissue-engineered blood vessel or indeed of a tissue-engineered human heart? Is it mechanical? Pharmacological? Biological? More importantly, does it even make sense to ask such a question? In other words, does it make sense to try to separate mechanics, biochemistry, and molecular biology? Taken to the extreme, is not the human body a combination product? If so, then from a regulatory perspective, the first question we must ask is, "What is the PMOA of the human body?"

> "Many complain about what FDA requires, but FDA can only do what Congress instructs them to do. And if you think it's difficult to change FDA, that's nothing compared to Congress! Interestingly enough, the OCP does not regulate anything. The OCP helps, for example, when a company submits what's called a request for designation, or RFD."

A few years ago, OCP spent considerable time and effort trying to develop a "better" definition of PMOA. When it was published in the Federal Register, it was some 15 pages long, which begs the question, "If we need 15 pages to define anything, perhaps that's part of the problem! After all, as Einstein said, "If we can't explain something simply, we don't understand it well enough."

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Combination Products: *The future of medicine*

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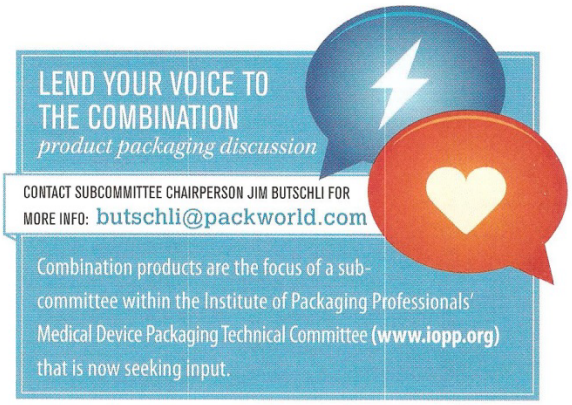

More important, some view those efforts largely as a waste of time. Why?

Because developing a "better" definition of PMOA is akin to rearranging the deck chairs on the Titanic—sooner or later, the ship is going down! Some within FDA are troubled by trying to apply the concept of the PMOA to more complex products. For better or worse, PMOA is still what appears in the Code of Federal Regulations (CFR). Many complain about what FDA requires, but FDA can only do what Congress instructs them to do. And if you think it's difficult to change FDA, that's nothing compared to Congress!

Interestingly enough, the OCP does not regulate anything. The OCP helps, for example, when a company submits what's called a request for designation, or RFD. The company makes a case that the PMOA of their combination product is device, drug, or biologic. OCP will consult with the other appropriate centers. They will agree or disagree with the company, and they will assign the FDA lead center. One

» CONTINUED ON PAGE 22

FDA ISSUES FINAL RULE ON COMBINATION PRODUCTS

A Final Rule on current Good Manufacturing Practice Requirements for Combination Products was published in the Federal Register Jan. 22, 2013.

The summary states, "The Food and Drug Administration (FDA or Agency) is issuing this regulation on the current good manufacturing practice (CGMP) requirements applicable to combination products. This rule is intended to promote the public health by clarifying which CGMP requirements apply when drugs, devices, and biological products are combined to create combination products. In addition, the rule sets forth a transparent and streamlined regulatory framework for firms to use when demonstrating compliance with CGMP requirements for 'single-entity' and 'co-packaged' combination products."

FDA received comments from regulated entities, trade associations, and individuals, and the agency responded to those comments, all of which are published in the Final Rule.

Describing the Final Rule's impact, FDA noted, "FDA estimates that approximately 300 manufacturers of combination products will be affected by the final rule. These manufacturers of combination products should benefit from the greater clarity provided regarding what regulatory provisions apply to their products and how they may comply with them. For both existing and future products, the streamlined approach set forth in the final rule will help ensure that CGMP requirements for co-packaged and single-entity combination products are consistent and appropriate, without duplicative or otherwise unnecessary aspects. This codification of CGMP requirements for combination products will also help ensure predictability and consistency in the application and enforcement of these regulatory requirements with regard to all combination products across FDA.

"Firms must already comply with the CGMP regulations for drugs, devices, and biological products, including the current good tissue practice regulations for HCT/Ps, found at parts 211, 820, 600 through 680, and 1271, that are applicable to the constituent parts of their combination products. The cost of this final rule would be the incremental costs to modify or streamline existing standard operating systems. Because this final rule is codifying our current practice, any firms that choose to streamline or modify existing SOPs are doing so because the private benefits are greater than the private costs. If some firms choose to modify their SOPs as a result of this final rule, the net benefits of the rule will be greater than the costs.

"Some firms may incur one-time incremental costs reassessing compliance with the final rule. Because this final rule codifies Agency practice that is described in current guidance documents and because no new CGMP requirements are proposed, we believe the time required would be small and estimate it to be about 25 hours per product. The amount of these compliance assessment costs for an individual firm, and the impact of any such costs, will depend on the number and nature of the products the firm produces and how the firm has applied current regulations. Nonetheless, because the time required would be limited, the Agency believes the impact will not be significant on entities considered small based on the Small Business Administration's definition of a small entity (500 employees for device and biological product firms and 750 employees for drug firms)."

To read the Final Rule, visit www.healthcarepackaging.com/go/63

Combination Products: *The future of medicine*

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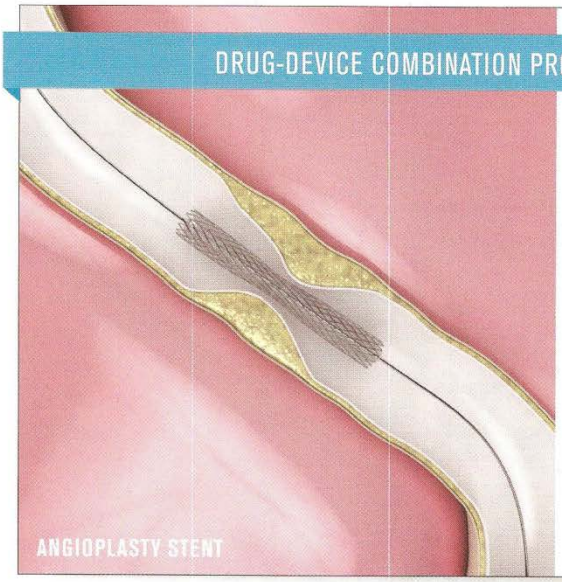

DRUG-DEVICE COMBINATION PRODUCTS SHOW HEALTHY GROWTH

A new BCC Research report predicts the global market for combination products to grow at a nearly 10% Compound Annual Growth Rate (CAGR) between now and 2017, when market value is expected to reach $30.5 billion.

- Antimicrobial catheters are expected to total $6.6 billion in 2012 and $11.7 billion in 2017, a CAGR of 12.1%.
- Photodynamic therapies as a segment should total $1.7 billion in 2012 and $2.6 billion in 2017, a CAGR of 8.9%.
- The segment made up of orthopedic applications (cements and bone substitutes) should be valued at $2.8 billion in 2012 and $4.1 billion in 2017, a CAGR of 7.9%.
- Coronary stents are expected to have a value of $5.8 billion in 2012 and $8.2 billion in 2017, a CAGR of 7.2%.
- Global drug-device combination products, valued at $18.5 billion in 2011, should reach $19 billion in 2012. BCC forecasts total market value to rise $30.5 billion in 2017 after increasing at a five-year CAGR of 9.9%.

SOURCE: BCC Research (www.bccresearch.com)

of the most important roles of the OCP is to serve as a monitor of sorts as drug, device, and biologics folks do not always speak the same language. OCP tries to bridge some of those gaps.

By the way, this is not limited to the FDA. How do you get a medical device company and a biotech company, for example, to come together to develop a combination product? There are huge knowledge gaps between industries. Education, in my opinion, is one of the biggest challenges in an area like combination products, which is, as I have said publicly many times over the past 20 years, clearly the future of medicine. I don't think there is any doubt about that anymore.

HCP: Why do you believe that to be the case and what are the challenges with advancing combination products?

DRUES: Slowly the rest of the world is coming around to the notion that combination products represent the future but it is taking a long time. Here's an interesting statistic from my combination product seminar: In 2012, an estimated 30 percent of all new healthcare products under development were "combination products" involving medical devices embedded with pharmaceutical or biologics components.

As for the biggest challenges, they are not what many may think. It is not the technology, the regulation, the intellectual property, or the manufacturing. While those are all challenges, the biggest hurdle is what's called "convergence." How do you get engineers, pharmacologists, and molecular biologists, whether they are in industry, at FDA, or in academic research, to come together to have an intelligent conversation about the synergistic benefits of combining their technologies when they may not understand the other technologies and they don't even speak the same language?

Here's a simple example: Engineers look at the world from an F=ma perspective, whereas molecular biologists look at the world from an A, T, G, and C perspective. There is not a lot of overlap between F=ma and A, T, G, and C. And for those not familiar with both references, that proves my point!

Most people may know lot about medical devices, or about drugs, or about biologics, but there are not a lot of people who have enough knowledge about all of these different areas to put them together in interesting and beneficial ways. So that, in my opinion, is one of the things that's really holding us back compared to what we could be doing [to advance medical treatment].

HCP: What are some of the exciting advances that you see in combination products and their place in the future of medicine?

DRUES: Combination products are clearly an area that is gaining in momentum. The drug-eluting stent remains the best-known example of a combination product, yet that technology is very much still in its infancy. I want to be able to put many different drugs and biologics all on a single medical device like a stent. I am using a stent as a metaphor for almost any medical device. For example, monoclonal antibodies, a type of therapeutic protein sometimes called a biotech-drug,

» CONTINUED ON PAGE 24

Combination Products: *The future of medicine*

CONTINUED FROM page 22

can be put on different medical devices to accomplish different objectives. What we have been doing thus far in drug-eluting stents has been very simple, almost primitive compared to what we could be and will be doing in the future.

What should be of interest to packaging professionals are issues like sterility and shelf life. Drugs are pretty stable molecules. Biologics on the other hand are very finicky, inherently unstable molecules. How do you sterilize a plain old bare metal stent? You can hit it with heat, gamma, ETO, and so forth, because you are not going to change the stent. But once you put a drug on it, or especially once you put a biologic on it, all bets are off. We don't sterilize most drugs—we manufacture them in an aseptic process. When it comes to sterilizing a biologic, such as a monoclonal antibody—or a gene inside a virus (i.e., gene therapy) on a stent, how do we do it? Does it make sense to even try, at least in the conventional sense? For biologics, sometimes changing the temperature or the ambient lighting is enough to denature the protein. So how do you sterilize it? There is a tremendous amount of education that has to happen here, not just in industry, but at FDA as well.

Now let's think of shelf life. The whole notion of putting a protein or some form of gene therapy or a stem cell (i.e., an endothelial progenitor cell) on a device in a package and placing it on a shelf for weeks or months is nuts. One thing I think we will see more and more in the future is that many of these products are not going to be combined in a manufacturing facility, but they are going to be packaged separately and combined at the patient's bedside, a so-called e(2) combination product. In January 2013, FDA issued a new guidance [see sidebar] meant to provide clarification on cGMP requirements for e(2) combination products, but that's still very primitive compared to what I'm describing.

Here's an example: In cardiology, just before the cardiologist inserts the stent—and again this is true for all these kinds of products, not just cardiology—the medical team is going to dip the stent in a little vial that contains monoclonal antibodies. Then that stent is going to be designed to attract those antibodies like a sponge, and hold them.

> "The bottom line is simple: These are all solvable problems if we think differently. That's the biggest challenge. We have got to move beyond what we have been doing in the past. We have got to be willing to think differently."

How do you make sure you have good coverage? One way to do it could be to design the stent to be white with the antibody solution red so that when you dunk this stent into the vial it could work similarly to litmus paper in that you could employ a color scale on the side of your bottle that tells the physician what the concentration (a.k.a. dosage) is. He or she pulls it out and can dunk it in again to attain the desired dosage of antibody for that particular patient. Can you say pharmacogenomics for medical devices?

Another trend is a concept I coined at FDA called "multiple combination product," where we have multiple drugs and biologics all being delivered by a single device. We are not there yet clinically. We don't even have many of those products in development, but that's clearly a trend for the future. These could be in the form of a liquid, a solid, a powder, or even a gel.

We can deliver these multiple combination products in many different ways. We could even use one combination product to deliver another combination product! For example, we could use a drug-eluting balloon catheter (or what I call a "biotherapeutic-carrying vehicle") instead of a stent. We can deliver gene therapy or nanoparticles, the mechanical equivalent of gene therapy, or a drug inside of a nanoparticle using this drug-eluting balloon and now we have one combination product delivering another combination product. That, as we would say in Boston, is wicked cool!

The bottom line is simple: These are all solvable problems if we think differently. That's the biggest challenge. We have got to move beyond what we have been doing in the past. We have got to be willing to think differently. **[HCP]**

Dr. Michael Drues is president of Grafton, MA-based Vascular Sciences, an education, training, and consulting company. He received his B.S., M.S., and Ph.D. degrees in Biomedical Engineering from Iowa State University. He has worked for and consulted with leading medical device, pharmaceutical, and biological companies, and for the FDA, Health Canada, the U.S. and European Patent Offices, the Centers for Medicare & Medicaid Services, and other regulatory and governmental agencies worldwide. He is an internationally recognized expert and keynote speaker on cutting-edge medical technologies and regulatory affairs and teaches graduate courses at several universities and medical schools. His specialties include combination products, clinical trial design, regulatory strategy, pharmacogenomics/personalized medicine, and business development. He can be reached on Linkedin®, by phone at 508.887.9486, and by e-mail at mdrues@vascularsci.com.

Q&A: COMBINATION PRODUCTS

Combination Products: Engineering and Biologics Make Good Bedfellows

Combination products are predicted to take off in the next few years, potentially equaling 50% of all U.S. medical device activity. Developing new combination products will face an uphill battle, however, unless medical device engineers and molecular biologists can combine their widely divergent talents. Michael Drues, president of medical device consulting company **Vascular Sciences Inc.** (Grafton, MA; www.vascularsci.com), spoke with *MPMN* about some of the challenges and opportunities associated with these devices.

MPMN: In what sense would you consider combination products to be the most current, yet the most misunderstood, topic in the medical device arena?

Drues: Probably the best-known example of a combination product is the drug-eluting stent, although I would argue that the drug-eluting stent is a very primitive, almost childlike example of a combination product.

The quintessential example of a combination product is what we're now starting to do in the area of tissue engineering. In terms of timeliness, the development of combination products for tissue-engineering applications is really, to a certain degree, a natural progression. It represents the future because the single biggest advantage of combination products, especially in applications like tissue engineering, is the ability to restore function that was lost because of illness or injury. A simple example: If a patient has a heart attack and a portion of the heart becomes necrotic, the simple reality is that you can do an angioplasty, you can put in a stent, you can put in a hundred drug-eluting stents if you want to, but from the perspective of the cells in the heart that have died, have you accomplished anything? Absolutely not.

The best outcome that you can hope for with current technologies is preventing the problem from getting worse. In the absence of something better, palliative treatment is OK, but we've faced that limitation in medicine for decades, and it's about time that we get past it. Thus, I don't want to simply prevent a medical problem from getting worse; I want to erase the damage in the heart caused by the heart attack as if the patient never knew that he or she had a heart attack to begin with, for example. This is not the next evolutionary advance in medicine; this is a revolutionary advance, a change in the whole ethos of how we approach medical problems.

> "This is not the next evolutionary advance in medicine; this is a revolutionary advance, a change in the whole ethos of how we approach medical problems."

MPMN: To achieve such devices, what new technology challenges do designers and manufacturers of combination products face?

Drues: There are plenty of challenges to go around on all fronts—clinical, regulatory, IP, and manufacturing. The list is endless. But with regard to the technology challenges from the device perspective, the most obvious would be getting whatever it is that you're trying to get to wherever it is that you're trying to go. That's probably the first thing that engineers are going to be thinking about. But that, in many ways, is the easy part. Dealing with drugs or very finicky molecules like biologics and therapeutic proteins, or delivering genes inside of a virus on a medical device to turn on angiogenesis or apoptosis, for example, is just the beginning of the discussion.

When dealing with drugs or biologics, there are all kinds of sterilization, shelf life, and stability testing issues. For example, you can sterilize a bare-metal stent with whatever you want—EtO, gamma, heat—and the stent is not going to change. But once you put a drug on it—or especially once you put a biologic on it—all bets are off. It's almost nuts to even ask the question of sterilizing a therapeutic protein or a gene inside of a virus on a medical device. Thus, how we deliver these kinds of things is really going to change.

This is a different conversation, but many new therapeutics are going to be put together at the patient's bedside immediately prior to being administered. Thus, the whole notion of putting together a product in a manufacturing facility and shipping it across the country or around the world and then putting it into a patient is going to change. Many industry professionals are going to be in for a bit of a paradigm shift because they're going to find that they're not going to be able to do that so easily anymore.

MPMN: How must medical device manufacturers adapt in order to collaborate with pharmaceutical and biologics companies?

Drues: The first and most important thing—and in some ways, the only thing—medical device manufacturers are going to need to do is to educate themselves. And that's also going to be the most difficult thing. Right now, there is no common language between medical device manufacturers and developers of drugs and biologics. Engineers are going to have to learn to speak some molecular biology, and molecular biologists are going to have to learn to speak some engineering.

This is not a trivial problem. I remember going into a stent company 15 years ago or more and trying to sell it on the idea of using a stent as a delivery system for gene therapy when they didn't know what a gene was. This was long before the advent of the drug-eluting stent. On the flip side, it would be equally difficult going to a biotech company today to make the same argument about using the stent as a delivery vehicle for gene therapy if they don't know what a stent is. Therefore, there's a tremendous amount of education that needs to happen, both in industry and FDA, in order to put these kinds of technologies together.

MPMN: What new technologies, materials, or systems will medical device designers need to be able to accommodate or deliver biologics?

Drues: The delivery systems that we're using today are sufficient—but not ideal by any means—for what we've been trying to do thus far. But what we've been doing is really the lowest of the low-hanging fruit. To get to the much more valuable, challenging stuff, we're going to have to come up with some totally new tools. In product development, there are two strategies: evolutionary vs. revolutionary. Most product development is evolutionary, or incremental improvements. But the problem with this is that the light bulb did not evolve from the candle; the car did not evolve from the horse. Thus, every once in a while you need to have a revolutionary leap—what Clayton Christensen at Harvard University calls a disruptive technology—to kick things up a few notches. And we need to see more of that. We need to see delivery systems that are not simply retrofits of medical devices that originally were designed to do something else. Instead, what we're going to need are truly new, truly novel delivery systems that were designed first and foremost to deliver whatever it is that we're trying to deliver.