

Letter-to-File 101:

Are you sure you're preparing yours correctly?

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 (March 4, 2022)

<https://www.greenlight.guru/webinar/letter-to-file-101>

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

Speaker Biography



Michael Drues, Ph.D., is President of Vascular Sciences, an education, training, & consulting company offering a broad range of services to medical device, pharmaceutical & biotechnology companies including stimulating & innovative educational programming, creative regulatory strategy & complete 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 Medicaid 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.

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](#) or LinkedIn [here](#).

Dr. Drues can be reached at:

Vascular Sciences
2105 Twain Avenue
Carlsbad, CA 92008

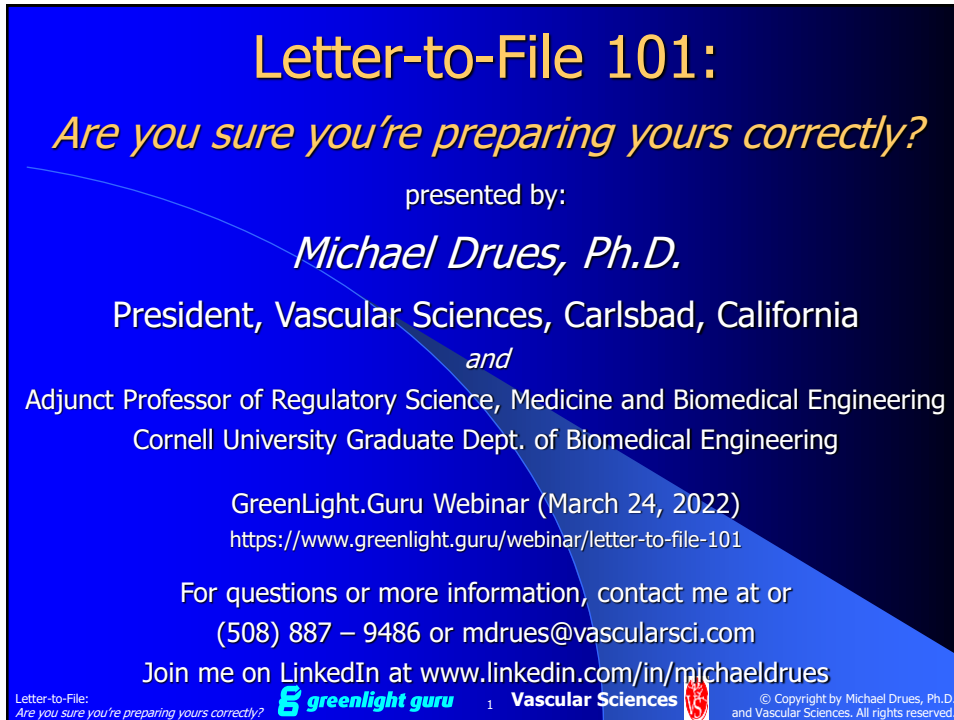
Phone: (508) 887-9486
Fax: (508) 861-0205
E-mail: mdrues@vascularsci.com

For additional information, contact Dr. Drues directly at (508) 887-9486, e-mail mdrues@vascularsci.com or via LinkedIn at www.linkedin.com/in/michaeldrues.

© Copyright 2022 by [Vascular Sciences](#). All rights reserved.

Letter-to-File 101:

Are you sure you're preparing yours correctly?





Letter-to-File 101:
Are you sure you're preparing yours correctly?

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 Webinar (March 24, 2022)
<https://www.greenlight.guru/webinar/letter-to-file-101>

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

Letter-to-File: *Are you sure you're preparing yours correctly?*  1  © Copyright by Michael Drues, Ph.D. and Vascular Sciences. All rights reserved.

1



Do you want more?

 **GLOBAL MEDICAL DEVICE PODCAST**
presented by greenlight.guru

 **Mike on Medtech**

 **LinkedIn**

 **REGULATORY & COMPLIANCE**
Guerilla Regulatory Strategy
Tips And Tactics
A guest expert series by Michael Drues, Ph.D., President, Vascular Sciences

Global Med Dev Podcast (GreenLight.Guru) [here](#)
Mike on MedTech (Medical Product Outsourcing) [here](#)
Medical Design and Outsourcing [here](#)
Guerilla Regulatory Strategy (MED Device Online) [here](#)
Healthcare Packaging [here](#)
LinkedIn [here](#)

 **Medical Design & OUTSOURCING**
A MassDevice Resource

 **Healthcare+
PACKAGING**

For columns, articles and podcasts... visit www.VascularSci.com

Letter-to-File: *Are you sure you're preparing yours correctly?*  2  © Copyright by Michael Drues, Ph.D. and Vascular Sciences. All rights reserved.

2

GreenLight.Guru Webinar (March 24, 2022)

<https://www.greenlight.guru/webinar/letter-to-file-101>

Letter-to-File 101:

Are you sure you're preparing yours correctly?

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!

Letter-to-File:

Are you sure you're preparing yours correctly?



3

Vascular Sciences



© Copyright by Michael Drues, Ph.D. and Vascular Sciences. All rights reserved.

3

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!

Letter-to-File:

Are you sure you're preparing yours correctly?



4

Vascular Sciences



© Copyright by Michael Drues, Ph.D. and Vascular Sciences. All rights reserved.


4

GreenLight.Guru Webinar (March 24, 2022)

<https://www.greenlight.guru/webinar/letter-to-file-101>

Letter-to-File 101:



Are you sure you're preparing yours correctly?



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

- ✓ What is a LTF and when / how should it be used?
- ✓ What goes into a LTF? What should it contain?
- ✓ How does a LTF compare to a special 510k or PMA supplement?
- ✓ Can a LTF be used for a class III PMA device?
- ✓ Is the LTF faster and/or less burdensome than notifying FDA?
- ✓ If you get sued, how can a LTF be used against you?
- ✓ Lots more tips and tricks... time permitting!
- ✓ Final thoughts...

Letter-to-File:
Are you sure you're preparing yours correctly?

  5

© Copyright by Michael Drues, Ph.D. and Vascular Sciences. All rights reserved.

5



Why is a LTF important?

Short answer:

Change management!

Two reasons:

Very common cause of 483 observations and warning letters

Industry standard is wrong!

Letter-to-File:
Are you sure you're preparing yours correctly?

  6

© Copyright by Michael Drues, Ph.D. and Vascular Sciences. All rights reserved.

6


GreenLight.Guru Webinar (March 24, 2022)

<https://www.greenlight.guru/webinar/letter-to-file-101>

Letter-to-File 101:

Are you sure you're preparing yours correctly?



What is a LTF and when/how should it be used?



First question:

You have a device on the market and want to change it in some way...


Do you notify FDA or not? and if so, how?

Letter-to-File: *Are you sure you're preparing yours correctly?*  7   © Copyright by Michael Drues, Ph.D. and Vascular Sciences. All rights reserved.

7

So you want to make a change to your existing medical device, i.e., a device already on the US market...

How to decide when to handle the change internally (via letter-to-file) vs. notifying FDA with a special 510k or PMA supplement






Ask these questions:

Can the proposed change(s) affect safety, efficacy, performance, etc. of the "new" device? What do you do to answer this?

What is the impact on labeling, usability, risk, etc.?

Recommendation:

You need your own process with specific criteria and validate it!

Letter-to-File: *Are you sure you're preparing yours correctly?*  8   © Copyright by Michael Drues, Ph.D. and Vascular Sciences. All rights reserved.

8

GreenLight.Guru Webinar (March 24, 2022)


<https://www.greenlight.guru/webinar/letter-to-file-101>

Letter-to-File 101:

Are you sure you're preparing yours correctly?


Question:
Whether you do a L2F or a s510k or PMA supplement...

What should you document





Short answer:
*FDA – easy (see guidance)
L2F – totally up to you!*

Here's a start:
What is the change, why are you making it, how did you test it, what are the consequences, how will you monitor them, etc. but...



Letter-to-File:
Are you sure you're preparing yours correctly?

 **greenlight guru**  **Vascular Sciences**

© Copyright by Michael Drues, Ph.D. and Vascular Sciences. All rights reserved.

9

Additional Resources

Contains Nonbinding Recommendations

Deciding When to Submit a 510(k) for a Change to an Existing Device

Guidance for Industry and Food and Drug Administration Staff

Document issued on October 25, 2017.

The draft of this document was issued on August 8, 2016.

This document supersedes *Deciding When to Submit a 510(k) for a Change to an Existing Device*, dated January 10, 1997.

For questions about this document regarding CDRH-regulated devices, contact the 510(k) Staff at 301-796-5640.

For questions about this document regarding CBER-regulated devices, contact the Office of Communication, Outreach and Development (OCOD) at 1-800-835-4709 or 240-402-8010.

U.S. Department of Health and Human Services
Food and Drug Administration
FDA U.S. FOOD & DRUG ADMINISTRATION
Center for Devices and Radiological Health
Center for Biologics Evaluation and Research

Contains Nonbinding Recommendations

Deciding When to Submit a 510(k) for a Software Change to an Existing Device

Guidance for Industry and Food and Drug Administration Staff

Document issued on October 25, 2017.

The draft of this document was issued on August 8, 2016.

For questions about this document, contact (CDRH) Linda Ricci, Office of Device Evaluation, 301-796-6325, Linda.Ricci@fda.hhs.gov.

For questions about this document regarding CBER-regulated devices, contact the Office of Communication, Outreach and Development (OCOD), by calling 1-800-835-4709 or 240-402-8010.



U.S. Department of Health and Human Services
Food and Drug Administration
FDA U.S. FOOD & DRUG ADMINISTRATION
Center for Devices and Radiological Health
Center for Biologics Evaluation and Research

Available [here](#). Available [here](#).

Recommendations:

- ✓ Like all guidance... nothing new but read anyway – I'm not going to read it to you! ©
- ✓ All guidance is a starting point only
- ✓ Think more broadly... CDRH>7 and FDA>30 guidance's in area of "Change Management"
- ✓ Most important: **develop your own process & apply your own test!** (think design controls)

Letter-to-File:
Are you sure you're preparing yours correctly?

 **greenlight guru**  **Vascular Sciences**

© Copyright by Michael Drues, Ph.D. and Vascular Sciences. All rights reserved.

10

GreenLight.Guru Webinar (March 24, 2022)

<https://www.greenlight.guru/webinar/letter-to-file-101>

Letter-to-File 101:

Are you sure you're preparing yours correctly?

Want to know more about change management?

Specifically, when you should notify FDA and when you don't need to?

Check out →

www.greenlight.guru/webinar/medical-device-change-management-best-practices

Letter-to-File:
Are you sure you're preparing yours correctly?



11

Vascular Sciences



© Copyright by Michael Drues, Ph.D. and Vascular Sciences. All rights reserved.

The screenshot shows a registration form for a webinar. The form includes fields for First Name, Last Name, Phone Number, and Company Name. Below these fields is a dropdown menu for 'Please Select' and an 'Email' field. A 'Watch the Webinar' button is at the bottom of the form. To the right of the form, there is introductory text about the webinar, a list of 'SPECIFICALLY YOU WILL LEARN' points, and photos of the presenter and moderator.

11

What is a LTF and when/how should it be used?



If you decide notifying FDA is not necessary...

LTF is the tool to use!

Note: not necessary ≠ not required!

Letter-to-File:
Are you sure you're preparing yours correctly?



12

Vascular Sciences



© Copyright by Michael Drues, Ph.D. and Vascular Sciences. All rights reserved.

12


GreenLight.Guru Webinar (March 24, 2022)

<https://www.greenlight.guru/webinar/letter-to-file-101>

Letter-to-File 101:

Are you sure you're preparing yours correctly?

Why create a LTF?





Several reasons:

- Document change (i.e., what, when, why, etc.)... not that important
- Show "new" (changed) device is substantially equivalent to "original" (predicate) device

Note: *pun intended!!!* 😊

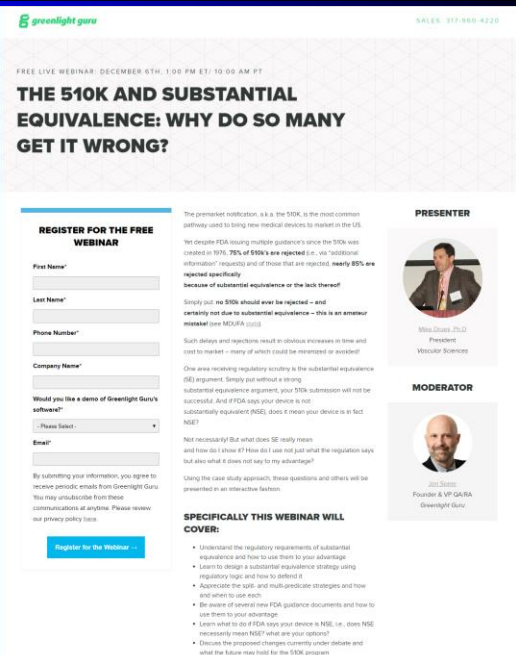
In other words...

A LTF is substantially equivalent to a s510k ...just "submitted" internally.

Letter-to-File: *Are you sure you're preparing yours correctly?*  13  © Copyright by Michael Drues, Ph.D. and Vascular Sciences. All rights reserved.



13

Want to know more about substantial equivalence?



Dec 6, 2018 available [here](https://www.greenlight.guru/webinar/510k-substantial-equivalence).

www.greenlight.guru/webinar/510k-substantial-equivalence


Letter-to-File: *Are you sure you're preparing yours correctly?*  14  © Copyright by Michael Drues, Ph.D. and Vascular Sciences. All rights reserved.

14 GreenLight.Guru Webinar (March 24, 2022)

<https://www.greenlight.guru/webinar/letter-to-file-101>

Letter-to-File 101:

Are you sure you're preparing yours correctly?



510(k) Substantial Equivalence In Plain English — Part 1
By Michael Drues, Ph.D., President, Vascular Sciences

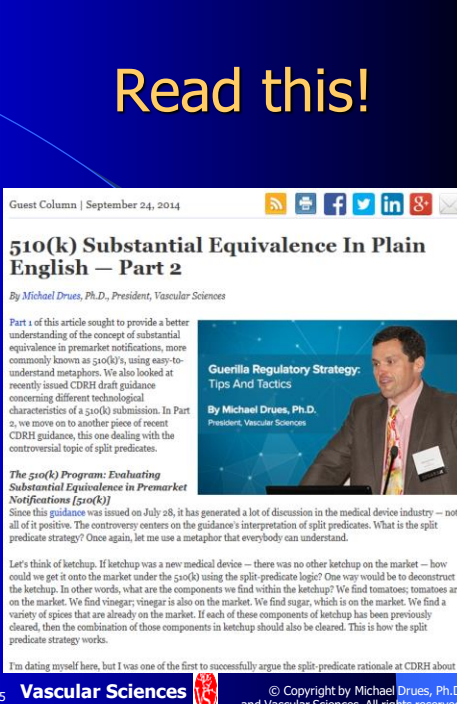
The 510(k), or premarket notification, process has been around since 1976, when it was introduced as part of the Medical Device Amendments to the Federal Food, Drug, and Cosmetic Act. In the nearly 40 years that have passed since its implementation, the 510(k) has become the most commonly used regulatory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

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

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

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

Read this!



510(k) Substantial Equivalence In Plain English — Part 2
By Michael Drues, Ph.D., President, Vascular Sciences



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

The 510(k) Program: Evaluating Substantial Equivalence in Premarket Notifications [510(k)]
Since this guidance was issued on July 28, it has generated a lot of discussion in the medical device industry — not all of it positive. The controversy centers on the guidance's interpretation of split predicates. What is the split predicate strategy? Once again, let me use a metaphor that everybody can understand.

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

I'm dating myself here, but I was one of the first to successfully argue the split-predicate rationale at CDRH about

510k In Plain English — Part 1 and Part II
(Med Device Online, Sept 2014)

Letter-to-File: *Are you sure you're preparing yours correctly?*  15 **Vascular Sciences**  © Copyright by Michael Drues, Ph.D. and Vascular Sciences. All rights reserved.

15



Guerrilla Regulatory Strategy: Tips And Tactics
By Michael Drues, Ph.D., President, Vascular Sciences



Simplifying Substantial Equivalence In FDA Premarket Notifications

The FDA's 510(k) premarket notification process is the most common pathway new medical devices take to market in the United States. And while most 510(k) submissions are eventually cleared, almost 75 percent of first-time applications are initially rejected. It's no wonder it's taking an average of 114 days for 510(k)'s to be review time in 2014, and that's actually an improvement over years past!

Staying current on 510(k) guidance is critical to making the process go as smoothly as possible, and the agency has issued quite a few related guidance documents in recent months. In this podcast, Michael Drues, Ph.D., author of the Med Device Online guest column series *Guerrilla Regulatory Strategy*, shares some 510(k) submission strategies and explains how two recent guidances — on the topic of substantial equivalence — should influence your approach.

Audio Podcast: 510(k) — In Plain English (MED Device Online, Sept 10, 2014) (20 min)

Letter-to-File: *Are you sure you're preparing yours correctly?*  16 **Vascular Sciences**  © Copyright by Michael Drues, Ph.D. and Vascular Sciences. All rights reserved.

16

GreenLight.Guru Webinar (March 24, 2022)

<https://www.greenlight.guru/webinar/letter-to-file-101>


For additional information, www.linkedin.com/in/michaeldrues, call (508) 887-9486 or e-mail mdrues@vascularsci.com

© Copyright by Michael Drues, Ph.D. and Vascular Sciences. All rights reserved.


Letter-to-File 101:

Are you sure you're preparing yours correctly?

Imagine this scenario:

Third reason: 


FDA knocks on your door. They say you changed your medical device but did not tell them.




What are the consequences of your decision

Consider:

*Regulatory?
Product Liability?
It's the "right" thing to do? ...or am I just being naïve?*




Letter-to-File:
Are you sure you're preparing yours correctly?  17  © Copyright by Michael Drues, Ph.D. and Vascular Sciences. All rights reserved.



17

**What goes into a LTF?
What should it contain?**

Short answer:

Same information as special 510k!



Letter-to-File:
Are you sure you're preparing yours correctly?  18  © Copyright by Michael Drues, Ph.D. and Vascular Sciences. All rights reserved.

18 GreenLight.Guru Webinar (March 24, 2022)

<https://www.greenlight.guru/webinar/letter-to-file-101>

Letter-to-File 101:

Are you sure you're preparing yours correctly?

How To Prepare A Special 510(k)

Contains Nonbinding Recommendations

The Special 510(k) Program

Guidance for Industry and Food and Drug Administration Staff

Document issued on September 13, 2019.

The draft of this document was issued on September 28, 2018.

This document supersedes the Special 510(k) content in "The New 510(k) Paradigm - Alternate Approaches to Demonstrating Substantial Equivalence in Premarket Notifications," issued on March 20, 1998.

For questions about this document regarding CDRH-regulated devices, contact ORP: Office of Regulatory Programs/ DRP1: Division of Submission Support/ Premarket Notification and Classification Team at 510K_Program@fda.hhs.gov or 301-796-5640. For questions regarding this document regarding CBER-regulated devices, contact the Office of Communication, Outreach and Development (OCOD) in CBER at 1-800-835-4709 or 240-402-8010 or by email at ocod@fda.hhs.gov.

CDRH website [here](#).

What are the most important sections?

Make a template!

CDRH guidance [here](#).

Letter-to-File: *Are you sure you're preparing yours correctly?* 19 **U.S. FOOD & DRUG ADMINISTRATION** U.S. Department of Health and Human Services Food and Drug Administration Center for Devices and Radiological Health Center for Biologics Evaluation and Research © Copyright by Michael Drues, Ph.D. and Vascular Sciences. All rights reserved.

19

Acceptance Checklists for 510(k)s

Contains Nonbinding Recommendations

Refuse to Accept Policy for 510(k)s

Guidance for Industry and Food and Drug Administration Staff

Document issued on: September 13, 2019.

Document originally issued on May 20, 1994.

This document supersedes "Refuse to Accept Policy for 510(k)s" issued February 21, 2019.

For questions about this document regarding CDRH-regulated devices, contact ORP: Office of Regulatory Programs, DRP1: Division of Submission Support, Premarket Notification and Classification Team by email at 510K_Program@fda.hhs.gov or at 301-796-5640.

For questions about this document regarding CBER-regulated devices, contact the Office of Communication, Outreach, and Development (OCOD) by email at ocod@fda.hhs.gov or at 800-835-4709 or 240-402-8010.

CDRH website [here](#).

And don't forget to update your QMS!

CDRH guidance [here](#).

Letter-to-File: *Are you sure you're preparing yours correctly?* 20 **U.S. FOOD & DRUG ADMINISTRATION** U.S. Department of Health and Human Services Food and Drug Administration Center for Devices and Radiological Health Center for Biologics Evaluation and Research © Copyright by Michael Drues, Ph.D. and Vascular Sciences. All rights reserved.


20

GreenLight.Guru Webinar (March 24, 2022)

<https://www.greenlight.guru/webinar/letter-to-file-101>

Letter-to-File 101:




Are you sure you're preparing yours correctly?



What does a LTF cost?

No MDUFA user fee... *obviously!*
Cost to company

Cost of not doing it properly... potentially **HUGE!**

Letter-to-File: *Are you sure you're preparing yours correctly?*  21   © Copyright by Michael Drues, Ph.D. and Vascular Sciences. All rights reserved.

21

Medical Device User Fee Act (MDUFA) 2022

User Fees for FY2022

Annual Establishment Registration Fee: \$5,672




All establishments must pay the [establishment registration fee](#). There are no waivers or reductions for small establishments, businesses, or groups.

Other fees for Fiscal Year 2022 (October 1, 2021 through September 30, 2022) are:

Application Type	Standard Fee	Small Business Fee†
510(k)	\$12,745	\$3,186
513(g)	\$5,061	\$2,530
PMA, PDP, PMR, BLA	\$374,858	\$93,714
De Novo Classification Request	\$112,457	\$28,114
Panel-track Supplement	\$281,143	\$70,286
180-Day Supplement	\$56,229	\$14,057
Real-Time Supplement	\$26,240	\$6,560
BLA Efficacy Supplement	\$374,858	\$93,714
30-Day Notice	\$5,998	\$2,999
Annual Fee for Periodic Reporting on a Class III device (PMAs, PDPs, and PMRs)	\$13,120	\$3,280

† **Small Business Fee:** For businesses certified by the Center for Devices and Radiological Health (CDRH) as a small business..

‡ **510(k) Fees:** All types of 510(k)s (Traditional, Abbreviated, and Special) are subject to the user fee. However, there is no user fee for 510(k)s submitted to the FDA on behalf of an FDA-accredited third-party reviewer.

Letter-to-File: *Are you sure you're preparing yours correctly?*  22   © Copyright by Michael Drues, Ph.D. and Vascular Sciences. All rights reserved.

22


GreenLight.Guru Webinar (March 24, 2022)

<https://www.greenlight.guru/webinar/letter-to-file-101>




Letter-to-File 101:

Are you sure you're preparing yours correctly?

How does a LTF compare to a special 510k or PMA supplement?




Short answer:
Principles (i.e., logic) is exactly the same!
Though less "freedom to operate" in Class III universe... why?


Letter-to-File: *Are you sure you're preparing yours correctly?*  23   © Copyright by Michael Drues, Ph.D. and Vascular Sciences. All rights reserved.




23

Can a LTF be used for a class III PMA device?



Short answer:
Yes but...



Letter-to-File: *Are you sure you're preparing yours correctly?*  24   © Copyright by Michael Drues, Ph.D. and Vascular Sciences. All rights reserved.


24

GreenLight.Guru Webinar (March 24, 2022)

<https://www.greenlight.guru/webinar/letter-to-file-101>

Letter-to-File 101:

Are you sure you're preparing yours correctly?



When is a PMA supplement required and when is it not?

Most important...

Why?!?

PMA Supplements and Amendments (Mar, 2022) [here](#)

Letter-to-File: *Are you sure you're preparing yours correctly?*

greenlight guru 25 **Vascular Sciences** © Copyright by Michael Drues, Ph.D. and Vascular Sciences. All rights reserved.

When to submit a PMA supplement (§814.39)

Changes that Require a PMA Supplement


After FDA has approved a PMA, an applicant must submit a PMA supplement for review and approval by FDA before making any change affecting the safety or effectiveness of the device unless FDA has advised that an alternate type of submission is permitted for a particular change. All changes must meet the requirements of the Quality System regulation (current good manufacturing practices) under 21 CFR Part 820 including the design control requirements under §820.30. Changes for which an applicant must submit a PMA supplement include, but are not limited to, the following types of changes if they affect the safety or effectiveness of the device:

- new indication for use of the device;
- labeling changes;
- the use of a different facility or establishment to manufacture, process, or package the device;
- changes in manufacturing methods, or quality control procedures;
- changes in sterilization procedures;
- changes in packaging;
- changes in the performance or design specifications, circuits, components, ingredients, principles of operation, or physical layout of the device; and
- extension of the expiration date of the device based on data obtained under a new or revised stability or sterility testing protocol that has not been approved by FDA. [If the protocol has been previously approved by FDA, a supplement is not submitted but the change must be reported to FDA in the postapproval periodic reports as described in §814.39(b).]

Changes without a PMA Supplement 814.39(b)

An applicant may make a change in a device after FDA's approval of the PMA without submitting a PMA supplement if: (1) the change does not affect the device's safety or effectiveness, and (2) the change is reported to FDA in a postapproval periodic report (annual report) required as a condition of approval of the device, e.g., an editorial change in labeling which does not affect the safety or effectiveness of the device. Trivial changes, such as changes in the color of a label, would not have to be included in the postapproval periodic report.

25



What types of PMA supplements exist?

Most important...

Why?!?

PMA Supplements and Amendments (Mar, 2022) [here](#)

Letter-to-File: *Are you sure you're preparing yours correctly?*

greenlight guru 26 **Vascular Sciences** © Copyright by Michael Drues, Ph.D. and Vascular Sciences. All rights reserved.

Types of PMA Supplements

The methods of notification and FDA involvement of changes to a PMA approved medical device depend on the type of change made. A summary of the types of notification and FDA involvement is outlined below. For additional information regarding the type of PMA supplement that should be submitted, please refer to the guidance document [Modifications to Devices Subject to Premarket Approval \(PMA\) - The PMA Supplement Decision-Making Process](#).

- **PMA Panel-Track Supplement - §814.39(c)**
 - For changes that request a significant change in design or performance of the device, or a new indication for use of the device.
 - Substantial clinical data are necessary to provide a reasonable assurance of safety and effectiveness.
 - A full PMA review which may include a review by an outside advisory panel will be required.
- **PMA supplement (180 days) - §814.39(a)**
 - For changes that affect the safety and effectiveness of the device.
 - For significant change in components, materials, design, specification, software, color additives, or labeling.
 - In general, the clinical data provided in support of the traditional device approval should still be applicable in supporting the approval of the changed device. In most cases, only new preclinical testing is needed to support safety and effectiveness.
 - In-depth review and approval by FDA is required before implementation of the change.
 - A full PMA review may be required. The criteria for a full PMA review includes changes in the device that may raise different types of safety and effectiveness questions or changes in which there may be no accepted test methods for evaluating the issues of safety or effectiveness.
- **Real Time Supplement - Food Drug & Cosmetic Act 737(4)(D)**
 - For a minor change to the device, such as a minor change to the design of the device, software, sterilization, or labeling, and for which the applicant has requested and the agency has granted a meeting or similar forum to jointly review and determine the status of the supplement.
 - For additional information about the type of changes that qualify for a real-time supplement, as well as the process for the real-time review program, please refer to the guidance document, "[Real-Time Premarket Approval Applications \(PMA\) Supplements](#)."
- **Special PMA Supplement - Changes Being Effectuated - §814.39(d)**
 - For any change that enhances the safety of the device or the safety in the use of the device.
 - For certain labeling and manufacturing changes that enhance the safety of the device or the safety in the use of the device.
 - May be placed into effect by the applicant prior to the receipt of a written FDA order approving the PMA supplement.

26

GreenLight.Guru Webinar (March 24, 2022)

<https://www.greenlight.guru/webinar/letter-to-file-101>

Letter-to-File 101:

Are you sure you're preparing yours correctly?

What more?




The image shows a promotional banner for a webinar. At the top left is the Greenlight Guru logo. The main text reads: "Free Live Webinar by greenlight guru + VASCULAR SCIENCES". The title of the webinar is "THE PRE-MARKET APPROVAL (PMA): IS IT REALLY AS BAD AS SO MANY THINK?". Below the title is a purple button that says "REGISTER NOW→". To the right of the button, the date and time are listed: "SEP 6TH @ 1:00PM ET / 10:00AM PT". On the right side of the banner, there are two circular headshots. The top one is for Michael Drues, Ph.D., President of Vascular Sciences, labeled as the "Presenter". The bottom one is for Jon Speer, Founder & VP QA/RA of Greenlight Guru, labeled as the "Moderator".

www.greenlight.guru/webinar/pre-market-approval

Letter-to-File: Are you sure you're preparing yours correctly?  27  © Copyright by Michael Drues, Ph.D. and Vascular Sciences. All rights reserved.

27



Is the LTF faster and/or less burdensome than notifying FDA?



Short answer: *Yes and no!*

Reminder:

LTF is not a shortcut... that's when you get in trouble!

Letter-to-File: Are you sure you're preparing yours correctly?  28  © Copyright by Michael Drues, Ph.D. and Vascular Sciences. All rights reserved.

28


GreenLight.Guru Webinar (March 24, 2022)

<https://www.greenlight.guru/webinar/letter-to-file-101>

Letter-to-File 101:

Are you sure you're preparing yours correctly?



What's the relationship between change management and product liability



Remember,



L2F and related documents (or the lack thereof) is the first place I point product liability attorney's!

Note: Who should you fear?

Letter-to-File: Are you sure you're preparing yours correctly?  29  © Copyright by Michael Drues, Ph.D. and Vascular Sciences. All rights reserved.

29

If you get sued, can a LTF be used against you?





Short answer:

Absolutely!

LTF's are one of the first things I ask for during discovery... why?

*Can be used against you if you have them...
can be used against you if you don't!*

Letter-to-File: Are you sure you're preparing yours correctly?  30  © Copyright by Michael Drues, Ph.D. and Vascular Sciences. All rights reserved.

30

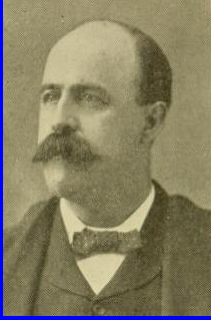
GreenLight.Guru Webinar (March 24, 2022)

<https://www.greenlight.guru/webinar/letter-to-file-101>

Letter-to-File 101:


Are you sure you're preparing yours correctly?

Advantages and Disadvantages of Documentation





*"Never write if you can speak...
never speak if you can nod...
and never nod if you can wink!"*

Martin Lomasney (1859–1933), Massachusetts politician
best remembered for being the ward boss of Boston's Ward Eight




Or put another way...

*"Never talk when you can nod...
never nod when you can wink...
and never write an e-mail because it's death.
You're giving prosecutors all the evidence we need!"*

Letter-to-File: Are you sure you're preparing yours correctly?  Eliot Spitzer (1959–) is a lawyer and former New York Governor (2007–2008).
31  © Copyright by Michael Drues, Ph.D. and Vascular Sciences. All rights reserved.

31



on the LTF

Positives



- ✓ More freedom
- ✓ Less formal
- ✓ Quicker... *or is it?*

Negatives

- ✓ No FDA review... *but is that a good thing?*
- ✓ Can get you in **BIG** trouble if not done properly!

Mike's Take

- ✓ Very useful tool... *when used properly by people who know what they are doing!*
- ✓ overall all... mixed bag

Letter-to-File: Are you sure you're preparing yours correctly?  32  © Copyright by Michael Drues, Ph.D. and Vascular Sciences. All rights reserved.

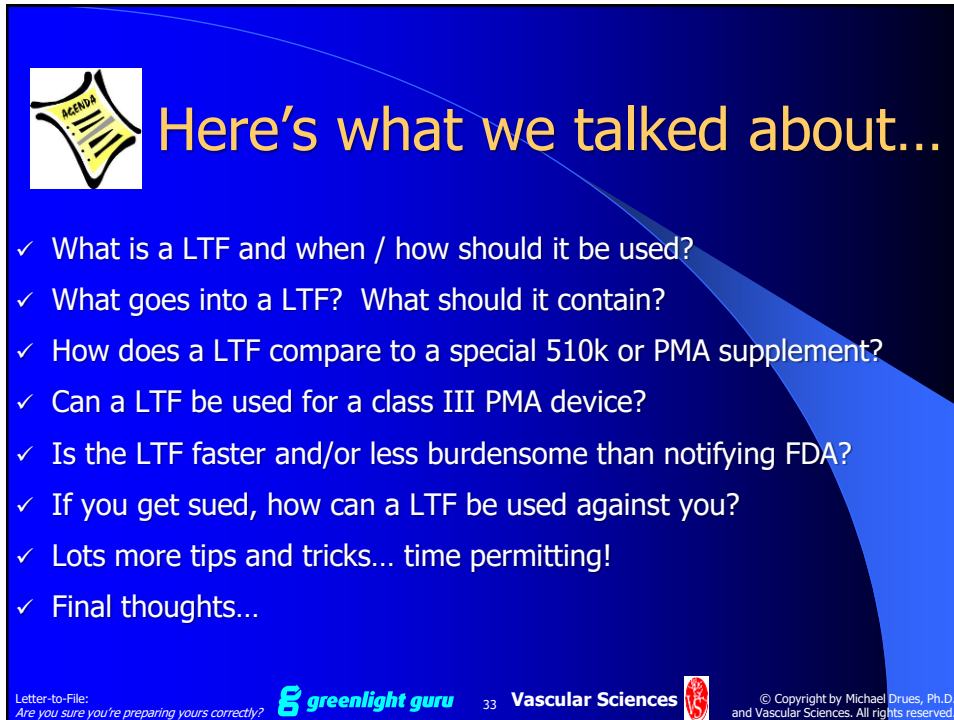
32

GreenLight.Guru Webinar (March 24, 2022)

<https://www.greenlight.guru/webinar/letter-to-file-101>



Letter-to-File 101:

Are you sure you're preparing yours correctly?



Here's what we talked about...

- ✓ What is a LTF and when / how should it be used?
- ✓ What goes into a LTF? What should it contain?
- ✓ How does a LTF compare to a special 510k or PMA supplement?
- ✓ Can a LTF be used for a class III PMA device?
- ✓ Is the LTF faster and/or less burdensome than notifying FDA?
- ✓ If you get sued, how can a LTF be used against you?
- ✓ Lots more tips and tricks... time permitting!
- ✓ Final thoughts...

Letter-to-File: *Are you sure you're preparing yours correctly?*  33  © Copyright by Michael Drues, Ph.D. and Vascular Sciences. All rights reserved.

33



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

Letter-to-File: *Are you sure you're preparing yours correctly?*  34  © Copyright by Michael Drues, Ph.D. and Vascular Sciences. All rights reserved.

34

GreenLight.Guru Webinar (March 24, 2022)

<https://www.greenlight.guru/webinar/letter-to-file-101>

Letter-to-File 101:

Are you sure you're preparing yours correctly?

Don't just follow the rules... think!

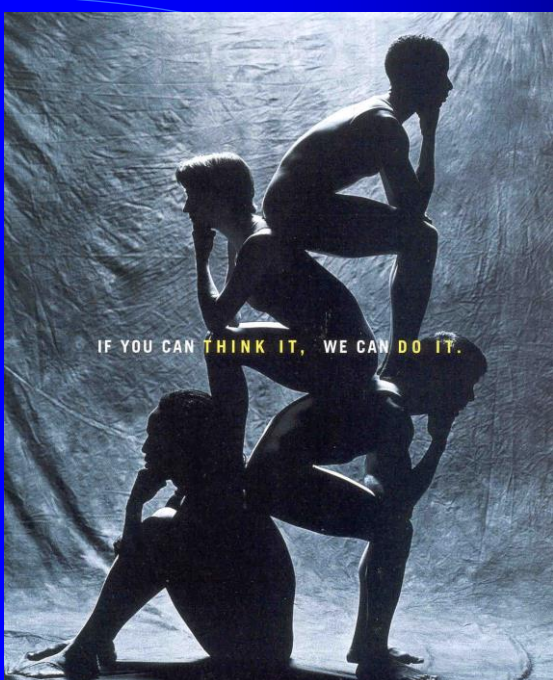


Rules are mostly made to be broken and are too often for the lazy to hide behind.

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.

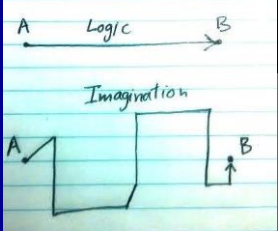
Letter-to-File: *Are you sure you're preparing yours correctly?*  35   © Copyright by Michael Drues, Ph.D. and Vascular Sciences. All rights reserved.

35






“Imagination is more important than knowledge, for while knowledge points to all there is, imagination points to all that can be.”

Albert Einstein



“Logic will get you from A to B. Imagination will take you anywhere.”

Albert Einstein

Letter-to-File: *Are you sure you're preparing yours correctly?*  36   © Copyright by Michael Drues, Ph.D. and Vascular Sciences. All rights reserved.

36


GreenLight.Guru Webinar (March 24, 2022)

<https://www.greenlight.guru/webinar/letter-to-file-101>

Letter-to-File 101:


Are you sure you're preparing yours correctly?

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.




Steve Jobs Heres To The Crazy Ones (1 min) 

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?



Letter-to-File: *Are you sure you're preparing yours correctly?*  37   © Copyright by Michael Drues, Ph.D. and Vascular Sciences. All rights reserved.

37



Questions?
Comments?
Suggestions?
Criticisms?
Complaints?

Letter-to-File: *Are you sure you're preparing yours correctly?*  38   © Copyright by Michael Drues, Ph.D. and Vascular Sciences. All rights reserved.

38 GreenLight.Guru Webinar (March 24, 2022)

<https://www.greenlight.guru/webinar/letter-to-file-101>