

**FDA Webinar: The Least Burdensome Provisions:
Concept and Principles Final Guidance**

**Moderator: Irene Aihie
March 14, 2019
1:00 pm ET**

Coordinator: Welcome and thank you for standing by. At this time all participants are in a listen only mode until the question-and-answer session of today's conference. At that time you may press star 1 on your phone to ask a question. I would like to inform all parties that today's conference is being recorded. If you have any objections you may disconnect at this time.

I would now like to turn the conference over to Ms. Irene Aihie. Thank you. You may begin.

Irene Aihie: Hello and welcome to today's FDA webinar. I'm Irene Aihie of CDRH's Office of Communication and Education.

On February 5 the FDA issued the final guidance titled The Least Burdensome Provisions: Concept and Principles.

This final guidance describes our use of the Least Burdensome approach through medical device regulation to remove or reduce unnecessary burden

that may delay the marketing of beneficial products while maintaining the statutory requirements for clearance and approval.

Today Joshua Silverstein Regulatory Adviser in the Office of Device Evaluation here in CDRH will discuss the final guidance. Following Joshua's presentation we will open the line to your questions related to the information provided during the presentation.

Additionally there are other central subject matter experts here to assist with the Q&A portion of today's webinar.

Now, I give you Joshua.

Joshua Silverstein: Good afternoon. Thank you for the introduction Irene. Thanks to the audience for joining today's webinar on the Least Burdensome Provisions: Concept and Principles.

As Irene noted my name is Joshua Silverstein. I'm a Regulatory Advisor in the Office of Device Evaluation. Sonja Fulmer from the Office of the Center Director is also here to help answer questions.

I will now go through our agenda for today's webinar.

This presentation will help stakeholders understand the background regarding Least Burdensome. We will summarize the Least Burdensome final guidance which was issued on February 5, 2019.

This final guidance is also on CDRH's fiscal year 2019 guidance priority A-list.

We will then give an update on implementation efforts before taking your questions.

At the end of this webinar you should know that the Least Burdensome principles apply across the total product lifecycle and enables the FDA to focus resources on the issues of highest public health concern.

But the FDA has identified principles to support the Least Burdensome approach to device regulation.

You should know selected examples of how the FDA and the industry have used the Least Burdensome approach.

How the FDA is implementing these changes to the Least Burdensome approach and how implementation of Least Burdensome upholds our stringent review standards and maintains the scientific integrity of our decision making process.

As a background, Congress added the Least Burdensome provisions to the Federal Food, Drug and Cosmetic Act passed in the FDA Modernization Act of 1997.

After the enactment of FDAMA, CDRH issued three guidances on Least Burdensome from 2000 to 2002.

The first guidance was the Least Burdensome provisions of FDAMA concepts and principles.

The second guidance was suggested for developing and responding to deficiencies in accordance with the Least Burdensome provisions of FDAMA.

And third a suggested approach to resolving Least Burdensome issues.

Congress updated the Least Burdensome provisions to clarify the standard in the FDA Safety and Innovation Act of 2012.

Congress further clarified Least Burdensome in the 21st Century Cures Act of 2016 and expanded Least Burdensome. 21st Century Cures expanded Least Burdensome to apply to a reasonable assurance and safety and effectiveness rather than just effectiveness. It also required the use of post market information to support a reasonable assurance of safety and effectiveness.

21st Century Cures also required training of FDA staff including the assessment of the effectiveness of this training.

And also that FDA documents how Least Burdensome requirements are considered for significant decisions in substantive summaries.

FDA issued final guidance developing and responding to deficiencies in accordance with the Least Burdensome provisions on September 29, 2017 which updated the 2000 guidance on pre-market deficiencies.

FDA issued a draft guidance of the Least Burdensome provisions concept and principles on December 15 of 2017.

And finally the Government Accountability Office published a report on December 15 of 2017 recommending that FDA develops metrics to evaluate whether it consistently applies a Least Burdensome approach in pre-market reviews.

We are discussing Least Burdensome today because the final concept and principles guidance was issued on February 5.

So I will now go through the current enacted Least Burdensome provisions.

Whenever the secretary requests information to demonstrate that devices with differing technological characteristics are substantially equivalent the secretary shall only request information that is necessary to making substantial equivalence determinations.

In making such requests the secretary shall consider the Least Burdensome means of demonstrating substantial equivalence and recommend - request information accordingly.

The second, any clinical data including one or more world controlled investigations specified in writing by the secretary for demonstrating a reasonable assurance of devices effectiveness shall be specified as a result of a determination by the secretary that such data are necessary to establish device effectiveness.

The secretary shall consider in consultation with the applicant the Least Burdensome appropriate means of evaluating device effectiveness that would have a reasonable likelihood of resulting in approval.

In requesting additional information with respect to a Pre-Market Approval Application or PMA the secretary shall consider the Least Burdensome appropriate means necessary to demonstrate a reasonable assurance of device safety and effectiveness.

The next is that the secretary shall consider the role of post-market information in determining the Least Burdensome means of demonstrating a reasonable assurance of device safety and effectiveness.

In all of the Least Burdensome provisions the term necessary means the minimum required information that would support a determination of substantial equivalence or a reasonable assurance of device safety and effectiveness.

And most importantly none of the least Burdensome provisions change the standards for pre-market approval or substantial equivalence.

I will now shift to a summary of the public comments received on the draft guidance. I will also discuss changes from the draft to the final guidance.

FDA received 79 comments from 13 external stakeholders which included device manufacturers, a law firm, trade association, academia and health care associations, as well as individuals.

Most comments were supportive of CDRH's proposal. There were revisions and additions requested regarding the least Burdensome definition and guiding principles.

There were multiple requests for the inclusion of additional examples. And stakeholders also requested more information regarding the implementation of the least Burdensome provisions and principles.

I will now discuss the final Least Burdensome policy.

Essential to the least Burdensome concept is our definition of Least Burdensome which is the minimum amount of information necessary to adequately address a relevant regulatory question or issue through the most efficient manner at the right time.

This definition has three parts that we would like to highlight.

Number one is that the minimum information is a nod to the statutory Least Burdensome provisions.

Number two most efficient manner acknowledges that there can be different answers to a regulatory question or issue.

And number three the right time concerns when in the total product lifecycle certain information should be captured or provided to the agency.

Now I will go over the scope of Least Burdensome.

The Least Burdensome concept applies to all products that meets the definition of a device, including device constituent parts of combination products.

The policy in this guidance applies to all activities pertaining to the regulation of devices including both pre-market and post-market actions. This policy also maintains FDA's gold standards.

And what we mean by that is that least Burdensome does not alter the statutory criteria for substantial equivalence or a reasonable assurance of safety and effectiveness.

Least Burdensome also does not alter the requirement for valid scientific evidence to support decisions.

I will now go through the seven (7) Least Burdensome guiding principles.

These guiding principles represent what the FDA and the industry should apply when taking the Least Burdensome approach and it also explains FDA commitment for Least Burdensome review.

Number 1 is that the FDA intends to request the minimum information necessary to adequately address the regulatory question or issue at hand.

Number 2, industry should submit material including pre-market submissions to the FDA that are Least Burdensome for FDA to review. That means that industry should submit well-organized, clear and concise information, that industry should not submit information unrelated to the regulatory decision to the FDA. And that industry should reference applicable FDA guidance documents where FDA recommendations were considered.

Number 3, FDA intends to use the most efficient means to resolve regulatory questions and issues. FDA intends to use all reasonable measures to streamline processes and policies as well as render regulatory decisions within appropriate timeframes such as MDUFA performance goals.

FDA intends to routinely use both formal and informal interactive approaches whenever possible to resolve questions and issues.

FDA intends to an industry should use reasonable tailored approaches that have been adapted to individual circumstances and needs to address regulatory

questions and issues. FDA intends to take appropriate consideration of the time and resource implications of our requests.

Number 4 is that the right information should be provided at the right time, for example, just in time data collection, to address the right questions.

FDA intends to, and industry should, consider the use of post-market data collection to reduce pre-market data collection wherever appropriate and feasible.

Number 5, regulatory approaches should be designed to fit the technology taking into account its unique innovation cycles, evidence generation needs, and timely patient access.

Number 6, the FDA intends to leverage data from other countries and decisions by or on behalf of other national medical device regulatory authorities to the extent appropriate and feasible.

Number 7 is that the FDA intends to apply Least Burdensome principles in international medical device convergence and harmonization efforts. The FDA intends to actively engage in the development, recognition, and use of voluntary consensus standards published by internationals and other standards development organizations.

The final guidance includes example to represent how Least Burdensome principles can be implemented. And I just wanted to note that these examples are for illustrative purposes only to show how Least Burdensome approach can be used.

The examples in the guidance are mapped to the Least Burdensome definition, but could be reasonably included in different sections.

And so the examples generally relate to different sources of reducing the burden of clinical data, using non clinical data, accepting alternative approaches, the use of benefit risk assessments, reducing administrative burden, smart regulation, global harmonization, balancing pre-market and post-market, and the use of just in time testing.

So examples of minimum information necessary include leveraging existing data. And so the first example of leveraging existing data is the use of peer-reviewed literature as it has been used to support the marketing authorization in both the De Novo requests and HDE applications as well as support expanded indication for use and other labeling changes in 510(k) submissions.

The guidance document includes a few examples of De Novo transparency and 510(k) summaries where peer-reviewed literature was used.

Additionally leveraging existing data has been to leverage information from pre-market approval applications to reclassify stair climbing wheelchairs and sharps needles destruction devices using the six-year rule.

Onto the most efficient means. Reducing the burden of traditional clinical studies using historical control groups, non-comparative clinical outcome studies, subject as own control, adaptive study designs, and alternatives to prospective sample collection.

There is also the example of global harmonization such as the use voluntary consensus standards which creates a consistent approach to device development, manufacturing, and evaluation.

Additionally the MDSAP program minimizes the number of audits, number of redundant requests, and disruption of business, while meeting the requirements of the multiple jurisdictions.

As examples of the right time as part of the Center's strategic priority to strike the right balance between pre-market and post-market data collection, FDA assessed 200 procodes of class III devices to consider whether these device types were candidates for a pre-market/post-market shift of data capture or reclassification.

Three final orders to reclassify these devices have been published thus far.

Additionally, the use of just in time testing for device evaluation strategies, early feasibility studies can be used to transparently establish a timeline for deferred or additional non-clinical testing as your company proceeds through subsequent clinical studies.

So we would also like to provide an update on implementation efforts in response to many of the comments that we received through the docket for the draft guidance.

And as many of you know the FDA published the FDA Report to Congress on the Least Burdensome training audit back in June of 2018.

Since the FDA report to Congress, CDRH finished training all staff with a targeted course entitled "How to Make the Most of the Least Burdensome: Case Study practice."

CDRH also conducted a pilot on a new approach to resolving issues in 510(k) submissions called the Least Burdensome Flag. And we will be discussing this program from here on out.

And so the Least Burdensome Flag is an opportunity for a submitter to request an informal review by upper management because they believe the FDA's request is not Least Burdensome or that they are being held in an inappropriate review standard.

CDRH ran a pilot on the Least Burdensome Flag from February until September of 2018 in seven review branches. What happened was that 510(k) request for additional information or deficiency letters for applicable branches that did not raise a potential not-substantially equivalent issue included an attachment offering the opportunity to use the Least Burdensome Flag.

Before using this program we had some pilot criteria that should have been satisfied.

And so number one was that submitters should discuss with branch or division management at least one time before being eligible to use the Least Burdensome Flag.

The Flag was limited to a deficiency or deficiencies in two different topic areas, for example, biocompatibility and sterility.

The Least Burdensome Flag would expire 60 days after the request for additional information or deficiency letter was sent.

If used, the Least Burdensome Flag feedback would be sent within 21 days of receipt by FDA.

And additionally the deficiency letter specifies that regardless of any Least Burdensome Flag use the due date to the document control center for the 510(k) submission did not change.

So I would like to now provide a summary of the pilot.

We were able to capture data by requesting feedback from one third of submitters who did not use the Flag and all submitters who did use the Flag.

The pilot sought to answer questions related to customer satisfaction, efficiency in submission outcomes.

In total 132 letters received the Least Burdensome Flag opportunity. Of these 132 letters, two (2) submitters or 1.5%, used the Flag.

I would like to first go through the feedback from the expire Least Burdensome Flags. The majority of respondents understood the purpose of the Least Burdensome Flag, its process, and appreciated the opportunity to receive feedback from senior management.

Respondents did not use the Flag because their issues were resolved either with the branch chief or a day 10 phone call or the deficiencies were reasonable.

A few respondents thought that the pilot was too restrictive or they were concerned about using official meetings.

All respondents said that they would use the Least Burdensome Flag if they did not agree with the FDA's request for additional information.

Now I would like to share feedback from the two submitters who did end up using the Least Burdensome Flag.

They thought that they were more likely to use the Least Burdensome Flag over an appeal. However, the timing of the Least Burdensome Flag with the day 10 call, submission issue meeting, or an appeal were not 100% clear. Respectively understanding the depth of review would have helped them before using the Least Burdensome Flag.

And finally if they were able to choose a particular program 510(k) would be the highest priority for the Least Burdensome Flag to be used.

So now I would like to sort of summarize the pilot data and as I already said the Least Burdensome Flag was used in 1.5% of submissions that were included in the pilot.

FDA was able to meet its self-designated 21-day deadline because each Flag was resolved in a straightforward manner. And we believe that the straightforward resolution was due to restricting the flag to two topic areas.

And finally submitters appreciated the opportunity to obtain senior management feedback.

So in conclusion for the Least Burdensome Flag pilot the result supports that the Least Burdensome Flag is simpler than an appeal based on the feedback that we have received. It's a useful process for our staff and it provided preliminary results that our staff is least burdensome.

Industry believed that the Least Burdensome Flag provided a valuable opportunity to raise concerns about their submissions.

CDRH is implementing the Least Burdensome Flag as a program for 510(k) submissions to act as a performance metric for the implementation of least Burdensome requirements.

CDRH implemented the Least Burdensome Flag on March 4 of 2019 for all 510(k) requests for additional information that are not potential not substantially equivalent decisions.

Before using the Flag and similar to the pilot submitters should discuss their concerns with the signatory authority or their manager before using the Flag.

Least Burdensome Flags should generally be within two topic areas and if they believe two topic areas - more than two topic areas - should be used, the submitter should contact the 510(k) staff for more information.

And finally the Flag should be used within 60 days after a deficiency letter or it expires.

Finally the Flag does not change the response due date for the submitter to the document control center.

In terms of how to use the Least Burdensome Flag, this is sort of a submission recommendation for the use of this program. And because this will be done through email, a submitter should email the lead reviewer, their manager and the 510(k) staff with the following information which should be within one to two pages.

Number one is a summary of the deficiencies being flagged including why the request is not Least Burdensome or the submitter is being held to a different review standard.

Number two, a summary of relevant communications with the signatory authority or their manager to show that the submitter has sought management input before throwing the Flag.

And number three a proposed path forward.

In terms of what submitter should expect.

Number one, the FDA will hold internal meetings only and schedule a teleconference with the submitter if they cannot adequately resolve the Least Burdensome Flag internally.

Number two, the Least Burdensome Flag response will be emailed on behalf of the director of the organizational unit in CDRH who is responsible for your 510(k).

And number three, the Least Burdensome Flag resolution is included as part of the administrative record.

So now I would just like to conclude with some resources that are available for our stakeholders.

Number one, there is a link to the final Least Burdensome concept and principles guidance. We have also included links to developing and responding to deficiencies in accordance with the Least Burdensome provisions.

We have also included reports to congress on the least Burdensome training audit as well as the GAR report on Least Burdensome medical device reviews.

So with that we have a few different resources for questions after this webinar. One of them is the 510(k) staff and the other is the Division of Industry and Consumer Education or DICE.

So with that this concludes the presentation part of the webinar and we are looking forward to hearing your questions.

Coordinator: Thank you. We will now begin the Question and Answer session. If you will like to ask a question please press star 1, unmute your phone and record your name clearly. Your name is required to introduce your question. If you need to withdraw your question press star 2.

Again to ask a question please press star 1. It will take a few moments for questions to come through. Please standby.

Joshua Silverstein: So while we are waiting for our questions to come in one of the common questions that we received is what is the difference between an appeal and the Least Burdensome Flag?

And so the Least Burdensome Flag is more about the fundamentals of the deficiency whereas we see an appeal being a deep dive into the administrative record.

So it looks like we have a few questions so I'm going to pause there.

Coordinator: Thank you. Our first question will come from Steven Silverman. Your line is open.

Steven Silverman: Hi, thank you very much for taking my question and thank you for this very informative webinar as well. I'm interested in hearing from you about what FDA is going to do in terms of metrics related to Least Burdensome practices.

Specifically how will FDA measure and track its staff application of Least Burdensome principles and application of those principles?

And in addition how will FDA document situations in which staff fails to apply Least Burdensome principles? For example, by tracking sponsor's assertions to agency practices or requirement are not Least Burdensome.

And in addition to developing these metrics what will FDA do to make these metrics publicly available and easily understood?

Joshua Silverstein: Thanks for your question. So just in general for performance metrics for the implementation of Least Burdensome requirements, we are required by statute to periodically assess the effectiveness of the training that we are required by statute to provide on Least Burdensome. So that is one part we have already had our initial report to Congress and we do have requirements on sort of periodically checking that.

And number two is the Least Burdensome Flag program which we just discussed we see as a key performance metrics for the implementation of Least Burdensome. And the reason why it's just for 510(k) submissions is that's where we see sort of these Least Burdensome issues being flagged by some of our stakeholders.

In terms of publicly available information. The FDA Report to Congress is already on the Web.

And in terms of any reporting on the use of the Least Burdensome Flag program that is something we will have to get back to you on.

Steven Silverman: Thank you for your response. We understand the points that you are making about mechanisms to evaluate application of Least Burdensome practices. And we will be very interested in seeing periodic reports of use of the Least Burdensome Flag like the information that you provided in today's webinar.

Joshua Silverstein: Thank you.

Coordinator: Thank you. Our next question comes from Allison Komiyama: Your line is open.

Allison Komiyama: Hello. Thanks for the webinar. I actually have two questions. The first one is, you mentioned that the Flag can be used for two specific topics are those being expanded now since the March 4 release or is that still going to stay within biocompatibility and sterility?

Joshua Silverstein: So biocompatibility and sterility are provided as examples of topic areas but those are not the topic areas that are restricted to you. So for example, if there was an issue related to nonclinical performance testing and electromagnetic compatibility those are examples of topic areas that would be included.

So if you did want to throw the Flag on say biocompatibility, sterility, electromagnetic compatibility and electrical safety that would count up to

four. And so that will be a little too much for the Least Burdensome flag program.

Allison Komiyama: Essentially putting burden on the Least Burdensome Flag. Okay. The other question that I had was you've mentioned that it's only allowed to be thrown within the first 60 days of the AI or then receipt of the AI whole letter.

If the sponsor feels like there is burden being placed on an interactive AI request that's done within the 30 days let's say of a 510(k), is that an opportunity as well to use the Flag in that scenario?

Joshua Silverstein: So do you mean - just so I can clarify. Do you mean the last few days of after responding to the deficiency letter?

Allison Komiyama: Yes. So typically we meet - to give you an example, we get a lot of toxicological risk assessment questions and we believe we adequately respond to them in the response letter and then we will get additional rounds of interactive requests for the toxicological risk assessment.

And each time we just feel like new questions are being asked and so I just wanted to know if that would be an adequate scenario where we could use the Flag.

Joshua Silverstein: Yes. So the Least Burdensome Flag is for the deficiency letter itself and one of the reasons for that is because it has already undergone management oversight as part of the sign-off process that we have here.

And so once you've responded to that letter you are a little bit out of the swim lane of the Least Burdensome Flag. But I would also just like to address another point from your question which is that you are kind of getting into a

very specific scientific issue -- and that's not really what the Least Burdensome Flag is about.

So to give an example of clinical testing. We typically would think the Least Burdensome Flag is for when, you know, FDA has requested a randomized controlled clinical study as part of the request for additional information and the sponsor does not agree with that request fundamentally.

A little bit different and I think it's more analogous to your situation as we don't think the Least Burdensome Flag is as applicable if you are disputing the clinical endpoint that's used as part of that study.

So it's really like a fundamental disagreement about the nature of that deficiency and not necessarily the nitty-gritty scientific aspects of it.

Hopefully that's helpful.

Allison Komiyama: Yes. It is. Thank you very much.

Joshua Silverstein: Thank you.

Coordinator: The next question comes from Nancy Cameron. Your line is open.

Nancy Cameron: Hi, also thank you for the webinar. It's very informative and one of my questions got answered already so thanks for the other questions.

And then I'm also knowing that you did say this applies to combination products and just wanted to clarify that that would include then requests that CDER is making that we feel are perhaps more than should be applied to a 510(k) product.

Joshua Silverstein: So I heard you until the last few words. Could you just clarify a little bit what you mean by a 510(k) product?

Nancy Cameron: So we have some combination products that are 510(k)s and yet in some of the interactions we have had CDER is applying their typical drug related requirements. And in some cases we feel that that's quite burdensome for a product that, you know, is not a drug product essentially, right?

Joshua Silverstein: Yes. Yes. I completely understand. So CDER is not formally signed onto this guidance however, they were consulted in the preparation of this guidance. And so device constituent parts of combination products being within the scope we do believe that there is space for Least Burdensome in that review.

Nancy Cameron: Okay. Thanks very much.

Coordinator: The next question comes from Jonathan Amaya-Hodges. Your line is open.

Jonathan Amaya-Hodges: Good afternoon. Thank you for the great webinar so far and I'm also speaking on my own behalf and on behalf of the Combination Product Coalition. So actually stemming off of the last question I'm glad this was opened up.

We do acknowledge and appreciate the fact that combination products are within the scope of this guidance. But I'm actually coming from a drug company angle where the submission would be NDA or BLA but we have a device constituent part to that product.

In those cases would Least Burdensome principles still apply and has there been any discussions on how that will be implemented from such products?

Joshua Silverstein: So as I said in the previous question device constituent parts of combination products are subject to the policy in this guidance. I'm not able to share any specific implementation efforts because they are not publicly available between CDER and CDRH though.

Jonathan Amaya-Hodges: Okay. Thank you.

Coordinator: The next question comes from (Jim Parineck). Your line is open.

(Jim Parineck): Hi, thank for taking my question and thanks for the webinar. We really appreciate it. My question is directed maybe at the software side of this whole guidance and one thing that was being discussed in Philadelphia - FDA had a great presence in one of the conferences there - and the pilot program was discussed in some detail.

And one of the questions that came up and I think continues to ring is FDA has made such great in-runs in terms of being relatively open to conversation, open to interaction, the relationships I would say have gotten much, much better.

There is a concern I think on the part of industry that the ability to throw a flag while useful in some situations could sour the relationship with the reviewer effectively going over their head. This may still be a useful technique to use at times.

But can you talk to that software side of the problem how and when and how do we ensure that this isn't just to going to sour reviewers on the relationship and make them fearful.

Joshua Silverstein: Yes. That's something that we have struggled with internally as you might expect as well. And so what I can say to that is we all have to be our own best advocates and so if you think that you have a legitimate issue I don't think that anyone internal to FDA is going to take it personally, you know, we are very professional and we are all public service oriented.

And so if there is a legitimate Least Burdensome issue that comes up in a submission I would expect that there will be no any kind of retaliation or sour relationship that you have been building over the last, you know, 2 to 10 years with a particular reviewer.

We are trying to get internally past the point where people take these kinds of decisions personally and it can be hard because there is a human aspect to it.

And so that's something that we are going to be working on internally and we hope that our external stakeholders are as well.

(Jim Parineck): So maybe the best practice there simply becomes to recognize that it isn't a completely neutral action to take but it is one in the tool box and everybody knows it and we act accordingly.

Joshua Silverstein: Yes. And just to expand on it a little bit more. You know, one of the conserved feedback - we did some internal meetings and surveys as well on this program and I didn't share in detail. But one of the points that we heard

from both external stakeholders and our staff was that everybody thought it was simpler and a lot less adversarial than an appeal.

And so many of our reviewers have gone through an appeal and that can be a lot more difficult and we thought that the Least Burdensome Flag kind of released a little bit of that tension both on the part of the submitter and as part of, you know, our staff.

(Jim Parineck): Because it sits in between the appeal and the (unintelligible).

Joshua Silverstein: Yes. It's kind of a - the Least Burdensome Flag is a way to sort of raise your hand before things get a little bit more hostile. And so I think that's - it's a really nice way to kind of just take a pause before we end up in an appeal situation.

(Jim Parineck): That's great clarification. Thank you so much and thanks for all the progress over the last few years.

Joshua Silverstein: Thank you.

Coordinator: The next question comes from (Francesca Curtis). Your line is open.

(Francesca Curtis): Hi, thanks for the presentation. It was very helpful. I have a couple of questions. So one is, so is a defici - so we receive a deficiency list and to make sure that I understand the process. If a deficiency list includes a deficiency we don't agree with so the step that would follow first is discuss this with a reviewer and the branch chief within that 10 days.

Then if we still can't agree on a resolution or we can't get an agreement at all then that's when we can further LB Flag, is that correct?

Joshua Silverstein: In general, that's correct, except for the 10 day part. So you do have 60 days and there is a sort of a menu of options that you can take and we have kind of left it to our external stakeholders to figure out what's the best option for them.

So to take the day 10 call is one of the options that could take. There is also the submission issue meeting. And also just an informal teleconference with the signatory authority is another option.

And so we are not being prescriptive in what you are doing but we just want to make sure that a reasonable effort has been taken to resolve the issue at the level at which the decision was rendered initially.

(Francesca Curtis): Got it. Okay. That's helpful and that clarifies it. Thank you. And my next question is will this end up - at least I was told when a reviewer - how sometimes depending on who the reviewer is they can have different opinions or recommendations.

Does the LB Flag sort of correct that or addresses that? Because I was told it was, like, well, think of a police, like, where - this is from a reviewer that if you are driving in a street and there is no police there it doesn't mean you are not speeding. And then if all of a sudden if a police is there and then you are speeding.

I mean, it sort of goes into depending on who the reviewer is you may get a different opinion.

Joshua Silverstein: I think that - I think that that perception is out there. Just one of the things I'd like to note is that even if you have a different reviewer between let's say

two different 510(k)s for a pretty similar product typically the manager who is signing off on that decision would be the same.

And so I can't really speak to that particular part. I will say that if there is a fundamental difference of opinion about a deficiency, the Least Burdensome Flag is the right program to use.

(Francesca Curtis): Got it. Okay. Thank you.

Coordinator: Our next question comes from Rebecca Miller. Your line is open.

Rebecca Miller: Yes. And I apologize if you've already said this, but I know we are mostly talking about 510(k)s here so is the Least Burdensome Flag also applicable to a PMA deficiency or a PMA supplement deficiency?

Joshua Silverstein: So the Least Burdensome Flag is only applicable to 510(k) submissions and we chose that in response to a lot of the feedback that we got both internal and external. And it's really just because that is the most down-delegated decision that we have in the Center whereas there is a lot more scrutiny around PMA and De Novo submissions.

Rebecca Miller: Okay. And then as far as, like throwing the Flag as you put it is there any guidance around on how to do that? Is that simply an email? Is that a written request? How is that?

Joshua Silverstein: So I have two elements of good news for you. One is that it's in the webinar slides so you can refer back to that.

Rebecca Miller: Okay.

Joshua Silverstein: And then two instructions for using the east Burdensome Flag are also included in each 510(k) request for additional information.

Rebecca Miller: Perfect. All right. Thank you.

Joshua Miller: Thank you for your question.

Coordinator: As a reminder you can press star 1 on your phone and record your name if you have a question. One moment please for any additional questions. We do have questions coming in. One moment please.

The next question comes from Kirsten Paulson. Your line is open.

Kirsten Paulson: Hi, thank you for this webinar. I'm very interested in the fact that you are putting on a program we are throwing in this flag after only two companies or two programs have done it. And were there any learnings even from that small sample size too that you were using to change the program or to change training since you have some ideas on why the number was so low?

Joshua Silverstein: So there can be a few reasons for that number being low. One is that in most situations we are being Least Burdensome and another option is that there could have been some resistance or hesitancy to use the flag.

And so maybe I think to number two there could be some resistance. We kind of already talked about that with one of the previous questions. And so we are providing an opportunity and if our stakeholders don't want to take that opportunity we are not really sure what else we can do to help you in a quick manner resolve Least Burdensome issues that come up from time to time.

I guess - does that answer your question?

Kirsten Paulson: More or less it just - I wonder about the value of the program that only two people have used it so far and I guess that remains to be seen.

Joshua Silverstein: Yes. I mean, part of the utility of this program is that GO - GAO recommended that we implement Least Burdensome metrics and we believe that this is an excellent way to do it in a Least Burdensome way for both industry and the FDA.

I mean, it kind of gets us to a point where we are having these really critical discussions about the validity of a request earlier in the review in the cycle rather than waiting for an NSE decision and then an appeal.

So it's allowing for us to sort of hit two birds with one stone. I just recalled that you also asked a little about changes between the pilot and the final.

And there was a little bit of hesitancy for some of the respondents with expired flags because they thought that the issue was being raised at such a high level that they were concerned about soured relationships.

And so the delegation for the Least Burdensome Flag is one level lower than it was in the pilot in the final program. And so the position right now would be Office of Device Evaluation Division Director even though our reorganization will be happening fairly soon.

Kirsten Paulson: Okay. All right. That's helpful. Thank you.

Joshua Silverstein: Thank you for your question.

Coordinator: The next question comes from (Edward Tidal). Your line is open.

(Edward Tidal): Thank you. Good seminar. And I think the Flag program sounds like a really good opportunity. One reason I kind of suspect that not as many people threw the flag as you might have is because as others have mentioned, it's been easier recently -- I believe -- to gain help and assistance from senior management without necessarily using a formal process and they have been quite helpful.

The one question I did have though is since it's a very new program some 510(k)s have been pending a for a good while and they have AIs that have been out there for a while and somebody might feel that they are burdened by fairly more so than is appropriate.

And so my question is for those 510(k)s and AIs that have been there for a while and that have already gone past the normal timeline for this is there any plan to accommodate for those? Obviously the timeline has worked very well for new AIs that come out since the program started.

But I wonder about those AIs or 510(k)s that may be out there in the past and perhaps it's kind of mute because many of those already have through informal means gotten some feedback and attention from senior management. But I appreciate your feedback on that.

Joshua Silverstein: Thanks for your question. So there are no immediate plans to extend - excuse me. There are no immediate plans to extend the Flag program to 510(k)s with request for additional information that were sent before March 4.

And one of the reasons why is that we don't want to set submitters up for failure. You know, we have the 60 day deadline for using the Flag and that day was very precisely chosen to fit into the 180 day response time that we have required for responding to our 510(k) deficiency letters.

And so to open the Flag up for those submissions we might be putting people in a place where they might end up with their 510(k)s being deleted or being NSEEd because they weren't given sufficient amount of time to provide additional information or performance testing to establish substantial equivalence.

(Edward Tidal): So that makes sense. I was just curious. Thank you.

Joshua Silverstein: Yes. Thank you for your question.

Coordinator: The next question comes from Katie Ferraro. Your line is open.

Katie Ferraro: Hi, my question is about the use of peerreviewed literature for Least Burdensome source of clinical data for expanding indication for use in a 510(k).

If peer-reviewed literature is used in this manner would it be FDA's expectation that that peer-reviewed literature was kind of not owned by the submitter of the 510(k) but that the submitter played a role in the publication of that data and may have the raw data available?

And in addition could peer review literature be the primary basis for extension and indication kind of as the main driver for that submission?

Joshua Silverstein: Okay. So you are - just so I can repeat your question back to you. One is, can the sponsor of the submission also have been involved in the...

Katie Ferraro: No. No. I'm asking is it FDA's expectation that the sponsor may have the raw data for that peer reviewed paper? Or is kind of the - if the peer reviewed article that is totally outside the scope of the submitter?

Joshua Silverstein: So I don't think it's an absolute yes or no answer. It will probably depending on the particular literature article that you are referencing. And so I think just as a best practice if you would like to take that route I definitely recommend reaching out to the reviewing division to kind of talk out what you are thinking.

But in terms of the second part of your question, has peer-reviewed literature ever been as the primary basis for expanded indications in a 510(k)? The answer is, yes.

We do have some examples of the use of literature in the final guidance and I would recommend taking a look at those summaries and hopefully they have the information that you are looking for.

But will definitely recommend early communication with the reviewing division if you would like to use that route.

Katie Ferraro: Okay. Thank you.

Joshua Silverstein: Thank you.

Coordinator: And again if you would like to ask a question at this time you can press star 1 on your phone and record your name when prompted.

One moment please for any additional questions. The next question comes from (Norman). Your line is open.

(Norman): Hi, just a quick question regarding the Burdensome Flag could that apply to the Pre-Sub process during the Pre-Sub discussions with CDRH with 510(k)s?

Joshua Silverstein: No. So the Least Burdensome Flag only applies to request for additional information or deficiency letters that are sent as part of a 510(k) submission.

In terms of what pre-submissions are, you know, that's just FDA's best feedback based upon that information that's provided at that time.

(Norman): Thank you.

Joshua Silverstein: Thank you.

Coordinator: We show no further questions at this time. I will now turn the call back over to Ms. Irene Aihie.

Irene Aihie: Thank you. This is Irene Aihie. We appreciate your participation and thoughtful questions. Today's presentation and transcript will be made available on the CDRH Learn Web page at www.fda.gov/straining/cdrhlearn by Friday March 22.

If you have additional questions about today's presentation please use the contact information provided at the end of the slide presentation. As always we appreciate your feedback.

Following the conclusion of today's webinar please complete a short 13 question survey about your FDA CDRH webinar experience. The survey can be found at www.fda.gov/cdrhwebinar immediately following the conclusion of today's live webinar.

Again thank you for participating. This concludes today's webinar.

Coordinator: Again that does conclude today's conference. Thank you for participating. You may disconnect at this time.

END