

**FDA Webinar: Combination Product Updates for “Acceptance and Filing Reviews for
Premarket Approval Applications” and “Refuse to Accept Policy for 510(k)s”**

**Moderator: Irene Aihie
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Coordinator: Welcome and thank you for standing by. Today's call is being recorded. If you have any objections, you may disconnect at this time.

All participants will be on a listen-only mode for the duration of the call. During the question and answer period if you would like to ask a question please press Star one. I would now like to turn the call over to (Irene Aihie).

(Irene Aihie): Hello...and welcome to today's FDA webinar. I am (Irene Aihie) of CDRH's Office of Communication and Education. On January 30th the FDA updated two final guidances. Refuse to accept policy for 510(k), and the Acceptance and Filing of Use for Pre-Market Approval Application.

The purpose of the guidances is to explain the procedures and the criteria the FDA intends to use in accepting or refusing a 510(k) or PMA submission. It includes checklists to identify the necessary elements and content of a complete application.

Today, James Bertram, Policy Analyst from the Office of Device Evaluation here in CDRH, will present an overview of the updates to the final guidances. Following the presentation, we will open the line for your questions related to information provided during the presentation.

Additionally, there are other Center subject matter experts here with us today who will assist with the Q and A portion of our webinar. Now I give you James...

(James Bertram): Thank you Irene for the opening comments and introduction. My name is James Bertram and I'm a Policy Analyst in CDRH's Office of Device Evaluation.

As Irene just informed you -- if you were not previously aware -- on January 30 of this year we updated two guidances as it pertains to our continued implementation of the statutory provisions associated with the 21st Century Cures Act. Specifically, the acceptance and filing a review for PMA applications guidance and the Refuse to Accept policy for 510(k) guidance.

All right, the intent of today's webinar is to explain the agency's recommendations regarding recent updates to these guidances. Twenty-first Century Cures -- or Cures -- amended the Federal Drug and Cosmetic Act to now require sponsors of combination products to appropriately self-identify their product as such.

Furthermore, if the product is a device-led combination product and it includes a drug constituent that has been previously approved by CDER -- which means the drug is listed in the orange book -- the sponsor must provide the appropriate patent certification, or statement as well as consider whether any new drug applications -- or NDA -- is protected by any exclusivity.

If so, this may affect the agency's ability to approve or clear the submission. As articulated in the two aforementioned guidances, FDA has updated its Refuse to Accept -- or RTA -- checklist to take into account these provisions, helping us to ensure the necessary information is present for the agency to

initiate review of your submission. I want to remind our listeners; these provisions only apply to combination products.

Today's webinar will begin with an outline of a number of provisions enacted under 21st Century Cures on December 13, 2016. After a brief introduction to these provisions we will provide an overview of your responsibility to accurately self-identify your product as a combination product, the need to include appropriate drug patent information in your submission, and ultimately the need to consider drug exclusivities that may have been previously granted by the agency for your drug constituent part.

We will then identify our intended review practices considering these provisions, provided - provide four case studies as examples, and take things home with a summary of what we've heard today. At that point we'll open the webinar up for participant questions.

Let's start with introductions. First a little history on the existence of the patent and exclusivity provisions currently in Section 505 of the Federal Food and Drug Cosmetic Act.

In 1984 Congress enacted the Drug Price Competition and Patent Term Restoration Act, which many know as the Hatch-Waxman Act. This included the first statutory provisions expressly pertaining to generic drugs, which created the basic scheme under which generic drugs are approved today.

Overall, Hatch-Waxman intended to encourage and speed the entry of generic drugs to market while at the same time providing additional protections to innovators of the listed drug. While we could arguably hold a separate webinar to discuss the Hatch-Waxman Act, for our interests with today's webinar it provided clarity regarding two aspects.

Drug exclusivities granted by the agency as well as patent protections and associated duties of both the innovator and subsequent applicants. Exclusivity is unique from patent protections and provides certain innovators limited protection from new competition for a prescribed period of time.

Meaning it could preclude submission of an NDA under Section 505(b) (2) or an NDA under Section 505(J). Regarding patent protections, Hatch-Waxman allowed innovators to submit relevant patents to the FDA for listing in the orange book. The orange book being a public repository that includes drug products approved by the agency.

It also includes listings of any applicable exclusivities and submitted patents for the listed drug. In turn, applicants of 505(B)(2) applications and ANDAs must certify to the patents listed for the relied upon listed drug.

For those new to this concept, patents and exclusivity work in a similar fashion but are distinct from one another and governed by different statutes. Patents are a property right granted by United States Patent and Trademark Office any time during the development of a drug and can encompass a wide range of claims.

Exclusivity refers to certain delays and prohibitions on approval of competitor drugs available under the statute that attach upon approval of a drug or of certain supplements. Periods of exclusivity and patent terms may or may not run concurrently.

Exclusivity was designed to promote a balance between new drug innovation and greater public access to drugs that result from generic drug competition. So, what did Cures do? It applied a number of these Hatch-Waxman

provisions -- of particular note those associated with drug patent and exclusivities -- to device-led combination products which contain a drug constituent.

As such we have updated our PMA and 510(k) RTA checklists helping to ensure that we have adequate information to not only initiate a review, but also helping to ensure consistency with these new provisions. Please note -- while the RTA updates apply to submissions received on or after April 2, 2018 -- the provisions have been in effect since December 13, 2016.

Since that time the agency has been considering appropriate processes for implementation. During this process -- to ensure consistency with the law -- CDRH has been checking submissions to determine if the drug constituent has unexpired patents or exclusivities for which an appropriate right of reference has not been provided.

Going forward CDRH is implementing processes to correct the necessary patent certifications -- and when appropriate patent statements -- from sponsors. These processes are believed to be consistent with the provisions in Cures. For purposes of our discussion and focus, the specific amended sections of 503 G are included here for reference.

Just to remind you, the first bill applies to all combination product types, not just those with a drug constituent part. Said another way, if you submit a combination product you are responsible for accurately self-identifying your product as a combination product.

Where Cures becomes a little more nuanced is the applicability of the second and third bullets to device-led combination products which include a quote

unquote approved drug. And approved drug is uniquely defined in Section 503(G). It is an active ingredient that meets all of the following criteria.

First, it must have been previously approved under Section 505(C). In other words, it was previously approved under a New Drug Application -- or NDA - - and thus is a listed drug in the orange book. Second, the sponsor submitting the application must rely upon the listed drug. A sponsor is believed to rely upon a listed drug if the sponsor themselves does not conduct and provide full reports of investigations that have been made to show whether the drug is safe and effective. And for which a right of reference is not obtained from the NDA holder for the listed drug.

As a general matter, if the drug is listed in the orange book we anticipate the sponsor submitting the application for the combination product would not provide a complete data set to reestablish all aspects of the safety and effectiveness of the drug. And therefore, would be relying upon the listed drug.

So, what submission types for your combination product should you consider the provisions? This would be all 510(k) types, de novo requests, original PMAs as well as PMA supplements including panel track, 180-day, and Real-time. As you probably realize, this includes submission types without an RTA checklist.

Section 503(G) is not limited to those submission types with RTA checklists. Therefore, we recommend you provide similar patent information and consider exclusivities for submissions with and without an RTA checklist.

For submissions without RTA checklists, staff will be evaluating whether these provisions are addressed and may request information accordingly.

Identification of combination products. The cited language from Section 503(G) is included here for reference as it pertains to a sponsor's responsibility to accurately self-identify their product as a combination product.

According to Section 503(G), whenever seeking agency action with respect to their combination product, a sponsor must identify the product as a combination product. Again, just a reminder, unlike the provisions associated with drug patents and exclusivity, this applies to combination products comprised of any combination of a drug, device, or biologic constituent part.

Although this is ultimately the responsibility of the sponsor, the agency will be verifying to ensure the sponsor's identification is accurate. If (such) identification is not included or is inaccurate -- for submissions with an RTA checklist -- this will be grounds for an RTA1 decision. For submissions without an RTA checklist, this would likely result in a request for additional information.

Now for a quick refresher on combination product classification and jurisdictional assignment. According to 21 CFR 3.2 there are technically four different types of combination products. The most common types being those that are physically or chemically combined or co-packaged together.

Less common are those that are sold separately but uniquely labeled for use together. While such classes of combination products may be submitted under a single application, it is somewhat common place for concomitant submissions to be submitted one to CDRH and then one to CBER or CDER.

In instances where there are concomitant submissions to two centers, reviewers of the device alone submission will select Not Applicable in the

RTA checklist for the question as to whether the product contains and approved drug as a constituent part.

If you are uncertain as to whether your product contains a drug constituent part and is potentially a combination product, in September of 2017 -- in collaboration with the centers -- the Office of Combination Products -- or OCP -- finalized its guidance on classification products such as drugs and devices.

This guidance provides clarity regarding the device exclusionary clause in Section 201(H)(3) of the Food and Drug and Cosmetic Act, cited here for reference. Notably this guidance provides the agency's interpretation of chemical action as well as primary intended purposes.

The Office of Combination Products is the agency entity responsible for adjudicating product classification and jurisdiction. Classification here meaning device, drug, biologic, or combination product. Not Class One, Two, or Three, which our audience here may be a little more familiar with.

If determined to be a combination product, the agency will first look to ascertain the primary mode of action of the product. This is the single mode of action of the combination product that provides the most important therapeutic action of the combination product.

For combination products regulated in CDRH based on PMOA, the device would be considered to provide the primary mode of action. However, in some instances the PMOA cannot be determined. And in such cases, we turn to the assignment algorithm. The first tier being center assignment based on which center regulates products rating similar questions of safety and effectiveness.

When there's no similar products OCP will then look to the second tier of the algorithm and assign the product to the center with the most expertise to evaluate the most significant safety and effectiveness questions raised by the product as a whole. Included here are a couple examples of combination products assigned based on PMLA.

The first example is a product that most of our audience is likely aware of, a drug-eluting stent. This is a combination product assigned to CDRH based on PMOA being that of the device, with the role of the coated drug in preventing (restenosis) being secondary.

The second example is a drug-eluting disc. The product is assigned to CDER. The PMOA was concluded to be that of the chemo-therapeutic drug, with the device being secondary as simply a means to ensure the sustained local delivery of the drug.

I'm not going to go through this list in totality, but included here for reference are some of the more common combination product types seen in CDRH. Assigned either on PMOA or via the assignment algorithm.

In summary, to ensure compliance with the provisions set forth in Cures -- regarding combination product self-identification -- we recommend that you include a statement in your cover letter and product description that basically states that you identify your product as a combination product.

This also facilitates our staff's review and effort to verify this expeditiously during the RTA phase. To further facilitate our review of the other provisions, if your product contains drug constituent parts we recommend you identify each of them in your product description section as well.

Ultimately, if unable to locate and identify the self-identification language in your submission, CDRH may RTA1 your submission or request additional information accordingly. If you have any questions as to whether your product is a combination product under CDRH purview, please feel free to reach out to CDRH at the cited inbox or the Office of Combination Products at combination at FDA dot gov.

Now on to an overview of the patent provisions. The cited language from Section 503(G) is included here for reference as it pertains to a sponsor's obligation to provide an appropriate patent certification or statement if their product contains an approved drug as previously defined.

With regard to responsibility to provide an appropriate patent statement or certification, you should first determine whether your active ingredient has been previously approved by CDER. This can be ascertained by searching the orange book. If listed, then the answer would be yes and you should identify a listed drug under an NDA for which you rely.

Depending on the status of any listed patents you should provide an appropriate statement or certification for each of the patents listed for the particular listed drug. Alternatively, a right of reference from the NDA holder may be provided in place of a patent statement or certification.

If you include a right of reference we ask that you state such in the cover letter of your submission, include or identify its location in the submission. This will greatly facilitate our review of ensuring compliance with these provisions.

You may be wondering what exactly patent certifications are. For each relied upon listed drug you provide either a statement that there are no relevant patents -- if appropriate -- or you provide one of the following four certifications to each listed patent in the orange book for the particular listed drug.

Paragraph One Certification may be appropriate if there are no patents listed in the orange book for the listed drug. A Paragraph Two Certification may be appropriate if there's either no patent listed -- as sometimes patents are delisted from the orange book after a period of expiration -- or the listed patent has expired.

A Paragraph Three Certification applies to situations when a sponsor intends to submit their application for review but fully appreciates the product won't be able to be fully approved for marketing authorization until the patent has expired. Finally, a Paragraph Four Certification is basically an assertion by the sponsor that the unexpired patent is invalid, unenforceable, or will not be infringed upon by the product for which the application is submitted.

When providing a Paragraph Four Certification a sponsor must provide notice to each owner of the patent and the NDA holder and include a statement of such certification. The Paragraph Four Certification is further described in Section 50 (B)(2) of the Federal Food and Drug Cosmetic Act.

After such notification each owner or holder of the patent has up to 45 days to file infringement suit. If the infringement suit is filed, this may stay the approval for up to 30 months. From an implementation standpoint, CDRH intends to RTA1 applicable combination products with submissions that do not contain appropriate patent certifications or statements.

As alluded to in the previous slide, if a Paragraph Three Certification is provided, CDRH cannot grant final clearance or approval until the patent has expired. And if a Paragraph Four Certification is provided, CDRH must wait 45 days before rendering a Marketing Authorization decision in case a suit is filed within the 45 days of notice. As previously stated, if an infringement suit is filed within the 45-day window, CDRH will delay clearance or approval for up to 30 months.

Recapping the patent provisions. If these provisions are met this means there is no attributed delay in approval or clearance when either the submission does not contain an approved drug -- that is it's not listed in the orange book -- or a right of reference by the NDA holder is provided in the submission.

Or a complete data set to establish safety and effectiveness of the drug is included in the submission. Again, we believe this scenario to be rare if the drug is listed in the orange book. Or an appropriate No Relevance statement patent or Paragraph One or Two Certification is provided.

Very briefly, the exclusivity provisions. The cited language from Section 503(G) is included here for reference as it pertains to the agency's obligation to consider any existing exclusivities for the approved drug as previously defined.

With regard to roles and responsibilities with drug exclusivities, you do not need to provide information related to exclusivity. The onus is on the agency to check for any existing exclusivities that may apply to your drug constituent.

That being said, we do recommend you be aware of any unexpired exclusivity that may be associated with your relied-upon listed drug. These too would be listed in the orange book under the NDA for the listed drug. Just a reminder --

as touched on in the introduction -- patents and exclusivity work in a similar fashion but are distinct from one another. If you have any questions or concerns regarding potential exclusivities, please don't hesitate to contact us at the listed inbox.

Here's CDRH's planned implementation procedures. From an implementation standpoint, CDRH will evaluate information related to these provisions at two stages in the review. At the beginning -- in the RTA phase -- as applicable. And then prior to clearance or approval. The second check -- prior to clearance or approval -- is necessary as the orange book is updated regularly and the patent and exclusivity landscape for the listed drug may change over the course of the product's review.

In addition, this practice is consistent with CDER's consideration of the orange book and the context of the review of NDAs and ANDAs. If determined to be inadequate during the RTA phase -- meaning the provisions are not met -- submission will likely not be accepted and an RTA1 decision will be made.

An RTA1 outcome may also occur if it's determined that the submission or ultimately marketing authorization is blocked by existing patents and exclusivities. If determined to be inadequate at the end of the review -- meaning prior to clearance or approval -- CDRH may not be able to issue a clean clearance or approval.

And the product could not be marketed until you either submit to the agency appropriate information addressing the outstanding patent -- or for exclusivity -- a letter of reference. Or the blocking conditions expire. And again, please remember that -- while RTA updates apply to submissions received on or after April 2, 2018 -- evaluation of the patent and exclusivity provisions prior to

clearance or approval has been in effect for submissions received on or after December 13, 2016.

So here are a few theoretical case studies that may represent combination products in CDRH. Just a reminder, the following are considerations that will influence your obligations as a sponsor and CDRH will be evaluating for adequacy. This includes your self-identification as a combination product and if inclusive of a drug constituent, whether it is listed in the orange book and subject to any unexpired patents or exclusivities.

The first case study, you have a combination product that includes a device coated with Drug A. Relevant background regarding Drug A is that the listed drug was approved under NDA let's say in this case zero one two three four five. Most notably there are no unexpired patents and no unexpired exclusivities.

As a sponsor your responsibility is to self-identify your product as a combination product, preferably in the cover letter and product description. Next you would be required to provide either a Paragraph One Certification, a Paragraph Two Certification, or a right of reference to the NDA holder. This too would be preferably identified in the cover letter.

Included here is example language say for a Paragraph One Certification. This could include the following. Paragraph One Certification to the specific NDA, to the best of our knowledge no patent information has been submitted to the FDA.

Case study two. You have a combination product that includes a device coated with Drug B. Relevant background regarding Drug B is that the listed drug was approved under NDA five four three two one zero. Notably there

are no unexpired exclusivities for Drug B, however there is a patent that does not expire until February 2, 2020.

Similar to Case Study One, your responsibility is to appropriately self-identify your product as a combination product. However, unlike the previous example, because of this unexpired patent you would now be required to provide a right of reference from the holder of the listed NDA. Or you will need to submit a Paragraph Three or Four Certification. Please be reminded though, submission of a Paragraph Three or Four Certification may delay clearance or approval of your product.

Case Study Three. You have a combination product that includes a device coated with Drug C. Relevant background regarding Drug C is it is not listed in the orange book. Therefore, your only obligation is to technically self-identify your product as a combination product.

A list of the extent of your obligation ensuring compliance with provisions discussed today, we recommend that you go one step further by not only identifying the drug constituent but also clarifying in your cover letter that the drug is not listed in the orange book. This too will assist staff in our review of your submission during the RTA phase.

All right, we're almost done. So maybe people on the East Coast will be able to get home before the roads get too bad. So Case Study Four. You have a combination product that includes a device coated with Drugs D and E.

Relevant background (of) Drug D is the listed drug was approved under the listed - the cited NDA. For Drug E, this was approved under another NDA. For both drugs there are no unexpired patents and no unexpired exclusivities.

As a sponsor your responsibility is first, again to self-identify your product as a combination product.

Next you will be required to provide either a Paragraph One Certification, a Paragraph Two Certification, or a right of reference to both NDAs. This too would preferably be identified in the cover letter. So example language for say a Paragraph Two Certification could include the following.

Paragraph Two Certification to the cited NDAs -- again noting both of them -- to the best of our knowledge. Patent information that has been submitted to the FDA has expired. In summary, the aforementioned provisions do not apply to your product if it is not a combination product.

However, if it is the provisions would be met if you first appropriately identify your product as a combination product and one of the following criterion apply. Your product contains a drug component that has not been previously approved by CDER -- i.e. not listed in the orange book -- or a right of reference is provided the NDA holder on your behalf.

Or a complete data set is included that establishes the safety and effectiveness of the drug. Again, we believe this to be rare if the drug is listed in the orange book. Or finally, there's no unexpired exclusivity for the relied upon listed drugs, there are no unexpired patents, and you provide an appropriate patent statement or certification for each of the listed patents.

On the contrary, if provisions are not met and or marketing authorization may be delayed if you do not appropriately identify your product as a combination product. Or your drug contains a drug listed in the orange book and you do not provide an appropriate patent certification statement or right of reference.

Or you provide a Paragraph Three Certification or Four Certification to unexpired patents listed for the relied upon listed drug. Or there's unexpired exclusivity and that affects the submission.

As you research further responsibilities and considerations associated with a future combination product submission, these resources may prove helpful and potentially answer some questions that that came to mind during the presentation. Please note, CDRH is looking into developing a CDRH website for stakeholders consolidating applicable combination product information and linkages to already existing FDA resources.

As I noted throughout the presentation, please don't hesitate to reach out with any questions to the CDRH (product jurisdiction) inbox. With that, this ends the presentation portion of the webinar. And I believe we'll be opening the line for questions.

Thank you for your attention and I hope this information proves useful in your upcoming combination product submissions.

Coordinator: We will now begin our question and answer session. If you would like to ask a question, please press Star one from your phone and unmute your line, speaking your name clearly when prompted. If you would like to withdraw your question, please press Star two.

Again, if you would like to ask a question please press Star one from your phone and speak your name clearly when prompted. One moment while we wait for the first questions.

(James Bertram): For the Q and A portion I want to introduce my colleagues in the room. I have Dr. (Andrew Yeatts), Policy Analyst and Jurisdictional Officer for

CDRH. I also have with me Ms. (Nisha Shah), who's a Regulatory Counsel in the Office of Regulatory Policy from the Center for - Drug Evaluation Research.

Also while we're waiting for questions to come into the queue, here's some - we'll go through some questions that we've received to date. So one being what if there is an unresolved patent or exclusivity issue at the end of the review?

CDRH would not be able to issue a clean approval or clearance. And the product could not be marketed until you either submit to the agency appropriate information addressing the outstanding patent. Or -- for exclusivity -- the right of reference. Or the blocking conditions expire.

Another question has been, my combination product was approved after December 13, 2016, but I did not provide a patent certification statement. Why now? Since December 2016 the agency has been considering appropriate processes for implementation of the respective provisions.

During this process to ensure consistency with the law, CDRH has been checking submissions to determine if the drug constituent has unexpired patents for which an appropriate right of reference has not been provided. Going forward, CDRH is implementing processes to collect the necessary patent certifications and where applicable statements from sponsors consistent with the Cures provisions.

Another question. Are patents and exclusivities approval clearance issues if I do not rely upon a listed drug in the orange book? No, because the patent exclusivity provisions apply only if you relied upon a listed drug or an active ingredient.

However -- as a general matter -- if the drug is listed in the orange book we recommend that you provide the appropriate patent certification or statement or right of reference as we anticipate that the application would not provide a complete data set to reestablish all aspects of the safety and effectiveness of the drug.

A complete data set to establish safety and effectiveness of the drug or right of reference would however obviate the need to certify to patents or wait for exclusivities to expire.

(Irene Aihie): Well take the other questions. We'll take our first question.

Coordinator: (Rhona Shanker), your line is now open.

(Rhona Shanker): Thank you. If - your - you keep saying that the product has to be declared as a combination product. If we have gone to the Office of Combination Product and FDA said it's a device but CDER will weigh in on the review process, is that considered a combination product?

(James Bertram): No. Technically if you have a determination from the Office of Combination Products that has clarified that you only have a device that would not be a combination product. It is relatively regular practice for the centers to reach out to the other centers for subject matter expertise.

So if you have a determination from OCP that your product is just a device then you would not be a combination product and would not be subject to these provisions.

(Rhona Shanker): Thank you.

Coordinator: As a reminder if you would like to ask a question please press Star one from your phone and unmute your line. If you would like to withdraw your question, please press Star two. One moment while we wait for any further questions.

(James Bertram): Well as we wait for other questions, another question that we've received. What if the drug is listed in the orange book under an ANDA? Can I certify to the ANDA? Very simply, no. You must certify to one approved under NDA. All right, looks like that may have stimulated another question?

Coordinator: One moment please. Our next question comes from (Liz Diamotto). Your line is open.

(Liz Diamotto): Hi. We currently have a device right now that's filed with CDRH. It's a device but it's classified as a combination product with CDRH.

It does not technically contain a drug but you can only use this device with a drug that's been reviewed on the CDER side. But the device doesn't come - it's not packaged with this drug. So will this fall into this classification for having to include patent certifications?

(James Bertram): May I ask a clarifying question?

(Liz Diamotto): Sure.

(James Bertram): It sounds like you have a separate NDA approval for the drug that your device is intended to be used with?

(Liz Diamotto): Yes.

(James Bertram): And it's not technically part of your product, so it's not co-packaged and not...

(Liz Diamotto): No.

(James Bertram): ...physically or chemically combined? Then...

(Liz Diamotto): No.

(James Bertram): ...no, these provisions would not apply. And that I believe I attempted to speak to that in an earlier slide.

(Liz Diamotto): So if we currently have a 510(k) already on this device and we need to submit another - basically an - another 510(k) for the same product -- because we're changing maybe the indication -- we don't have - it's not - I don't have to consider this a combination product? Even though the original 510(k) is classified as a combination product with CDRH?

(James Bertram): So technically your only obligation here would be to appropriately identify your product as a combination product.

(Liz Diamotto): Okay. So I would just state in the cover letter that we are combination product and that's it.

(James Bertram): Yes.

((Crosstalk))

(Liz Diamotto): Okay.

(James Bertram): ...it may help to further clarify your situation specifically to help the reviewer.
But...

(Liz Diamotto): Okay.

(James Bertram): ...your only - from what you said it sounds like your only obligation here
would be to appropriately ID.

(Liz Diamotto): Okay. And there's no requirements for any type of patent certifications to be
submitted? Is what...

(James Bertram): Correct.

(Liz Diamotto): ...I understand. Okay. Great. Thank...

(James Bertram): Because it was separately submitted to CDER under an NDA.

(Liz Diamotto): Okay. Thank you.

Coordinator: Again, if you would like to ask a question from the phone please press Star
one from your phone.

(Irene Aihie): Looks like we have one question...

Coordinator: Our next question comes from (Lena Cantos). Your line is open. (Lena)?
Your line is open.

One moment while I get the next question. And our next question comes from
(Nancy Cameron) with Medtronic.

(Nancy Cameron): Hello. I'm wondering, if you do the orange book search and all of the NDAs that come up with your drug are listed as D-I-S-C-N -- which I'm assuming means discontinued -- do you still have to make any designation? Or can you just state that in your cover letter that all your - all the applicable NDAs are discontinued?

(James Bertram): Thank you for the question. So you would still appropriately identify as a combination product. You would still need to provide the appropriate certification. So that would be you identify one of the NDAs, that is identified as discontinued and that you relied upon. And that you would provide either a Paragraph One or Paragraph Two Certification statement.

(Nancy Cameron): Okay. Thank you.

(James Bertram): Yes.

Coordinator: And our next question comes from (Simir Shah), your line is open.

(Simir Shah): I wanted to clarify what I thought I heard you tell a previous speaker. Did you say that if it's a single entity combination product or a co-packaged combination product then one has to do the patent certification? But if it's a cross-labeled combination product -- where they're sold separately -- then one does not have to do the patent certification?

(James Bertram): Correct. Because arguably if you're doing a cross-labeled that's assuming that there were concomitant submissions. You would have had CDER who would have considered the appropriate patents and exclusivities in the context of the NDA.

(Simir Shah): Okay.

(James Bertram): Does that answer your question?

(Simir Shah): Yes, that does.

Coordinator: Next we have a question from (Anne Leonard). (Anne), your line is open.

(Anne Leonard): Hi. I'm going to try to articulate this clearly, but this is looking forward. And it's kind of - well it does involve biologics. And potentially impacts to combination products that contain a device and a biologic and not necessarily a therapeutic biologic. But a biologic maybe such as insulin.

I'm aware that you know, most of these biologics, some of them that were approved under NDAs will be converted to BLAs around 2020. And I think -- with this legislation and another piece of legislation -- we now have the follow on biologics element.

And I was wondering if you can speak to something that might be emerging that is similar to like the use of the 505 (B)(2) in the RLD scheme for drugs. If that's going to evolve in some manner for biologics? I'm not sure if you heard me.

(Irene Aihie): We heard you. Just one second while we get that answer for you.

Coordinator: While we're waiting again if you would like to ask a question from the phone line please press Star one from your phone.

(James Bertram): Okay, can you hear me? Hello, (Anne), can you...

((Crosstalk))

(Anne Leonard): Yes, I can hear you.

(James Bertram): ...okay. Hi, thank you...

(Anne Leonard): Yes, I can.

(James Bertram): ...sorry. Thank you for your patience. So we'll probably likely recommend you follow up to the CDRH product jurisdiction inbox with your question. But our current thinking right now -- just on a quick discussion -- is that you would likely comply with the provisions.

Given that these biologics that are currently under NDA, you would provide the appropriate sort of patent certification statements. Regarding the point at which they become BLAs, then these provisions do not apply. Again to biologics as these provisions are exclusive to drug constituents.

I think your question regarding sort of future plans for 505(B)(2) et cetera is somewhat out of the scope of this discussion. But again I would ask that you - include that in your email and reach out we can either clarify our response or provide additional information as we've had a little more time to think about what you have.

(Anne Leonard): Okay. Thank you.

Coordinator: Our next question comes from (Xin Wong), your line is open.

(Xin Wong): Yes, hi. My question is so we have a combination product approved under PMA. The question is if we make changes to this product that there's - that's

not drug related, do we need to include patent certification in the PMA supplement?

(James Bertram): So, thank you for your question. That depends on the modification and the supplement type. So yes if let's say the modification you're making just to the device constituent necessitates a 180-day supplement. Then arguably you would need to provide that information in that submission, even if it's not a change to the drug constituent.

(Xin Wong): Okay. So but if it's like RTR or 30-day notice do we still need to do that? Or it's only limited to 180 day PMA?

(James Bertram): Sorry, that's correct. That's what the - I forgot the exact number on the slide. But so for example if you were making a modification say 30-day notice...

(Xin Wong): Yes.

(James Bertram): ...you would not need to provide that information.

(Xin Wong): Okay, thank you.

Coordinator: At this time I would like to turn the call back over to (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/training/CDRH-Learn by Wednesday, March 28. 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 [W-W-W dot F-D-A dot gov forward slash CDRH webinar](http://www.fda.gov/forward/slash/CDRH/webinar) immediately following the conclusion of today's live webinar.

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

Coordinator: Thank you for your participation in today's conference. You may disconnect at this time.

END