ANNE RADWAY:
Hello, everyone, thank you for joining us today and welcome, I'm Anne Radway, the Associate Director in the Division of Regulatory Project Management in CTP's Office of Science. I've worked with CTP and the Office of Science for the last nine years. I started as a regulatory health project manager and moved up through many leadership positions and took my current role. As Associate Director, among many other things, I'm responsible for the training and development of the division. One of the main priorities is to prepare the regulatory health project managers to serve as industry liaisons and the regulatory experts and the Office of Science.

ANNE RADWAY:
Prior to joining CTP, I spent several years in the military and as a contractor working with biological select agents. I started my current role as Associate Director in the Division of Regulatory Project Management in October 2019. We are really excited to welcome everyone to the public meeting as we share the latest updates on Deemed product review. During today's meeting, we'll cover a range of topics related to deemed product review, including an overview of the CTP OS planning and preparation for the September 9th deadline. We will highlight our current review progress and current metrics and reporting and also provide information on the public lists of products.

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After the presentation, we will also have time to answer your questions during an open panel discussion with you and representatives from the Office of Science. I encourage you to submit your questions at any time during the meeting by entering your name and your question in the chat box below and then pressing post. You will not see a confirmation, but after pressing post, your question will be successfully submitted to us. Feel free to submit multiple questions as well. Please be aware that we will not take questions that are not related to the topic of this meeting or any questions about individual applications.

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If you have questions about your specific applications, please reach out directly to your assigned regulatory health project manager or email askCTP@fda.hhs.gov. Now, I'd like to start the meeting by introducing Dr Matthew Holman, the director of the Office of Science at the Center for Tobacco Products. Dr Holman has 20 years of experience working as a regulator at FDA, including over 10 years at CTP. During his first six years at CTP, he headed the division of Product Science. In this position, he oversaw evaluation of the composition and design of tobacco products. In addition, he was involved in chemical microbiological and engineering research on tobacco products,

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resulting in numerous publications and peer reviewed scientific journals. He was appointed to his current position as director of the Office of Science in January 2017. In addition to reviewing tobacco product applications, the Office of Science provides scientific support for regulations and guidance, evaluates the knowledge basis for regulatory decisions, and carries out research to fill the gaps in scientific knowledge related to tobacco product regulation. Many thanks to Dr Holman for joining us today. I will now turn it over to Matt to share more information on deemed product review.

MATTHEW HOLMAN:
Great, thanks for the introduction and and good afternoon to everyone. I wanna start by thanking all of you for attending and participating in this meeting by submitting the many questions that have already been submitted and I'm sure additional ones that will be submitted throughout the meeting. I am the director office of sciences and indicated I do wanna note that throughout the meeting you will hear me and my colleagues refer to the Office of Science at (UNKNOWN). So I wanted to go ahead and let you know about that abbreviation we'll be using and as we use other abbreviations or acronyms Will, we'll be sure to define what they mean as we're going through.

MATTHEW HOLMAN:
But for those of you who are not aware, the Office of Science has primary responsibility within the Center for Tobacco Products for reviewing marketing applications for new tobacco products. During this meeting, we will review OS's planning and preparation for the September nine, 2020 deadline. We'll also talk about the highlighted current review progress and current metrics of reporting of our progress and then we'll have an open panel discussion with you, the audience and representatives from the Office of Science. CTP's director, Mitch Zeller, previously pledged that the agency would keep stakeholders up to date on the agency's progress throughout this bullish year.

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We're now at that point in the review of these applications where we can share some updates on our progress. Our aim is that this meeting increases your understanding of the preparation and planning that we did prior to September 9th to streamline the intake and review process, but I also want to provide some updates on the review status of timely applications by sharing the latest metrics and reporting, and then during the last part of the meeting, as I said, we'll have a panel of leaders from within LS who will address the questions and potential concerns that we receive from meeting attendees. We received many questions ahead of the meeting, which we'll try to answer,

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but we also will address questions that were received during the meeting. So please remember to submit your questions at any time, down the meeting and described at the outset. Let's begin with some brief background on the review process and how we got here. There are three pathways available to bring a new tobacco product onto the market in the United States, and they are the three market tobacco product application pathway, which you'll hear us talk about or refer to as PMTA's throughout this meeting. The second way to bring a product to market, a new tobacco product to market our substantial equivalence reports or what we call SC reports,

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and then the third is our request for exemption from substantial equivalence, which we shorthand as exemption requests. The SC pathway continues to be the most commonly used pathway of the three for applications for cigarettes, small, bookless tobacco products, cigars, hookah tobacco products, pipes and roll your own tobacco products. In contrast, all applications that we receive for e-cigarettes devices as well as e-liquids were submitted through the PMTA pathway. And we did also receive a small percentage of PMTA's for other product categories in addition to the e-cigarette devices and e-liquids. For PMTA's we determine whether marketing in tobacco product meets four main criteria.

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First, we consider whether the product is appropriate for the protection of public health. And this is determined with respect to the risks and benefits to the population as a whole, which includes users and non users. This consideration also take into account whether there's an increased or decreased likelihood that existing users of tobacco products will stop using tobacco, new tobacco products, as well as the increased or decreased likelihood that those who do not use any tobacco products will start using the new tobacco products. Additionally, the other three criteria that we evaluate for each PMTA are whether the manufacturing of the product conforms with requirements in Section 906E of the FD$C Act

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or the Federal Food Drug and Cosmetic Act, whether the proposed labeling would be false or misleading, which could cause the product to be misbranded under Section 903 and the last criteria is whether the product conforms to any product standards under Section 907, which would that are applicable to that given new tobacco product. Lastly, in terms of background, let me remind everyone of how we got here. In the summer of 2019, the courts ruled or ordered that marketing applications for e-cigarettes, pipes, hookah and certain cigars on the market had to be submitted to FDA, more specifically to CTP by September 9th of last year.

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That court order allowed products for which applications were submitted by September 9th deadline to remain on the market, on enforcement discretion for up to a year while pending FDA review. This undertaking represents a major milestone for tobacco product regulation and for public health as a whole. By implementing the free market review requirements for all deemed new tobacco products, we are taking steps to transform the marketplace from one where all tobacco towards one where all tobacco, new tobacco products available for sale will have undergone a careful science based review and oversight by the agency. A couple more points that I wanna make,

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one, as a result of the court decision, we will not be as a result of a different court decision, that is, we will not be enforcing this requirement for premium cigars. It's also important to note that any tobacco products, including deemed tobacco products on the market in the United States as of February 15, 2007 are considered grandfathered and they are not required to meet them to have a market authorisation from FDA to be sold in the United States. Our preparation ahead of the September 2020 deadline has allowed us to be much more agile, efficient and effective. Across the entire center, we've worked towards a system of continuous process improvement,

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and for the last several years we have been preparing for the receipt and pre market review of what we knew would be a large number of deemed new tobacco products. These efforts include improving our information technology systems, engaging with stakeholders, significantly increasing our hiring, as well as streamlining our review procedures themselves, among other things. And that's what I wanna talk about, I wanna walk through and give you some more details about that planning and preparation over the next few slides here. Since 2011, the Office of Science has increased tenfold. In just 10 years, we've

gone from about 40 staff members and less to over 500 full time staff members today.

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The majority of these staff are scientific and regulatory experts who spend most of their time on application review. And we aren't done yet. We continue to hire and train even more staff to conduct application review, increase our review capacity, strengthen our reviews, as well as increase our efficiency during the review process. Ahead of the September 9th, 2020 deadline, we used a multifaceted approach to provide resources and information to applicants. On this slide and the next few slide show examples of such approaches. I just wanna point out a few things on this slide. First, we issued a final guidance with a detailed description of information

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and data that we recommended be included in the PMTAs for e-cigarette devices and e-liquids. The second point is that all the materials from the October 2019 meeting, including transcripts, video recordings, the presentations, text themselves, all those things continue to be available on the FDA website. And I would say that the guidance document, as well as the meeting materials from the October 2019 are still valuable resources that I would encourage applicants to utilize as appropriate when responding to deficiency letters from (UNKNOWN) or when assembling new marketing applications to be submitted to CTP.

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Again, here are more examples of approaches that we use to reach stakeholders ahead of the September 2020 deadline. I do think it's worth talking about the electronic submissions. We recognize that in the past, some applicants chose not to submit applications electronically or if they did choose to submit electronically, they had some difficulties doing that. Therefore, we put a lot of effort into helping applicants understand how to submit market applications electronically. I think one of the most significant aides that we provided to facilitate submission of market applications was that we allowed applicants to group submissions, so many applications could be included in a single submission from a given applicant.

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For example, let's say a cigar manufacturer in the past would have submitted separate (UNKNOWN) reports for each of its say 75 new cigars. But instead, to meet the September 2020 deadline, that cigar manufacturer actually would have sent in just a single submission through the portal and that submission would have contained the (UNKNOWN) reports for all 75 new cigars. And to help facilitate the grouping of multiple applications in a single submission, we also provided an example of a spreadsheet that could be used by applicants to organize their submission and clearly identify the applications and products in each submission. I'm very happy to report today that a lot of manufacturers,

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manufacturers did in fact submit electronically. A lot of manufacturers or applicants did choose to submit their applications as group submissions, and they did use either the spreadsheet example that we provided or similar spreadsheet to help organize their group submissions. And as a result, we were

and I really want people to really stop think about this as a result of all that preparation and support that we provide to applicants. We were successful in receiving over six and a half million market applications within a window of just a few weeks. Also, as a result, we were able to process that huge number of voluminous submissions to identify all the products

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and market applications that we received by the September 9th, 2020 deadline. Lastly, we have 25 reviewer guides and memos on a variety of review topics covering numerous scientific disciplines and topic areas. These documents have a lot of useful information for applicants, so if you haven't looked at them, please take the time to look at them for again responding to your deficiency letters or even assembling new applications. One of the other actions that we took ahead of the September 9th, September 2020 deadline was to provide more information to stakeholders on TPMF or tobacco product master files. We all we gave a lot of time

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and attention to explaining how TPMFs could be useful to the applicants themselves, to, say, third parties and then to FDA and our review of the information. TPMFs were introduced in part to decrease the burden on applicants because a single TPMFs can be used multiple times. In other words, that TPMF can be seven months with information and we can look at that over and over again for different CPMT's as reports or exemption request, which makes it much easier on the applicant or submitter and also makes it less resource intensive for us. And I'm happy to report as a result of the education that we did around TPMFs, we we saw a tenfold increase on TPMFs received by CTP.

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When you compare what we received at the time when the (UNKNOWN) as compared to what we had seen up until that point in time. So currently we have about 100 TPMFs that we've received. There they generally are really four types of are the TPMF owners at least fall into four categories. The almost half of the TPMFs we got were from suppliers to actually the finished product manufacturers so that those account for almost 50%. Another third are a little bit more than third came from manufacturers of the tobacco products. So some manufacturers, for example,

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might have different groups within their company that have certain information. So there's different parts of the company may have submitted information and TPMF...

MATTHEW HOLMAN:
That then could be relied on for the overall application review. About 10% of the TPMF we got were from testing labs. So, typically these are analytical methods, methodologies used to do product analysis or different types of studies. And then lastly, we got a small number of TPMFs from consultants that were just providing information on behalf of the finished product manufacturer.

MATTHEW HOLMAN:
I did talk about group submissions just a few moments ago and how they've been really helpful, I think, to both applicants and to CTP and I do want to talk, though, about a related IT tool that we developed,

which is a new cloud based product data service that houses the submission product data. So, as I said, many of the applications were grouped in submissions, each submission contains multiple applications. Each application is for an individual or single product. So, this new service houses that product information for each and every one of those products and the six and a half million plus mark applications that we got by the September 2020 deadline. With a large number of products that we expect to receive from applications for, we knew it was gonna be important to improve our IT systems.

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And data from this new IT tool is being used to generate the list of submissions and products received from industry. It's also being used to help us efficiently determine what products are in a particular review. And then lastly, really useful in helping us report out on those products that are under review. So, population of this new database was significantly... I wanna point out early that population of this new database was significantly facilitated by submission of the spreadsheet that I talked about a minute ago, either the one that we provided as an example, to help applicants organize their submissions and provide information on each individual product, or, as I said, if they used a similar spreadsheet really help facilitate population of this new product data service that we have created.

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Now that I've highlighted the planning and preparation that we did ahead of the September 9, 2020 deadline, I wanna discuss how we created a fair process to review applications and really what's working well. As part of this section of the talk I'll also describe how we're allocating our review resources.

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As anticipated, we receive thousands of tobacco products submissions covering millions of tobacco products and the vast majority of which came in very close to the September 9, 2020 deadline. The submissions, as you might imagine, very substantially a number of tobacco products containing each submission, the size of each submission, the format and organization of its submission. However, despite these challenges and then really, really significant challenges, due to our preparation and a continued engagement with stakeholders, the intake of this large number of submissions went very smoothly. Part of the reason for the success, I think is due to applicants using the group submissions, using the (UNKNOWN) and then using the product spreadsheet provided by FDA or similar spreadsheet.

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We've completed the work to go through the submissions and identify all the products contained within them, which has allowed us to create the product lists that we recently released, as well as helping us move the applications through a review process. I'm sure you all can appreciate that this was not an easy task, and I just wanna say I'm very proud of my colleagues for the work they've done which have enabled this to happen. And as a result of that work, acceptance ,filing and substantive scientific review of applications are moving forward with no major issues from this intake process.

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Processing of the pre-market applications has historically been conducted, I think most you guys know, on a first in, first out, or what we call FIFO basis. This really means that when an application is received, it immediately enters phase one or acceptance review and then move to the review phases to a final

action. This process has worked very well when processing and review capacity each phase of the review process is one to one. In other words, it works really well when our capacity at all three phases of review of an application are adequate so that we don't see delays at each phase. However, due to the September 9th deadline and anticipated increase in applications that we had expected, as well as the volume of the size, I guess I should say, of each applications, or each submission being so large, we expected that if we followed this FIFO process for defining review order, it would result in significant delays that all the phases of the review process for all three pathways for PMTAs, (UNKNOWN) reports.

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Therefore, to address this issue, CTP developed a triage process that we think is very fair and ensures that the greatest possible public health impact results from our review of these applications.

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OK, to determine which reports and exemption request would enter review and in which order, we simply randomized all applications by manufacturer and then by product type, meaning we took all of the SE Reports and randomized by manufacturing product type. For example, if manufacturer X submitted SE Reports for cigarettes and cigars, the cigarette SE Reports got one place in the randomization and the cigar SE Reports got a different place in the randomization. We did this again for both SE Reports and Exemption REQs, but I do wanna just point out and be clear that SE Reports and exemption requests were randomized separately so that there is a separate queue for SE Reports and a different queue for exemption requests, they weren't all combined. It's just that we followed the same process for both of those pathways.

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And most of the PMTAs that we received were, in fact, randomized using the process that I just described for SE Reports and exemptions. However, we did use a triage approach for PMTAs that included a separate queue for those PMTAs from current manufacturers with the largest market share of ENDS products and use that as a primary criterion to determine the order of tobacco product review. The reason is we wanted to ensure that we reviewed these PMTAs is that regardless of our conclusion, whether we issued a positive order or a negative order, those actions on these products will have a significant impact based on the high level of use of these products currently by end users.

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I do want to make an important point about the product types you include in the triage and therefore undergoing review. All types of products are included, whether the products are statutory, meaning cigarettes, smokeless tobacco products or (UNKNOWN) tobacco products, or whether the products are covered by the deeming regulation. So, (UNKNOWN), cigar, pipe and waterpipe. So, for example, SE Reports for cigarettes and cigars are included in our triage and are being reviewed and being treated the same, they're not being treated different in that triage process I just described our previous slide

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Another important point that I wanna make is that we completed two rounds of triage for PMTAs. For the first round we took all of the applications received between April and August of last year and we apply that triage process. By doing this we were able to know the review order and begin review at the

very beginning of September. For the second round we took all the applications received by September 9th and applied the triage process. Therefore, PMTAs that were received by August of last year had two chances to be pulled in the scientific review. For example, manufacturer A submitted PMTAs, say last July, their applications would have had a chance to be prioritized for scientific review in early August and then a second opportunity to be prioritized for scientific review later in the year last year.

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In contrast, for example, if manufacturer B submitted PMTAs, let's say, on September 6 of last year, their applications would have had a chance to be prioritized for scientific review in late fall of last year. But they would have not had an opportunity to enter scientific review at the very beginning of September.

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Despite all the great progress that I've described, having been made on intake and review thus far, we know that we will not be able to review all the submitted applications by September 9th of this year merely due to a number of factors. The large number of applications that we are currently moving in to review all at the same time, the uniqueness or novelty of the products and and consider policy and scientific issues to be considered, realistically the finite nature of (UNKNOWN) review resources. And I think also importantly, that the necessary time to make sure that we are consistent and our review process and continue to apply the appropriate level of rigor to that process. So, with that being said, I'd like to go into some more detail on our review process and share some of the latest stats on the large number of applications that have made it through the different phases of review.

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We completed the intake processing step for all pre-market tobacco applications submitted by the September 9th deadline. Again, we completed and take up all of these at this point in time. You can see on the slide the number of different SE Reports, Exemption Requests and PMTAs that received. I think you all quickly recognize that this number of applications exceeds anything that we've ever seen by orders of magnitude. This was very challenging due to the size, complexity and diversity of these submissions.

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For example, some applicants provided separate submissions for each section of the marketing application, such as submitting the clinical data separately from the product identification and manufacturing data, while others included up to many thousands of products within a single submission. In fact, one firm actually submitted information on more than four million tobacco products in a single submission. The amount of content in each of these submissions also varied greatly, with some (UNKNOWN) including up to two million files, where each file contains multiple pages of content for FDA to review.

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So, the ability to process all these applications and identify the products subject to each application is really a huge accomplishment. And as I said earlier, I'm really very proud of my colleagues for getting us to this point. That being said, there's more to be done and on this slide here, I think a lot of us have seen

this, so I'm not gonna spend a lot of time on, but the Chevron diagram here shows all the phases of application review for all three pathways.

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I will just point out really quickly that the time needed for each step in this phase of the review is not reflected in this Chevron diagram. Also want to point out that the final review in phase two only applies to PMTAs, there is no filing review for SE Reports or potential requests. And similarly, phase four, the post market reporting only applies to PMTAs as well. If a product is found appropriate for protection of public health, which you'll hear sometimes referred to as APPH, then the order letter will identify post market reporting requirements.

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I'm gonna kind of quickly walk through the different phases of the review to describe them and then also I think more importantly, to share progress at each phase I'll limit my discussion to really just phases one through three. And phase one to start, OS completes an acceptance review to ensure that the products fall under our jurisdiction. If, in fact a product and an application falls under CPD's jurisdiction, OS completes a high level plenary review to determine if the application on its face contains basic statutory and regular requirements in accordance with our refuse to accept or what we call RTA regulations.

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The RTA regulations apply to all the pathways, PMTAs, SE Reports and exemption requests. We may RTA applications if any of the 10 criteria listed in the RTA regulations apply to a given application. You'll see common deficiencies on the slide that have led to RTAs in all three pathways. I'm not going to read them, but I do wanted to share some examples just to help you understand what might lead to or what has led to an RTA.

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But I do think it's worth taking a minute here just to delve into what full identification of the tobacco product means so that you can understand why we would RTA for lack of product identification. The product properties that are required and considered for full identification of a tobacco product are listed here on the slide. Failure to include any of these product properties would lead to an RTA.

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When receiving marketing applications for tobacco products we need to identify the individual product that is subject of each application and the piece of information that uniquely identify tobacco products are referred to as properties. For example, the product name is a property that helps us identify each tobacco product. However, I think you all recognize that the product name alone would not be sufficient to uniquely identify each tobacco products in order to determine the properties needed to uniquely identify which tobacco product, it's necessary to determine which properties are actually applicable to a given product.

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So, as each product type has a different set of properties that would be needed to uniquely identify that

tobacco product. I should say to that point, by knowing the type of product or the product category, in other words, of a given product, FDA inherently knows some of the product properties associated with that product. However, additional identifying properties are needed in order to distinguish an individual product within a given category or subcategory from other products within that same category, subcategory. And this determination of these properties, identifying properties, is really dictated by the product category and subcategory.

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It should be noted that the properties needed to uniquely identify tobacco products are determined by FDA based on our experience in reviewing regulatory submissions for these products to date and we have developed memos over the years that are periodically updated and posted on our website. And FDA recently updated our unique ID memo and I do want to point out that new or updated unique identification properties will be captured in Appendix A of our letters to applicants starting very soon. So, it will actually be directly included in the letters as an appendix.

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This latest unique ID memo includes a particular item of interest that I wanna point out, I really just want to highlight that we've identified a new product category, what we're calling heated tobacco products or HTPs, that are captured in our newest memo and.

MATTHEW HOLMAN:
HTPs are further divided into specific sub categories such as closed or open HTPs. On this slide, I've included one example of a unique ID for closed HTPs. I'm not going to go through all the properties line by line, but I will point out that the properties can be the same or very similar to those of vapes or E cigarettes. Really, the primary difference between HTPs and vapes is that HTPs can use multiple types of consumables while vapes or E cigarettes can, cannot be used with solid tobacco.

MATTHEW HOLMAN:
Now that I've talked through the substance of acceptance reviews, I want to provide you an update with on the status of acceptance reviews across all three pathways. As of April 11th of this year, a couple months ago, we've accepted over 320,000 total applications across the three pathways, resulting in issuing more than 55,000 RTAs or to say so, to say differently as of April 1st, we had completed acceptance review of over 375,000 PMTA, SE reports and exemption request.

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We do continue to conduct acceptance reviews of applications received by the September 9th 2020 deadline for all three pathways, and we are providing updates on the progress on our tobacco products, applications, metric and recording web page. But I do want to share a number of important factors in context that I think need to be considered when you review the metric data on our website.

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And what we found is due to the large volume of applications received by the September 9th deadline, and the real time changes to the status taking place, as applications move through our groups or applications moved through the review process, we're seeing constant changes in the month of month

data over time. Although the data may be accurate at a given point in time, when it's shared publicly, there are corrections and adjustments that often need to be made. And in some cases, they need to be made retroactively.

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For example, an action taken on a set of applications toward the end of a reporting period may not be captured in our systems until the next reporting, that beginning of the next reporting system. So, as the data for the next reporting system is being collected, we would go back and look at the data that we previously reported and updating that data, if in fact updates were needed to be made. And given that many of the submissions include very large numbers of applications, even updating the acceptance review metric, for example, for just a single submission, could change the metric by tens of thousands of applications.

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For example, if the last reporting period (INAUDIBLE), you know, say, right ahead of the April 1st deadline that we last reported, we had accepted a submission, but it didn't make it in the report, when we go back in our next update and provide that data, we would include that acceptance number. But again, if that submission was, say, 25,000 products, that is going to make a huge difference in our acceptance metrics. So, just wanted to point that out.

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And in light of this, what we decided to do was start reporting on a monthly basis, but really start recording cumulative fiscal year to date, data to share with stakeholders. I also do want to point out again, because of these issues I'm just talking about, that data is generally accurate within 10%, is what we're finding. But again, it is truly a snapshot in time on, you know, the data that we have in hand. And because we are processing so many applications through all the various phases of review, these data can change in pretty large ways and, you know, even as frequently as daily.

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But despite all these challenges that I'm talking through, we are providing the updates, because we do think it's important to be as transparent as possible, while at the same time, you know, trying to make sure that we're providing accurate and timely data around some of these metrics. OK, I want to shift from phase one to discussing phase two, which is the filing review. As I mentioned, we do filing reviews for PMTA's but not for SE reports or exemption requests. The purpose of a filing reviews to determine if the application contains sufficient information to initiate substantive scientific review.

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So, during filing, we conduct a more in depth multidisciplinary review of the PMTA to determine if all statutory requirements have been provided, as outlined in Section 910B, in specific parts A through G of the FD and C act. So, at the end of the filing phase, one of two things happens. If we find that PMTA has all the information, basic information that is, that we would need just to kick off substance scientific review, we would issue a filing letter to notify the applicant of such.

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If we find any information that that we need in Section 910B is not present, then we would issue refuse to file a what we call RTF letter. That RTF letter will include the reason for or will identify the information that was not submitted that led to the RTF decision. Here are some common deficiencies that lead to RTF. Again, I'm not going to read through this list. But I think you'll recognise as you read through this that there really is some basic information that we need in order to be able to conduct our substantive scientific review.

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And if we don't have that information, we won't file the PMTA, we won't move it into substance scientific review. And I think again, what's laid out here is really what's captured in statute under Section 910B of the FD and C act. OK, let me share the status of filing reviews for PMTAS, the date on the slide is again as of April 1st of this year. But as I said earlier, with acceptance reviews, we are updating our metrics on the website. So, no, so, the new data on the status of filing reviews should be posted soon on our website.

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That being said, as of April 1st, we've completed a total of nearly 45,000 PMTAs, but we've completed filing reviews for nearly 45,000 PMTAs with over 90% being filed. This, the number of filing reviews completed continues to increase significantly each month, as is the case for acceptance reviews as well. If accepted and filed by CTP then a PMTA moves into phase three, which deals with the substantive scientific review and results in an action from the CTP.

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For SC, an exemption request, they would just need to move through acceptance. And then if accepted, they would move into phase three of substantive scientific review. The sub notes of scientific review is a multi display review of the data submitted in the application to determine if, in fact, the data is sufficient to meet the requirements for marketing under the three different statutes. And really, we ultimately issue three types of letter, we issue a deficiency letter, which may also include environmental information requests, will issue a marketing granted order or the third type of letter we issue is a marketing denial or a letter.

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And generally what we expect when an applicant submits, you know, applications that there's that application contains all the information we need to determine that it would be appropriate to allow marketing of that product. However, you know, we've recognized that additional information may for some applications be needed in your review of that application. So, if FDA has questions or identifies additional information needed to render such a decision, we may choose to or that's when we may choose to issue a deficiency letter.

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The deficiency letters that we issue include a timeframe by which the manufacturer would need to respond to us and the applicant can submit an amendment and response to that deficiency letter within that timeframe. But I do want to point out that, from the date that we issued that deficiency letter until we received that amendment, if we in fact receive one, the review of those, that application is

suspended. We do not work on our review clock stops.

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If for example, during that review, we identify, as I said earlier, the need for additional information around the environmental assessment that we would need to do to prepare either an environmental impact statement or EIS or finding a no significant impact or (UNKNOWN). We would, we would issue that environmental information request typically as part of the deficiency letter, because we do need to find scientifically that a product can be marketed after reviewing application.

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But we also have to make sure that we meet the requirements of the National Environmental Protection Act or NEPA, that require us to either complete an EIS or (UKNOWN) before we allow marketing of a product. And as I said, I mentioned earlier, if we do issue a marketing granted letter, order, I want to just point out for PMTAs, we would also identify in that marketing granted order, any post market requirements, so, if there are any restrictions, for example, on sales or distribution, we would describe them in that marketing branded order.

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And then lastly, I'll just say with the marketing denial order, if it, if we do issue that we will identify what deficiencies led us to that conclusion. OK, I want to do, I do want to say one more thing about specifically, just about PMTA deficiency letters. So, what I'm putting on this slide is really specific to the PMTA pathway. We recently inserted additional text into these deficiency letters for the the intent of clarifying the purpose and really the intention of the deficiency letters.

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These deficiency letters are intended to notify the applicant where FDA needs additional information. And you'll see the new language shown on this slide clarifies that the letter is not intended necessarily to convey a list of concerns about the product. Or, and I also want to point out that this new language also makes it clear that a complete just responding to our complete response to a deficiency letter does not in and of itself guarantee that the application will lead to receive a positive marketing order.

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As a decision about whether marking the new product is appropriate for the protection public health or a PH is made after FDA reviews all available information, including whatever information is provided in response to a deficiency letter. For example, a deficiency letter may seek additional information related (INAUDIBLE) testing, testing and validation of test methods. And although an applicant may provide that information to adequately respond to the deficiency, that and we still need to analyse the totality of information in that application, determine whether the information and total supports marketing application.

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It takes a lot of work by FDA staff to move an application from receipt to completion of substantive scientific review, which like I said, and either positive or negative order letter. But that being said, we have issued marketing orders under the SC and EX pathways. As of April 1st, we issued a total of nearly

300 order letters on both positive and negative under these two pathways. We have not yet issued any marking orders for PMTAs, however, we do expect to issue order, order letters, again, with some possibly being positive, some possibly negative, by September 9th of this year.

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I also want to point out that we have issued many deficiency letters under all three pathways. And we have completed many thousands of scientific reviews for all three pathways at this point in time. OK, I just want to say thanks everyone for staying with me so long. I just needed a few more minutes and then we'll get to our panel discussion. And the last section of my presentation, I want to discuss the product list that we made public earlier this year.

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The SC and EX lists were originally posted in February, and they included over 2000 products, including 1100, about 1100 cigars, over 330 pipe products and over 660 water pipe products. The PMTA list, which posted in May, includes over 6000 products. We made these lists available to the public in an effort to be transparent and increased stakeholder knowledge of these products. But I do want to point out that we had to ensure that the development and posting of these lists was done in accordance with applicable laws.

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For example, FDA needed to contact each individual applicant to request the dates of initial marketing, as well as current marketing status of each product for which an application was submitted by the September 9th 2020 deadline. So, I, you know, as part of that, I want to note that we use this information to determine if the existence of the pending application could be disclosed to the public or not. And when we have not independently verified the information provided by applicants about the current marketing status of their products.

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It's important to note also that these are not comprehensive lists. They are not intended to cover all currently marketed deemed new tobacco products that a firm might be manufacturing distributed selling. For example, the lists do not include products from companies that did not provide their information in time to be included, it does not include products that are subject to a positive marketing order from FDA between, before, I should say, April 5th of this year, and they don't include products that were a commercial market the United States as of February 15 2007, I, grandfather products, which have not been modified.

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The list also do not include products that are subject to negative actions from FDA before April 5th of this year, or products with a pending submission that were not submitted by the September 9 2020 deadline. Furthermore, as manufacturers are not required to submit more than one application for products that may have different names and or labels if the products are physically identical. Some products on list may also be marketed under different names and are under different labels.

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And lastly, certain products on these lists may also be subject to warning letters notifying a manufacturer on alleged violation of the FD and C act or applicable regulations. To determine if a product has been subject to a warning letter alleging failure to comply with applicable statutory and regular requirements, you can visit our warning letters webpage to find that information. And now I will hand the meeting back over to Anne to begin to our q&a session section of the meeting.

ANNE RADWAY:
Matt, thank you for sharing the latest updates on Dean product review. And for remaining with us for the rest of the meeting to answer questions. I just wanted to also give a reminder that the PowerPoint slides as well as the recording of this event will be posted to our website. FDA will notify all registered attendees when they are made available. And now I'd like to introduce the rest of our panelists from the Office of Science and open the meeting to address questions.

ANNE RADWAY:
As a reminder, like I said in the beginning, you may submit questions at any time by entering your name and your question in the chat box below and then pressing post. You will not see a confirmation but after pressing post, your question will be successfully submitted to us. Feel free to submit multiple questions and also as a reminder, we will not address questions that are not related to the topic of this meeting or about individual applications. Therefore, if you have a specific question about your product application, please reach out directly to your regulatory health project manager or email askCTP@FDA.HHS.govt

ANNE RADWAY:
Our first panellist is Dr. Todd Cecil. He is the Deputy Director for Regulatory Management in the Office of Science. Dr. Cecil joined CTP as a chemistry review scientist in 2015, and progressed through managerial positions until he served as the Associate Director of the Division of Product Science. In this position, he oversaw the evaluation of the composition and design of tobacco products.

ANNE RADWAY:
In addition, he served on the leadership team, which was involved in chemical, microbiological and engineering research on tobacco products, resulting in numerous publications and peer reviewed scientific journals. In 2020, Dr. Cecil became a Deputy director of CTP's Office of Science, the leadership team in the Office of Science share responsibilities for reviewing tobacco product applications. Dr. Cecil's particular focus is on substantial equivalence and exemption from se requests.

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In addition, Dr. Cecil participates in aspects of pre market tobacco application review, provides scientific support for regulations and guidance, evaluates the knowledge basis for regulatory decisions, and carries out research to fill gaps in the scientific knowledge related to tobacco product regulation. Before his tenure at CTP, Dr. Cecil worked for over 20 years at the United States Pharmacopeia Convention, USP, including 10 years as the vice president of Standards Development.

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USP is a nonprofit standard setting organization for the pharmaceutical industry. In this role, Dr. Cecil

authored and contributed to hundreds of pharmaceutical standards and chapters with broad industry impact, including a revised standard for metal impurities and pharmaceuticals. In this role, Todd travelled extensively and presented at hundreds of national and international symposia and training sessions throughout the world. Next, we are joined by Miss Crystal Allard, the Director of the Office of Science Division of Regulatory Science Informatics.

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Miss Allard's team supports all IT activities in the Office of Science. They provide OS with systems to help automate mundane processes so, they can focus on interesting relevant information to make good research and review decisions. These systems include review process automation, research, activity tracking, and data storage and analysis. Miss Allard has worked at CTP since January 2019. And before CTP, she worked at FDA Centre for Drug Evaluation and Research, the Office of the commissioner and the Centre for Biologics Evaluation and Research.

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Crystal has been at FDA since 2008. And before that, she worked in industry, preparing electronic submissions and standardized study data for submission to FDA. I'd also like to welcome Dr. Joanna Randazzo. She's the Acting Chief of the Science Policy branch in the Office of Science. In her role, Dr. Randazzo is responsible for supervising science policy activities, and staff to analyse the needs of the Office of Science. This includes drafting regulatory and policy proposals and developing plans to provide consistency in the regulatory and scientific approaches addressing public health concerns in the context of pre market review and implementation of the Tobacco Control Act.

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Dr. Randazzo has been in the Office of Science at CTP for the last eight years, originally serving as a regulatory health project manager prior to transitioning to policy work in 2014. Prior to joining CTP, Joanna was in private practice as a chiropractor and also worked as a personal trainer. We are also joined by Miss Cristi Stark. She is the Director of the Office of Science Division of Regulatory Project Management. Miss Stark has over 18 years of regulatory experience at FDA including over 10 years at CTP.

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Within her time CTP, she has served in project management, DFO and policy roles. In these positions, she has aided with the proposal development and implementation of rules, guidance, policies and procedures around the handling and review of submissions. In her current role, she is responsible for the oversight of regulatory processes and review procedures associated with submissions handled within the Office of Science. Prior to working at CTP, Cristi worked FDA Centre for Drug Evaluation and Research and Centre for Biologics Evaluation and Research. And before that, she worked as a biologist for the National Cancer Institute.

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Thank you to all our panel members for joining us today. Now, let's get started with our first question. OK, here's our first question. Will FDA grant extensions to timely submitted applications that have passed acceptance and filing milestones and have proceeded to scientific review if FDA has not yet

completed review by September 9th 2021? Cristi, I'm gonna give this question to you.

CRISTI STARK:
Good afternoon. Can you hear me?

ANNE RADWAY:
Yes, we can hear you.

CRISTI STARK:
OK, fantastic. So, in short, we're planning and striving to review as many applications as possible during this one year period described in the court order that said that September 9 2020 application deadline. In addition, FDA does have the discretion to defer enforcement action against a particular product on a case by case basis, as that one year period for review comes to an end in September 2021. But I'm noting it's case by case specific to that particular product and circumstance.

ANNE RADWAY:
Thank you, Cristi. OK, next question. When metrics are reported, does a single number represent a single SKU or in it, or an application that may be bundled into multiple SKUs? I'm going to give that to Crystal.

CRYSTAL ALLARD:
The numbers that are listed on the metrics and reporting web page called Tobacco Product Applications, Metrics and Reporting, report the number of products, but it's important to note that one product listed on that page may represent multiple products on the market. So, for instance, an example is, we may have received an application for a single product called alpha e cigarette, but it can also be sold as beta e cigarette or gamma e cigarette.

CRYSTAL ALLARD:
And the manufacturers only submitted one application and this example for one single physical product which is identical but is marketed under three different product names. It's also important to note that the products that are listed on the web page are counted differently from the way that they're registered and listed, and I know that the registration and listing uses the SKU, sometimes we call them SKUs. But we don't use those SKUs (INAUDIBLE) using doing our product review. So, that's a slightly different counting method.

CRISTI STARK:
If possible, I'd like to add one point regarding registration and listing versus the product counts. Registration and listing is purely for domestic products. With the requirements we still require regulation to include foreign, our product counts include both foreign and domestic manufacturers for the products.

ANNE RADWAY:
Thank you both. Our next question is, is the FDA prioritizing review by market share, for example, is FDA prioritizing review, reviewing PMTA applications for the products that dominate the market? Todd, can

you take this one?

MATTHEW HOLMAN:
Todd, we can't hear you. (INAUDIBLE)

ANNE RADWAY:
Maybe alright. Oh, there you go. We can hear you now.

TODD CECIL:
(INAUDIBLE) sorry. So, due to the large number of AMS products currently marketed and for which we anticipated receiving submissions, FDA decided to dedicate a portion of its resources to reviewing the products that count for the most of the market, current market. The continued marketing these products has the potential to have the greatest public health impact either positively or negatively, as they hold the largest overall market share and therefore unlikely used by the largest number of people.

TODD CECIL:
For this reason, FDA pulled several applications into separate review, a separate review queue, and dedicated resources to their review. These reviews were done alongside reviews for other products as well. By identifying and sharing these review, first review to these applications, we believe that we can achieve the greatest public health impact most quickly. If FDA finds that a widely used currently marketed product does not meet the standard and law for marketing. the agency will not grant a marketing order and the product must be removed from market.

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Conversely, if FDA finds the widely used currently marketed product does not meet the standard or does meet, sorry, the standard for law for marketing, the agency will grant a marketing order and that product may remain on the market (INAUDIBLE) of the conditions of that order. In either case, earlier review ensures a faster transition to the market, a marketplace of products that has been scientifically reviewed for their impact on public health.

ANNE RADWAY:
Todd? OK, next question. Does FDA see any opportunity for common data sharing amongst competitors, market data, literature review, etcetera, to cut time and costs from the process? Cristi, I'll let you kick this one off.

CRISTI STARK:
Sure. And I want to echo one of the statements on in Matt's earlier presentation, regarding the use of a tobacco product masterfile, applicants may share information without any release of trade secret or confidential commercial information. Through that process, I encourage everyone to look up TPM apps, we have a dedicated section on our website and discuss any open questions regarding that with their assigned regulatory health project manager. It's a quick and easy way to share information without handing over the keys to trade secret a commercial confidential info.

CRYSTAL ALLARD:

And I would just like to add that while FDA can't share industry submitters proprietary data, there are opportunities for submitters to make data publicly available and to share and use already publicly available data. And there are some pretty good examples of data sharing that exists in HHS and FDA for public health initiatives.

ANNE RADWAY:
Thank you both. OK, next question. Are you still reviewing MRTP applications during this time period? And what queue are they in? Todd, can you take this one?

TODD CECIL:
Yeah, absolutely. So, yes, we are still reviewing MRTPAs during this time period. We do have separate resources or groups of reviewers in the Office of Science that are dedicated to continued review of applications received for this programme. There are relatively few of them, relative to the huge number of applications received for the PMTA programme and the large number for SC as well. So, we are working through those and that is something we will continue to work through no ongoing process.

ANNE RADWAY:
Thank you. Next question, is a product's in market history considered while reviewing applications? Or is each product reviewed as a truly new product without consideration of its in market history? Joanna, I'm gonna give this one to you.

JOANNA RADAZZO:
Sure. So, yeah, to answer that question, a product in market history would potentially be considered when reviewing PMTAs that have been submitted to us. We use all available data when reviewing a pre market application. So, this may include real words, real world data, or it could include also marketing trends, based on a product's prior revealed availability on the market. This information is important for FDA as it may help identify or informed concerns for use appeal, or other factors that go into our (INAUDIBLE) analysis.

ANNE RADWAY:
What will happen if there are no ends products authorised by FDA by September 9 2021? I'm going to give this one back to you, Todd.

TODD CECIL:
Thank you. Well, given the unprecedented number of applications as well as other factors, the likelihood of FDA reviewing all of the applications received by September 9th, is extremely low. Given that this would be an unprecedent number of applications, and several orders of magnitude greater than anything agency has experienced in the past. We will continue to allocate our resources with the goal of working as quickly as possible through transition. The current marketplace for deemed products to one in which all products available for sale have undergone a careful science based review by FDA.

TODD CECIL:
We will focus resources on products for Scientific Review will have the greatest public health impact based on their market share, while also committing to providing an opportunity for review during the

one year period to all companies regardless of size prior to this September 9th 2021 deadline, at which time we, they risk FDA enforcement per FDA's guidance. FDA also has the discretion to defer enforcement action against a particular product on a case by case basis, as the one year period for that review comes to an end in September.

ANNE RADWAY:
Thank you Todd. Next question, what does FDA consider major and minor amendments for PMTA? Cristi, do you want to answer the phone?

CRISTI STARK:
Sure. So, in short, a major amendment is going to be substan of large amounts of data that FDA would have to review. So, an example of this similar to other FDA centres could be the addition of a new clinical trial, it could be reanalysis of previously submitted data, significant amounts of manufacturing information or data not previously submitted. Minor amendments, in short, are anything outside of that. So, it could be, let's just say that there was a change with some of the contacts updates for some of the SOPs or other things such as that, those would be considered minor.

CRISTI STARK:
The important thing with a major amendment is, when you look at it, this is something that would cause a large amount of time and FDA staff and resources to review. So, in essence, it would reset our PMTA clocks when we're looking at that full review timeframe. So, it's really important when you're looking at the type of information that you're placing within your applications, they are complete upon submission, because submissions such as reanalysis of your data, or a new clinical study, could trigger a reset of that clock and timeframe.

ANNE RADWAY:
Thank you. Next question. How is the Office of Science managing the challenge of maintaining consistency across the tens of thousands of reviews and reviews conducted by hundreds of reviewers? Crystal, do you want to start us off on this one?

CRYSTAL ALLARD:
Sure. Matt covered this really well during his presentation. But FDA has expanded their review teams to prepare for the high volume of applications. Part of our preparation prior to kicking off review of the applications was to ensure that we had consistent process and consistent decision making process and review of data. Part of that was a process whereby we paired staff working on the process with staff who were working on building IT systems and building new databases to ensure that we could consistently provide the same types of information to the reviewers during a consistent process so that our reviewers were able to understand what was expected them and to work a very consistent and efficient process.

CRISTI STARK:
I'm gonna add a little bit as well to what Crystal started with. In addition, I wanna note that during the preparation for our review teams, we have focused staff on particular application pathways and focus TPLs on that, in addition to some of the tools and training that we provided to them. So, we have the

same staff reviewing PMTAs from start to finish and then separate staff reviewing SC reports, exemption requests, and so on. This also addresses consistent decision-making as we're looking through our portfolio

TODD L. CECIL:
And to add one last bit. One of the parts that Matt talked about is we've got a lot of scientists, but we've also got a lot of disciplines. And all of the disciplines are involved in all of their views of PMTAs. And so, within those disciplines, we're actually asking each of those separate disciplines to meet regularly. And they're meeting something on the order of once a month and talking about what they're finding their reviews so that they can share their information and share the knowledge that's gained as they work their way through any problems that they've had, any issues that have come up or any unknowns that they've crossed over, so that we have consistent knowledge for every review that comes up.

MATTHEW R. HOLMAN:
Yeah. And I guess I would add one other piece to it too, which is there are a small number of us that sign all of these final actions. So, if you looked at all the letters that we issue, you'll just see a couple of names on it. And so, we look at, for example, can I look at every one of these actions, letters, and we make sure that we do maintain that consistency across these programs. And so, we do have a small group within the center that really looks at all these things from out the door, out the door for just that reason. And so, I think the bottom line as you heard from the four of us chiming in the responses, we've done a lot. We believe consistency is a really important thing. We've put a lot of pieces in place ahead of the deadline and also are doing a lot of things now post that line to make sure that we do our best to be as consistent as possible.

ANNE RADWAY:
OK. Next question. How will the FDA consider the impact of flavors on youth initiation of products? Will any applications be denied for the inclusion of a flavor that is highly appealing to youth?

TODD L. CECIL:
Well, it's a really important question. I think FDA has made it clear that we are concerned about the impact of flavored products on Youth Tobacco Initiation. Including by prioritizing enforcement discretion or enforcement against flavor, cartridge-based ENDS products, and also stated that the determination of whether a flavor ENDS product is appropriate for the protection of public health will be determined for our pre-market review process. Therefore, in its scientific review in PMTA, CTP considers the potential impact to youth of any new products, including the potential impact of flavors on youth initiation.

ANNE RADWAY:
Next question. Since a random number generator was used to determine the order of review for the application submitted by September 9th, is there a way to determine where submissions are in the list? And will the assigned numbers be provided to applicants upon request? Cristi, do you wanna take this one?

CRISTI STARK:
So, because the order of review of applications is, or will be constantly evolving. For example, due to we

have large numbers of applications being withdrawn, refuse to accept or refuse to file decisions, providing that individual review number, that random number wouldn't be particularly helpful or illustrative for companies as it really wouldn't provide that greater context for what it means, what it may happen to those ahead of them in order in the queue. It's also an additional burden on FDA's resources during this period. Again, we've been focusing our resources on efficient review of applications rather than pulling other data to provide it out to applicants. So, what we've done instead is we are communicating, when I say we, the assigned Regulatory Health Project Manager is communicating with the applicant, they provide a courtesy call to inform them when their application has been moved into that substantive review process. This is at the start of it. And it will typically give you a sense for when you may see a type of letter to come out of it. Again, if there's a question you may reach out to your assigned RHPM to see the status.

If you haven't had that call yet, they'll likely say it's still in queue.

ANNE RADWAY:
Alright, thank you. Next question. Given that review of many PMTAs have not yet begun, how will CTP prioritize any new PMTAs or supplemental PMTAs submitted in 2021 or before the backlog of September 9th, 2020 submission reviews have completed?

MATTHEW R. HOLMAN:
Yeah, another good question. And so, let me just start by saying, we have focused our resources on review of the applications that were submitted by September 9th of last year. We think in light of the court order and the ending of enforcement discretion or at least broad enforcement discretion, it's important for us to complete the review of as many of those applications as possible. That being said, we are setting some, we have set some resources aside to work with some other things. So, for example, Todd mentioned just a few minutes ago, he got a question, he fielded a question that we got about MRTPAs. Yes, we do have some resources that Todd said are dedicated to working on evaluation of MRTPAs. It is greatly dwarfed, those resources devoted in MRTPA, are greatly dwarfed compared to the resources devoted to applications received by last September 9th, but they are there.

MATTHEW R. HOLMAN:
Similarly supplemental PMTAs or new PMTAs, we do have some resources there. What we're doing again is trying to balance the need to be able to evaluate all the applications we get in, whether they came in by September 9th or not, try to balance that against the fact that the courts have put this deadline for the September 9th in place. And so, it really, you know... For example, if we got a PMTN that identified a product that we thought may really mitigate youth access to ENDS products, we would likely pull that into review and review that. And so, we do have some staff available to sort of do these assessments and to be able to review either new applications or supplemental applications as warranted. But again, I wanna be be very clear that the amount of progress or the degree of resources, the extent of resources we were committing to that is really small, relative to the larger set of applications that are going through, or the largest set of products that are gonna lose enforcement discretion on this September if we don't in fact, take a final action.

ANNE RADWAY:

Alright. And in phase two, as noted in the presentation, if CTP determines there is insufficient information to initiate scientific review, does CTP provide the applicant with the opportunity to update their application? Cristi, do you wanna address this?

CRISTI STARK:
Sure. So, I think the main premise that I stated before is an application should be complete when submitted. When OS polls for a review, as of the date that we initiate that review, we pull the application and all amendments received as of that date. So, if we haven't yet initiated review either in phase two for filing, or if we are going to phase three for substantive review and an applicant has information to amend, submit it so it's been received before that start date. I wanna note that once we have initiated review at that point, FDA is not obligated to review those amendments when considering information, and we'll issue an appropriate letter at that time. Our letters typically do state in the appendices, what has and has not been considered for part of it.

CRISTI STARK:
The other thing I wanna note for letters, some in industry may not have a lot of experience with receipt of our letters. In addition, when you look at appendix A, it will list every product related to that review. So, for example, if an applicant has submitted 100,000 products, our review will list if it's for a100,000 products, or maybe we only reviewed 50,000, 100. So, I just want you to pay attention to those appendices. And at the end of the day, if you still have clarifications or questions, your assigned Regulatory Health Project Manager, their information is listed in that letter. We have email addresses, phone numbers, please reach out and contact them with clarifying questions.

ANNE RADWAY:
OK. This next one is for you Todd. FDA has stated bridging may be appropriate, but has not further defined or provided examples that it would find suitable. Is bookmarking acceptable? For example, high and low wattage enough for devices, high and low nicotine strengths enough for E-Liquids?

TODD L. CECIL:
OK. it's a broad question. And what I can say is it could be appropriate to identify like low extremes and high extremes. However, these extremes may be different depending upon the discipline that reviews your submission. So, for example, if we're gonna use this bracketing approach, it may be reasonable to provide a low and a high concentration of nicotine for one PG VG combination to bridge the concentration of nicotine at this PG VG ratio. However, there may be other factors to consider. Such as if an applicant is using a salt form of nicotine, other PG VG ratios, the types of bottles being used. So, while the low extreme and high extreme may be reasonable, other considerations may also play with that and have to be resolved in additional testing needed to bridge the product lines between the two extremes.

TODD L. CECIL:
So, ENDS design parameters and product characteristics, you know, temperature of the heating element, voltage, wattage, control scheme, power duty cycle, and so forth may affect aerosol characteristics, including particle size distribution and user exposure to nicotine and other HPHCs. If the ENDS product has different options for device settings, an applicant should consider providing testing

for the range of the operating conditions. So, various temperatures, wattage, voltage levels as appropriate, and provide a scientific rationale for the choice of the settings that were used in their study. Including how we should be using that information to interpret the results or to bridge the data to other settings. So, we do think that using bridging to provide a easier way to provide us the data and allows us to review a lot less data is a great opportunity. However, we do wanna make sure that we understand all of the implications that bridging brings to that table when you provide that information,

ANNE RADWAY:
OK, Cristi, this one is for you. In the past, we have seen multiple rounds of deficiency questions for an application. For example, advice information requests, questions followed by preliminary findings questions, and even rounds of environmental questions. Given the current challenges facing CTP, how likely is this process and the number of rounds of question to change?

CRISTI STARK:
OK. So, I'm gonna just be completely honest. In order to be most efficient with our review processes for the very large number of September 9th, 2020 applications received, FDA has streamlined the process for all review programs and has generally limited the application review to one deficiency letter. FDA will continue to issue environmental information request letters as appropriate. These letters, the environmental information requests differ from our deficiency letters, as those letters have already determined scientifically that the application is supported. So, you would see an appropriate letter at the end. And I'm just gonna note, if there are additional clarifications or anything in response to the deficiency letter, the RHPM will reach out to contact you for quick discussion. But I do want all applicants to be aware that in general, we are limiting review rounds to one deficiency letter.

ANNE RADWAY:
Thank you. This kind of leads to our next question. I'm gonna let Joanna answer it. What is the process for obtaining case-by-case extensions of the compliance period?

JOANNA C. RANDAZZO:
OK. So, FDA certainly understands the interest in this topic. And as you've stated in previous responses and during the presentation, we are striving to review and resolve as many applications as possible before September 9th, 2021. Broadly speaking we know as with all unauthorized products, generally, if a product has not received marketing authorization by the end of the one-year review period, the product risks FDA enforcement. Questions about enforcement plans and policy beyond the end of the compliance period are outside of the scope of this meeting and what FDA plans discussed today. But when we do have information to share, we will be sharing it publicly with all interested stakeholders.

ANNE RADWAY:
Alright, thank you. Next question. What percentage of applications were for flavored products? Crystal, do you wanna take this one?

CRYSTAL ALLARD:
Sure. We don't currently track this data in a way that makes it easy for us to do that type of reporting and to give a precise number, but we can say that the majority of ENDS PMTAs are for flavored

products.

ANNE RADWAY:
Thank you. Many PMTAs submitted to FDA on or before September 9th, 2020 were without laboratory testing. Will these manufacturers receive deficiency letters? Go Todd. Yeah.

TODD L. CECIL:
So, it really depends. If an application is severely deficient, if it's missing great swabs of information that we need to be able to evaluate the products that is the subject of that PMTA, you know. Or is missing the product characterization, lack of testing, lack of scientific evidence and so forth. There's a lot of things that can be missing and have been seen to be missing. The application may receive a denial in lieu of a deficiency letter. However, in cases where the tobacco product contains, or it has the potential, well, cases where there's enough information for us to progress from the application through filing and into the scientific review and we find that there is enough information for us to really start to dig into what is there.

TODD L. CECIL:
We are looking for testing in cases where there's a potential that a tobacco product contains or has the potential to contain or to create HPHCs through reactions or degradation of the constituents. In those cases, we will expect there to be laboratory testing for each of the products or testing of the subset of products with a rationale for bridging. As I talked about earlier, the results from one product to another. Where this information is not available, the manufacturers are likely to receive a deficiency letter requesting that HPHC data.

ANNE RADWAY:
Thank you, Todd.

ANNE RADWAY:
OK, please explain the process for the continued review of provisional products and applications that were not associated with deemed product submissions, but were in scientific review at the time deemed product submissions were received. Deficiency letter responses for products that were already in phase three substantive review before September 9, 2020, appear to have been treated as new submissions and placed in queue with deemed product submission submitted on or before September 9, 2020. When will review of these deficiency letter responses commence? And Cristi, you can take this one.

CRISTI STARK:
I figured that one was mine. So, in short, and this was talked about in one of the slides that Matt presented, with the large number of applications moving into review at the same time, the novelty of reviewing over 6 million products, the finite nature of our review resources, and ensuring consistency, we really had to develop a process for the review order for all applications. As stated on our website with some of the recent updates and in Matt's presentation, all new applications and responses to deficiency letters were placed in with that randomized queue and FDA will actually notify us (INAUDIBLE) the project manager will call when it's moved into the substantive review.

CRISTI STARK:
This does include the provisional products that previously received a deficiency letter and they responded, they are included in there with part of that random number generated. Again, if an applicant is unsure, contact your assigned regulatory health project manager to verify if you've been moved into that phase three substantive review or not. Your project manager can let you know if it is under review or if it's still in queue waiting to be reviewed. I want to know that they're not treated... Responses to deficiency letters, whether it's provisional or for a regular product in the SE program, are not treated as new applications. They were just placed in an assigned random number generated, similar to our new applications.

ANNE RADWAY:
Thank you. Are applications progressing through review at the planned pace, or more slowly due to the high number of applications? Matt, I'll let you address this.

MATTHEW R. HOLMAN:
Yeah, good question. Let me try to answer this in a couple of ways, I guess. First, let me just say, we didn't know ahead of September 9 exactly how many applications we'd get, but we knew the number was going to be very, very large, much, much larger than we'd ever seen before and of course that has come true. So, we did a lot of work ahead of September 9. I highlighted just few things, and then my presentation to get ready. I'll just share another couple examples.

MATTHEW R. HOLMAN:
I mean, we really put a lot of effort into training. As I said, we've hired so many new staff both ahead of the bolus, during the bolus, in order to deal with this workload, and we've put a lot of effort into training them and getting them up to speed. We also, in addition to streamlining our review process, really restructured it in some ways to really have folks more or less kind of specializing in different parts of the review process. All these things in an effort to, again, apply the same rigor that we always apply to our review, but to try to do it with a higher level of throughput so that we could complete review as many of these applications received by last September 9, as possible, by this September 9.

MATTHEW R. HOLMAN:
With all of that, we set pretty... I would say, pretty aggressive goals for ourselves on the pace we could achieve during this one-year period and the reality is we are achieving it. These are very novel set of products with issues that we haven't really had to tackle before in the ways we're having to tackle them to complete our application review. And as I said, we're attacking this in terms of getting the work done in a very different way, but we are on pace by and large. There are some places where we may not be exactly where we wanna be or where we thought we could be, but there are other places where we're well ahead of where we thought we would be. And I think at the end, when we get to this September 9, and we look back, I think we will have achieved all that we expected to achieve by that date and probably a little bit more than we expected to achieve, at the pace we're going.

MATTHEW R. HOLMAN:
I'm privileged to work with folks, colleagues that are super-dedicated to their jobs, super-motivated.

And in spite of working in 100% virtual, in spite of having so many new staff come aboard, in spite of having such large workload of such novel applications, and in spite of just a multitude of challenges, my colleagues, both in and outside of OS, are really working extremely hard and really, I think, will exceed our very ambitious goals by this September 9.

ANNE RADWAY:
I just want to throw in a follow-up question, this is something that Cristi stated, for major amendments, what does a reset mean?

CRISTI STARK:
Oh, yeah. So essentially, we have, within the statute, a 180-day timeframe for issuing a decision on a PMTA. So, a major amendment essentially resets that 180-day clock. Typically, when we issue a deficiency letter, it would pause the clock. So, say we issued at day 90 when we receive the response, that would start at day 91 for us to pick up. If it's a major amendment though, such as a re-analysis of previous submitted data, that would have been something needed for filing at the start, therefore we reset the clock for the full 180 days.

ANNE RADWAY:
Thank you. OK, next question. And I think Christi has already addressed this a little bit, but Crystal, I'll let you add to it. How do we know our applications have been received?

CRYSTAL ALLARD:
Yeah, so if an application was submitted electronically through the CTP portal, then there are a number of available ways to track the application. So, for example, when it's received through the portal, there's a green check mark displayed and there are also automated acknowledgments. And a user is able to enter the portal and view what they've submitted. This is one of the major benefits to using the portal to submit electronically to CTP and we highly recommend that users use the portal to submit electronically to CTP. And I'll let Cristi weigh in on this if she thinks it's necessary, but if an application was submitted in some other way using physical media like a hard drive or submitted in paper, then when an RHPM completes their acceptance review, they would place a call to the submitter and prepare a letter for either acceptance or refuse to accept.

CRISTI STARK:
In short, and I think Crystal has it right, any application that comes in, whether it's electronic or physical, receives a decision. And that's either going to be an acceptance letter or refuse to accept letter. And I do want to kind of give an update. I know that we had numbers as of April 1 in the presentation, but let's just talk about the three premarket pathways right now, so folks have a sense. 100% of applications submitted under the exemption request pathway and under the substantial equivalence pathway have completed acceptance.

CRISTI STARK:
If an applicant has not received a letter, either an acceptance or refuse to accept, I'm going to have them take a look at what was submitted with the date, make sure it was by September 9, 2020 and contact the assigned regulatory health project manager. If they are not sure who that is, we also have

the AskCTP@fda.hhs.gov available where we can get you in touch with the right person.

CRISTI STARK:
With respect to PMTAs, I can tell you that by the end of July, we expect to complete 100% acceptance for the millions of applications received through that pathway. We are through a significant percentage right now, but I do want to give folks the date so that they know if they haven't seen something for their PMTA by mid to late July, by the end of July, start of August, please start reaching out to your project manager because we will have 100% completion there.

ANNE RADWAY:
Thank you. OK, Joanna, the next question is for you. For PMTA submissions made after September 9, 2021, does FDA plan to maintain an approach where only one deficiency letter is provided prior to making a decision on the application, or will this process change where there will be an option for FDA to issue additional deficiency letters for a submission?

JOANNA C. RANDAZZO:
OK, so Cristi and Matt both touched on this a little bit. As part of our preparations for the influx of the large volume of PMTAs we received, and other premarket applications, we did streamline the review process to generally issue just one deficiency letter to promote efficiency. We are planning to re-evaluate the effectiveness of this process change after the compliance period.

ANNE RADWAY:
Thank you, Joanna. OK, the next question is for Todd and it's a very long one, so I can break it up in pieces if you need me to. We are a very small operation and undertaking a study together, health risk data in comparison to products in the same category, which would mean other e-liquids for open take systems as well as products in different categories, such as cigarettes. It's simply not financially nor logistically feasible in the response period allotted in a deficiency letter.

ANNE RADWAY:
Understandably, large companies have the means to conduct their own analysis of products on the market, conduct varying market research, and chemical analysis of the competing products. We do not have such an operation. We only focus on small-volume manufacturer of e-liquid only for open take vaporizers. Therefore, questions are, given internal confidential data of various companies, how does the FDA suggest we obtain sufficient, detailed information on health risk data and other user data of other tobacco products to compare? That's just the first question, Todd. Do you want me to...

MATTHEW R. HOLMAN:
Todd, you're muted.

TODD L. CECIL:
I should never mute myself. Alright, why don't we go ahead and do all of the questions here. If we can talk about them in a larger context, rather than piecemeal.

ANNE RADWAY:

OK, sure. The next one is, likewise, how can we collect chemistry data or health data of products like ours, existing e-liquids, if other similar products are also currently in the PMTA process as well, and such data is not available publicly? And then the next part is, can articles or general information we can find on public sources, essentially web-based sources, be sufficient for comparison to our PMTA products? And does the comparison need to be specific to flavors or more broadly to the category of e-liquids?

TODD L. CECIL:
OK, there's a lot going on here. Let me try and, at least, address a lot of these questions. So, while evaluating a new tobacco product to determine whether it's appropriate for protection of public health, we do not consider the size of the company. We may have to make a determination as to whether or not the product itself is appropriate for the protection of public health, whether it's large or small. The same goes with the time to respond. As stated earlier, we have a relatively short timeframe, 90-day timeframe, to respond to queries for information that's missing, or that we need to be able to evaluate more fully the information that has been submitted. If we had an extended period of time or were to extend that longer, there'd be no way we can evaluate the products within the timeframe set out by the court.

TODD L. CECIL:
So, we have to maintain these short timeframes. It gives us the best opportunity to review the most products that are available. So, as we take a look at this, it is each applicant's responsibility to support a scientific finding for authorization. The standard does not change based upon the company size or means. As the specific questions pose, it is the responsibility of the applicant to pull together the data, the studies, literature, and findings necessary to demonstrate that the tobacco product is appropriate for the protection of public health. These studies and literature may be peer-reviewed journals, they may be studies conducted by the applicant, they may be studies conducted by a third-party laboratory at the request of the applicants. Where the studies are conducted using tobacco products that are not the subject of the application, the applicant may want to consider relating how the study relates to their products with appropriate scientific justification.

TODD L. CECIL:
As to data concerning competitor products for ENDS, we realized there are no ENDS products that have received marketing orders, and therefore you're free to compare your product to any other product, with adequate justification as to why you chose the competitor and the knowledge about how it responds under the same testing or study conditions that you were reporting for your product. So, one of the things that a application is intended to do is an opportunity for you to tell the story of your product, why you think it's appropriate for the protection of public health, with the data to support your statements. And if you need to find ways of getting testing done, it is your responsibility to find a way to get us the information we need to help us make the decision as to whether or not that product does protect public health, or may protect public health.

TODD L. CECIL:
I don't know if I've answered all the questions, but perhaps.

ANNE RADWAY:

We may get a couple of follow-ups, but that's OK.

TODD L. CECIL:
Fair enough.

ANNE RADWAY:
I think this question has already been addressed and a few other questions, but I'll ask it anyways. And Cristi, if you want to add anything to it that you didn't get in the other questions. But this question says, how does FDA balance, prioritize those reviews with reviews of PMTAs submitted after September 9 and how long can they expect to receive an acceptance letter and, potentially, enter into substantive review?

CRISTI STARK:
Sure. So, I do think the presentations, some of the updates on our website for the progress on our deemed applications, as well as previous answers touched on all of those questions. In short, we are following our defined process with our randomization for our review programs, for the order in which we're reviewing. With respect to acceptance, as I stated earlier, we have completed phase one acceptance for 100% of the exemption requests and SC reports submitted by September 9, 2020. We are complete with a significant number of PMTA applications that were submitted and we expect 100% completion by mid to late July of this year. Any questions regarding status, if an application was received, again, reach out to your assigned regulatory health project manager. And if you don't know who they are, please utilize AskCTP@fda.hhs.gov so we can get you in touch with the correct person.

ANNE RADWAY:
Thank you, Cristi. OK, what is the time period used to determine the number of applications submitted by the September 9 deadline? Crystal, do you want to take this one?

CRYSTAL ALLARD:
Sure. So, after looking at the submission of all applications, we've found that the majority of the applications for deemed new tobacco products on the market as of August 8, 2016, were submitted to the agency within the five-month period before the application deadline of September 9, 2020 at 11:59:59 pm Eastern Time, just to be very specific here. So that basically means that five period goes from approximately April of 2020 to that very specific time on September 9.

CRYSTAL ALLARD:
So for that reason, we're using the time frame to estimate the numbers of applications submitted and received by the deadline for our metrics and reporting. And it's important to know, as Matt mentioned earlier, that these are estimates and that we estimate them to be accurate to within 10%. So approximately 90% accurate, but keep in mind that at any given time, because of the flux in the way that the process works, those numbers are generally mostly accurate, but may not be 100% completely accurate.

ANNE RADWAY:
As FDA continues its review of PMTAs submitted by September 9th, how will it balance prioritize those

reviews? I feel like we've answered this already.

MATTHEW R. HOLMAN:
Yeah, I was gonna say let me jump on this here, because I try to touch upon this earlier, which it is a balancing act and we are prioritizing the applications received by September 9th of last year, but we are using some of our resources, a small percentage, but some resources to address (UNKNOWN) applications they received after September 9th of last year full applications as well as supplemental applications. So, again, I mean, I think you're hearing a similar theme from all of us, which is we recognize the loss of enforcement discretion from the September 9th. And in light of that, we are focusing on the majority of our resources and efforts on completing as many reviews as possible.

MATTHEW R. HOLMAN:
Doesn't guarantee there will be positive orders necessarily, but we think it's important that we at least finish a review, even if some of them are gonna result in negative marketing orders.

ANNE RADWAY:
OK, next question I'll give to Joanna, will any applications be denied for high concentrations of nicotine?

JOANNA C. RANDAZZO:
In short, no, I mean, so there is currently no product standards in place that can be applied to e-liquid categories broadly. So this means that all information that's submitted in support of your PMTAs is considered in its totality. And we consider everything on a case by case basis based on the product in making our APPH determination.

ANNE RADWAY:
Alright, next question. What happens to applications that were submitted by the deadline but have not been notified of their application status or accepted due to the backlog of PMTAs. I feel like Cristi has already addressed this, but, Todd, do you have anything to add?

CRISTI STARK:
Todd, you're on mute.

ANNE RADWAY:
You're on you mute.

TODD L CECIL:
Well I get. I should not mute again, I would say Cris Cristi answered it very well. I'm not sure that I can add anything other than to reiterate that the PMTAs in general by mid-July, all the applications submitted by mid-September, September 9th will be notified if they have been accepted or not, and if they have not received that notice that they should come contact the RHPM for status and if you don't know who our RHPM is, you should contact the AskCTP@fda.hhs.gov for a response.

ANNE RADWAY:
Thank you, Todd. Next question, Cristi, this one's for you. FDA is known for issuing deficiency letters that

request additional data test results within a 90 day response period. Companies are not always able to respond within that period due to the limitations on capacity of labs and other service providers. What is it? What is FDA doing to address this in situations where applicants are otherwise willing to comply in good faith with FDA's request for additional data?

CRISTI STARK:
OK, so we do understand applications were submitted without lab testing with the original application sent September 9 2020, but as I stated earlier, we also expected applicants to continue to have complete applications. And if they didn't have that testing in there, they were to continue testing and amend it with results once received, 'cause I noted that when we go to initiate a review process, we would pull the original application and all amendments received as of that date. If an applicant receives a deficiency letter and they're unable to respond within the 90 days outlined in that letter for a PMTA. It's important that they still respond with what they have and then also give us a detailed plan with a timeline for all remaining data.

CRISTI STARK:
Broadly speaking, I'm gonna note that as with all unauthorized products, generally, if that product hasn't received marketing authorization by the end of the one year review period due to lack of data, it does risk FDA enforcement. So in short, work with due diligence for completion of lab testing and then where possible and we can discuss certain cases with the project manager when we're looking at that application.

ANNE RADWAY:
Thank you, Cristi. Next question for the applied millions of NS products, how could CTP deal with such huge burdens and push for the PMTA process still in time, Matt? Oh you were muted.

MATTHEW R. HOLMAN:
No, Todd seems to be the only one of us that can't figure out the mute unmute button.

TODD L CECIL:
(INAUDIBLE)

MATTHEW R. HOLMAN:
I have no problem being unmuted. It's being muted that that really is a struggle for me. Yeah, I'm not sure I exactly understand the question. How do we push for the PMTA process still in time? And so I'm gonna try to answer as best I can and it's gonna repeat, I think, a lot of things you guys have already heard, which is we we know that we're not gonna be able to review all six plus million of these applications by the September 9. We will review way more. We'll complete the review way more applications than we've ever done in our history within this one year period. For sure, we will we will get a lot done.

MATTHEW R. HOLMAN:
We have done a lot of work ahead of time. We're doing a lot of things new now. We are making adjustments along the way to make sure that we can review as many of these as possible by the

September 9, but we are not gonna get through all 6 million, and that's for sure. And and that's why we came up with what we believe is a very fair triage prioritization process that also is really geared towards having the most significant public health impact that we can in light of what the court has ordered. And so I don't really have anything new to add in responses that we we already haven't said. But again, I reiterate that we are not only on track, I think to achieve what we we had hoped to achieve by the September

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9th, I think we're going to actually have achieved some things that we we didn't necessarily think we would be able to do by the September 9th, in part because of gonna hire and train some more people. And as I said earlier, really a lot of folks across the center that are really dedicated, motivated to try to complete as many reviews as possible by the September 9.

ANNE RADWAY:
Thank you, Matt. OK, next question, can an application use General HPHC testing from other countries? Todd, this one's yours.

TODD L CECIL:
Okeydokey, well I think that we need to break this question down a little bit. When we talk about general HPHC testing, I presume that the the individual who sent the question is indicating that they want to take a look at data that's either been published in literature or that is available on the Internet somewhere. And whether that data comes from in this case have come from different countries. So, the question that I think they're asking is, can I bridge my product with that other material that's been tested out there? And so absolutely it is possible to bridge from your product to other products, regardless of where those products were tested.

TODD L CECIL:
And this can work for HPHC testing from other comparable product types. Now, all data for HPHC is including data from other countries, should be collected using test methods that are suitable for purpose, adequately validated and conducted using an uncredited testing laboratory. And those are the sorts of things we'll be looking for when we take a look at the data that's presented. Now, the applicant may want to include this sort of documentation in their information or in their application. So if you are using General HPHC testing that is descriptive of all of the HPHC collected for all of the ends devices out there and wanna compare your product to it,

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it is certainly a one way to do it and if you're going to go that route, you need to provide data showing why your product lives within this greater context. And those decisions are sometimes more difficult than those that are compared one to one to another product. So it is, again, your opportunity to tell the story. That's your opportunity to to use the data that you have at hand to demonstrate that your product is appropriate for protection of public health.

ANNE RADWAY:
Thank you, Todd. OK, next question. Cristi, this one is for you. Can FDA provide more specific thresholds

for acceptance, filing and scientific review as acceptance letters are received. It appears as if statutory PMTA requirements are not the standard unless there is no EA. Industry is aware of several consortium PMTA templates and specific applications that fail to include a compliant ingredient list. A number identify only the complex ingredients and and a description of the manufacturing and controls. Section 910B 1B and C require the information and the applications are non-compliant. Why are they not immediately rejected? The number of applications to review would be drastically reduced.

CRISTI STARK:
OK, so when we talk about a PMTA, I just wanna note acceptance is gonna be determined by jurisdiction. So basically, is it a regulated tobacco products? And under 21 CFR, it's 1105 and that's that final RTF rule, which includes items such as is the application in English or translated to English. Does it contain product identifying information? Does it contain an EA? And so on. And to date, I haven't seen any issues around acceptance for that. So I will ask if there is an issue or we've seen it that an example is provided to to us and OS, you can send it to myself. You can send it to your (UNKNOWN) health project manager, and we'll look into that. With respect to filing when answering questions such as around ingredient lists,

CRISTI STARK:
I wanna remind folks that some manufacturers don't have access to complex ingredients. So they may rely on tobacco product master files. And as Matt gave a breakdown of the large number of TPMF that's we have, those complex ingredients are considered trade secret information. So it may be reasonable for filing purposes to call it out by the name that it's purchased under or that particular number. Therefore, that substantive review phase when we go into phase three is gonna tackle some of the more finite details for the breakdowns, for the complex ingredients. But I just I kind of wanna note, we are still hitting the requirements in 910B1B for those ingredient lists when we have the full list.

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We're just also trying to be very careful about protection of information as required. And the same holds true for manufacturing. We do have tobacco product master files that describe manufacturing controls and processes in detail through a master file. Therefore, we would take some of the broad statements for filing under the PMTA and look under the tobacco product master file for that and really dig into it during substantive review. But I will state lack of those items would be a basis for RTF. So let's say that you've submitted a closed ends where you neglected to provide any details on your e-liquid in that closed system. If we do not see details such as PGVG or nicotine concentrations or things such as that,

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while you may have a complex flavor, ingredients, something else, but we're missing those items that would be a basis for an RTF. Same thing like for your manufacturing. If you have five different facilities performed for your different stages of manufacturing and let's say three of them, you've completely forgotten or misplaced and they're not in the application that may result in a basis for an RTF as well. I hope that's a little bit more helpful with where we're coming from and also respecting confidentiality of data.

ANNE RADWAY:

Thanks, Cristi. The next question, if there is no long no long term health data about how a product will impact public health, would that product receive a deficiency letter? Matt, do you wanna take this one?

MATTHEW R. HOLMAN:
Sure. Yeah, I would, I think in that scenario, we would like to send a deficiency letter. I mean, I think once we get a substantial scientific review, as we've said a couple of times this afternoon, our intent is to issue a signal deficiency letter. And as I explained with the new language we put in the PMTA deficiency letter, specifically, the intent of those letters is to identify information that we think is necessary to complete our review and make it and make our final determination on whether to issue marketing, brand or marketing denying order. So if there is missing information like no long term health data about the product, we would likely put a deficiency, likely send the deficiency letter,

MATTHEW R. HOLMAN:
and that would certainly be one of the deficiencies. I will reiterate what I believe Todd and maybe even Cristi talked about, which is such data does it, can be public data, it can be public data that. So I guess just to clarify, if if there is no data specific to that, none of this long term data specific to the product that is subject to application that wouldn't necessarily result in the deficiency, because if they did actually give us some public data and they the application clearly explain how that data is applicable to the product subject to the application. If we we agree with that, we would actually send it officially.

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Now, if they submitted some general public health for a long term data and they didn't link it to their didn't adequately link it to their product, then again, that would result in deficiency.

ANNE RADWAY:
OK, next question is for Crystal, CTP's website has frequent updates. Is there a good way to know when those changes are made?

CRYSTAL ALLARD:
There are a couple of different ways to tell when our website's changed, all of our websites have content current as of dates on them up at the top right corner. You can also always sign up for email. It's from CTP, which would give you notifications when ever CTP has something like to share with you. For instance, there are multiple types of email outreach that describe things like regulation, updates, guidances ,enforcement actions, compliance related announcements, etc. and CTP's also on social media, so, for instance, you can follow us on CTP on Twitter @FDATobacco. And if you have any specific questions about content on the websites, you can always email the e-submissions Help Desk or the AskCTP email address.

ANNE RADWAY:
Thank you. OK, we have a follow up for Todd on controls and standards. The question is, we manufacturer NS devices, how do we know what controls and standards to test vapor output against when there is there are no known standard e-liquids.

TODD CECIL:

Well, you are asking a fundamental issue having to do with all of the tobacco products. The numbers of standards that are available to us are fairly limited, and it is something that we would love to see change over time, whether that is an ISO change or whether it's a progressive change, whether there are other standards that are developed, all of those would be tremendously helpful. However, none of that is the case at the moment. And so what we recommend is that, again you tell your story, choose the standard product that you think is appropriate. Explain to us why you say that standard is the appropriate for material to use and then go ahead and do your testing. And if we disagree with your use of that material we'll include a deficiency requesting more information and provide more guidance as to what information would be necessary for us to consider it. However, it really does come down to what it is you think you need to do to provide information about your product so that we can make that determination.

ANNE RADWAY:
OK, thanks, Todd, I have another question for you and some of this you may have already touched on, but what are the stability testing requirements at a minimum for PMTA? Stating a variety is not always helpful. What time points are required is liquid in aerosol testing needed at all time points for E-liquid manufacture? Manufacturers. Do device manufacturers need to test devices at a later time point to understand how device functions with older liquids, other liquids?

TODD CECIL:
Yeah, no, older liquids makes sense. So, the choice of which endpoints to track and the number of time points to collect are the responsibility of the applicant. It's going to depend upon the type of shelf life you're using for your product, and it's going to look at what are the critical modes of failure for your given product. So, in the case of a E-liquid, I think that's most of the questions here have to do with E-liquid. We're looking for and are concerned with a number of things, including microbial growth and physical degradation over the shelf life of the tobacco product.

TODD CECIL:
So those are the sorts of things we're going to be looking for. Now, whether how often you test that and what are the specific time points are e-material. You do the ones that you think are appropriate, you provide as many as you need to demonstrate that there is a trend or there's not a trend in the either microbial growth or the growth of TSNA's caused by microbial growth or other signal events that are going to give us an understanding of the stability of the materials and that should be provided in the application. So, now if you have not completed your full study at the time of submission, so back in September when you submitted you only finished six months of your intended two-year study, we would recommend that you go ahead and include that additional information as it becomes available through amendments and until such time as you've completed your full study. Going more to the question. Another question is, should we be looking at aerosol testing of all E-liquids that have been sitting on the shelf for two, three, four years? That will depend upon those critical modes of failure.

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And if there's a, if you believe that there is a potential for failure of an E-liquid, that it's going to see degradation that may result in a change to the constituents that a user is exposed to, then you should provide that information to us. If that is not the case, then that information may not be necessary. But it

all depends upon your product, which you should know better than anybody else.

ANNE RADWAY:
Thanks, Todd. Next question, will deferred enforcement past September 9th, 2021 happen for all applicants or only on a case by case basis? And will the FDA need to petition Judge Groome's court to extend that time? Joanna, I'm going to give this one to you.

JOANNA RANDAZZO:
Yeah, I'll take this one, and this one we kind of touched on this in a couple of other responses. So, similar to what we had said earlier, we definitely understand the interest in this topic and we're not planning to discuss it outside of the scope of this meeting. But FDA does have the discretion to defer enforcement action against that particular product on a case-by-case basis after the one-year period for review comes to an end this coming September. But broadly speaking, it's important to remind everyone if products are not authorized by September 9th of 2021 and you knock them off the market at that time, they risk FDA enforcement.

ANNE RADWAY:
In recent deal deficiency letters received CTP has stated, to maximize review efficiency, we do not intend to issue additional deficiency letters for these applications. If we respond to the first deficiency letter in our best with our best attempt but CTP has follow-up questions, will CTP issue an NAC or no market order letter, or will we have a way to respond to any follow-up questions? Cristi, can you take this?

CRISTI STARK:
Yes. So I touched on this earlier based, to maximize our review efficiency we intend to make a decision based on the response to the deficiency letter. In short, we're looking to issue only one deficiency letter. If there are additional clarifications, FDA will contact you. You'll hear from your regulatory health project manager. Our goal is to issue a decision via order after we review that first response. But there is a small opportunity if there are clarifications for FDA to reach out and discuss.

ANNE RADWAY:
Thank you, Cristi. OK, how long is the process of checking the content likely to take? When can the first approvals be expected? Are there already positive results? Thank you very much for your effort. Matt, I'm going to let you take this.

MATTHEW HOLMAN:
Yeah, let me jump because I did touch on this towards the end of my presentation for SENEAX, we have already issued hundreds of order letters. As of April 1st, it was nearly 300. That number is even higher today. The vast majority of those letters under the EXNC programs have been positive order letters, although there have been some negative as well. For the PMTA program as I stated, we have not yet issued any final orders, but we do anticipate issuing orders by the September 9th. I don't know when we will issue. It's hard for me to predict when will issue our first order letters. I know this ask about approval. I'm just going to use same more broadly ordered letters which could be positive or negative. It's hard for me to say when we'll issue those under the PMTA program. Again, these are really novel

products with a lot of scientific and policy, and regulatory issues that we're grappling with. But we are on track to be able to issue orders by September 9th. I just don't know again, how far ahead of September 9th, you'll see our first order letters under the PMTA program.

CRISTI STARK:
Anne, I just want to jump in with one bit of terminology, Matt probably knows, I'm going to say this. Our center, we do not approve products. We do not approve tobacco products. There is no safe tobacco products. And actually stating it's an approved tobacco product is a violation where you could have enforcement action. So, our orders we either authorize so you would receive a marketing order where it's authorizing or we deny. We do not approve, though, in CTP.

ANNE RADWAY:
All right, next question, what is the status of the PMTA and SE final rules, Joanna?

JOANNA RANDAZZO:
I'll take this one. So, as many of you are probably already aware, on January of this year, the PMTA and SE rules were displayed in the Federal Register but did not publish. And subsequently, the next day, a memo from the White House ordered the withdrawal of any rules that did not publish in the Federal Register by noon that day. So, these rules have been withdrawn, but FDA is working closely with the new administration to advance regulations and policies that were withdrawn and would be in line with the agency's public health mission. So, stay tuned for more. You monitor our Web site, of course, and everybody will be made aware when that happens.

ANNE RADWAY:
OK, next question. What would be the approach for product improvement, modifications, and design, or process during the MTA scientific review process? Cristi, you want to address this?

CRISTI STARK:
Sure. So, I want folks to remember what the definition of a new tobacco product is in 9.10. Any modification to a product renders it new. Any new product is going to be required to be authorized through one of our three pre-market pathways. Therefore, when we're looking at applications, each application is specific to that product. If an applicant is proposing to modify a product, then they will need to submit the application. And the one thing that I want to note, there is a little bit of confusion over this. If you've previously received authorization via PMTA, one quick route to modify a product is to submit what we call a supplemental PMTA, where you're referencing that original PMTA.

CRISTI STARK:
But I want to note a supplement can only be sent in once that product has been authorized. It cannot be sent in prior to that because FDA has not rendered a decision authorizing it. This is different than an amendment which you've heard us talk about earlier. An amendment is where you're sending additional information to a pending application or decision. So, you could amend either your original application or you could even amend a supplement later. Therefore, when you're looking at modifications, I do recommend some discussions with your assigned regulatory health project manager. We have three premarket pathways. There may be options that you haven't considered. So, we may want to look at a

supplement for a PMTA.

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You may want to look at an option for an exemption request depending on if it's a minor modification of a tobacco additive. Or we may want to look at the SE pathway if you've received authorization through there. I know this question is specific to PMTAs, but I just want to do a reminder when we're talking about all three programs and let you know that your RHPM is a great resource for it and a general reminder that a supplement is only when the PMTA has been authorized.

ANNE RADWAY:
OK, thank you. We have a few more minutes for a few more questions. Will the FDA weigh tobacco industry-sponsored versus academic research similarly, while reviewing the public health standard and PMTA's, Todd?

TODD CECIL:
I will try to be brief. The FDA considers all available evidence in reviewing PMTAs. If the research and the data were derived from an appropriately designed study and fit, that is fit for purpose then is considered consistently across all sources.

ANNE RADWAY:
OK, thank you. Let's get one more in. When our product was added to the product list, did that provide us an extra year of enforcement discretion? Cristi, you want to take this one?

CRISTI STARK:
Yep. In short, the answer is no. So, if the application was submitted by September 9th, 2020, FDA generally intends to continue to defer enforcement discretion for one year. So, that's up to September 9th, 2021. I want to note that the product list is one source of information to know the applications for the particular products that were submitted. But I want to note that that is not the only source of information. To be added to the product list there were several criteria that needed to be established. And I want to note that there may be some applications submitted where we do not have products listed on our product list due to an applicant's not responding to FDA. When there were questions about the marketing status of their particular products or lack of a timely response to the specific question that was asked. So retailers, if you're out there, I encourage you to talk to manufacturers to see what your options are. If a product can continue to be sold and can take advantage of that one-year enforcement discretion.

CRISTI STARK:
But in short, the enforcement discretion period is from September 9th, 2020 to September 9th, 2021, and less during that time period, that particular product has received a negative decision from FDA, such as they refused to accept, refuse to file or a denial such as found not exempt NSC or the marketing denial order.

ANNE RADWAY:
OK, thanks, Cristi. We, I don't think we have much time for any other questions, but if you all have

additional questions or if your question did not get answered, please reach out to the CTP. To CTP by using the appropriate email address, which will be listed on screen after the meeting. So, I want to thank everyone again for joining us today. We thank you for all of your questions and hope we are able to provide you with more information on dim product review. Again, the presentation slides along with the recording of the meeting, will be posted to CTPs website in the coming weeks. And we also want to encourage you to access health, access the helpful resources CTP has available on its website for additional information on submitting tobacco product applications, updates on the review, progress, and other helpful guidance. So, we just want to thank you guys again. And Matt, do you want to say the last word?

MATTHEW HOLMAN:
Yeah, sure. Just a couple of things, one, thank you to everyone who attended this, we had a really good turnout. I hope you found the information of some of the information here very useful to you and want to especially thank those who took the time to submit questions. I don't know what the total tally is, but I know we receive hundreds of questions both before and during the meeting and I really appreciate you guys taking the time to submit those to us so that we could try to do our best to provide useful information to everyone. But really, lastly, I want to thank all the folks on the screen right now for being willing to join me here and try to answer some really challenging but really important questions that we're receiving from stakeholders.

MATTHEW HOLMAN:
Really appreciate all the work you guys are doing, both before and during the meeting, to make this successful. And then also want to thank, there's a lot of folks both inside and outside the Office of Science that you're not seeing on video right now that have been instrumental ahead of the meeting and during it and making this successful. So, I just want to thank all of my colleagues within CTP for their work to pull this off. And really just want to point out to everyone that as it came out over and over again during this meeting, we all have a lot of work within CTP ahead of us still on our plates, and all the folks you see on screen, all the folks behind the scenes that you're not seeing, they've all, put in the extra effort to make this meeting a possibility without losing pace, because we got some little inkling that people are worried about how many reviews we can get through by the September 9th.

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And, you know, we are able to pull this morning because so many of my colleagues are willing to put in that extra effort without losing pace on the work we're doing by September 9th so that we could spend this time this afternoon trying to help stakeholders understand where we're at and clarify a lot of issues that the US might have. So, with that, just thanks to everyone and I hope you all have a wonderful weekend.