# User fee negotiations in US offer hope for improvements to interactive review for medical device submissions

*Kristin M Zielinski* discusses the shortfalls of the Food and Drug Administration's interactive review programme and the improvements "on the table".

The US Food and Drug Administration's interactive review programme for medical device marketing applications is a critical process aimed at ensuring that companies are able to understand and meet the agency's expectations and bring their products to market in a timely fashion.

The programme was formalised in the Medical Device User Fee Amendments of 2007 (MDUFA) as part of the reauthorisation of the Medical Device User Fee and Modernization Act (MDUFMA) of 2002, following successful negotiations by the medtech industry. Its creation was intended to improve interactions between FDA reviewers and companies during a product review, both to resolve minor issues informally and to alert the applicant to major issues identified by the FDA in advance of the agency issuing a formal letter.

Despite the issuance of a guidance document governing the interactive review process, the programme has been applied inconsistently and its results have generally not met expectations. While the FDA and industry both agree that the programme is important, some agency officials appear to be concerned that, if overused or used incorrectly, the process can lead to increased reviewer workload and can delay submission timelines (rather than streamline them as intended).

In today's shifting regulatory climate, with impending changes to the FDA's 510(k), or pre-market notification, programme, increasing scientific data requirements for devices and departures from regulatory precedent, companies are more unsure than ever as to what is needed to gain regulatory clearance or approval of their products.

Accordingly, FDA and industry representatives are currently engaged in negotiations regarding the reauthorisation of the medical device user fee legislation and proposed improvements to the interactive review programme are on the table. These negotiations offer hope that the programme will be further "institutionalised" within the FDA and that formal mechanisms to track its use and outcomes will be implemented starting in Fiscal Year 2013.

This article examines the issues surrounding the interactive review programme and discusses the improvements to the process that are being considered ahead of the reauthorisation of MDUFA, which must be enacted by 30 September 2012 to prevent the user fee programme from expiring. It also recommends steps that companies can take to improve the efficiency of product submission reviews in the meantime. This article is based solely on a review of the minutes of stakeholder negotiations for MDUFA's reauthorisation and other publicly-available information.

## The original goals

Medical device user fees were first authorised around nine years ago as part of the enactment of MDUFMA to allow the FDA to collect fees from industry for several types of pre-market device submissions such as 510(k) submissions, pre-market approval applications and PMA supplements, and biologic licence applications.

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In return, the agency committed to certain performance goals for the timely review of the submissions. Other goals included improving the scheduling and timeliness of pre-approval inspections, holding annual stakeholder meetings, and holding formal and informal meetings. The user fee legislation must be reauthorised every five years in order for the FDA to continue collecting user fees.

In 2007, Congress passed the FDA Amendments Act of 2007[1], which reauthorised MDUFMA and set additional performance goals. A 27 September 2007 letter from the Secretary of Health and Human Services to the Chairman of the Committee on Health, Education, Labor, and Pensions of the Senate[2] outlined the goals of MDUFA 2007 (see section 201(c) of FDAAA), including a formalised process of interactive review for pre-market submissions. In this letter, the agency committed to issuing a guidance document that described the interactive review process within three months of FDAAA's enactment. In December 2007, the FDA issued a final guidance document on interactive review, which was updated in February 2008[3]. The updated guidance, entitled Interactive Review for Medical Device Submissions: 510(k)s, Original PMAs, PMA Supplements, Original BLAs, and BLA Supplements, was immediately placed into effect.

According to the 2008 guidance document, the interactive review programme aims to:

- improve the interaction between the FDA review staff and the applicants during the review process;
- prevent unnecessary delays in the completion of the review, thus reducing the overall time to market;
- try to ensure that the FDA's concerns are clearly communicated to the applicant during the review process, as appropriate;
- minimise the number of review cycles;
- minimise the number of review questions conveyed through formal requests to applicants for additional information; and
- ensure timely responses from applicants.

In the guidance, the FDA indicates that all appropriate forms of communication (e-mail, facsimile (fax), phone calls, meetings and letters) may be used. However, the preferred method of communication is informal written communications (e-mail or fax) for documentation reasons; meetings are cautioned against because of the administrative requirements and time required to schedule and execute them. In terms of timelines, the guidance outlines that the FDA is to communicate with the sponsor "as needed", but not prematurely (ie not in the middle of the review of a particular section of the submission), and is to establish timelines for applicants to respond on a case-by-case basis according to the review clock for that submission.

The guidance describes the role not only of the FDA, but also of the applicant, in the review of pre-market submissions. In terms of the applicant's role, the agency outlines a number of steps they can take to facilitate the interactive review process.

One recommendation, which is always a key factor in a successful review, is that the sponsor provides a complete submission that contains all of the required elements, and complies with guidance documents or relevant material/testing standards for that type of device. The FDA also recommends providing complete responses to any issues or deficiencies raised by the agency informally during the review, or in a formal hold letter. Finally, the guidance emphasises that it is important to provide complete contact information in the cover letter for each submission.

Situations described in the guidance where it is appropriate for the applicant to contact



 

the FDA review team include to:
- clarify or discuss deficiencies cited by the FDA during the review;
- discuss timelines for responses or other procedural questions;
- clarify or correct information previously submitted;
- indicate an intent to submit additional information; or
- request a meeting.

The agency cautions against contacting the review team simply to ask for status updates, as this can distract from the review.

In terms of the FDA's role in the review of 510(k) notices and PMAs, the guidance outlines the types of "minor" requests that can likely be handled informally through the interactive review process. Examples of these types of requests include:
- revisions to administrative items for 510(k)s or certifications for PMAs;
- additional information concerning the device (details regarding features, or engineering drawings, for example);
- clarification of test methods or results for pre-clinical studies or sterilisation validation;
- omitted manufacturing documents for PMAs;
- published literature;
- post-approval studies for PMAs; and
- edits to labelling.

For such informal requests, the FDA does not typically intend for the responses to be filed as formal submissions with the agency's Document Mail Center (DMC), as this would introduce the administratively burdensome requirement of processing the submission. Rather, the guidance specifies that responses to informal requests should typically be provided to the requesting reviewer directly.

In addition to more minor issues that can be resolved informally, the guidance also indicates that the FDA should (where appropriate) informally alert the applicant to "major" issues concerning the marketing submission prior to the issuance of a formal hold letter (ie so that there are no surprises). Examples of major issues include requests for additional pre-clinical testing; additional data to address a safety issue; or additional analyses of clinical data included in the application. The guidance specifies that the purpose of such an alert is as a courtesy to the applicant, and to allow the applicant to begin work on collecting the information requested to address the agency's concern in the meantime. The FDA cautions that the applicant should wait until receipt of the formal hold letter before submitting a formal response. If the response is submitted following the informal communication, but prior to receipt of the formal hold letter, it will be treated as an unsolicited major amendment, which could delay the review process.

## Programme changes contemplated

It has been widely recognised, by both industry and the FDA, that the interactive review programme has not been as successful as was originally hoped. Industry often complains that the process is being applied inconsistently by the agency. The willingness of a reviewer from the FDA's Center for Devices and Radiological Health to interact informally with a company regarding an application can vary from division to division, from branch to branch, and even within branches.

> Despite the FDA's stated commitment to interactive review, opinions within the agency appear to be at odds

Some reviewers choose not to use interactive review at all, which can be extremely frustrating for applicants, who feel as though their submissions have entered a "black hole". In addition, while reviewers may use interactive review to communicate minor issues, companies often feel "blind-sided" by major issues that arise in formal "hold" letters, as the process to alert sponsors to these issues (eg management review) is generally not practical in the timeframes given. All parties appear to agree that improvements are needed, as discussed in recent negotiations regarding the reauthorisation of MDUFA[4], described below. While it appears likely that the interactive programme will remain in the new legislation, and there is hope it will be strengthened or expanded, its ultimate format is yet to be determined.

## The programme in practice

Despite the issuance of the interactive review guidance document, the programme is voluntary and its use is at the discretion of individual FDA reviewers. Unlike goals for review times for pre-market applications, the agency has not issued specific performance goals or metrics to track the use of the interactive review process. In updates published by the agency regarding MDUFA (FY 2009 Performance Report to Congress for the Medical Device User Fee Amendments of 2007[5]; FDAAA Implementation – Highlights One Year After Enactment[6]; and FDAAA Implementation – Highlights Two Years After Enactment[7]), only general statements regarding interactive review are included – specifically that staff have been trained and interactive review is "standard operating procedure".

In addition, despite the FDA's stated commitment to interactive review, opinions within the agency appear to be at odds. Although interactive review has been touted as a method to streamline review processes, some agency staff believe it can also add additional workload for FDA reviewers. In an environment where many reviewers are already stretched to their limit, there may be a disincentive for them to use the process in some cases.

As evidence of this, pre-market submission review times have been increasing in recent years, despite review goals associated with the user fee programme. Along with other factors, the interactive review process has been blamed for part of this increase, either through its overuse, or because it has been used to handle issues beyond its scope.

At a 9 February 2011 meeting on MDUFA's reauthorisation[8] as outlined in the meeting minutes, the agency presented an analysis of original PMAs and panel track supplements received by CDRH under MDUFA II from fiscal years 2008-2010 to determine factors contributing to review times in excess of the 180 day Tier 1 goal. It was reported that seven submissions that missed the Tier 1 goal had used interactive review extensively. The FDA concluded that using the interactive review process more broadly than intended may result in "excessive" back-and-forth communications regarding an application while the review clock is running, causing the agency to miss review goals.

In addition, the FDA's Transparency Task Force highlighted this issue in its January 2011 report: FDA Transparency Initiative: Improving Transparency to Regulated Industry[9]. As part of the transparency initiative, the agency considered comments from industry encouraging informal communications and meetings between industry and the FDA on product submissions. In the task force report, the agency acknowledges the importance of such informal communications, but states that "meetings and frequent informal communications are resource and time-intensive" and concludes that "given current resources, it is not feasible to significantly increase the number of meetings and informal communications with FDA staff without decreasing review efficiency".

## Current negotiations

FDA and industry representatives have been negotiating MDUFA's reauthorisation in a series of meetings this year[10]. The agreements reached by both parties will form the basis for user fee legislation, which must be enacted by 30 September 2012 if the user fee programme is to continue. Part of these negotiations relate to goals for the interactive review process.

At a 30 March meeting[11], the FDA presented its perspective on the interactive

review programme. According to minutes of the meeting, the agency indicated that it views the programme to be of help primarily for exchanging information regarding minor deficiencies noted during the review of a submission. The agency does not use this process to alert sponsors of 510(k) submissions that it has reached a not substantially equivalent (NSE) decision because such communications require sign-off by FDA management, but interactive review requests do not require management sign-off. Industry noted that the interactive review guidance, in fact, allows the FDA to alert sponsors to major issues. However, the agency responded that for practical reasons (primarily the requirement for management sign-off regarding communication of major issues, and the fact that sponsors may want to try to "negotiate" on the issue), this is not generally done interactively.

As outlined in the minutes, the FDA also provided more detail on how it has implemented the interactive review internally. Specifically, in addition to releasing the interactive review guidance, the agency added an interactive review log to the document tracking database and trained staff on the interactive review procedure in November 2007. The FDA confirmed at the March meeting that interactive review is an element of the core competencies for reviewers.

The agency also reported that, to identify issues concerning the interactive review process, it had conducted interviews as part of a 2010 survey that assessed the perception on the use of the programme by staff from its Office of Device Evaluation and Office of In Vitro Diagnostic Device Evaluation and Safety. The FDA also looked at data from the interactive review log. According to the meeting minutes, the agency found that reviewers do not always track their interactions on the interactive review log because it is time-consuming, and those that do, do so inconsistently (some count each interaction, others provide an overview of interactions, etc). Despite these limitations, the FDA's data showed that the number of 510(k) notices with at least one interactive review logged in the tracking system decreased from 2008 (47%) to 2010 (36%); the agency theorised that this was due to increased reviewer workload.

The ODE/OIVD survey also revealed the following trends since 2005:

- 38% of staff reported increased use of interactive review, 43% reported no difference in use, and 9% decreased use;
- 10% of staff believe that instances in which interactive review benefitted the overall review have decreased, 64% said it remained the same, and 20% said it increased;
- 7% of staff reported that interactive review "does not work at all";
- reviewers' reasons for choosing not to use interactive review include:
  - they were planning to send a letter anyway for more significant issues (32%);
  - there was not enough time left on the clock (32%); and
  - they believed the data being requested would take too long to collect to use the interactive review process (31%).

Finally, at this meeting, the FDA outlined potential considerations that reviewers take into account in deciding whether to use interactive review, including whether the questions are minor or major, the review clock, and even the historical responsiveness of the sponsor.

## Engaging in the pre-IDE process prior to submitting a marketing application offers an opportunity to develop a relationship with the review team

At a 13 April meeting[12], the FDA responded to a call by industry for the interactive review process to be tracked by proposing mandatory tracking as part of the MDUFA reauthorisation. According to minutes from the meeting, the agency also noted that it would identify best practices and incorporate them into its good review management practices guidance, establish interaction goals for 510(k)s and PMAs, and hold yearly meetings. The agency stressed that the proposal does not include mandatory use of interactive review, as it is not always needed. At meetings on 4 May[13] and 1 June[14], industry expressed concern and frustration regarding the implementation of the interactive review policy, which is extremely important to industry.

### Recommendations for industry

While interactive review is left largely to the discretion of the reviewer, and changes to the process are yet to be determined, there are things that companies can do in the meantime to contribute to interactive and productive review cycles. These include the following:

- **Begin interacting early.** Engaging in the pre-investigational device exemption process prior to submitting a marketing application not only provides an opportunity for you to gain important feedback on the data requirements for your submission, but also offers an opportunity to develop a relationship with the review team. Because most, if not all, of the review team involved in the pre-IDE process will eventually be involved in the review of the subsequent marketing application, developing a working relationship with these individuals can increase the chances the review team will be willing to work interactively during their review.
- **Follow the FDA recommendations in the interactive review guidance.** The FDA provides several recommendations in the guidance to facilitate this process. Specifically, the agency recommends that companies submit complete submissions that contain all of the required elements, comply with guidance documents or relevant material/testing standards, provide complete responses to any issues raised by the FDA previously, and provide complete contact information. By ensuring that there are no major "gaps" in your submission, it may be possible for the reviewer to focus on more minor issues that can be resolved interactively.
- **Initiate interactive review where appropriate.** The FDA guidance outlines the situations in which sponsors of applications may contact the review team to clarify or resolve issues interactively. For example, if you have discovered an error in your submission, or something that is not clearly presented, it is appropriate to contact the reviewer to alert them to the situation. Likewise, if you identify additional information that you plan to submit in an unsolicited manner, you may choose to alert the reviewer to this upcoming amendment. In most cases, reviewers will appreciate such communications, because it facilitates their review. It is not recommended, however, to contact the reviewer simply for status updates.
- **Get to know your reviewer.** To the extent possible, develop a working relationship with your reviewer. In the event that communication is warranted, for example, if the reviewer has asked an interactive question, consider accompanying email responses with phone calls to discuss issues. If you plan to submit multiple applications to the same branch (eg a string of 510(k) notices for products within the same therapeutic area), this may be an opportunity to develop a long-term relationship with members of the review team who will likely overlap for each submission. As noted above, be careful not to "bother" the reviewers, and respect the review process.

### Conclusions

In today's uncertain regulatory climate, interactive review is more important than ever to medical device companies. As part of the user fee negotiations, as outlined in the minutes of recent stakeholder meetings, the



 

FDA appears to have agreed that the interactive review process is an important programme and that it needs to be improved to ensure its success. Such improvements will likely include a more formal method of tracking use and outcomes of the programme.

While the ultimate outcome of the user fee talks is unknown, the negotiations offer hope to companies that the interactive review process will be used more widely and/or consistently in the future, at least for the resolution of minor issues related to product submissions. However, it appears that the issue of alerting companies to major issues (eg an NSE decision) will require significantly more negotiations. Nevertheless, there are things companies can do in the meantime to promote interactive product reviews.

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