FDA INSIGHTS

How to (Or Not to) Impede FDA Reviews

The little things can mean a lot in facilitating or derailing the review process.

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The views and opinions in this article are those of the author and do not necessarily reflect those of the US FDA, the US Department of Health and Human Services, or the Public Health Service.

Imagine this scenario: your clinic is full of patients waiting to be seen. Per protocol, records have been pulled for these patients in anticipation of their visits. Unfortunately, these records have been thrown into several bins outside of your office. Worse yet, the pages are loose. There is no staff to help organize the files. Each patient must be seen at his scheduled time.

Such chaos in absence of changes in deadlines is not uncommon in submissions to FDA. The Peripheral Vascular Devices Branch of the Division of Cardiovascular Devices has identified some of the common problems that should be easily avoided. They are presented here, accompanied by analogies that illustrate how they might translate into an average day in the clinical setting.

DEAR MR./DR./MS. NAMELESS

FDA: There have been times when a reviewer would like to ask for more information, but accurate contact information has not been provided.

Clinic: You need to call a patient to reschedule his appointment, but the contact information is incorrect.

THE DISAPPEARING ACT

FDA: Many submissions reference attached appendices, drawings, or tables, but when flipping to the point of reference the data surprisingly have disappeared, moved, or partially vanished.

Clinic: The record references blood work, but no results are attached.

THE NAME-TRADING GAME

FDA: From the device description to the engineering drawings, the whatcha-ma-call-it gets changed to the dingle-hoo-ha. We are left to guess whether these two devices are truly one and the same.

Clinic: The first page of the patient's record identifies him as Mr. Smith. The CT identifies the patient as Mrs. Jones. Was it really Mrs. Jones that had the CT, or was it Mr. Smith?

THE GREAT TRANSFORMATION

FDA: Tables are often the most concise way to provide data for review, but they can also be the most confusing. From one table to the next or from the tables to the text, the numbers of patients, adverse events, and endpoints can change and/or disappear. The reviewer may in turn worry more about data integrity, spending more time adding up the numbers in the tables than looking at the science behind them.

Clinic: The size of the aneurysm is listed as 4.5 cm in the letter from the referring physician, but the attached exam notes state that the aneurysm is 5.4 cm.

A HOP, SKIP, AND A JUMP

FDA: Thousands of pages of data are reviewed by the FDA every day. It seems simple, but often there are no page numbers in the submission, rendering it nearly impossible to find all of its relevant pieces.

Clinic: First you see the patient's 6-month follow-up imaging, then his preop, followed by his 2-year…

I'LL HAVE MINE IN COLOR, PLEASE!

FDA: The stress analysis is the key data needed to demonstrate that the device should not break when used clinically. Unfortunately, the data that are color-coded are provided in black and white.

Clinic: The CT scans for your patients are black and white copies of copies.

DOES ANYONE HAVE THE TIME?

FDA: The impossible does creep into submissions from time to time. Credibility is lost when the Data Safety and

Monitoring Board was to have met on February 29 when it was not a leap year.

Clinic: The patient's death was reported to the FDA; however, the patient is standing right in front of you.

NOW THAT TAKES TALENT

FDA: Reviewers do read submissions, every word, but that does not mean that the submissions have been memorized. Often, modifications to devices are written with the assumption that the reviewer is intimately familiar with the previous design. Similarly, certain questions are answered by the sponsor, but the questions themselves are not identified.

Clinic: The person in charge of documenting the patient's comorbidities assumes that you remember what year the patient had an MI.

DO A DOUBLE TAKE

FDA: Files arrive with inconsistent numbers reported, missing pages, incomprehensible sentences, conflicting data and results, typographical errors, as well as with the problems as described above. Proofread, please!

Clinic: You plan to do surgery on the lower right leg based on the referral, but this leg had been amputated in 1993.

PLAYING HIDE-AND-SEEK

FDA: Investigational Device Exemption (IDE) letters inform sponsors that future correspondence regarding the IDE are required to be submitted in triplicate, the IDE number must be referenced, and the package needs to be sent to the IDE Document Mail Center. Triplicate means (at least) three copies. The IDE number is the number identified as such on the FDA letter. The IDE Document Mail Center is not the reviewer. When submissions are not clearly marked, extra copies and appendices can end up on a shelf in the Document Mail Center rather than with the reviewer, leaving the reviewer to wonder where, oh where, have the appendices gone (see The Disappearing Act, above). Similarly, if documents are sent straight to the reviewer, bypassing the Document Mail Center, the company will be wondering where, oh where, its review has gone.

Clinic: Data from the following physician is sent to your home address rather than the office.

THE EXPENSE OF SAVING POSTAGE

FDA: Multiple submissions often get sent in the same package and can be mistakenly logged in as one submission. When this happens, only the top document enters the review queue until the problem is identified by the reviewer.

Clinic: The appointment book only lists Mr. Smith, but Mrs. Smith and her mother were also to be seen that same day.

NEED AN ANSWER PRONTO!

FDA: A request for a live case comes in for a meeting that starts next Sunday. A patient needs to be treated as soon as possible, but prior FDA approval is needed as the treatment would involve a protocol deviation. These requests come in with the other piles of submissions and can be tucked into the review queue without being identified as urgent.

Clinic: There is no triage in the ER.

WHATEVER HAPPENED TO "HEADS UP"?

FDA: Not infrequently, major submissions show up without warning. Reviewers manage many projects at one time. Knowing what files are arriving when is critical in planning how best to allocate our resources.

Clinic: Your favorite referring physician sends a case to you, but fails to let you know before the patient shows up that he has a ruptured aneurysm.

YOU WANT US TO SHARE?

FDA: Two copies of a response to a 25-page IDE deficiency letter arrive on the desk of the reviewer. There are statistical, clinical, engineering, animal study, and biocompatibility concerns that need to be reviewed by the respective consulting reviewers who incidentally reside in four different buildings. Extra review time is not added on to the mandatory deadlines to make or get additional copies.

Clinic: Three copies of the angiographic results are needed—one each for the surgeon and the cardiologist, as well as one for the patient's record. Only one is provided, and the patient requires emergency treatment necessitating clearance by the cardiologist and planning by the surgeon.

THE GOAL

The goal in submitting a file to the FDA should be to allow the reviewer(s) to understand the information provided such that at least intelligent questions can be asked, if not a full approval granted. To facilitate the review, common sense should be applied, which will greatly improve not only the efficiency of the review, but also the mood of the reviewer. Communicating with the reviewer, numbering pages, thoughtful organization, proofreading, proofreading, proofreading, sending a copy of the FDA letter with the responses, and sending enough high-quality copies to the right place can go a long way toward establishing a successful, collaborative relationship with FDA. ■

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