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Your Dataset Looks Fine – But Does It Comply with ’99?

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ABSTRACT

This paper highlights the role of best practices in Clinical Programming as it relates to regulatory compliant submission of New Drug Applications to the Food and Drug Administration. FDA Form 356h lists 20 Items to be included as part of this application. A Guidance document published by the FDA in 1999 gives detailed requirements for electronic submission of Form 356h. Item 11 on this list is, “Case Report Tabulations (CRTs)”. CRTs are the main work products produced by the Clinical Programming teams in the form of datasets.

More recent Guidance from the FDA address eCTD formats and Electronic Signatures on electronic submissions, but the 1999 Guidance on Item 11 remain current. This paper discusses suggested best practices for Clinical Programming to produce ’99-Compliant datasets.

INTRODUCTION – PROGRAMMING TO A PURPOSE

Clinical Programming teams need to have a good understanding of how their work products will be utilized so that they can ensure that requirements are being met even during the initial set up processes. A seemingly minor assumption made at the beginning of the programming phase can make the resulting dataset non compliant and thereby trigger expensive rework.

Given the long, complex process of drug development today that involves multiple parties adhering to exacting regulatory standards, it is relatively easy for individual statisticians and programmers to lose sight of the overall goal. Clinical Programming teams need to do all they can to help with quick, accurate and complete submissions.

The New Drug Application form (FDA Form 356h) lists 20 items to be included in the application. Item 11 is of immediate interest to Clinical Programming as it relates to Case Report Tabulations (CRTs). Other items on the Application Form are important but Item 11 serves as the end goal for Programming teams.

All organizations have quality control or regulatory teams set up to review datasets produced by Programming teams and to evaluate compliance with FDA Guidance of 1999. The time, effort and costs associated with this compliance check can be lowered substantially if Programming teams are involved before they start any programming work.

THE GOAL – NEW DRUG APPLICATION VIA FDA FORM 356H

Submitting an application for New Drug approval is a team effort. The Application Form has 20 Items that need to be completed. Different teams are responsible for assembling and formatting material required to be submitted for each Item in this list. Clinical Programming needs to contribute to Item 11 (Highlighted in the full list below).

ITEM 1: TABLE OF CONTENTS (INDEX)

ITEM 2: LABELING

ITEM 3: SUMMARY

ITEM 4: CHEMISTRY, MANUFACTURING, AND CONTROL (CMC)

ITEM 5: NONCLINICAL PHARMACOLOGY AND TOXICOLOGY

ITEM 6: HUMAN PHARMACOLOGY AND BIOAVAILABILITY/BIOEQUIVALENCE

ITEM 7: CLINICAL MICROBIOLOGY

ITEM 8: CLINICAL

ITEM 9: SAFETY UPDATE

ITEM 10: STATISTICAL

>>>> ITEM 11: CASE REPORT TABULATIONS (CRTS) <<<<

ITEM 12: CASE REPORT FORMS

ITEM 13: PATENT INFORMATION

ITEM 14: PATENT CERTIFICATION

ITEM 15: ESTABLISHMENT DESCRIPTION (CBER ONLY)

ITEM 16: DEBARMENT CERTIFICATION

ITEM 17: FIELD COPY CERTIFICATION

ITEM 18: USER FEE COVER SHEET

ITEM 19: FINANCIAL INFORMATION

ITEM 20: OTHER

It will be helpful for programmers to see how their work fits into the overall application structure. FDA's Guidance of 1999 gives details on how each one of these items need to be formatted for an electronic submission. Item 11 is submitted as datasets. Apart from the formatting and naming conventions, Item 11 Guidance highlights best practices for these datasets. Datasets in compliance with these conventions are processed easier by FDA reviewers using their toolsets.

THE FDA GUIDANCE FOR CASE REPORT TABULATIONS

The efficient use of datasets by the reviewer can be significantly improved if some basic principles are followed in setting up the datasets.

1. Each subject should be identified with a single, unique number for the entire application. The unique number needs to be provided in each dataset. This is essential for joining different datasets.
2. For a data table, each variable should be represented as a single field in the dataset or column heading. Each row should contain a single observation or result for an individual patient. In some datasets, this will result in multiple rows per patient.
3. The variable names and codes should be consistent across studies. This is necessary when combining datasets and reduces the time for learning the datasets. For example, if glucose is checked in a number of studies, use the same name to describe this variable in all of the studies. Conversely, do not use the same name for different variables.
4. The format of variables for similar types of data should also be consistent within and across studies. For example, all variables that are a calendar date (e.g., birth date, screening visit date, randomization date, date of death) should use the same format for representing the date.
5. Duration is frequently part of an analysis. Time, start and stop times, and dates should also be provided as duration of treatment based on the start of study treatment and expressed in minutes, hours, or days, whichever is appropriate. When expressed in days, the following formula should be used to calculate study day: ((testdate)-(date of first dose) + 1).
6. Results are frequently analyzed based on the study, center/site, treatment assignment, sex, age, and/or race of the subjects. To save time for the reviewer, each dataset should include these variables.
7. For treatment assignment, all placebo subjects should be 0, and in fixed dose studies, the treatment assignment variable should be the prescribed dose.
8. Data variable names should be limited to 8 characters with a more descriptive name, up to 32 characters, provided as a data variable label.
9. Text should be used instead of, or in addition to, arbitrary number codes. For example, for the variable concomitant medications, if there is a number code for each type of medication, a separate column should be included that has the actual name of the concomitant medication.

All suggestions in these guidelines are in the control of the Programming team and can be addressed easily with little effort as long as the importance is understood at the right time.

CHALLENGES FOR PROGRAMMING TEAMS

Clinical Programming teams can end up with a number of inefficiencies if the submission guidelines are not understood in context. All of these can add up quickly and impact timelines, costs and completeness. The challenges can be observed in the following areas.

- **Scheduling -** Compliance check is done when the datasets are ready and it is usually done by Regulatory department. If the datasets fail the Compliance Check, they have to be sent back to the programmers to rectify it.
- **Rework -** Since it is the last step in the submission process, the timelines are tight. more often than not, the programmers forget to drop the unwanted/ work variables. These variables don't have label and are not needed in the final dataset, so they need to dropped and the dataset has to be rerun.
- **Staffing -** If the specification is not done correctly upfront then chances of a lot of rework are high
- **Consistency -** Different datasets are done by different programmers, so there is inconsistency among the variables
- **Team Morale –** Frequent rework under tight deadlines causes stress which in turn generates miscommunication and errors in a vicious cycle. Team spirit and camaraderie are victims of this process.

CONCLUSION - SOLUTIONS

The Clinical Programming team can be much more effective in dealing with the challenges of submission guidelines if tangible effort is made in the following areas.

- Education - Educate the programmers about the submission process
- Communication - Better communication among Statisticians, Programmers and Regulatory Staff
- Automation 1 - Have a Macro in place that can pull out the variables from the specs directly this will reduce manual error.
- Project Planning – Allocate sufficient time for 99 Compliance Check
- Automation 2- Have a macro/product in place to run the Compliance Check and generate a report.

REFERENCES

- Application to Market a New Drug, Biologic, or an Antibiotic Drug for Human Use; US Department of Health & Human Services, Food and Drug Administration- Form FDA 356h (10/05)
- Guidance for Industry – Providing Regulatory Submissions in Electronic Format-NDA's, US Department of Health & Human Services, Food and Drug Administration, Center for Drug Evaluation and Research (CDER), IT3, January 1999

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