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Commentary

Graphical display of histopathology data from toxicology studies for drug discovery and development: An industry perspective

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ABSTRACT

Histopathology data comprise a critical component of pharmaceutical toxicology studies and are typically presented as finding incidence counts and severity scores per organ, and tabulated on multiple pages which can be challenging for review and aggregation of results. However, the SEND (Standard for Exchange of Nonclinical Data) standard provides a means for collecting and managing histopathology data in a uniform fashion which can allow informatics systems to archive, display and analyze data in novel ways. Various software applications have become available to convert histopathology data into graphical displays for analyses. A subgroup of the FDA-PhUSE Nonclinical Working Group conducted intra-industry surveys regarding the use of graphical displays of histopathology data. Visual cues, use-cases, the value of cross-domain and cross-study visualizations, and limitations were topics for discussion in the context of the surveys. The subgroup came to the following conclusions. Graphical displays appear advantageous as a communication tool to both pathologists and non-pathologists, and provide an efficient means for communicating pathology findings to project teams. Graphics can support hypothesis-generation which could include cross-domain interactive visualizations and/-or aggregating large datasets from multiple studies to observe and/or display patterns and trends. Incorporation of the SEND standard will provide a platform by which visualization tools will be able to aggregate, select and display information from complex and disparate datasets.

1. Introduction

Pharmaceutical research generates enormous amounts of data during the conduct of nonclinical safety studies and informatics solutions are needed to allow users within the pharmaceutical industry and regulatory agencies to query and analyze the data as efficiently as possible. In addition, study results can be further enriched with metadata, documents, external resources and other contextually relevant information which can aid with interpretation and hypothesis generation. Unfortunately, significant amounts of data reside in "static or locked formats" or lack standardized representations which can create challenges for using the data beyond analysis of a single study. In order to more fully use research data, combine them in proper context with other data, and enrich the collective knowledge base, standardization, extraction and exchange technologies need to be developed. Similarly, as data and content resources become more readily accessible, new tools and techniques need to be developed or refined to better search, display, model and/or analyze the data. The range of needs and challenges that exist for the pharmaceutical industry and health authorities are significant, but many of the challenges are shared among key stakeholders which provide opportunities for mutually

Abbreviations: CDISC, Clinical Data Interchange Standards Consortium; ESTP, European Society for Toxicologic Pathology; US FDA, United States Food and Drug Administration; IND, Investigational New Drug; NDA, New Drug Application; PhUSE, Pharmaceutical Users Software Exchange; SDTM, Study Data Tabulation Model; SEND, Standard for Exchange of Nonclinical Data.

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beneficial collaboration (Cases et al., 2014).

The FDA-PhUSE (Pharmaceutical Users Software Exchange) Nonclinical Working Group (PhUSEa) is a collaborative interaction between various stakeholders within the pharmaceutical and allied software industries, and the US FDA in which ideas and concepts for managing and analyzing nonclinical safety data are openly discussed (Kropp et al., 2013; Kasturi et al., 2014). The collection and submission of toxicology data to the FDA to support IND and NDA filings in accordance with the SEND standard (Standard for Exchange of Nonclinical Data; a subpart of CDISC-SDTM or Clinical Data Interchange Standards Consortium – Study Data Tabulation Model) are central topics for this collaboration (US FDA Guidance Documents; see References (US Food and Drug Administration 2014a, 2014b, 2014c)). The SEND standard is intended to provide a means for standardizing and submitting nonclinical safety data to the FDA in an electronic format to better enable data warehousing efforts for scientific and regulatory review. Data standards provide a common controlled terminology/language and format that supports the exploration and use of diverse study results and metadata (Harland et al., 2011). Projects for the Nonclinical Working Group are conceived based on opportunities presented by the SEND standard, new regulatory submission requirements, and informatics solutions to enhance and accelerate data review and analyses.

Histopathology (also known as microscopic pathology) data comprise a critical component of general toxicology and carcinogenicity studies, and are required to be electronically submitted in SEND-compatible datasets (Keenan and Goodman, 2014). These data are typically reported in a tabular fashion in study reports in which histomorphologic finding incidence and/-or severity are organized by tissue or organ type. The data are oftentimes presented on numerous pages, which create challenges with respect to review and correlation with data across different organs, from other domains (e.g. organ weights, clinical laboratory tests) within a study or across studies. However, data capture, reporting and submission in conformance with the SEND standard provides a uniform process that can enable informatics systems to be utilized for data searches, conducting analyses and/or graphical displays in a flexible and dynamic fashion (Nigsch et al., 2011). Data mining and visualization technologies have the potential to allow for presentation of data in more novel or intuitive formats that can enhance hypothesis-driven data analysis or conduct focused investigations of study findings and their relationships to specific biomarkers or other cross-domain data sets (Parkinson et al., 2012).

During sessions of the FDA-PhUSE Computational Sciences Symposium in March 2015, a subgroup was created within the FDA PhUSE Nonclinical Working Group to evaluate the use of graphical displays of histopathology data. Individuals representing various pharmaceutical companies, contract research organizations, software vendors/developers and pharmacology/toxicology reviewers at the FDA comprised this subgroup. A survey was prepared to obtain information and opinion from members of the subgroup on current methods of data visualization, and their benefits and limitations for use. In addition, a live survey was conducted during a session at the 2015 European Society for Toxicologic Pathology (ESTP) annual meeting. This paper provides the results of these surveys and discussions, as well as representative examples of graphical displays of histopathology data from toxicology studies, along with points for consideration regarding use of this technology.

2. Methodology

2.1. FDA-PhUSE survey

During the 2015 FDA PhUSE Computational Sciences Symposium (held March 15–17 in Silver Spring, MD, USA), the Nonclinical Working Group endorsed the formation of the Visualization of Group-Related Differences in Histopathology Data (PhUSEb) as a project with the expressed goal of canvassing opinion regarding the use of graphical displays of histopathology data and sharing/discussing case-examples. The working group consisted of approximately 25 individuals from various pharmaceutical and software companies, contract-research organizations and the US FDA. Multiple teleconferences were held during 2015 to meet project goals. Open-ended survey questions were developed and distributed by email to working group members with the request to provide written responses. The questions (Table 1) were organized into three major themes: A) rationale for graphical displays and their advantages, B) available tools and their application, and C) benefits and limitations. Responses to each question were collected and collated together in an anonymous fashion followed by group review. Case examples and demonstrations utilizing different graphical display tools were presented during working group meetings, which aided with evaluation of the survey results. Responses to each question were summarized to reduce redundancy from which common themes were identified by the working group. General consensus was obtained for the summarized results which formed the basis for a poster presented at the 2016 FDA PhUSE Computational Sciences Symposium (March 13–15 in Silver Spring, MD, USA; Brown et al., 2016).

2.2. ESTP survey

A live survey was conducted during a presentation on data visualization and visual communication at the annual meeting of the European Society of Toxicologic Pathology (ESTP) held in Surrey, England, UK on 25 September 2015. The survey responses were collected using polling hardware and software from Turning Technologies, OH, USA. Survey questions were displayed during a single session using on-screen PowerPoint slides. The questions had multi-option answers which were numerically labelled for answering using a response card which was distributed among the audience (one per person, with 41–69 responses collected per question). For each survey question, the poll was open until no further responses were received which lasted less than 1 min. The poll was closed and the answer distribution promptly displayed by PowerPoint. In addition, all data received were automatically stored in an Excel file.

3. Results

3.1. Collated survey responses from the FDA PhUSE Nonclinical Working Group

Collated answers from the survey of the FDA PhUSE Nonclinical Working Group members suggested that mortality, organ weight, macroscopic and microscopic pathology, and clinical pathology data would be the most appropriate data sets for graphical display, and should be displayed by treatment group, sex and/or tissue. Responses suggested that graphical displays be prepared to simplify the comparison of data within a study, within multiple studies with a single compound and/or to aggregate data across studies from multiple compounds. Visual or graphical display of histopathology data could provide value if they enhanced the understanding of treatment- or dose-related effects within a study as well as correlating effects between different data in other domains (i.e., clinical pathology, organ weight, biomarkers). Additionally, a tool that allows the aggregation of data from multiple studies would enhance the ability to recognize patterns across multiple studies within a project or therapeutic area, which would enhance