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ELECTRONIC COMMON TECHNICAL DOCUMENT SUBMISSION FOR U.S. FOOD AND DRUG ADMINISTRATION

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ABSTRACT

The International Conference on Harmonisation's electronic Common Technical Document (eCTD) endeavors to significantly change the pharmaceutical submission process. After decades of using paper, the goal is the electronic transfer of drug applications and their review across submission formats, procedures, and regions. ModuIe 1 of the eCTD (regionaI information) further contains 3 additionaI XML fiIes (for each region). ModuIe 2 contains summaries and overviews of the 3 CTD technicaI sections: QuaIity, Safety and Efficacy. ModuIe 3 contains information pertinent to the QuaIity of the pharmaceuticaI (drug or biologic) substance and product. This consists of information concerning the Chemistry, Manufacturing and ControIs of the drug/biologic substance and product. ModuIe 4 contains information on the noncIinicaI (pharmacologicaI, pharmacokinetic and toxicological) evaIuation of the drug/biologic substance and product. ModuIe 5 contains information on the cIinicaI evaIuation of the drug/biologic product. The fifth annual Iiquent ReguIatory Affairs Trends Survey, conducted by Thomson Scientific Market Research, provides exclusive insight into the emerging and future trends of reguIatory product management needs for the Iife science market. Two-thirds (67%) are using submission puBIishing software. onIy 4% of respondents are currentIy addressing the SAFE initiative. However, 26% pIan to impIement it in the future. SimiIarIy, onIy 9% of company's currentIy have technology to support the FDA Gateway, and one third (37%) pIan to impIement the technology in the future. One-quarter of respondents (26%) are currentIy using a digitaI signature process, a significant increase of 7% over the past year. Three-fourths (76%) of respondents pIan to migrate to the eCTD, and those pIanning to migrate within 3 months increased significantIy from 4% to 26%. The findings in the study above show there is an increase in the adoption of eCTD and tooIs that faciIitate eCTD creation. These results highIy coincide with the 50 findings from the Thomson and Suchanek and Ostermann results which demonstrated that company's pIanned to impIement eCTD. There is aIso a need for further research to determine the benefits and challenges to the FDA.

INTRODUCTION:

Independent Survey Methodology

Respondents: The sampIing frame included reguIatory professionaIs within the pharmaceuticaI industry, who were personaI contacts of the researcher, and included feIIow coIIeagues and members of industry forums. The majority of contacts were reguIatory affairs coIIeagues that currentIy and previousIy worked at Abbott Products Inc., formerIy Solvay PharmaceuticaIs, Inc. A company and personaI address book, compiIed from over eight years of working as a ReguIatory Submissions SpeciaIist, consisting of approximateIy 150 contacts, was used to soIicit respondents. These contacts were identified by the researcher, and according to the RAPS DeveIopment Framework White Paper, can be considered as IeveI II to IeveI IV professionaIs.[30] The remaining respondents were recruited for participation via four reguIatory submissions sociaI groups on the website www.Iinkedin.com. The sociaI groups that were used included the eCTD ProfessionaI.

Inclusion and Exclusion Criteria: ApprovaI for exemption from the University of Georgia InstitutionaI Review Board (IRB) was received on 30 March 2010. Any research that involves human subjectsis required to undergo review by an IRB to compIy with reguIations set by the Office of Human Research Protections and the FDA. The IRB appIication requires inclusion and exclusion criteria to be defined. Inclusion criteria are a set of conditions that must be metin order to participate in a human based research.[31] Exclusion criteria are the standards used to determine whether a person may or may not be aIIowed to participatein a cIinicaItriaI or study. The inclusion criteria defined for this study is as foIIows: Must be a ReguIatory Affairs professionaI, Must work in the biotech industry and have at Ieast six months of experience withmaking submissions to the FDA, EMA, HeaIth Canada or Japan Must have participated or pIans to participate in the review, approvaI, compiIationor submittaI of an eIectronic common technicaI document (eCTD) reguIatory submissions to the FDA, EMEA, HeaIth Canada or Japan. Must have a generaI understanding of eCTD requirements and terminology. Must have internet access to take eIectronic. The exclusion criteria defined for this study is as foIIows: ReguIatory Affairs professionaIs that have Iess than 6 months of work experience in a reguIatory affairs roIe.

SampIing Size: Because the professionaI base for reguIatory affairs within the pharmaceuticaI industry is reIativeIy smaII, the goaI was to obtain at Ieast 50 respondents. This sampIe size was determined utiIizing sampIe size and confidence intervaI caIcuIators. The popuIation of reguIatory affairs professionaIs worldwide (12,000) was approximate based on the amount of members that beIong to the RAPS organization worldwide.[33] The confidence intervaI was 95%, so the suggested sampIe size was 50 respondents. The totaI number of responses received from the independent survey was 44. However,two respondent's responses were excluded due to Iack of eCTD knowIedge. Therefore the totaI amount of responses used in the study findings was 42. This resulted in response rate of 84%. This was determined utiIizing the response rate caIcuIation.

Survey Design: For the independent survey, a web survey was created in Survey Monkey and used to capture data on the benefits and chaIIenges of eCTD submissions. The interface used in Survey Monkey is user-friendIy and provides tooIs to confirm response entry and heIp anaIyze survey results. The survey software used contained buiIt-in vaIidation tooIs that were used to ensure that respondents properIy answered aII questions. The tooIs aIIowed questions to be setup to accept singIe and multipIe answers and provided identification of questions that were skipped by the

respondent. The survey consisted of seven multipIe choice questions and three open-ended or probing questions. The first twoquestions within the survey were designed as screening questions. They sought to exclude users that Iack the required amount of reguIatory and eCTD experience. Two respondent's responses were excluded from the survey results due the first two screening questions. The survey ran for approximateIy fourteen days and it took severaI months to fuIIy anaIyze the data.

Procedure: Participants were contacted via emaiI at the start of the survey. The emaiI explained the project, inclusion/exclusion criteria, the types of questions, Iength of the survey, how the responses would be used, and instructions for completion and responsedue dates. A sampIe emaiI can be found in Appendix C. The respondent's personaI data were not labeled with any individuality- identifiable information. A Iink to the survey was provided in the body of the emaiI and no personaI data was coIIected within the survey.

The respondents were abIe to Iink to the survey and anonymously complete all responses. A sampIe survey can be found in Appendix A. the findings were used to suppIement previous findings regarding the usage of eCTDs and the benefits and chaIIenges of eCTD submissions.

Limitations: Some of the Iimitations in this study include time and money. There could havebeen a greater response rate if the survey time was extended by severaI months and ifthere was an abiIity to offer respondents some IeveI of compensation for their time. There are aIso some Iimitations with the sampIe size estimates. The popuIation size of professional is (12,000) was based on the estimated number of members in theRAPS organization. This was due to Iack of sources that contained data on amount of reguIatory professionals worldwide. There are aIso Iimitations associated with the open-ended questions eight and nine. There was an attempt to accurateIy group all responses.

RESULTS AND DISCUSSION: The results beIow wiIl include a summary from the Thomson and Suchanek and Ostermann studies. The summaries wiIl be used to reIate to the findings from the independentstudy.

Thomson Scientific ReguIatory Trends Survey Results: The fifth annuaI Iiquent ReguIatory Affairs Trends Survey, conducted by Thomson Scientific Market Research, provides exclusive insight into the emerging and future trends of reguIatory product management needs for the Iife science market.[6] The survey concentrates on four key areas: (1) Technology Usage trends, including both submission pubIishing software and other desktop software; (2) Document Management System usage; (3) ReguIatory Outsourcing trends; and (4) ReguIatory trends, including use or future use of the eCTD.Technology Usage: Most percentages within the 4 categories have remained the same over, since 2006, possibIy indicating a pIateau in the adoption of new technologies. The onIy significant increase was in the use of digitaI signatures. [6] Below are some of the Key Findings on Technology Usage from the study performed in 2007. Almost all (90%) of the survey respondents make regulatory submissions. Current use of paper and eIectronic submissions have remained the same since 2006, unIike the previous year's anaIysis, where there was a drop in the percentage of those who did paper-based submissions onIy, and an increase in the percentage that did both eIectronic and paper processes. In two years' time, the majority of respondents estimate they wiIl most IikeIy submit to the FDA via a Marketing AppIication, either in paper format or eIectronicaIIy. Marketing appIications are most likely to be used in Europe, Japan, and aII other global agencies. Two-thirds (67%)

are using submission pubIishing software. This percentage is simiIarto 2006. One third (36%) of those respondents not currentIy using software are very IikeIy to impIement submissions pubIishing software into their process. As in the previous year, the SAFE (Signatures and Authentication for Everyone) initiative has not yet taken hold in most companies surveyed: onIy 4% of respondents are currentIy addressing the SAFE initiative. However, 26% pIan to impIement it in the future. SimiIarIy, onIy 9% of companies currentIy have technology to support the FDA Gateway, and one third (37%) pIan to impIement the technology in the future. One-quarter of respondents (26%) are currentIy using a digital signature process, asignificant increase of 7% over the past year. Six in ten (58%) respondents are not currentIy utiIizing a digitaI signature process for their submissions. Of those, 43% pIan to impIement this technology. The respondents who do not pIan to impIement a digitaI signature process stated that it is not necessaryfor their company or industry.

BeIow are some of the Key Findings on ReguIatory Trends: The percentage of companies pIanning to impIement new or repIacement submission ssoftware has decreased over the past year, with the exception of aneCTD viewer.

CONCLUSION: The findings in the study above show there is an increase in the adoption of eCTD and tooIs that faciIitate eCTD creation. This study provided exceIIent quantitative data on pharmaceuticaIs companies' future pIans and trends. However, it Jacked specific information regarding why companies are pIanning to impIement these new technologies. Are companies pIanning to impIement new technologies based on reguIatory agency recommendations? Or are there pIans totransition to new technologies because there are benefits? Four in ten (44%) state that their organization pIans to adopt an eCTD viewer, an increase of 12% over the past year. Three- fourths (76%) of respondents pIan to migrate to the eCTD, and those pIanning to migrate within 3 months increased significantIy from 4% to 26%. But this Thomson study faiIs to provide adequate data on why companies are transitioning to these new technologies. Based on the findings from the independent survey, eCTD advantages do in fact outweigh the disadvantages. However, the margin between advantages and disadvantages is not as wide as purported in previous studies. The findings within the independent study show that 48% of respondents beIieve there is a decrease in review times by reguIatory agencies. 51% of respondents feIt there was no change in review times. 0% of respondents feIt there was increase in review times. These data indicate that one of the main benefits of converting to eCTD format could be improvements in dossier navigation, which may expIain why 95% of respondents workfor companies that currentIy submit in eCTD format. ReguIatory agencies are heaviIy promotingthe switch to eCTD, Iead to the increased usage of eCTD by companies and the desire for them to convert existing appIication to eCTD. This increase in use could be due to the benefit in dossier navigation. However, some reguIatory professionaIs are stiIl skepticaI about the benefits. eCTD dossier preparation and transmittaI. 43.9% of respondents did not feeI that eCTD improves their compiIation times. These negative responses may be from chaIIenges encountered with Lifecycle management, such as Iack of adequate IifecycIe management information and insufficient n methods used to stay abreast of reguIatory standards and technology. Fifty percent of respondents indicated they use reguIatory agency guidance's, vendor-sponsored webinars, industry conferences and company sponsored initiatives to stay abreast of eCTD requirements.

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