Electronic Submission Capability to FDA for Academic Investigators—The Process, Challenges, and Opportunities Affecting the Translational Research Enterprise

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Introduction

The Prescription Drug User Fee Act (PDUFA) has undergone authorization five times, most recently as part of the FDA Safety and Innovation Act (FDASIA) signed into law on July 9, 2012. PDUFA V covers fiscal years 2013–2017 beginning on October 1, 2012. Section 1136 of FDASIA includes a requirement that submissions to FDA be in electronic format. To implement this requirement, FDA's Center for Drug Evaluation and Research (CDER) and Center for Biologic Evaluation and Research (CBER) issued a Draft Guidance (January 2013) on the standards and format of electronic submissions including electronic Common Technical Document (eCTD) format.[1] FDA will issue the Final Guidance no later than 12 months from the close of the 60-day public comment period upon the Draft Guidance. The Final Guidance and subsequent revisions will be binding on sponsors, applicants, and manufacturers no earlier than 24 months (36 months for Investigational New Drug [IND] submissions) after issuance of the Final Guidance. In short, the transition to mandatory eCTD compliance for drugs and biologic submissions is swiftly approaching. The Center for Devices and Radiologic Health (CDRH) has already issued its Final Guidance for "eCopy" standards in December 2012.[2]

For drugs and biologics, PDUFA V electronic submission mandates for eCTD do not apply to noncommercial research conducted by academic sponsor-investigators. However, academics are required to comply with the eCopy guidelines of CDRH. One could then question if eCTD capability for academia is even desirable given that transition from paper can be a resource-intensive process. The fact is that with PDUFAV mandates, the FDA submission practices of eCTD-compliant industry and academia will continue to diverge. On a number of levels, this divergence can complicate the translation of academic discoveries into private sector opportunities and biomedical advances.

Clinical research at academic medical centers significantly and increasingly contributes to discovery, development, and repurposing of FDA-approved products. In addition to Institutional Review Board approval, such studies commonly require FDA oversight through IND or Investigational Device Exemption (IDE) submissions to FDA. An increasing number of academic medical centers offer regulatory support for their academic sponsor-investigators who hold these INDs and IDEs. First described by Dr. Harvey Arbit, these support units offer significant value to investigators and the university; they can reduce regulatory compliance risk while accelerating biomedical advances.[3] We propose that like industry, academic regulatory affairs units, technology transfer offices, and the university research enterprise could benefit from the efficiencies and benefits of "eSub" capability.

Presently, we describe one high-volume regulatory support program at a large academic health center and its acquisition of eSub capability for drugs (paper IND to eCTD) and devices (paper IDE to eCopy). We describe the steps involved and their challenges, some of which are likely unique to a non-industry setting. We also discuss our use of expert technical consulting and software solutions. Finally, we postulate how eSubmissions will impact our regulatory operations metrics, our agency interaction, and our industry interaction. It is our hope that sharing this information will assist other academic health centers that are thoughtfully considering an investment in this technology.

Methods

Setting

The Michigan Institute for Clinical and Health Research (MICHR) is funded by the National Institute of Health's Clinical and Translational Science Award (CTSA); the CTSA Consortium is funded by the National Center for Advancing Translational Sciences (NCATS) of the National Institutes of Health (NIH). The MICHR IND/IDE Investigator Assistance Program (MIAP) is a program of MICHR that provides full service regulatory support services to faculty investigators including regulatory consultation, FDA submissions, FDA meeting preparation, clinical protocol and informed consent guidance, and regulatory education. Approximately 50% of currently funded CTSAs have some form of regulatory support for academic investigators.

MIAP is staffed by five full-time regulatory professionals who hold various certifications from the Regulatory Affairs Professional Society, the Association of Clinical Research Professionals, the Society of Clinical Research Associates, the National Association of IRB Managers, and the American Society for Quality. The staff has varied backgrounds in academia and industry with expertise in life sciences, chemistry (drug discovery R&D), nursing, Human Subjects Research Protection, Good Clinical Practice, Good Laboratory Practice, Good Manufacturing Practice, quality assurance, and clinical trial operations. The mean years in research (clinical + preclinical) is 14.8 (±2.8 SEM) and in regulatory affairs is 9 (±2.6 SEM). MIAP's volume of FDA submission activity is significant; annual

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estimates are 30+ new IND and IDE submissions, 100+-related lifecycle submissions, and several presubmission meeting requests and briefing packets. Prior to this electronic submissions pilot project, all FDA submissions were in paper. In addition, all IND submissions were in Traditional Format,[4] not in Common Technical Document format.

Submissions

For this pilot project, the legacy paper IND was a repurposed FDA-approved drug to improve renal function in renal transplant patients. This model was selected because INDs for repurposed drugs represent a significant percentage of our FDA submission portfolio. The paper IND was 406 pages (1,218 pages total for three paper copies) and included Appendix material such as the Letter of Authorization to cross reference the industry-held Drug Master File, Investigator CVs, draft Informed Consent, approved drug package insert, and reference articles. The legacy paper IDE was for a multicenter, pivotal study with an industry-provided cardiac device. The paper IDE was 2,812 pages (8,436 pages total for three paper copies) and included extensive Appendix material including Case Report Forms, Letter of Authorization, Instructions for Use, Informed Consent documents, charters for the Clinical Events Committee and the Data Safety and Monitoring Board, the Monitoring Plan, Sample Investigator Agreements, Investigator CVs, device and packaging labels, and reference articles. Documents contributed by the investigators (.doc files) were not created using a template and lacked significant or consistent formatting. PDF documents like the Investigator's Brochure, approved drug label, patient Instructions for Use, and device designs were obtained from the internet or were provided by the manufacturer.

Training and software

Training for electronic submissions began with attendance at the Regulatory Affairs Professional Society "Preparing Compliant eCTD Submissions" conference held in March 2011. The conference instructor was Ms. Antoinette Azevedo, CEO and founder of Sage Submissions (San Diego, CA, USA) and of e-Submissions Solutions (San Diego, CA, USA). Ms. Azevedo is expert in the technologies, practical techniques and processes for producing paper and electronic submissions for the pharmaceutical, biotechnology, and medical device industries. A pilot project to obtain eSubmission capability at MICHR was subsequently undertaken under the guidance of Ms. Azevedo. Software used in the pilot project included: Microsoft Word 2010 (Microsoft); Adobe Acrobat X Professional (Adobe); ISI Toolbox Pharma (Image Solutions, Inc. Whippany, NJ, USA) for PDF remediation; LORENZ eValidator (LORENZ, Frankfurt, Germany) and GlobalSubmit VALIDATE+VIEW (GlobalSubmit, Philadelphia, PA, USA) to validate eSub compliance of PDFs; and eCTD Manager (EXTEDO, Berwyn, PA, USA) for eCTD assembly and publishing.

Paper IND to eCTD—process and approaches

The steps for eCTD compilation were compliant with current CDER guidelines.[1]

Format documents using MS Word Styles

The academic investigator provided documents with inconsistent formatting and without the assistance of a template; this is common practice in academic environments that often have diverse authors with varied medical writing experience. Specifically, the documents had inconsistent formatting for headings, subheadings, table and figure captions, tables of contents/list of figures/list of tables, and internal hyperlinks. MIAP used MS Word Styles, a formatting feature within Microsoft Word, to generate these attributes. The use of Styles automates the bookmarking features of Adobe Acrobat upon PDF conversion. In addition, Word Styles enabled the generation of captions, table of contents, list of figures, and list of tables, all of which can be rapidly updated as needed through multiple rounds of document editing.

Remediate PDFs rendered from MS Word Documents

Word files (.doc) were converted to PDF using the PDFMaker plug-in within MS Word. This approach, rather than "Save as PDF," preserves the formatting required to generate bookmarks in the resulting PDF file. After PDF conversion, quality control (QC) was done on the generated bookmarks, and modifications to the file were conducted to comply with FDA guidelines for PDFs[5] including security settings, fonts, page orientation, page size and margins, hypertext linking, initial view settings, page numbering, and file naming. If bookmarks were missing or incorrect, the original MS Word file was inspected for the cause of the error, followed by conversion to PDF and subsequent QC.

Remediate PDFs from Non–MS Word Documents

As with the rendered PDFs from .doc files, investigator-provided PDF documents like the FDA-approved drug label or Investigator's Brochure often required the assignment or correction of bookmarks. In large documents, ISI Toolbox Pharma was used to quickly generate bookmarks based upon heading and subheading size and font. Bookmarked documents were then QC'd for missing or incorrect bookmarks, and PDF compliance was assessed using the same guidelines for rendered PDFs as described earlier. Bookmarks were manually added or corrected using Adobe Acrobat X Professional.

Map to CTD, assemble, and publish

Individual documents were mapped to CTD format using the FDA's Comprehensive Table of Contents Headings and Hierarchy, Version 1.2.[6] The eCTD was assembled and published using EXTEDO eCTD Manager.

Establish Electronic Submission Gateway (ESG) account and submit to FDA

The following steps were conducted in accordance with FDA recommendations as published on fda.gov.[7]

Request your WebTrader account

An email was sent to esgprep@fda.hhs.gov to request a WebTrader test account, and the e-mail provided the following information: company name ("Michigan Institute for Clinical and Health Research"); submitter's legal name ("E M. Seymour"); phone number; and submission method ("WebTrader").

Complete Preparatory Activities

A digital certificate is needed to exchange secure email with FDA and to submit via the ESG. A 1-year digital certificate for the first author and ESG submitter (E M. Seymour) was purchased from

GlobalSign (Cambridge, MA, USA). FDA requires that all digital certificates for use with the ESG have an expiration date between 1 and 3 years from the time they are presented to the FDA. Also, the digital certificate's public key (.p7b or .cer file) must meet FDA standards.[8]

In addition to the digital certificate, a Letter of Non-Repudiation Agreement was submitted to FDA prior to registering as a transaction partner for the FDA ESG; this process is described on fda.gov.[9] The letter was submitted in paper form on company letterhead and signed by E M. Seymour with a handwritten signature. Two test submissions were then prepared—a guidance-compliant submission and a load test. The guidance-compliant test was the .XML file of our legacy Paper IND-to-eCTD submission. The load test submission need not be guidance compliant (the submission is not reviewed by FDA), but should be representative of the file types you will be submitting in a typical submission. The load test requirements are 2GB for CDER/CBER.[7] The load test files were provided by our consultant, Antoinette Azevedo.

Register your test account

The test account was then registered at WebTrader. The digital certificate public key was needed to complete this step. The Primary Contact in the test account must be a person and not a group or shared email. The "Company Name" entered during the registration process is actually the account name and must be unique throughout the entire ESG test system. Toward this end, FDA recommends appending the users' initials to the company name (e.g., "Michigan Institute for Clinical and Health Research_EMS")

Set up machine/PC for ESG

Once we received the activation email, the laptop dedicated to electronic submissions needed to have the correct Java configuration (Sun's Java Runtime Edition [JRE] 1.5.0_18, for the browser plug-in files). JRE Installation and firewall configuration instructions were provided by FDA in the account activation email.[10]

Send test submission

We logged in to our ESG WebTrader test account (same URL used to register for the ESG WebTrader test account) with the user ID and password created when registering for the test account. We then sent a small (20KB) text (.txt) file to the "Testing (GWTEST)" center with submission type "Connectivity Test." We then sent the guidance-compliant test submission to CDER with the appropriate submission type (eCTD). Finally, we sent a load test to "Testing (GWTEST)" center and submission type "Size Test." The FDA reviewed the guidance-compliant test submission which took 2 weeks; we were notified by email regarding submission status.

Set up production account

After successfully completing the test submissions and the guidance compliant submission, the FDA ESG sent an email with information on how to register for an ESG production account. The production account will be used for all subsequent eCTD submissions, and production account approval signals that you are eCTD "ready." This registration requires the digital certificate public key and must use the same computer used for your test account submissions. The production account was approved (and activated) in less than 48 hours.

Paper IDE to eCopy—process and approach

Our process aligned with the Final Guidance "eCopy Program for Medical Device Submissions" issued December 31, 2012.[2]

Format documents using MS Word Styles

The approach was similar to that employed for eCTD as described above. Additional steps were taken to locate and remove any external hyperlinks with the document, including email addresses of investigators and external hyperlinks links to references.

Remediate PDFs from MS Word Documents

As above, .doc files were converted to PDF using the PDFMaker plug-in within MS Word. After PDF conversion, QC was done on the generated bookmarks. If bookmarks were missing or incorrect, the original MS Word file was inspected for the cause of the error, followed by conversion to PDF and subsequent QC.

Remediate PDFs from Non-MS Word Documents

The IDE contained layered PDFs of engineering specifications and patient or provider instruction manuals. Attachments must be removed from PDFs; if they cannot, it is advisable to scan the PDF and then perform an eSubmission compliance check on the scanned document. Larger documents were bookmarked using ISI Toolbox Pharma, while others were bookmarked manually using Adobe Acrobat X Professional. ISI Toolbox-generated bookmarks were QC'd and corrected, as needed.

Copying and assembly of the files onto a CD was done using a volume/folder structure, because some files exceeded the 50 MB size limit dictated by CDRH. *Figure 1* shows the volume and file structure with an added view of folder content. Each folder (e.g., "VOL_023_CVs") contained at least one PDF file (e.g., "001_PI CVs 1 to 7.pdf"). Each folder and individual PDF followed CDRH-defined naming conventions.[2] The eCopy burned to CD was an exact duplicate of the hard copy and was sent to FDA by mail with two paper copies of the IDE. The eCopy was accompanied by a cover letter stating that the eCopy was an exact copy of the paper copies as required by CDRH guidelines.[2]

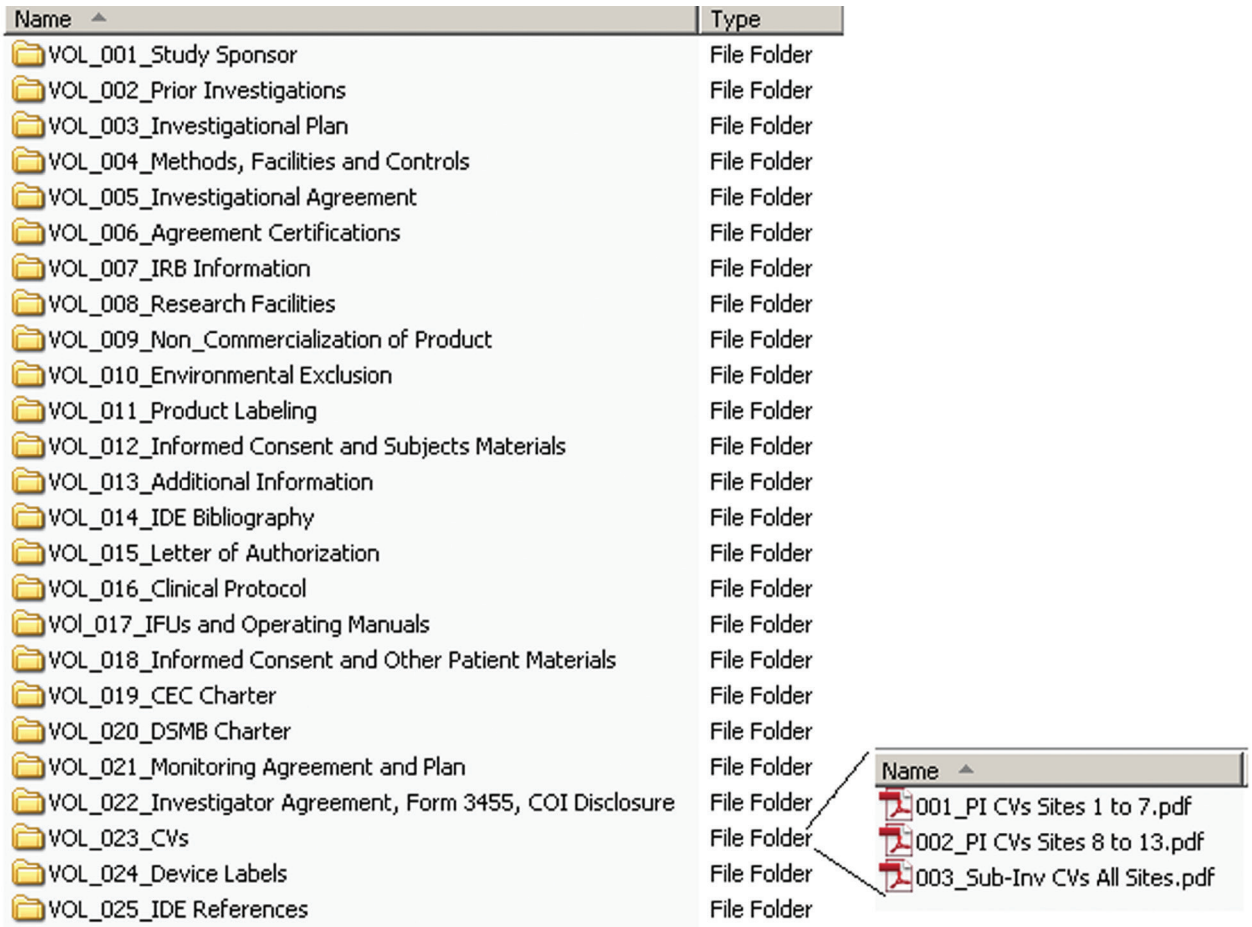
Metrics

Given the benefits of properly formatted Word documents, we now assume that we will continue to create and/or edit .doc files using MS Word Styles. However, the PDF remediation or PDF formatting required to create eSub-compliant documents is an effort that is not shared with paper submission practices. Paper-related tasks and materials for the legacy IND are listed in *Tables 1* and *2*.

Results and discussion

The formatting tasks and remediation for .doc and .pdf files comprised the majority of effort. Even with the use of MS Word Styles, rendered PDFs often revealed small errors that required correction in the MS Word document. In addition, the creation and addition of internal hyperlinks can add significant time to .doc formatting and .pdf QC and remediation. Scanned documents like CVs posed a problem for bookmarking because they were not scanned with a scanner using Optical Character Recognition (OCR). Bookmarks had to be created by hand for all CVs. For eCopy, some external hyperlinks can be hard to detect in some documents, even after using tools within Adobe Acrobat or ISI Toobox. If the external hyperlinks cannot be removed, we could scan the document and manually add bookmarks.

Figure 1. Volume and file content of CD sent as an eCopy to FDA.



Task	Hours (mean)	Cost[1]
Make and print labels and dividers	1	$54.75
Make and print ACCO® folder labels	0.4	$21.90
Make shipping label	0.35	$19.16
Print 1st copy	0.41	$22.45
Assemble 1st copy	0.9	$49.28
QC 1st copy	1.5	$82.13
Print 2nd and 3rd copy	0.75	$41.06
Assemble 2nd and 3rd copy	1.5	$82.13
QC 2nd and 3rd copy	1.8	$98.55
Total hours	9.81	–
Total cost	–	$471.41
Cost per page[2]	–	$0.39

QC, quality control. Hours (mean) calculated from data from five FTEs. [1]Cost determined by $/hour for salary + benefits. [2]total pages = 1,218.

Table 1. Cost of paper-related tasks for the legacy Paper IND.

Surprisingly, assembly of the .xml file took comparatively minimal time. The FDA Contents Hierarchy assisted us in mapping the Traditional Format[4] IND content to eCTD format along the XML backbone. There are many gaps in CTD content for a repurposed drug IND, gaps that are typically occupied in a submission for a New Molecular Entity (NME), including significant Module 3 content ("Quality" or Chemistry/Manufacturing/Controls) and Module 4 content ("Safety" or preclinical/toxicology). These gaps are expected and do not affect the acceptability of the .xml file to FDA. Acquiring an ESG test account and then production account was a layered and time-consuming task, so this step should be started early in a transition to eSubmissions.

IT resources and training needs

Through the licenses of our consultant, several vendor products were used during the pilot submission process for this eSub transition. While completing the pilot submission to the ESG, we also released a Request for Proposals to several eCTD vendors to provide our permanent, in-house eCTD technology. The RFP response was an iterative process of discussion and clarification. Not surprisingly, the vendors were unfamiliar with academic client needs. Larger pharmaceutical companies typically have separate divisions for regulatory affairs,

Material	Cost
ACCO® folders (three)	$12.00
Labels/Dividers (three sets)	$26.97
Appendix labels/dividers (three sets)	$26.97
Paper (500-page ream)	$18.00
Cost of shipping carton (24 × 12 × 12)	$2.40
Shipping by next day air (20 pounds)	$140.00
Total cost	$226.34
Cost per page[1]	$0.19

[1]total pages = 1,218.

Table 2. Cost of paper-related materials for the legacy Paper IND.

medical writing, and regulatory operations/publishing. The latter is the group responsible for eSubmission expertise and execution. However, by adding eSubmission capability, MIAP would now perform all three roles. Despite our relatively large submission volume, we determined that our transition to eSubs must be gradual given our diverse roles and responsibilities. As such, a low initial software investment coupled with a pay-per-submission model (LORENZ docuBridgeONE) was the most nimble approach for this gradual transition from paper. Should our eSubmission volume become heavy, an annual license with unlimited submissions may become a more cost-effective option. Another emerging option from eCTD vendors is cloud-based deployment. In the cloud, the ability to phase-in your use paying on a *per* submission or monthly rate (versus an annual rate) may also be desirable for academic units.

Based on our experience, formal training in eCTD is very important to begin the eSub transition process. Ideally, more than one staff member should become conversant in the vernacular, skills, and tools of electronic submissions. Following training, the assistance of a consultant was a very valuable asset and can significantly reduce implementation time. In addition, eSub knowledge and technical skills must be maintained by keeping abreast of changing industry and submissions standards, ideally by periodic attendance at relevant professional conferences. These continuing education costs should be considered a requirement for maintaining eSubmission capability.

Proposed operational impact

Given the resource impact of poorly or inconsistently formatted documents, it would be ideal if all investigator-provided documents would adhere to a house style guide and/or use a MIAP-provided template, though this may be hard to enforce in academia where documents are authored and sourced by many people. Often, a funded NIH grant is the main document provided to MIAP by the investigator rather than a developed clinical protocol; this situation requires significant writing and editing effort from our group. Mandated use of eCTD-compliant .doc templates would initially burden investigators but would greatly reduce time spent on .doc file formatting and downstream PDF remediation activity.

Prior to considering an eSub transition, it is valuable to track the costs associated with your paper submission activities across your submission portfolio. As a sample, *Table 1* details the costs associated with paper-associated tasks for the legacy IND used in this study, while *Table 2* details the paper-related materials costs. It is logical to conclude that operational costs for paper, printing, assembly, and shipping are curbed by electronic submissions. However, with the initial formatting considerations, the cost for the initial submission of an IND or IDE may not significantly differ between paper and electronic format. Instead, we expect that the resources for IND and IDE maintenance activity (the majority of our FDA submission volume) will be significantly reduced by eSub capability. Therefore, our long-term expectation is to save both money and time by converting to eCTD.

Proposed FDA interaction impact

By statute, INDs and IDEs have a 30-day review window by which FDA must formally respond. Electronic submissions are rapidly funneled to the division and Regulatory Project Manager to begin assignment and review. In contrast, it is estimated that a paper IND could take up to 2 weeks to reach the desk of a Regulatory Project Manager.[11] Given FDA's 30-day timeline for IND/IDE review, electronic submissions could more than double the time allowed for FDA review and even for communication with the academic sponsor-investigator. Such communications may help avoid select Clinical Hold issues being imposed on the IND. eSubmission format therefore benefits both the sponsor and FDA. In 2011, 17.2% of IND submissions to CDER were "Research" INDs from an academic sponsor.[11] Following broad eCTD adoption by industry, paper INDs from academia will become a growing operational burden to FDA. In addition, FDA reviewers strongly prefer electronic format, and there is some evidence that eCTD format (vs. paper) enables a more favorable regulatory review.[12] As the preferred and increasingly adopted submission format, there are likely both quantitative and qualitative benefits of eCTD adoption for Agency interaction.

Proposed industry interaction impact

Given the risk and rising cost of R&D, industry is increasingly approaching academia for licensing and partnering opportunities. This cooperation could involve eventual NDAs/BLAs for new drugs or biologics or 510k/PMA submissions for new devices. Given that drug repurposing research is common in academic health centers, industry partnerships could also likely utilize the 505(b)(2) NDA pathway. Section 505(b)(2) of the Federal Food, Drug and Cosmetic Act was established by the Hatch–Waxman Amendments of 1984 and allows approval of NDAs containing investigations of safety and effectiveness that were not conducted by/for the applicant. The 505(b)(2) can avoid unnecessary duplication of studies already performed on the approved drug, but sponsors must provide data to ensure that the differences from the approved drug (like a new formulation or patient population) do not compromise safety and effectiveness. Because approval can rest in part on data already accepted by the FDA or otherwise available in the public domain, fewer and smaller studies may be required which mitigates risk, costs, and development time. For drugs, 505(b)(2) has become the leading regulatory pathway in recent years; in 2012, approximately 50% more products were approved through the (b)(2) path than through the 505(b)(1) path (the traditional NDA pathway for a new entity). Given that drug repurposing research is common in academic health centers, it is very likely that industry trends in 505(b)(2) activity will extend into academia; this presents an exciting new frontier for translational research.

Regardless of regulatory strategy, academic alliance with industry submission standards would improve opportunities for commercial development. When forming such a relationship with academia, industry would assume the resource and logistical burden of transitioning paper submissions into eCTD format. As such, it is possible that opportunities for partnership and the financial terms of those relationships could be favorably leveraged by academic eCTD compliance.

Summary

Electronic submission capability to the FDA provides both challenges and opportunities for those in an academic environment. The main challenges include changed medical writing practices, initial and continued staff training, and initial and recurring technology expense. Opportunities include reduced operational expense for paper-related tasks, reduced environmental footprint, reduced operational costs over the lifecycle, improved regulatory interaction, and improved industry alliance. While eCopy to CDRH is now required even in academic environments, we expect that investigators, institutions, and FDA could benefit from eCTD capability within the academic research enterprise.

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