Table 10: Opportunities and Challenges of Regulatory Submissions in the Digital Age

Session 1:
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Session 2:
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SCOPE:

What are the dream scenarios for the industry/regulators for submissions in a digital environment? What are the biggest opportunities and pitfalls? How do we advance to the future of electronic submissions beyond eCTD? There is tremendous potential for new tools, view, connectivity driven by the digital advances in the pharmaceutical industry. The transition of Q12 to Step 4 is an additional driver. What are you considering? Imagine in your future variation, a virtual tour of the change proposed, data presented in different ways according to regulators needs, leading to faster approvals and flexible life cycle management of your product portfolio.

QUESTIONS FOR DISCUSSION:

1. Do you expect changes in regulatory submissions as the environment is more digitally focused? What changes do you anticipate?
2. What drivers do you see for changes in regulatory submissions in the next few years? Regulator approaches, industry needs?
3. A few regulatory bodies are driving a digital agenda. How would you manage in this environment, particularly with regions that are not ready yet?
4. Are dossiers connected via a digital backbone to the source information, specifications, established conditions for example? How is it connected to your control strategy?
5. How will companies anticipate regulator requests for raw data, specifications?
6. Has your company already changed how submissions are provided to regulators, managed internally?
7. Have you introduced Artificial Intelligence driven dossier authoring and query responses?
8. Are there changes you want to make that require new agreements with regulators?
9. Do the changes you are considering facilitate trend analysis, specification development?

DISCUSSION NOTES:

Session 1:

- Have you introduced AI driven dossier or query responses?
  - Desire to utilize AI to find similar Health Authority question/responses across countries and projects
  - Limiting factors/Challenges include:
    - Standardization: how to put into format after it is addressed so that the information can be used by AI
    - Resource availability: It is valuable, but from personal resource mindset setting up the meta data is not
      - Human error challenge of time limitation by RA CMC Lead
  - Natural language processing (NLP) could identify keywords to enable finding related queries; reduces barrier to have to fully characterize queries

- Usefulness in creating an ontology= glossary of terms and data model, how it relates your model and how does it categorize to support NLP
  - Language differences between Agencies and scientists (terms, country-language, translations)
    - Published concept: digital twin- how do you integrate AI into system; not relevant to regulatory submissions yet; Monitors the difference between current process vs. desired process eg. gap analysis to allow control.
      - It is all online and is continually evaluated so that it is possible to see what the difference is and control
      - Able to observe raw material characteristics and be able to determine what future impact could be retroactively looking at data; Example: Identify that soybeans which are produced in the dry season yield more byproduct X compared to soybeans harvested in wet season.
  - How do we validate this software? What is the system to store the data?
    - Looking to other industries...
      - Consider medical device space with wearable devices. FDA Guidance on medical device and AI is available; this could be a good basis for biotech to learn as starting point
      - In sales there is customer optimization by machine learning on sales calls. Translating to analytical development there is a need to have data in a consumable format in order to be useful to AI. This is a challenge at this point as companies are established in how they acquire data. Consideration of storing data in a cloud
        - Consider something like a 'product history file' which includes development input, data collection and is continuously updated and stored digitally
    - Eventually expect that it will become a raw data repertoire that AI will utilize
- How much raw data will we submit to Agencies?
  - Challenge of sending standardized data sets (via cloud or hub) that can be sent to and utilized by agency
  - Questions to what are the standardized data sets; what is the data set that HA/FDA wants?
    - Agency is not ready to accept control strategy that would be necessary to support filing that relied on AI-driven product development
    - Currently there is a lack of correlated models (ex. sequence variation to structure model) and lack of harmonious models across industry. However, presenting our data is irrespective of if we have better models
  - Providing raw data (eg. chromatograms, stability tables)
    - challenge globally because some countries require notarized documents, declarations, etc. → Blockchain would provide validation to countries that the information is "real" eg. regional HA are able to trust industry by having direct access to data
    - Where is the data stored so that it is easily accessible?
      - Standardized data set/ product history file (provides phase appropriate experiments and once complete where would it store)
      - Possible to build regional templates that would pull the data as needed and accept that the health authorities will continue to require them (ex. Chromatograms)
        - Tag chromatogram with lot, data, etc. store in cloud use a Vendor agnostic viewing platform could be used by HA to instantly or quickly observe
  - Batch record submission (electronic) – they're still required in US CFR

- - Where do these fit in digital age? Are established conditions appropriate to be put in here and do we need to be held accountable

- Is it possible to have central data hub where industry inputs their data and all agencies access?
    - This would enable the review by multiple countries, enable concurrent review
    - Third party companies are doing this for FDA, why can't it be done for all countries
    - It would help to align global dossier, answer redundant queries
    - Security risk is one concern

- Regarding ICHQ12, Established conditions: Data digitization provides electronic connection of established condition to section in dossier. This could be linked to change control, dossier management
    - Noting that there is already standardized Japan AAF, Russia normative document – these are already EC's in theory
    - The Dossier as an output (structured offering)- standardize or "template-ize" the dossier and complete the template using something like a product history file.
        - Predetermined where is the data located, is it complete, is it changing etc.
        - Consider that attribute/value pair is already built into CMC dossier already
        - Recipe-driven approach: qualification, validation reports; automating report authoring is the easy part; the challenge was to determine what the output would be/ what the report would look like/ what data and stats would be included
            - "One click NDA"
            - Searchable
- How to generate the dossier and how to provide them. What are the drivers?
    - Speed of review (shareholder input), ease of management, compliance (Agency driven), ethical component (lifesaving pharmaceutical with limited resources)
        - Leverage system where it is possible to get data to agencies faster so that approval can occur more quickly and patients are able to get medicine
- Are there any industry consortiums/Trade Associations that are pushing these topics, championing our ideas, needs, etc. to help align the process globally and across industry?
    - CASSS, DIA, BioPhorum, NIIMBL all have programs which discuss
    - Proposal to have CASSS workshop (CMC Strategy Forum in Summer 2020)
    - WHO initiatives to push reliance on other agencies for review, testing, data requests
- Does digitization require a new way to work with regulators?
    - Yes, if FDA analyzes our data the industry would also need tools that FDA/HA uses so that same analysis of dataset can be done by industry
    - Possibility to lookback at other agencies (Japan, Russia) for lessons learned on how to manage EC's
        - How to make non-EC's visible requires level of trust consideration that Agency needs to trust Industry MA-holder and inspectors
        - Non-EC's need to be visible, but update to dossier does not need to be provided
    - Dataset, data integrity, faster access to data, supply chains needs are better indicated (regional requirements)
        - More harmonization on review timing if we are able to categorize what type of change
    - Regulators have a desire to have more detail over less, but industry is risk-averse and therefore there is a challenge
    - Integrating into local legislation is a rate limiting step, upcoming regulatory agencies to become aligned

- Consortium where industry and regulators met to produce proposal that takes into consideration what limiting factors are
- Need for digitization will come from need to creation of dossiers faster, which could come to fruition in near future
- Possible that an external influence (disrupter), such as new modality might force agency to review of data digitally
- General impression that companies and agency want to enable data digitization

Session 2:

Challenges and opportunities:

1. Expecting changes in the digital age –

    a. eCTD and what works around the world. Opportunity to minimize the dossiers (get rid of the fluff).

    b. OneDrive technology (check in/checkout) real time review internally, limited access are changes for technical writers

    c. Currently, no CMC utilization of AI and data lake, though some efforts to start digitization of data from documents and build dossier as you go

    d. Need a merger from scientific and IT systems and processes (e.g. Spotfire linkage with LIMS), QULIK also been used for developing reportable data maps. Online webinars (data revolution sponsored by QULIK)

    e. KASA (FDA), PQ/IQ is data use of system (currently being used for small molecules)

    f. Use as a pilot for CMC data - CDISK (used by clinical for data sets)

    g. Reduce the timeline which is needed to prepare a dossier for Module 3 and have one for all agencies and know when questions are coming in to an organization

    h. Global harmonization (including nomenclature) and data integration (vendor support/alignment), sustainable demonstration of data integrity

2. New guidance's on P21 and S21 (manufacturers); creating a common data standard on how manufacturers are identified. Submit sections of dossier directly submitted vs a PDF.

3. Overall process still same (i.e. technical writers, publish, etc)

    a. Bring on board a document management system for edit/review cycles

4. Any strategies to streamline submissions to different agencies/authorities

    a. as the expectations are different in preparation of the dossier, it makes it difficult to have single source of content

    b. harmonizing requirements would be beneficial for digital age

    c. modular system and need to piece together – occur automatically using a DMS

    d. Veeva Vault system – with content plans to be able to generate content for filings

5. Addressing challenges with different expectations – how to manage

    a. ICHQ12 and establish conditions that contains all requirements (build to highest bar); also be supportive of life cycle management (e.g. submission of variations, etc)

    b. Each organization will need its own customization (example Japan submissions requirement of acceptance criteria for assays)

6. Potential issue if reduce content to smallest bits may loose big picture of full story

    a. Some sections are easier for digitization vs others (Mfg, stability, methods, etc)

    b. Example to link data from LIMS system straight to dossier (current processes have potential for transcription error).

    c. Example to also consider nomenclature when transferred from LIMS data system to how presented in filing.

    d. Revisions of LIMS/data systems could impact any established templates and transfer applications

        i. Constant maintenance on templates/applications to ensure appropriate functionality

7. Is there any opportunity to learn from the clinical side on data transcription into a filing?

    a. For CMC is raw data requested from agency (usually from PMC) another example is data related to PS80

    b. Looking forward to Q12 outcomes, implementation process, expectations and lastly interpretation from other countries. (example "defining an established condition)

8. Challenges with working young organizations

    a. External partners (BOX, Goggle Docs, Drop Box) for exchange of external documents

    b. Version management is key in DMS; need to establish best practices includes renaming files from vendors (i.e. scanned PDFs with file names that don't match the title of the document)

9. Regulatory filings

    a. Single source for all filings (easier for IND to IMPD) but beyond for global markets not feasible

    b. Core/Reduced document to start a new filing application (ie. New market); judgement to send more than needed usually

    c. Core team plate with colored template for guiding what goes where, also hidden text in templates. (easier for analytical section)

    d. Template for key three agencies (buy in from FDA, EMA, PMDA); build with hidden text instruction