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PEER REVIEWED

DIGITIZATION OF VALIDATION FOR EFFECTIVE OFF-SITE REGULATORY "REVIEW" AND "INSPECTION"

INTRODUCTION

In the on-going COVID-19 pandemic, the U.S. Food and Drug Administration has postponed domestic and foreign routine surveillance inspections on a case-by-case basis; it is prioritizing mission-critical inspections that it seeks to conduct with appropriate safety measures in place. In the broader context of extreme uncertainty and emergency use principles, the FDA is relying on firms to self-regulate – "we believe most FDA-regulated firms understand and appreciate their responsibility to ensure the safety of the products they manufacture or produce. We consider these firms to be our partners in public health" (1,2).

It is unlikely that we will return to the pre-pandemic "normal" course of regulatory inspection for some time; perhaps, the remote, virtual, "office-based" inspections may now be a part of the norm across the ICH region (3,4). This alternate means of inspections will, among other things, require firms to provide electronic copies of documents and additional information for off-site regulatory "review" with follow-up tele/video conferences and email. Inspecting and investigating deviations from Good Laboratory, Clinical, and Manufacturing Practices is a distinct complementary function to off-site regulatory review of documents supplied by a company. There is a need to appreciate the value of this distinction and to progress evidence-based policies and procedures to incorporate technological solutions that provide remote "hands-on" and "eye-on" interactive inspectional capabilities.

Paperless validation systems are already in place at many facilities. They can be utilized for interactive inspections and provide opportunities for regulators and companies to improve efficiencies and provide assurance to patients. This paper outlines key advantages and points to consider for leveraging a paperless validation platform to enhance the efficiency of remote pre-approval and pre-license remote inspections.

CURRENT SCENARIO

In and beyond the COVID-19 pandemic, there is high uncertainty, anxiety, and eroding trust. Supply chain disruptions are juxtaposed with constrains on regulatory oversight, emergency use authorization, and unprecedented efforts by the life science sector to find therapeutic and vaccine solutions. The assurance patients and the public derive from regulatory oversight is, if not compromised, in a delicate balance. The consequence of incidents of external quality failures can be more severe if not catastrophic. Historically many pharma companies have been in a reactionary mode, i.e., correcting after regulatory observations and warning letters. Pharmaceutical corporations and professionals need to, and have an opportunity, to be trusted partners in public health. The maturity of their quality management systems, the ability to showcase these systems to regulators, and to be considered a low-risk facility are essential success factors for industry. To be able to demonstrate the maturity of their quality management system, technological solutions such as a paperless validation platform are crucial, and these solutions can also enhance the efficiency of remote pre-approval and pre-license remote inspections.

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TECHNOLOGICAL SOLUTIONS

The use of technology for the manufacturing process is not new to the regulated firms. Technology to manage the manufacturing process continues to evolve at a lightning pace. Most firms are adopting technologies for Quality Management Systems (QMS), Document Management Systems (DMS), Enterprise Resource Planning (ERP), Learning Management Systems (LMS), and Electronic batch records (eBMR), etc. Traditionally, validation is managed as a paper-based process, with the advent of the digital Validation Lifecycle Management System (VLMS), validation can be managed 100% paperless. With the help of all these digital systems, the entire Pre-Approval Inspection (PAI) can be managed remotely with a high degree of confidence. Firms (foreign and domestic) can use VLMS to manage the following activities:

- Digitally manage all the development studies, risk assessments, validation studies, including facility and equipment C& Q, Analytical method validation, cleaning validation, process validation, etc.
- VLMS can archive the raw data associated with every test result without any data integrity concerns
- Augmented reality enabled VLMS can support virtual real-time audit; auditee can walk around the facility to be audited, and the auditor can view the facility in real-time. All the activities during the audit will be recorded as objective evidence to use during the follow-up audits as required.
- Firms can conduct decision-tree driven assessment with required objective evidence based on the digital templates provided by the agency. VLMS will rank the risk level of the firms based on the responses provided by the firm under the following criteria:
  - Facility risk
  - Product risk
  - Process risk.

Science-based risk assessment and effective CAPA are essential aspects of a quality management system. The ability to assess the maturity of QMS – in the rigor and sufficiency of product, process, and facility risk-management and effective system-wide CAPA, will enable regulators to prioritize for more frequent inspections firms that poses high risks. Firms can provide access to regulatory agencies for the required studies through the audit portal available in VLMS; regulatory agencies can access the information remotely as needed. In addition to streamlining inspections by replacing a pen-and-paper checklist with a digital validation system, augmented reality can enhance an auditor's ability to view the facility in real-time.

Electronic transmission of information between manufacturers and importers to FDA has been widely used, for example, in NDA, ANDA, NADA, and ANADA submissions and responses to FDA 483 observations. Standard formats, content, and software facilitate transmission and review of large volumes of data and information. For pre-approval and surveillance inspections, a broad scope and a large volume of data are required, including records review, facilities inspections, operations witnessing, quality management systems evaluation, and quality culture assessment to name a few. At present, no standard shared protocols, software, or framework exists to cover the myriad aspects of verification required to complete a satisfactory inspection remotely. FDA and manufacturers/importers/suppliers need systems to retrieve and share information conveniently and quickly, and this could include arrangements for verification with a camera and video systems for virtual witnessing and inspection of operations, facilities, procedures, and records.

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SOLUTIONS

FDA established the New Inspection Protocol Project (NIPP) to address pre-approval inspections (PAI), surveillance inspections, and for-cause inspections. Digital Validation Lifecycle Management Solutions (VLMS) or similar data, information, and knowledge management systems in the industry can readily collect and provide information to assist in the inspection process. The focus for PAI is primarily on process design (Stage 1 Validation) and process qualification (Stage 2 Validation). In contrast, Surveillance and For-Cause Inspections focus mainly on Continued Process Verification (Stage 3 Validation). In an ideal state, digital or electronic systems used by industry would provide raw data, assessments, and reports which could be processed and delivered electronically to the agency for review in a standard format as currently practiced with the CTD for NDA, ANDA, NADA, and ANADA submissions.

Standardized digital templates based on FDA manufacturing site inspection guidelines would be generated for investigators to use for inspections. The templates would cover all focus areas based on guidance and investigator experience. Flexibility would be designed into the templates to ensure prioritization of focus areas, including follow up on findings from prior inspections, current regulatory compliance priorities, or other factors designated by the FDA. Leveraging investigator guidelines for question-based inspection, the investigator would be prompted to collect semi-quantitative data and information. Models, algorithms, and/or analysis of keywords and phrases would be designed into the system to provide an assessment of quality and "intelligence" performance of the firm. Information captured from the inspection would be exported to populate a template-based draft report, which could be assessed for any critical gaps during the inspection to direct further assessments either to complete during the current inspection or for follow-up during subsequent inspections.

As with the standardized digital templates for the inspection, reports templates would be set up based on the inspection process and inspection output. Assessments would capture benefits as well as insights for continuous improvement of the inspection process. The process for conducting virtual or on-site inspections and for sharing information in the automated draft report would be driven by inspection type. Virtual Pre-Approval Inspection (PAI) would be conducted based on the current three objectives used for on-site inspections. Likewise, Surveillance Inspections would be organized based on the existing six systems and elements of quality culture currently specified for on-site inspections. Based on the output, the system would provide standard ratings for semi-quantitative and compliance ratings based on inputs collected and shared. These outputs can be used by the FDA to give feedback to the firm and consider for follow up during future inspections. Perhaps most importantly, the output provided would enable the firm to track and improve performance proactively and well in advance of any future inspections.

Several features of output from the inspection would provide deeper insights into quality and compliance. Ratable elements would be scored by the inspector according to the level of performance, providing a list of possible areas for coverage that fit within the scope of each ratable element. Example questions for each element would guide the investigator to areas of coverage. Negative ratings reflect degrees of failure in areas requiring action to achieve compliance. Zero ratings reflect good practices that achieve compliance. Positive ratings reflect good practices exceeding compliance up to best practices. A draft inspection report will be reviewed, edited, and issued for communication with the agency and to the inspected entity. Sharing this output with the firm inspected will provide a more comprehensive framework for providing additional information to the agency, as required, more in-depth insights into areas for improvement, as well as general direction on developing enhancements to the QMS or

procedures. More specifically, the output of the process would highlight best practices, identify gaps or opportunities, and recommend actions to implement best practices or to close gaps. Furthermore, the output would track implementation for continuous improvement actions for the digital tool, inspection process, ratings, and reports.
The benefits of this approach include a standard inspection format, ratings, and reports which will provide for consistent assessments and harmonize performance level assessment between PAI and Surveillance Inspections. Knowledge could be integrated from multiple observations as well as from prior inspections, ratings, and reports; this will provide more efficient use of time for the agency and inspected entity. Overall, the result would be enhanced clarity and reduced errors on administrative tasks freeing up resources to focus on the core principles of quality and compliance.

FDA would maximize the value of time and resources spent on inspections thus providing more consistent inspectional coverage and observations. The digital process would facilitate faster and more consistent review of inspection reports, provide inspection data for trending within and between sites, and thereby produce an assessment of the relative health of the facility being inspected. The assessment would provide more structured data for trending and facility comparisons, help determine the need for future inspection frequency, and support more consistent enforcement actions.

The proposed approach would provide industry with more consistent inspectional coverage and operations and provide more clarity of expectations for industry practices. Firms with high levels of manufacturing quality and performance would benefit from fewer inspections, particularly for areas with high performance because the process would recognize and reward positive behaviors in cases where facilities exceed essential compliance.

To test and further build out this concept, a digital VLMS provider with a lead BioPharma company would engage FDA to develop a pilot to demonstrate the viability of the digital and virtual inspection approach compared to on-site, paper-based inspections. Gaps in the process would be identified, measured, and addressed. Outcomes, including benefits and challenges, would be assessed to inform a decision to improve the process and move forward with replication or abandonment if not viable.

CONCLUSION

The current paper-based on-site inspections present challenges to the efficient and effective utilization of FDA and industry resources for verification and enhancement of quality and compliance. Travel restrictions presented by COVID-19 further exacerbate the challenges of continuing the current construct. Digitally enabled remote inspections would reduce administrative burden, allowing both the agency and inspected entities to focus more effort on addressing gaps, continuous improvement, and implementation of best practices. Standardized output and communications would reduce time to understand opportunities, set action plans, and implement improvements that provide benefits to FDA, inspected entities, and enhanced quality and safety to patients.

In and beyond the COVID -19 pandemic, the need for a transparent method of evaluating and communicating quality management maturity is acute and critical (5). Using technological solutions, manufacturers can demonstrate the rigorous oversight of their systems. Their supervision should demonstrate understanding and control over their manufacturing processes. When regulators such as the FDA can observe the rigor and maturity of a corporate QMS, they can exercise a more flexible regulatory approach.

Such a flexible approach should create opportunities that are genuinely aligned with the notion of partners in public health, reduce the need for "extensive regulatory oversight," and encourage continual improvement of manufacturing processes. One can expect that a formal rating system to measure and rate quality management maturity will need to emerge soon. Now is the time that firms seriously consider investing in technologies that contribute to maturity and oversight of their QMS and enable drawing a distinction from others with less mature systems.

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