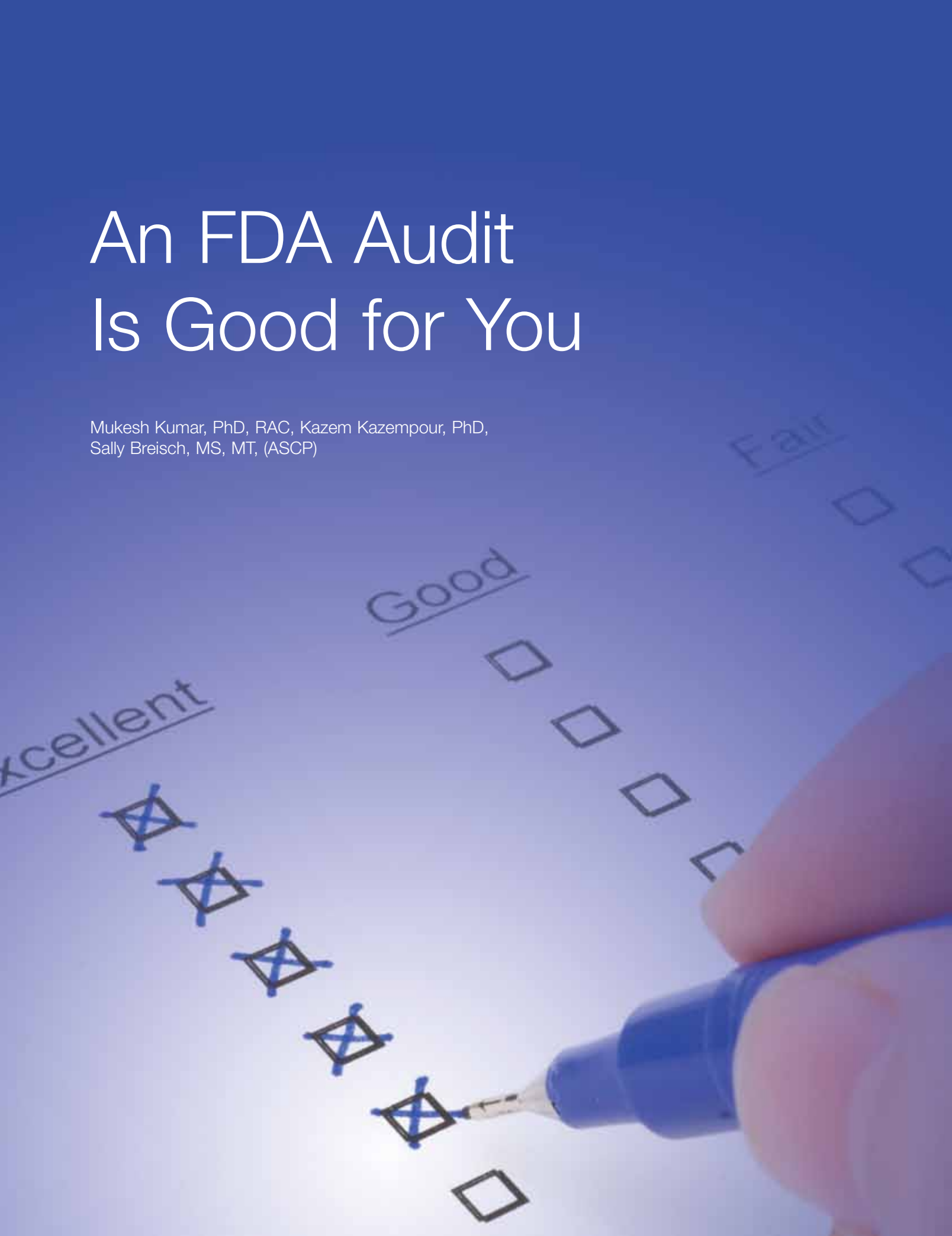
An FDA Audit Is Good for You

Mukesh Kumar, PhD, RAC, Kazem Kazempour, PhD,
Sally Breisch, MS, MT, (ASCP)



Audits by the US Food and Drug Administration (FDA) are perhaps the most intimidating of all events at a regulated facility. Each year, FDA conducts several thousand audits, approximately half of which lead to findings that result in Form FDA 483s. Most Form 483 findings are amicably resolved, but a few lead to serious consequences for the audited parties, starting with Warning Letters and ending with heavy fines and jail time for a few. It is the major offenders who get most of the publicity, for obvious reasons.

It can be argued that the risk of getting caught by FDA for noncompliance is well appreciated by the industry and no organization wants to be known as a willful offender. It can also be argued that compliance with all current regulations is in the self-interest of any organization for business and financial reasons. Further, regulatory enforcement via FDA audits is well-accepted as necessary for ensuring regulatory compliance.

However, the general perception of FDA audits fails to acknowledge their mutual beneficence for the regulators and industry. Most organizations and trainers fail to appreciate the benefits of being audited. Almost all discussions about compliance are done from the regulators' perspective. From a sponsor's viewpoint, an FDA audit, if managed properly, could be one of the best things to happen to a facility.

Independent Verification of Processes

All FDA-regulated organizations, big and small, prepare diligently to comply with FDA requirements. Preparation may involve detailed study of the regulations and guidance documents, extensive review of processes, creating detailed documentation systems, training staff and hiring expert consultants to validate systems.

Depending upon the type of facility—clinical site, laboratory or manufacturing facility—meeting basic compliance requirements could take few weeks to several months and require an enormous amount of resources. As evident from **Figure 1**, regardless of the facility type, several operational areas need to be reviewed. There are several common requirements and a few specific requirements for each facility.

No matter how well a facility prepares, it is difficult to ensure that no stones have been left unturned. To audit themselves, organizations frequently approach independent parties, such as accreditation organizations and overseas regulators able to evaluate ISO and international requirements and independent auditors.

None of these independent organizations can guarantee FDA auditors will not find anything. An FDA audit is the only guaranteed method to ensure absolute compliance with FDA requirements at a given facility. FDA audits also provide an unbiased opinion on compliance status, which may be suspect when the auditor is hired. At best, self-audits offer a sense of comfort from knowing the organization has done the most it possibly could.

Credible Assessment of Compliance Status

Independent audits of a given facility by contract auditors or accreditation organizations are excellent resources to evaluate compliance status and are highly recommended. These auditors could vary significantly in their assessment of a given process and suggestions for remedies to fix an identified deficiency, depending upon their personal experience and depth of knowledge. Regulations are mostly general and subject to interpretation.

Although guidance documents on specific processes could aid in clarifying issues, in most cases, an organization has to identify its own most practical, most feasible and least burdensome approach to compliance. An approach selected by an organization might be deemed lacking by one or more auditors.

The biggest dilemma is when conflicting opinions are provided by different auditors. In such situations, FDA's audit offers the most credible assessment of a given process. FDA audits

Figure 1. Compliance Requirements for FDA-regulated Facilities

Requirements	Clinical Site	Laboratory	Manufacturing Site
Regulation	GCP	GLP	GMP
Standard operating procedures	●	●	●
Trained personnel	●	●	●
Validated equipment	●	●	●
Validated processes	●	●	●
Documentation	●	●	●
Quality control processes	●	●	●
Investigational product handling	●	●	●
Facility design	○	●	●
Warehouses	○	●	●
Environmental monitoring	○	●	●
Testing laboratory	○	●	●
Independent quality assurance	○	○	●
Patient/subject interactions	●	●	○
Independent review board	●	○	○
Complaint handling	●	●	●

Legend: ● = Required ● = May be required ○ = Not required

are comprehensive, involving every regulated aspect of a given facility, and are legally binding in the US. They are conducted by some of the most experienced auditors in the world. FDA auditors are trained to review processes in full detail, assess the scientific basis for a given decision made by an organization and provide an opportunity for the audited party to explain the cause for a perceived deficiency.

Usually, the audited organization can find ways to address FDA's concerns, thereby eliminating any ambiguity about compliance status. More importantly, FDA audits are internationally recognized as among the best in the industry. Most regulators in other countries tend to agree with FDA's finding of compliance or noncompliance. A successful FDA audit provides credibility to an organization beyond the US.

Focused Compliance Saves Time and Resources

Regulatory compliance is a moving target due to constantly changing requirements. This is particularly true for organizations involved with investigational products, such as clinical trial sites, due to changes in Good Clinical Practice (GCP) requirements. Good Laboratory Practice (GLP) and Good Manufacturing Practice (GMP) requirements do not change as much but do require a close eye on the regulatory landscape.

For any organization, evaluation of compliance is an ongoing task. Most organizations use elaborate regulatory intelligence and training systems to identify changes in any relevant regulations, assess potential impact on operations and suggest possible remedial actions. The burning question is whether its compliance status is current. An FDA audit is a good way to confirm compliance.

Facilities involved in operations governed by different standards (GCP, GLP or GMP) are audited by FDA at different rates. While GMP facilities could be audited by FDA once every two years, GCP audits are mostly scheduled only at the time of submission of marketing authorization applications or when triggered by a specific episode. GLP facilities are mostly audited for cause only.

Depending upon the type of operations, some organizations may be assured of regular FDA supervision while others may not be so fortunate. An FDA audit provides the best opportunity to stay compliant by focusing additional resources to address audit findings.

Addressing Audit Findings in Form 483s

For every audit, FDA creates an investigational team comprising the auditors who visit the audited site, their supervisor/team leader and, if needed, additional reviewers. The FDA auditors discuss their findings at the end of every day of the audit and summarize them in the exit interview.

Any findings that cannot be resolved to the auditor's satisfaction at the end of the audit are listed in a formal letter called the Form FDA 483 Inspectional Observation Report or simply the Form 483. The observations cited in the Form 483 indicate that, in the auditor's judgment, listed conditions or practices at the facility are in violation of FDA's requirements.

FDA investigators are trained to ensure that each observation noted on the Form 483 is clear, specific and significant. FDA investigators are also required to discuss the Form 483 with the company's senior management with the goal of seeing changes made quickly.

The Form 483 does not constitute a final FDA determination of whether any condition is in violation of the *Federal Food, Drug, and Cosmetic Act* or other relevant regulations. Upon return to the FDA office, the auditors submit a report of their visit and findings to their supervisors and/or team leaders.

The supervisor/team leader discusses the findings with the investigational team, comes to a final conclusion regarding the completeness of the audit and recommends a final action. The investigational team then creates an Establishment Inspection Report or EIR, which is released to the audited organization.

The EIR includes inspectional evidence that will be considered in totality of the overall situation. The agency will consider all of this

information and then determine what further action, if any, is appropriate. The audited party should consider the Form 483 along with the EIR.

The investigational team may indicate one of three actions in the EIR:

- No Action Indicated (NAI): The facility is in full compliance.
- Voluntary Action Indicated (VAI): The findings are usually minor, corrective measures should be implemented voluntarily, operations mostly can continue.
- Official Action Indicated (OAI): Major violations need to be addressed immediately, before resumption of operations.

Someone unfamiliar with the FDA audit process may incorrectly assume that receiving a Form 483 is an indication the facility has failed the FDA audit. However, most Form 483s are satisfactorily addressed by the audited party.

Companies are encouraged to respond in writing to the Form 483 with their corrective action plan and then implement that plan expeditiously. Once FDA is satisfied with the company's response, the Form 483 is closed and a close-out letter is issued to the company.

Undergoing an FDA audit and addressing all concerns raised by the FDA auditors could be one of the best measures of the competence of a given organization. Issued Form 483 and close-out letters are usually used by organizations to demonstrate their compliance status.

Successful completion of FDA audits is one of the best ways to build confidence and increase morale at an FDA-regulated organization. FDA audits could be perceived as a training exercise by an organization where the personnel demonstrate their professional excellence. These audits are also a good exercise to evaluate the ability of personnel to interact with regulatory authorities. Successful completion of an FDA audit is known to boost employees' self-esteem and investors' confidence.

FDA Inspections Are Inevitable

FDA has the legal authority to inspect all facilities involved with development, testing, manufacture, storage and marketing of therapeutic, preventive and diagnosis products. It is illegal to deny a request for inspection by FDA or withhold access to any relevant areas of the facility.

All regulated organizations need to be prepared at all times for an eventual FDA inspection. It is important to understand the scope and logistics of an FDA audit, identify personnel to be involved, review dos and don'ts, and plan follow-up in case there are findings. Most FDA audits are announced a few days to a couple of weeks in advance. Without adequate preparation, this lead time is too short to prepare for an audit. Preparation must be done well ahead.

Getting ready for an audit helps an organization assess not only its basic operations, but also the level of training and preparedness of the overall facility and personnel. An organization should periodically conduct mock FDA audits to assess its strengths and weaknesses on a holistic basis. These mock audits should include assessment of any deficiencies identified, and these should be addressed appropriately.

These rehearsal audits should ideally be done by independent experts. In addition, mock audits of critical suppliers and vendors should be conducted. There are several resources and training programs available from a variety of sources that can be tailored to a given organization.

Conclusions

FDA audits are good for business. Successfully undergoing an FDA audit is the best and the only way to demonstrate guaranteed compliance with FDA requirements. Organizations routinely use their FDA audit history for business development activities, because they provide independent, industry-acknowledged verification of the compliance status of the audited facility.

Unfortunately, it is not possible for an organization to request an FDA audit. However, when an audit does happen, it benefits the organization being audited as much as FDA and the consumers who are affected by the company's products.

Authors

Mukesh Kumar, PhD, RAC, is a senior director, regulatory affairs at Amarex Clinical Research, LLC, located in Germantown, MD, which is a full-service CRO offering regulatory support, strategic planning, trial management, data management and statistical analysis services for global clinical trials. Kumar is a member of the RAPS Board of Editors for *Regulatory Focus* and can be reached at mukeshk@amarexcro.com. **Kazem Kazempour, PhD,** is the CEO and president of Amarex Clinical Research LLC. He is an experienced regulator and statistician and has worked as a reviewer at the US Food and Drug Administration and several large and small pharmaceutical companies. He specializes in helping companies prepare for marketing authorization applications and advisory committee meetings. He can be reached at kazemk@amarexcro.com. **Sally Breisch, MS, MT (ASCP),** is the COO and vice-president of Amarex Clinical Research LLC. She is an experienced clinical project manager and compliance auditor with more than 35 years experience in hundreds of clinical trials all over the world. She can be reached at sallyb@amarexcro.com.