Quality Oversight in Regulatory Inspections

A Toolkit work product of the DIA Quality Oversight Working Group

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Introduction to the DIA Quality Oversight Working Group

The primary objective of the DIA Quality Oversight Working Group (QOWG) is to increase awareness, provide educational opportunities, and share best practices in support of vendor* quality oversight in the pharmaceutical industry.

Outsourcing is here to stay. Good business practices dictate that when work is assigned to a vendor, such work should be performed consistent with sponsor expectations and contractual obligations. Further, FDA has made it clear that a formal transfer of responsibilities by a sponsor to a vendor does not absolve the sponsor of the responsibility for the quality of the work performed. Finally, FDA has demonstrated via recent regulatory activity, e.g., warning letters, that vendor oversight is a major responsibility of the pharmaceutical sponsor.

Quality oversight (QO) of vendors has become a frequent topic at industry symposia and commercial programs. However, definitions remain unclear as to what, exactly, quality oversight should entail and how optimal quality oversight programs can be effected. Regulatory authorities have suggested a risk-based approach, but even that is subject to different interpretations. For example, for some sponsors, oversight is focused entirely at the site level. While a start, such an approach does not adequately capture trial components such as vendor monitoring processes. Anything less than a truly holistic approach will provide sub-optimal oversight.

*The QOWG is organized within the DIA Global Outsourcing SIAC, and therefore emphasis is placed on vendor oversight vis-à-vis oversight applied to a sponsor's own internal initiatives. Clearly, most of the principles apply equally.

The QOWG has chosen the issue of QO in regulatory inspections as its first project. Our experience is that regulatory inspectors are frequently asking sponsors about their oversight efforts, e.g., "How do you know that your CRO is performing according to requirements and expectations?" It is no longer acceptable to rely on contracts, trust, and audits, although these three elements are indispensible.

In response, and in an effort to assist sponsors in answering this and similar questions, the DIA QOWG has developed a Toolkit. The Toolkit addresses a

series of questions, that when answered, will assist sponsors in addressing this evolving issue. The QOWG is not providing suggested answers to these questions, as that is for the individual sponsors to decide. However, we are providing some commentary that should help the sponsor be prepared for the questions and subsequently help frame their response.

The Toolkit consists of five modules, and is comprised of a brief commentary and questions that will assist sponsor firms in addressing the salient issues. The Toolkit modules are:

What have you contracted, and to whom?

How do you know your CRO partner performed according to expectations?

Which regulatory agency will be performing the anticipated inspection, and what are the associated implications?

How does oversight pertain to investigational sites?

How are you preparing for the inspection (specifically for QO?)

What have you contracted, and to whom?

Commentary

This is the simplest of the questions, as the answers provided will be totally objective. It is important to provide appropriate specificity in answering this question. The answer 'We outsourced data management to Mega-CRO' could easily be interpreted as outsourcing all data management activities to the CRO, whereas the more accurate answer might be 'We outsourced select components of data management, listed separately, to Mega-CRO.' Health authorities are also taking a keen interest in other suppliers, such as central laboratories, electronic data capture, interactive voice/web response system suppliers and others. It is helpful to consider the primary and secondary measures for the study protocol to consider what specific suppliers could be targeted for inquiries. For example, if a primary efficacy measure for a neuroscience indication relies on a patient reported outcome tool and this is done electronically, there is a higher probability that the health authority will ask probing questions about the selection and management of that ePRO supplier. Another example: if a primary efficacy variable is associated with a specialty lab measure, then that small lab may be of specific interest for inquiries as well. In addition, sponsors must realize the 'hidden' outsourced partners, i.e., sub-contractors. A central laboratory may subcontract out to a reference lab. A CRO may subcontract out monitoring in remote locations. It's valuable to consider the broader scope of suppliers used in today's environment for preparing for inspection, since the questions from health authorities are now extending well outside traditional CRO outsourcing. In this case, the sponsor will ideally have the list prepared in advance of the inspection.

Questions for consideration

Do we have full transparency into the sub-contracting practices of our CROs?

Have we prepared documentation to answer the 'What have you contracted, and to whom?' question in advance?

How do you know your CRO partner performed according to expectations?

Commentary

Answering this question isn't simply a matter of checking and finding isolated human error. Such observations are useful insofar as they focus the sponsor on quality-enhancing activities and initiatives. Insignificant one-off observations involving isolated human error are not the focus of a robust Quality Oversight program.

Rather, the focus is on…

"…data that can be used without further revisions or data that will produce conclusions and interpretations that are equivalent to those that would be derived from error-free data, that is, data that are accurate, reliable, and fit for use."

> Davis, J, Nolan, V, Woodcock, J, and Estabrook, R. Editors "Assuming Data Quality and Validity in Clinical Trials for Regulatory Decision Making. A Workshop Report." The Institutes of Medicine. National Academies Press, Washington, D.C., 1999.

A regulatory inspection is a sponsor's opportunity to demonstrate its quality oversight methodology.

Questions for consideration

How well are the sponsor expectations clearly communicated, and even more important, documented, for the CRO? Are the expectations documented in the contract or were they captured via other means (kick-off meetings, high level supplier governance, quality agreements, etc.)?

What metrics have we employed to assure ourselves and the regulatory agencies that work performed by our vendors is adequate?

What trial-level organizational structures have we put in place to provide an infrastructure for optimal quality oversight, e.g., an oversight committee?

Have we prepared a Quality Oversight Plan that encompasses the CRO activities including the interface of the CRO to the sponsor and other suppliers used in the trial? Can we show documentation that we implemented the oversight plan (perhaps via meeting minutes, issue management, corrective actions, communication mechanisms, etc.)?

Which regulatory agency will be performing the anticipated inspection, and what are the associated implications?

Commentary

While all regulatory agencies share the common goal of assessing safety and efficacy of investigational products, their methods can differ substantially at the level of field investigations. An ideal inspection readiness program will take into account the various nuances of the different regulatory bodies, and will be flexible enough to add specificity to the planning and approach for individual differences when an actual inspection is announced.

There isn't much peer-reviewed published literature on this subject. However, there is a plethora of anecdotal evidence. For example, FDA investigators typically review documents first, and then ask questions to cement understanding. European inspectors, on the other hand, tend to interview in-depth to establish the process, and then review documents to verify the answers they were given.

European inspectors tend to specialize, whereas most FDA investigators are generalists (who certainly may have a specialty or special interest).

While these general patterns tend to be well-established, sponsors should understand that they can change based on the regulatory and inspection landscape.

Questions for consideration

What have we put into place to appreciate the differences between regulatory bodies?

Has a health authority inspected our organization previously? If so, it's possible that they could compare their general observations with other health authorities. Although mutual recognition *per se* may be some time in the future, it is clear that FDA and EMA desire more joint inspections and the sharing of information.

For example:

Section 903(b)(3) of the Federal Food, Drug and Cosmetic Act

"…shall participate through appropriate processes with representatives of other countries to reduce the burden of regulation, harmonize regulatory requirements, and achieve appropriate reciprocal arrangements."

And…

Title 21 CFR 20.89 permits FDA officials to share non-public information with a foreign government or international organization that performs counterpart functions to FDA as part of cooperative law, enforcement or regulatory efforts

Lists of Participating Countries

Confidentiality Commitments

http://www.fda.gov/InternationalPrograms/Agreements/ConfidentialityCommitments/default.htm

Memoranda of Understanding and Other Cooperative Arrangements

http://www.fda.gov/InternationalPrograms/Agreements/MemorandaofUnderstanding/default.htm

FDA vs. EMA Mission

FDA	**EMA**
Oversees clinical trials	Coordinates activities National authorities oversee clinical trials
FDA staff perform inspections	GCP inspections are conducted by EU Member State inspectors.
FDA takes enforcement actions	Enforcement actions are the responsibility of the Member States and subject to local regulations.

How does oversight pertain to investigational sites?

Commentary

When sponsors talk of preparing for a regulatory inspection, much of the planning occurs at the level of the sponsor headquarters. While sponsor inspections are a critical component of the overall regulatory inspection process, we must not neglect the fact that considerably more time is actually spent by regulatory bodies (particularly FDA) at investigational sites.

Not infrequently, findings at the site level are what cause delays and even submission withdrawals. Even if the sponsor is generally satisfied with the work of their external service provider, this does not mean that it should be taken for granted that the sites are inspection-ready.

Questions for consideration

What have been the recent findings from health authorities regarding oversight of the investigator sites and have we put a focus on these findings for your trial?

Have we communicated to the suppliers BEFORE they begin work regarding our expectations for their future role in preparing sites for inspection so they build in "inspection readiness" as a routine requirement at the sites?

What processes have we put into place to insure that our sites that have been monitored by a third party are prepared for a regulatory inspection (example: quality oversight visits to sites by sponsor or independent third party)?

Is the TMF at the site aligned with the sponsor's requirements?

How are you preparing for the inspection (specifically for QO?)

Commentary

Most sponsors routinely prepare for regulatory agency inspections, either as a regularly scheduled process or in response to an anticipated inspection tied to a new product submission. However, because of the relative newness of the quality oversight model, sponsors may not have fully thought out how to prepare for specific quality oversight questions that might be raised in a regulatory inspection.

Questions for consideration

Are we fully prepared to answer the previous questions in this Toolkit?

Have we identified the appropriate personnel to interact with the regulatory authorities in terms of quality oversight?

What written procedures do we have in place for quality oversight?

Does our mock inspection program adequately cover issues of quality oversight?

Is there a mechanism for notifying suppliers of inspections (mock or actual HA inspections)?

Do we involve our suppliers in the mock inspections so they can prepare and practice?

Do we invite our CRO project leader to our sponsor site for the sponsor monitor inspection?

Do we have any strategic planning meetings for inspection readiness and if so, have we involved your CRO?

Is it possible that the CRO that helped our program years ago may need to regroup the resources for today's inspection preparation needs?