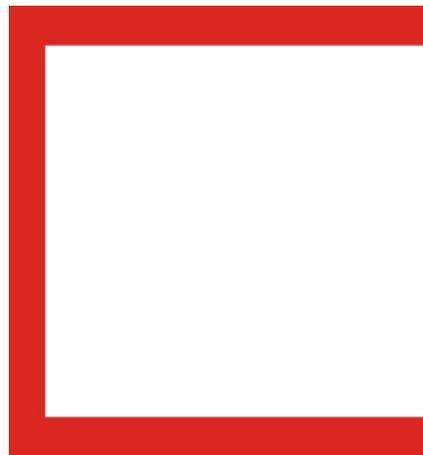


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Vendor Management through Conforming Contracts

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Redica Platforms

Benchmark Report

Compare Sites and Organizations across multiple variables, including inspections and enforcement actions

Groups Report

A custom Site/Organization profile based on your pre-defined Groups

Barb 2.0 Report

Deep-dive into enforcement actions, aggregated by topic area

Annual Trend Report

View year over year trends for a specific GxP tagging model

Comparison Report

Compare and contrast two objects using a specific GxP tagging model

Top Issues Report

View the top issues for a given data model over a defined time frame.

CFR Citation Report

View Chart by [Percentages](#) Count

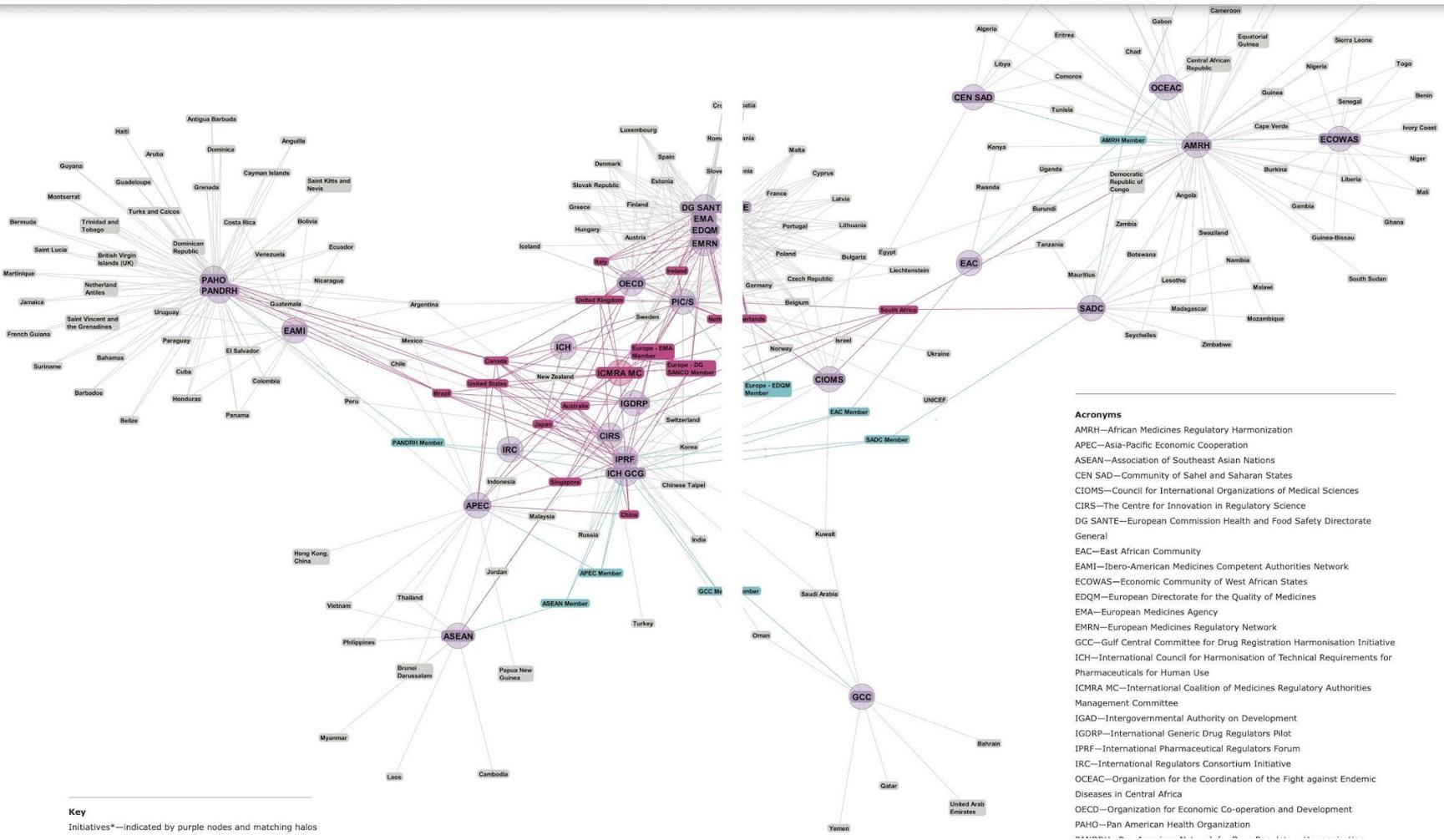
Sort by Highest Averages

All Topics (300)

2022	<div style="width: 98.27%;"><div style="width: 98.27%;"></div></div>	98.27%	Investigator (295)
2023	<div style="width: 98.43%;"><div style="width: 98.43%;"></div></div>	98.43%	
2022	<div style="width: 1.73%;"><div style="width: 1.73%;"></div></div>	1.73%	Data Integrity (5)
2023	<div style="width: 1.57%;"><div style="width: 1.57%;"></div></div>	1.57%	

Harmonization Efforts

- Technical content/requirements for submissions (incl. conduct of development work under GLP/GCP/GMP)
- QMS/QA/QC
 - WHO Pre-qualification, PIC/S, and Mutual Recognition Agreements
- Upstream Supply Chains
- Downstream distribution (e.g., serialization; transfer of transaction statements/Information/history) through pharmacy
- Post-approval monitoring/reporting
- US = 503A (traditional) and 503B (outsourcing facilities) pharmacies



Examples: When Companies are tracking

- Major BioPharma Company ships an expensive biologic from Brussels to Middle East. The transportation carrier is a common carrier (airline). Validated shipping studies were successfully performed. About 50% of the time, following testing, the batches are refused entry. QA was asked to investigate.
 - After product release, the product is turned over to the company's trade group that manages exports, pays the cost of the carrier, manages any import duties on arrival, etc.
 - QA identifies the problem. Anyone know what the issue was (hint: what is the cheapest way to fly?)
- Major international Indian generic company maintains two manufacturing facilities on its campus. One is a state-of-the-art facility for the production of solid orals to be exported to the US and EU. The other is an older facility that has several, easily identifiable GMP deficiencies (e.g., handling of incoming and out going materials, wearing dirty sandals, etc.), but the product from this facility is intended for low-income countries. In discussions with a non-executive (independent) Board member, he was asked what happens if the company missed specifications in the new facility?
 - His response was that it would be thrown over the wall to the ROW facility for distribution. Two major issues here: going to ROW doesn't ensure it stays in the country of import, and secondly, if this happens with any frequency, what does it say about having a validated process?
- Head of Brand Security at Pharma Co. is in India. Is walking through a local market, and sees a product that looks remarkably like Pharma Co's. He purchases a package, takes it to Pharma Co's contracted-for manufacturing facility where he speaks to the GM. The GM verifies that this is a Pharma Co. product. This is a product that requires cutting of certain material as part of its production. Upon further inquiry, the GM explains that the contract with the cutting and packaging company requires a yield of at least 91%. For the last 4 months, the claimed yield was exactly 91%.

Examples: When companies are not tracking

- Large pharma distribution facility broken into (2010). 2 years later, stolen insulin ends up on the shelves of Kroger pharmacies.
- “Avastin” initially shipped into the US via two small distributors (Tennessee and Montana). The product was labeled as Altuzan (the Roche brand for Turkey). Labeling is in Turkish and Arabic - intended for the Egyptian market. From Egypt transshipment through UK to a distributor in the Caribbean. From there, to two small distributors in the US (Tenn and Mont). Acquired by multiples of tens of cancer infusion centers in the USA. Zero active ingredient. Clearly produced in a high speed manufacturing line. Ultimately traced back to Turkey.
- Heparin/over-sulfated chondroitin
- NECC
- Excipients (ethylene glycol and its related chemicals)
- Everything we all see in Warning Letters and 483s

Current State: Quality Agreements

Quality Agreement Responsibility Matrix				
Client may audit all listed CMO functions for cGMP Compliance				
Item	Task	Client	CMO	Shared
1	Training			
1.1	Responsible for ensuring personnel have the appropriate education, training, and/or experience to perform assign job duties		X	
1.2	Ensure there is an adequate number of qualified personnel to perform and supervise the manufacture, processing, packing, and holding of drug product		X	
2	Buildings and Facilities			
2.1	Buildings that facilitate cleaning, maintenance, and proper operation		X	
2.2	Provide adequate space for the orderly placement of equipment and materials to prevent mix-ups between different component, drug product containers, closures, labeling, in-process materials, or drug product		X	
2.3	Perform operations within specifically defined areas of adequate size		X	
2.4	Provide adequate ventilation		X	
2.5	Provide equipment for adequate control over air pressure, micro-organisms, dust, humidity, and temperature when appropriate for the manufacture, processing, packing, and holding of drug product		X	
2.6	Air filtration system shall include pre-filters and particulate matter air filters when appropriate		X	
2.7	Potable water shall be supplied under continuous positive pressure in a plumbing system free of defects that could contribute contamination to any drug product		X	
2.8	Drains will be of adequate size and will not be directly connected to the sewer		X	
2.9	Immediately disposing of sewage, trash, and refuse from the building and the immediate premises		X	
2.10	Provide adequate washing facilities including hot and cold water, soap or detergent, air driers, and single-service towels, and clean toilet facilities easily accessible to work areas		X	
2.11	Maintain building used in the manufacture, processing, packing, and holding of drug product in a clean and sanitary condition		X	
2.12	Maintain a pest control system and written procedure such that the building is free from infestation by rodents, birds, insects, and other vermin.		X	

Current State: Quality Agreements

- Quality Agreements (QAs): How to implement?
- If covered by a DMF, not going to have access to most of the manufacturing information.
- It is a best practice to put the QA as an appendix to the Supplier/ Manufacturing Agreement and having QA Heads sign that appendix. Why?
- FDA Investigators do not want to read contracts; they want to know what cGMP requirements are being transferred to a vendor (non-applicant, except for DMFs) - including CMOs for finished dosage forms.
- Also consider who is implementing and tracking the obligations stated in the QA. The legal department or the Quality Assurance department.

Current State: Transfer of Regulatory Obligations

Program Title:				
Protocol/IND No.: _____				
Code of Federal Regulations (CFR) or Good Clinical Practice (GCP) Guidance	Description of Responsibility	Responsible Party		
		Organization name	CRO/Organization Name	Not Applicable
312.50	General Responsibilities of Sponsors			
(a)	Ensuring that the investigation is conducted in accordance with the general investigational plan and protocols. (ICH GCP 5.6.3a)	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
(a)	Maintaining an effective IND with respect to the investigations. (ICH GCP 5.10)	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
(a)	Ensuring that Food and Drug Administration (FDA) and all participating investigators are promptly informed of significant new adverse effects or risks with respect to the drug. (ICH GCP 5.16.2)	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
312.52	Provide FDA with a transfer of obligations (TORO) for each contract research organization: Prior to initiating a trial, the sponsor should define, establish, and allocate all trial-related duties and functions. (ICH GCP 5.7)	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
312	All submissions and correspondence with the FDA	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
312.53	Selecting Investigators and Monitors			
(a)	Selecting qualified investigators (ICH GCP 5.6.1)	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
(b)	Controlling the shipment of investigational test article (ICH GCP 5.14.1, 5.14.2)	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

A note on the important function of Quality Assurance

- If you are using a CRO or a site, how long is that CRO/Site going to keep the clinical records?
- If you're a CMO making clinical batches for the Sponsor, are you being told what phase of clinical development for the current clinical batch is being used?
- Too much variability in content uniformity of trial batches - even if within early specifications allowed by FDA - can lead to trial failure.
- BLUF: QA is simply an important part of overall organizational success.

Monitoring your Quality Agreements and TOROs

- Most of you engaged in Quality Assurance already have SOPs covering qualifications of vendors for specific functions.
- You also likely have a monitoring plan in place:
- For Quality Agreements, full CoA testing for new chemical suppliers, followed by periodic testing, and audit schedule.
- For TOROs, it depends upon who is managing the CRO and site selection, and who is responsible for the monitoring visits.
- If fully out-sourced and managed within your QMS, audits should be a complete part of the transferred sponsor obligations, including audits of the CRO, qualifications of the PIs and site personnel, and reviews of the monitoring plans and subsequent monitoring reports.

Monitoring your Quality Agreements and TOROs (Cont.)

- Just because you have a Quality Agreement or TORO in place doesn't mean a Sponsor or Applicant is off the hook (human and animal drugs and biologics regulations explicitly allow for transfer of responsibilities...Device regulations do not, even though it is common). If something goes terribly wrong, both you and your vendor(s) will be closely inspected.
- So, what do I think are the most important objectives of these agreements may be?
- Ensuring that the respective QA heads are on the same page
- Ensuring that there is frequent and direct communication between the QA heads or their designees
- Ensure there is always a plan to manage non-conformance (i.e., deviations from GxP)
- Utilize the confidentiality provisions of the contract and educate your vendor as to the status of your investigational or commercial marketing applications.
- Remember, with Vendors, unless you find a practice violative of a regulation, you should be prepared to modify your own SOPs, not expecting them too. When you enter into an agreement with them, you are one of many customers "leasing" their internal procedures, each of whom is conducting audits and reporting their findings back and expecting them to be addressed. Your job is to assess the validity of the work they do.

Enforcing your Quality Agreements and TOROs

- Work together with your in-house attorneys and outside counsel to ensure all are armed with FDA guidance, Compliance Program Guides, Inspections Operations Manuals, Manual of Processes and Procedures, and your own internal SOPs.
- Make no assumptions about what anyone else knows
- Contact your RPM at FDA. They are not consultants, but they will help you if they think you are wrong.

Additional Protections Through Vendor Agreements

- Vendor's reporting requirements
- Carefully-crafted Audit provisions
- Obligations post-termination and Survival Clauses
- Confidentiality and non-use;
- Redundancies/Multiple Vendors

Additional Protections Through Vendor Agreements

- Vendor's reporting requirements
 - Requirements for timely reporting of various events
 - Anything impacting ability to fulfil duties under agreement
 - e.g. non-regulatory-related sourcing or manufacturing/supply problems)
 - E.g., Issues from a regulatory perspective, e.g. (e.g., w/24 hours):
 - Inspections (e.g. when they are happening)
 - 483s
 - Official Action Indicated (OAI), e.g., Warning letters, injunction, other penalties;
 - Voluntary Action Indicated (VAI)
 - NAI
- Breach; implications of breach (e.g., audit, responsibility for fees/costs)

Additional Protections Through Vendor Agreements

- Carefully-crafted audit provisions
 - Go beyond the rote audit provision
 - Timing/number of audits
 - Specify what the audit includes
 - Encompassing of anything that relates to the obligations of the vendor under the agreement, e.g.:
 - Documents/records, including financial documents
 - On-site facility inspection
 - Implementation and maintenance of safeguards, e.g., confidentiality and trade secrets protections
- Post-termination obligations and audit rights; Survival clauses
 - Confidentiality, trade secrets, non-use
- Redundancies/Multiple vendors

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