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Mini Summit XIX
Focus Clinical/R&D, FMV, Monitoring, & Contracting Considerations

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Panel introductions

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Co-moderator introductions

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Oliver is a strategic business consultant with more than 15 years experience. Oliver gained a deep understanding of the Life Science Industry while working for some of the leading Management Consulting firms across a vast variety of clients. He has helped global life science clients to enhance their organizations and processes in respect of regulatory information management, different compliance related issues, and risk management with a focus on Pharmacovigilance and Regulatory.

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Mark A. DeWyngaert, PhD, is a Managing Director in the Life Sciences Regulatory and Operational Risk Deloitte & Touche LLP. Dr. DeWyngaert trained as a molecular biologist and has been actively involved in both research and business development roles for the past 30 years. He has provided operational, clinical, managerial, consulting, and litigation services to various segments of the health care industry. He specializes in assisting pharmaceutical manufacturers, biotechnology, and medical device companies with identifying and mitigating regulatory risks, valuing intellectual property and litigation support.

Agenda

01 **Introduction of speakers**

02
- ***Overview of the Discussion Topics:***
  - Topic 1: Outsourcing of traditional pharmaceutical company functions, such as pharmacovigilance (PV).
    - The role of Safety Data Exchange Agreements, and what to include in those documents.
  - Topic 2: Industry support of non-registrational clinical studies – potential risks and proposed mitigation steps
  - Topic 3: Fair market value assessments for research services Phase IV and Outcomes Research
  - Topic 4: New compliance risk areas for consideration

03 **Q & A**

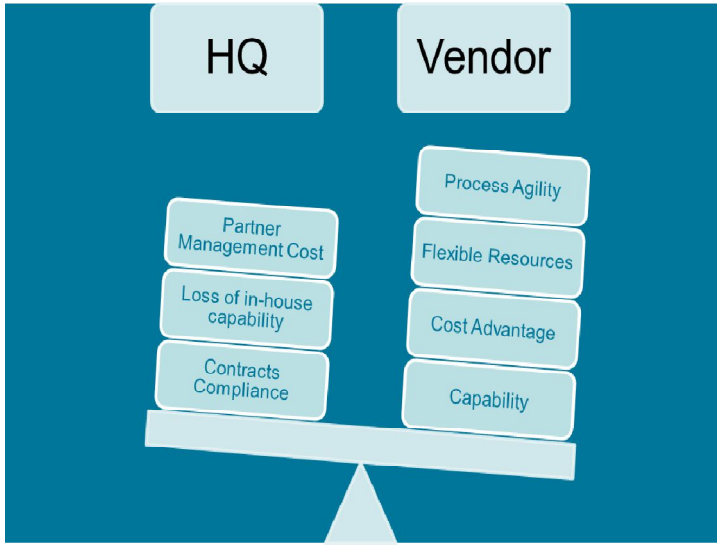
Topic 1

Outsourcing of traditional pharmaceutical company functions, such as pharmacovigilance. The role of Safety Data Exchange Agreements, and what to include in those documents.

Outsourcing is a key part of resourcing strategy for PV functions across the industry

Drivers for PV outsourcing

The swinging pendulum of outsourcing



Many different drivers

- Pressure to reduce costs per case
- Manage spikes (e.g. new product launch, seasonal spikes etc.)
- Free resource to focus on other value services (reactive/proactive PV)
- Lack of in house capabilities
- Company strategy

Options that can help achieve key PV strategic objectives

Optimize Internally

The delegation of the operations or jobs from within a business to an internal (but stand-alone) entity that specializes in that operation.

Shared Services

The provision of a service by one part of an organization or group where that service had previously been found in more than one part of the organization or group.

Outsourcing

The transfer of the management and/or day to day execution of an entire business function to an external third party service provider.

However, automation is starting to play a more dominant role and could soon change the question from ‘What and how to outsource ?’ to ’What and how to automate ?’

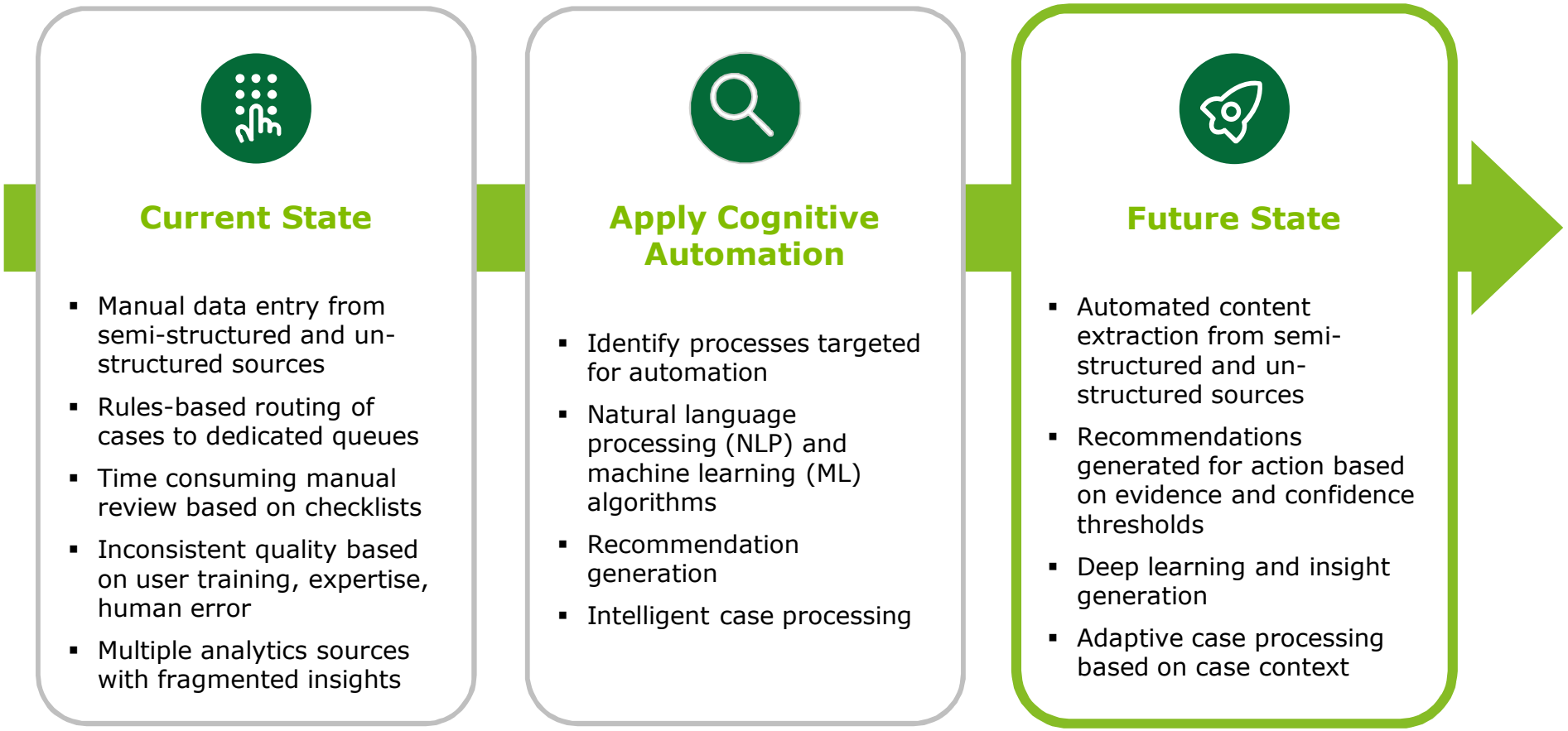
Robotic & Cognitive Automation *(RPA / RCA) Capabilities*

Enable machines to replicate human actions and judgment with robotics and cognitive technologies

Robotics	Intelligent Automation	Cognitive Automation	Artificial General Intelligence
“Mimics Human Actions”	***“Mimics/Augments Quantitative Human Judgement”***	***“Augments Human Intelligence”***	***“Mimics Human Intelligence”***
Rules-based / repetitive process automation, screen scraping data collection	Data input and output in any format; pattern recognition in unstructured data; replication of judgment based tasks; basic learning capabilities for continuous improvement to quality and speed	Natural language recognition/ processing; hypothesis based predictive analysis; self-learning rules continuously rewritten to improve performance; predictive decision making	Completely replicate human interactions

Case study automation: changing the case intake and processing paradigm

PV organizations need to fundamentally shift the case intake and processing paradigm from labor intensive manual processing to cognitive enabled automation with intelligent triage and assessment



Automating PV Functions will raise some fundamental questions:

Who is accountable if something goes wrong ?

- The Vendor?
- The Pharmaceutical Company?
- Both ?

What are risks if something does go wrong?

- FDA Enforcement (but against whom?)
- Risk to new drug approvals
- Product liability risk if PV signals go undetected
- Reputational risk
- Decline in shareholder value

What happens to the resources who are conducting the work right now ?

Safety Data Exchange Agreements (SDEAs)

A Critical Component To Successfully Outsourcing Safety Operations

- When outsourcing safety reporting or PV operations, we recommend entering into an SDEA
  - The SDEA should be a standalone agreement, which is typically an exhibit to the main outsourcing agreement
  - We recommend keeping the SDEA as a separate agreement for two reasons:
    1. If FDA inspects PV operations, the company can provide a copy of the SDEA to the inspectors without having to produce a copy of the outsourcing agreement, which will contain financial and commercial terms
    2. Having a standalone SDEA gives safety staff a dedicated procedural document they can consult for their day-to-day operations

- SDEAs generally include the following elements:
  - Clear definitions of reportable safety data and product complaints
  - Identification of the party who has the duty to submit safety reports to FDA
    - Both parties may have FDA reporting obligations, depending on the nature of the relationship
  - Timelines for both parties to deliver safety data to the other party
  - Assignment of responsibility for making final determinations about the severity, relatedness, and expectedness of AEs
  - Assignment of responsibility for signal detection [Note: Many drug companies are unwilling to outsource this function]
  - Description of how and where safety data will be stored and which party will maintain the master safety database
  - ***But how should automation issues be handled in the SDEA?***

Topic 2

Industry support of Investigator-Sponsored Trials, Post-Market Studies, and Expanded Access Use: Potential risks and mitigations steps.

Compliance Risks With Investigator-Sponsored Trials (ISTs)

- An "IST" is a clinical study in which the principal investigator also serves as the study sponsor
  - FDA's regulations at 21 CFR 312.3 explicitly recognize the role of "Sponsor-Investigator," who is often the person who initiates and conducts and IST
- It is a common practice for drug and device companies to support ISTs by:
  1. Providing free drugs/devices for the study
  2. In some cases, also providing a research grant to support the study
- Although industry support of ISTs is a common and accepted practice, potentially significant compliance risks can arise:
  - Depending on the number and types of ISTs a company supports, these studies could be viewed as a form of promotion
    - For example, if a company supports an excessive number of ISTs all evaluating similar off-label endpoints, the government could view the company's conduct as inappropriate promotional activity
  - If any particular research grant is excessive – or if an IST lacks scientific merit – the research grant could potentially be viewed as inappropriate under the Anti-Kickback Statute

Steps to Address and Mitigate Compliance Risk in ISTs

We strongly recommend implementing a company policy on research grant that states:

- IST proposals must *not* be solicited by the company
- The company must establish a review committee to evaluate and approve all requested support for ISTs
- Support for ISTs must *not* be provided with the intent of influencing or encouraging prescribing decisions
- ISTs the company supports must have scientific merit and be likely to produce meaningful information
- The size and scope of the proposed research activities (e.g., number of subjects, duration of study, number of sites) and amount of the grant is reasonable and does not exceed what is necessary to produce meaningful results
- The IST will be routinely audited and monitored

For each IST a company supports, there should be a contract in place that specifies:

- The total value of ***ALL*** support that the company will give to the investigator over the life of the study
- The investigator's obligations to submit reports, data, and safety information to the company
- Funding milestones clearly tied to measurable study progress
- The requirement that study results will be published

Similar Risks Exist with Post-Market Studies

- There are many forms of post-market studies and data collection activities:
  - *FDA mandated post-approval commitments*
  - *Safety registries*
  - *New indications*
  - *Collection of real world data (RWD) and real world evidence (RWE) from novel sources such as electronic health records and claims and billing activities*

Similar risks exist with these studies as with ISTs. Some questions to ask are:

- *Do the post-market studies have scientific merit?*
- *Is the size and scope of the proposed study appropriate?*
- *Are the parties involved in the research being paid fair market value?*
- *Will the study be routinely audited and monitored?*
- *Will the data be published? If so, by whom and where?*
- *Will safety data be collected, assessed, and submitted to FDA?*
- *What compliance policies and procedures do you covering post-market studies?*

Potential Compliance Risks Associated With Expanded Access?

- In the last several years, there has been a tremendous amount of focus on "expanded access," sometimes referred to as "compassionate use" or "treatment use"
- Under FDA's IND regulations (21 CFR 312 Subpart I), the agency may permit companies to make their unapproved drugs available to treat patients
  - In some cases, FDA will authorize (a) the treatment of "Intermediate-size patient populations," or (b) widespread treatment use (21 CFR 312.315 and 312.320)
- Some reports state that FDA approves 99% of expanded access requests
- Although there is an accepted regulatory pathway for expanded access, companies should be aware of potential compliance risks. Some interesting questions include the following:
  - ***Could large-scale treatment use before approval be perceived as a form of pre-approval promotion?***
  - ***Is it acceptable for drug companies to pay doctors who treat patients under expanded access protocols?***
  - ***If it is acceptable to pay doctors, what rules should companies follow for these payments?***
- **This area could get more attention if a federal "Right to Try" law is enacted**

Topic 3

Fair market value assessments for clinical research services

Relevant regulation

Many laws, regulations and standards relating to clinical research require Fair Market Value to be determined, acknowledge that Fair Market Value can be used as a safe harbor or defense, or influence the determination of FMV (not exhaustive).

- Federal False Claims Act
- "Stark Laws" regarding physician self-referral
- National Physician payment Transparency Program: Open Payments
- OIG testimony regarding FMV and enforcement actions related to the Anti-Kickback Statute
- OIG Compliance Program Guidance
- PhRMA Code of Ethics on Interactions with Healthcare Professionals
- EFPIA Code of Ethical Business Practice
- Applicable Anti-Kickback Statute safe harbors including 42 CFR 1001.952, Personal Services and Management Contracts
- Recent CIA requirements
- Other country pharmaceutical codes, including
  - Global transparency regulation including the US Sunshine Act of 2010, the French Sunshine Act of 2012, the Japan Pharmaceutical Manufacturers Association (JPMA) Promotion Code for Prescription Drugs of 2012, and the UK Bribery Act of 2010
  - Foreign Corrupt Practices Act ("FCPA") of 1977

Business sense

As the average cost of developing a single drug can range from hundreds of millions of dollars to well over $1 billion, it is **critical that clinical research payments meet the high regulatory standards required of the pharmaceutical industry**.

In addition to reducing regulatory risk, creating a process for determining Fair Market Value:

- Creates the potential for **substantial savings;**
- **Aligns different parties** within the organization to the key budget components and streamlines budgeting process; and
- Lays the foundation upon which **exceptions can be addressed and documented**.
- Need for documented Process

Types of clinical research considered

Category	Activity
Pre-clinical Research Agreements	Compound Testing
	Development of diagnostic or testing methodology
	Pre-clinical disease state research (excludes administration of compounds, composition or materials to humans)
	Other pre-clinical research studies
Clinical Trial Agreements	FDA approved clinical studies – Phases I through III
	Post-FDA approved studies (Phase IV studies, e.g. product development studies, epidemiological studies, observational studies, etc.)
	Facilitate a 2-hour meeting to present assessment observations, recommended next steps, and timing as well as to facilitate a broader discussion on current clinical compliance considerations with senior Clinical leadership
Investigator Initiated Studies (IIS) and HEOR	Investigator Initiated Studies and Health Economic Outcomes Research
Other Activities	Publication activities
	Protocol Development

Topic 4

New compliance risk areas for consideration

RISK EXAMPLES BY FUNCTION

Function	Enduring Risks	Emerging Risks
Market Access	• PAPs, Coupon and Co-Pay programs • GPO/Specialty Pharmacy/Hub Relationships • Government Pricing: Discounts, Rebates and Reporting • Service Fee FMV: Wholesalers and other Distributors	• Value-Based Contracting (i.e., innovative financing/ payment options) • Real world evidence: increased reliance on outcomes research and Outcomes Liaison
Corporate/ Multi-Functional	• Advisory Boards and Other HCP Consultancy • Charitable Donations • Corporate Sponsorships • Federal and State Transparency Reporting • Third Party Vendor Relationships	• International Transparency Reporting Requirements • Social Media
Medical Affairs	• Medical Education Grants • Medical Science Liaison Activities • Off-label Medical Communications	• Globalization of the Medical Science Liaison (MSL) role • Publication Practices
Sales & Marketing	• Interactions with HCPs • Joint HCP Interactions with Medical Affairs • Promotional Materials • Promotional Sponsorships • Speaker Programs	• Patient advocacy: ○ Engagement of individual patients, and ○ Sponsorship/ support of patient advocacy groups • Joint HCP/Payer Interactions with Market Access
Clinical/R&D	• Clinical Trial Registries and Results Databases • Investigator Initiated Trials • Research Grants	• Oversight of large Contract Research Organizations managing multi-national, global trials

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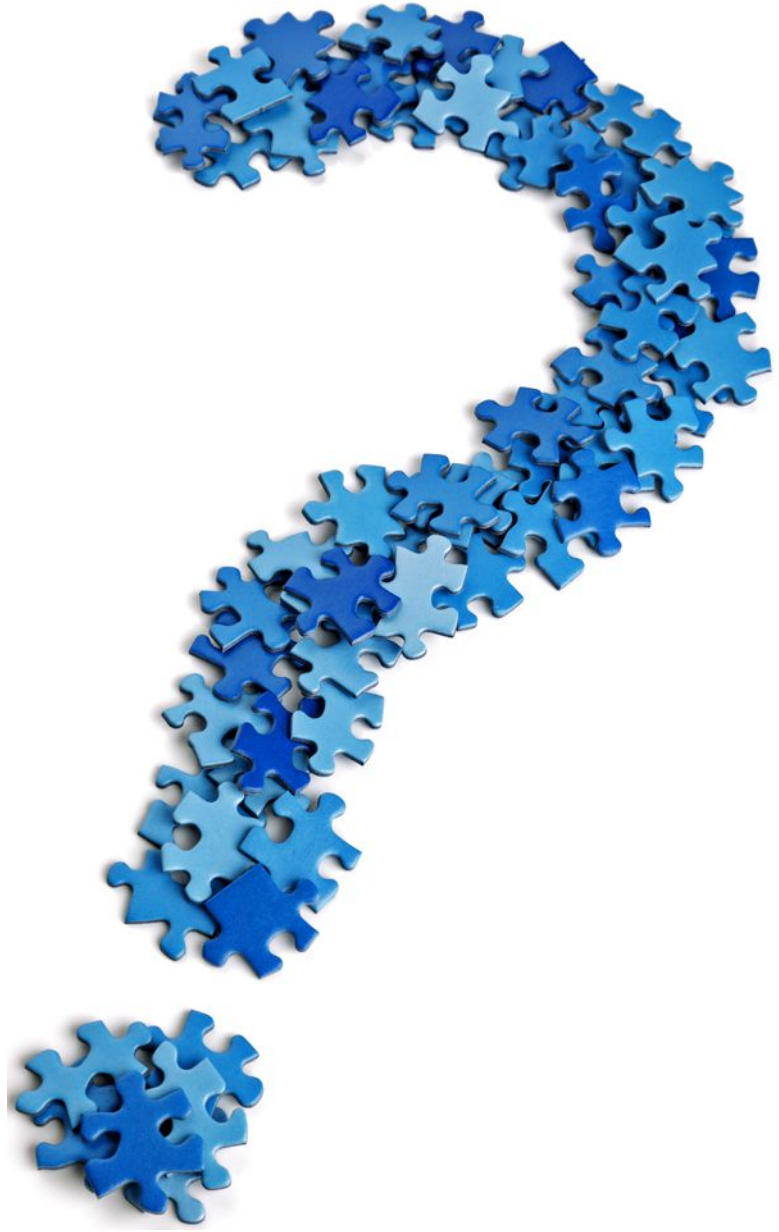
ClinicalTrials.gov: A new enforcement frontier?

- ***Very Brief History of ClinicalTrials.gov:***
  - ***In 2007***, Congress overhauled the CT.gov reporting requirements
    - These changes included a number of ***penalty provisions*** to help ensure better compliance with reporting requirements
  - ***In 2016***, HHS issued a final rule expanding the requirements for CT registration and results submissions
    - Notably, the final rule requires submission of results information for completed clinical trials, ***even for unapproved products***
    - The final rule also describes potential consequences of noncompliance, including civil and criminal actions
- **Compliance risks associated with ClinicalTrials.gov**
  - Failure to comply with the clinical trial registration and results reporting requirements is a prohibited act under the FDCA and may result in civil or criminal actions or penalties of up to $10,000 per day
  - Notably, drug and device applicants must also submit a Certification of Compliance with the CT.gov requirements in most applications (NDAs, BLAs, PMAs, etc.).
    - Failure to submit the Compliance Certification and the knowing submission of a false certification are prohibited acts under the statute.
    - ***A willfully and knowingly false statement on the certification is a criminal offense***.

We are seeing signs that FDA and HHS are starting to take compliance with CT.gov more seriously

Question: Because results reporting is a significant transparency issue, could CT.gov violations become a component of OIG enforcement?

Questions



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