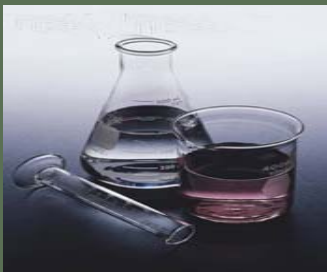


Understanding the New Complexities of Clinical Trials from Results Reporting and FMV to Off-label Communication and Aggregate Spend

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Agenda

- I. Clinical Trials Results Reporting
- II. Clinical Trials and Fair Market Value
- III. Clinical Trials and Aggregate Spend
- IV. Clinical Trials and Off-Label Communication
- V. Future Considerations

I. Clinical Trial Results Reporting

Laws Associated with Clinical Transparency

Recent Guidance

- September 27, 2008: U.S. Food and Drug Administration Amendments Act of 2007 (FDAAA)
 - Required that clinical trials results be made publicly available on the Internet through an expanded “registry and results data bank”
 - Non-compliance may result in penalties as well as possible loss of funding
- Effective October 1, 2009: PhRMA endorsement
 - Measures to increase transparency and reporting requirements around clinical trials
 - Provide medical research results summaries (safety and effectiveness data) for all interventional clinical trials involving patients regardless of whether the medicines are approved or the particular research programs have been discontinued
- Proposed June 9, 2009: changes to Maine’s clinical trial reporting regulations
 - Would expand the types of trials and number of data elements that must be reported
 - Would apply to future and prior postings and
 - Would result in revisions to summaries currently in ICH-E3 format as well as the reporting of additional data elements for studies already posted
- Effective July 1, 2009: Vermont legislation
 - bans gifts to health care providers by any manufacturer of a prescribed product. However, expenditures (i.e. payments) that are not banned include bona fide clinical trials. those provided in support of
 - Will government consider duplicative/non-actionable research to be *bona fide*?

Laws Associated with Clinical Transparency (cont'd)

Recent Guidance

- 2008: Revised ICMJE Uniform Requirements for Manuscripts (URM)
 - ICMJE member journals will require, as a condition of consideration for publication in their journals, registration in a public trials registry.
 - The ICMJE does not advocate one particular registry, but registry
 - Must be accessible to the public at no charge
 - Must be open to all prospective registrants and managed by a not-for-profit organization
 - Must have a mechanism to ensure the validity of the registration data
 - Should be electronically searchable
 - Obligation to publish negative studies:
 - Editors should consider seriously for publication of any carefully done study of an important question, relevant to their readers, whether the results for the primary or any additional outcome(s) are statistically significant.
 - Failure to submit or publish findings because of lack of statistical significance is an important cause of publication bias.

II. Clinical Trials and Fair Market Value

Regulation related to Fair Market Value (FMV)

Recent Legislation and Guidance

- OIG testimony regarding Fair Market Value
- Enforcement actions related to the Anti-Kickback Statute
- Federal False Claims Act
- OIG Compliance Program Guidance for Pharmaceutical Manufacturers
- “Stark Laws”: 42 CFR Parts 411 and 424 regarding physician self-referral
- State Laws for:
 - District of Columbia (“Act A17-0282”)
 - Maine (“22 Me Rev. Stat. Ann. § 2700-A”)
 - Vermont (“18 Vt. Stat. Ann. § 4632”)
 - West Virginia (“W.Va. Code § 5A-3C-13”)
 - Massachusetts (“Mass S.B. 2863”)
- PhRMA Principles on Conduct of Clinical Trials and Communication of Clinical Trials Results
- Food and Drug Administration Amendments Act of 2007 (FDAAA)
- Food and Drug Administration – Device Regulation and Guidance
- <http://www.oshpd.state.ca.us/Chargemaster/>
- <http://www.ClinicalTrials.gov>

The Anti-Kickback Statute

Constraints on the Offer or Payment of Anything of Value

Companies should be aware of the federal Anti-Kickback Statute and the constraints it places on the marketing and promotion of products reimbursable by federal health care programs, including, but not limited to, Medicare and Medicaid. In the health care sector, sales, marketing, discounting, and purchaser relations potentially implicate the Anti-Kickback Statute.

- The Anti-Kickback Statute is a criminal prohibition against payments (in any form, whether the payments are direct or indirect) made purposefully to induce or reward the referral or generation of federal health care business.
- The Anti-Kickback Statute addresses not only the offer or payment of anything of value for patient referrals, but also the offer or payment of anything of value in return for purchasing, leasing, ordering, or arranging for or recommending the purchase, lease, or ordering of any item or service reimbursable in whole or part by a federal health care program.
- Companies should be aware that, in addition to any explicit payments received for work done on clinical research, HCPs may receive additional value from participating in a clinical trial by gaining publicity and/or increased reputational value by the publication of results or by the positive perception of being involved in “cutting edge” treatments by their patients.



Risks Associated with HCP Arrangements

Considerations in Identifying Risk

The OIG has highlighted issues and areas of risk related to physician interactions. The result can impact multiple areas within an organization. Within its guidance, the OIG has articulated issues that it feels all manufactures need to address in assessing risk.

There are several considerations that can be useful in identifying activities at greatest risk of prosecution. In particular, manufacturers should ask the following questions, among others, about any problematic arrangements or practices they identify:

- Does the activity have a potential to interfere with, or skew, clinical decision-making? Does it have a potential to undermine the clinical integrity of a formulary process? If the arrangement or practice involves providing information to decision-makers, prescribers, or patients, is the information complete, accurate, and not misleading?
- Does the arrangement or practice have a potential to increase costs to the federal health care programs, beneficiaries, or enrollees? Does the arrangement or practice have the potential to be a disguised discount to circumvent the Medicaid Rebate Program Best Price calculation?
- Does the arrangement or practice have a potential to increase the risk of overutilization or inappropriate utilization?
- Does the arrangement or practice raise patient safety or quality of care concerns?



Activity between HCPs and Manufacturers

AdvaMed & PhRMA Code Impact

Between July and December of 2008, new PhRMA Code and the AdvaMed Code guidance was approved to enhance the codes and further distinguish the appropriate and inappropriate activity between HCPs and manufacturers.

AdvaMed Code

- In light of the recent DPAs faced by the “Big 5” Medical Device manufacturers, the revised AdvaMed code makes direct references to the federal Anti-Kickback statute.
- Restrictions on third-party support of Educational Conferences emphasize that the focus of such sponsorships should be on the educational value of the program.
- Interactions with HealthCare Professionals (HCPs) must be for *bona fide* consulting purposes and compensated for at Fair Market Value. Entertainment expenses are expressly prohibited, and some new guidelines around royalty payments to consultants have been issued.

PhRMA Code

- Includes new provisions that require companies to ensure that their representatives are sufficiently trained about applicable laws, regulations, and industry codes of practice – including this Code – that govern interactions with healthcare professionals
- Provides that each company will state its intentions to abide by the Code and that company CEOs and Compliance Officers will certify each year that they have processes in place to comply

Definition of *Bona Fide* Clinical Research

Bona Fide Clinical Research Based on Industry Guidance

The OIG recognizes the value and importance of manufacturers' support for research conducted by institutions and healthcare professionals for the advancement of science and medicine.⁽¹⁾ The *bona fide* purpose of clinical research must be defined and documented in order for consideration of fair market value. Current legislative and industry compliance references provide guidance on criteria that determine what constitutes bona fide clinical research.

Research Type	Definition	References
<i>Bona fide</i> Clinical Trial	<ul style="list-style-type: none"> • Has been approved by the U.S. Food and Drug Administration (FDA) or by a duly constituted Institutional Review Board (IRB) • Assesses the safety or efficacy of drugs or the relative safety or efficacy of drugs in comparison with other drugs or other therapies • Results can be published freely by the investigator and reasonably considered to be of interest to scientists or medical practitioners in the particular field of inquiry 	FDA, OIG, State laws for ME, VT, WV, MA, RI
<i>Bona Fide</i> Research	<ul style="list-style-type: none"> • Systematic investigation designed to develop or contribute to conclusive knowledge when the results can be published freely by the investigator • Results can be reasonably can be considered of significant interest or value to scientists or health care practitioners in the particular field of inquiry 	FDA, OIG, State laws for ME, VT, WV, MA, RI

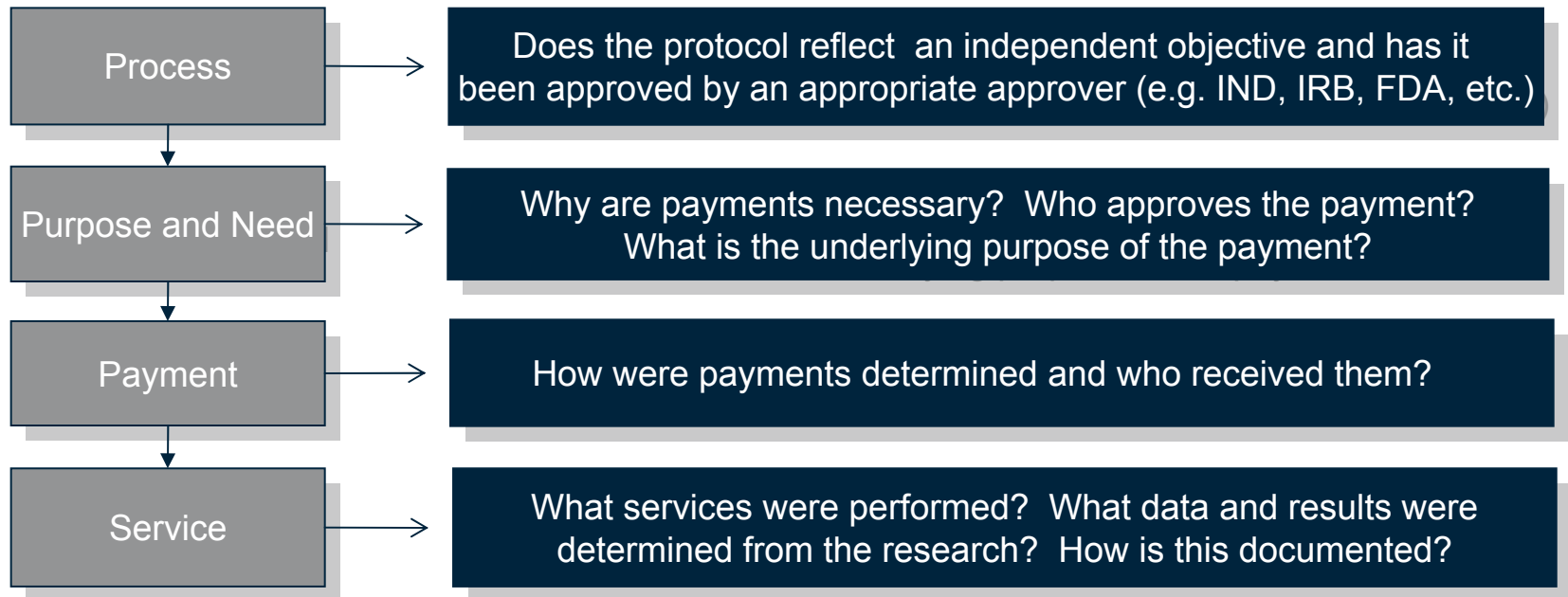
(1) "OIG Compliance Program Guidance for Pharmaceutical Manufacturers". Federal Register / Vol. 68, No. 86 / Monday, May 5, 2003, p. 23736

Demonstrating *Bona Fide* Clinical Research

Considerations for Demonstrating *Bona Fide* Clinical Research

Determining or confirming the FMV of a clinical research arrangement requires demonstration of the *bona fide* purpose of the research. Companies should consider the following four key areas to documenting, monitoring, and reconciliation processes to demonstrate *bona fide* purpose as well as delivery of research activities. Companies may be at risk of facing anti-kickback issues if clinical research is left unfinished or is never performed.

Documenting *Bona Fide* Research Activities



III. Clinical Trials and Aggregate Spend

State Reporting Compliance Guidance

Mitigating Risk and Managing State Filings

Manufacturers should identify and track key issues related to state reporting and tracking aggregate spend. Laws vary by state and manufacturers must carefully follow new legislation as it is enacted to make the appropriate change to remain compliant.

Gift Disclosure Laws:

MA, ME, MN, VT, WV, and DC

- File a report identifying the value, nature, and purpose of any gift, fee, payment, subsidy, or any economic benefit greater than \$25 (greater than \$50 in MA)

Prohibition & Disclosure Law:

MN

- Prohibits certain gifts over \$50 to any one HCP per year
- Requires disclosure of compensation and reimbursements valued at more than \$100

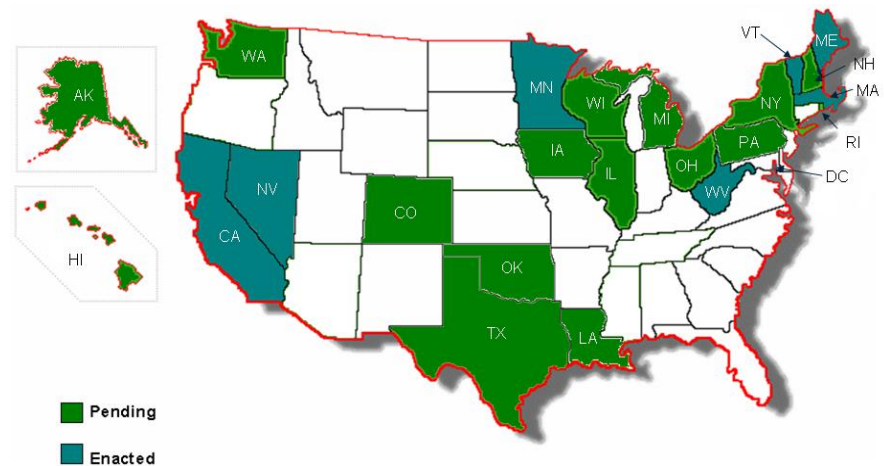
Comprehensive Compliance & Reporting Law:

CA

- Establish annual, per-physician limits on gifts, promotional marketing materials and other items or activities (limits established by each company)
- Compliance with PhRMA Code and OIG Guidelines

MA and NV

- Adopt a written marketing code of conduct, a training program, identify a compliance officer, conduct annual audits of compliance with marketing code, and adopt policies for investigating non-compliance with the marketing code



Pending – Grassley subcommittee inquiries and Federal Sunshine Act disclosure provisions.

The Sunshine Act

Impact on Compliance Risk and Operations

The Sunshine Act is a federal law that would require reporting of payments on a national level. However, the federal law may not pre-empt the state laws, creating further compliance operations issues as companies work to track spending that adheres to both state and federal legislation.

- Represents continued efforts of Senator Grassley and Kohl
- Would establish a nationwide requirement for reporting payments \$100 or greater to physicians
- Includes consulting fees, honoraria, gifts, entertainment, food, travel, education, research, charitable contributions, royalty or license payments, ownership or investment interests, compensation for serving as faculty or as a speaker for a continuing medical education program, and grants
- Information would be posted on HHS website
- Penalties
 - Subject to CMPs of \$1,000 to \$10,000 per violation (maximum of \$150,000)
 - Subject to CMPs of \$10,000 to \$100,000 for knowing violations (maximum of \$1,000,000)

Recent Medical Device DPA Requirements

DPA Requirements Are More Invasive and Require More Public Reporting

The DPAs alleged that certain companies in the medical device industry conspired to violate the Anti-Kickback Statute, used consulting agreements with HCPs as inducements to use a particular company's products, and paid surgeons tens to hundreds of thousands of dollars per year for consulting contracts and often received trips and other expensive benefits.

▪ Code of Conduct Requirements

- Commitment to full compliance with all federal, state, and local laws and regulations
- All of the company's Covered Persons must comply with all federal health care program requirements and with the company's own policies and procedures .
- All of the company's Covered Persons shall be expected to report to their Compliance Officer, or other appropriate individuals designated by the company, suspected violations of any federal health care program requirements or of company's own Policies and Procedures .

▪ Required Policies & Procedures

- Tracking of HCP contracts in a database
- An internal review and approval process
- Tracking of remuneration to and from sources of health care business or referrals.
- Reporting Requirements include:
 - All services made available by payment, per consultant, by region and by total payments with a list of services yet to be rendered (HCP Payment tracking).
 - Consulting payments must not exceed \$500 per hour.

“The Big 5” medical device companies are now required to publish individual payments to all contracted HCPs on their company websites.

This information is now available for scrutiny by any individual, company, government entity or law firm.

Recent Medical Device DPA Requirements

DPA Requirements Are More Invasive and Require More Public Reporting

In order to be compliant with the anti-kickback statute, companies were required to create procedures to ensure that each existing and new or renewed Arrangement, including Contractual and Non-Contractual Arrangements, does not violate the Anti-Kickback Statute (taking into account the regulations, directives, and guidance related to this statute). These procedures shall include

- Creating and maintaining a database of all existing and new or renewed Arrangements,
- Tracking remuneration to and from all parties.
- Tracking service and activity logs to ensure that parties to an Arrangement are performing the services required under the applicable Arrangement.
- Monitoring the use of leased space, medical supplies, medical devices, equipment, or other patient care items to ensure that such use is consistent with the terms of the Arrangement (if applicable).
- Establishing and implementing a written review and prior approval process for all Contractual Arrangements, including but not limited to, a legal review by counsel with expertise in the Anti Kickback Statute and appropriate documentation of all internal controls.
- Requiring the Compliance Officer to review the Arrangements Database, internal review and approval process, and other Arrangements Procedures at least quarterly and to provide a report on the results to the Compliance Committee
- Implementing effective responses when suspected violations of the Anti-Kickback Statute are discovered including disclosing Reportable Events

“The Big 5” medical device companies are now under extreme scrutiny for all of their HCP arrangements.

Compliance with contractual obligations must be documented and reviewed within multiple levels of the organizations.

This includes not just typical FFS activities, but also activities related to clinical and R&D work.

IV. Clinical Trials and Off Label Communication

Off Label Concerns and Regulatory Responses

States AG's OIG and FDA all are focused on Potential for Off-Label Discussions

Industry increasingly uses more media venues to communicate, advertise and promote their products (i.e. internet web sites, blogs, patient advocacy sites) in addition to TV, radio and other print media.

- Areas of potential risk include:
 - Pre-approval discussions
 - Off-label dissemination of reprints or abstracts
 - Lack of fair balance in the presentation of product's benefits and risk (e.g. false or misleading information)
 - Medical Affairs activities must be consistent with FDA guidelines regarding education, advertising and promotion
 - Emphasis should be on education and scientific exchange of information and less on “product promotion”
 - FDA is more concerned about the content and activity and less on the title of the provider of information
 - Manufacturers may respond to unsolicited requests for medical information (21 U.S.C. § 360aaa-6(a))
 - Request must be truly unsolicited
 - Response must be tailored to the question asked
 - Response must be balanced and non-promotional
 - See 59 F.R. 59820 at 59823 (Nov. 18, 1994)
 - Agents and distributors need appropriate training and monitoring to ensure compliance

Recent Cases of Scientific Misconduct

Investigations and Allegations Related to Clinical and Research Studies

Issue	Examples of Cases	Outcome
Falsified Research	<ul style="list-style-type: none"> The Army found that Dr. Kuklo, a former Army surgeon at Walter Reed, had forged the names of four other Walter Reed doctors he claimed to be his co-authors on the study, and presented data that appeared to have been fabricated because it did not match Walter Reed patient records. Medtronic received a subpoena in May 2009 regarding its financial relationship with the surgeon. 	DOJ Investigation (still open)
Ghostwriting	<ul style="list-style-type: none"> Eli Lilly, Wyeth, Pfizer, and Merck have all faced allegations of ghostwriting, wherein these manufacturers, to a varying degree, write the paper or study and then have a medical doctor add his or her name to the publication to provide the appearance of third party objectivity. 	Ghostwriting was a factor in several multi-million dollar settlements
Failure to Obtain IDE	<ul style="list-style-type: none"> Inspection revealed that Stryker failed to obtain an Investigational Device Exemption (“IDE”) prior to initiating a clinical investigation. 	FDA Warning Letter
False Claims	<ul style="list-style-type: none"> The complaint against EBI alleged that King and McNair, while implanting Ionic Spacers, “took studies that failed in laboratory animals, and then, without any reasonable basis to conclude that they would be successful, began to experiment on humans” by implementing similar surgical techniques. After the surgeries and the implantation of the Ionic Spacers, King and McNair, with EBI’s full knowledge, allegedly submitted claims for payment to Medicare and Medicaid for the cost of the surgeries. 	Qui Tam Action
Documented Research Needs	<ul style="list-style-type: none"> Several medical device manufacturers were found to be lacking adequate documentation/substantiation for multiple research and educational grant related activities. 	Annual Needs Assessment is Required

Recent Corporate Integrity Agreements (CIA)

Implications for the Life Sciences Industry

- Recent settlement with the Justice Department stemming from allegations of off-label promotion
- Substantial requirements for internal controls and monitoring of clinical research processes:
 - Must develop policies and procedures addressing sponsorship, funding of, and disclosures relating to research and development-related activities (including clinical trials, market research or authorship of articles and other publications)
 - Must develop a monitoring program for all continuing medical education and certain charitable contributions to healthcare related charitable organizations
 - Must establish a needs assessment process and develop a monitoring program for publications activities
- Other disclosure initiatives
 - All authors of biomedical manuscripts expected to fully comply with the ICMJE criteria regarding authorship and disclosure
 - Company to register every Company-sponsored clinical Phase I-IV interventional study in patients on www.clinicaltrials.gov

FDA Issues Warning Letters For Paid Internet Search Ads

FDA Cracking Down on DTC Internet Advertising

On April 3rd, the Food and Drug Administration (FDA) issued letters to 14 pharmaceutical companies warning them to stop using what it called “misleading” and “misbranded” internet ads for 48 drug products.

- Sponsored web-links that accompanied internet searches failed to communicate any risk information associated with the use of the drug products.
- Application of the "one-click rule" for a product web ad that provides a link to the package insert or brief summary is not sufficient.
- As companies become involved in social media, there is greater responsibility to address some of technical aspects of the Internet, which the FDA has responded to with increased regulatory parameters that are not always clearly defined. This continues to be an evolving area of regulation and risk for both pharmaceutical and device companies.



Recognizing the Risks and Responsibilities of Social Media

Identifying and Mitigating Compliance Risk

Current guidelines regarding various media in which pharmaceutical and medical device manufacturers may promote their products is vague and incomplete. Social media is an area involving a high level of risk associated with promotion of off-label or egregious information.

- Social Media is not free- it still takes considerable resources (both financial and human)
 - The same rules of DDMAC review apply as well.
- As with other mediums there is a continuum of risk and complexity. Social media sponsored by pharmaceutical companies appears to represent the highest level of risk –visitors are not controlled, they may leave off-label posts and any editorial control may be viewed as an endorsement.
- Examples of risks involving social media are:
 - High Risk
 - Developing corporate disease awareness social networks/bulletin boards-risk of off-label discussions and possible adverse event reporting
 - Branded Corporate Wikis-risk of off label promotion, adverse event reporting and unfair balance
 - Branded Participation in social media- leaving posts, comments in forums-concern with off-label and fair balance being maintained
 - Medium Risk
 - Branded advertising on SM platform some risk for off label perception
 - Non-branded disease awareness blogs
 - Branded Blogs
 - Low Risk
 - Branded Corporate podcasts
 - Non-branded advertising on SM platform

Suggestions to Mitigate Risks Related to Social Media

Identifying and Mitigating Compliance Risk

To mitigate risks involving social media, clear guidelines should be set to reflect the Company's views towards off-label and unapproved promotion of the Company's products. Below are a list of actionable measures to take in order to prepare your company to prevent social media abuse.

- Educate senior management, legal and compliance staff on what is social media, your objectives, and importantly your metrics.
- Create “what if” scenarios for discussion with legal and compliance.
- Rules of engagement –what will you do with negative information or adverse event reports.
- Develop clear written guidelines for adverse event reporting, employee conduct on company sponsored sites (and other sites), presentation of user-generated content, measurement of trends in discussions.
- Provide adequate training to designated individuals.
- Limit or avoid off label communications in any social media strategy
 - Monitor medical content on sponsored or supported web sites
 - Support arms-length unbranded educational web sites and do not require content approval or review
 - Have Legal and Regulatory review of all content for company sponsored sites
 - Don't circumvent your review and approval process

Suggestions to Mitigate Risks Related to Social Media (cont'd)

Identifying and Mitigating Compliance Risk

- Set up specific framework and process to review social media materials
 - Clearly establish Company's interpretation of FDA regulations.
 - How will Company incorporate new rules in a rapidly changing environment?
- Ensure Compliance Clarity
 - Develop criteria for assessing adverse event reporting.
 - Train employees to monitor social media activity using specific criteria.
 - Work with FDA to develop a customized monitoring protocol that meets the needs of a specific medium.
- Discourage the use of personally identifiable information
 - Add warnings to the terms of use section
- Consider the use of independent moderators if you are considering facilitated or moderated discussion forums.
- Consider strict limitations on discussion topics on Company sponsored sites and review of postings (make sure this is transparent to community).
- Consider reviewing links to ensure Drug name is not included in conjunction with a claim.
- Consider disabling links to post on your Twitter accts and other sites to prevent confusion until rules become more settled.
- Set strict guidelines on use of information gathered from social media sites particularly for sales or marketing purposes.

V. Future Considerations

Preparing for Future Requirements

Enhancing Clinical Trial Transparency

Manufacturers must identify key areas of compliance risk and enhance their policies and processes to minimize risk commonly associated with IIS and other clinical research activity. Prior to conducting such research, manufacturers must ensure proper registration on clinicaltrials.gov.

- Prepare for future reporting requirements
 - Identify which studies may need to be revised and the effort it will require to make these compliant
 - Manufacturers can expect to face similar regulatory trends international, as seen in EMEA
- Proactively develop a transparent and documented review and approval process
 - Ensure validity of research and avoid unnecessary duplication of research
- Track all research, and the associated investigators, which is being conducted with manufacturer's products
- Incorporate appropriate language into contracts to ensure compliant SAE reporting
- Conduct FMV determinations, where necessary, and create supporting documentation
- Develop compliance policies related to communicating via social media

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