Research Compliance
2012: A Year in Review

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Agenda

- A Year-in-Review and Special Topics: What should you know?
  - FY 2012 OIG Work Plan (with continuing investigations from 2011)
  - Affordable Care Act and Clinical Research
  - Human Subjects Research Protections
  - HIPAA & HITECH
  - Conflicts of Interest
  - Research Misconduct
- Special Topics
  - FDA Guidance: Oversight of Clinical Investigations
  - FDA Guidance: Humanitarian Use Device Designations
  - FDA Guidance: Responding to Unsolicited Requests for Off-Label Info
  - FDA Request for Information: Scientific Exchange
  - Off-Label Marketing and Promotion: Major cases from 2011
FY 2012 OIG Work Plan

Research Oversight

- The Food and Drug Administration’s Oversight of Investigational New Drug Applications
  - The OIG “will review FDA’s process for evaluating investigational new drug (IND) applications.”
    - Drug sponsors submit IND applications to FDA for review, and the agency has 30 days from receipt of the applications to review them, after which the sponsors may start clinical trials without FDA’s approval.
    - They “will assess FDA’s timeliness and identify challenges to the IND review process.”

(OEI: 00-00-00000; expected issue date: FY 2013; new start)
FY 2012 OIG Work Plan

Research Oversight

- FDA’s Policies and Procedures for Resolving Scientific Disputes
  - FDA will describe the extent and nature of formal internal scientific disputes that occurred during the approval of medical devices.
  - FDA will assess the extent to which regulations, policies, and procedures were followed during the dispute resolution process.

- FDA’s 510K Process for Device Approval
  - FDA will review documentation of devices that FDA cleared using the Premarket Notification process, known as the 510(k) process, and describe characteristics of the cleared devices.

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FY 2012 OIG Work Plan

Research Oversight

- National Institutes of Health and Colleges’ and Universities’ Compliance With Cost Principles
  - The OIG “will review colleges’ and universities’ compliance with selected cost principles issued by OMB Circular A-21, Cost Principles for Educational Institutions.”
  - They will also “conduct reviews at selected schools based on the dollar value of Federal grants received and on input from HHS operating divisions and the offices of the Assistant Secretary for Financial Resources and the Assistant Secretary for Administration.”

(OAS; W-00-11-50037; various reviews; expected issue date: FY 2012; work in progress)

- Review of Extra Service Compensation Payments Made By Educational Institutions
  - OIG will determine whether payments for extra compensation charged to federally sponsored grants, contracts, and cooperative agreements by educational institutions complied with Federal regulations.

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FY 2012 OIG Work Plan

Research Oversight

- Informed Consent and Privacy Protection Procedures for NIH Grantees Conducting Genetic Research
  - They will determine the extent to which NIH grantees conducting genetic research comply with regulations and guidance on informed consent procedures.
  - They will assess the informed consent and privacy protection procedures used by these grantees and determine the extent to which they ensure that human subjects’ private information stored in biobanks is protected in future research.
  
  *(OEI; 01-11-00520; expected issue date: FY 2012; work in progress)*

- Use of Data and Safety Monitoring Boards in Clinical Trials
  - OIG will determine the extent to which Data and Safety Monitoring Boards (DSMB) monitor data in clinical trials.
  - They will also determine how and to what extent NIH is ensuring that grantees comply with the NIH policy for DSMBs in multisite clinical trials.

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FY 2012 OIG Work Plan

Research Oversight

- NIH Oversight of Grants Management Policy Implementation
  - The HHS Grants Policy Directives and the NIH Grants Policy Statement provide guidance on implementing regulations at 45 CFR Parts 74 and 92 which establish uniform administrative requirements governing HHS grants.
  - OIG will examine the NIH Office of Extramural Research’s (OER) oversight of the grants administration processes implemented by the 24 Institutes and Centers (IC) that award extramural grants.
  - They will also examine OER’s oversight of each IC’s compliance with regulations, department directives, and agency policies.

  *(OEI; 07-11-00190; expected issue date: FY 2012; work in progress)*

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FY 2012 OIG Work Plan

Research Oversight

- National Center for Research Resources’ (NCRR) Oversight of Clinical and Translational Science Awards (CTSA)
  - The OIG “will review the NCRR process for overseeing CTSA grantees.”
    - The CTSA program began in 2006 (to be fully implemented in 2012) to encourage intellectual discussion and dissemination of clinical research results and technologies among scientific investigators at 60 institutions that facilitate the creation of translational science networks and biomedical informatics tools.
    - The CTSA program awards 5-year grants to 12 academic health centers annually.
    - NCRR oversees this program and its milestones for compliance with CTSA program objectives and HHS grant administration requirements at 45 CFR pt. 74.
    - Congress awarded over $300 million during the first 2 years of this program, with funding of the full CTSA initiative expected to exceed $500 million annually by 2012.
  - They “will also examine NCRR’s monitoring of programmatic involvement with CTSAs, particularly awardee-generated goals and milestones.”
    (OEI; 07-09-00300; expected issue date: FY 2012; work in progress)

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FY 2012 OIG Work Plan

Research Oversight

- Inappropriate Salary Draws From Multiple Universities
  - The OIG “will determine whether faculty members working on NIH grants were inappropriately drawing salaries from multiple universities.”
  - This follows a recent indictment that alleged that two professors were inappropriately drawing salaries from two universities.
    (OEI; 00-00-00000; expected issue date: FY 2010; new start)

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FY 2012 OIG Work Plan
Research Oversight

- Cost Sharing Claimed by Universities
  - OIG noted in a recent audit that, a university waived its claim for Facilities and Administrative (F&A) costs to meet cost-sharing requirements.
    - The university then relied on a Cost Accounting Standards (CAS) exemption to directly claim costs that are normally treated as F&A costs. A CAS exemption allows, in exceptional circumstances, normally indirect costs, such as clerical salaries, postage, memberships, subscriptions, telephone charges, and office supplies, to be charged as direct costs.
    - However, by waiving F&A costs to meet cost-sharing requirements and claiming the costs directly, the university is not complying with the intent of cost sharing. Indirect costs may be claimed in matching or cost sharing instances only with the prior approval of the Federal awarding agency. (OMB Circular A-110)
  - OIG will determine how universities are meeting cost-sharing requirements
    (OAS; W-00-12-58207; expected issue date: FY 2012; new start)

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Affordable Care Act and Clinical Research

Physician Payment Sunshine Act
(The Transparency Act) Provisions
(Section 6002)
Physician Payment Sunshine Act Provisions

Overview

- The “Physician Payment Sunshine Act” (in some form) was introduced each year in the U.S. Congress since 2007.
- In 2010, Physician Payment Sunshine Act provisions were included in the Affordable Care Act (Section 6002).
- Section 6002 is designed to encourage transparency in the relationships between manufacturers and physicians.
- Requires manufacturers of covered drugs, devices, biologicals, and medical supplies ("applicable manufacturers") to submit on an annual basis certain payments or other transfers of value made to physicians and teaching hospitals ("covered recipients") during the course of the preceding calendar year.
- Requires searchable payment information to be posted on the Internet in a format that is clear, understandable, and able to be easily aggregated and downloaded by 2013.
- Preempts state “sunshine” laws requiring manufacturers to submit the same data
- Includes penalties for non-compliance (failing to report)

CMS Proposed Rule

- Section 6002 requires reports to be submitted (in electronic format) to HHS by March 31, 2013 for payments or other transfers of value made during calendar year 2012, with subsequent reports due on the 90th day of each calendar year thereafter.
- CMS proposed rule to implement Section 6002 was issued on December 14, 2011 — missing the October deadline, as written in the statute.
- Because a final rule was not published in time for manufacturers to begin collecting the information required on January 1, 2012, as indicated in the statute, CMS is not requiring manufacturers to begin collecting the required information until after the publication of the final rule.
- Depending on the publication date of the final rule, CMS is considering requiring the collection of data for part of 2012, to be reported to CMS by the statutory date of March 31, 2013. (i.e., It now looks like 2012 data reporting will be voluntary.)
- Comments to the proposed rule were submitted to CMS on or before February 17, 2012. The Final Rule is expected any day now.

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Two types of reports must be submitted to CMS under the proposed rule:

(1) payments or other transfers of value from applicable manufacturers to covered recipients; and

(2) physician ownership and investment interests in applicable manufacturers and applicable GPOs.

Who must report?

"Applicable manufacturers": any entity that is

(1) engaged in the production, preparation, propagation, compounding, or conversion of a covered drug, device, biological, or medical supply for sale or distribution in the US (or US territory); or

(2) under common ownership with such an entity and that provides support to such entity with respect to the activities described above, or with respect to marketing, promotion, sale, or distribution of a covered drug, device, biological, or medical supply for sale or distribution in the US.

CMS is proposing that common ownership exist where the same entity or entities directly, or indirectly, own any portion of two or more entities.

– CMS seeks comment on an alternate threshold such as a minimum 5 percent ownership threshold
A "covered drug, device, biological, or medical supply" is any drug, device, biological, or medical supply for which payment is available (either separately or as part of a composite payment rate) under Medicare, Medicaid, or CHIP.

- Includes only drugs and biologicals that require a prescription and only devices and supplies that require premarket approval by (or notification to) the FDA.

A "covered recipient" refers to:

- A physician under section 1861(r) of the Social Security Act (e.g., MDs, Dos, DMDs, DPMs, ODs, and Licensed Chiropractors).
  - Does not include PhDs, NPs, PAs or Allied Health Professionals
- A teaching hospital that receives indirect medical education ("IME"), direct graduate medical education, or psychiatric hospital IME payments.

Note: manufacturers are responsible for identifying covered recipients.

- Must use the National Plan & Provider Enumeration System to identify physicians.
- CMS will annually publish a list of hospitals that qualify as teaching hospitals.

A "payment or other transfer of value" is a transfer of anything of value.

- Manufacturers must report all payments or transfers of value to a covered recipient, regardless of whether the covered recipient specifically requested the payment.
- Payments or transfers of value made to a physician through a group practice should be reported under the name of the physician as the covered recipient.
- The nature of payment or other transfer of value could be, for example:
  - Consulting Fees
  - Honoraria
  - Gifts
  - Entertainment
  - Food
  - Travel
  - Education
  - Charitable contributions
  - Royalty or license
  - Direct compensation for serving as a faculty member / speaker for CME program
  - Grants and other compensation for research activities, including payments pursuant to clinical trial agreements.
**CMS Proposed Rule**

*Excluded payments and other transfers of value*

- Payments or other transfers of value excluded from the required reporting:
  - Anything of value that is made *indirectly* to a covered recipient through a third party in connection with an activity or service in the case where the applicable manufacturer is *unaware* of the identity of the covered recipient.
  - Anything < $10, unless the aggregate during the calendar year exceeds $100.
  - The loan of a covered device for a short-term trial period, not > 90 days
  - Other excluded items include:
    - Product samples for patient use.
    - Educational materials for patient use.
    - Items or services provided under a contractual warranty.
    - Discounts (including rebates)
    - “In-kind” items used to provide charity care.
    - Interest payments or dividends from publicly traded securities or mutual funds.

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**CMS Proposed Rule**

*Indirect payments*

- Payments or transfers of value made to an individual or entity at the request of or designated on behalf of a covered recipient must be reported under the name of the covered recipient.

- (As noted in the previous slide) Payments or transfers of value do *not include* anything of value that is made *indirectly* to a covered recipient through a third party in connection with an activity or service in the case where the applicable manufacturer is *unaware* of the identity of the covered recipient.
  - However, exclusion does not apply when the manufacturer has “*actual knowledge, or acts in deliberate ignorance or reckless disregard of the identity of the covered recipient.*”
  - CMS is proposing that awareness by an agent of the manufacturer be attributed to the manufacturer.
Limited to payment for *bona fide* research activities, including clinical investigations that are subject to both a written agreement or contract between the applicable manufacturer and the organization conducting the research, as well as a research protocol.

When reporting payments or other transfers of value designated as research, applicable manufacturers must report the payment or other transfer of value as either ‘indirect research’ or ‘direct research.’

**Indirect research payments:**
- Research payments made to a clinic, hospital (other than a teaching hospital), or institution conducting the research (either by an applicable manufacturer or a CRO entity) and that organization in turn pays the physician covered recipient (or multiple physician covered recipients) serving as a principal investigator(s).

**Direct research payments:**
- Research payments made directly to a physician covered recipient or teaching hospital covered recipient by an applicable manufacturer or CRO entity.

Both indirect and direct research payments must be reported under the individual names and NPIs of physician covered recipients serving as principal investigators.

- For indirect payments, this includes:
  - the physician covered recipient(s) serving as principal investigator(s) who would ultimately receive payments from the clinic, hospital, or other research institution, assuming the applicable manufacturer is aware of the identity of the principal investigator(s).
  - the name of the entity or individual that received the payment.

- For direct research payments provided to teaching hospitals and ultimately to physician covered recipients, payments must be reported for both the teaching hospital covered recipient, and the physician covered recipient(s).
  - Payments to the teaching hospital covered recipient are to be reported as direct research payments;
  - Payments for the principal investigator(s) (physician covered recipient(s)) are to be reported as indirect research payments.
CMS Proposed Rule
Payments for research (cont.)

- CMS acknowledges “that reporting the amount of the payment or other transfer of value may be difficult because neither the applicable manufacturer nor the CRO generally know how the research payment is distributed because the payment includes all items and activities associated with the research project, not only the physician’s time and services.”
- Therefore, for both direct and indirect research payments, CMS is proposing that manufacturers report the entire payment amount for each research payment (whether to the covered recipient or research institution), rather than the specific amount that was provided to the covered recipient.
- Finally, some of the reporting requirements of Section 6002 will duplicate requirements already mandated by the FDA for manufacturers who submit marketing applications (containing clinical study data): 21 CFR part 54—Financial Disclosure by Clinical Investigators.

CMS Proposed Rule
Manufacturer registration

- CMS is considering requiring that all applicable manufacturers register with the agency, even if they have no information to report.
  - In doing so, the chief executive officer, chief financial officer, or chief compliance officer would be required to submit an attestation that the company had no reportable payments or other transfers of value during the previous calendar year.
- The stated purpose of this universal registration and attestation process would be to help CMS better understand the relationships within the industry, as well as encourage applicable manufacturers to perform a more thorough evaluation to determine if they have any reportable information.
CMS Proposed Rule
Report format for payments or other transfers of value

- CMS is proposing that the following information be required:
  - Name of the covered recipient (and entity that received the payment, if applicable)
  - Business address and National Provider Identifier (NPI) (if applicable)
  - Amount of the payment or other transfer of value
  - Date(s) on which the payment or other transfer of value was provided
  - Description of the form of payment or other transfer of value (e.g., cash or in-kind)
  - Description of the nature of the payment or other transfer of value (e.g., research)
  - Name of the covered drug, device, biological, or medical supply (if applicable)
  - Whether the payment or other transfer of value was provided to a physician holding ownership or investment interests in the applicable manufacturer
  - Whether the payment or other transfer of value should be granted a delay in publication because it was made pursuant to a product research agreement, development agreement, or clinical investigation.
  - Any other categories of information CMS deems appropriate

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CMS Proposed Rule
Delayed publication for payments made pursuant to product R&D

- CMS will delay publication of payments (or other transfers of value) made pursuant to product research or development agreements or clinical investigations in order to maintain confidentiality of proprietary information.
- Request for delay in publication will be required for each reporting year.
- Publication of payments granted delay will be made available to the public after the earlier of the following:
  - The date of the approval or clearance of the covered drug, device, biological, or medical supply by the FDA; or
  - Four calendar years after the date such payment was made.
- Payments or other transfers of value granted delayed publication are limited to relationships for bona fide research or investigation activities, which, if made public, would damage the manufacturers' competitive and/or proprietary interests.

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CMS Proposed Rule
45-Day Review Period

- Applicable manufacturers and covered recipients will have the opportunity to review the data submitted for a period of at least 45 days prior to the data being made available to the public.
- After the submission due date has passed, CMS will aggregate the data and notify all applicable manufacturers and covered recipients about the review process, which will include the specific instructions for performing this review.
- CMS is proposing a few different plans for notifying covered recipients.
  - One such plan requires applicable manufacturers to collect and report to CMS the contact information and preferred method of contact for each covered recipient or physician owner or investor.

CMS Proposed Rule
Public Availability

- CMS suggests a data structure that includes all of the content from the submitted reports, less the following information:
  - Whether the payment or other transfer of value was provided to a physician holding ownership or investment interests in the applicable manufacturer; and
  - Whether the payment or other transfer of value should be granted a delay in publication because it was made pursuant to a product research agreement, development agreement, or clinical investigation.
- The Internet website will include all other information, as required by the statute (e.g., any enforcement actions taken for the previous year; and background or other helpful information on relationships between the drug and device industry and physicians and teaching hospitals).
- In addition to this information, CMS intends to clearly state on the website that "disclosure of a payment or other transfer of value on the website does not indicate that the payment was legitimate nor does it necessarily indicate a conflict of interest or any wrongdoing."

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CMS Proposed Rule
Penalties for non-compliance

- Manufacturers will be subject to civil monetary penalties for failure to report accurate and complete data on a timely basis in accordance with final regulations:
  - Failure to report may result in a civil monetary penalty of not less than $1000 but not more than $10,000 for each payment or transfer of value not reported (not to exceed $150,000).
  - A “Knowing Failure to Report” may result in a civil monetary penalty of not less than $10,000 but not more than $100,000 for each payment or transfer of value not reported (not to exceed $1,000,000).
    - The term “knowingly” is given the meaning from the False Claims Act, 31 U.S.C. 3729(b).

CMS Proposed Rule
Penalties for non-compliance

- CMS proposes that the following factors be considered in determining the amount of the CMP:
  - The length of time the manufacturer failed to report, including the length of time the manufacturer knew of the payment or other transfer of value;
  - The amount of the payment or other transfer of value the manufacturer failed to report;
  - The level of culpability;
  - The nature and amount of information reported in error; and
  - The degree of diligence exercised in correcting information reported in error.
CMS Proposed Rule
Audit, Evaluation or Inspection

- CMS is proposing that it, the Secretary of HHS, the OIG, or their designees be allowed to audit, evaluate, or inspect applicable manufacturers for their compliance with the submission of required information.
- To enable an audit, evaluation, or inspection, applicable manufacturers will be required to maintain all books, records, documents, and other materials sufficient for a period of at least five years from the date the payment or other transfer of value is published publicly on the website.

Implications for Manufacturers

- Manufacturers will need to develop and implement:
  - policies, procedures and training for Clinical Development, Medical Affairs and possibly Commercial personnel so that they understand the rules;
  - a payment tracking and reconciliation process (if one does not already exist) to ensure that payments are being made according to the clinical trial agreement, for bona fide research only;
  - mechanisms for reporting payments made to covered recipients; and
  - mechanisms to monitor and/or audit payment reporting to ensure that all payments are being reported in a timely and accurate manner.
Implications for Research Sites

- Teaching hospitals and other research sites will need to:
  - review and possibly edit their conflict of interest policies, procedures and disclosure mechanisms in order to determine if they are consistent with the Sunshine Act and the various state reporting rules in place in their states;
  - educate physician covered recipients to ensure that they properly disclose any payments or other transfers of value made to them by manufacturers; and
  - develop and implement mechanisms to ensure compliance with the institution’s disclosure policy and to reconcile disclosers made by physician covered recipients with payments and other transfers of value reported by manufacturers.

Human Subjects Research Protections
Human Subjects Research Protections
Advance Notice of Proposed Rulemaking


- The proposed changes are intended to:
  - streamline review and approval processes,
  - reduce bureaucratic inconsistencies,
  - appropriately include new research technologies and categories of human subjects research, and
  - expand protections for human research participants.

Some notable proposed changes include:
- Requiring domestic institutions receiving funding from Common Rule agencies to extend Common Rule protections to all of their human subjects research.
- Use of a standardized, yet flexible and streamlined set of data elements to enable customized safety reporting and compliance with Federal agency reporting requirements for unanticipated problems and adverse events
- A mandate that all domestic sites in multi-site research studies rely upon a single IRB as the IRB of record.
- Elimination of continuing review for minimal risk research which received expedited review.
- Increased auditing of IRBs by the Institution
Human Subjects Research Protections

FDA Guidance

- In March of 2011, the FDA issued final guidance, titled “Exception from Informed Consent Requirements for Emergency Research”

  - The purpose of the guidance is to ‘assist Institutional Review Boards (IRBs), clinical investigators and sponsors in the development, conduct, and oversight of investigations to determine the safety and effectiveness of FDA regulated products in emergency settings when an exception from the informed consent requirements is requested’

  - The guidance offers FAQ type of information on topics ranging from processes for submitting proposed emergency research to the FDA to how IRBs should document their review of emergency research

The guidance defines emergency research as: a planned clinical investigation that requires prior written FDA authorization to proceed and involves subject(s) who are in a life-threatening situation for which available treatments or in vitro diagnostic tests are unproven or unsatisfactory.


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Health Insurance Portability and Accountability Act (HIPAA)

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Health Information Technology for Economic and Clinical Health (HITECH)
The HIPAA Privacy Rule was the first comprehensive Federal protection for the privacy of personal health information (PHI).

- Research institutions and investigators may or may not be covered by HIPAA.

Prior to HIPAA, investigators were already required to take measures to protect PHI from inappropriate use or disclosure.

- As we discussed, these measures are included in the HHS and FDA Protection of Human Subjects regulations 45 CFR part 46 or 21 CFR parts 50 and 56, respectively.

HITECH Act (part of ARRA) supplemented and/or modified certain provisions of the HIPAA Privacy Rule

- State Attorneys General may bring civil actions in federal court on behalf of the state’s residents.
- Civil monetary penalties for HIPAA violations have increased.

**Authorization for Research Purposes**

- Pertains only to a specific research study, not to future, unspecified projects.
- An Authorization is different than Informed Consent
  - An Authorization is an individual's permission for a covered entity to use or disclose PHI for a certain purpose, such as a research study.
  - Informed Consent is the individual's permission to participate in the study.
- An Authorization can be combined with an Informed Consent Form (ICF)
  - Must include the core elements and required statements. See: [http://privacyruleandresearch.nih.gov/authorization.asp#samplelang](http://privacyruleandresearch.nih.gov/authorization.asp#samplelang)
Covered entities may permit researchers to review PHI in medical records or elsewhere during reviews preparatory to research, as long as the covered entity receives representations from the researcher that:

- The use or disclosure is sought solely to review PHI as necessary to prepare the research protocol or other similar preparatory purposes.
- No PHI will be removed from the covered entity during the review.
- The PHI that the researcher seeks to access is necessary for research purposes.

On May 31, 2011, the DHHS, Office for Civil Rights ("HHS-OCR") issued a proposed rule, the HIPAA Privacy Rule Accounting of Disclosures Under the Health Information Technology for Economic and Clinical Health ("HITECH") Act. The proposed rule would:

- modify the existing accounting of disclosures of protected health information ("PHI") obligations under the HIPAA Privacy Rule,
- obligate covered entities and business associates to provide "access reports" identifying who has accessed PHI in an electronic designated record set maintained by a covered entity or business associate for up to three years prior to the access report, and
- require covered entities to modify their Notices of Privacy Practices to include a statement that individuals have the right to receive an accounting of disclosures and an access report.
Conflicts of Interest

HHS Financial Conflict of Interest Final Rule

- On August 25, 2011, HHS published a final rule on financial conflicts of interest (FCOI) affecting investigators and institutions that apply for or receive Public Health Service (PHS) funding (e.g., NIH grants, contracts and cooperative agreements).

- The revised regulations—Responsibility of Applicants for Promoting Objectivity in Research for which PHS Funding is Sought (42 C.F.R. Part 50, Subpart F) and Responsible Prospective Contractors (45 C.F.R. Part 94)—implement substantial reporting requirement changes to the 1995 PHS conflicts of interest regulations.

- Institutions that are covered by the Final Rule must be in full compliance with all of the regulatory requirements:
  - no later than August 24, 2012, or
  - immediately upon making its investigator FCOI policy publicly accessible (as required in the revised regulations).

- In the interim institutions comply with 1995 regulations, revise their policies, establish procedures for compliance, and train Investigators.
HHS FCOI Final Rule
Rationale for rule changes

- Since the promulgation of the PHS conflicts of interest regulations in 1995, biomedical and behavioral research and the resulting interactions among government, research institutions and the private sector have become increasingly complex.
- This complexity, as well as a need to strengthen accountability, led to changes that expand and add transparency to investigators’ disclosure of significant financial interests (SFI), enhance regulatory compliance and effective institutional management of investigators’ financial conflicts of interests and increase HHS compliance oversight.
- The Final Rule reflects an expanding national effort to increase transparency and FCOI reporting to assure scientific objectivity and integrity.

HHS FCOI Final Rule
Regulatory framework

The basic FCOI framework remains the same

- Disclosure of SFI
- Compliance with Institutional Policy

- Institutional Policy
- Implementation
- Evaluation of SFI
- Identification of FCOI
- Management

- Oversight

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HHS FCOI Final Rule

Major areas addressed

- The major areas that are addressed in the revised regulations include:
  - Definition of Significant Financial Interests
  - Extent of investigator disclosure
  - Information reported to the PHS awarding component (e.g., NIH)
  - Information made accessible to the public
  - Investigator training

HHS FCOI Final Rule

Major changes to the 1995 regulations

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<thead>
<tr>
<th>Topic</th>
<th>1995 Regulations</th>
<th>2011 Final Rule</th>
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<tbody>
<tr>
<td>Significant Financial Interests (SFI)</td>
<td>De minimis threshold of $10,000 for disclosure generally applies to payments or equity interests.</td>
<td>De minimis threshold of $5,000 for disclosure generally applies to payments for services and equity interests. Includes any equity interest in non-publicly traded entities.</td>
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<tr>
<td>Exclusions</td>
<td>Income from seminars, lectures, or teaching, and service on advisory committees or review panels. for public or nonprofit entities.</td>
<td>Income from seminars, lectures, or teaching engagements sponsored by and service on advisory or review panels for a federal, state, or local government agency, an Institution of higher education as defined at 20 U.S.C. 1001(a), an academic teaching hospital, a medical center, or a research institute that is affiliated with an Institution of higher education.</td>
</tr>
<tr>
<td>Which SFIs need to be disclosed (once the threshold is met)</td>
<td>Only those SFI the Investigator deems related to the PHS-funded research.</td>
<td>All SFI related to the Investigator’s institutional responsibilities.</td>
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### HHS FCOI Final Rule

**Major changes to the 1995 regulations**

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<tbody>
<tr>
<td>Types of SFI excluded</td>
<td>All forms of remuneration are included – specific questions such as mutual funds and blind trusts are addressed in FAQ on the NIH website.</td>
<td>Excludes income from investment vehicles, such as mutual funds and retirement accounts, as long as the Investigator does not directly control the investment decisions made in these vehicles.</td>
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<tr>
<td>Travel reimbursements and sponsored travel</td>
<td>Travel reimbursement is not mentioned explicitly in the regulations but is not excluded from the SFI definition.</td>
<td>Disclose the occurrence of any reimbursed travel or sponsored travel related to Institutional responsibilities (including purpose of trip, sponsor/organizer, destination, and duration). NOT required to disclose travel that is reimbursed or sponsored by a federal, state, or local government agency, an Institution of higher education as defined at 20 U.S.C. 1001(a), an academic teaching hospital, a medical center, or a research institute that is affiliated with an Institution of higher education. The Institution will determine if any travel requires further investigation, including determination or disclosure of the monetary value.</td>
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### HHS FCOI Final Rule

**Major changes to the 1995 regulations**

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<td>Information on an identified Financial Conflict of Interest (FCOI) reported by the Institution to the PHS Awarding Component</td>
<td>•Grant/Contract number&lt;br&gt;•Project Director/Principal Investigator (PD/PI) or Contact PD/PI&lt;br&gt;•Name of Investigator with FCOI&lt;br&gt;•Whether FCOI was managed, reduced, or eliminated</td>
<td>INITIAL REPORT&lt;br&gt;Requirements in 1995 reg, plus:&lt;br&gt;•Name of the entity with which the Investigator has a FCOI&lt;br&gt;•Nature of FCOI, e.g., equity, consulting fees, travel reimbursement, honoraria&lt;br&gt;•Value of the financial interest $0-4,999; $5K-9,999; $10K-19,999; ams between $20K-$100K by increments of $20K; amts above $100K by increments of $50K or statement that a value cannot be readily determined&lt;br&gt;•A description how the financial interest relates to PHS-funded research and the basis for the Institution’s determination that the financial interest conflicts with such research&lt;br&gt;•Key elements of the Institution’s management plan</td>
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<td>ANNUAL REPORT&lt;br&gt;•Status of the FCOI&lt;br&gt;•Changes to the management plan</td>
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### HHS FCOI Final Rule

**Major changes to the 1995 regulations**

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<th>Topic</th>
<th>1995 Regulations</th>
<th>2011 Final Rule</th>
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| **Subrecipient Institutions / Investigators and Reporting of identified FCOIs** | Institutions must take reasonable steps to ensure that Investigators working for subs comply with the regs by requiring those Investigators to comply with the Institution’s policy or by requiring the entities to provide assurances to the Institution that will enable the Institution to comply with the regs. | • Incorporate as part of a written agreement terms that establish whether the FCOI policy of the awardee Institution or that of the subrecipient will apply to subrecipient Investigators and include time periods to meet disclosure and/or FCOI reporting requirements.  
• Subrecipient Institutions who rely on their FCOI policy must report identified FCOIs to the awardee Institution in sufficient time to allow the awardee Institution to report the FCOI to the PHS Awarding Component (e.g., NIH through the eRA Commons FCOI Module) to meet reporting obligations. |
| **Public Accessibility** | No requirement | Make the institution’s FCOI policy and certain information available concerning identified FCOIs held by senior/key personnel via a publicly accessible Web site or by a written response to any requestor within five business days of a request, and update such information as specified in the rule. |

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### HHS FCOI Final Rule

**Major changes to the 1995 regulations**

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<th>1995 Regulations</th>
<th>2011 Final Rule</th>
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| **FCOI training** | No requirement | Each Investigator must complete training prior to engaging in research related to any PHS-funded grant or contract and at least every four years, and immediately under the designated circumstances:  
• Institutional FCOI policies change in a manner that affects Investigator requirements  
• An Investigator is new to an Institution  
• An Institution finds an Investigator noncompliant with Institution’s FCOI policy or management plan. |
| **Retrospective Review** (*"Mitigation plan," discussed in NPRM*) | Not mentioned | Institution is required to conduct a retrospective review in those cases of non-compliance with the regulation but is not required to report the review to the PHS Awarding Component. The Institution will be required to notify the PHS Awarding Component promptly and submit a report to the PHS Awarding Component only in cases where bias is found. The report will address the impact of the bias on the research project and the actions the Institution has taken, or will take, to eliminate or mitigate the effect of the bias. |
HHS FCOI Final Rule

*What’s still missing from the HHS COI regulations?*

- **Non-financial conflicts of interest:** Non-financial competing interests (sometimes called “private interests”) can be personal, political, academic, ideological, or religious. For example:
  - Personal recognition, academic/career advancement or visibility in the media;
  - Bestowing favor on a relative, friend or colleague;
  - Allegiance to a school of thought;
  - Publishing or not publishing results; and
  - Political commitment or influence.

- **Institutional conflicts of interest:** Although the revised regulations require PHS grantee institutions to have a written policy for identifying and managing investigator FCOI, there currently are no federal requirements in place that apply to the grantee institutions, themselves.
  - Institutions have their own financial interests, such as royalties for helping a pharmaceutical company invent a drug, which could improperly influence other institutional decisions.

SNR DENTON

Revised FDA Guidance

*Financial Disclosure by Clinical Investigators*

- In May of 2011, the FDA published “Guidance for Clinical Investigators, Industry, and FDA Staff: Financial Disclosure by Clinical Investigators.”
  - Intended to assist clinical investigators, industry, and FDA staff in interpreting and complying with the regulations governing financial disclosure by clinical investigators, 21 CFR part 54.
  - Addresses issues raised by the Office of the Inspector General (OIG), Department of Health and Human Services, in its report, OEI-05-07-00730, “The Food and Drug Administration’s Oversight of Clinical Investigators’ Financial Information” as well as questions FDA has received from industry and the public.
  - Includes several Frequently Asked Questions (FAQs)

- The current Financial Disclosure by Clinical Investigators regulation (21 CFR part 54) were last revised in 1999.


SNR DENTON
Research Misconduct

- Department of Health and Human Services Policy on Research Misconduct
  - All institutions that apply for or receive PHS support for biomedical or behavioral research, biomedical or behavioral research training, or activities related to that research or research training share responsibility for the integrity of the research process.
  - Institutions and institutional members have an affirmative duty to protect PHS funds from misuse by ensuring the integrity of all PHS supported work, and primary responsibility for responding to and reporting allegations of research misconduct

Subpart A- 42 CFR Part 93.100

Public Health Services (PHS) policies on Research Misconduct (42 CFR Parts 50 and 93) have not changed since the issuance of the Final Rule in 2005.
Research Misconduct

Brief Regulatory Overview

- Public Health Services (PHS) Policies on Research Misconduct; Final Rule
  - Regulations at 42 CFR Parts 50 and 93 provide a definition of research misconduct:
    - “Research misconduct means fabrication, falsification, or plagiarism in proposing, performing, or reviewing research, or in reporting research results”
      - Fabrication is making up data or results and recording or reporting them.
      - Falsification is manipulating research materials, equipment, or processes, or changing or omitting data or results such that the research is not accurately represented in the research record.
      - Plagiarism is the appropriation of another person’s ideas, processes, results, or words without giving appropriate credit.
    - Research Misconduct does not include honest error or difference of opinion

SNR DENTON 57

Research Misconduct

Brief Regulatory Overview

- Public Health Services (PHS) Policies on Research Misconduct; Final Rule
  - Findings of Research misconduct requires that:
    - There be a significant departure from accepted practices of the research community
    - The misconduct be committed intentionally, knowingly, or recklessly
    - The allegation be proven by a preponderance of the evidence

SNR DENTON 58
Research Misconduct

Brief Regulatory Overview

- Public Health Services (PHS) Policies on Research Misconduct; Final Rule
  - Examples of “Bad Science,” Not Research Misconduct:
    • Poor design, inappropriate experimental methodology
    • Poor scientific assumptions
    • Use of wrong statistical methodology
    • Keeping poor research records
    • Poor technique
  - Examples of Errors or Carelessness, Not Research Misconduct:
    • Misinterpretation of data
    • Calculation errors
    • Not checking chemical labels
    • Miscalculations of amounts of solutions

SNR DENTON

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Research Misconduct

Brief Regulatory Overview

- Public Health Services (PHS) Policies on Research Misconduct; Final Rule
  - Regulations at 42 CFR Parts 50 and 93 provide the scope of authority of the final rule:
    • HHS [US Department of Health and Human Services] has ultimate oversight authority for PHS supported research, and for taking other actions as appropriate or necessary, including the right to assess allegations and perform inquiries or investigations at anytime.
    • Each institution that applies for or receives PHS support for biomedical or behavioral research, research training or activities related to that research or research training must comply with this part.
  - The Final Rule delegates responsibility for addressing research misconduct issues to the Office of Research Integrity (ORI).
Research Misconduct

Brief Regulatory Overview

- Public Health Services (PHS) Policies on Research Misconduct; Final Rule
  - Regulations at 42 CFR Parts 50 and 93 provide the responsibilities of institutions for compliance. Institutions must:
    • Have written policies and procedures for addressing allegations of research misconduct that meet the requirements of this part;
    • Respond to each allegation of research misconduct for which the institution is responsible under this part in a thorough, competent, objective and fair manner.
    • Foster a research environment that promotes the responsible conduct of research, research training, and activities related to that research or research training.
    • Take all reasonable and practical steps to protect the positions and reputations of good faith complainants.
    • Provide confidentiality to all respondents, complainants, and research subjects.

SNR DENTON [1]
Research Misconduct
Brief Regulatory Overview

- The signature on these documents establishes an assurance

Institutions maintain their assurance by:
- Filing the Annual Report on Possible Research Misconduct (between January 1 and March 1 each year),
- Submitting their policy for responding to allegations of research misconduct for review when requested by ORI,
- Revising their policy when requested by ORI to bring the policy into compliance with the PHS regulation, and
- Complying with the PHS regulation.
Research Misconduct
Recent cases settled in 2011

April 27, 2011—“Lab sabotage deemed research misconduct (with exclusive surveillance video)”

- Vipul Bhrigu, a former postdoctoral fellow at the University of Michigan, was caught on video engaging in the sabotage of a graduate student’s research.

Does ORI regularly pursue cases of sabotage? The answer: “It depends.”

SNR DENTON

The Palm Beach Post
Recent cases settled in 2011

May 16, 2011—“Judge: Scripps scientist told lies”

- Philippe Bois, former postdoctoral fellow in the Department of Biochemistry at St. Jude Children’s Research Hospital, knowingly and intentionally falsified data reported in two (2) papers
  - In an article in the Journal of Cell Biology, Bois conducted two 2003 experiments into a protein’s effect on certain types of childhood tumors. Only one of the two experiments supported Bois’ hypothesis that a malfunction of a particular gene led to soft-tissue cancer; he didn’t report the other experiment, which did not favor his theory.
    - The Journal of Cell Biology retracted the article in 2007, but not before it was cited seven times by other scientists.
  - In an article in Molecular and Cellular Biology, Bois altered an image that appeared in the journal, and then when investigated, blamed it on a fellow graduate student
    - Molecular and Cellular Biology issued a correction in 2007.

SNR DENTON
## Research Misconduct
### Recent cases settled in 2011

### FUNDSCIENCE.ORG
#### FUNDSCIENCE BLOG
- **February 10, 2011**—“Findings of Research Misconduct”
  - **Meleik Goodwill**, a former postdoctoral fellow at Wadsworth Center, a research laboratory at the New York State Department of Health, was found guilty of fabricating data for growth curves and using unrelated western blot images in a 2007 *Journal of Neuroimmunology* article.
    - The article was subsequently retracted in 2008
    - Goodwill entered into a Voluntary Settlement Agreement and will still be allowed to participate in PHS-supported research, but only with an ORI-approved supervisory plan to ensure the integrity of her work over the next three (3) years.

### THE CHRONICLE of Higher Education
- **November 4, 2011**—“Former Researcher at U. of Virginia Is Penalized for Plagiarism”
  - **Jayant Jagannathan**, former Resident Physician at UVA Medical Center, engaged in research misconduct by plagiarizing PHS-funded research
    - In five (5) publications, he plagiarized large amounts of text and an illustration taken from other publications supported by NIH grant awards.
    - Jagannathan entered into a Voluntary Settlement Agreement for a period of four (4) years, beginning on October 20, 2011.
      - Like the Goodwill case, Jagannathan will still be allowed to participate in PHS-supported research, but only with an ORI-approved supervisory plan to ensure the integrity of his work.
Research Misconduct
Recent cases settled in 2011

THE CHRONICLE
of Higher Education

- Oct 19, 2011—“Former Graduate Student at Pitt Is Penalized for Falsifying Data”
  - Marija Manojlovic, a former graduate student in the Department of Chemistry at the University of Pittsburgh, falsified data in a poster presentation and in a draft paper submitted for publication.
    - Found guilty of research misconduct after an inquiry was conducted and written admission obtained by the University of Pittsburgh (UP), and additional analysis conducted by ORI in its oversight review.
    - Manojlovic entered into a Voluntary Settlement Agreement for a period of four (3) years, beginning on September 26, 2011.
      - Like the prior two cases, Manojlovic will still be allowed participate in PHS-supported research, but only with an ORI-approved supervisory plan to ensure the integrity of his work.

Research Misconduct
Recent cases settled in 2011

ST. LOUIS POST-DISPATCH

- December 16, 2011—“[PPS Clinical Research] admits falsified drug testing”
  - PPS is a St. Louis-based multi-specialty clinical trial management company, who contracted with the German drug manufacturer Boehringer Ingelheim to test a drug dubbed the "female Viagra."
  - PPS staffers reported the falsification of patient visits to the drug manufacturer in 2009, and the company reported it to the FDA five days later.
  - In 2010, FDA investigators found:
    - That a former study coordinator falsified records about multiple patient exams that never occurred, and failed to properly store investigational drug.
    - Conflicts between what patients reported about "their interactions with PPS versus what PPS' patient records purported to document."
  - PPS plead guilty in May 2010 to a federal felony charge of obstructing the FDA’s investigation and agreed to a $68,000 fine and to forfeit $7,000.
    - Without admitting liability, PPS also agreed to pay $206,000 in the civil settlement.
Research Misconduct
Recent cases settled in 2011

Other cases settled in 2011:

- April 27, 2011—Junheee J. Shin, a former graduate student, New York Medical College, falsified data in a manuscript sent to the journal *Infection and Immunity*.
- August 5, 2011—Sheng Wang, who has been an Assistant Professor, Department of Medicine, Boston University School of Medicine Cancer Research Center (BUSM), fabricated data that were included in two (2) published papers.
- October 4, 2011—Scott Weber, a former Assistant Professor, University of Pittsburgh School of Nursing, plagiarized text and falsified data from two publications supported by PHS funding in two unpublished manuscripts. He also included large portions of that plagiarized text in two grant applications to the NIH.
- October 11, 2011—Shamarendra Sanyal, a former postdoctoral scholar at Duke University, falsified data in a grant application to the NIH.
- October 13, 2011—Nicola Solomon, a former postdoctoral fellow at the University of Michigan Medical School, included false information in a manuscript based on research supported by two grants from the NIH.

Research Misconduct
Notable allegations from 2011

"Deception at Duke"

- In 2007, Duke University announced that they had discovered how to match a patient's tumor to the best chemotherapy drug.
  - The research was published in the most prestigious medical journals.
  - Researchers enrolled 112 patients into clinical trials using this new method.
- In 2010, the new method was deemed a failure. What wasn’t known, until recently, was that the discovery that led to using this new method wasn’t just a failure, it may end up being one of the biggest cases of research misconduct ever.
“Deception at Duke” (continued)

- **Dr. Anil Potti** was the researcher behind the “breakthrough” matching method. He decoded the genetic makeup of hundreds of tumors, generating massive amounts of data—the underlying proof in research papers published in the top medical journals.

- Then, researchers—first, two doctors from the MD Anderson Cancer Center, and then later, others from the National Cancer Institute—questioned some of the data and results that were published in Dr. Potti’s journal articles.

- This prompted Duke to begin an investigation. Duke suspended the enrollment of patients and asked an outside review committee to analyze Dr. Potti’s discovery.

- After three months, the review committee concluded that Dr. Potti was right.

- Then Dr. Potti’s laboratory Director, Dr. Joseph Nevins, discovered that Dr. Potti’s Rhodes scholarship, which was included in his biosketch on their applications for federal grants, was a lie.

- Having been deceived about the Rhodes scholarship, Dr. Nevins, whose own reputation was at stake, reviewed the original data (which justified the clinical trials) and found that the underlying data should have disproved Dr. Potti’s theory, but they had been changed.

- It was abundantly clear to Dr. Nevins that the data were fabricated.

- Dr. Potti resigned from Duke and is now facing an ORI investigation into research misconduct.

- Duke’s Vice Chancellor, Dr. Rob Califf, is implementing new procedures for Duke to prevent and/or detect cases of research misconduct. He is also overseeing the retraction of Dr. Potti’s papers from the medical journals, one of the most significant retractions in the history U.S. medical research.
July 12, 2011—A University of Pennsylvania psychiatry professor, Dr. Jay D. Amsterdam, accused his department chairman and four colleagues of publishing an article that was ghostwritten on behalf of the pharmaceutical company, GlaxoSmithKline (GSK), and "was biased in its conclusions," "made unsubstantiated efficacy claims and downplayed" negative side effects of one of its best-selling drugs, Paxil.

- The research was supported by both the NIH and GSK.
- The complaint was filed with the Office of Research Integrity.

Is ghostwriting a type of plagiarism? Is it "research misconduct?"

"To protect the integrity of science, we must look beyond falsification, fabrication and plagiarism, to a wider range of questionable research practices"

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**Research Misconduct**

**Notable allegations from 2011**

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**THE CHRONICLE of Higher Education**

- **July 12, 2011**—A University of Pennsylvania psychiatry professor, Dr. Jay D. Amsterdam, accused his department chairman and four colleagues of publishing an article that was ghostwritten on behalf of the pharmaceutical company, GlaxoSmithKline (GSK), and "was biased in its conclusions," "made unsubstantiated efficacy claims and downplayed" negative side effects of one of its best-selling drugs, Paxil.

- The research was supported by both the NIH and GSK.
- The complaint was filed with the Office of Research Integrity.

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**Research Misconduct**

**Resources**

- ORI website: [http://ori.hhs.gov/](http://ori.hhs.gov/)
- Statutes and Regulations
  - ORI Statutory Authority - 42 U.S.C. § 289b
    View: [HTML](#) | [PDF](#)
  - HHS Debarment Regulations - 45 CFR Part 76
- ORI Sample Policy and Procedures for Responding to Research Misconduct Allegations
- ORI Guidelines for Institutions and Whistleblowers; Responding to Possible Retaliation Against Whistleblowers in Extramural Research
- ORI Handbook for Institutional Research Integrity Officers

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FDA Guidance
Oversight of Clinical Investigations

- In August of 2011 the FDA published “Guidance for Industry: Oversight of Clinical Investigations — A Risk-Based Approach to Monitoring”
  - The purpose of this guidance is to enhance human subject protection and the quality of clinical trial data by helping clinical research sponsors develop risk-based monitoring plans and strategies.
  - The guidance provides clarifications to help sponsors tailor their monitoring activities for each trial to focus on critical data elements— the processes for protecting human subjects, maintaining the integrity of study data, and compliance with applicable regulations.

The guidance defines monitoring as, "the methods used by sponsors of investigational studies, or CROs delegated responsibilities for the conduct of such studies, to oversee the conduct of and reporting of data from clinical investigations, including appropriate investigator supervision of study site staff and third party contractors.”


SNR DENTON 71
FDA Guidance

Humanitarian Use Device Designations

- In December of 2011 the FDA published draft “Guidance for Industry and Food and Drug Administration Staff: Humanitarian Use Device (HUD) Designations”
  - The purpose of the guidance is to help with the preparation and submission of HUD designation requests, and assist FDA reviewers in their analysis and evaluation of HUD designation requests
  - The guidance lists specific information that should be in designation requests
- The draft guidance does not address the Humanitarian Device Exemption (HDE) marketing approval process
  - A HUD approved designation is a prerequisite for HDE approval

A HUD is a medical device intended to benefit patients in the treatment or diagnosis of a disease or condition that affects or is manifested in fewer than 4,000 individuals in the United States per year.

For HDE approval, the device must demonstrate safety but does not have to demonstrate a reasonable assurance of effectiveness in order to be go to market.


SNR DENTON

FDA Guidance

Responding to Unsolicited Requests for Off-Label Information

- On December 27, 2011, the FDA issued draft “Guidance for Industry: Responding to Unsolicited Requests for Off-Label Information About Prescription Drugs and Medical Devices”. The draft guidance covers both:
  - responding to requests made directly and privately to companies, and
  - requests made in public forums, including through emerging electronic media.
- FDA Policy on Responding to Unsolicited Requests for Off-Label Information:
  - For decades, the FDA has said that companies can respond to unsolicited requests for off-label information with "truthful, balanced, non-misleading, and non-promotional scientific or medical information that is responsive to the specific request," without subjecting their products to the strict regulatory requirements for promotional labeling or advertizing.
  - This draft guidance does not deviate from the FDA's long held position. Merely, it explains in detail the FDA's recommendations for responding to each type of request for off-label information --"non-public" and public.
FDA Guidance

Responding to Unsolicited Requests for Off-Label Information

Background:

- By law, drug and device companies (manufacturers and distributors) are prohibited from marketing and promoting their products for uses beyond those approved or cleared by the FDA. However, once a drug or medical device has been approved or cleared by the FDA, physicians can (in most cases) lawfully use or prescribe that product for indications that are not included in the product's approved labeling on a case by case basis (or, in the case of a medical device cleared under the 510(k) process, in the product's statement of intended uses).

- Because "off-label" uses may provide important treatment options for patients and may even constitute a medically recognized standard of care, physicians, patients and/or their advocates often seek information about such off-label use – sometimes requesting off-label information directly and privately to firms.

- According to the FDA, a growing number of consumers (patients and providers) are turning to the Internet as a source for information about treating medical conditions. Moreover, drug and device companies, are increasingly using the Internet to disseminate information about their products.

SNR DENTON K

Background (cont.):

- Companies may receive requests for off-label information about their products through product websites that they maintain and over which they have full control. However, the FDA acknowledges that there exist a number of third-party websites, including online discussion boards, chat rooms, and other public, web-based forums that are either entirely independent of a company's control and influence or not fully controlled by a company, and in which may also reveal questions about off-label uses of that organization's products.

- Often, such questions about off-label uses are directed to users of the website generally, rather than directly and privately to companies who, according to the FDA, "are capable of responding to requests about their own named products in a truthful, non-misleading, and accurate manner."

- The FDA deems it to be in the best interest of public health for a company to respond to unsolicited requests for information about off-label uses of its products that are addressed to a public forum, since other respondents may not be able to provide the most accurate and current information about the company's products.

SNR DENTON K
FDA Guidance
Responding to Unsolicited Requests for Off-Label Information

Non-Public Responses

- For a company’s response to a non-public unsolicited request for off-label information about its product that was specifically directed to the company privately via a 1-on-1 communication, the FDA gives seven (7) recommendations:

1. Information distributed in response to an unsolicited request should be provided only to the individual making the request [and handled] as a private, one-on-one communication.

2. Information distributed in response to an unsolicited request should be tailored to answer only the specific question(s) asked.

3. Information distributed in response to an unsolicited request should be truthful, non-misleading, accurate, and balanced.

4. Information distributed in response to an unsolicited request should be scientific in nature.

5. Responses to unsolicited requests for information should be generated by medical or scientific personnel independent from sales or marketing depts.

SNR DENTON

Seven recommendations for responding to non-public unsolicited requests:

6. Information distributed in response to an unsolicited request should be accompanied by the following:

- A copy of the FDA-required labeling, if any, for the product (e.g., FDA-approved package insert and, if the response is for a consumer, FDA-approved patient labeling or, for new animal drugs, FDA-approved client information sheet)

- A prominent statement notifying the recipient that FDA has not approved or cleared the product as safe and effective for the use addressed in the materials provided

- A prominent statement disclosing the indication(s) for which FDA has approved or cleared the product

- A prominent statement providing all important safety information including, if applicable, any boxed warning for the product

- A complete list of references for all of the information disseminated in the response (e.g., a bibliography of publications in peer-reviewed medical journals or in medical or scientific texts; citations for data on file, for summary documents, or for abstracts)

SNR DENTON
FDA Guidance
Responding to Unsolicited Requests for Off-Label Information

Seven recommendations for responding to non-public unsolicited requests:

7) A company should maintain the following records:
   - The nature of the request for information, including the name, address, and affiliation of the requestor
   - Records regarding the information provided to the requestor
   - Any follow-up inquiries or questions from the requestor

Public Responses

- The FDA is concerned about the possibility that companies may respond to public unsolicited questions about off-label uses of their products in a manner that promotes off-label use to individuals who have not requested such information, because product information posted to websites and other electronic forums is likely to remain "available to a broad audience for an indefinite period of time."
- Citing the availability of new data on product risks becoming available in the future, the FDA expressed additional concern that publically posted responses may become outdated.
FDA Guidance
Responding to Unsolicited Requests for Off-Label Information

- In support of a company's response to a public unsolicited request for off-label information about its product, including questions encountered through websites and other emerging electronic media, the FDA gives four (4) recommendations:

1) If a [company] chooses to respond to public unsolicited requests for off-label information, the [company] should respond only when the request pertains specifically to its own named product (and is not solely about a competitor's product).

- For example, a company should not respond to non-specific questions or requests, such as "What drug/device can be used for Condition X?".

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Four recommendations for responding to public unsolicited requests:

2) A [company's] public response to public unsolicited requests for off-label information about its named product should be limited to providing the firm's contact information and should not include any off-label information.

- The [company's] public response should convey that the question pertains to an unapproved or uncleared use of the product and state that individuals can contact the medical/scientific representative or medical affairs department with the specific unsolicited request to obtain more information.

- The [company's] public response should provide specific contact information for the medical or scientific personnel or department (e.g., e-mail address, telephone number, facsimile [number]) so that individuals can follow up independently with the firm to obtain specific information about the off-label use of the product through a non-public, one-on-one communication.
FDA Guidance
Responding to Unsolicited Requests for Off-Label Information

Summary

- Regardless of where the unsolicited request for off-label information was made—in a non-public or public forum—the FDA recommends that a company only provide the requested off-label information about its product to the specific individual who requested the information in a private, one-on-one communication.

- The FDA does not intend to use the responses of companies to unsolicited requests for off-label information as evidence that a company is purposefully promoting its product(s) off-label, if such responses conform to the recommendations provided within the draft guidance.
  
  – Additionally, responses that conform to this guidance would not be expected to comply with the disclosure requirements related to promotional labeling and advertising.

- The complete FDA draft guidance can be found here. Those planning to submit comments or suggestions regarding the draft document will have 90 days from the date of its publication in the Federal Register.

SNR DENTON
FDA Request for Information and Comments
Communications and Activities Related to Off-Label Uses

- On December 28, 2011, the FDA issued a “Request for Information and Comments,” entitled “Communications and Activities Related to Off-Label Uses of Marketed Products and Use of Products Not Yet Legally Marketed”.

- Background: On July 5, 2011, a citizen petition was submitted by lawyers for a group of seven manufacturers requesting that the FDA clarify its policies for drug products and devices governing certain communications and activities related to off-label uses of marketed products and use of products that are not yet legally marketed for any use. Specifically, the petition requests clarification in the following areas:
  1. Manufacturer responses to unsolicited requests;
  2. Scientific exchange;
  3. Interactions with formulary committees, payors, and similar entities; and


The FDA has considered these issues for over a decade.
- The Agency is already considering what actions to take in the areas specified by the petitioners with respect to manufacturer responses to unsolicited requests; interactions with formulary committees, payors, and similar entities; and the dissemination of third-party clinical practice guidelines.
- Therefore, under this Request for Information, the FDA is only seeking comments and information “on all aspects of scientific exchange communications and activities related to off-label uses of marketed drugs, biologics, and devices and use of products that are not yet legally marketed.”
### FDA Request for Information and Comments

**Communications and Activities Related to Off-Label Uses**

- The FDA is particularly interested in responses to the following questions:
  - How should FDA define scientific exchange?
  - What types of activities fall under scientific exchange?
  - What types of activities do not fall under scientific exchange?
  - Are there particular types and quality of data that may indicate that an activity is, or is not, scientific exchange?
  - In what types of forums does scientific exchange typically occur?
  - Should the use of certain forums be given particular significance in determining whether an activity is scientific exchange or an activity that promotes the drug or device? If so, which forums?
  - What are the distinctions between scientific exchange and promotion? What are the boundaries between scientific exchange and promotion?
  - Generally, who are the speakers involved in scientific exchange, and who is the audience for their communications?

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**SNR DENTON**

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### FDA Request for Information and Comments

**Communications and Activities Related to Off-Label Uses**

- The FDA is particularly interested in responses to the following questions (cont.):
  - Should the identity of the participants (either speakers or audience) be given particular significance in determining whether an activity is scientific exchange or an activity that promotes the drug or device? If so, which participants would be indicative of scientific exchange and which would be indicative of promotion?
  - How do companies generally separate scientific roles and promotional roles within their corporate structures?
  - How should the Agency treat scientific exchange concerning off-label uses of already approved drugs and new uses of legally marketed devices? And should there be any distinctions between communications regarding uses under FDA-regulated investigation (to support potential approval) and communications regarding uses that are not under express FDA-regulated investigation.

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**SNR DENTON**

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FDA Request for Information and Comments
Communications and Activities Related to Off-Label Uses

• The FDA is particularly interested in responses to the following questions (cont.):
  – How should the Agency treat scientific exchange concerning use of products that are not yet legally marketed (that is, products that cannot be legally distributed for any use outside of an FDA- or institutional review board (IRB)-approved clinical trial)?
  – Should investigational new drugs and investigational devices be treated the same with respect to scientific exchange? Why or why not?

• Under the regulations, an investigational device is considered to be ‘‘commercialized’’ if the price charged for it is more than is necessary to recover the costs of manufacture, research, development, and handling. Similarly, FDA considers charging a price for an investigational drug that exceeds that permitted under its regulations (generally limited to cost recovery) to constitute ‘‘commercialization’’ of the drug. What other actions indicate the commercialization of drug and/or device products? If there are differences in the steps taken to commercialize drug products and the steps taken to commercialize device products, either before or after approval, what are these differences?

• Comments are due by March 27, 2012.

SNR DENTON  

3/22/2012
Off-Label Marketing and Promotion
Major Cases in 2011

**January 17, 2011**: GlaxoSmithKline (GSK) set aside $3.4 billion for the probable settlement with the U.S. Government related to civil and criminal investigations into its sales and marketing practices for numerous drugs from 1997 to 2004.

**November 3, 2011**: GSK announced that it has reached an agreement in principle with the U.S. Government to pay $3 billion to settle (among other charges):
- the investigation into GSK’s sales and marketing practices by the U.S. Attorney’s offices of Colorado and Massachusetts; and
- the DOJ’s investigation of the marketing of Avandia, a diabetes drug that was severely restricted last year after it was linked to heart attack risks.

The final settlement is expected to be finalized in 2012. The settlement of $3 billion will be paid using existing cash resources that were set aside in January.

When all is said and done, this settlement will be the largest settlement by a pharmaceutical company for off-label marketing in history, surpassing the previous record of $2.3 billion paid by Pfizer in 2009.

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Off-Label Marketing and Promotion
Major Cases in 2011

**February 28, 2011**: Elan Pharmaceuticals, Inc., the U.S. subsidiary of Irish drugmaker Elan Corporation PLC, plead guilty, finalizing a $203.5 million settlement agreement that was reached in December 2010—in connection with the illegal marketing of its epilepsy drug, Zonegran®.

**AstraZeneca**

**March 10, 2011**: in a settlement that did not include an admission of guilt by the company, AstraZeneca PLC agreed to pay a civil settlement of $68.5 million to 37 states and the District of Columbia to resolve allegations that it promoted off-label prescribing of its schizophrenia drug, Seroquel®.
- This was the largest multi-state, consumer protection-based pharmaceutical settlement on record; and
- It was separate from the $520 million federal settlement over similar allegations announced last year.
Off-Label Marketing and Promotion
Major Cases in 2011

May 13, 2011: The Wall Street Journal reported that according to unnamed sources, federal prosecutors are seeking approximately $1 billion to settle a six-year investigation into whether Janssen Pharmaceutical Inc., a Johnson & Johnson (J&J) company, promoted the off-label use of its antipsychotic drug, Risperdal®.

- Prosecutors are using the 2009 Eli Lilly settlement (which involved a $1.4 billion payment relating to the marketing of the antipsychotic, Zyprexa®) as a benchmark to resolve the Janssen matter.

- The attorneys general of over 40 states have either already filed — or intend to file — actions against Janssen seeking repayment of Medicaid funds, civil penalties, and other compensation for Risperdal® prescriptions written for off-label use.

January 19, 2012: J&J agreed to pay $158 million to Texas settle a lawsuit filed by the state attorney general. Settlements with other states are expected to follow in the coming months.

June 9, 2011: UCB Inc., the U.S. subsidiary of Belgian pharmaceutical company UCB SA., pleaded guilty and will pay more than $34 million for promoting the off-label use of its epilepsy drug Keppra®.

June 10, 2011: the U.S. subsidiary of Danish pharmaceutical company Novo Nordisk Inc. agreed to pay $25 million to settle allegations of off-label promotion of Novo-Seven®, its hemostasis management drug.
Off-Label Marketing and Promotion

Major Cases in 2011

**Abbott**

- **October 19, 2011**: Abbott Laboratories disclosed in its quarterly SEC filing that it recorded a $1.5 billion charge for the third quarter to cover a potential settlement stemming from a government investigation of allegations it promoted its anti-seizure drug, Depakote®, for a variety of unapproved uses, including agitated and aggressive dementia. Just two days later...
- **Bloomberg News** reported that Abbott agreed to pay at least $1.3 billion to settle claims by the U.S. Government and 24 states involved in the suit.

**Pfizer**

- **October 20, 2011**: Pfizer Inc. agreed to pay $14.5 million to settle off-label marketing charges brought by a pair of former Pfizer sales reps in 2006 who accused Pfizer of illegally marketing Detrol® as a treatment for enlarged prostate or BPH (benign prostate hyperplasia), even though the pill had only been approved to treat overactive bladder.
- The U.S. DOJ declined to join the suit, but 22 states joined the whistleblowers, charging that their Medicaid programs were defrauded between 1998 and 2008.
- **May 25, 2005**: One of the whistleblowers wrote a letter to the Senior VP of Human Resources and the Vice Chairman, General Counsel, that informed them (with documented evidence) of illegal promotion of Detrol® and Bextra®, which violated Pfizer’s existing 2004 Corporate Integrity Agreement, a result of illegally marketing Neurontin®.
Off-Label Marketing and Promotion

Major Cases in 2011

MERCK

- **November 22, 2011**: Merck & Co. agreed to pay $950 million to resolve criminal charges and civil claims related to its promotion and marketing of the painkiller Vioxx®, which was withdrawn from the marketplace in September 2004 after it was linked to increased risk of heart attacks and other cardiovascular injuries.
  
  - Under the terms of the resolution, Merck will plead guilty to a one-count information charging a single violation of the Federal Food Drug and Cosmetic Act (FDCA) for introducing a misbranded drug into interstate commerce.
  
  - Under the terms of its plea agreement with the U.S., Merck will plead guilty to a misdemeanor for its illegal promotional activity and will pay a $321,636,000 criminal fine.
  
  - Merck will pay a $628,364,000 civil settlement to resolve additional allegations regarding off-label marketing of Vioxx® and false statements about the drug’s cardiovascular safety.

Thank You!