Medical Science Liaisons and Requests for Medical information: Mitigating Regulatory Risks

Ann E Lewis
VP and Senior Counsel, US Healthcare Law Compliance, BMS
Douglas Young
Vice President, Medical Affairs, BMS
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A few questions to warm us up to the topic

• The role of the Medical Science Liaison was started by what company in what year?

• What are the specific regulations governing the role of Medical Information, the Medical Science Liaison, or the field medical role by any other name (Medical Science Manager, Field Medical Information)?

• Can you name a case that is specifically associated with the misuse of MSLs?
What is the role of MSLs?

- Dr. Jane Chin, Ph.D. (http://www.mslinstitute.com) "...catalysts of collaboration between pharmaceutical companies and thought leaders, medical science liaisons are essential conduits to the quality and success of transmission of timely information, research resources, and business intelligence."
- MSLs are often described as “Key opinion or thought leader managers”
- MSLs can also be seen as the field based extension of the medical information function; companies and MSLs may see their role as first and foremost that of providing unbiased scientific information with no objective other than the safe and appropriate use of prescription drug products.
- View themselves as peer communicators and providers of education
What are the basic laws and regulations that apply to MSLs and MI?

FD&C Act: FDA regulates the activities of pharmaceutical manufacturers:

- Manufacturers can only promote their products within approved indications and consistent with approved product labeling (PI) (NDA=limited license)

- FDA recognizes that Health Care Professionals (“HCPs”) may want access to information that is outside the PI; implicitly recognized that companies are the best source of information about their products

- FDA does not regulate the practice of medicine

- Recognition of the existence of information outside the label and the manufacturer’s right (and obligation) to provide that information rests on laconic regulatory authority
FDA does not regulate responses to unsolicited questions from HCPs as *promotion*

- Responses to unsolicited requests from health care professionals about unapproved products or product use... “These types of legitimate requests from scientists/individuals for drug information will be regarded and treated as a personal communication between the requestor and the firm. . . . This type of exchange is not being regulated at this time so as not to restrict the full exchange of valid and legitimate information about the drug. . . . Abuses will result in the material being regulated as labeling within the law and regulations....”

- April 22, 1982 DDMAC Position on the Concept of Solicited and Unsolicited Requests
With the enactment of FDAMA addressing the dissemination of peer reviewed scientific literature following certain required steps, this section was added to the Food, Drug and Cosmetic Act and a corresponding section was added to the regulations:

- **SEC. 557.** [21 U.S.C. 360aaa–6] (a) UNSOLICITED REQUEST.—Nothing in this section shall be construed as prohibiting a manufacturer from disseminating information in response to an unsolicited request from a health care practitioner.

- Also see 21 CFR section 99.1(2)(b)
FDA regulation key to our topic

- FDA exempts the following from regulation as promotion if conducted appropriately:
  - The full exchange of scientific information, including dissemination of scientific findings in scientific or lay media . . . 21 CFR 312.7(a)
  - Industry-supported scientific and educational activities that are independent of the influence of the supporting company . . . 62 Fed. Reg. 64074 (Dec. 3, 1997)
What is true scientific exchange?

- Scientific exchange is not a loophole that permits the “dissemination of off-label information”
- Scientific exchange is about the uptake of publicly disclosed important scientific findings, and about discourse in appropriate scientific fora
- It is not the basis for off-label dialogue between manufacturers’ field medical personnel and HCPs (would be an exception that vitiates the rule)
- Although there may not be complete consensus in industry, it is generally agreed that proactive dissemination of off-label information is not permitted outside the above contexts
The other basic legal concern: kickbacks

- The Anti-kickback Statute 42 USC sec.1320a-7b(b) ("Fraud and Abuse"
- Criminalizes the offering or payment of remuneration to influence the referral of federal health care program business
- As applied to pharmaceuticals, prohibits payments to anyone to induce someone to purchase, prescribe or recommend a pharmaceutical product reimbursable under a federal healthcare program
- "Manufacturers ..frequently cultivate relationships with physicians through a variety of practices, including gifts, entertainment and personal services compensation arrangements... These activities have a high potential for fraud and abuse...” OIG Compliance program Guidance for Pharmaceutical Manufacturers April 2003
Key MSL Activities

- Provide clinical trial support
- Deliver on-label medical presentations
- Answer unsolicited off-label questions from HCPs
- Identify and educate contracted speakers
- Provide managed care support
- Acquire and communicate medical intelligence
- Provide medical training for Sales Representatives
MSL Activity Differs Depending on Product Lifecycle

Pre-Approval

- Disease state presentations
- Investigator interactions
- Answer unsolicited questions
- KOL mapping

Post-Approval

- Product presentations
- Formulary presentations
- Speaker training
- Medical congress support
Key Opinion Leaders

• Definition
  – Key Opinion Leaders (*KOLs*) are accomplished medical or scientific professionals who are recognized by their peers

• Examples
  – Professors
  – Board Members
  – Board Officers
  – Editors of Major Journals
  – Authors
  – Patient Access Experts
  – Speakers
  – Clinical Leaders
  – Investigators
MSL Profile

- Advanced scientific training
  - Typically PharmD, PhD or MD
- Significant clinical experience
- In depth scientific knowledge of one or more therapeutic areas
- Ability to interact with a wide variety of individuals
- Comfortable presenting to large groups
- Ability to interact with external and internal customers ethically and within compliance standards
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<th><strong>Pros</strong></th>
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<td><strong>Medical Affairs</strong></td>
<td>• Clear medical role &lt;br&gt;• Less likely &lt;br&gt;Sales/Marketing influence</td>
<td>• Must establish value of MSLs to organization</td>
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<td><strong>Business Unit</strong></td>
<td>• MSLs clearly aligned with business unit objectives</td>
<td>• More difficult to define MSL role &lt;br&gt;•Potential to use MSLs inappropriately</td>
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The Government’s Focus on Off-label Promotion

• A key area of current Government focus is company interactions with HCPs that encourage off-label promotion; recent focus on Med Info and MSLs
• What is the Government concerned about?
  – Corruption of independent clinical decision-making (kickback issues)
  – Over-utilization/Improper utilization (off-label promotion)
    • Costs
    • Patient Safety/Outcomes
• Fundamentally, government does not believe in the “relationship model” which has long been the basis of industry interactions with prescribers and ‘influencers’
• Purpose of interactions need to be well defined
Key areas of concern enunciated under recent CIAs

- **MSL/MI Activities:**
  - MSLs and Medical Information responses to off-label requests
  - MSL interactions with field reps
  - MSL compensation

- **BMS CIA:**
  BMS must have policies and procedures that address:
  1. the handling of and/or response by sales representatives, MSLs and Medical Information to requests for information about off-label uses
  2. appropriate mechanisms by which the Medical Information Department receives and responds to requests for off-label information, including the form and content of the response and the internal review process for the information
Key Areas of Concern: BMS CIA

1) Internal review of generation of Medical Information Request Forms by therapeutic area and representative frequency

2) IRO review of medical information process and “BMS policies and procedures applicable to the manner and circumstances under which medical information personnel (including MSLs) participate in meetings or events with HCPs”
Other CIAs

Jazz Pharmaceuticals: requires development of a database of requests for information made to the MI department and review monthly by Compliance, to assess whether improper promotion has occurred; also IRO review

Purdue: requires policies on development and provision of information by MI and for MSL dissemination; also database review for suspect inquiries; also IRO review

Schering-Plough Addendum: Requires quarterly review of MI by top requestors, and IRO review of process, form and content for MI; also IRO review of policies and procedures governing MSLs participating with sales representatives in meetings or events with HCPs
The government is skeptical about MI and MSL activities

- MSLs have special expertise based upon professional education, clinical training and experience

- BUT ... the Government’s view of proactive MSL or MI activities is that they are regulated as promotional activities

- Government recognizes the need for Medical Information...

- But there are more limits on the discussion of drug information within the heavily regulated pharmaceutical industry than in other environments (such as hospitals, academia, MCOs)
The Neurontin Case: MSL Whistleblower

- Neurontin only initially approved as secondary treatment for epilepsy. Drug use grew to approx. 90% off-label; promotion for bipolar, pain control, ADD, restless legs, and other uses.
- Company decided not to seek supplemental indications for certain uses, but to promote the uses anyway.
- Use for which the FDA rejected a supplemental application was promoted.
- Methods of off-label promotion:
  - Inducements to HCPs to encourage off-label prescribing (e.g., consulting and research arrangements)
  - CME
  - Sales Reps and MSLs
Neurontin Case: MSL Role

- MSLs reported to Sales & Marketing:
  - After an MSL presentation to local medical society that included off-label uses: “a . . . Medical Director praised the event as ‘another great example of use of the medical liaisons’ and an Area Business Manager called it an ‘outstanding utilization of . . . One of the medical affairs liaisons.’ ” (Crim. Information)
  - May 1996 Medical Director voicemail to MSLs in that region: “What’d we like you to do is, any time you’re called out just make sure that your main focus out of what you’re doing is on Neurontin . . . When we get out there, we want to kick some ass, we want to sell Neurontin on pain. All right? And monotherapy and everything that we can talk about, that’s what we want to do.” (Crim. Information)

- MSLs made misleading statements about use of Neurontin for off-label uses

- MSLs were encouraged to inflate their credentials and misstate data
Neurontin Case

Key Take-away: Neurontin established the principle that off-label promotion can trigger liability under False Claims Act, in addition to criminal liability under the Food, Drug and Cosmetic Act.

The government’s big stick: In addition to criminal fines under the FDCA, under the FCA, potential consequences include treble damages, civil penalties of up to $11,000 per false claim, Corporate Integrity Agreement and potential exclusion from government healthcare programs (e.g., a company’s products would not be covered by Medicare/Medicaid)
Enforcement and the use of Med Info: Eli Lilly – December 2005

• Evista (raloxifene) approved indication: prevention of osteoporosis in post-menopausal women

• Competitive landscape → marketing plans touted Evista as effective for off-label uses (prevention/reduction of risk for breast cancer, cardiovascular disease) – 3 for 1 “value proposition” identified Evista as the only agent to protect against osteoporosis, breast cancer and CV disease

• Sales representatives were encouraged to push medical letters out to promote Evista for unapproved uses: May 17, 1998 email from a DM to his reps: “…we should be making all product medical letters available, especially bone, lipid, breast cancer”

• On or about Nov. 12, 1998, an Eli Lilly representative met with a doctor in Missouri and promoted Evista for the reduction of breast cancer...(evidence from informants)

• Lilly paid a criminal fine, pled guilty to introducing a “misbranded drug” into interstate commerce, disgorged profits, engaged an IRO
Heightened Scrutiny of MSLs

• If the government views MSL activities as governed by the same promotional standards as sales representatives, why are inappropriate interactions between MSLs and Sales Representatives (or managed care account managers) and Customers identified as a key risk area?

• Concern is the prompting of off-label questions and the blurring of the lines between sales and medical functions
Issues that need to be addressed with Policies and Standard Operating Procedures

Off-label and other information requests:
• How do sales representatives capture questions for Medical Information or MSLs to answer? Should you capture on-label questions as well as off-label inquiries?
• What is the auditable trail between the inquiry and the response?
  – Do you have a process for capturing e-mail and phone inquiries?
  – Do your MSLs have a system for recording their interactions?
• How do you avoid the appearance of prompting unsolicited questions? Can representatives schedule time for MSLs to ‘come in and answer questions’?
Issues that need to be addressed ..cont’d

Standards for Responses to requests for Information:

- MSL verbal response to unsolicited off-label question must:
  - Appropriately disclaim the information as off-label; confirm that company is not promoting or recommending off-label use
  - Answer only the question asked
  - Provide an accurate and complete answer with fair balance

- Similarly, Medical Information requests captured through MI must follow the same steps
- SOPs or procedures must address the appropriate sources for response; the compilation of responses and the process for review to ensure balance and fairness
  - Who is ensuring that responses to requests for off-label information are non-promotional (the xmas tree test)?
How do you address research activities

- Range of permitted activities varies by company
- Need to have in place standards for investigator sponsored research; what are the criteria for funding an investigator sponsored trial?
- Concerns are both kickback and off-label promotion
- Submission and Review process must be rigorous enough so that no inference can be drawn that funding is for relationship building
Other issues to address

- Are MSLs allowed to bring in food? If so, are processes in place for capturing MSL expenses to ensure adherence to company policies like the PhRMA Code modest meal requirement and compliance with state law requirements?
- Are MSLs allowed to make joint calls with sales representatives? Do sales representatives get to record the visit as a call? Are sales representatives allowed to be present for an off-label discussion?
- Business rules that are not well defined become compliance issues, and the activities are not auditable
Other business rules and processes required

- If gathering business or scientific intelligence is described as an MSL role, a process to capture that information and use it in strategic development is important.
- Equally important to define appropriate parameters for gathering such information.
- Like any other activity, cannot be used as a rationale for interactions unless there is substance to the interaction (minimize "relationship building").
- Speaker interactions, selection and training: what are the criteria for speaker selection, the role the MSL plays, and the role the MSL plays in speaker training.
- Compensation: how are MSLs compensated that differentiates them from sales representatives?
Potential Methods to Assess MSL Productivity

- Number of visits to KOLs
- Number of unsolicited questions answered
- Number of speakers trained
- Time spent in the field (i.e. Field Days)
- Number of formulary presentations
- Number of physicians recruited for clinical trials, advisory boards
- Number of abstracts and publications submitted
- Extent of therapeutic knowledge
- Number of scientific conference attended
Monitoring Framework

- Review policies, procedures, laws, regulations
- Determine processes, risks, issues
- Identify compliance attributes
- Develop protocols for frequency, scope (using compensation metrics)
- Establish sampling strategy
- Select and test sample
- Identify and report findings
- Corrective and preventive action
- Continuum ... Review, Test, Report, Check