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Management of Pharmacovigilance in Licensing and Outsourcing Arrangements

2nd International Pharmaceutical Regulatory and Compliance Congress

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29th May 2008

Pharmacovigilance in licensing/outsourcing arrangements

Basic legal principles everybody knows, but not everybody applies:

- PhV obligations are the legal responsibility of the MAH
- If you are the MAH and things go wrong, for regulatory purposes, it is irrelevant that the problems were due to the actions or failures of a 3rd party working for the company or on its behalf

Pharmacovigilance in licensing/outsourcing arrangements

- **Key: Is the third party part of the MAH's PV System?**

  e.g.
  - co-marketer who has agreed to perform PV tasks for/on behalf of both MA-holding parties
  - consultant who provides literature searching service
  - consultant who provides QPPV services

Risk factors for non-compliance with legal obligations

- Entering into contractual relationships is a calculated risk that may lead to an authorisation holder's failure to comply with legal obligations

- On 9th July 2004 at DSRU meeting on Compliance in pharmacovigilance, Priya Bahri (EMEA) first listed a number of risk factors for non-compliance these included:
  - small companies
  - large corporate structures
  - contractual agreements
  - multiple licensing partners

Pharmacovigilance in licensing/outsourcing arrangements

- Licensing arrangements – one company who holds IP rights authorises another to use them in connection with activities related to a products or products

- Outsourcing arrangements – MAH buys a service from a separate entity/person (eg company or natural person)

Pharmacovigilance in licensing/outsourcing arrangements

"Management" of licensing and outsourcing relationships involves steps taken:

- Before the contract is signed
- Whilst the contract is in place
- To provide for a period after the arrangement is over

Pharmacovigilance in licensing/outsourcing arrangements: minimising risk

Therefore:

- Choose partners and contractors with care
  - Perform adequate due dilligence before entering the contract
- Ensure that the structure of the arrangements is optimal
  - Address the impact of the regulatory requirements on the way a marketing deal/service contract is structured early on
  - Provide checklists for negotiators
- Have a contract dealing comprehensively with PhV issues*
- Actively manage the relationship: are the parties performing their obligations? How do you know?
  - Reserve the right to audit and implement monitoring processes
  - Have a process for addressing problems arising

Minimising risk: tailor the contract terms to the circumstances

Scale and scope may differ in different circumstances and depending upon who is the partner company – take care with templates!!!!

- **A.** Licensor has no continuing commercial interest
- **B.** Co-promotion
- **C.** Co–marketing: partner operates in a small number of territories
- **D.** Co-marketing: partners both operate in several territories

- **A.** Minimal provision– PhV responsibility of licensee
- **B.** Co-promoter must ensure training of sales force and reporting of any AEs/ADRs to MAH
- **C.** Licensor weights control in his favour ,ensures full, timely exchange of all safety info.
- **D.** Licensor and licensee may "share" PhV functions and complex agreements are needed

Protection afforded by a contract: managing risk

A contract affords an opportunity to manage risk:

- records and specifies the scope and details of the arrangements
- satisfies the regulators
- there are civil remedies for breach

Protection afforded by a contract : satisfying the regulators

Does the law require them?

Applications:

Art 8.3(ia) detailed description of the PhV **system**

Art 8.3.(n) proof of necessary means for notification of ADRs

After Grant:

Art 23 para. 3 supply of information which might require amendment of the documents or particulars referred to in Art 8.3 inter alia ie the description of the system

Art 103 obligation to “maintain” system

(References are to Directive 2001/83/EU see also Regulation 726/2004 Articles 16 and 23)

Protection afforded by a contract : satisfying the regulators

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- Guidance explains the legal obligations
- What is the “system”?
  - Includes “contractual arrangements” (relating to transfer of PhV tasks and functions), stresses the need for detailed and clear documentation of arrangements for meeting PhV obligations between MAH and persons or organisations “involved in the fulfilment of “PhV obligations
  - See Introduction, Part 1,Sections 1.2 and 1.3

Protection afforded by a contract : satisfying the regulators

- MAH to provide information of “such arrangements” to CA
- Contractors to implement QA and QC and must accept being audited.
- Co-marketers to avoid duplicate reporting to Eudravigilance
- Part I section 2 deals with the requirements for systems. Section 2.2 requires updates, product-specific addenda for product-specific arrangements arising in licensing situations, documentation, quality management systems.

What do regulators expect?

- DOCUMENTATION!!!
- Typical findings:
  - relationship not properly regulated
  - functions not well-defined
  - “rules” not complied with
  - lack of review of data supplied by contractors
  - lack of review of performance of contractors
- MHRA statistics suggest contracts and agreements were being handled better in 2007 than in 2006
- That commercial considerations should not outweigh public safety

Issues in contractual relationships (1) : keeping track

- Having an accessible, centralised record of agreements and what products are affected by them NB MAHs must notify record holder
- Keeping the record current – terminations/expirations/variations
- Reviewing the agreements when there are changes to law and guidelines
- Reviewing “old” arrangements and contracts
- Ensuring obligations are met – auditing self and 3rd parties

Q. Do your SOPs cover all of these?

NB. Relevance to description and management of of pharmacovigilance system.

Issues in contractual relationships (2): time

When does time run against the MAH: expedited ADRs?

Article 104, 2001/83/EEC (Art. 24 Reg. 726/2004)

- Obligation to report is that of the MAH
- Obligation bites when information is “received”
- What is “receipt” for a corporate MAH? Personnel and agents
- Report at least within “15 days from receipt of the information” - all paragraphs of Art 104/24

Issues in contractual relationships (2): time

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- Introduction and Part 1 section 2.3.4 refer to “receipt” by MAH
- Part 1 section 4.2 clarifies that it is receipt of “minimum information”
- BUT section 4.2 says Day 0 is when “an organisation having a contractual arrangement with the MAH “ receives information
- What kind of “contractual arrangement”?
  - contracts for “the fulfilment of the PhV obligations” of the MAH

Issues in contractual relationships (2): time

Importance?

- What obligations should a MAH impose on a 3rd party
- Whether the failure of the third party is a breach by the MAH
- Good practice v technical compliance
- Other safety-related information

Issues in contractual relationships (3): balance

Co-marketing – balancing the relationship

- Each party as MAH is subject to regulatory obligations:
  - To have a system in place and to maintain it
  - To have a QPPV
  - To report ADRs
  - To file PSURs
  - To answer regulatory authority queries
  - To refer information that may be relevant to risk benefit evaluation to the authorities

  Note: The obligations of the QPPV and of the MAH exist in parallel

Issues in contractual relationships (3): balance

The licensor tends to want to exert more control :

- How comfortable is the licensee in relying on the licensor eg re expedited reporting, PSUR production/filing, preparing answers to enquiries, preparing/ amending CSI, drafting and amending the RMP?
- How much influence, input and information does the licensee have?
- Is the MAH in effect “contracting in “ a service from the other party related to performance of its PhV obligations?

Issues in contractual relationships (4) : undergoing inspections

National provisions

- Powers to review and take documents are generally very wide
- Disclosure of audit results by MAH of contract partner?
  - obligation to co-operate
  - extent of disclosure necessary
- Inspection of contractual partner as part of the inspection of the MAH or leading to inspection of the partner

Issues in contractual relationships (5): managing safety issues

WHAT IF THE PARTIES DISAGREE?

E.g.

- co-marketer raises an issue/refers to regulatory authority
- co-marketer makes a label change
- regulatory action is taken

Actions affect a “product” as a whole.

Issues in contractual relationships (6) : divestments

- Transitional provisions:
  - Managing the "overlap" before all MAs are in the hands of the divestee
  - Complete v partial divestment
  - Post divestment support?