Position Paper

Title: When is a Pharmacovigilance Agreement ("PVA") required for a Marketing Authorization Holder (MAH) according to EU Good Pharmacovigilance Practices (GVP)?

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Executive Summary

Between a MAH and a non-MAH, a PVA with case exchange is only required:

- If there are PV relevant services delegated by the MAH to a Service Provider (e.g. including direct interaction with patient and/or HCPs or digital media/social media screening);
  Or
- If a commercial distribution/wholesale arrangement is not purely logistic (e.g. distributor is listed on package leaflet, package, or other materials, or doing promotional activities);

Between MAHs, no PVA is required:

- In case of off patent licensing to another MAH, who obtains a stand-alone MA.

The "manufacturer set-up" (Licensor/Supplier/Manufacturer might be listed on the package leaflet and/or package as manufacturer and might receive AE reports for the licensed product):

- is already covered by GMP and Manufacturer SOP regulating the forwarding of such inadvertently received AE report to the MAH. So, no additional PVA is required.

1 When is a PVA required according to GVP?

("PVA" shall include also a PV Annex to or a PV Clause in a principle agreement).

According to GVP Module I (Pharmacovigilance systems and their quality systems), PV contractual arrangements are required:

- When a marketing authorisation holder intends to establish a partnership with another marketing authorisation holder, organisation or person that has a direct or indirect impact on the pharmacovigilance system. (GVP I.C.1.1.)
- When subcontracting tasks to another organization (GVP I.C.1.5)

According to GVP module Module II (Pharmacovigilance system master file (PSMF)), such contractual relationships should be categorized according to (GVP II.B.4.2.):

1) Service providers (e.g. medical information, auditors, patient support programme providers, study data management, etc.)
2) Commercial arrangements (distributors, licensing partners, co-marketing etc.)
3) Technical providers (hosting of computer systems etc.)
   (for note: this is a service as well and could be subsumed under Service providers)

The Paper will further focus on licensing commercial arrangements between MAHs only (co-marketing, licensing partners).

a) Licensing agreements for off patent products.

A licensor out-licenses the rights to an off patent registration dossier and the rights to market this product in certain territories to a licensee/MAH. Such selling of a dossier including the manufacturing of product is also called "Industrial Business" and deviates considerably from the co-marketing/licensing approach for innovative products described under b).

Usually

- The licensing is related to a commercial supply agreement (licensee is required to buy supply from the licensor).
- After the initial term of the commercial agreement (e.g. 5 years), the right to use the MA will stay with the licensee, who can decide to manufacture the product by themselves or have it contract manufactured by a 3rd party.
- There is no "co-marketing". There is rather a firewall between the Industrial Business unit of the licensor and the commercial business unit of the MAH legal entity of the licensor and consequently, there is no "partnership" with the off patent licensee.

The approach with regards to PVA requirements differs considerably between the off patent companies. In part B below (PVA / case exchange requirements for off patent products between MAHs) the different approaches, associated issues, and preferred options are described.

b) Co-marketing agreements (= licensing for innovative products).

This business model allows two companies/MAHs to market a drug under at least two distinct trademarks in any particular country.

Usually:

- It concerns an innovative drug when the deal is named "co-marketing".
- it's in the form of a license and supply agreement, based on which the licensor/innovator provides product at an agreed supply price to the licensee.
- There is also co-operation in other areas, e.g. medical information.
- After termination of partnership the MA(s) will need to be transferred back to the innovator.

A PVA is required. With regards to exchange of AE reports: always from licensee to licensor/innovator. If required in licensee territory, also exchange of AE reports from licensor/innovator to licensee.

2 PVA / case exchange requirements for off patent products between MAHs

<u>In the following situations no PVA is required in any case, since the marketing authorisation/dossier is not the same:</u>

- Licensing of a MA or dossier / selling of a MA or dossier without commercial supply: licensee has all rights to manufacture the product by themselves or have it contract manufactured.
- Licensing or divestment or acquisition, once the commercial supply relation has ended and the licensee has all rights for their territory to produce the products themselves separately (or let produce by a contract manufacturer) – in line with the term and termination clause/agreement.
- Licensing with royalties for Intellectual Property rights, but no commercial supply relationship (separate, independent manufacturing)

Reason:

- The 3rd party licensee or divestment/acquisition partner has all rights to the products for their territory.
- There is no ongoing commercial supply arrangement.
- Due to independent manufacturing, even if it was once the same dossier, the product will deviate due to different manufacturing processes and dossier maintenance.

The approach with regards to PVA requirements differs considerably between the off patent companies with regards to licensing agreements between MAHs with licensing of the same dossier and supply by the licensor from the same manufacturing site.

Option 0:

- Some off patent Marketing Authorization Holders (MAHs) interpret EU and UK GVP (and potentially other international PV legislation) to contain a requirement to collect cases from 3rd party licensees (MAHs) or licensors (MAHs) from outside their territory for off patent medicinal products. E.g. GVP Module VI.C.2.2. requirement to collect AE reports when having concluded a commercial agreement with a company outside EEA holding MAs of the same medicinal product (interpreted by these MAHs as containing the same dossier, supplied by licensor from the same manufacturing site); or the equivalent UK requirement to collect and report world-wide cases from such companies.

The different interpretation by off patent companies is due to the lack of standard definition of the “same medicinal product”, “commercial arrangements”, and “partnership with another marketing authorisation holder”.

- This is associated with following issues:
    - multiplication of an AE report, exchanged between many off patent MAHs, each applying modifications per company case processing SOPs, reported to each applicable competent health authority multiple times.

- duplicates (or rather “multiplicates”) in authority databases requiring creation of a Master Case out of the various versions of the AE report.
- Authorities and MAHs allocating huge resources into limited added value activities i.e. multiple case exchange, reconciliation, and Master case creation. Such resources should rather be allocated to safety analysis.

Moreover, the “manufacturer set-up” (Licensor/Supplier/Manufacturer might be listed on the package leaflet and/or package as manufacturer and might receive AE reports for the licensed product) is covered by some off patent companies with PVAs. 3rd parties, products, and territories are detailed and presented in the PSMF Annex of contractual relationships

Impact/Issue:
Big off patent companies have hundreds, even thousands of such out- and in-licensing relationships (Industrial Business) with other MAHs.

- it costs huge resources to keep track of all active products and territories where a manufacturer might be listed – while there is no increase in safety.
- in practice receipt of such cases by Licensor/Manufacturer is a very unlikely scenario; it’s never or very rarely occurring that the small listed manufacturer is approached instead of the prominent and big listed, and obviously responsible MAH/Licensee.
- it duplicates the GMP requirements and processes according to which a manufacturer is collecting such (never or very rarely occurring) adverse events and is forwarding them to the MAH.

Besides the above presented GVP interpretation with its associate issues, the following compliant options could be used by off patent companies:

For note: such specific requirement like in EU and UK GVP module VI.C.2.2. is not included in other legislation and the below options are therefore considered compliant for other territories as well.

Option 1: no PVA is required.

Rationale (for the example of a MAH in EEA):

- No exchange of AE reports is required as the outside EEA 3rd party’s MA is a stand-alone MA, independent from the MA in EEA and they are therefore not considered the same product/MA (even if it’s containing the same dossier; is supplied by licensor from the same manufacturing site).
- Off patent Industrial Business (selling the rights to an off patent dossier to a 3rd party, including manufacturing and/or supply of the product) is not considered to fall under the terms of GVP (“commercial arrangements”, and “partnership with another marketing authorisation holder”) and therefore does not require entering into a PVA or including such business contract into the PSMF.
- Avoiding the multiplicity of exchange between off patent companies, which would ultimately lead to each off patent MAH becoming a “Global Safety Database Holder (GSDH)” not only for its product but for world-wide cases of the active ingredient (as case collection and distribution in companies and authorities is generally active ingredient driven and not product/dossier driven).
- Maintaining multiple global safety databases would not be proportional to the risks of a well-established off patent product.

- In addition, there is no comprehensive database with all world-wide AEs required for signal detection for an active ingredient: In an example of 5 big databases, a combined dataset of all cases will only show a signal, if there was already a signal in one of the 5 databases. Rather a signal may not be identified in the combined dataset.

The "manufacturer set-up" (Licensor/Supplier/Manufacturer might be listed on the package leaflet and/or package as manufacturer and might receive AE reports for the licensed product):

- is already covered by GMP and Manufacturer SOP regulating the forwarding of such inadvertently received AE report to the MAH. So, no additional PVA is required.
    - E.g. Volume 4, EU Guidelines for Good Manufacturing Practice for Medicinal Products for Human and Veterinary use contains such guidance regarding handling of suspected AE in Part I, 8.7.
    - Manufacturer SOPs or Quality Agreements contain the forwarding of such AE to the MAH.

The above handling is the clearly preferred option in order to save PV resources for covering the receipt of cases from patients or HCPs by a listed manufacturer (which in practice is never or very rarely occurring). As this process is already adequately covered by GMP.

Following option for covering the "manufacturer set-up" could be used as well, which involves entering into an agreement by PV and tracking in the PSMF:

Option 1B – Memorandum of Understanding (MoU)

Background: In case companies and/or authorities would see a need to enter into agreements between the PV departments of the MAHs in addition to GMP coverage of the "manufacturer set-up", following considerations could be taken into account – to reduce the complexity described in option O.

- already by GVP guidance and best practice the off patent companies are exchanging such accidentally received AE reports from the manufacturer set-up.
- Already at the initial step of case triage at the Licensor/Manufacturer, there is a check if a case is related to a product of the company – or related to a product of another MAH.
- → So, no knowledge of contractual relationships and products and territories of 3rd parties is required for this check and fulfilling this duty.

Solution:

Instead of various PVA with detailed tracking of products, a Memorandum of Understanding (MoU) could be signed between two parties to cover all such products.

MoU content:

- If no company product is related to an AE, but only the product of another MAH, the AE report should be sent to the other MAH who will process the case and report it to the competent health authority.
- If a company product is related to an AE and additionally a product of another MAH, the AE report should be processed by the company and reported to the competent health authority, but not sent to the other MAH to avoid duplication (in line with EMA Q&A: EMA/390861/2018, Question 2.133).

- No detailed product/territory lists are required, as the scope is for all products and territories between the companies for this set-up. So, a PSMF entry like “all products/territories” can be applied.

Impact/Issue:

- Still, additional resources are invested and PSMF tracking is done for a process which is already covered by GMP and companies SOPs and/or Quality Agreements.

Option 2:

Per GVP Module VI.C.2.2. the MAH (in EEA in this example) does not need to receive AE reports from all outside EEA MAHs (which are contractually related), but the receipt can be restricted and is not required when the outside EEA MAs are connected with:

- 3rd party commercial agreements concluded with an EEA legal entity
  (Rationale of GVP is likely that an EEA 3rd party legal entity will have EEA MAs and report outside EEA cases to Eudravigilance by themselves).

A potential “manufacturer set-up” could be covered as described in Option 1.

Issue: reducing only some multiplication of cases.

Option 3:

In addition to the restrictions in Option 2, receipt of AE reports is also not required if:

- the commercial agreement of the MAH (in EEA in this example) is with a 3rd party legal entity outside EEA, but the group of companies of the 3rd party has EEA MAs for the same INN and therefore reports to Eudravigilance by themselves.
  (Rationale: this is in analogy to the literal restriction in GVP Module VI.C.2.2. presented in Option 2 and avoids duplicate reporting to authority)

A potential “manufacturer set-up” could be covered as described in Option 1.

Issue: reducing only some multiplication of cases; but adding complexity for the MAH: keeping track of 3rd party authority reporting obligations of all license partners.

In Summary:

The presented Option 1, no PVA required, manufacturer set-up covered by GMP processes, is clearly preferred due to:

- Maintaining multiple global safety databases would not be proportional to the risks of a well-established off patent product.
- Avoiding multiplication of an AE report, exchanged between the many off patent MAHs.
- Avoiding duplicates (or rather “multiplicates”) in authority databases requiring creation of a Master Case out of the various versions of the AE report.

- Avoiding authorities and MAHs allocating huge resources into limited added value activities i.e. multiple case exchange, reconciliation, and Master case creation. Such resources should rather be allocated to safety analysis.
- Avoiding waste of PV resources for covering the "manufacturer" set-up as it is already covered by GMP processes, which cover forwarding of inadvertently received cases (very rarely or never occurring) to the MAH.

In addition, there is no comprehensive database with all world-wide AEs required for signal detection for an active ingredient. In an example of 5 big databases, a combined dataset of all cases will only show a signal, if there was already a signal in one of the 5 databases. Rather a signal may not be identified in the combined dataset.

In case the authorities would nevertheless aim for a comprehensive database containing (nearly) all AEs for an active ingredient, the following should be aimed for.

Suggestion for Process and Legislation improvement:

- While for innovative products the originator is GSDH, for off patent products the authority databases (or a reference database, e.g. WHO) should be considered as reference repository for signal detection and safety analysis.
- Health authorities should therefore aim to implement a system with following principles:
    - MAHs to report AEs only in the country of reporter to the competent health authority.
    - Health authorities exchanging such AE reports once, electronically, in a worldwide network of participating authorities.
    - Health authorities having the possibility to a) analyze the safety data in one reference authority database (e.g. WHO) or b) a health authority could import each of the network AE reports to their authority database and use it for analysis of the safety data.
    - Health authorities clearly not requiring the MAH to set-up PVAs with the (Contract) manufacturer due to coverage of this set-up by GMP processes.

For note: the above principles could also be implemented for innovative products to have a harmonized approach:

- Innovators would still collect AE reports from all commercial partners and co-marketing arrangements if/as required by company policy.
- But an AE report would only be submitted by the MAH in the country of reporter to the competent health authority. Health authorities exchanging the AE electronically in the worldwide network of participating authorities.

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