efpia European Federation of Pharmaceutical Industries and Associations

IFPMA International Federation of Pharmaceutical Manufacturers & Associations

Vaccines Europe

Registration of Multiple Manufacturing Sites in One Product License

Joint Position from EFPIA, IFPMA and Vaccines Europe

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Executive Summary

Supply of medicinal products and vaccines is critical for patient access. The registration of multiple manufacturing sites is a key enabler for flexible supply. While most countries allow multiple manufacturing sites in one license, some countries issue a new license for each additional manufacturing site. This often leads to inefficient use of resource and delays in approval due to

- repeated review of a full dossier for additional manufacturing site
- a proliferation of additional licenses requiring long-term maintenance

which ultimately limits supply flexibility.

As industry associations, we urge all countries to adopt a 'multiple-site-to-one-license' approach in line with WHO[1] and other guidelines[2,3]. We believe this will result in a reduction of duplicate work for all stakeholders, help to build agility and speed in supply chain management and improve patient access to medicines and vaccines.

Background

Supply chain resilience is an important component of uninterrupted patient access to products. To ensure supply chain flexibility, a well-established approach is the registration of multiple manufacturing sites in one product license ('multiple-site-to-one-license') which is accepted by many Health Authorities (HAs) worldwide.

However, there are significant challenges and delays when registering additional manufacturing sites in countries, where the local HAs only accept the 'one-site-to-one-license' approach. This requirement was often established due to concerns from HAs about the traceability of products in case of surveillance and product recall. HAs consider it easier to identify and recall the affected product from the affected manufacturing site under "one-site-to-one-license" approach, despite the technical and digital developments in batch numbering and track and trace systems. The addition of a new manufacturing site is usually treated as a New Marketing Authorization with a considerably longer approval timeline than a variation and the issuance of a new license upon authorization. This

can sometimes cause a delay in processing other regulatory procedures submitted to the same Health Authority.

One-site-to-one-license: Challenges, Issues and Risks

1) **Repeated review of a full single site dossier is an inefficient use of resources and delays approval.** Under the one-site-to-one-license approach, a "repeated" full New Drug Application (NDA) or Biologics License Applications (BLA) package needs to be created by the company when adding a manufacturing site. HAs repeated the review of previously evaluated information in this new site registration (e.g. Drug Substance data, preclinical and clinical data). This not only requires unnecessary efforts from both industry and HAs, but also delays the approval of the new sites, as supply-critical new site registrations are often subjected to an NDA/BLA-level review timeline.
2) **Proliferation of additional licenses that need maintenance requiring additional resources.** The one-site-to-one-license approach adds complexity to regulatory lifecycle maintenance due to a proliferation of additional licenses that need to be maintained. This requires duplicate efforts from both industry and HAs without enhancing the value of regulatory oversight, especially when there is a need to submit identical changes affecting multiple manufacturing sites and therefore multiple licenses.
3) **Limit global supply flexibility - regulatory filing perspective**. Given the duplication and difficulty in maintaining multiple licenses, applicants may opt to limit the supply site alternatives for a country with the 'one-site-to-one-license' requirement. If this approach is taken it may reduce product sourcing flexibility and affect continuity of supply leading to increased risk for product shortages and/or stock outs and thus may potentially restrict patients' access to products.
4) **Limit global supply flexibility - supply chain impact.** In the context of global supply management, the allocation of products to countries at the latest possible step of manufacturing is critical to be able to respond quickly to constantly evolving demand. Having to segregate products depending on the way licenses are managed, represents a strong limitation to the supply flexibility.
5) **May result in additional administrative procedures, which could delay the supply of product from the new manufacturing sites to patients**. In some countries, pricing, hospital listings, tendering and reimbursement policies are connected to the product license number unique to each product. If with the 'one-site-to-one-license' approach a new site is approved under a new license, the entire access process has to be undergone before the product can be provided. This could further delay patients' access to products from the new site and limit the flexibility to switch among approved sites in case of supply emergency.

Benefits of a Multiple-sites-to-one-license:

- **Reduce regulatory burden.** Implementation of 'multiple-sites-to-one-license' can reduce the burden of regulators to maintain oversight of multiple licenses, avoiding the need to perform duplicate review of identical changes affecting multiple licenses and reduces the burden of industry to maintain separate licenses.
- **Building supply agility and speed.** Improving source flexibilities though 'multiple-sites-to-one-license' can prevent product shortages and ensure supply continuity, which ultimately will improve patient access to pharmaceutical products. This is especially critical during pandemic situations which have been observed in past years. A similar impact can be expected during natural disasters or geopolitical crises.

- **Batch numbering can ensure traceability of products under multiple-sites-to-one-license situations**. According to cGMP[1*] and GDP[**] basic traceability of products supplied by different manufacturing sites has been already assured by integrating specific codes in the batch-numbering structure, directly visible on the packaging materials as well as accompanying certificates. Compliance to cGMP and GDP is regularly verified during routine inspections by regulators. Batch numbering is suitable for product recalls and pharmacovigilance, no matter which site the product is manufactured. Furthermore, track and trace systems mandated by many HAs have been implemented widely by manufacturers, which provides enhanced tracking of the products from production to the end user.
- **Allowing multiple-sites-on-one-license is a common practice of ICH members and most PIC/S members**. More and more countries are considering adopting a similar approach. APEC also recommended[4] adopting the practice of 'multiple-site-on-one-license' in line with WHO guidelines. This practice was considered by APEC member economies as one of the key performance indicators to measure the progress towards achieving regulatory convergence for pharmaceutical products. From 2008 to 2020, the percentage of regulatory authorities in APEC accepting 'multiple-sites-on-one-license' increased from 9/21 to 15/21 (28% increase)[4]**.**

Industry Recommendations

The industry recommends adaptation of current procedures in all concerned countries to avoid the issues created by the 'one-site-to-one-license'. This is based on a principle that supports the drive to regulatory convergence. It allows alignment with the best practices of ICH members and WHO that promotes greater work efficiency for product life-cycle management for both regulator (review) and Industry (dossier preparation / maintenance).

In particular, the following recommendations should be considered:

- An additional site should be approved as a post-approval variation, and subsequently be included in the same license. This is in line with recommendations under the International Standard of WHO[1] and other Guidelines (eg. EMA[2], Health Canada[3], etc.).
- The data required for an additional site change should consist of relevant data generated from the new site, and is a reduced package compared to the full New Drug Application (NDA) or Biologics License Applications (BLA) package.
- The reporting required for review and approval of a new manufacturing site should be subject to the relevant change categorization, i.e. minor, moderate or major changes and not those of a new application.

Conclusion

'Multiple-sites-to-one-license' is a well-adopted approach by ICH Countries and most PIC/S members to enable supply chain resilience and uninterrupted patient access to medicines and vaccines. It reduces redundancy, avoids duplication of effort to save resources for both Industry and regulators. It will also simplify the life-cycle maintenance of licenses and consequently contribute to ensure continuous supply of medicinal products. Regulatory convergence to enable

[1*] Current Good Manufacturing Practice
** Good Distribution Practice

wide acceptance of ‘multiple-sites-on-one-license’ is expected to enhance timely access of medicinal products and vaccines to patients worldwide by focusing the use of resources in building regulators and industry agility in the way they operate.

Reference:

1. WHO Guidelines on procedures and data requirements for changes to approved biotherapeutic products Link
2. EU Guidelines on the details of the various categories of variations, on the operation of the procedures laid down in Chapters II, IIa, III and IV of Commission Regulation (EC) No 1234/2008 of 24 November 2008 concerning the examination of variations to the terms of marketing authorisations for medicinal products for human use and veterinary medicinal products and on the documentation to be submitted pursuant to those procedures. Link
3. Canada Guidance Document : Post-Notice of Compliance (NOC) Changes: Quality Document Link
4. Measuring Progress of Regulatory Convergence and Cooperation Among Asia-Pacific Economic Cooperation (APEC) Member Economies in the Context of the COVID-19 Pandemic, Ther Innov Regul Sci. 2021 Jul Link

Appendix

WHO - Guidelines on procedures and data requirements for changes to approved biotherapeutic products

Description of change	Conditions to be fulfilled	Supporting data	Reporting category
38. Change involving a drug product manufacturer/ manufacturing facility, involving the following:			
a. Replacement or addition of a manufacturing facility for the drug product (including formulation/filling and primary packaging)	None	1–7	Major
	1–5	1–3, 5–8	Moderate
b. Conversion of a drug product manufacturing facility from single-product to multi-product facility	None	9, 10	Moderate
c. Replacement or addition of a secondary packaging facility, including secondary functional packaging (that is, assembly) facility	2, 3	1–3	Minor

Table *continued*

Description of change	Conditions to be fulfilled	Supporting data	Reporting category
d. Deletion of a drug product manufacturing facility or packaging site	6, 7	None	Minor

EU Variation Guidelines

B.II.b) *Manufacture*

B.II.b.1 Replacement or addition of a manufacturing site for part or all of the manufacturing process of the finished product	Conditions to be fulfilled	Documentation to be supplied	Procedure type
a) Secondary packaging site	1, 2	1,3, 8	IA_{IN}
b) Primary packaging site	1, 2, 3, 4, 5	1, 2, 3, 4, 8, 9	IA_{IN}
c) Site where any manufacturing operation(s) take place, except batch release, batch control, and secondary packaging, for biological/immunological medicinal products, or for pharmaceutical forms manufactured by complex manufacturing processes			II
d) Site which requires an initial or product specific inspection			II
e) Site where any manufacturing operation(s) take place, except batch-release, batch control, primary and secondary packaging, for non-sterile medicinal products		1, 2, 3, 4, 5, 6, 7, 8, 9	IB
f) Site where any manufacturing operation(s) take place, except batch release, batch control, and secondary packaging, for sterile medicinal products (including those that are aseptically manufactured) excluding biological/immunological medicinal products		1, 2, 3, 4, 5, 6, 7, 8	IB

Canadian Guidance Document: Post-Notice of Compliance (NOC) Changes: Quality Document

1. Pharmaceuticals

3.2.P.3 Manufacture

23. Replacement or addition of a drug product manufacturer / manufacturing site, involving

a. production of a modified release or a sterile drug product; or production of an immediate release product that does not meet the conditions for Annual Notification
- **Conditions to be Fulfilled:** None
- **Supporting Data:** 1-6, 8-10
- **Reporting Category:** Supplement

b. production of an immediate release product [e.g., tablet, capsule, liquids, semi-solids]
- **Conditions to be Fulfilled:** 1-4
- **Supporting Data:** 2-5, 8-11
- **Reporting Category:** Annual Notification

c. primary packaging
- **Conditions to be Fulfilled:** 1-3
- **Supporting Data:** 2-3, 5-6, 9
- **Reporting Category:** Annual Notification

d. testing [e.g., release, stability]
- **Conditions to be Fulfilled:** 3
- **Supporting Data:** 2-3, 5, 7-8
- **Reporting Category:** Annual Notification

e. storage and distribution
- **Conditions to be Fulfilled:** 3
- **Supporting Data:** 2-3
- **Reporting Category:** Annual Notification

2. Biologics

3.2.P.3 Manufacture

43. Change involving a drug product manufacturer/manufacturing facility, such as:

a. replacement or addition of a manufacturing facility for the drug product (includes primary packaging facility)
- **Conditions to be Fulfilled:**
  - None
  - 1-5
- **Supporting Data:**
  - 1-6,8-9,11-14
  - 1-4,6,8-9,11-14
- **Reporting Category:**
  - Supplement
  - Notifiable Change

b. replacement or addition of formulation/filling suite to an approved formulation/filing facility
- **Conditions to be Fulfilled:**
  - None
  - 1,8
- **Supporting Data:**
  - 3,5-6,8-9,11-14
  - 3-4,6,8,10,12, 14-15
- **Reporting Category:**
  - Supplement
  - Notifiable Change

c. replacement or addition of a secondary packaging facility; a labelling/storage facility; or a distribution facility
- **Conditions to be Fulfilled:** 2-3
- **Supporting Data:** 1-2,4
- **Reporting Category:** Annual Notification

d. modification to a manufacturing area or modification to an existing service/system [e.g., change to WFI systems or HVAC systems, moving a wall]
- **Conditions to be Fulfilled:** 6-7
- **Supporting Data:** 7,12,14
- **Reporting Category:** Annual Notification

e. qualification of a new room or change in classification of an existing room
- **Conditions to be Fulfilled:** 6-7
- **Supporting Data:** 7,12,14
- **Reporting Category:** Annual Notification

f. deletion of a drug product manufacturing facility
- **Conditions to be Fulfilled:** None
- **Supporting Data:** None
- **Reporting Category:** Annual Notification