EAEPC Good Parallel Distribution Practice Guidelines for Medicinal Products

Due to its role in the production and handling of products related to public health, the Community pharmaceutical sector operates at a high level of quality assurance. Parallel distributors are an established component of the distribution process in Europe for medicinal products for human use. They follow exactly the same manufacturing and distribution regulations as other market players, including multinational companies.

These guidelines have been prepared to give an overview of the detailed requirements to be followed by parallel distributors. Compliance is a condition of membership for all parallel distributors affiliated to the European Association of Euro-Pharmaceutical Companies (EAEPC).

1) PARALLEL DISTRIBUTION

Parallel distribution, in a European context, is an activity limited to within the European Economic Area (EEA)[1]. It is both legal and desirable, socially as well as economically.

Parallel distribution involves the transfer of genuine, original branded products, authorised in accordance with Community legislation, marketed in one member state of the EEA at a lower price – the source country - to another EEA member state – the country of destination - by a parallel distributor, and placed on the market in competition with a therapeutically identical product already marketed there at a higher price by or under licence from the owner of the brand's intellectual property (the directly-distributed product).

The process allows third-party payers and consumers to realise savings. These are both:

- direct (from the lower cost of parallel-distributed products); and
- indirect (from price competition entered into with the parallel product by the directly-distributed version)

Parallel distribution acts as a counterweight to the monopoly situation of manufacturer patent protection, yet it avoids governments implementing more interventionist or market-distorting cost-containment measures. It gives pharmacists and patients a choice, and accelerates the integration of the EU Internal Market.

Parallel distribution embodies two fundamental principles of the Community's founding Treaty of Rome: the free movement of goods and Community-wide exhaustion of IP rights. It is also referred to as parallel trade and also, less correctly (the EEA is a single market with no internal borders), as parallel importing.

2) MARKETING APPROVAL

Despite all parallel-distributed medicines already having been subject to the rigorous EU approval process that all directly-distributed products need to undergo before first marketing, they are required to be subject to a second regulatory assessment before their distribution in parallel takes place. No parallel-distributed product may be marketed until specific authorisation for this is given.

If the directly-distributed product has been subject to the national approval process, described in Directive 2001/83/EC (as amended by Directive 27/2004/EC), then the parallel distributor must obtain from the same competent authority a **simplified marketing authorisation** for the product to be distributed in parallel.

Together with any applicable fee, the applicant must indicate the EEA source country and the product's marketing authorisation number there. The competent authority then conducts checks, in conjunction with the competent authority in the source country, to assure itself that there are no differences of therapeutic significance from the directly-distributed product covered by a full marketing authorisation in the country of destination.

The general principles to be considered by national competent authorities when granting simplified marketing authorisations for parallel-distributed products were first outlined in a 1982 Communication from the European Commission.[2] They have subsequently been adapted by decisions of the European Court of Justice (ECJ). For example, parallel-distributed products no longer have to have a common origin to the directly-distributed product (ECJ cases C-201/94 & C-112/02). Judgement in case C-112/02 also reaffirmed the burden of proof is on the competent authority in the country of destination to show if the criteria for parallel distribution are not satisfied.

If the directly-distributed product has been approved centrally by the European Commission following a positive opinion from the European Medicines Agency (EMEA) and in accordance with Regulation 726/2004 then no further regulatory approval is necessary, as the product on the market is by definition authorised and identical in every member state. However, a linguistic compliance check on the pack labelling and patient package leaflet of the parallel-distributed product by the EMEA is required in accordance with Article 57.1(o) of Title IV of the Regulation, resulting in the issuance of a **Parallel Distribution Notice**.

The notification procedure is described at
http://www.emea.eu.int/pdfs/human/parallel/23680en.pdf

3) OTHER REGULATORY REQUIREMENTS

In accordance with Article 76.3 of Directive 27/2004/EC, parallel distributors are required to notify the full marketing authorisation holder and the competent authority in the member state of destination of their intention to parallel distribute a product.

Parallel distributors are required to hold a pharmaceutical **wholesaling authorisation** issued (in accordance with Article 77 of Directive 2001/83/EC, as amended) by the competent authority in the member state in which they are located. The only exception is if a manufacturing authorisation (see below) includes provision for wholesale dealing. In accordance with the wholesaling authorisation, parallel distributors are obliged to follow **Good Distribution Practice** (GDP) guidelines in accordance with Article 84 of the Directive[3], employ an EU Responsible Person and are subject to periodic inspection by the competent authority.

Separate and additional authorisation must be obtained from the relevant competent authority in order to handle and distribute controlled drugs (narcotics).

After receipt of a simplified marketing authorisation from the national competent authority or filing a notification with the EMEA, the parallel distributor in the country of destination has to adapt the packaging/labelling of every incoming batch to access the local market, in accordance with the marketing authorisation, national law and decisions of the ECJ.

As a manufacturing operation, all repackaging/re-labelling requires a pharmaceutical **manufacturing authorisation** issued by the competent authority in the country of destination. Holders of manufacturing authorisations are obliged to follow **Good Manufacturing Practice** (GMP) guidelines[4], employ an EU Qualified Person and are subject to periodic inspection by the competent authority.

4) PRACTICAL ACTIVITIES UNDERTAKEN BY PARALLEL DISTRIBUTORS

Maintenance of the integrity of the supply chain

Parallel distributors only purchase medicinal products with marketing authorisations from authorised wholesalers or manufacturers in other EEA countries. The supplying wholesaler should make available before sale a copy of its wholesale authorisation and provide assurance that the supplies were obtained from the original manufacturer and/or an authorised wholesaler within the EEA.

Parallel distributors only sell or supply medicinal products with marketing authorisations to authorised wholesalers, registered pharmacies or other persons entitled to sell medicinal products to the general public. A copy of the authorisation should be requested if there is any doubt about this entitlement.

Qualified person

Each parallel distributor in the country of destination involved in repackaging/re-labelling must employ at least one EU Qualified Person (QP), who has received the relevant education and training (in accordance with

Article 48 of the Directive), with responsibility to personally ensure that a quality system is implemented and maintained.

Control of incoming stock

Each incoming lot must be checked against the marketing authorisation and an authentic reference sample of the product received from the source country. The check should cover the actual product itself, its immediate and outer packaging, and the label and package leaflet. The following is documented and retained:

a) Product name, dosage form, pack size and strength.
b) Name and address of supplier.
c) Date of purchase.
d) Quantity received.
e) Batch number (if different batches are received in a single shipment each one should be handled separately).
f) Expiry date.
g) Any difference in the appearance of the product (carton, label, blisters, leaflet or the actual product itself) from the authentic reference sample.

Re-labelling/Repackaging

The goods should remain in their original packaging as long as possible. However, once the received product is approved for processing, re-labelling may be undertaken in accordance with the national simplified marketing authorisation of the parallel-distributed product, under conditions of GMP, i.e. exactly the same procedures as those followed by all pharmaceutical manufacturers.

This either involves replacement of the original outer carton with a brand new one or over-stickering the original outer carton, with both providing the approved label text in the language of the country of destination. In all cases, the existing package leaflet is removed and replaced by a new one originated by the parallel distributor in accordance with the simplified marketing authorisation in the language of the country of destination.

Both the original cartons - if these are replaced - and the original leaflets must be destroyed.

No handling of the actual product (e.g. open units of tablets or capsules) within its immediate packaging (e.g. blister or foil packs) takes place during replacement of the original carton.

Replacement packaging should always be considered in order to produce a finished product of the highest quality, but is subject to meeting the 'necessity' criterion laid down by the ECJ in linked cases C-443/99 and C-143/00. Furthermore, the ECJ (in cases C-427/93, C-429/93 & C-436/93) has given four conditions that have all to be met if repackaging takes place:

- The product inside the packaging must not be affected
- The new packaging must clearly state who repackaged the product and the name of the manufacturer
- The reputation of the trade mark owner must not be damaged

- The trade mark owner must be given adequate prior notice before the repackaged product is put on sale and, on demand, be supplied with a specimen of the repackaged product

The relevant case law on repackaging was reviewed by a 2003 Commission Communication[5]. It emphasised the rights of parallel distributors to repackage products to obtain effective access to the market.

As with any other pharmaceutical manufacturer, parallel distributor operators involved in re-labelling and/or repackaging are given regular training in GMP.

Batch documentation is retained for each batch.

Final release

No product may be sold or supplied to the market by a parallel distributor until its relabelled/repackaged batch is released by the QP. The release is based upon:

a) The requirements of the simplified marketing authorisation
b) Checks on the documentation on the product received
c) Checks on the re-labelling/repackaging batch documentation, including documentation on line-clearance performed to ensure no mix-up with other products/batches has taken place and yield
d) Checks on the finished product, including its labelling and leaflet

All parallel distributors should have written procedures in place to ensure traceability and recall for any batch received, relabelled/repacked or distributed should serious quality or safety problems with a medicinal product occur.

Storage conditions

Medicinal products must be stored apart from other goods, in clean, safe and secure areas, and under conditions specified by the manufacturer and the marketing authorisation.

When specific storage conditions are required, storage areas are equipped with temperature recorders, which are monitored regularly. Any products that have been exposed during storage to a temperature outside the acceptable range must be quarantined for assessment.

A system to ensure stock rotation applies. Medicinal products beyond their expiry date must not be supplied.

Transport conditions

Conditions for the transport of stock must be in accordance with GDP and in compliance with the requirements for each individual product.

Cold chain products must be shipped by appropriate specialised means, involving either the use of temperature recorders or a validated transport system. Any product that has been exposed during shipping to a temperature outside the acceptable range must be quarantined for assessment.

Inspections

Regular GMP inspections are undertaken at parallel distributors (performing re-labelling/repacking activities as described above) by the competent authority in the member state concerned to ensure that EU GMP Volume 4 is adhered to. After every inspection, the competent authority shall report to the parallel distributor on GMP compliance, with the latter taking remedial measures and informing the competent authority of these, if any deficiency has been shown. As wholesalers, all parallel distributors are also subject to regular GDP inspections by the competent national or regional authority.

5) POST MARKETING ACTIVITIES

Pharmacovigilance

The parallel distributor in the country of destination may be subject to the normal obligations of all marketing authorisation holders as regards adverse reactions, abuse and defect reporting, and provision for product recall.

Changes in the original marketing authorisation

Parallel distributors must adopt as soon as possible all changes in the full marketing authorisation approved by the competent authority in the country of destination or by the EMEA, including those made at the request of the marketing authorisation holder. This requires parallel distributors to constantly monitor with all their marketed products changes in the wording of the summary of product characteristics (SmPC).

As soon as a change has been identified, the parallel distributor has to implement this itself and/or submit a variation/notification to the competent authority for authorisation of the change.

Withdrawal of original marketing authorisation

In accordance with ECJ decisions (case C-172/00 and linked cases C-15/01 & C-113/01), withdrawal of a full marketing authorisation at the request of its holder for reasons other than the protection of public health, does not require the automatic cessation of the validity of any corresponding simplified marketing authorisation allowing parallel distribution of the same product.

Complaints

Customer complaints are handled by parallel distributors in the country of destination according to written procedures, and are thoroughly investigated and promptly responded to.

6) RECALLS

Recalls are handled by parallel distributors according to written procedures. A specific person is designated responsible for execution and co-ordination of recalls, with 24 hour availability seven days a week.

In the case of a recall initiated by the original manufacturer or by the competent authorities, all customers (other wholesalers, retail or hospital pharmacies and other persons entitled to sell medicinal products to the public) to whom the product or batch/batches have been distributed should be informed to quarantine all the affected packs and return them to their supplier. The recall message will normally include information as to whether the recall should be carried out at the wholesale level only, or whether it should also be carried out at the retail level.

All suppliers are required to inform the responsible person of their parallel distributor customers in the country of destination immediately, by telephone and in writing, of a recall in the source country affecting a product or batch(es) previously supplied.

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[1] The EEA consists of the 25 EU member states plus Norway, Iceland and Liechtenstein
[2] Commission Communication C115/5, Official Journal of 6 May 1982
[3] General Guidelines for good distribution practice of medicinal products for human use (94/C 63/03) http://pharmacos.eudra.org/F2/pharmacos/docs/Doc2001/may/GDPGuidelines1.pdf
[4] Eudralex, EU GMP Volume 4, Good manufacturing practices, Medicinal products for human and veterinary use
[5] Commission Communication COM (2003)839, of 30 December 2003