European Commission
Ms. Maria Figuerola
DG Sanco Unit D3 Pharmaceuticals
Rue de la Loi 200
Brussels

E A E P C
European Association of Euro-Pharmaceutical Companies

Brussels 22 Oct. 2011

**Consultation: Review of Commission Regulation (EC) No 1234/2008**

Dear Ms Figuerola,

With the present submission the EAEPC would like to participate in the public consultation ending today.

The EAEPC is the European voice for parallel distribution of medicines in Europe. Many of its some 70 member firms have experienced the positive outcome of the move of EMA to apply the principles of "eliminating red tape without compromising public health" on the process of granting variations to parallel distribution notices.

Parallel import (PI) is regulated by national authorities as well as the EMA; in the latter context we speak about parallel distribution, whereas in the context of non-centrally approved medicines the terminology of "parallel import" is prevalent. The Commission has issued a communication in 2003 on “on parallel imports of proprietary medicinal products for which marketing authorisations have already been granted”; COM (2003) 839 final.

Since the entry into force of the Variations Regulation, the EMA has introduced an adapted regime for dealing with notifications of change to a parallel distribution notice – the equivalent of a variation to a parallel import licence. With a view to maintaining distribution notices up to date in case of changes (variations) to the original marketing authorisation the EMA has for a set of mainly administrative changes to the original marketing authorisation introduced the “do and tell” concept in the granting of variations to the parallel distribution notice.

EAEPC Members estimate the share of “do and tell” notifications to be close to 70 percent of the overall number of notifications for change.

Against this background and drawing from the lessons learnt in the EMA context, we certainly welcome the basic idea of the Commission to extend the principles of the "variation regulation" to nationally approved medicines.

We therefore submit that the revision of the variations regime as outlined in the Commission consultation document also extends to authorizations by national regulators for granting parallel import authorizations, and that an eventual Commission proposal should include clear rules to instruct Member States to treat these authorizations according to the same rules as will be proposed for any other national approval of medicines.

According to the communication cited above, PI authorizations issued by national authorities must be considered a marketing authorization, albeit obtained in an abbreviated procedure, as no pharmaceutical product may be placed on the market without a marketing authorisation. Whatever the name, it is clear that the public health function of the regulatory decision for granting a parallel import authorisation is that of a marketing authorisation. We see no reasons for treating parallel import authorisations as authorizations sui generis which could not justifiably fall under the principles envisaged in the consultation document as these principles focus on facilitating the administrative burden for regulators and economic operators alike without, however, reducing the high level of public health.

Unlike in the EMA procedure for variations (notification of change) the national procedure must focus on establishing that the parallel imported product matches the reference product already approved on that market (originator product). This is normally established in an initial licence. But a large part of variations do not have an adverse impact on patient safety. EAEPC members report that most of the changes (to existing authorizations) result from changes of the address of the manufacturer or its representative, or from other mainly administrative modifications to which the parallel importer must adjust.

Some statistics:

Parallel imported pharmaceuticals have an average share of the total EU drug market of some 3 to 4.5%, but in certain member states where the concept has evolved over some 30 years can reach market shares in retail pharmacy (data for 2010) of 11% in Germany, 16% in Denmark, 8-9% in Sweden, ca. 14% in the Netherlands and ca. 5% in the UK (at its peak in 2002 it was 17% in UK), and is also gaining ground in markets such as Poland where it accounts for 1% of retail pharmacy sales.

Following communication COM (2003) 839 final, placing on the market of a parallel imported medicine is conditional on obtaining a marketing authorization issued by the national competent authorities in an abbreviated procedure. An individual authorization fore each importer is required for each medicine (and different strengths and pack sizes), and for each country of sourcing of that medicine, which explains the relatively higher number of national authorizations granted for PI compared to authorizations granted for new molecules to originator companies.

In Germany, for example, which is currently the largest market for parallel import of pharmaceuticals in the EEA area, in 2010 the BfArM issued a total of 2907 authorizations for new and existing medicines, and among this figure 540 authorizations, or 18.7 percent, for parallel imports. (Source: BfArM Bearbeitungsstatistik der Zulassungen for 2010, published at www.bfarm.de/DE/Arzneimittel/4_statistik/statistik-bearbeitung.html?nn=1009778).

The published data on parallel import authorizations cover new PI products, or new dosage forms or new source countries of PI medicines already marketed. But they do not include the rather more numerous number of applications/approvals of variations to existing marketing authorizations.

EAEPC Members in Germany and in Poland estimate that the number of authorizations for variations is a factor of 5 to 7 greater than the number of basic product authorizations. Members in Sweden report that the MPA in 2010 issued 451 new licences, and in addition approx. 900 variations.

Statistics from the UK MHRA demonstrate the quantitative importance of variations compared to initial PIPL (parallel import product licenses):

Over the period June to September 2011, the MHRA granted 259 Initial Parallel Import licences, and in addition it granted 5159 Variations. (Source: MHRA PLPI Post, monthly newsletter).

The MHRA subdivides variations into three categories: Administrative; scientific; pharmaceutical. EAEPC members in the UK estimate the volume of administrative variations to be about 30 percent of the total variations submitted/granted.

From these data it is obvious that the average annual workload of the economic operators in the parallel import sector is more determined by nationally approved products than by those approved by EMA. Correspondingly, the burden on national regulatory authorities will be significant. There is thus headroom for productivity gains for the regulators and the parallel importers also in the facilitation of authorizations of parallel import approvals.

In response to the specific consultation items, we have the following views:

Consultation items no 1 and 2:
Worksharing in cases where dossiers are not harmonised would not appear feasible in the case of parallel imports. We further think that in the context of parallel import it would not be compatible with the public health mandate of member states to forego the right to deal with variations that may have an impact on patient safety.

Consultation item 3:
Agree.

Consultation item 4:
Drawing from EMA experiences, and those of MHRA, purely administrative variations could either be adopted with shorter timelines, or even better should fall under the “do and tell” principle.

Consultation item 5:
Implementation of variations that have no or limited impact on public health should be treated under “do and tell” and not need waiting for pre-approval by a regulator; this will also help increasing self-responsibilty of applicants.

Consultation item 6:
Introducing a deadline would appear in the interest of public health, but changes to product information significant for public health should enter into the public domain, eg. by asking Member States to publish such approved changes on the regulator’s website. For a parallel importer, as an example, this would improve its capability to adjust in a timely manner to any relevant changes to the PIL.

Consultation item 7:
We share the view that a proliferation of small changes to the SmPC is not in the interest of public health.

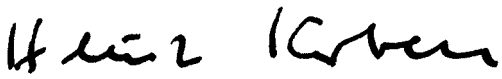
Consultation item 8:
Bulk variations to PLPI licences are currently practiced by the MHRA for mainly administrative variations in that the MHRA offers the industry a possibility of group variations of connected PIPLs.. This does not normally pose problems of timing. We

would however understand the need for more time in the case of more complex group variations, but this should not lead to prolonging procedures which in the past have been running smoothly.

Consultation item 9:
Parallel import in specific circumstances can help alleviating access to medicines in a pandemic setting as necessary repackaging (of medicines procured in one country and sold in another) can be carried out as a matter of routine. This can also include vaccines. Given their special storage conditions and shorter expiration periods, flexible procedures to accommodate such situations are certainly helpful.

We thank you for the possibility to participate in this consultation and are available for any further explanations that you may wish.

Yours sincerely,
Heinz Kobelt



Director European Affairs EAEPC

Annex 1:

What is Parallel Distribution?

Parallel distribution occurs when products which are purchased at a lower price in one country are transported and repackaged for resale to other countries where they are more expensive. This process puts the parallel traded product in the destination market in competition with the same product which is marketed, in the destination market, by the original trade mark owner, i.e. the manufacturer or its local licensee of the product.

Parallel distribution of medicinal products is the result of collaboration between two types of operators: a licensed pharmaceutical wholesaler in country 'A' who holds excess stock and a parallel importer in country 'B' who has regulatory approval to market these pharmaceuticals - repackaged according to the requirements of the destination market.

Parallel distribution is 100% legal and encouraged by many governments and regulators in order to foster competition.

The flow of medicines within Europe is diverse, and price differences vary greatly across therapy areas and geographic markets. Parallel distribution is the logical consequence of the difference in prices of medicines between member states in the European Union. Parallel distribution provides the only form of price competition to patent-protected pharmaceutical products and helps patients and governments to control spiralling healthcare costs.

Parallel distribution can exist wherever there are price differentials for identical products. This process has existed globally ever since goods were first traded, and is found across Europe in a wide range of sectors involving many branded products. The overall level of

parallel distribution with medicines in Europe is unremarkable in this context, and only becomes an issue when original manufacturers attempt to hinder competition.

Almost all EEA countries are involved in parallel distribution, either as a source of products or as a destination market. Some countries are both the source of exported medicines as well as the destination for other kinds of medicines. Consequently, parallel distribution boosts intra-Community trade, which the European Commission sees as a decisive vehicle for the completion of the EU internal market in medicines.

It is important to note that the parallel distribution of medicines in Europe has nothing to do with EU trade with third countries.

'Know your supplier' principle

The EAEPC and its members strongly believe in the principle of "know your supplier".

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

According to GDP, each purchaser of medicines must ensure goods come from an authorised source. This applies equally to all parallel importers and distributors, as they must use a GDP license.

The regulators in the importing Member States, such as the UK or Denmark, request from the parallel importers that they have a file of authority-approved exporting wholesalers. In France the authority requires that the exporting wholesalers, included its number of authorization, is identified, in the application for parallel import.

A PI company in Germany and Austria has to verify that its suppliers are in possession of a valid wholesale licence in accordance with the requirements of their respective countries. This verification has to be kept on file and at the disposal of the authorities for verification or inspection purposes.

The importer must also ensure that the goods obtained are in free circulation within the EEA. Any PI product licence is restricted to named countries of origin. Therefore the products marketed must have their origin in these specified countries. No specific proof of origin is required. It would be a violation of the law - and the trademark rights of the owner- if PI companies marketed products from outside the EEA.

Further, the importer must check and ensure that the storage conditions are observed during transport, e.g. cold chain requirements. These procedures are regulated in GMP and GDP rules and transposed in detail into the Standard Operating Procedures (SOP) of the parallel distributor. SOPs underpin the operation of the manufacturing authorisation (at initial issue, and through regular inspections).

According to SOPs, the detection of defective medicines, as well as possible counterfeits, is part of the regular quality control in place, i.e. first at the point of entry of a shipment when numbers and volumes of incoming batches are checked against the invoice, and in

case of mismatch, a report is sent to the supplier. A second time, controls are made at the workplace for repackaging or re-labelling, when the blisters are taken out of the packages (to exchange the PIL). If there were any obvious differences or changes in the visible quality of the medicine, the product will be eliminated, scrutinised and clarified under the supervision of the Qualified Person.

As mentioned in the previous submission to DG Enterprise [1], if a parallel distributor does not repack or re-label goods in his own facility, they will have to subcontract these processes to an authorised re-packer, who will have to demonstrate that he operates under GMP conditions. In these cases, all legal and technical requirements that must be observed by the parallel importer/distributor will be laid down in a technical agreement between them and the re-packer. This ensures full compliance with all legal and technical requirements.

Hence, parallel importers/distributors are fully compliant with GDP and GMP standards to ensure security of product sources.

The EMEA or the national authorities normally have a list of authorised pharmaceutical manufacturers for internal use. There is a European database of all pharmaceuticals having obtained the marketing authorisation. EMEA has recently started a database on all parallel distribution authorisations it grants every month, in line with its wish to increase the transparency of the market.

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. 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.

[1] "Safe medicines in parallel trade", EAEPC submission to DG Enterprise consultation, 30 March 2007.

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.

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, 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, employ an EU Qualified Person and are subject to periodic inspection by the competent authority.

Annex 2:

Statistical information on UK parallel import authorisations.

Source: PLPI Post September 2011 and October 2011; Newsletter of MHRA Parallel Import Section

## Monthly statistics

Every month a series of reports from the Sentinel database are run to monitor various aspects of Parallel Import Licence granting performance. Each month we will include the current statistics for some key parameters in The PLPI Post so that you can see how we are doing. Please let us know if there is something you would like included.

| Measure | June 11 | July 11 | August 11 |
|---|---|---|---|
| Initial Parallel Import Applications received | 123 | 83 | 109 |
| Initial Parallel Import Licences granted | 100 | 93 | 33 |
| Minimum time to grant (months) | 6.1 | 5.0 | 5.7 |
| Median time to grant (months) | 9.3 | 8.1 | 8.3 |
| Time to start assessment (months) | 6.6 | 9.4 | 7.3 |
| Variations received | 2039 | 1411 | 1532 |
| Variations granted | 973 | 1368 | 1750 |
| Time to grant leaflets (months) | 3.6 | 3.0 | 3.2 |
| Time to grant pharmaceuticals (months) | 5.5 | 4.9 | 5.1 |
| Time to grant admin (months) | 1.6 | 1.6 | 1.6 |

**For any PLPI related queries contact: RIS.PLPI@mhra.gsi.gov.uk**
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October Newsletter:

| Measure | July 11 | August 11 | September 11 |
|---|---|---|---|
| Initial Parallel Import Applications received | 83 | 109 | 112 |
| Initial Parallel Import Licences granted | 93 | 33 | 33 |
| Minimum time to grant (months) | 5.0 | 5.7 | 5.8 |
| Median time to grant (months) | 8.1 | 8.3 | 9.0 |
| Time to start assessment (months) | 9.4 | 7.3 | 5.5 |
| Variations received | 1411 | 1532 | 1912 |
| Variations granted | 1368 | 1750 | 1068 |
| Time to grant leaflets (months) | 3.0 | 3.2 | 3.2 |
| Time to grant pharmaceuticals (months) | 4.9 | 5.1 | 5.7 |
| Time to grant admin (months) | 1.6 | 1.6 | 1.9 |

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