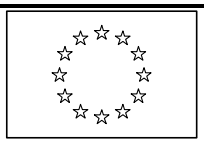

U.S. Food and Drug Administration

EUROPEAN COMMISSION
ENTERPRISE DIRECTORATE-GENERAL

European Medicines Agency

CONFIDENTIALITY ARRANGEMENTS CONCLUDED BETWEEN THE EU (EC AND EMEA) AND THE US FDA/DHHS

IMPLEMENTATION PLAN FOR MEDICINAL PRODUCTS FOR HUMAN USE

Finalized September 16, 2004

I. INTRODUCTION

Reference is made to the Confidentiality Arrangements concluded on 12 September 2003 between the EU (European Commission and EMEA) and the U.S. FDA of the U.S. Department of Health and Human Services in the context of regulatory co-operation and transparency between the U.S. Government and the European Commission.

In order to allow for a successful exchange of information and documents between the EU and the FDA in accordance with the terms of these Confidentiality Arrangements, this Implementation Plan is agreed. The objective of this Implementation Plan is to describe at high-level the processes by which each party will undertake the exchange of information and documents as envisioned by the Confidentiality Arrangements, as well as a process for the monitoring of the implementation of this Implementation Plan.

The outcomes of preliminary discussions of these matters at recent EU/FDA bilateral meetings have been taken into account when drafting this Implementation Plan.

II. IMPLEMENTATION PLAN

II.1 Extent of the Regulatory Co-operation

The Confidentiality Arrangements concluded on 12 September 2003 establish a framework for, among other things, the possible exchange of information on advance drafts of legislation and regulatory guidance documents, as well as non-public information related to ensuring the quality, safety and efficacy of medicinal products for human and veterinary use, including orphan medicinal products, authorised or under review both in the USA and the EU.[1]

It should be noted that the sharing of product-related information is limited to medicinal products evaluated or authorised in accordance with the EU Centralised Procedure, as well as medicinal products authorised at national level by the EU Member States, that are subject to arbitration or referral in accordance with European Community procedures.

In order to utilise the framework established by the Confidentiality Arrangements, a step-wise approach is envisaged. In the initial phase, a limited implementation programme will be established. At a later stage, the scope of information sharing

[1] This will also include information on maximum residue limits.

and other regulatory co-operative activities can be reconsidered in accordance with the Confidentiality Arrangements and on the basis of accumulated experience.

II.2 Regulatory Co-operation between the European Commission, the EMEA, and the US FDA/DHHS

The regulatory co-operation between the European Commission's Directorate General Enterprise and the US FDA/DHHS may include the ad-hoc exchange of

1) advance drafts of legislation, including the adaptation of existing legislation to emerging technologies,
2) the implementation of new legislation, and
3) "non-papers" on regulatory issues prior to the drafting of new legislation.
4) implementing technical texts, such as guidelines

II.3 Regulatory Co-operation between the EMEA and the US FDA/DHHS

Initial Phase

It is agreed that the implementation programme - in its initial phase - will consist of the following pillars:

1) The establishment of an educational programme.

   This educational initiative should lead to a culture of increased awareness at all impacted staff levels at both the FDA and EMEA about the strengthening of regulatory co-operation between both organisations permitted by the Confidentiality Arrangements, with particular emphasis on the limitations of the scope of such co-operation and on the agreed processes for requesting and responding to requests for documents/information covered by the Confidentiality Arrangements.

2) The establishment of procedures for the request of documents/information to be exchanged, for the subsequent exchange of such documents/information, and for the documentation of such exchanges.

   Two types of exchange are envisaged: regular exchange and ad-hoc exchange.

   a) <u>Regular exchange</u>

      (i) On a quarterly basis, the routine exchange of a listing of agreed specific information on applications, both pre-and post-authorisation[2],

      (ii) On a quarterly basis, the routine exchange of a listing of inspections (GMP, GCP and pharmacovigilance inspections) performed the previous quarter, and inspections likely to be performed during the

[2] The quarterly exchange of information should include (1) for pre-authorisation applications: a listing of newly submitted applications, applications still undergoing review, applications upon which a marketing authorisation decision have been made that quarter (and what the decision was); as well as (2) for post-authorisation applications: a listing of newly submitted applications, applications still undergoing review, and applications upon which a marketing authorisation decision have been made that quarter (and what the decision was), the scope of such applications being limited to issues of major public health interest, such as extensions of indications, certain additional formulations (e.g. paediatric formulations) and important safety concerns which have an impact on the use of the medicinal product.

next quarter, at a select group of manufacturing sites of interest to each party.

(iii) On a quarterly basis, the routine exchange of a listing of the guidelines under development.

In case further information on any topic contained in the listings is required, such additional information should be obtained through the primary contact points identified at the level of each organisation.

b) Ad-hoc exchange

By their very nature, ad-hoc exchanges are not subject to planning, however they should, nonetheless, be tracked and documented and provide mutual benefit. During 2004 and 2005, the scope of ad-hoc exchanges should be limited in order to obtain as much experience as possible with the regulatory cooperation. Therefore, in 2004 and 2005, staffs will be asked to limit their non-emergency ad hoc exchanges to the following areas, i.e.:

(i) provision of scientific advice (parallel scientific advice procedure) based upon a formal pilot programme (including a General Principles Document) that will be developed by both parties;

(ii) encountered difficulties in relation to the evaluation of applications for marketing authorisation;

(iii) pharmacovigilance related issues[3],

(iv) advance notice, before the release of information into the public domain, of significant regulatory sanctions of mutual interest concerning one another's market (i.e. actions taken by a Regulatory Authority to restrict the distribution of a product and/or to restrain the conduct of manufacturing facilities, such as license suspension/revocation, seizure/injunction action, embargoes, detentions), as a result of GMP, GCP and pharmacovigilance inspections;

(v) issues of general public health concern (e.g. TSE-, vCJD-, counterterrorism measure – related issues);

(vi) a pilot benchmarking exercise with at least 2 medicinal products to be chosen by the FDA and the EMEA to compare pre-market review assessments for an application (one in which the decision on marketing authorisation differed, and one in which the decision was similar);

At the level of each organisation, a primary contact point will be responsible for tracking the regular and ad-hoc exchange of information.

3) The possibility for staff of the EMEA, EU experts representing the EMEA and staff of the FDA to be exchanged between, or seconded to respective organisations including attendance at the other's scientific meetings.

Second Phase

One year after the initiation of the Initial Phase of this Implementation Plan in accordance with the Confidentiality Arrangements, the EU and the FDA will jointly develop and implement an audit plan designed to evaluate whether exchanges were timely, relevant, and mutually beneficial for the effort expended, and include

[3] The current concept of videoconference meetings between the EMEA/CPMP Pharmacovigilance Working Party/FDA will be reviewed in order to take into account the terms of the Confidentiality Arrangements.

recommendations for changes to the scope of the interaction, in accordance with the terms of the Confidentiality Arrangements.

Actions and Status

The actions to be undertaken in order to implement the Initial Phase of this Implementation Plan, as well as the status of such actions, are described below:

Establishment of an Educational Programme	
Actions	**Status**
Familiarise the staffs of both the EMEA and the FDA with the elements of this Implementation Plan and the consequences of the Confidentiality Arrangements, ▪ horizontally between both organisations; ▪ vertically within each organisation. This should be conducted in 4 phases: **First phase:** ▪ Familiarisation between (senior) management Staff of both organisations, responsible in each organisation for the management of this Implementation Plan.	▪ Completed.
Second phase: ▪ Creation of awareness within all impacted components of each organisation.[4]	▪ Ongoing.
Third phase: ▪ Familiarisation between key Staff of both organisations within each identified area of activity.	▪ Ongoing.
Fourth phase: ▪ Possibility of EMEA Staff to second at the FDA as Visiting Experts and vice-versa, in order to further strengthen the familiarisation concept.	▪ Ongoing

Establishment of Procedures for Requesting the Exchange of Documents / Information and for the Subsequent Exchanging of such Documents / Information	
Actions	**Status**
The following phases are envisaged: **First phase:** Identification at the level of both organisations of primary contact points in order to establish the necessary link between the EMEA and the FDA and to subsequently channel both the requests for and the transmission of documents and information through such contact points.	▪ Ongoing.

[4] This includes at EU level involvement of the EMEA Scientific Committees Members and Experts.

Establishment of Procedures for Requesting the Exchange of Documents / Information and for the Subsequent Exchanging of such Documents / Information	
Actions	**Status**
<u>Second phase:</u> Start of exchange of documents and information:	
<u>Regular exchange</u> ▪ Through a quarterly exchange of agreed specific information on applications, both pre-and post-authorisation. ▪ Through a quarterly exchange of planned/performed inspections. ▪ Through a quarterly exchange of guidelines under development.	 ▪ Start date: 1 October 2004. ▪ Start date: 1 October 2004. ▪ Start date: 1 October 2004.
<u>Ad-hoc exchange</u> ▪ During 2004 and 2005, the scope of the ad-hoc exchange should be limited as described under Section II.1.	 ▪ Start date: 1 October 2004.

Attendance by the EMEA and FDA Staff at each other's Scientific Meetings through exchange/secondment of Staff and Experts	
Actions	**Timeframes**
▪ Establishment of a procedure at the level of each organisation describing the practical arrangements to be established.	▪ Ongoing.

III. MONITORING OF THE IMPLEMENTATION

In order to ensure a smooth implementation of this Implementation Plan, an appropriate organisational structure shall be established.

Such organisational structure shall consist of:

- A Steering Committee:

  The main role of such Steering Committee, composed of senior representatives of both the FDA and the EU (European Commission and EMEA), should be to closely monitor the implementation of this Implementation Plan, to prioritise activities to be undertaken as part of this Implementation Plan, and to take any corrective action if deemed necessary.

  The Steering Committee shall also discuss any request for disclosure to third parties of non-public information.

  The Steering Committee should meet every six months either in person or by using tele- (or video) conference facilities in order to monitor the progress made. A status report should be made available for discussion at EU/FDA bilateral meetings.

- An adequate operational process:

  An adequate operational process, capable to achieve the objectives of the Implementation Plan, shall be established internally at both the FDA and the EMEA. Taking into account the different organisational structures and resources of the

EMEA and the FDA, such operational processes may be different in each organisation.