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Interim report on the International API Inspection Pilot Programme

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1. Objective

The objective of this report is to provide an interim update on the achievement of the Pilot Programme after 18 months and to check if the results so far are in line with the expected deliverables.

2. Background of the pilot programme

In the context of the Transatlantic Administrative Simplification Workshop organised in Brussels November 2007 and the 2nd International Summit in Dublin in December 2007 it was proposed, as an initial effort to improve international sharing of information and to facilitate more risk based approaches to inspection planning, that a small group of interested regulators establish a pilot project for Active Pharmaceutical Ingredients (API). This would, build on equivalent API GMP standards and taking into account a risk based approach, foster mutual confidence between regulators.

The pilot phase is restricted to inspections of API manufacturers carried out outside the participating regions.

3. Activities of the pilot programme

Between December 2007 and May 2008, EMA approached a number of EU Member States active in the area of inspections of active pharmaceuticals: France, Germany, Ireland, Italy, United Kingdom, as well as the European Directorate for the Quality of Medicines and Healthcare (EDQM) from the Council of Europe, the United States of America Food and Drug Administration (US FDA) and the Australian Therapeutic Goods Administration (TGA).

A start date of the operational phase of December 2008 was marked by the actual sharing by all parties of their inspection plans according to a previously agreed template and the sharing of information on inspections carried out in the last 24-36 months. The pilot phase was supposed to last for 18 months from the date it became operational but as setting up the practical details to implement the project took some time it was decided in November 2009 during a plenary meeting in Washington to extend the pilot an additional 6 months. This would have the advantage of two full years of functioning and it was agreed to publish a final report in December 2010 where the outcomes will be analysed and a recommendation for future action made.

Nevertheless it was decided to publish after June 2010 the present interim report, the date when the programme was originally supposed to end.

4. Expected deliverables and key performance indicators

The following items were originally identified as key performance indicators:

- Increased transparency and visibility of inspections performed by participating authorities
- Decrease in "duplicate inspections", (inspections of the same product or sites carried out by more than one participating authority within a similar time period)
- Increase in the number of inspections performed of value to more than one authority
- Overall increase in the number of API sites inspected by participating authorities for all inspections
- Positive assessment of the deliverables by the participating authorities

Increased transparency and visibility of inspections performed by participating authorities

The key element of increased transparency and visibility is the elaboration, based on the contributions of all participants, the maintenance and sharing of a Master List which records the sites of interest for the participants including (when available) the APIs produced at the site, the date and outcome of the last and the date of the next, planned, inspection.

To date the participants submitted the following into the Master List:

1046 site entries were provided by the participants together, from which:

- Europe submitted 499 sites (*France: 44; EDQM: 173; Ireland: 4; Italy: 11;EMA: 112; UK: 51; Germany: 104)*
- US FDA submitted 352 sites
- Australian TGA submitted 195 sites

In the Master List the sites which are of interest to more than one participant i.e. "shared" are highlighted in order to identify them easily as they are the starting point for collaboration.

Not all participants have yet submitted all the API manufacturing sites which supply APIs to their national territories but based on the present information the tables below show the number and manner in which the sites are shared:

	# of sites provided (15/06/2010)	**# of shared sites (and %)**	**# of sites shared between 2**	**# of sites shared between 3**
Europe	499	190 (38 %)	**100** 29 TGA 71 FDA	90
FDA	352	192 (54 %)	**102** 71 EU 31 TGA	90
TGA	195	150 (78%)	**60** 29 EU 31 FDA	90

The Master List also contains the inspection dates and outcome of inspections performed during 2009 and 2010, about 250 inspections in total done by the participants of the 3 regions, Australia, Europe, and US, which were submitted by the participants.

With all those elements organized and easily available to all participants, the Master List has increased transparency and visibility of the inspection activities.

Decrease in "duplicate inspections"

The number of joint inspections organised so far, thus avoiding duplicate inspections are:

- Europe *(EMA, EDQM)* participated in 6 joint inspections: 5 with TGA and 1 with FDA.
- FDA participated in 2 joint inspections: one with 1 Europe *(EMA)* and 1 with TGA.
- TGA participated in 6 joint inspections: 5 with Europe *(EMA and EDQM)* and 1 with FDA.

In total: 7 joint inspections were performed:

1. Europe (EDQM) / TGA : India

2. Europe (EDQM) / TGA : India
3. Europe (EDQM) / TGA : India
4. Europe (EDQM) / TGA : India
5. Europe (EMA) / FDA : Croatia
6. FDA / TGA : Mexico
7. Europe (EMA) / TGA : Japan

- 2 planned and confirmed joint FDA/TGA inspections in Japan were ultimately cancelled.

However, it has been noted that a number of duplicate inspections were still performed and the reasons for this will be explored in the final report:

Country of the inspected sites	Inspectorates	Dates of the duplicate inspections
Japan	US / Europe *(ZLG)*	2009 February / September
China	US / Europe *(EDQM)* US / Europe *(EDQM)*	2009 July / October 2009 February / February
India	US / Europe *(EDQM)* US / Europe *(EDQM)* Europe (E*MA)* / US US / Europe *(AFSSAPS)* Europe *(ZLG)* / US US / Europe *(EDQM)* US / Europe *(EDQM)*	2009 March / April 2009 April / June 2009 October / 2010 February 2009 February / September 2009 February / April 2009 April / 2010 February 2009 January / April

Increase in number of inspections performed of value to more than one authority

The exchange of inspection-related information included in the Master List allows participants to know about inspections performed by other participants and their outcome. In case they need more information they can request a copy of the inspection report. Based on the information regarding the planning of inspections, the participants can also contact each other to ask for an already planned inspection to have its scope extended so that the shared report covers more products and is therefore of value for more than one authority.

The number of inspection reports requested is as shown in the below table:

	Requested by Europe	**Requested by FDA**	**Requested by TGA**
From Europe	-	20	7
From FDA	47	-	8
From TGA	16	16	-

Overall increase in number of sites of API inspected by participating authorities

It is not possible to be concise about an overall increase in the number of sites inspected, but because of the sharing of information and inspection reports it is self-evident that resources were freed up for other priorities including inspection of sites which are not shared by other participants and/or which were never inspected before.

Region-specific analysis will be developed in the final report based on the feedback of the participants.

Positive assessment of the deliverables by the participant authorities

This will be developed in the final report based on the feedback of the participants and will look at a wider range of deliverables.

5. Conclusion

There is an unquestionable strong commitment of the participants in the pilot programme and there is an essential public health incentive to collaborate on the inspections of API manufacturers worldwide.

The achievements of the pilot to date are promising because collaboration has started and palpable results of team work within the pilot programme are already available. However, a full continuous collaboration between the participants will certainly need additional effort as there still appears to be some duplicated inspections.

Still, the tools developed during the pilot programme, especially the Master List and its wide ranging information on the API manufacturing sites supplying APIs to the three participating regions is a precious source of information. It is also a model which can be used to design the future Eudra GMP module for sharing of inspection planning.

To further develop collaboration, tools will have to be adapted and improved to better suit the intended use and national systems will have to be adapted to make better use of international cooperation opportunities.

The project is contributing substantially to the better understanding of regional approaches to inspection and building mutual confidence.

A more comprehensive analysis of learnings will be provided in the final report.