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Final report on the International API inspection Pilot Programme

Executive summary

A pilot programme on International collaboration on GMP inspections of API manufacturers was conducted between December 2008 and December 2010 involving competent authorities from Australia, Europe and the United States. The purpose of the programme was to foster cooperation and mutual confidence between participating regulators through better communication and exchange of information on inspection planning.

New tools for work sharing and exchange of information were developed and used by the participants to share inspection reports and to organise joint inspections of API manufacturers located outside the participating regions. Increased transparency and visibility of inspections performed by participating authorities allowed a successful collaboration between authorities on sites of common interest and increased the number of inspections performed of value to more than one authority.

Following the successful conclusion of the pilot it was agreed to maintain the cooperation established and to extend participation, initially to other European authorities.

The increased cooperation established as a result of this pilot programme increased information sharing between the regulators concerned and facilitated work sharing. It also promoted more efficient use of international inspectional resources combined with wider global inspectional coverage to the benefit of public health and patients worldwide.

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Table of contents

1. Objective

The objective of this report is threefold:

- provide a final update and a conclusion on the achievement of the International API Inspection Pilot Programme after 24 months,

- assess if the results are consistent with the expected deliverables,

- based on the experience gained, make recommendation for the continuation and development of the programme.

2. Background and purpose of the pilot programme

In the context of the Transatlantic Administrative Simplification Workshop organised in Brussels November 2007 and the subsequent 2nd International Summit of Heads of Medicines Agencies in Dublin in December 2007 it was proposed as an initial effort to improve international sharing of inspection information and to facilitate more risk based approaches to inspection planning, that a small group of interested regulators establish a pilot project on Active Pharmaceutical Ingredients (API) inspections.

This pilot phase was restricted to inspections of API manufacturers carried out outside the participating regions: Australia, Europe and the United States of America.

The purpose of the pilot programme, building on equivalent API GMP standards: ICH Q7 shared by the participating authorities and taking into account a risk based approach, was to foster mutual confidence between regulators through better communication, coordination and collaboration on inspections of manufacturing sites of common interest. In addition the pilot programme would foster a better use of international inspectional resources allowing an increase in the number of inspections performed of value to more than one authority and a better inspectional coverage.

3. Activities of the pilot programme

Between December 2007 and May 2008, EMA approached a number of EU Member States known to be active in the area of inspection of active pharmaceutical ingredients (API) manufacturers: France (AFSSAPS), Germany (ZLG), Ireland (IMB), Italy (AIFA), United Kingdom (MHRA), 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). All those approached agreed to participate and welcomed the initiative. Confidentiality agreements or equivalent agreements signed between the participants allowed the sharing of non-public information.

The main activities proposed and developed within the program and based on the sharing of inspections planning were exchange of inspection reports and organisation of joint inspections.
The start date of the operational phase of the API Pilot in December 2008 was marked by the actual sharing by all parties of their inspection plans according to a previously agreed template. Participants were also asked to submit retrospective data about the inspections performed in countries outside the participating regions between 2005 and 2008 in order to highlight possible “duplicate inspections” (similar inspections of the same site performed separately by 2 participating authorities within a short period of time) and identify a base line for the pilot programme. From the information exchanged, 85 sites were identified which had been inspected by more than one participant and for which inspection dates were available.

The following results were found:

- 8 sites had been inspected by at least 2 of the participants during the same month
- 7 other sites had been inspected by at least 2 of the participants within a 3 month period
- 11 other sites had been inspected by at least 2 of the participants within a 6 month period
- 20 other sites had been inspected by at least 2 of the participants within a 12 month period
- 14 other sites had been inspected by at least 2 of the participants within a 2 year period
- 25 other sites had been inspected by at least 2 of the participants over more than 2 years.

Although the scopes of the inspections were not taken into account and different scopes may justify several of the "duplicate inspections", the figures collected from the retrospective data submitted confirmed a tendency of the participating regulators to perform duplicate inspections in third countries during the 3 years prior to the start of the pilot programme.

The pilot phase was initially intended to last for 18 months from the date it became operational but as setting up the practical details to implement the project took more time than expected it was decided in November 2009 during a plenary meeting of the pilot programme's participants in Washington to extend the pilot for an additional 6 months until December 2010. Hereafter a final report on the outcomes of the pilot programme would be published, including a recommendation for future action.

In addition it was decided to publish an interim report after the date when the programme was originally supposed to end (June 2010). This report was published by EMA and TGA in October 2010 and by FDA in January 2011.

4. Tools of the pilot programme

Work sharing tools

The 3 tools proposed and used for work sharing were:

- exchange of inspection reports of past inspections,
- exchange of inspection reports of planned inspections with or without extension of scope,
- joint inspections with or without extension of the scope of the inspection.

The tool which was the most used during the pilot, because easily organised, was the exchange of inspection reports from past or planned inspections, but without extension of the scope.

The extension of the scope of a planned inspection was only used twice because it was difficult for the inspectors to cover more products than initially planned, mainly for logistic and administrative reasons, but also due to constraints on duration of the inspection.

Although the planning of joint inspections required extensive organisation and collaboration between the inspectors as well as with the site to be inspected, several joint inspections were organised and considered successful as the inspection team agreed on the conclusions and on a common list of GMP deficiencies on every occasion.

Work sharing was made possible through frequent and regular use of bilateral or plenary teleconferences as well as by the exchange of countless e-mails.

Master List

A so called "Master List" was built up at the very start of the Pilot programme with initial information on API manufacturing sites (Name, address, API(s) manufactured, last inspection date and outcome, planned inspection date…) provided by each participant. This list was regularly amended by additional information provided regularly by the participants: new sites, new inspection dates, planned inspection dates and APIs manufactured.

The EMA assumed responsibility for updating regularly the Master list, including for tracking purposes, the relevant activities proposed for each site, e.g. sharing of inspection reports or planning of joint inspections.

The updated Master List was sent regularly by the EMA (at least once a month) to each participant.

When received, the Master List was intended to be used by participants as a source of pertinent information for the planning of their inspections helping them to avoid unnecessary duplication of inspections and supporting the exchange of inspection reports and/or the organisation of joint inspections.

Feed back forms

Feed back forms were developed and distributed to the inspectors in order to identify possible differences between an inspection done by a national team of inspectors and an inspection done by an international team. Inspectors were also asked to identify and report on all issues faced during the joint inspections, make recommendations when relevant and also report on the experience gained.

No notable differences were identified and reported by the inspectors during the preparation, conduct and conclusion of the joint inspections. However the issues which were raised already during the earliest inspections were on the necessity to foresee, in addition to preparatory teleconferences, meetings before the inspection for preparation involving all inspectors of the team and after the inspection, to discuss and agree on the deviations and the conclusion. This was considered especially important when the inspectors in the team were working together for the first time.

5. 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”
- 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

5.1 Increased transparency and visibility of inspections performed by participating authorities

The key element which provided increased transparency and visibility was the elaboration, based on the contributions of all participants, the maintenance and sharing of the Master List which recorded 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 by any of the participants.

By the end of the pilot the participants had submitted the following inspection information into the Master List:

1110 site entries were provided by the participants together, from which:

- **Europe** submitted **538** sites (*France: **44**; EDQM: **202**; Ireland: **5**; Italy: **11**;EMA: **119**; UK: **53**; Germany: **104**)*
- US **FDA** submitted **355** sites

- Australian **TGA** submitted **217** sites

The entries corresponded partly to sites inspected between 2005 and 2008 and partly to sites planned to be inspected as part of the 2009 and 2010 inspection programmes of the participants.

As several sites submitted by the participants were sites shared by more than one participant, the Master List finally consisted of a total of 642 sites of which 408 sites were of interest to one of the participants only and 238 were sites of shared interest to 2 or 3 of the participants; these were therefore the sites on which collaboration was possible.

Based on the information available at the end of the pilot in December 2010, the table below shows how the shared sites were distributed between the participants:

Number of sites shared between 2 participants : 137		
Europe (DE, EDQM, EMA, FR, IE, IT, UK)	TGA	**36**
TGA	FDA	**28**
FDA	Europe (DE, EDQM, EMA, FR, IE, IT, UK)	**73**
Number of sites shared between all 3 participants : 97		

For the majority of the sites, the Master List also provided the inspection dates and outcome of inspections performed during 2009 and 2010. About 250 inspections were performed on sites listed in the Master List by the participants of the 3 regions, Australia, Europe, and US during the pilot period. The inspection dates and outcomes were submitted by the participants and this information could be used by all participants to request inspection reports.

Conclusion : With all those elements as listing of sites, details of APIs manufactured, last inspection date, next planned inspection date, organized and easily available and shared with all participants, an increase in transparency and visibility of inspection activities was achieved.

5.2 Decrease in "duplicate inspections"

In addition to the sharing of inspection reports which increased the number of inspections of value for more than one authority (see next section), a total of 9 joint inspections, were organised. The joint inspection which allows two authorities to share resources by sending one shared inspection team to the same company helps to avoid duplicate inspections which require more resources from the inspectorates and from the sites inspected twice instead of once.

Europe *(EMA, EDQM, UK)* participated in 8 joint inspections: 5 with TGA and 3 with FDA.

FDA participated in 4 joint inspections: 3 with Europe *(EMA)* and 1 with TGA.

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

All 3 Australia, Europe and US took part together in one joint inspection.

The 9 joint inspections performed were:

Joint inspection team	County of the inspected site	Inspection date
Europe (EDQM) / TGA	India	June 2009
Europe (EDQM) / TGA	India	June 2009
Europe (EDQM) / TGA	India	June 2009
Europe (UK) / TGA	India	June 2009
Europe (UK on behalf of EMA) / FDA	Croatia	June 2009
FDA / TGA	Mexico	November 2009
Europe (Italy on behalf of EMA) / TGA	Japan	June 2010
Europe (France on behalf of EMA) / FDA / TGA	China	September 2010
Europe (Slovenia on behalf of EMA) / FDA	India	October 2010

However, it was noted that, particularly in 2009 when the programme was still at the beginning, and the tools not yet fully developed and in use, a number of duplicate inspections were still performed. This was less evident in 2010.

Several reasons can explain and sometime justify the duplicate inspections:

- The Master List, which is not exhaustive, didn't contain relevant information about a planned inspection, the date of a very recent one or the scope of the inspection.
- The Master List, although containing the pertinent information wasn't examined by the participants before planning the inspection;
- Although the information was in the Master list and known by the participant the inspection couldn't be postponed or cancelled because of internal, logistical or administrative reasons, or because the duplicate inspection was justified in view of a different scope.

Conclusion: Efforts to reduce the number of duplicate inspections should be continued as it allows saving costly inspectional resources and it also reduces the number of repeated often similar inspections to which the API manufactures are subjected.

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

The exchange of inspection-related information included in the Master List allowed participants to know about inspections performed by other participants and their outcome. Whenever more information was needed a copy of the inspection report could be requested. Based on the information available on the

planning of inspections, the participants could also contact each other to ask for an already planned inspection to have its scope extended so that the inspection would cover more products and therefore be of value for more than one authority.

The number of inspection reports (IR) exchanged is as shown in the below table:

	Received by Europe (DE, EDQM, EMA, FR, IE, IT, UK)	**Received by FDA**	**Received by TGA**
IR from Europe (DE, EDQM, EMA, FR, IE, IT, UK)	-	12	7
IR from FDA	50	-	7
IR from TGA	12	5	-

Close to 100 reports were exchanged and examined by the participants. According to the feed back received, the information contained in the report was used for different purposes.

- When the API(s) covered by the scope of the inspection were different from the API of interest, the reports were examined for information about the quality management system in place and about the weaknesses identified and also for the preparation of an inspection with a different scope.

- When the API(s) covered by the scope of the inspection were the same as the API of interest, the reports could be used as an information for the preparation of the planned inspection, or if the conclusions were satisfactory to postpone or cancel a planned inspection.

- In several cases, a firm's corrective actions mandated in one agency's final inspection report were verified by a different agency during their subsequent inspection, and the final outcome was shared with the original agency.

- In some cases actions have been taken based on information received by exchanging inspection reports, which could lead in the case of reported GMP non compliance to the organisation of follow up joint inspections or national enforcement measures against the non compliant manufacturers.

Although, from a legal perspective, the exchange of GMP certificates was the preferred option within Europe, consideration should be given to the advantages of an exchange of inspection reports between worldwide competent authorities as it allows to share an essential technical record of the full inspection process and outcome and is for the receiving party an essential source of relevant information for its risk management process.

Conclusion: the exchange between authorities of inspection reports and use of the information they contain for the planning of next inspections increase the number of inspections performed of value to more than one authority

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

It was difficult to accurately assess an overall increase in the number of sites inspected; information on whether participants increased or decreased their inspectional resources during the pilot for reasons not related to the programme was not available. However, because of the sharing of inspectional information and of inspection reports, it was certainly possible that resources that would previously have been used for certain inspections could have been allocated to other priorities for example to

inspection of sites which were not shared with other participants and/or which were never previously inspected.

From the feed back given by the participants it appears that the sharing of inspectional information, in combination with the impact of joint inspections led to confidence building and to the firsthand knowledge that either the inspections performed by the participants were comparable, or that differences were understood. Although a small number of joint inspections were performed during the pilot, helping to build confidence, the number was limited because of the additional work and time needed to organize them. As a result, work sharing was not always accompanied by the possibility to reallocate resources. In addition, the need expressed by inspectors in the feed back forms to meet before a joint inspection to prepare and afterwards to discuss outcomes contributed to the reduction of efficiencies.

Conclusion: Based on the experience to-date, it is expected that more efficient and consistent organization of joint inspections , combined with timely sharing of information on past and planned inspections should lead in the future to the possibility to free up inspectional resources and thus improve inspection coverage.

5.5 Positive assessment of the deliverables by the participant authorities

1. Overall experience/impressions

The exercise was found to be very positive by all the participants and a good step forward for information exchange and confidence building between authorities in an informal and efficient manner. It also allowed the participants to examine and assess their internal processes in comparison to those of the partner agencies and to promote best practices towards better collaboration. The reliance on other equivalent regulatory authorities was found to be a major asset for participants although some aspects of the cooperation were found to be logistically more complex than anticipated.

2. Systems/database support

The excel spreadsheet used for the Master List was found to be suitable for the compilation of retrospective and prospective inspection data at the initial stages of the project. However, as was pointed out during several teleconferences, the exchange was not fully satisfactory as it was dependent on regular forwarding of information from the participants to EMA, update of the Master List by EMA and then distribution to all participants of the updated Master list by the EMA.

It would be preferable to identify a secure host for a simple database, which enables the agencies to record and share data in real-time. The use of the future EUDRA GMP database module on inspection planning may solve the problem, though this won't be until 2012 at the very earliest.

A closely related issue is the need to better standardize the identification and nomenclature of sites and manufacturing processes to avoid misunderstandings especially with a view to the planning of joint inspections.

3. Communication and Program Coordination

Coordination of the pilot programme which was done by the EMA was found to be essential, although it was a major resource cost. In addition organization of periodic teleconferences was found to be of high importance for overall cooperation and program coordination although the key information was

exchanged by e-mails. The location of the participants in different time zones was an additional difficulty.

Recommendation: A common, live data source posted on a secure web page with timely updates by all participants would reduce some of the coordination efforts although some management will always be required.

4. Project Metrics

Project metrics were clearly defined and agreed upon in order to establish reporting. The project metrics included the number of requested and received inspection reports, joint inspections, extended scope reports and inspection outcomes. Recording of metrics were managed by the EMA for all participants and centralised in the Master List. Counts often were not entirely in agreement due to the definition of 'request' versus 'completed request', timeframe of counts, which firms were part of the pilot, as well as by type of information (full report versus inspection outcome summary) for example.

5. Tracking of information sharing and timeliness

Several logistical time challenges were met when the Pilot started. Specific contact persons and dedicated electronic mailboxes had to be identified and created in order to avoid delays in receiving requests and in sending reports. Some agencies' laws and regulations mandated redaction of these reports, which added delays to the overall exchange process. This was especially true when 'batches' of 10 or more reports were requested all at once. However, noticeable improvements were achieved by the end of the Pilot when participants had streamlined their own internal processes for the benefit of all participants.

6. Notification of joint inspections

Although joint inspections were not originally intended to be a major focus of the pilot, a number of joint inspections did take place. In addition a couple of joint inspections had to be cancelled due to the absence of effective advance planning and logistical issues. For all participants, planning has to begin very far in advance because available inspectors need to be identified early to enable pre-inspection planning, logistics etc to be undertaken. Inspection dates had to be found when inspectors of two participating authorities were available and when no restrictions on the possible inspection dates occurred due to specific public holidays or festivals typical in Asian countries.

A number of 'duplicate' inspections were identified, reflecting either inspections were inadequate to meet the needs of other parties, or lost opportunities for work sharing.

Recommendation; Planning of joint inspections should commence as early as possible and include the identification of the inspectors, so that the contact between the future inspection team can be established at the earliest stage possible.

7. Inspection Reports.

Although during the pilot, and in accordance with the agreed terms of reference, each participant issued a different report according to their own national/regional format after a joint inspection, the participants support the idea of preparing one single inspection report that could be used by all

participating agencies as it would maximize the benefits of the project. This could be further extended to include agreement to manage the inspection close-out by one agency on behalf of all participants (noting each agency would continue to have prerogative to determine any subsequent regulatory action). However, most participants have constraints that may limit from moving forward with this proposal, specifically, if the joint inspection report requires a modification to the existing format and structure.

Recommendation: As an interim measure a joint inspection report format and basis for content should be developed, so as to standardize what is used and understood in terms of coverage.

8. Feedback Forms

The feedback forms were considered to provide meaningful contribution to the evaluation of a joint inspection and to identify differentials between the participants. Feedback is critical to ensure a posteriori that the parties were able to inspect together using equivalent inspection procedures and GMP interpretations. One of the main information reported repeatedly on the forms was the usefulness of a pre and post inspection meeting of the inspection team to prepare and conclude optimally the inspection.

6. Conclusion

There was 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 are promising because collaboration is in place and palpable results of team work within the pilot programme were made available. However, a full continuous collaboration between the participants will certainly need additional efforts and innovative tools for real time exchange of information as there still appears to be some unnecessary duplicated inspections.

However, some of the tools developed during the pilot programme, especially the Master List with its wide ranging information on the API manufacturing sites supplying APIs to the three participating regions were found to be a particularly rich source of information. The master list also represented a model which could be used to design the future Eudra GMP module for sharing of inspection planning.

The project has contributed substantially to a better understanding of regional approaches to inspection and the building of mutual confidence.

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

7. Recommendations for future action

It appears from the experience gained so far that following measures could be envisaged rapidly in order to improve international collaboration for the benefit of public health:

- to include in a shared database an all extensive list of API manufacturers registered in the different participants countries in order to identify, all shared sites which should be subjected to regular work sharing but also identify other “critical” sites for example in terms of monopoly position, etc.;

- to consider the development and implementation amongst the participants of a common policy related to the re-inspection of shared sites located in third countries (frequency based on risk).

All partners are supportive in principle of continuing the API inspection collaboration, and extending the project to new partners. Some issues however need to be addressed for example caution was expressed about the possibility of opening the project wider at this point due to the added complexity.

New partners should have a clear understanding of expectations. They should be active contributors and there are some pre-requisites such as a functioning API inspectorate, implementation of ICH Q7, API sites of common interest and have the necessary confidentiality agreements in place with other partners.

In the short term, collaboration will continue within the existing format and will be extended to all EEA Member States rather than the initial limited number. Full integration of all EEA Member States may be dependant on the establishment of confidentiality agreements or equivalent, between the programme participants that do not already have such an agreement in place.

Nevertheless it is recognised that extending the programme to more comparable regulatory authorities and possibly the World Health Organisation would certainly need to be considered as a long term goal, as an efficient worldwide programme of inspections of APIs would be a notable benefit for public health globally.