March 2018

Report on the International Active Pharmaceutical Ingredient Inspection Programme 2011 – 2016

1. Executive summary

The purpose of the International Active Pharmaceutical Ingredient Inspection Programme is to create a framework for greater international collaboration and information sharing on Good Manufacturing Practice (GMP) inspections of Active Pharmaceutical Ingredient (API) manufacturers worldwide. This framework supports a better distribution of inspection capacity, allowing more sites to be monitored to increase the GMP oversight, and a reduction of unnecessary duplication by avoiding inspections of the same product or sites carried out by more than one participating authority within a similar time period.

The International API Inspection Programme has been operating since 2008, first as a pilot in late 2008 to late 2010, and as a full programme since January 2011. At the close of the pilot, a final report detailing the activities, accomplishments, challenges and path forward was issued. It was agreed that a formal assessment of the programme should occur, and to revise terms of reference if need be.

Since then, the programme has continued and has grown in both membership and sites of common interest. Increased cooperation and information sharing has kept duplication in check, and overall inspection coverage grew, benefiting global public health.

However, the analysis of the results from the past 6 years also indicates that some challenges remain to be addressed, such as a more active participation from all members of the group, the need for a formal electronic sharing platform and performing regular reviews of the programme results.

2. Objective

The objective of this report is to provide an overview of the functioning of the International API Inspection Programme for the period between 2011 and 2016. The report discusses the expected deliverables and key performance indicators as per the terms of reference of the programme. Finally, based on the results, future revisions to the objectives and operations of the programme are suggested.

3. Background and purpose

3.1. API Pilot

As a result of a Transatlantic Administrative Simplification Workshop organised in Brussels in November 2007, a pilot programme aimed at increasing international cooperation in the field of GMP inspection was conducted between 2008 and 2010, among a group of international partners. The pilot programme participating regions were Australia, European authorities and organizations (AFSSAPS/now ANSM, AIFA, EDQM, EMA, IMB/now HPRA, MHRA and ZLG) and the United States of America[1]; its scope included API manufacturer inspections in countries outside the participating regions.

The purpose of the pilot programme was to increase mutual confidence between regulators worldwide in the field of inspections and to achieve a better use of international inspectional resources through better communication, better co-ordination and collaboration on inspections of manufacturing sites of common interest. It was also aimed at facilitating a more risk based approach to 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.

At the end of the Pilot Programme a report was prepared to analyze the effectiveness of the programme in achieving its objectives, and to make recommendations for the continuation and development of the programme. For further details on the API Pilot Programme please refer to the API Pilot final report at the link below:
(http://www.ema.europa.eu/docs/en_GB/document_library/Report/2011/07/WC500108655.pdf)

Following the successful conclusion of the pilot it was agreed to maintain the cooperation established and to extend participation, to other interested authorities. A set of references on the programme operations and pre-requisites for participating authorities were drafted to support the operations of the programme and collaboration between partner organisations but also the expansion of the programme with new members. Details on the API Programme Terms of Reference can be found at

[1] Pilot participating authorities and organizations: France - Agence française de sécurité sanitaire des produits de santé (AFSSAPS) now Agence Nationale de Sécurité du Médicament et des Produits de Santé (ANSM), Germany - Zentralstelle der Länder für Gesundheitsschutz
bei Arzneimitteln und Medizinprodukten (ZLG), Ireland– Irish Medicines Board (IMB) now Health Products Regulatory Authority (HPRA), Italy - Agenzia Italiana del Farmaco (AIFA), United Kingdom - Medicines and Healthcare products Regulatory Agency (MHRA), 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 Australia - Therapeutic Goods Administration (TGA).

the following link:
(http://www.ema.europa.eu/docs/en_GB/document_library/Other/2012/02/WC500123489.pdf).

3.2. Member and observing authorities, changes since API pilot

Following conclusion of the Pilot and decision to continue the collaboration, the German ZLG left the programme due to necessary confidentiality commitments with all the German Laender inspectorates which is a requirement per the terms of reference. In addition, the Danish Medicines Agency (DKMA) joined the programme in 2011. All other members remained the same.

In January 2012, the World Health Organization (WHO) joined the programme as an observer (and therefore has been counted as a member for data purposes in this report). Two additional regulatory authorities joined the programme as observers: in 2015, Health Canada (HC) and in 2016 Pharmaceuticals and Medical Devices Agency (PMDA) Japan. However as the data received from these organization was limited to a short period of time, this was not incorporated in the report. All three observer organizations were formally designated as full members in 2016.

4. Activities of the programme

The main goal of the programme is to ensure an efficient channel of sharing of information and collaboration on GMP inspections of API manufactures in countries outside the participating region.

Over the past 6 years, the working group's activity has focused predominantly on sharing plans for and outcomes of inspections. On specific sites of high interest this includes exchange of inspection reports.

Joint inspections conducted during the pilot phase indicated a high degree of confidence among participating authorities. The practice was continued during the 2011-2016 reporting period as a means of continuing to enrich that confidence. This further created opportunity to exchange more information among all members on the inspections performed jointly, and as such a reporting form was setup to routinely capture inspectors' feedback.

5. Tools of the programme

5.1. Work sharing tools and platform for exchange

Work sharing tools in the program focus on exchanging of plans, outcomes and reports of inspections and joint inspections. The open lines of communication and individual member programs' own internal mechanisms for providing the inspection reports stabilized during the Pilot Programme, establishing a sound foundation as more participants joined.

As noted, joint inspections have been a commonly used tool for work sharing since the beginning of the programme. Participants acknowledge that these require substantial planning and resources compared to simply sharing inspection information. For example, an additional level of communication is required to coordinate the background information as well as the logistics within and across the inspection teams. These logistic challenges extend to the site to be inspected to accommodate inspectors from more than one region working together.

In addition to information directly exchanged during the programme meetings, additional information on inspection outcomes can be obtained through specific authority resources like EudraGMDP (EU), the DCIQA/"COMSTAT" platform (US FDA), and WHOPIRS (WHO).

It is noted that the level of information shared by each participant (members and observers) has varied, but overall has greatly increased over the 6-year period.

The majority of the information exchange has been done through either the monthly programme teleconference, or through bi-lateral or multi-lateral electronic exchanges. The US FDA organized the teleconferences and maintained the related documents, such as meeting minutes and an "active" subset of the Master List provided during the monthly teleconference. These teleconferences were aimed at sharing information about upcoming inspections, as well as the outcome and, if applicable, the follow-up of inspections performed. The information shared upfront via the teleconferences formed the basis of further bi- or multilateral exchange of documents and/or the organization of joint-inspections.

5.2. Master List and Inspection Planning Module

The programme maintains a Master List of mapping of API manufacturing sites of interest to the participating authorities, which is a tool envisaged as a priority since the beginning of the programme. The list consists of sites of common interest (i.e. of interest to at least 2 participating authorities) and serves as the primary focus for communication, information sharing and is designed to ultimately facilitate decision making for each individual participating authority. Specifically, the participating authorities agreed upon entry to the program that for sites of common interest they would:

- Take into account the results of an inspection conducted or to be carried out by another participating authority in planning their inspection activity covered within the scope of this project.
- Consider whether, instead of conducting an independent inspection, request one of the participating authorities to expand the scope of their already planned inspection to cover areas of interest to more than one participating authority.

The Master List has been expanded to include all third country (countries other than those participating in the programme) API sites of interest to any participant). For the sites included in the database, information is captured on the inspection history and future plans for the participating

authorities including, where available, the scope of these inspections. This spreadsheet is periodically published on the protected module of EudraGMDP for reference of participants.

How best to use and maintain data and information, such as that included in the Master List has been a persistent challenge in managing the programme. The volume of information included makes updating labour intensive, especially as only one party can have control of the document while collating written and verbal updates from all participants. The group currently lacks a common IT sharing platform and relies solely on bilateral access to information or emailing of data.

To improve exchange of information and to facilitate timely and accurate information availability, a proposal was made to use the European database for GMDP inspections and certification for this purpose (EUDRAGMDP planning module) instead of the current Master List.
This has been discussed and has been accepted by all the participants in the programme, and arrangements have been put in place e.g. writing access has been granted to the non-EEA partners, special templates have been created for entering information.

Technical details for implementation of the EudraGMDP planning module were finalized and representatives from the participating authorities have been trained as of mid-year 2017. The next phase of the implementation will be for each authority to enter data into the module. This step is recognized as being the most difficult part and requires a transition period when both the Master List and the EudraGMDP module should be used and a cut-off date agreed. It is expected that the full migration to EudraGMDP will continue throughout 2018, with the final steps depending on participating authorities' resource deployment.

5.3. Non-compliance Alerting and Regulatory action

One of the areas of exchange implemented within the programme is early feedback on sites identified as GMP non-compliant. Within the scope of existing confidentiality agreements, the participating authorities regularly exchange information on sites that are GMP non-compliant before they are made publicly available by the relevant authority (such as through Warning Letters or Statements of GMP Non-Compliance).

Such information not only covers overall outcome of inspections, but also specific areas where deficiencies were identified and are in need of enhanced oversight. Future re-inspection plans are also shared and, in some cases where interest is shared, other participating authorities in the program may choose to follow-up by proposing a joint inspection. In addition to inspection outcomes, participating authorities also exchange early notices of regulatory actions or license suspensions or any other national enforcement measures against non-compliant manufacturers.

6. Assessment 2017: Deliverables and key performance indicators

For the purpose of assessing the performance of the International API Programme between 2011 and 2016, it was agreed by the participating authorities that the same expected deliverables and key

performance indicators used to assess the Pilot Programme should be employed in the new review. The assessment itself was conducted through use of a survey sent to all participating authorities that included a set of ten questions with responses that often required specific objective indicators, but also sought more qualitative input on the workings of the programme.

The following expected deliverables were assessed in accordance with the programme's terms of reference (and will be discussed in details in the next section of the report):

- Increased transparency and visibility of inspections performed by participating authorities
- Overall increase in the number of API sites inspected by participating authorities
- Decrease in "duplicate inspections"
- Increase in the number of inspections performed of value to more than one authority
- Assessment of the deliverables by the participating authorities

6.1. Increased transparency of inspections performed by participating authorities

All participants acknowledged that communication and centralized updates of the Master List have evolved over the six-year study period of the programme. As such, more information shared by participating authorities was documented and circulated on a routine basis. Additionally, transparency and visibility of the participant's inspection programmes increased substantially. It was noted by some, however, that the goals of the programme depend upon full participation of all members and this participation level varied due to resource constraints, staff turnover and evolving priorities in the participant authorities.

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

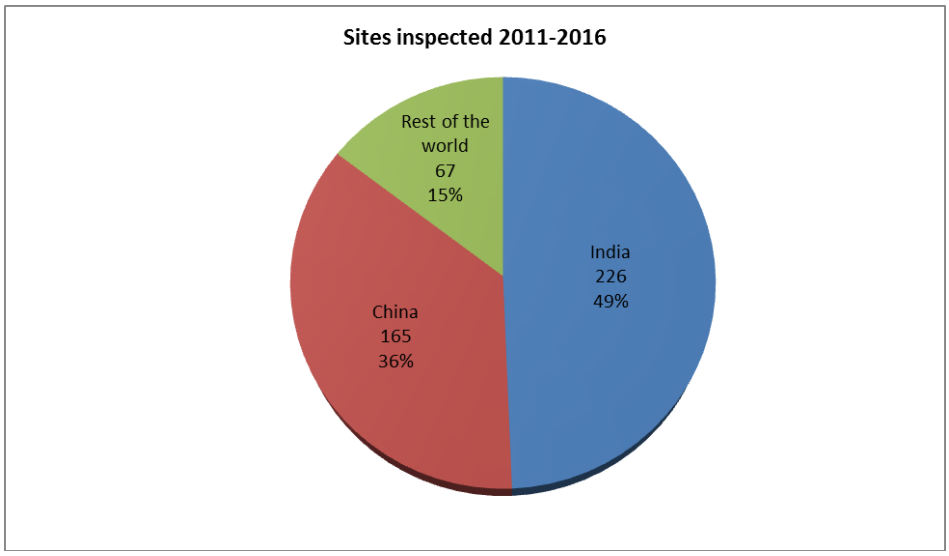
For the time period of calendar years 2011-2016, a retrospective review was conducted separate from the use of the Master List. Authorities were asked to submit all third country API inspections performed in the time period with dates, outcome and whether or not it was a joint inspection, as well as indicate any sites of common interest that were not inspected in that time frame. [Note that in the data below, the term "European" in the context of sites of common interest or firms that were inspected refers to manufacturing plants that are part of EDQM's Certification of Suitability scheme, centrally authorized medicinal products and national marketing authorisations in EU member states participating in this programme.]

- 944 unique sites* were submitted by 9 reporting authorities (EMA, AIFA, ANSM, DKMA, MHRA, EDQM, FDA, TGA, WHO).

  **"Unique" refers to an inspectable unit (that may be part of a larger campus of multiple 'sites'), that was submitted by one or more authority. It is noted that this number is slightly smaller than the inventory during the pilot. There are many potential reasons for the change, including removal of duplicates, change in participating authorities, sites that permanently closed or sites that are no longer of interest to the participant authorities.*

- 458 unique sites (49% of all sites submitted) were of common interest.
- These 458 sites were located in 18 countries: primarily India with 226 sites, China with 165 sites, and the remaining 67 located in 16 countries around the world.

Figure 1.



An overview of the number of sites of common interest (i.e. of interest to at least 2 participating authorities) shared between the authorities is provided below.

Table 1.

Number of sites of common interest shared between at least 2 participating authorities			
	TGA	FDA	WHO
European Authorities*	136	350	41
TGA	x	176	17
FDA	x	x	50

*Including EDQM

Table 2.

Number of sites of common interest shared among 3 participating authorities	
European Authorities*-TGA-FDA (no WHO)	117
European Authorities*-TGA-WHO (no FDA)	15
European Authorities*-FDA-WHO (no TGA)	30
FDA-TGA-WHO (no European Authorities*)	17

*Including EDQM

Table 3.

Number of sites common interest to all participating authorities	
All Participants	15

Of the 458 sites of common interest, there were 1333 total unique inspections by the participating authorities over the 6-year period, resulting in an average 2.9 inspections per site in the review period.

Table 4.

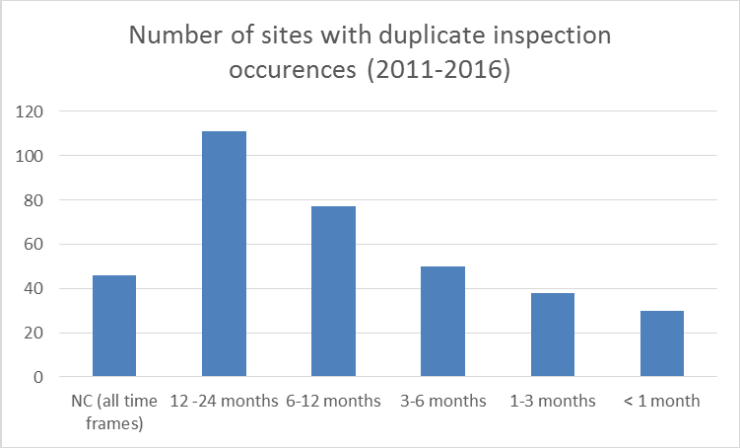
Total inspections by all participating authorities (2011-2016)	
European Authorities*	310
FDA	762
TGA	130
WHO	131
Total Unique Inspections	1333

* Including EDQM

6.3. Decrease in "duplicate" inspections

For the purposes of the API Programme, a "duplicate" inspection is defined as two or more authorities inspecting the same site, within a proximity of time (in intervals of less than 1 month, 3 months, 6 months, 12 months, 24 months.) In the API Pilot report, the time window of "greater than 24 months" was also used. However, for the purpose of this report, it was decided that inspections conducted on an interval greater than 24 months would not be considered duplicates, as in some cases an authority may consider 24 months to be an appropriate time frame for re-inspection following recognition of an outcome from a trusted authority. To also note that an additional level of complexity, in some cases it might not be appropriate to classify an inspection of the same site as duplicate if the scope of inspections was different.

Figure 2.



Sites that received 'duplicate inspections' as a result of a GMP non-compliant outcome of an inspection were reported separately as these are not necessarily considered as a duplication of inspection. The reason for this is that most participants have a policy to inspect a non-compliant site after non-compliance information is received from a partner authority in order to decide if further regulatory action is required. It was noted that industry wasn't aware of this approach and sometimes regarded these re-inspections as duplication.

Table 5.

Number of sites with duplicate inspections 2011-2016			
	Number of sites	**Number of inspections**	**Avg. number of inspections/site**
Duplicate inspections for site with at least one Non – Compliance	46	107	2.3
Duplicate inspections for compliant sites	205	358	1.7

Overall, 28% of the total number of sites inspected during this period had at least one non-compliant inspection, and were inspected on average 3.6 times. This is compared to the 72% of sites with a compliant history that were inspected 2.7 times per site in the study time frame. It can be concluded that the inspection rate of sites that have been deemed non-compliant following an inspection is higher than the duplication rate for sites that have positive inspection outcomes. Most participants in the programme did not specifically track how often use of the Master List or information from the programme led to a decision to not inspect a site that otherwise would have been. However, some did. For example, in 2016 EDQM took into account 36 inspections

performed by EU authorities, which led to their removal from EDQM's inspection plan.

There are several reasons that could explain some of the duplicate inspections:

- The Master List 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; or was not updated in a timely manner to allow for alternate planning.

- 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, administrative or legal reasons. For example, inspections triggered by company requests to be granted a EU GMP certificate. Also, not all authorities have procedures in place yet to extend the validity of a GMP certificate based on an inspection with the same scope performed by one of the other participants.

- Delayed communications within different entities of the participants' organization regarding the timing for notification to the companies.

In conclusion, efforts to reduce the number of duplicate inspections should be continued as it allows more strategic use of inspectional resources and reduces the burden to all participants, including on the API industry.

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

There are ways that knowledge about another region's inspection can be of value to more than one participating authority beyond simply minimizing duplication of inspections, overall:

- Authorities may recognize each other's inspection outcomes, allowing them to defer inspection. EDQM reported that inspections of 22 sites were postponed, because they had been subject to on-site inspections by non-EU participants of the API project.

- Simply sharing reports of an authority that performed an inspection facilitates oversight without the need to perform an on-site inspection. This was noted by participants as part of the value of the programme, often leading to clarifying conversations in monthly programme teleconferences as well as follow-up meetings for more detailed discussion. For example, EDQM provided more than 25 inspection reports to authorities in 2015-2016.

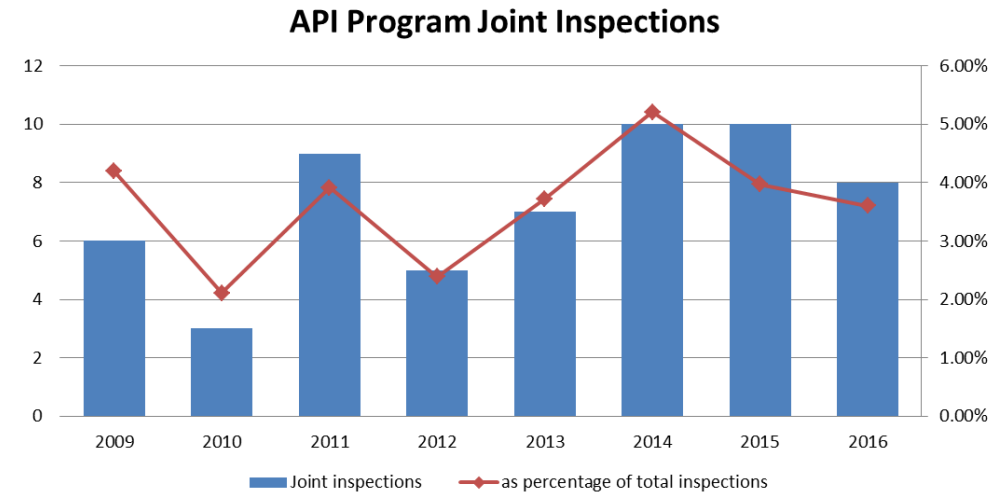
- Review of an inspection report by another authority can help a region prepare for their own inspection and/or if mutually agreed to follow-up the Corrective and

Preventive Actions (CAPA) implementation related to selected severe GMP violations.

- In some cases, review of another authority's report may stimulate interest in conducting a joint inspection.

There were 47 joint inspections conducted at 43 sites in the six-year period of review. Four sites hosted joint inspections twice in the time period.

Figure 3.



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6.5. Assessment of the deliverables by the participating authorities

One of the key performance indicators identified was the positive assessment of the deliverables by the participating authorities. To assess this indicator, a questionnaire was developed and circulated amongst the participants in 4Q 2016. The objective was to assess the level of satisfaction of the responders with regards to how the programme has managed to achieve a better international collaboration and information sharing to help to better distribute inspection capacity on API Inspections in third countries.

Overall, all the authorities participating to the study indicated that they are satisfied with the programme operation, with 64% of respondents indicating a high level of satisfaction. Participating authorities indicated that the programme is a good example of international communication and collaboration and building mutual confidence, and improvements to the programme should come with more involvement of the individual participating authorities in the activities of the group.

The survey provided information on the general opinion of authorities that participate to programme and their support for the programme to be continued. This type of information had not been captured in previous reports, and the survey proved to reveal information that would

otherwise not have been identified during the analysis of the expected deliverables and key performance indicators.

7. Overall assessment of deliverables

Based on analysis of the individual deliverables and key performance indicators as communicated above, the migration from a Pilot Programme into a permanently running scheme can be considered successful as the clear majority of the objectives were achieved.

The data show that there was an increase in the number of API sites inspected by participating authorities included in the programme and this increase has supported the exchange of information on inspections which in return supported a better GMP oversight for the participating authorities.

More information was shared by participating authorities and therefore the programme brought more transparency and efficiency for the planning and realization of GMP inspections.

Some of the recommendations that had been put forward as a result of the report on the pilot international API inspection programme were not achieved within the period covered by this report. These recommendations were to develop and implement:

- A shared database with a comprehensive list of API manufacturers registered in the different participants' countries
- A common policy framework related to the re-inspection of shared sites located in third countries

These ambitious undertakings would likely require many years of work beyond what has occurred to date. Nonetheless, overall the level of satisfaction of the participants to the survey indicates that the programme is beneficial for the authorities in a number of ways. All believe that this also translates into value for the API industry because of reduced workload to host inspections.

8. Recommendations for future action and path forward

Going forward, based on the conclusions of this report, the participating authorities recommend the continuation of this international collaboration on API Inspections. In addition, while the goals of the programme remain the same, several recommendations for improvement were proposed during the review.

The following proposals for further development to the programme are made:

- Establishment of a formal, central repository with write access hosting the Master List, inspection reports, etc.
- Amplify the usage of the EudraGMDP planning module by all EEA members and API Programme participants

- Guidelines and further remote training sessions amongst participants on how to prepare, conduct and follow-up on joint inspections
- Encourage participants to the API Programme to a more active participation and input during the monthly teleconferences, as well as integration of information within the respective authorities as necessary

It is also agreed that the participants should determine clear deliverables to be assessed at regular intervals within the programme, to include:

- Review of re-inspection frequencies/schemes amongst participants
- Explore how to maintain metrics such as: number of inspections deferred, number of inspection report exchanged
- Increase visibility of the programme to industry
- Promote the approach of this group to other authorities worldwide, and include new participants if there is interest
- Promote the need to amend national regulations in order to lift the legal requirements that lead to technically unnecessary duplication of inspections

With increased participation, deeper collaboration and enhanced information sharing including technological and legal advancements, the full goals of the programme can be met.