API manufacturer's experience with a global change: a case study

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A global change: a case study

What / who is Marieke van Dalen

- Working for Aspen Oss B.V. in the Netherlands as Global Regulatory Specialist
- Over 30 years of experience in the regulatory field
- Board member of APIC (the European Active Pharmaceutical Ingredients Committee)

A global change: a case study

- Description of the change
- The strategy
- Countries and customers involved
- Informing the customers
- Feedback from the customers
- Informing the health authorities
- Timelines
- Discussion
- Conclusion

Description of the change

- The API in focus is produced in a two step synthesis from the Regulatory Starting Material (RSM) with additional purifications. (Note: the RSM itself is also an API).

- RSM -> Intermediate -> Intermediate pure -> API crude -> API semi pure -> final API

- In the first purification step of the API (the step leading from API crude to API semi pure) trichloroethylene was used.

- As a result of the publication of EU Commission regulation 348/2013 (published April 18, 2013) trichloroethylene needed to be replaced in production.

Description of the change

- After investigations it was shown that replacement by toluene was the best way forward.
  As toluene was new in the synthetic route from the RSM to the API and as it would be used in the final steps of the synthesis, a specification for toluene in the API thus also needed to be introduced. And obviously the trichloroethylene specification could be removed.

- We evaluated this proposed change as a **major change**.

- We took the opportunity to combine this (SHE induced) change with the replacement of dimethylformamide (ICH limit 880 ppm) by less toxic (ICH limit 3000 ppm) methanol in the same step.

Description of the change

- Methanol was already used in the process (final purification step) so no additional specification was needed there. The specification for dimethylformamide (no longer used) could obviously also be deleted.

- Since benzene may be present in small amounts in toluene, as a confirmation some API batches were again tested on the absence of benzene. As the results were consistently found to be <0.6 ppm (LOD of the method), that means below 30 % of the ICH Q3C option 1 limit for benzene, there was no need for routine testing in the API.

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The strategy

The strategy was as follows:

•Production of three full scale validation batches, and issuance of a validation report.

•All customers with a regulatory commitment were informed to
* get an idea of what they expected from us (with respect to information and to amounts of validation material) and
* inform them of what we expected from them in terms of timelines and information. Extremely important as the EC regulation dictated the cease of use of trichloroethylene as per April 2016.

The strategy

- Following authorization of the validation report, a so-called qualification document was written which could be used as supportive information for both customers and regulatory authorities and in which the equivalence of post-change material vs. pre-change material was shown.

- Also customers without a regulatory commitment (usually customers operating in countries with less or less clear regulatory requirements) need to be informed as the proposed changes in solvents and specifications also impact the customer files and certificates of analysis.
  Note: we do not always know where these files (“open part information”) are being used as regulatory documents!

The strategy

- In all customer correspondence we communicated a date from which we expected to only produce and deliver post-change material.
- As the final purification step remained unchanged there was no expectation for different behaviour of the API in Drug Product formulation.
- As the final date was set by a EU regulation, it was not subject to negotiation. It was therefore very important that customers gave us their feedback in a timely manner on the amount of bridging stock of pre-change material they would need.

The strategy

- Obviously, as this change is a Prior Approval Supplement in the US and a Partial Change Application in Japan, we acknowledge that authority approval needs to be obtained in some regions before introduction of the changed material.

- It is however the customer's responsibility to provide us with information on their bridging stock requirements.

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Countries and customers involved

- Europe: CEP (15 customers, 82 applications)
- USA (2 customers)
- Canada (1 customer, veterinary application)
- Japan (3 customers)
- India (1 customer, Import Licence)
- Russia (1 customer, no Drug Master File, a Normative Document)
- Taiwan (2 customers, using CEPs, no Drug Master File)

- Please note: more countries may be involved (dealt with by customers using the Open Part information).
- Some customers are active in more than one region.

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Informing the customers

- All customers were informed of our intention in January/February 2015 by means of a Customer Notification: a letter including the qualification document and replacing modules for the customer files that were in their possession.

- It was clearly stated what the reason for the change was, what the timelines were and what type of feedback we expected from them.

- For customers not having any regulatory commitment we announced that we expected to start shipping post-change material as from September 2015, which gave them more than 6 months to make arrangements if any.

Informing the customers

- In the meantime we had requested a revision of our CEP at EDQM.

- When the revised CEP was received we sent another letter (with the completed CEPs) to all CEP users (end of June 2015), indicating that we would start supplying them by September 2015.
  Using the CEP this was a Type Ia change for them, meaning that the variation needs to be filed within one year after implementation of the change (do and tell).

Informing the customers

- In September 2015 we could start supplying post-change material to the majority of the customers.

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Feedback from the customers

- Most responses were confirmations of receipt and acceptance of our proposals and timelines: for customers operating within the EU and using the CEP, obviously no problems were expected since use of the CEP means that for them this is just a Type Ia variation.

- Not so many questions for material to be used for in-house studies by our customers. A few questions on the date of availability of 6 months stability data for the API.

- One customer required an additional assurance for our claim that polymorphism would not be changed as the final purification step was not altered. Additional proof was sent.

Feedback from the customers

- Japanese customers had an additional problem: at that time the average time for a Partial Change Application was still up to 18 months and we had informed them that there would most probably be an additional Partial Change Application for this API within a 2 years time period. Two of them preferred to wait for that second one and then file one Partial Change Application.
- This meant they had to make very detailed and correct bridging stock calculations.
- As per PMDA advice (following a consultation), we put the changed process in the J-DMF as an alternate process to the pre-change process in order for our customers to have the possibility to use the stock of pre-change material. This also meant two sets of (residual solvents) specifications!

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Informing the health authorities

- EDQM: EDQM was informed in December 2014. As there are customers who operate both in the EU and other countries with the CEP and in non-CEP countries, we started with the request for revision of the CEP.

  One question was raised by EDQM (not related to the change) in February 2015 and once the question had been answered and the answer was found acceptable, the revised CEP was issued in April 2015.

- FDA: The amendment for the FDA was sent in January 2015, so approximately at the same time as the Customer Notifications. The customers filed their PAS and received approvals without further questions from the FDA.

Informing the health authorities

- Canada (veterinary): The authorities were also informed in January 2015. No questions were raised and the customer could be delivered with the post change material as from September 2015 (as announced in the customer notification).

- Japan: The package to inform the PMDA was prepared and sent through the in-house caretaker in February 2015.
  A series of questions was asked in February 2016, only few related to the actual change (e.g. questions on implementation of Q11). Answers were submitted and lead to a second set of questions in June 2016.

Informing the health authorities

- Japan (continued): from the Japanese customers one has submitted the PCA and has received approval. The other two customers want to file the change at a later date (to combine with the other Partial Change Application). In practice this means that these two are still supplied with and using pre-change material.

- Russia: as this change leads to changes in the normative document, our Russian agent was supplied with all information In February 2015. The addendum to the normative document was issued on June 30, 2016, so the Russian customer could from that moment onwards also be supplied with post-change material.

Informing the health authorities

- India: Informed through our Indian agent in February 2015. Many non-related questions (procedural: attestations etc.), but no questions were raised on the change itself.

Informing the health authorities

- So far, so good….
  All countries have evaluated the change and are okay..
- But remember “some customers have registered in some countries with just Open Part information”….
- Japanese customers delayed.

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Timelines

- Our planning was to cease production of this API using trichloroethylene as from September 2015.

- The last batches actually produced were released in November 2015.

- However, supply of pre-change material is still ongoing:
  * to two Japanese customers
  * to customers who have (also) obtained registrations in other countries, often countries with unclear change regulations. In fact these customers have no idea when to expect approvals in such countries.
  * one customer still needs to file the change in Brazil.

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Discussion

- As said, not many questions on the change itself.
- Often the opportunity was taken by the health authorities to get one or more unrelated points clarified
- “The regulated world” has fixed timelines. Even though these are not harmonized this gives the opportunity to the finished dosage form manufacturers to estimate the bridging stock they need.
- The less regulated countries have different or no guidelines, not always clearly described, and often the outcome is unpredictable.
- This is a problem for the finished dosage form manufacturer, but in the end also for the API producer

Discussion

- A more harmonized change control approach would be very welcome.
- Harmonization of timelines would also be a step forward.
- Acceptance of CEPs outside the EU has proven to be very useful, we are happy that more and more countries are willing to accept/recognise the CEP system.
- ICH Q12 may be able to help te reduce differences.

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Conclusion

- It is impossible to predict a timeline for the worldwide acceptance of a change that needs to be filed globally.
- There is a need for harmonization on the classification of changes and of the timelines that are being set.
- Questions not related to the change can slow down the change introduction, which is undesirable, specifically for changes that are made because of SHE reasons.

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