The Zelboraf story

Sharing experience on different drug substance designations

Cinzia Gazziola, PhD
Pharma Technical Regulatory Manager
F. Hoffmann-La Roche, Switzerland

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Table of contents

Background on Zelboraf

Zelboraf drug product

General information on drug product

- Marketed globally as Zelboraf, 240 mg film-coated tablet for the treatment of BRAF V600 mutation-positive unresectable or metastatic melanoma.

- The INN of the compound is vemurafenib, BRAF Kinase Inhibitor .

- Manufactured using conventional pharmaceutical technology and operation steps as dry granulation (roller compaction), compression and film-coating.

Zelboraf drug substance

Crystalline vs co-precipitated non-crystalline/amorphous with polymer

Active ingredient: a crystalline powder that can exist in several polymorphic forms, the process consistently delivers one of them

Challenge:
BCS Class IV compound, practically insoluble in aqueous media across the pH range from 1 to 7.5. ⇒ very low bioavailability ⇒ dose escalation during Phase 1 was not possible

- To achieve a higher bioavailability a new process developed to stabilize the non-crystalline form of API: non-crystalline solid dispersion of vemurafenib and of the polymer hydroxypropyl methylcellulose acetate succinate (HPMC-AS):
- The more soluble non-crystalline state was stabilized in form of a Micro-precipitated Bulk Powder (MBP)
- 5 fold increase in bioavailability observed using the MBP formulation compared to the formulation using micronized crystalline API

Regulatory Strategy

Regulatory Strategy in Clinical Phase

IND/IMPD approach

- Phase 1 clinical trial started with capsules containing API crystalline form and a conventional dry blending process. Due to several challenges on dissolution and dose escalation, the non-crystalline micro-precipitated bulk powder (MBP) was developed and used.
- For further clinical phases the MBP was used for new strengths and dosage form (i.e. film coated tablets).
- The definition of API was challenged during clinical submissions (see question below):

  The blending of an active substance and an excipient is considered as the first step in the manufacture of the medicinal product, and therefore does not fall under the definition of an active substance. Upon future registration, the dossier should be re-structured to describe vemurafenib in the drug substance section and the manufacture of the API-polymer complex in the drug product section; relevant sections should be amended where appropriate. Since the drug substance manufacturing site(s) perform the first steps of the drug product manufacture, GMP requirements for finished products are applicable. (Belgium)

Regulatory Strategy for NDA/MAA

Pre-discussed the proposal to submit the stabilized API (MBP) as drug substance with EMA and FDA (2009)

- **The question:** «Does the agency agree that the co-precipitated non-crystalline API-polymer complex may be designated as the drug substance?»
  - **EMA**: Agreed to the designation of drug substance to be the co-precipitated non crystalline API with stabilizer (MBP) as considered to be " *essential to produce an oral drug product of optimal stability and bioavailability"* (Scientific Advice received in 2009). This is in line with the EMA Q&A document on API mixes ("in certain circumstances, i.e., stability or safety reasons, the applicant can submit data on such a mixture under part 3.2.S).
  - **FDA**: Did NOT agree with the proposal because "*the API-polymer complex cannot be designated as the drug substance because of the absence of chemical bonding (covalent or ionic) between the pharmaceutically active moiety and the hydroxypropyl methylcellulose acetate succinate polymer. Since the interaction of the API and the polymer is physical in nature, the polymer is considered an excipient, which may influence the form, bioavailability and dissolution of the API. The non-crystalline API should be designated as the drug substance.*" As a consequence the co-precipitated API-polymer is designated as "DP intermediate".
  - Canada and Japan aligned with FDA, whereas all remaining countries followed EMA opinion.

Considerations

Consequences on dossier structure and review

Different designations for API vs stabilized API (MBP)

- **Different** regulatory dossier structures for different markets with complex life cycle maintenance (see Slide 11)

- **Extensive Q&As** on the MBP on characterization, uniformity, stability, control of shipping conditions during the complete transport chain, sound justification of hold time for the amorphous material supported by stability studies with “aged” MBP (see Slide 12)

- **Start and estimation of DP shelf-life** (crystalline API designated as DS): the start of shelf-life with tableting instead of manufacturing date was questioned (see Slide 12)

✓**Start of shelf-life:** despite the different designations for drug substance, agreement was reached on the start with the tableting step (usually is the mix of API with excipients)

Considerations on dossier structure

Examples of Sections for EMA/Global and FDA/HC/PMDA

Section	FDA/HC/PMDA (i.e.MBP as DP intermediate)	EMA/Global (i.e. MBP as API)
S.2.2_Drug Substance Manufacturing Process	Last step is API (not MBP)	Last step is the MBP
P.3.3_Drug Product Manufacturing Process	MBP as DP intermediate	MBP as DS
S.2.4_Control of Critical Steps and Intermediates	Description of API intermediates	Extensive description of the API as one of the intermediates for the MBP
P.3.4 _Control of Critical Steps and Intermediates	Extensive description on MBP incl control strategy and stability	Standard controls for manufacturing process of solid dosage forms
S.7.1_Stability Summary and Conclusions	Stability on the API	Stability on MBP
S.2.6_Manufacturing Process Development	Control strategy focussed on API	Control strategy focused on MBP
P.2_Pharmaceutical Development	Drug substance forms a solid dispersion with a polymer	Drug substance is a solid dispersion of API with a polymer

Considerations on review of NDA/MAA

Examples of questions received from EMA (i.e. MBP agreed as API) and FDA (i.e.MBP as DP intermediate)

- Drug Product Expiry: The proposal that expiry of the MBP begins at the milling step is acceptable if the milling is completed within 30 days of the initial manufacturing step, in accordance with GMPs.(FDA + discussions with Office of Compliance)
- Shipping of the MBP -Provide the quality control measures for the shipping and handling of the MBP to assure the absence of crystallinity in the MBP after shipping to the milling site and then to the tablet manufacturing site. What are the controls for temperature and relative humidity during the entire shipping, including time spent at the loading dock. Please provide a shipping protocol. (FDA)
- Manufacturing - The Applicant is requested to discuss the uniformity of content of drug substance in MBP in more detail. The discussion should encompass moment, speed, order and amount of precipitation as both the active moiety and the polymer are fully dissolved and precipitation is performed slowly by acidification and cooling. Moreover, absence of a drug substance specification test for the uniform distribution of vemurafenib in the drug substance should be justified. (EMA)
- Stability of the drug substance - The manufacturing date of the drug substance is assigned by the Applicant as the date of milling of MBP. This is not acceptable. As the stabilization of the active substance (vemurafenib) can be seen as an intermediate production step, the date of manufacturing should be set at the date of manufacturing vemurafenib, i.e. at the end of step 4 of the synthesis. (EMA)

Consequences of co-precipitated non-crystalline API/ polymer as “DP Intermediate”

GMP aspects

2 options for manufacturing the designated “DP intermediate”:

1. **At the drug substance facility**

   Risk analysis was performed for the manufacturing in chemical plant against GMP requirements and **several potential gaps identified:** e.g. flow of materials, zones, storage, pest control, water, cleaning validation

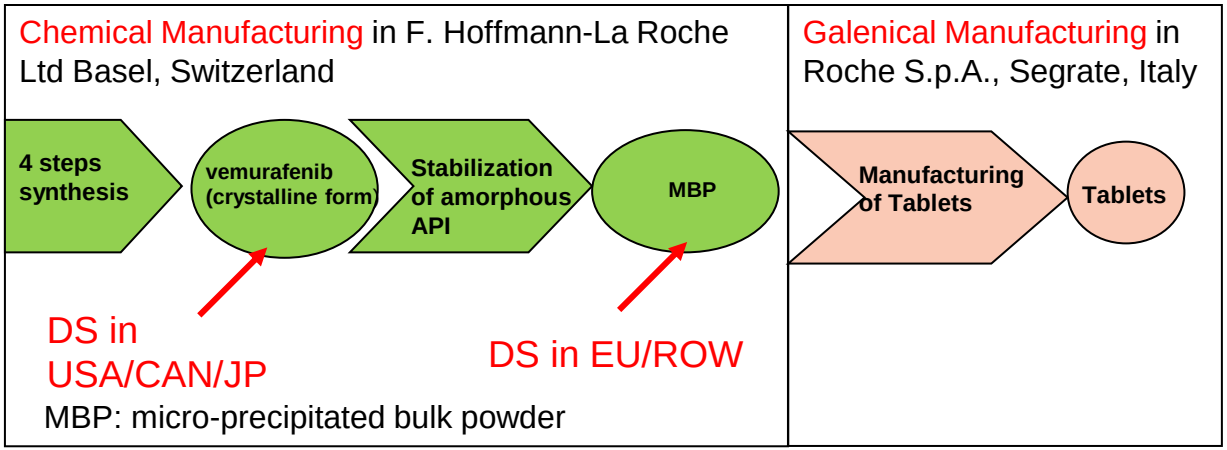
   ⇒ **significant re-design and time needed to close the gaps**

2. **At the drug product facility**
   - Large amounts of organic solvents used in manufacturing: quality and safety risk
   - **Not possible to manufacture without significant transformation of the facility with disruption of the supply for commercial products**

✓**Followed up with** FDA compliance division: **agreement reached** to manufacture the drug product intermediate according to ICH Q7 regardless of the drug substance designation (see slide 14)

Manufacturing of Zelboraf and API designation

DS and DP manufacturing sites



Considerations for subsequent submissions

Non-crystalline API stabilized with excipient proposed as drug substance or DP intermediate

- An holistic control strategy approach is key for the overall quality of the product delivered to the patients regardless of the API vs DP intermediate designation
- Different API designation results in different regulatory dossier with high burden on lifecycle
- GMP aspects of manufacturing DP intermediates in a chemical facility or in a drug product facility should be pre-discussed with HAs along with in depth risk assessments
- Lean supply chain needed to minimize risk of stock out due to shelf life limitation considering hold and manufacturing times of the DP intermediate

Conclusions

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The challenging experience with Zelboraf discouraged the company to invest more time and effort in getting global acceptability of the designation of an API mix with an excipient as API.

Nevertheless, there is still interest in getting global approval of API with excipients/co-processed API designated as API due to several aspects:

- Improved quality, supply security and flexibility;
- A globally harmonized dossier with easier/faster lifecycle maintenance;
- More innovative and sustainable manufacturing (e.g. co-processed API, greener manufacturing technologies).

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Doing now what patients need next