MIRELLA CALCINAI, M.D.

Dr. Calcinai graduated from Medical School and then specialized in Otorhynolaryngology at the University of Pisa, Italy, where she also lives. Dr. Calcinai joined one of the companies that at a later stage merged into Kedrion in 1991. She has been working in the regulatory office since 1997 and has been leading the Italian office since 2004. After the acquisition of HUMAN Bio Plazma Kft (HU) and the setting up of Kedrion Biopharma Inc. (US) Dr. Calcinai took responsibility for Kedrion's global regulatory activities.

KEDRION BIOPHARMA

Managing Post-Market Changes in Diverse Regulatory Landscape

Case study: non-EU Europe and Asia

Mirella Calcinai
Global Regulatory Affairs Director
Kedrion

Changes

- Two variations submitted in EU through MRP and national procedure

  addition of an intermediate manufacturer

  July - August 2012

  addition of a new therapeutic indication

  May 2012

- Submission and approval in Europe non EU and ASIA between 2012 and 2016

Addition of an intermediate manufacturer

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Type of application according to Reg. 1234/2008 and further amendments:

Type II B.I.a.1. Change in the manufacturer of a starting material/reagent/intermediate used in the manufacturing process of the active substance or change in the manufacturer (including where relevant quality control sites) of the active substance, where no Ph. Eur. Certificate of Suitability is part of the approved dossier
e) The change relates to a biological active substance or a starting material/reagent/intermediate used in the manufacture of a biological/immunological product.

SCOPE	**Addition of an intermediate manufacturer**		
		Intermediate:	**Medicinal product**
		Cryo-paste	FACTOR VIII
		Fraction II	IVIG
		Fraction V	HUMAN ALBUMIN
APPROVAL TIME (AIFA Approval)	FACTOR VIII		14 months
	IVIG		9 months
	HUMAN ALBUMIN		9 month

Addition of an intermediate manufacturer EU package

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‘‘core’’ EU package

Module 2.3 (QOS) Amended sections)
Module 3 Amended sections

- Stability of the intermediate manufactured at the proposed manufacturing plant (3 lots)
- Stability of the FP manufactured with the intermediate of the proposed manufacturing plant (2 lots)
- Process and Analytical Technology Transfer Reports
- Process Validation of the intermediate
- Comparability Study of the intermediates manufactured by the current and proposed manufacturer (3 batches vs 3 batches)

Comparative table between batch analysis on 2 FP production batches manufactured with the intermediate of the proposed manufacturing plant and 3 FP production batches manufactured with the intermediate of the current manufacturing plant

List of non EU European and Asian countries

VARIATION REQUIRED

- ALBANIA
- INDIA
- IRAN
- ISRAEL
- KOSOVO
- MACEDONIA
- SERBIA
- SINGAPORE
- SRI LANKA
- SWITZERLAND
- THAILAND
- TURKEY
- UKRAINE

VARIATION NOT REQUIRED (*change implementable*)

- BANGLADESH
- BOTSWANA
- GEORGIA
- HONG KONG
- INDONESIA
- LEBANON
- MACAU
- PAKISTAN
- RUSSIA
- VIETNAM

VARIATION INCLUDED IN THE RENEWAL DOSSIER

- AZERBAIJAN
- BELARUS
- ISRAEL
- KUWAIT
- BOSNIA HERZEGOVINA
- IRAQ

non EU European and Asian countries where variation is required

KEDRION BIOPHARMA

VARIATION REQUIRED

- ALBANIA
- INDIA
- IRAN
- ISRAEL
- KOSOVO
- MACEDONIA
- SERBIA
- SINGAPORE
- SRI LANKA
- SWITZERLAND
- THAILAND
- TURKEY
- UKRAINE

PARALLEL APPLICATION ALLOWED
Submission in parallel with Italian Variation

PARALLEL APPLICATION NOT ALLOWED
Submission after Italian Approval of the Variation

Overview of requirements and timing

KEDRION BIOPHARMA

COUNTRY	VARIATION PACKAGE &OTHER LOCAL REQUIREMENTS	DOCUMENTS REQUESTED BY LOCAL AUTHORITY DURING REVIEW	APROVAL TIME
ALBANIA	EUROPEAN PACKAGE	none	9 months
KOSOVO	EUROPEAN PACKAGE	none	2 months
MACEDONIA	EUROPEAN PACKAGE	none	6 months
SERBIA	EUROPEAN PACKAGE	none	9 nonths
INDIA	EUROPEAN PACKAGE	none	6 months (if no feedback from local CA)
SWITZERLAND	EUROPEAN PACKAGE	None	5 months
TURKEY *	EUROPEAN PACKAGE + commitment to provide AIFA approval and updated stability data (once available) until study completion	None	3 months (ALBUMIN) 8 months (IVIG and FVIII)
IRAN	EUROPEAN PACKAGE	See following slide	Still pending
SINGAPORE	EUROPEAN PACKAGE + list of countries where new manufacturer is approved	None	8 months
SRI LANKA	Only admin docs + batch analyisis data	None	3 months
THAILAND	EUROPEAN PACKAGE	None	8 months
UKRAINE	EUROPEAN PACKAGE	None	10 months

Iran

- **A "parallel application" was accepted by the Iranian MOH without the AIFA approval at time of submission (which is a standard variation requirement) in September 2012**
- **KEDRION S.p.A. submitted a letter committing to provide the AIFA approval once available**
- **A standard requirement from the Iranian MOH is the inspection of the new manufacturing sites**
- **During the evaluation of the variation dossier, the MOH required the following additional data (provided on August 2013):**
  - ✓ List of countries where the variation was approved
  - ✓ Updated stability data
  - ✓ AIFA approval
  - ✓ Site Master File of the proposed intermediate manufacturing site
- **Based on the last provided data and the agreement on the inspection dates (March 2014), a special import license for unlimited quantity and validity specifically for the medicinal product ALBUMIN manufactured starting from the new intermediate was issued by the Iranian MOH (August 2013)**
- **The GMP inspection was carried out in March 2014**
- **Additional MOH requests were made by Iranian MOH in June 2015:**
  - ✓ Certificate of analysis of FP manufactured from intermediates of the new manufacturer
  - ✓ CPP
  - ✓ Updated stability data on FP
  - ✓ Validation data and in-process controls results
  - ✓ Replacement pages of the dossier (sections 3.2.S.2.1 and 3.2.S.2.2)
- **The variations are still pending.**

Turkey

- **A "parallel application" was accepted by the Turkish MOH in September 2012 without AIFA approval at time of submission.**
- **KEDRION S.p.A. submitted the complete European package + commitment letters to provide the updated stability data upon study completion and the AIFA approval, once issued**
- **At the end of the evaluation process, the Turkish MOH issued the variation approvals based on the above mentioned commitments fulfillment (most updated stability data + AIFA approval).**
- **For IVIG the Turkish authorization was issued after the approval of the same variation in Italy. For FVIII and HUMAN ALBUMIN the Turkish authorization was issued before AIFA Approval.**

Product	AIFA Approval in Italy	Approval in Turkey
FACTOR VIII	09/09/2013	25/05/2013
IVIG	09/05/2013	16/06/2013
HUMAN ALBUMIN	02/04/2013	14/12/12

Addition of a new therapeutic indication

Type of application according to Reg. 1234/2008 and further amendments:

Type II – C.I.6.a) Change(s) to therapeutic indication(s) – Addition of a new therapeutic indication

SCOPE	**Addition of a new therapeutic indication: "*Chronic inflammatory demyelinating poliradiculoneuropathy (CIDP)*"**
	Medicinal product: **IVIG**
APPROVAL TIME (AIFA Approval)	**10 months (EOP) + 14 months price negotiation phase TOTAL 25 months**

Addition of a new therapeutic indication

KEDRION BIOPHARMA

“core” EU package

Revised Product Information

Module 2.5 – Clinical Overview
Module 2.7 – Clinical Summary

Module 5 – Clinical Study Report

List of non EU European and Asian countries

VARIATION

REQUIRED:

- ALBANIA
- BOSNIA HERZEGOVINA
- HONG KONG
- IRAN
- KOSOVO
- PHILIPPINES
- SERBIA
- SRI LANKA
- TURKEY
- SWIZERLAND
- VIETNAM

All countries involved required a variation application

VARIATION INCLUDED IN THE RENEWAL DOSSIER

- INDIA

List of non EU European and Asian countries

KEDRION BIOPHARMA

VARIATION

SUBMITTED:

- ALBANIA
- BOSNIA HERZEGOVINA
- HONG KONG
- IRAN
- KOSOVO
- PHILIPPINES
- SERBIA
- SRI LANKA
- TURKEY*
- SWITZERLAND
- VIETNAM

PARALLEL APPLICATION ALLOWED
Submission in parallel with Italian Variation

PARALLEL APPLICATION NOT ALLOWED
Submission after Italian Approval of the Variation

** Parallel submission of this variation was not made as per company decision (planning allocation flexibility)*

List of non EU European and Asian countries

KEDRION BIOPHARMA

COUNTRY	VARIATION PACKAGE	DOCUMENTS REQUESTED BY LOCAL AUTHORITY DURING REVIEW	APROVAL TIME
ALBANIA	EUROPEAN PACKAGE	None	2 months
BOSNIA HERZEGOVINA	EUROPEAN PACKAGE	None	4 months
HONG KONG	EUROPEAN PACKAGE	Approval of the variation in Switzerland, Germany and Portugal	Pending approval since 12/2014
IRAN	EUROPEAN PACKAGE	None	8 months
KOSOVO	EUROPEAN PACKAGE	None	1 month
PHILIPPINES	EUROPEAN PACKAGE	None	13 months
SERBIA	EUROPEAN PACKAGE	None	9 months
SRI LANKA	EUROPEAN PACKAGE	None	Pending approval since 10/2014
SWITZERLAND	EUROPEAN PACKAGE	None	17 months
TURKEY	EUROPEAN PACKAGE	None	8 months
VIETNAM	EUROPEAN PACKAGE	Leaflet adjustments and clarifications on the submitted clinical study	Pending approval since 08/2014

Conclusions

- all countries required a pre-approval submission for a new therapeutic indication
- half of the countries did not require a pre-approval submission to introduce a new intermediate manufacturer
- the EU package data was widely accepted
- two countries followed specific pathways
- most countries do not allow to submit the application in parallel with the country of origin
- timing of approval is the main difference between countries, in three countries the applications are still pending