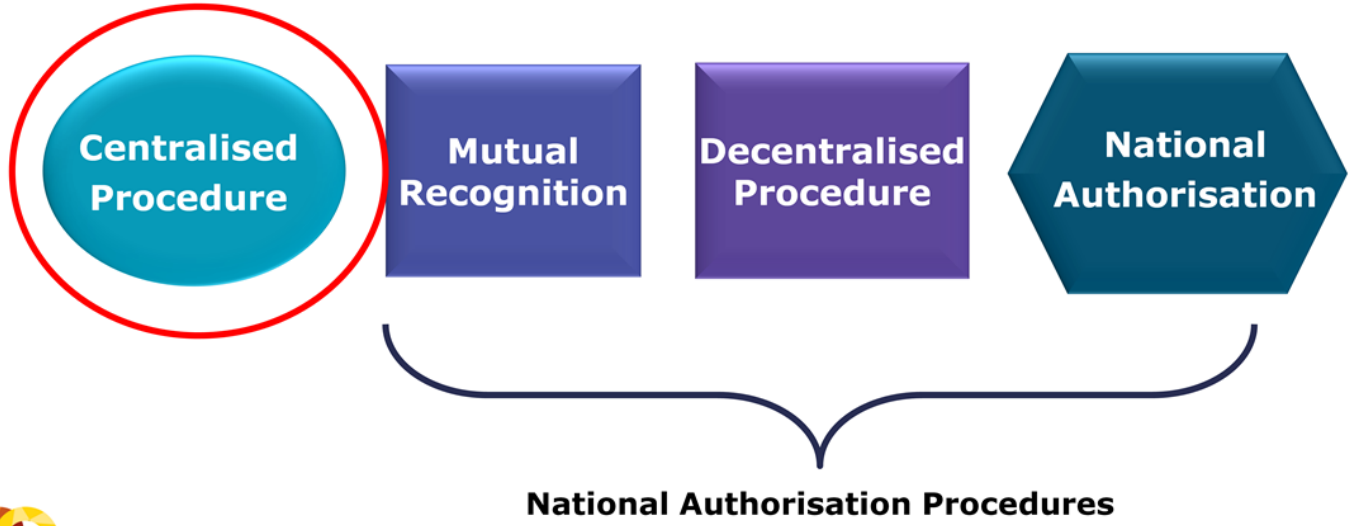
Singhrix™ as a case study to illustrate marketing autorisation procedure

famhp
federal agency for medicines and health products
.be

The European System

Marketing authorisation: allows a medicine to be placed on the market for sale and supply

Two ways of obtaining a marketing authorisation: Centralised procedure and National Authorisation procedures



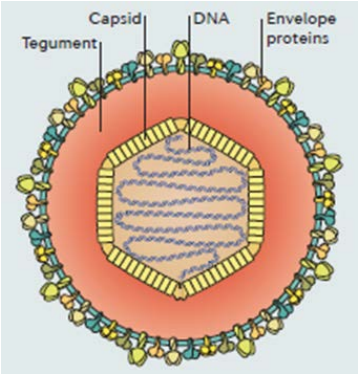
1 The Centralised Procedure

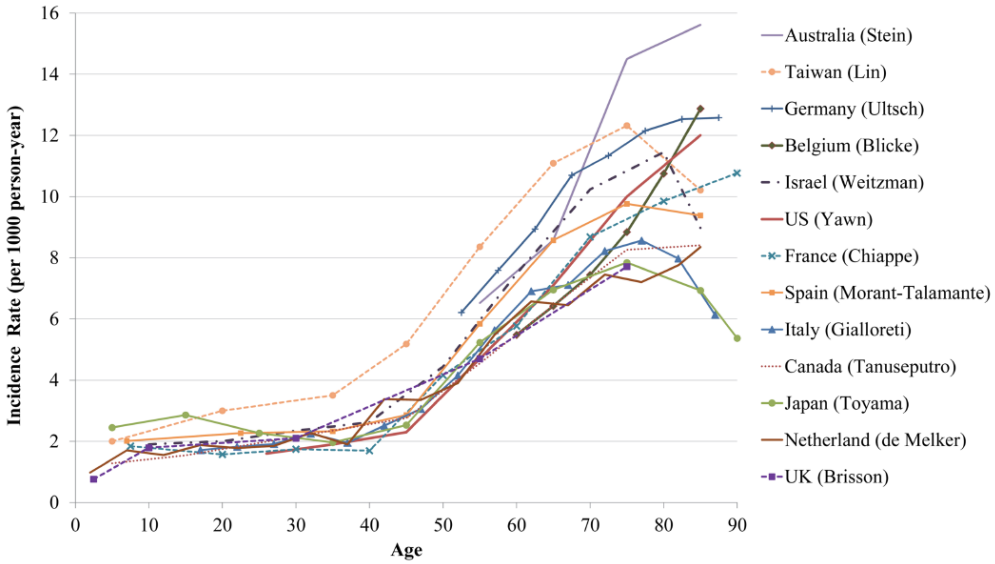
Shingrix

4.1 Therapeutic indications

Shingrix is indicated for prevention of herpes zoster (HZ) and post-herpetic neuralgia (PHN), in adults 50 years of age or older (see section 5.1).

The use of Shingrix should be in accordance with official recommendations.

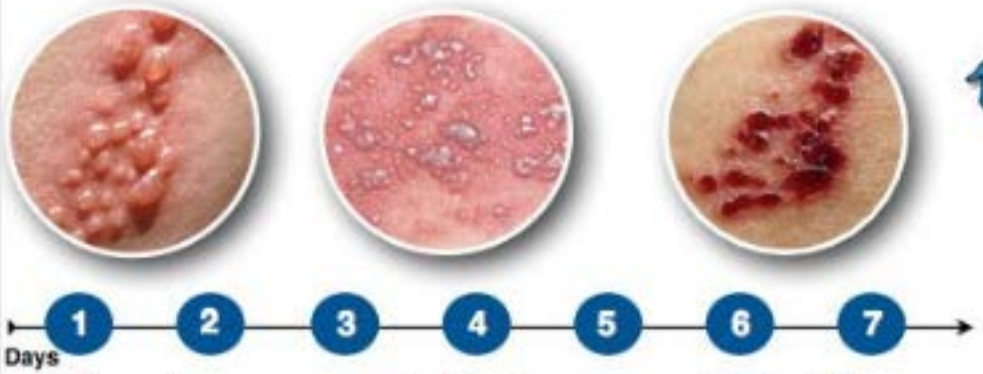




Age-specific incidence rate of herpes zoster in North America, Europe and Asia-Pacific.

Herpes Zoster (Shingles)

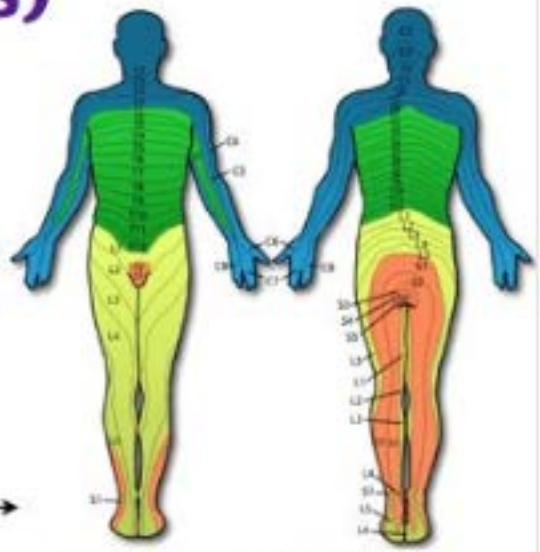
Varicella-zoster virus



Erythematous papules

Pustular/ Hemorrhagic

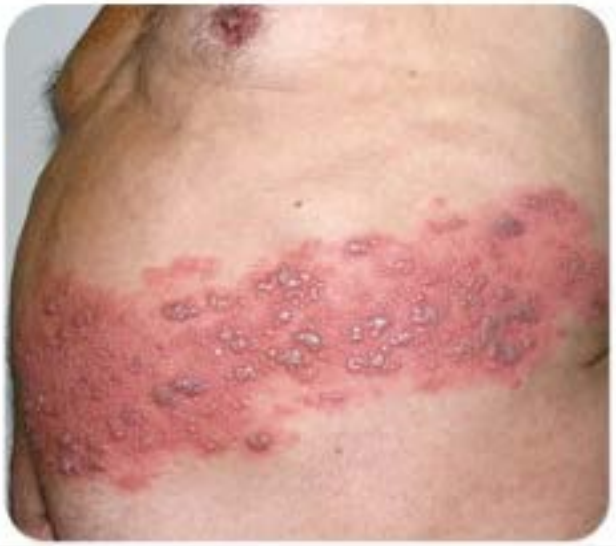
Crusted/No longer infectious



Dermatomal distribution
(Thoracic/Lumbar most common)

Clinical
- Rash
- Acute neuritis (pain)

Complications
- Postherpetic neuralgia (8%)
- Bacterial skin infection (2%)
- Uveitis/Keratitis (1.5%)
- Motor neuropathy (1%)
- Meningitis (0.5%)
- Zoster oticus (0.2%)



Centralised procedure

Data on the new vaccine are submitted to the European Regulatory Authority

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

ONE

Marketing Authorisation application

Evaluation

- Authorisation in all EU MS
- Invented name
- Product information
  - Summary of Product Characteristics (SmPC)
  - Labelling
  - Package Leaflet (PL)

ALL

EU languages

Marketing authorisation → positive risk-benefit balance

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

-> 7 Scientific Committees

CHMP, PRAC

CHMP (Committee for Human Medicinal Products) : provides a **comprehensive scientific evaluation** of data; determines whether a medicine meets the necessary **quality, safety and efficacy** requirements and that it has a positive **risk-benefit balance**

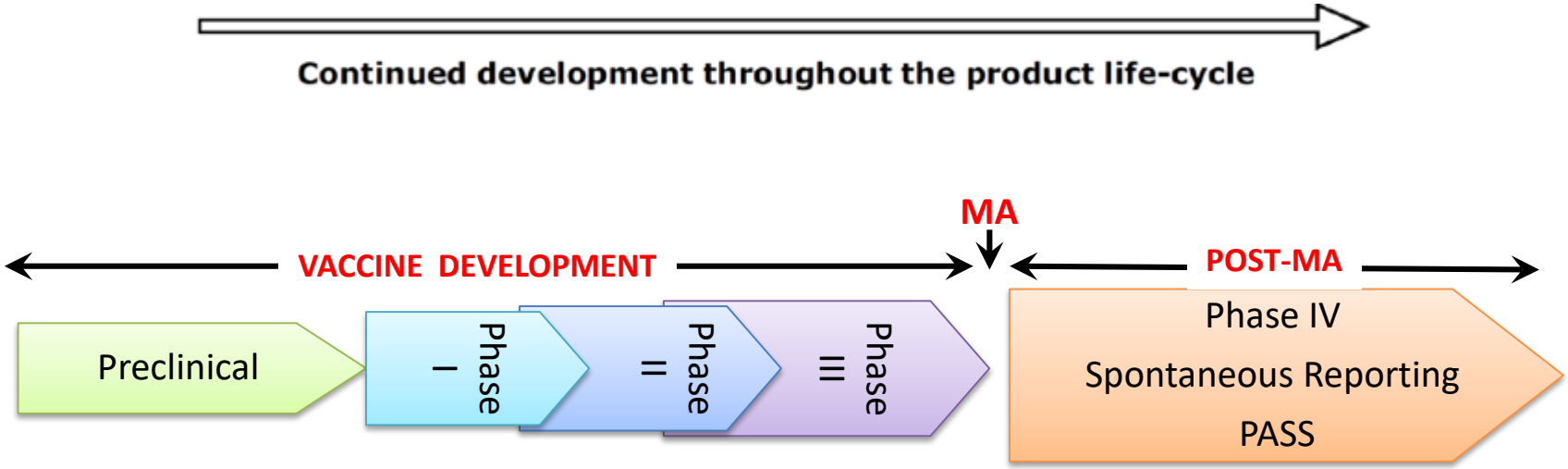
BE : 1 member + 1 alternate + 1 co-opted member for pharmacoepidemiology, team of assessors

-> Working Parties : Biologics Working Party, Vaccine Working Party, Scientific Advice Working Party

PRAC (Pharmacovigilance Risk Assessment Committee): is responsible for assessing all aspects of the **risk management** of medicines for human use (signal detection, risk minimisation, risk communication, PASS, PhV audit); provides **recommendations** on questions on pharmacovigilance and risk management systems, to, among others, the CHMP and European Commission

BE: 1 member + 1 alternate, team of assessors

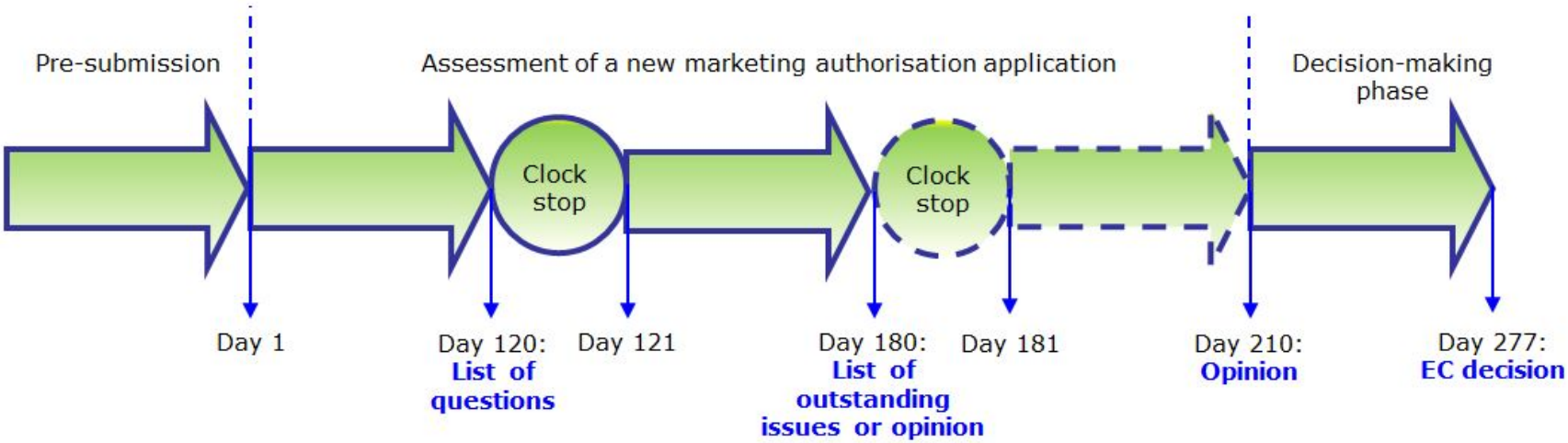
Marketing authorisation → positive risk-benefit balance (2)



Scientific advice, dialogue
Guidelines
Clinical trials methods
Biomarkers
…

Safety managment
Periodic B/R evaluation report
Variations
Health Technology assessment, reimbursement
…

Marketing authorisation application: steps

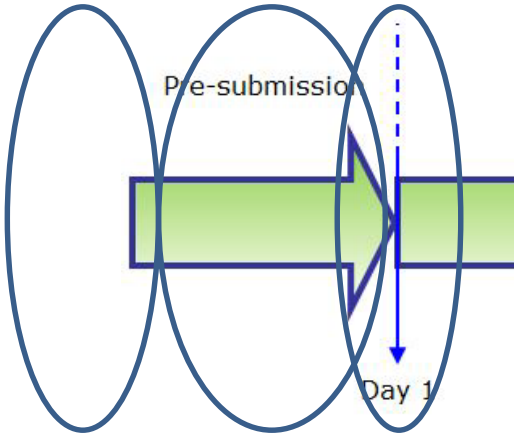


August 2016

January 2018

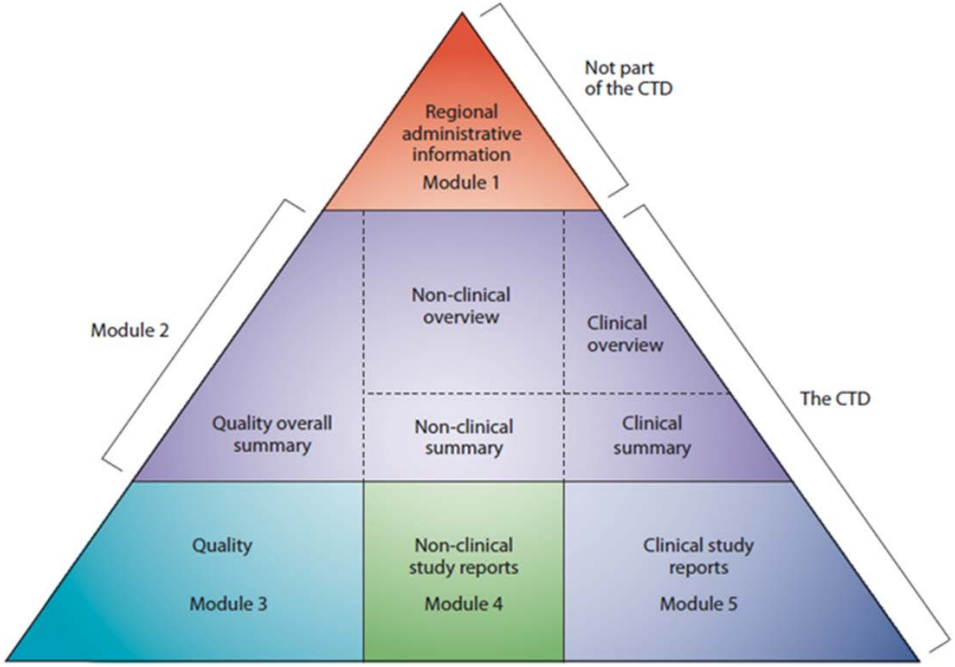
EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

Marketing authorisation application: steps (2)



LoI
Rapporteur and Co-Rapporteur
Peer-reviewer

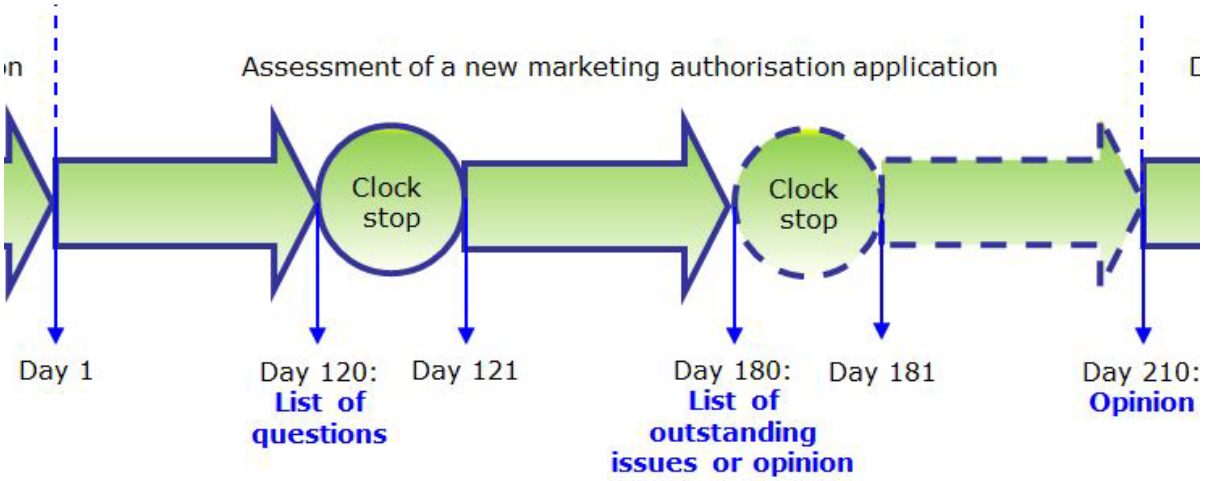
CTD



xx documents >40 studies >20 studies

-> Thousands of pages

Marketing authorisation application: steps (3)



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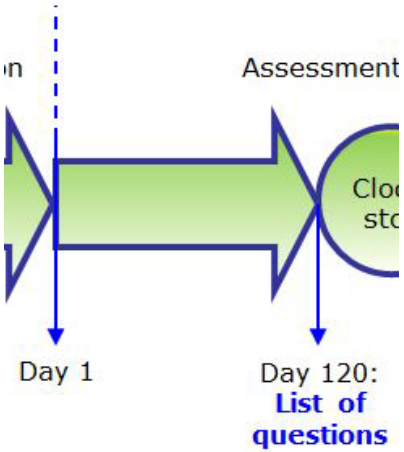
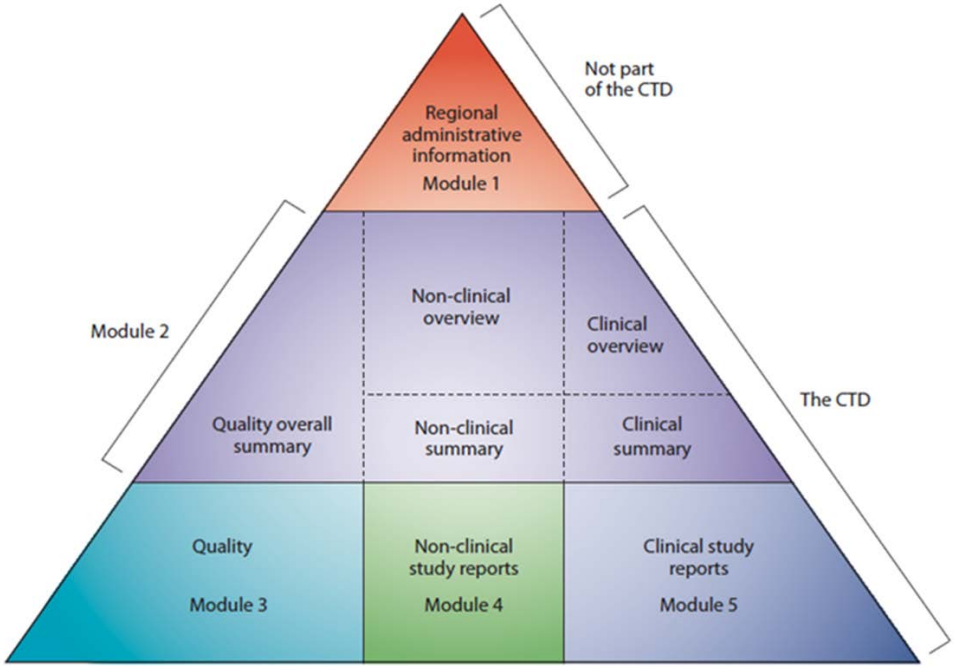
SCIENCE MEDICINES HEALTH

Guidance document for the content of the <Co->
Rapporteur day <60*><80> critical assessment report

Marketing authorisation application: steps (4)

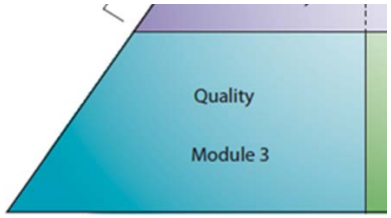


CTD

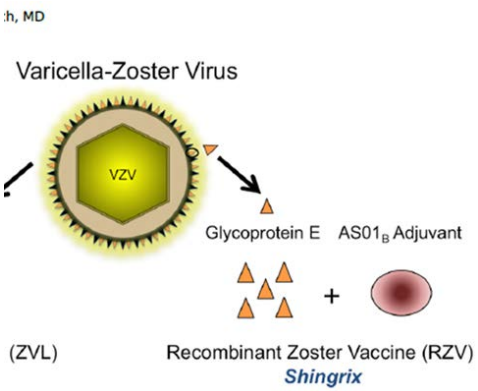


xx documents >40 studies >20 studies

Shingrix - quality



Drug substance, Drug product
GMP

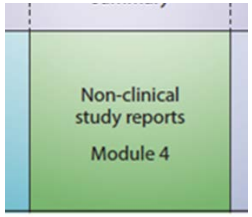


2-vial presentation : lyophilised antigen reconsituted with liquid adjuvant

Vaccine antigen: Recombinant VZV glycoprotein E (gE) produced in CHO cells
Vaccine adjuvant: $AS01_B$

Conclusion:
No major objections were raised for quality, there were several questions (other concerns) regarding the manufacturing process validation.

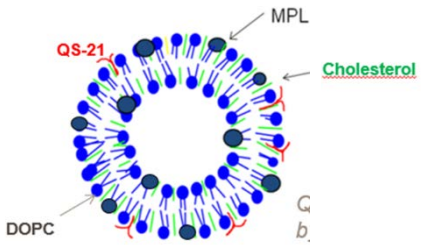
Shingrix – non-clinical

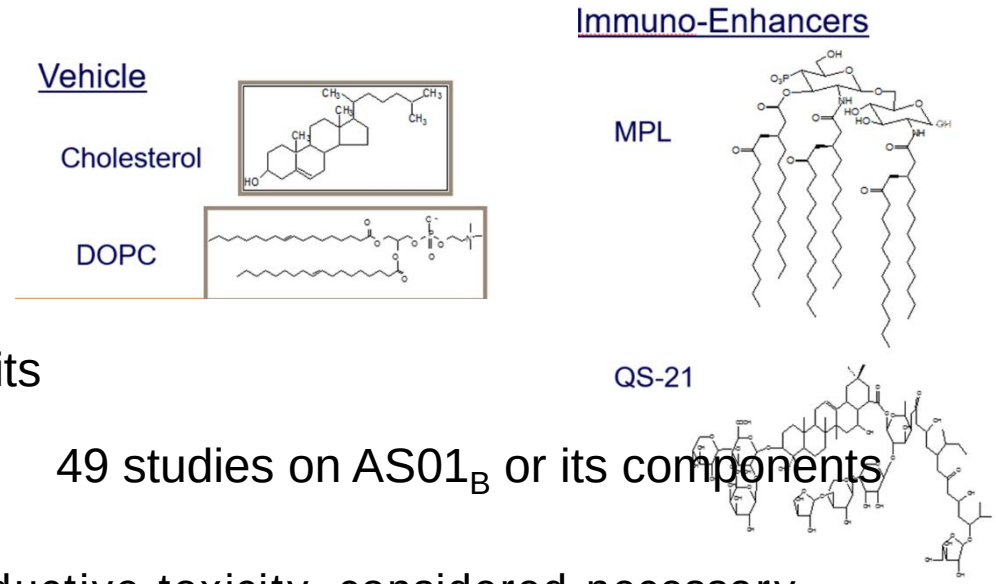


Pharmacodynamics and toxicity
GLP

Vaccine :VZV gE + $AS01_B$

$AS01_B$: Liposomes, QS-21, MLP



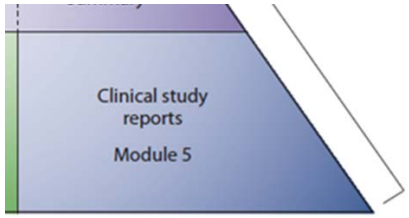


17 studies in mice, rats and rabbits

49 studies on $AS01_B$ or its components

Conclusion:
No major objections
Other concern related to reproductive toxicity, considered necessary despite initial indication ≥50 yoa (extended indication to IC subjects ≥18 yoa)

Shingrix - clinical



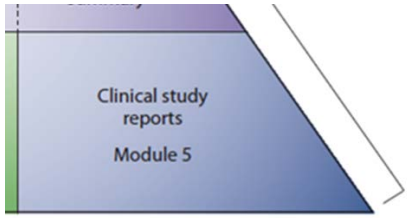
Pharmacodynamics
Clinical efficacy
Clinical safety
GCP

22 studies submitted, 14 studies completed at the time of MAA

Overall:
Efficacy trials included 30,000 subjects
Safety database included ~17,000 subjects (exposed to at least one dose of the vaccine)

High VE demonstrated
Reactogencity
No major safety concern

Shingrix - clinical



GCP inspection requested

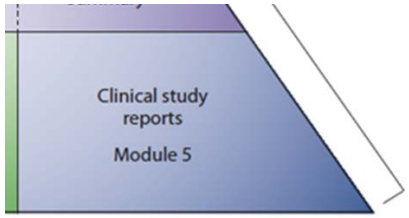
No major objections.
Limited number of other concerns related to real-life settings (population, reactogenicity and safety)

At licensure, VE was demonstrated over 4 years

Ongoing studies:
FU immunogenicity
FU of the trials for long term protection (10 years)
Co-administration studies

Additional studies were requested (→ Pharmacovigilance plan)

Shingrix – clinical (PRAC)



RMP

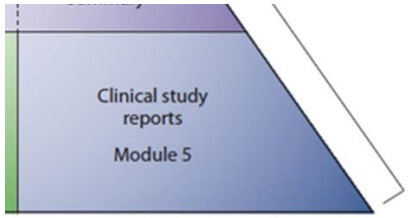
Summary of safety concerns	
Important identified risks	None
Important potential risks	• Risk of potential Immune Mediated Disorders (pIMDs) following *Shingrix* vaccination • Virus reactivation in immunocompetent individuals with a history of Herpes Zoster
Missing information	• Long-term efficacy and assessment of the need for additional doses in adults 50 years of age and older. • Long-term immunogenicity in adults 50 years of age and older. • Use of *Shingrix* in frail adults 50 years of age or older • Use of *Shingrix* in immunocompromised adults • Use of *Shingrix* in adults with pre-existing pIMD • Effectiveness of *Shingrix* in preventing HZ, PHN and HZ-related complications

Pharmacovigilance Plan

Phase III and non-interventional studies

- → EPI-ZOSTER-030 vs
- → ZOSTER-062, 056
- → ZOSTER-049, 060
- → ZOSTER-064, 063
- → ZOSTER-002, 039, 041, 028
- → ZOSTER-069
- → EPI-ZOSTER-031

Shingrix – clinical



SPC and Patient Information Leaflet

1. NAME OF THE MEDICINAL PRODUCT

Shingrix powder and suspension for suspension for injection
Herpes zoster

2. QUAL

After reconsti
Varicella Zos

[1] Varicella Zc
[2] adjuvanted v
plant e:
3-O-de

[3] glycoprotein
technology

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Shingrix is indicated for prevention of herpes
50 years of age or older (see section 5.1).

The use of Shingrix should be in accordance v

4.2 Posology and method of administrati

Posology

The primary vaccination schedule consists of
second dose 2 months later.
If flexibility in the vaccination schedule is necessary, the second dose can be administered between 2 and 6 months after the first dose (see section 5.1).

The need for booster doses following the primary vaccination schedule has not been established (see section 5.1).

Shingrix can be given with the same schedule in individuals previously vaccinated with live attenuated HZ vaccine (see section 5.1).

4.8 Undesirable effects

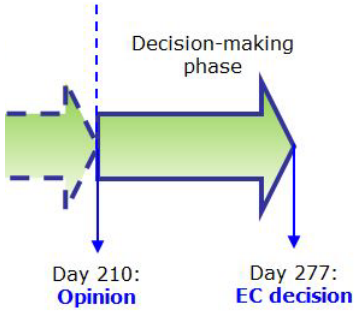
Summary of the safety profile

gia (PHN), in adults

The most frequently reported adverse reactions were pain at the injection site (68.1% overall/dose; 3.8% severe/dose), myalgia (32.9% overall/dose; 2.9% severe/dose), fatigue (32.2% overall/dose; 3.0% severe/dose) and headache (26.3% overall/dose; 1.9% severe/dose). Most of these reactions were not long-lasting (median duration of 2 to 3 days). Reactions reported as severe lasted 1 to 2 days.

The incidence of adverse reactions was higher in subjects aged 50-69 years compared to those aged ≥70 years, especially for general adverse reactions such as myalgia, fatigue, headache, shivering, fever and gastrointestinal symptoms.

Final opinion



Risk-Benefit balance

	certainties	uncertainties
Efficacy	high efficacy >< HZ and PHN in ≥50 yoa	duration of protection
		need of a boost
		effectivness
	can be used in IC subjects	efficacy and safety in IC subjects
reactogenicity/safety	severe reactogenicity not uncommon (but temporary and manageable)	theoretical risk of acquiring vaccine induced pIMD or of exacerbation of pre-existing pIMD
	no major safety concern	potential risk of HZ recurrence in subjects with previous history of HZ

3.8. Conclusions

The overall B/R of Shingrix is positive.

The divergent positions are appended to the opinion.

European Public Assessment Report – EPAR

https://www.ema.europa.eu/en/medicines/field_ema_web_categories%253Aname_field/Human/ema_group_types/ema_medicine

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

25 January 2018
EMA/88588/2018
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Shingrix

International non-proprietary name: herpes zoster vaccine (recombinant, adjuvanted)

Procedure No. EMEA/H/C/004336/0000

Shingrix received a marketing authorisation valid throughout the EU on 21 March 2018.

Adults ≥ 50 YOA, Healthy (initial proposed indication)

	Study	Scope	Remark
Phase I	ExploCRD004	Exploratory safety and CMI	
	ZOSTER-018;019	FU ExploCRD004	
	ZOSTER-023	Adults of Japanese ethnic origin	
Phase II	ZOSTER-003	Antigen and adjuvant dose selection	
	ZOSTER011;12;13	FU ZOSTER-003; Y1,2,3	
	ZOSTER-024	FU ZOSTER-003; Y6	
	ZOSTR-060	FU ZOSTER-003	*ongoing*
	ZOSTER-010	Adjuvant dose selection	
Phase III	ZOSTER-006	Pivotal + pooled	
	ZOSTER-022	Pivotal + pooled	
	ZOSTER-049	FU 006/022; 6 years FU	*ongoing*
	ZOSTER-004	Coadmin Flu-D-QIV	
	ZOSTER-035	Coadmin Pneumovax23	*ongoing*[2]
	ZOSTER-042	Coadmin Boostrix	*ongoing*[2]
	ZOSTER-007	Lot to Lot consistency	
	ZOSTER-048	Previous Zostavax administration	*ongoing*
	ZOSTER-033	Adults with previous episode of HZ	
	ZOSTER-026	Schedule comparison	
	ZOSTER-032	SC vs IM	
	ZOSTER-056	Safety in 006/022 placebo recipients	*ongoing*

Adults ≥ 18 YOA, Immunocompromised (proposed extension of indication)

Phase I/IIa	ZOSTER-001	Autologous HCT recipients	
	ZOSTER-015	HIV-infected adults	
Phase II/III	ZOSTER-028	Solid Malignant Tumours chemotherapy	*ongoing*[2]
Phase III	ZOSTER-002	Autologous HCT recipients	*ongoing*
	ZOSTER-039	Hematologic malignancy patients	*ongoing*
	ZOSTER-041	renal transplant	*ongoing*

Contact

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