AGENZIA ITALIANA DEL FARMACO

Tutela Ricerca e Sviluppo per la Salute

Junior Clinical Trials Assessors Training: VHP Guideline

Massimiliano Sarra, Ph.D.

26.06.2019

Public Declaration of transparency/interests*

The view and opinions expressed are those of the individual presenter and should not be attributed to AIFA

Interests in pharmaceutical industry	NO	Current	From 0 to 3 previous years	Over 3 preavious years
DIRECT INTERESTS:				
1.1 Employment with a company: pharmaceutical company in an executive role	X	☐	☐	☐ mandatory
1.2 Employment with a company: in a lead role in the development of a medicinal product	X	☐	☐	☐ mandatory
1.3 Employment with a company: other activities	☐	☐	☐	X optional
2. Consultancy for a company	X	☐	☐	☐ optional
3. Strategic advisory role for a company	X	☐	☐	☐ optional
4. Financial interests	☐	☐	☐	X optional
5. Ownership of a patent	X	☐	☐	☐ optional
INDIRECT INTERESTS:				
6. Principal investigator	X	☐	☐	☐ optional
7. Investigator	X	☐	☐	☐ optional
8. Grant or other funding	X	☐	☐	☐ optional
9. Family members interests	X	☐	☐	☐ optional

*Massimiliano Sarra, in accordance with the Conflict of Interest Regulations approved by AIFA Board of Directors (25.03.2015) and published on the Official Journal of 15.05.2015 according to EMA policy /626261/2014 on the handling of the conflicts of interest for scientific committee members and experts.

N.B. I am not receiving any compensation

Before May 2004

Different **processes and requirements** for clinical trial authorisations in each Member States…

… resulted in **delays and complications** detrimental to effective conduct of clinical trials in the EU.

Directive 2001/20/EC

First step to harmonise **processes and requirements** for clinical trial authorisations.

Implementation **1 May 2004**.

Concerns expressed soon after its implementation.

Regulation (EU) 536/2014

Published **on 27 May 2014.**

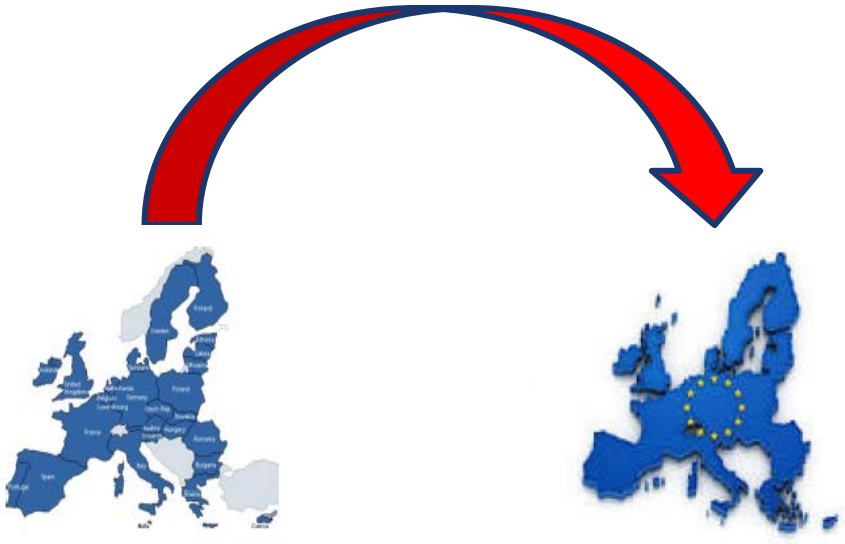
Application 6 months after confirmation published in the OJ of **full functionality of EU portal and EU database**, in any event **not earlier than 28 May 2016.**

Transitional arrangements.

Directive 2001/20/CE

Regulation 536/2014/CE

Regulation 536/2014: Key changes



2001/20/CE

536/2014/CE

- New evaluation process
- Development of a portal/database (CTIS) for submissions/communications
- New transparency roles
- Collaboration in managements of safety reports and issues

Directive versus Regulation

Implemented in national laws

Directly applicable

"[...] experience indicates that the legal form of a Regulation would present advantages for sponsors and investigators, for example in the context of clinical trials taking place in more than one Member State, since they will be able to rely on its provisions directly, but also in the context of safety reporting and labelling of investigational medicinal products. Divergences of approach among different Member States will be therefore kept to a minimum".

Overall objective: Make EU attractive for R&D.

The Voluntary Harmonisation Procedure (VHP)

VHP applies to all phase I-IV MN CTs involving 2 or more Member States. It allows the joint assessment of the same documentation provided by the Applicant in a specific timeline, thus leading to the harmonized conclusion on the possibility to approve or reject the CT Application in all the Members States involved.

VHP: Main Characteristics

- Harmonization of the Documents (Protocol, IB, IMPD, risk/benefit) shared by the NCA through the VHP-DB
- A rigid and specific Timeline
- Nomination of a Ref-NCA that leads the assessment and collect the comments of the P-NCA
- Coordinated assessment of the CTA, thus leading to a single harmonized decision among the Member States involved

Documents sharing procedures

An Application via VHP should be submitted by the Applicant to the VHP-Administrator (DE-PEI), which forwards the request to the NCAs of the Member States involved in the trial. The request and all notifications are circulated through specific email addresses given by the NCAs.

- No communications among Sponsor and NCAs until day 0
- Starting from day 0 all the communications with the Sponsor are handled by the Ref-NCA.

List of documents accepted in VHP

- General Information (Cover letter, CTA form)
- IMPD and related documents
- Investigator's Brochure
- Study Protocol
- Additional information (Scientific advices, PIP etc.)

Documents circulated by the VHP-Administartor trhough Eudralink and stored in the VHP-Area

VHP: Main Characteristics

- Harmonization of the Documents (Protocol, IB, IMPD, risk/benefit) shared by the NCA through the VHP-DB
- A rigid and specific Timeline
- Nomination of a Ref-NCA that leads the assessment and collect the comments of the P-NCA
- Coordinated assessment of the CTA, thus leading to a single harmonized decision among the Member States involved

Timeline

timelines for VHP

VHP Application Date: 01.10.2015 Date of Start VHP: 08.10.2015

type of deadline	due on	Day
Confirmation of receipt to Sponsor	03.10.2015	-5
Date informing NCA on VHP/VHP-Dossier location in VHP area	03.10.2015	-5
Final acknowledgement of receipt to Sponsor	08.10.2015	0
DAR/GNAs to be stored in VHP-area/VHP-Database by Ref.-NCA	28.10.2015	20
Statement on ASR/GNAs by P-NCAs and additional GNA to be entered in VHP-DB	02.11.2015	25
Date of consolidated List of GNAs by Ref-NCA in VHP-Database due by	05.11.2015	28
Date acceptance P-NCA of consolidated list of GNA	06.11.2015	29
TC on GNA before	07.11.2015	30
Info of Sponsor on GNAs by	09.11.2015	32
Response on GNA by sponor due by	19.11.2015	42
Assessment of response by Ref.-NCA in VHP-area / VHP-Database by	26.11.2015	49
Response of P-NCAs on assessment by Ref.-NCA in VHP-Database by	03.12.2015	56
Final ASR by Ref-NCA to be stored in VHP-area by	04.12.2015	57
TC on unsolved GNA before	05.12.2015	58
End of VHP / final info to Sponsor	07.12.2015	60
National applications by Sponsor	27.12.2015	80
National approvals by NCA	06.01.2016	90

Validation and nomination (7 days)

Assessment phase (60 days)

National Approval (10 days)

*NB1. Changes of the timeline occurs in case of ATMP

*NB2. The timeline is not changing in case of SW but a streamline approach is encouraged

VHP: Main Characteristics

- Harmonization of the Documents (Protocol, IB, IMPD, risk/benefit) shared by the NCA through the VHP-DB
- A rigid and specific Timeline
- Nomination of a Ref-NCA that leads the assessment and collect the comments of the P-NCA
- Coordinated assessment of the CTA, thus leading to a single harmonized decision among the Member States involved

Single discussion involving all the NCAs concerned

- The technical / scientific evaluation is carried out by an NCA (Reference-NCA) involved in the clinical trial application which will deal with drawing up a document (Assessment Report) made available for all the other NCAs (Participant-NCAs).
- This assessment usually includes a list of “objections” which if not resolved by the Applicant preclude the authorization of the study (Grounds for Non Acceptance - GNA).
- The other P-NCAs participate in the technical/scientific discussion by providing their comments on the Ref-NCA and adding GNAs (if any).
- The final list of GNAs is provided by the Ref-NCA who takes into consideration all the comments received and operates to harmonize the feedback received by all the NCAs involved.

VHP: Main Characteristics

- Harmonization of the Documents (Protocol, IB, IMPD, risk/benefit) shared by the NCA through the VHP-DB
- A rigid and specific Timeline
- Nomination of a Ref-NCA that leads the assessment and collect the comments of the P-NCA
- Coordinated assessment of the CTA, thus leading to a single harmonized decision among the Member States involved

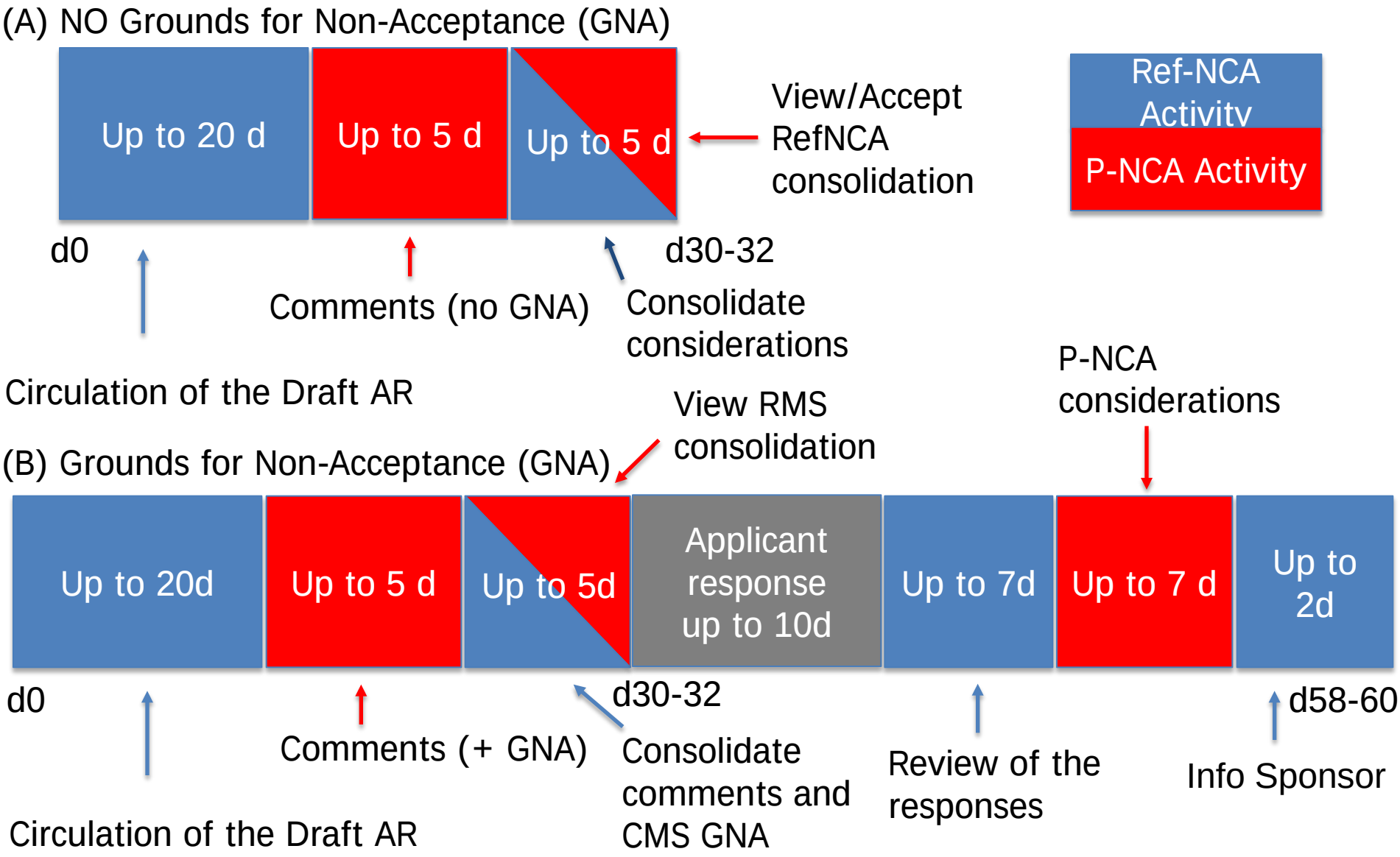
Single decision applicable nationally in all the MS involved

- The outcome of a VHP can be the following:

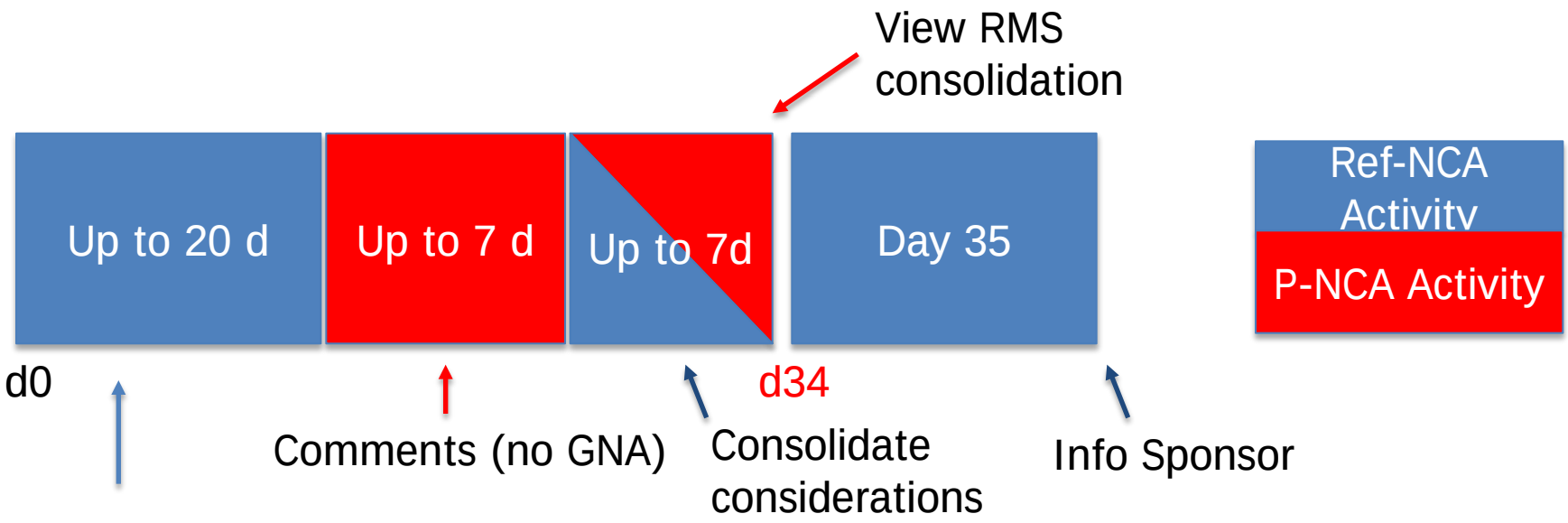
- *VHP approvable*
- *VHP approvable with conditions*
- *VHP to be rejected*

N.B. In case of a positive decision a fast-track national authorization will follow

Schematic overview of timelines and workflow for an Clinical trail application submitted via VHP


(A) NO Grounds for Non-Acceptance (GNA)
Up to 20 d
Up to 5 d
Up to 5 d
View/Accept RefNCA consolidation
Ref-NCA Activity
P-NCA Activity
d0
d30-32
Comments (no GNA)
Consolidate considerations
Circulation of the Draft AR
View RMS consolidation
P-NCA considerations
(B) Grounds for Non-Acceptance (GNA)
Up to 20d
Up to 5 d
Up to 5d
Applicant response up to 10d
Up to 7d
Up to 7 d
Up to 2d
d0
d30-32
d58-60
Comments (+ GNA)
Consolidate comments and CMS GNA
Review of the responses
Info Sponsor
Circulation of the Draft AR

Schematic overview of timelines and workflow for a Substantial Amendment application submitted via VHP



N.B. No possibility to raise GNAs in VHP SA

Grounds for non Acceptance

- Issues that if not solved by the Applicant before the VHP conclusion will lead to a negative opinion.
- No possibility to raise question to have information nice to know/have.
- The GNA should lead to a request of document modification or a request of a rationale/justification on specific issues.

Outcome of the assessment

The feedback of the P-NCAs is always given to the decision of teh Ref-NCA

Positive: The ref-NCA decision is agreed by the other P-NCAs

The VHP is closed

Neegative: The ref-NCA decision is not agreed by one or more P-NCAs

Divergent decision

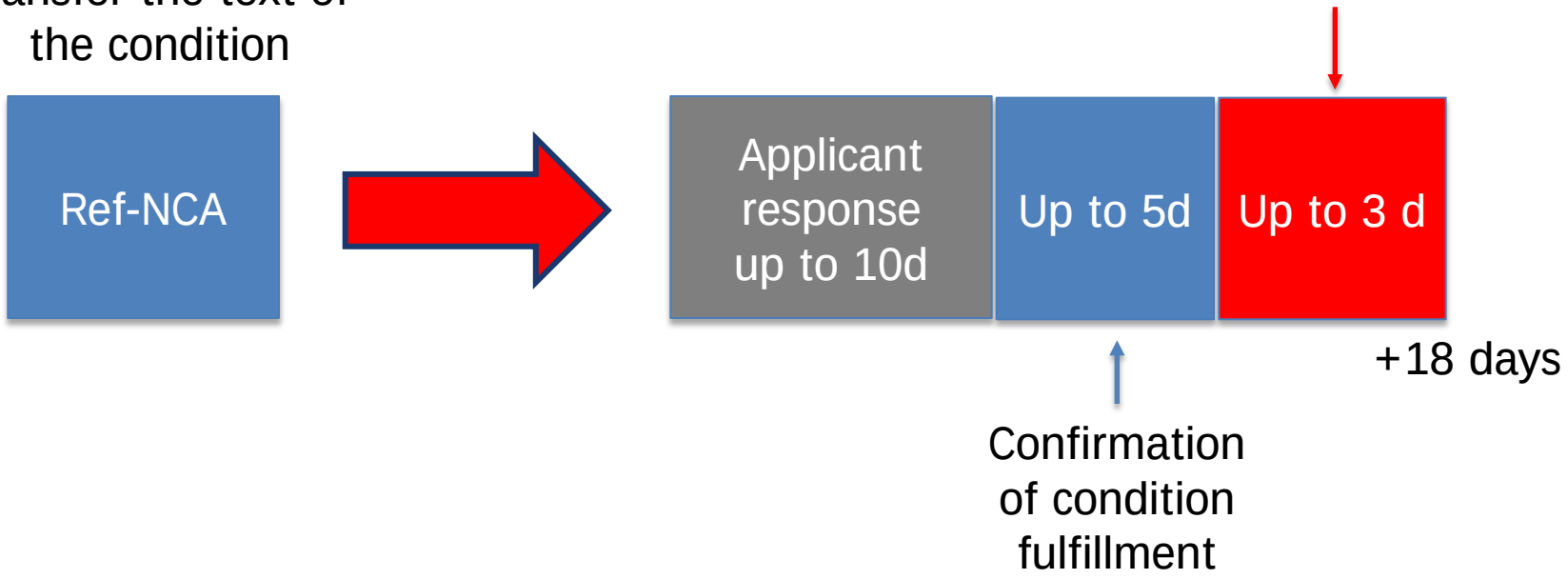
Outcome of a VHP

VHP approvable	The VHP received a positive feedback and the Sponsor can submit the CTA nationally in the MS involved
VHP approvable with conditions	The VHP can receive the positive opinion only after the fulfillment of a specific condition. The national submission can be done only after the conclusion of the VHP
VHP to be Rejected	The VHP received a negative opinion and the study cannot be submitted nationally. A resubmission in VHP is usually encouraged.

VHP Conditional Approval

The Ref-NCA inform the Sponsor and transfer the text of the condition

P-NCA acceptance / non-acceptance



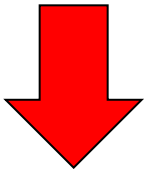
Definition of Condition in VHP

"In case of conditional approval the conditions of the NCAs should be clear and the change request should be self-explaining. This means that the changed documents should not require a scientific assessment again, but only the check if the condition is fulfilled. If a condition is not clear, clarification shall be provided by the Ref-NCA"

- Request of additional data/information
- Request of clarification/justification/rationale
- Request to amend the document at the next regulatory opportunity

Divergent Decision

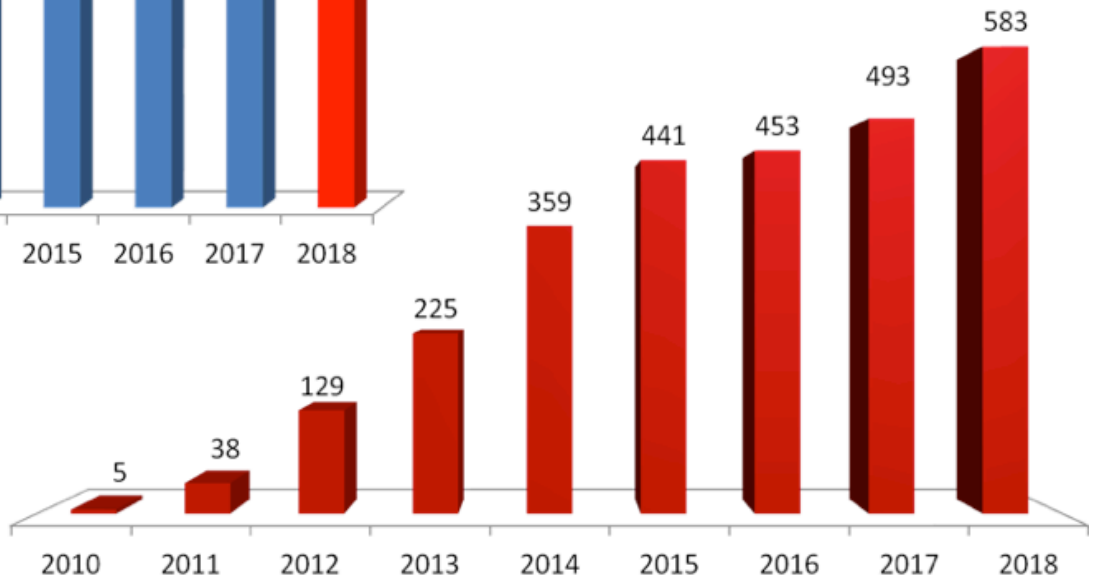
If no harmonized position are reached, the outcome of the VHP may be different between the various NCAs involved in the experimentation



Different position among the MS

Differences of the documents

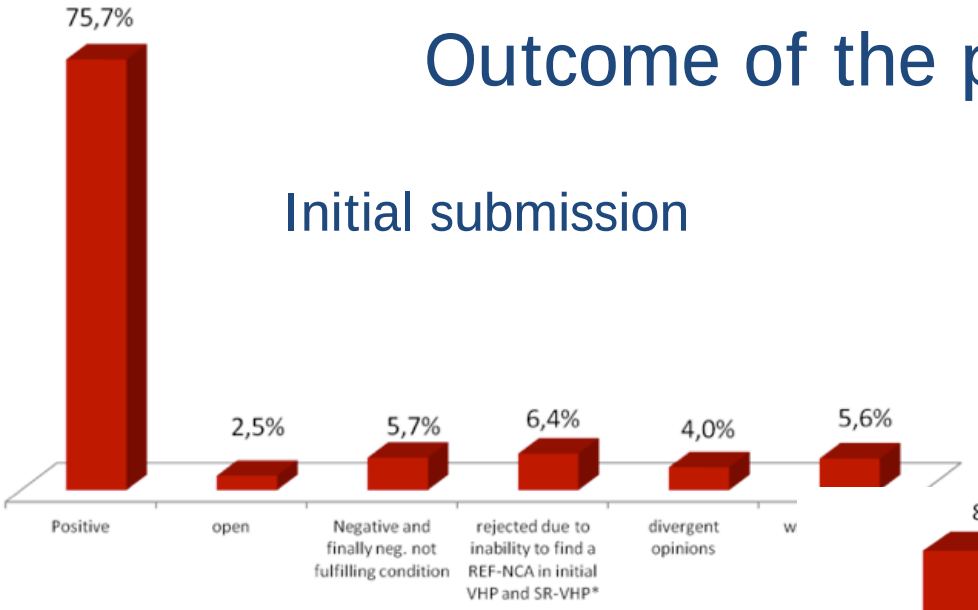
Results of the VHP (2009-2018)
Nr. of VHP per year



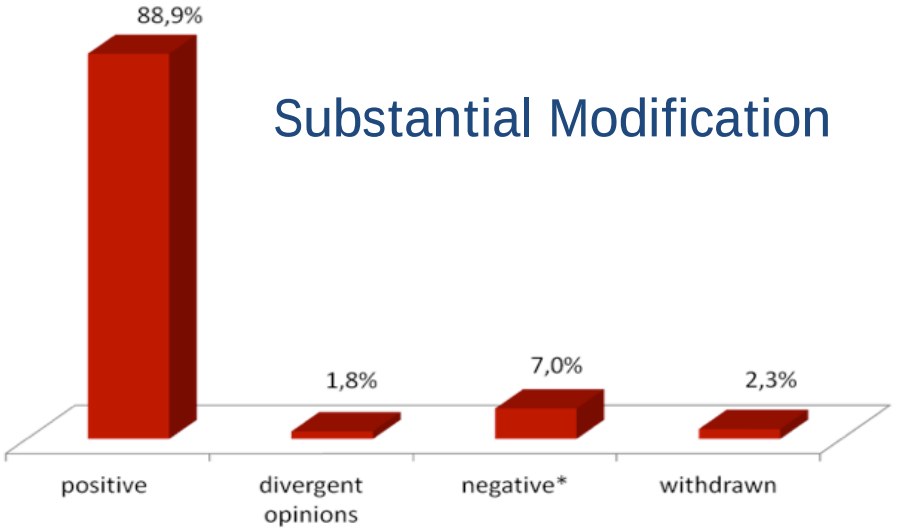
Substantial Modification

Results of the VHP (2009-2018)
Outcome of the procedures

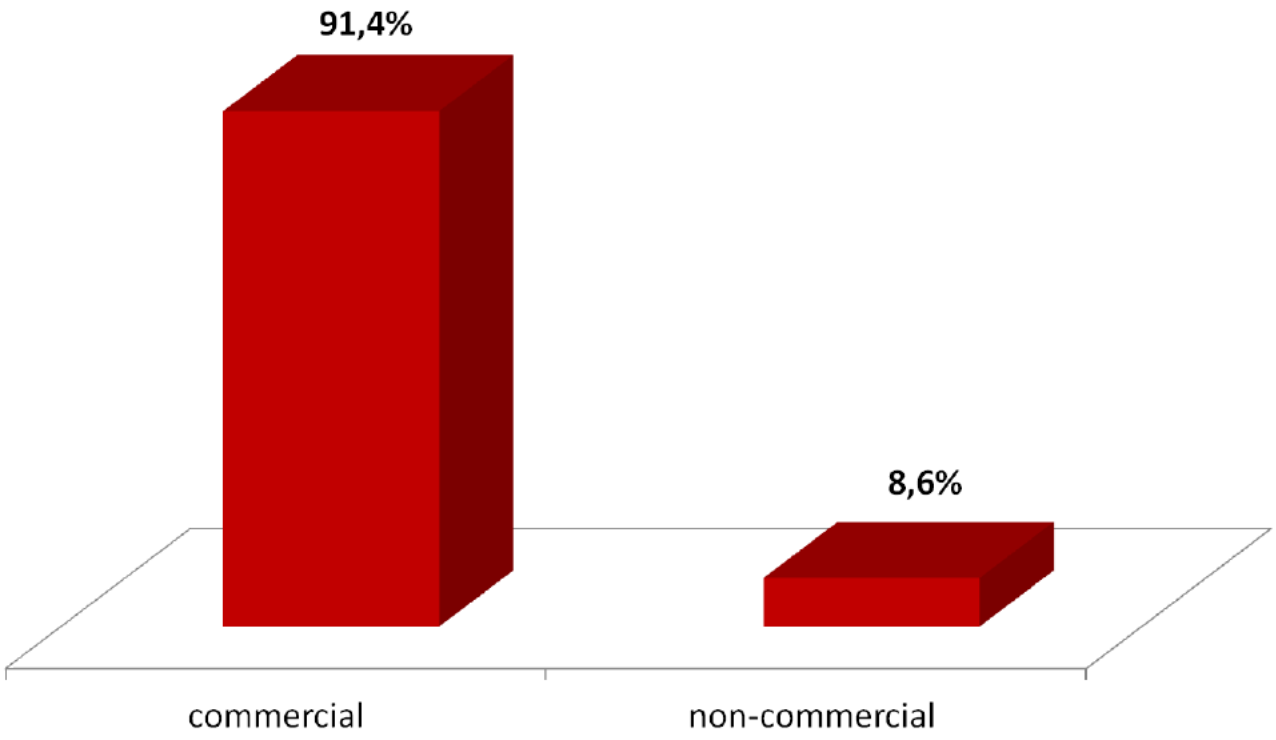
Initial submission



Substantial Modification



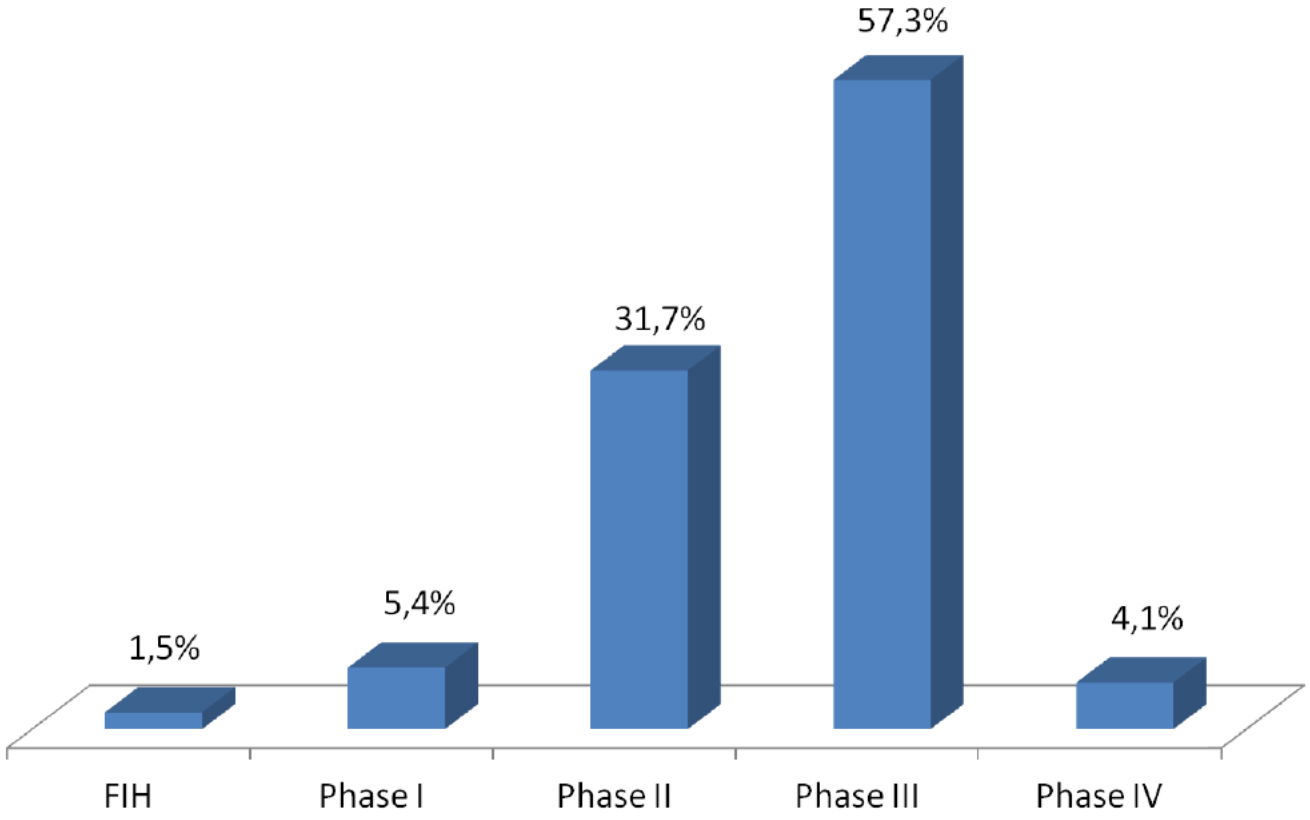
Distribution of commercial / non-com. Sponsors in VHP



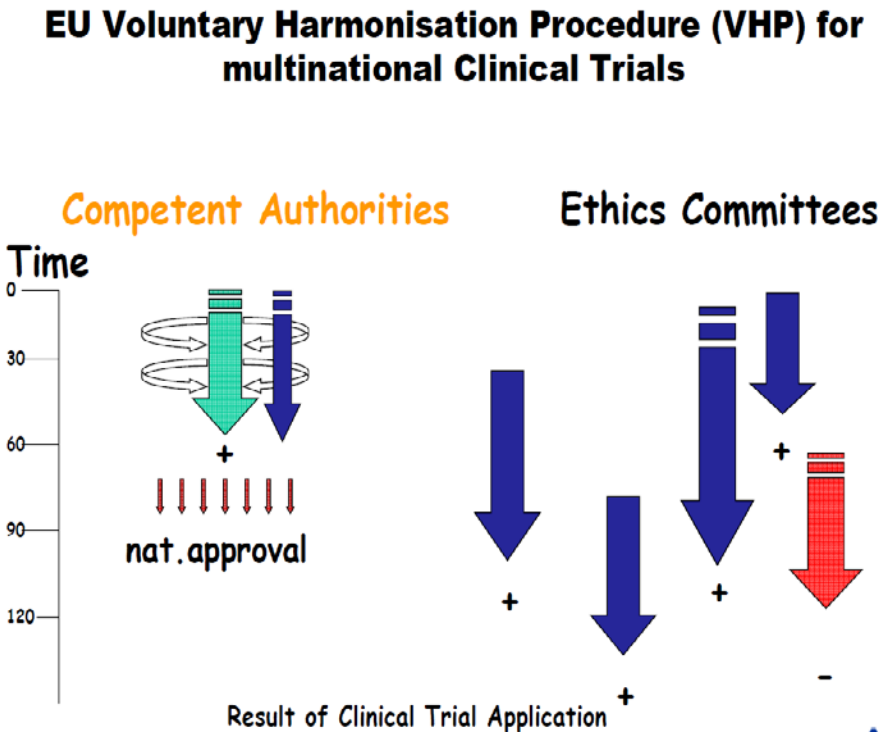
Distribution of IMPs

Group IMP	Percentage
Chemicals	51,0
Biologicals	49,0

Distribution of VHPs by phase of the clinical trial

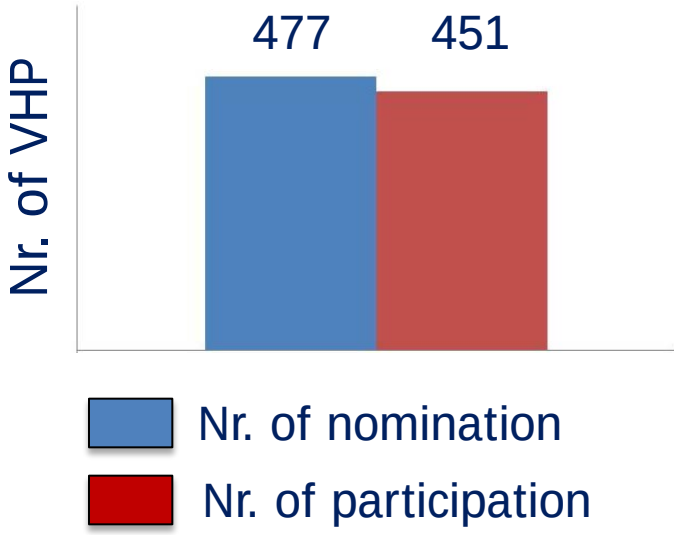


Involvement of Ethics committes in VHP: VHP Plus

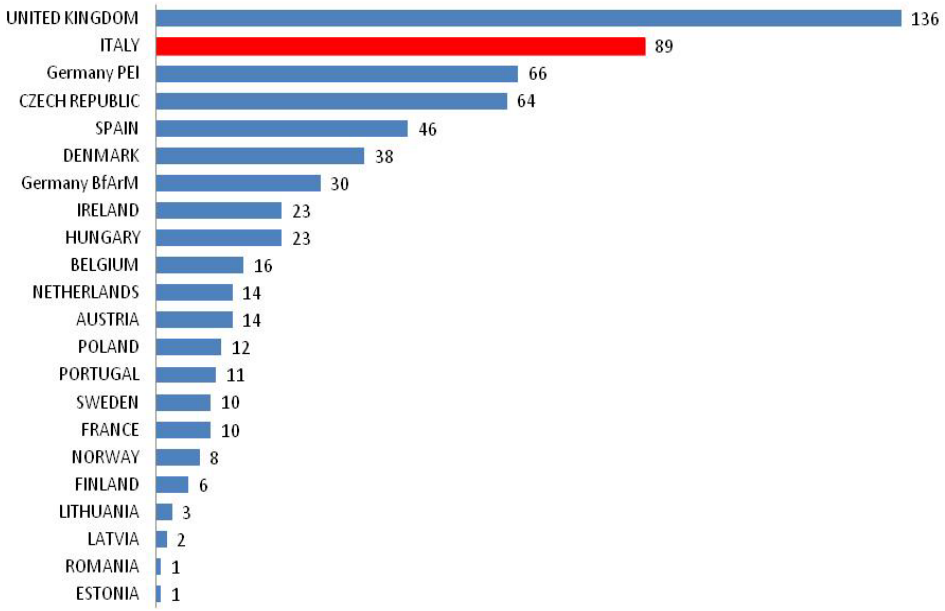


VHP-plus is a VHP involving Ethics Committees in the assessment of benefit/risk, IB and protocol in some Member States

Involvement of Italy in VHP procedures (Cumulative data 2015-2018)



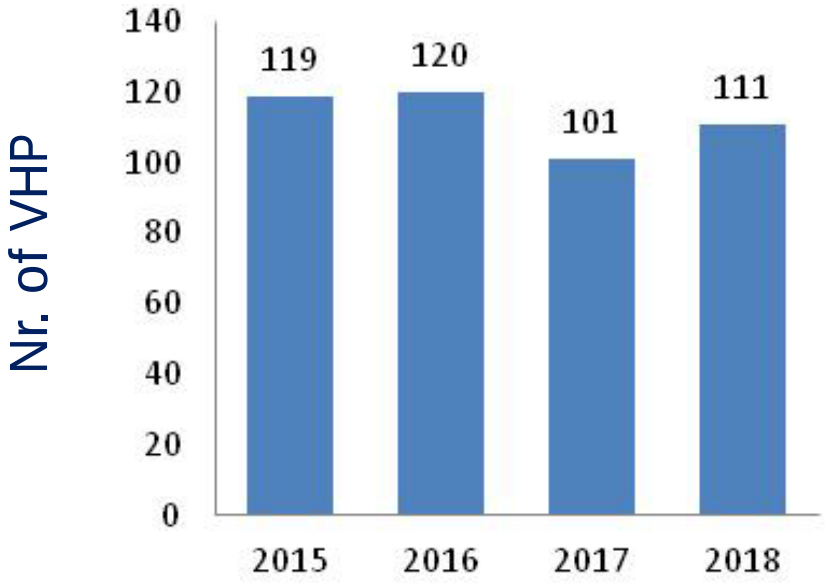
Nr. di VHP as Ref-NCA

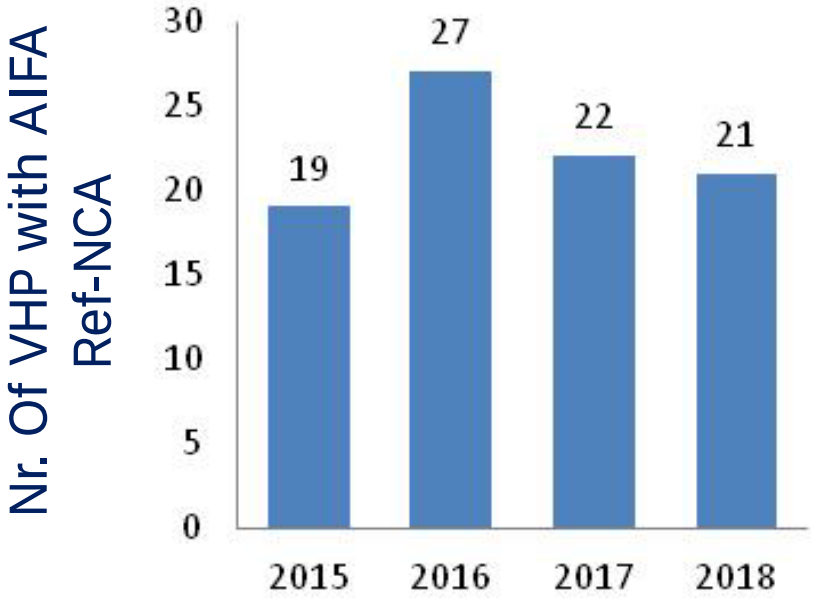


Source: HMA website

Involvement of Italy in VHP procedures (01.2015-09.2018)

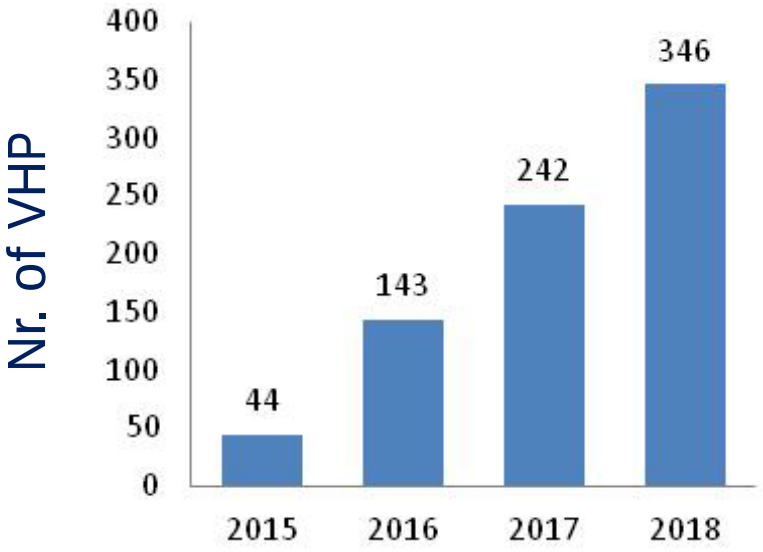
Initial submissions involving Italy

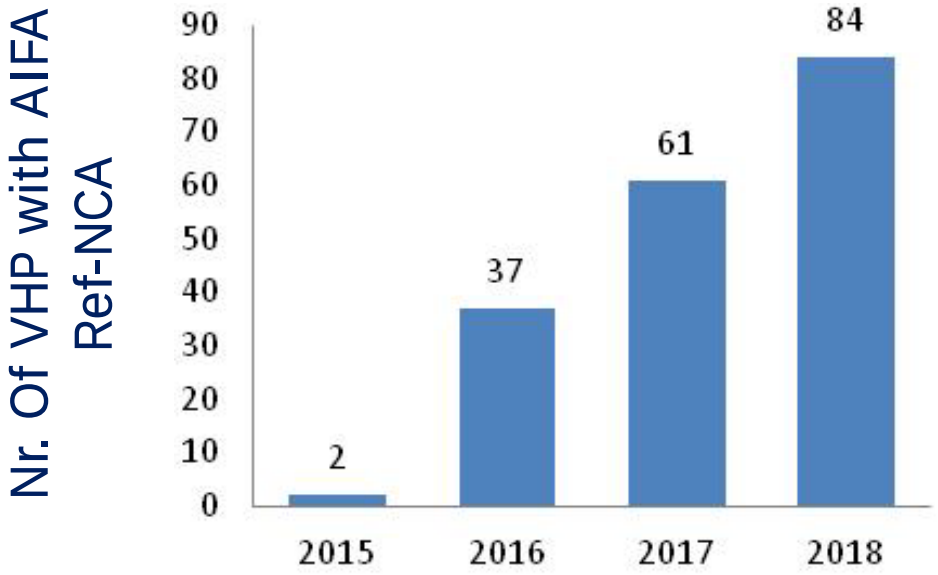




Involvement of Italy in VHP procedures (01.2015-09.2018)

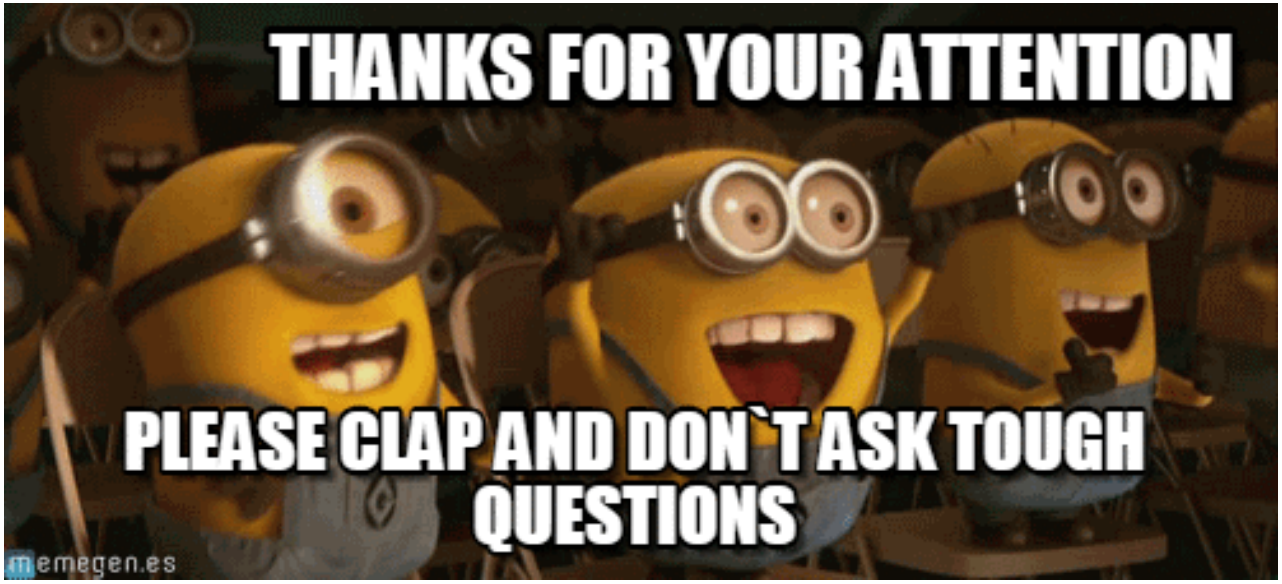
Substantial Amendments involving Italy





Conclusions: looking forward at the implementation of the new regulation

- Harmonization of the decisions with a very small percentage of divergences.
- Harmonization of the documents.
- Clear and defined timeline for providing a final decision.
- Streamline approach to the assessment.



Massimiliano Sarra, PhD
Pre-authorization Dept.
Italian Medicine Agency (AIFA)
m.sarra@aifa.gov.it
Tel. +39 06.59784075