EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

6. Referral procedures

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What is a Referral?

Procedure used to resolve issues over concerns on

QUALITY

EFFICACY

SAFETY

BENEFIT/RISK

...of a medicine or class of medicines

What is a Referral?

Medicine(s) is **REFERRED** to the Agency's committees

CHMP

PRAC

…to make a recommendation for a common approach across the European Union

Information on referrals:

http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general_content_000150.jsp&mid=WC0b01ac058002240d0

http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/landing/referral_search.jsp&mid=WC0b01ac05805c516f

Types of safety referrals

Directive 2001/83/EC

- **Article 31** “Union Interest”
- **Article 107 i** “Urgent Union Procedure”

Regulation EC No 726/2004

- **Article 20**
- **Article 5(3)** “Scientific Opinion”

Safety Referrals
New Pharmacovigilance legislation

The main pillars of change:

- Systematic involvement of PRAC
- Increased transparency
- Public involvement
- Character of urgency reinforced

Article 107i
Urgent Union Procedure

In which cases?

As a result of the evaluation of data resulting from PhV activities
+ urgent action is needed:

- *consideration of*
  - suspension/revocation of a product(s),
  - prohibition of supply,
  - non renewal of the license of a product;
  - new contra indication for its use,
  - reduction in the dose,
  - restriction to the indications.

- *based on safety concerns, from MAH*
  - interruption of placing on the market,
  - product withdrawn;

New Safety Urgent issue identified with a medicine with urgent action needed in view of public health protection

Urgent Union Procedure

- ***Who can start?***

  Member States of the Union or the European Commission
  (justification of the action(s) proposed/taken)

- ***How?***

  Notification circulated to the Agency, (other) Member States and European Commission

- ***Which products?***

  ALL medicines affected by urgent safety issue
  (e.g. a class of products, just one product approved in more than one MS and regardless of route of authorisation – nationally or centrally authorised)

  Products involved are identified by each Member State

Urgent Union Procedure

Keys points

- PRAC performs the assessment following
  - ⇨ Collection of data;
- Very short timeframe (max. of 60 days);
- Public hearing may be held;
- SAG and ad-hoc expert meeting may be held;
- PRAC issues a recommendation;
- Temporary measures can be taken at any time;

Announced on the Agency's website

Urgent Union Procedure
Collection of data

ANYONE CAN SUBMIT DATA
to be considered to the assessment

DEDICATED MAILBOX

TEMPLATE SUBMISSION FORM

Data submitted will be part of the assessment that will be publicly available

Urgent Union Procedure
Announcement

Summary of the Safety issue and Action proposed

Notification + scientific background

Draft list of all products concerned

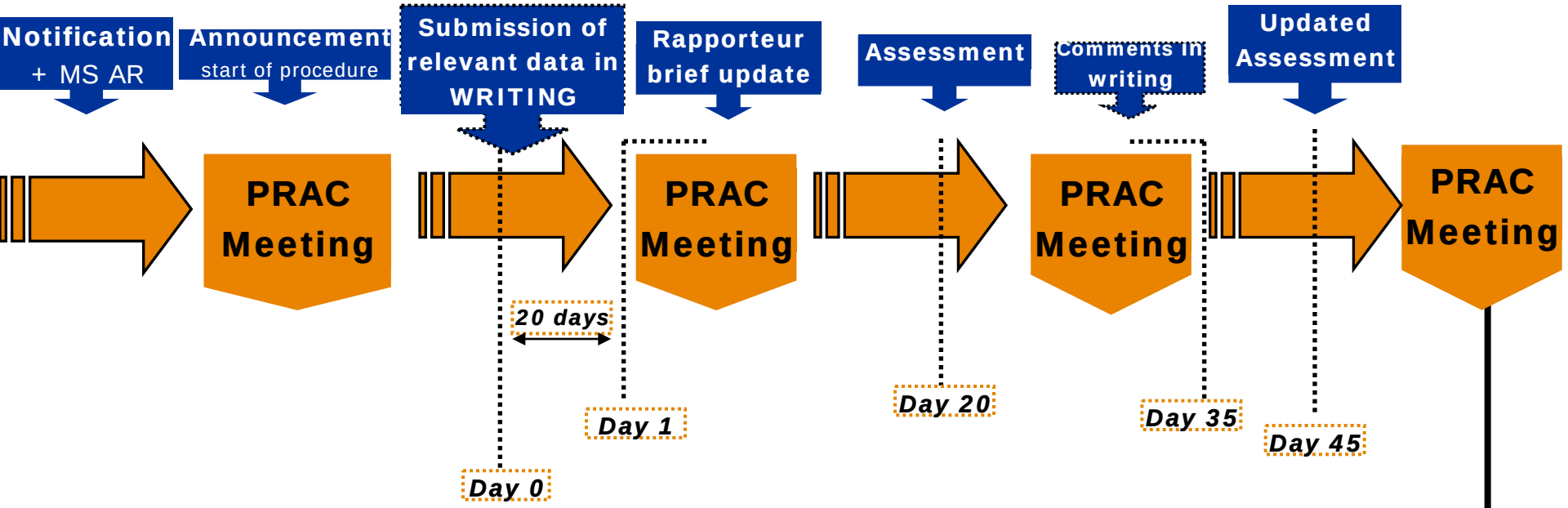
Questions + timetable for assessment

Information on Public hearing

Submission of data
(dedicated mailbox and template form)

Example: Diclofenac-containing medicinal product
http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/human/referrals/Diclofenac-containing_medicines/human_referral_prac_000009.jsp&mid=WC0b01ac05805c516f

Overall PRAC assessment



- Consideration of the matter;
- Temporary measures needed?
- SAG/Ad-hoc expert meeting
- Public Hearing?
- Which data to ask?
- When & how to submit?

- Public Hearing?
- Temporary measures;
- SAG/Ad-hoc expert meeting
- Preliminary discussion;

- Public hearings held?
- Non-Public hearing
- Discussion

PRAC RECOMMENDATION

Urgent Union Procedure
PRAC recommendation

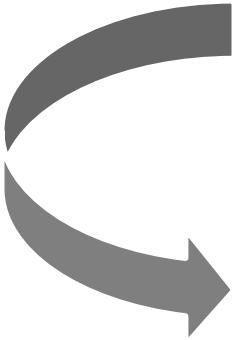
A. PRAC outcomes defined

- no further evaluation or action is required at union level;
- the MAH should conduct further evaluation of data together with the follow-up of the results of that evaluation;
- the MAH should sponsor a post-authorisation safety study together with the follow up evaluation of the results of that study;
- the MS or MAH should implement risk minimisation measures;
- the MA should be suspended, revoked or not renewed;
- the MA should be varied

B. TT for implementation (if NAPs/MRP/DCP)

C. PRAC divergent position(s)

Urgent Union Procedure
PRAC recommendation



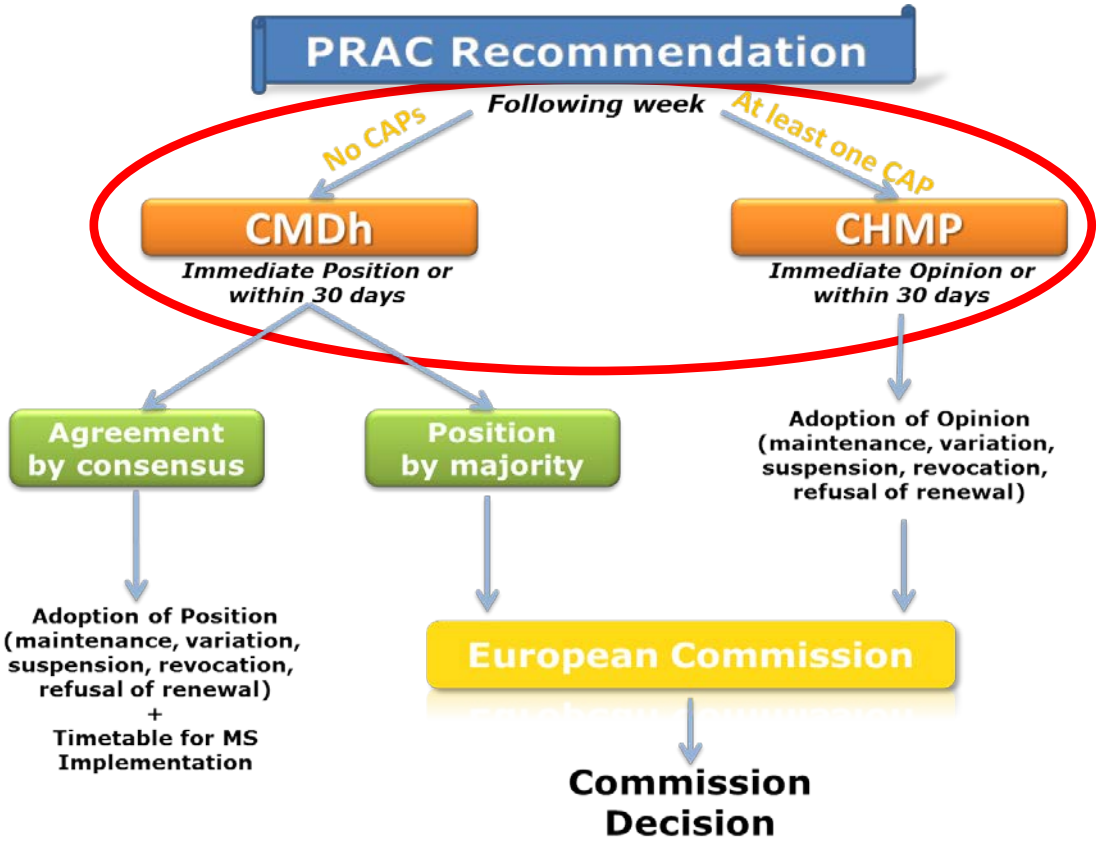
Publication

PRAC highlights

- *Friday* of the PRAC plenary
- Press release (if applicable);
- Question & Answers-type document in lay language

Urgent Union Procedure

Overall process of decision



Urgent Union Procedure

CHMP Opinion, CMDh position / agreement

Publication

CHMP / CMDh highlights

- *Friday* of the monthly plenary
- CHMP Opinion + CHMP AR
- CMDh position/agreement
- Press release (if applicable)
- Question & Answers-type document in lay language

Article 31
Quality, safety or efficacy issues

- **When?**
  - ✓ shall be applicable where the interests of **the Union** are involved;
  - ✓ following concerns relating to the **quality, safety or efficacy;**
  - ✓ a medicine or a class of medicines;
  - ✓ No urgent action required (possible clock stop);
  - ✓ urgent action to protect public health possible.
- **Safety Art.31 vs. Q&E driven Art.31**
  - ✓ involvement of different Committees;
  - ✓ pathways of announcement;
  - ✓ Possibility of a Public hearing.

PHARMACOVIGILANCE CONCERNS

NAP/MRP/DCP → ARTICLE 31 PROCEDURE

Initiated by	MS/EC/MAH
Time Limit	60 + 60 + 30 days (Possible clock stop)
Consultation	MAHs (Written +/- oral) Public hearing
Outcome	PRAC recommendation CHMP opinion or CMDh agreement/position
Urgent Action to protect public health	Commission decision if applicable No specific provisions but MSs can suspend any time

RE-EXAMINATION

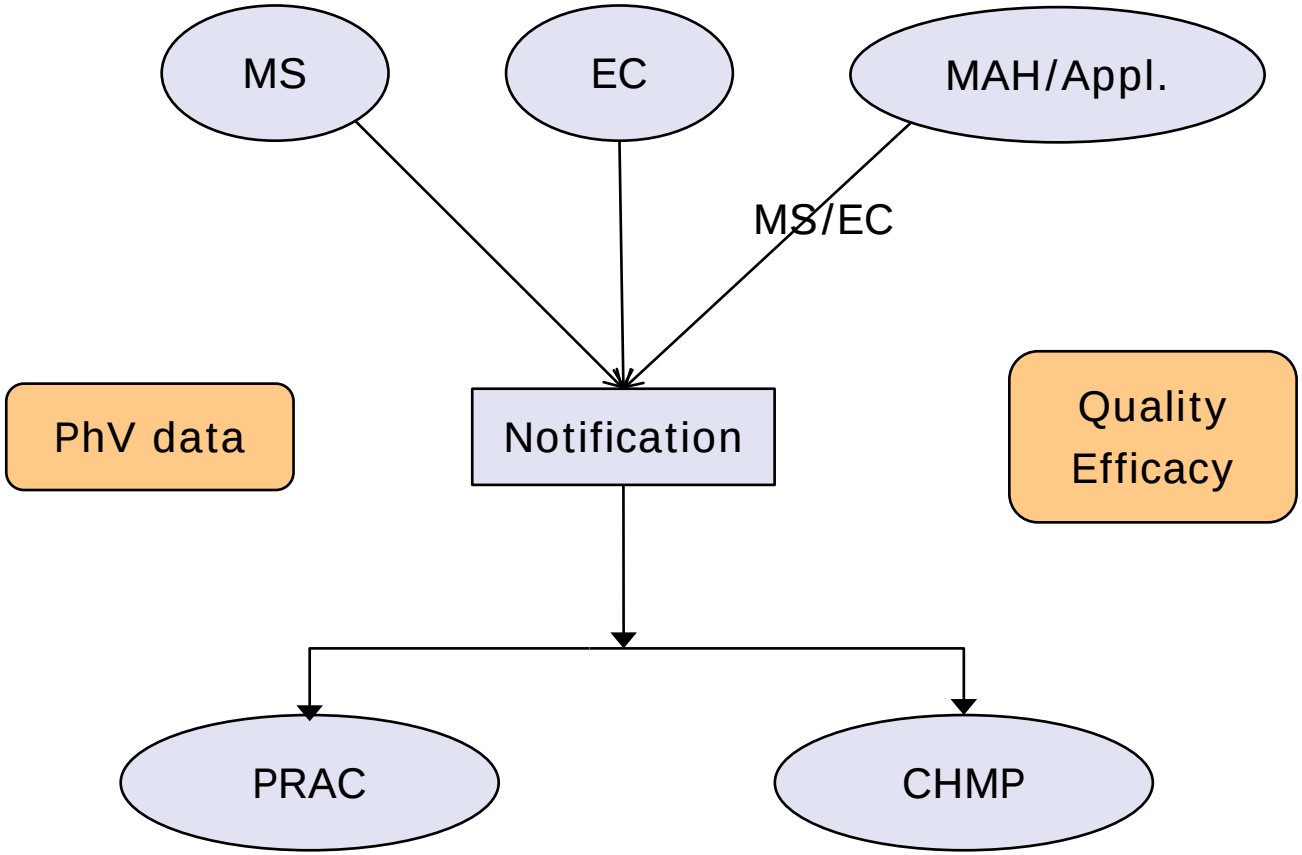
EFFICACY, QUALITY CONCERNS

NAP/MRP/DCP → ARTICLE 31 PROCEDURE

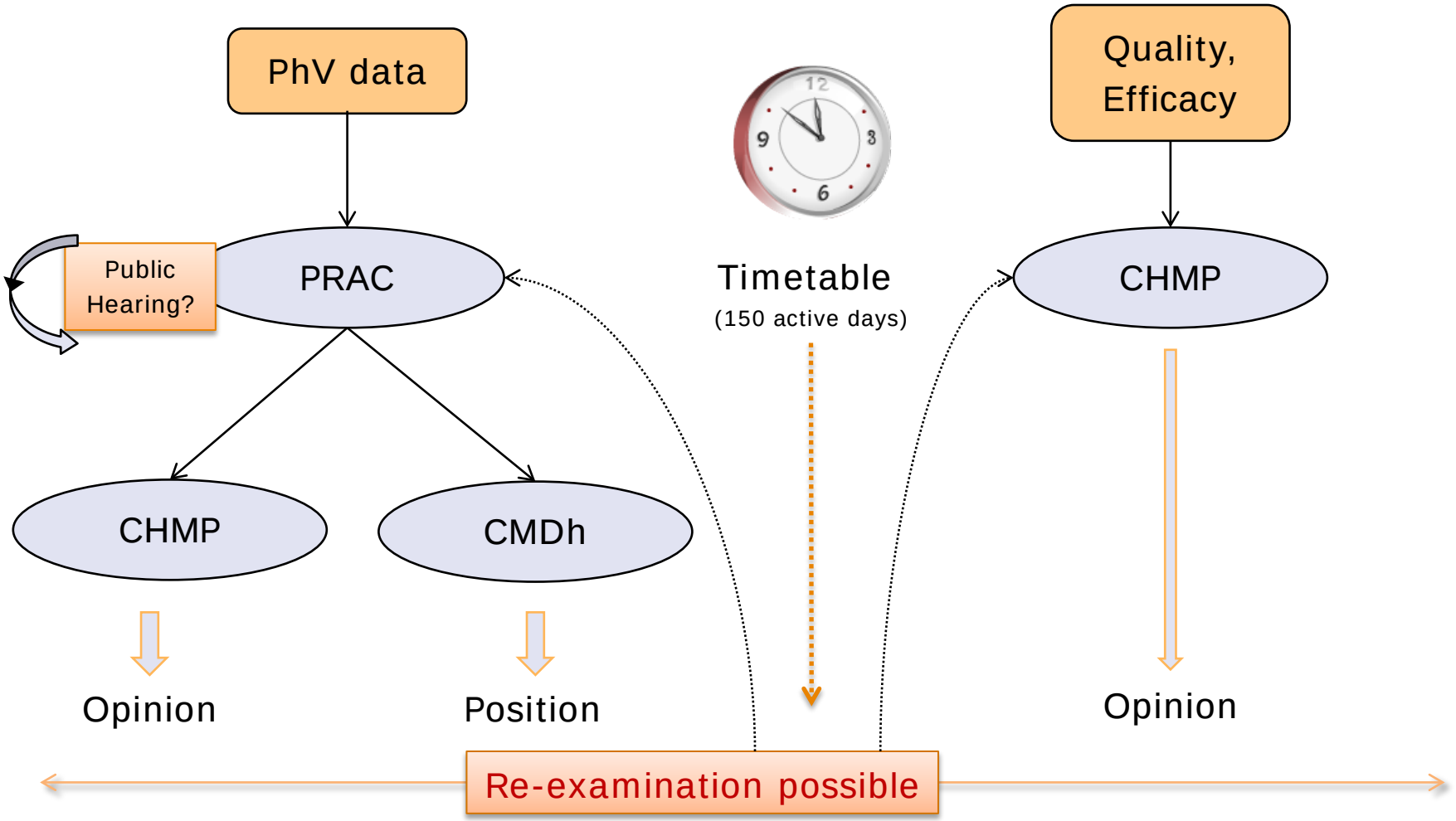
Initiated by	MS/EC/MAH
Time Limit	60 + 90 days (Possible clock stop)
Consultation	MAHs Written +/- oral
Outcome	CHMP opinion Commission Decision ♦ Final (measures)
Urgent Action to protect public health	No specific provisions but MSs can suspend any time during procedure

RE-EXAMINATION

In summary: NO urgent action required (1/2)

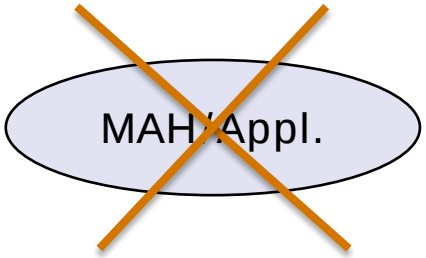


Timelines: (2/2)



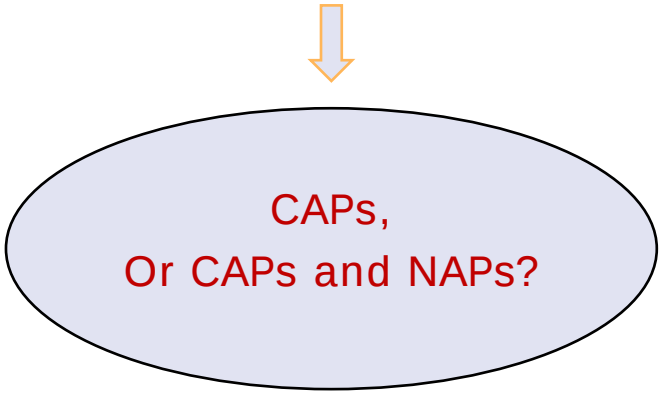
Article 20
Quality, efficacy or safety issues

- *Manufacturing and qualities issues?*
  - ✓ Art.20 of the Reg. (EC) 726/2004 remains *(Manufacturer/importer established within the Community territory no longer fulfilling the obligations laid down in Title IV of Directive 2001/83/EC)*
  - ✓ For CAPs
  - ✓ Triggering body: EC or MS
  - ✓ To ensure public health:
    - ✓ provisional measures tool
    - ✓ possibility of MS to suspend the use of the product
  - ✓ No re-examination foreseen



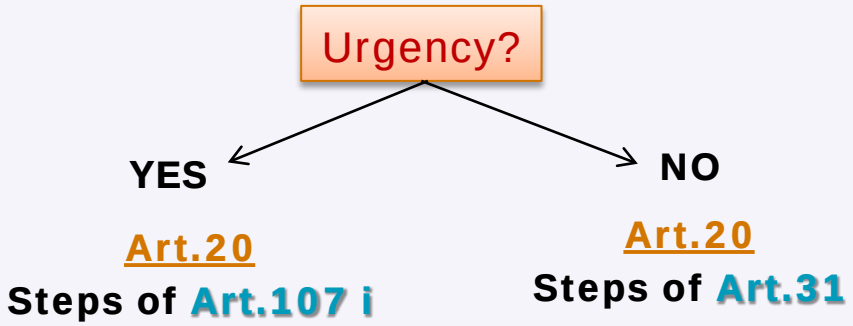
Article 20 - safety issues

- *When **pharmacovigilance data** are concerned*
  - ✓ involvement of different Committee
  - ✓ pathways of announcement
  - ✓ possibility of public hearing



Centrally (CAPs) + Nationally (NAPs) authorised products

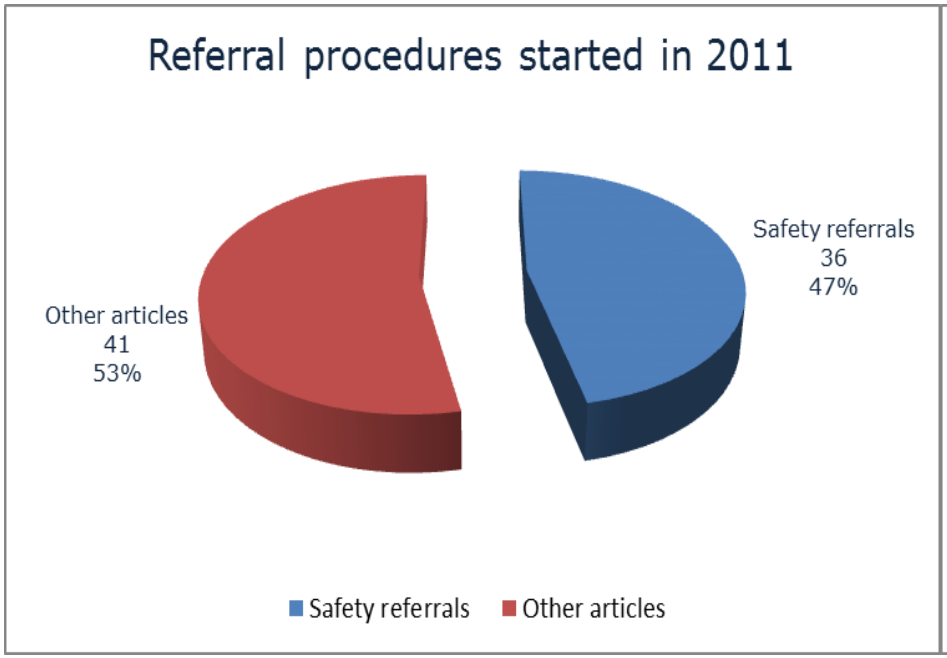
Article 20(8)	Art 20(9)
only CAP(s)	**CAP(s)+NAP(s)**
Procedural steps followed: the ones defined under the article 31 or 107i (depending upon the urgency of the PV matter)	Procedure followed: article 31 or 107i (depending upon the urgency of the PV matter)

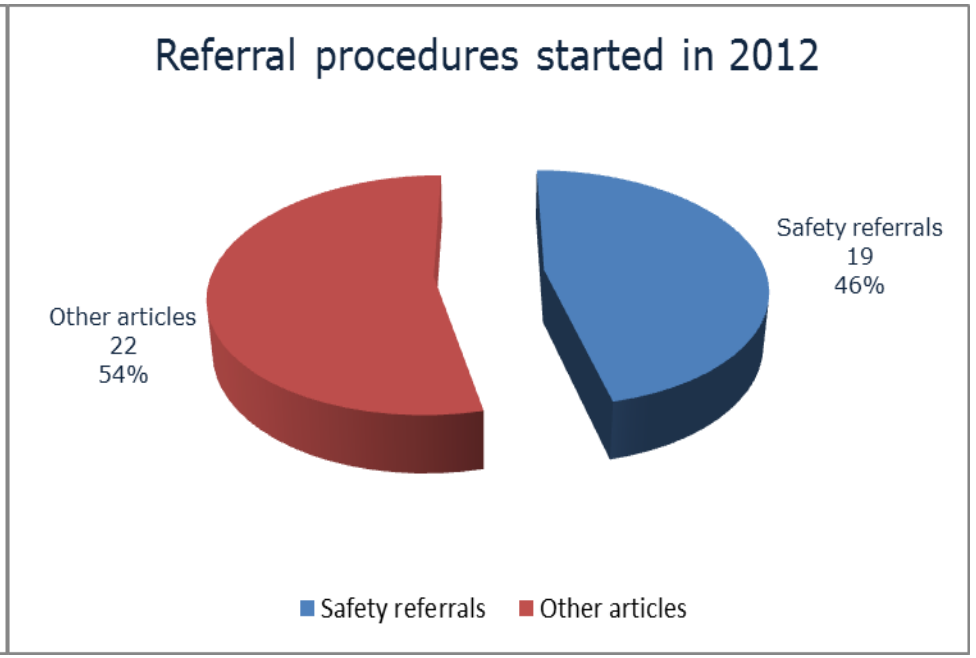


CAPs only: procedural steps (art. 107i vs. art. 31)

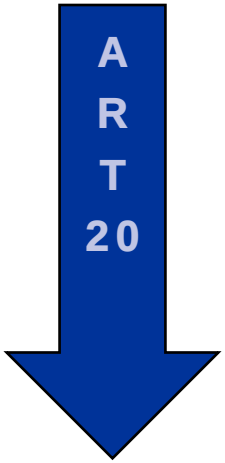
Procedural steps defined under the art. 107i (urgent action needed), including:	Procedural steps defined under the art. 31 (non urgent action needed), including:
PRAC involvement	PRAC involvement
Announce start of procedure in the web portal	Announce start of procedure in the web portal
Possibility for healthcare professionals and public to submit to the Agency relevant information to the procedure	-
Possibility for public hearing, non public hearing and oral explanation	Possibility for public hearing, non-public hearing and oral explanation
60 days for PRAC recommendation following submission of the information	Timelines to be followed are the ones established in Article 32 of Directive 2001/83/EC
Issue of a PRAC recommendation	Issue of a PRAC recommendation
Adoption of temporary measures at any stage of the procedure	-
CHMP to adopt an Opinion within 30 days of the receipt of the PRAC recommendation	CHMP to adopt an Opinion within 30 days of the receipt of the PRAC recommendation

Safety Referrals
Some numbers





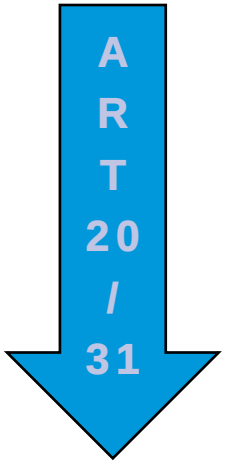
Safety Overview Pre PRAC



Gilenya

Rasilez

Avandia

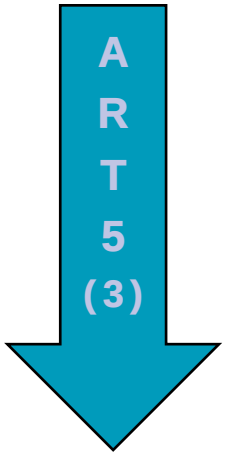


MMR vaccines

Fibrin sealants (fibrinogen)

Biphosphonates

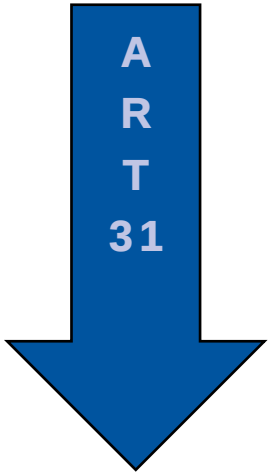
Somatropins



Pandemic vaccines

Angiotensin II receptors antagonists

Safety Overview Pre PRAC

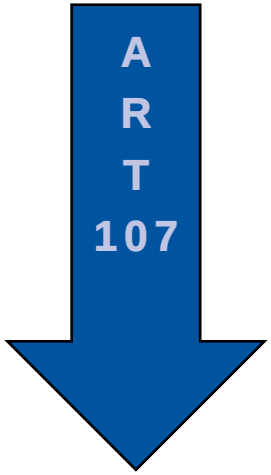


Ergot derivates

Terpenic derivatives

Nicardipine (B/R)

Nimesulide



Buflomedil

Meprobamate

Sibutramine

Safety Overview – post PRAC

ART 31

PRAC

Codeine
Diclofenac
Short Acting Beta Antagonists
Hydroxyethyl Starch
Almitrine
Diacerein

Thank you

Any question?