

CAST analysis of pregnancy adverse events DURING/AFTER isotretinoin administration

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1st November 2018, ESWC 2018

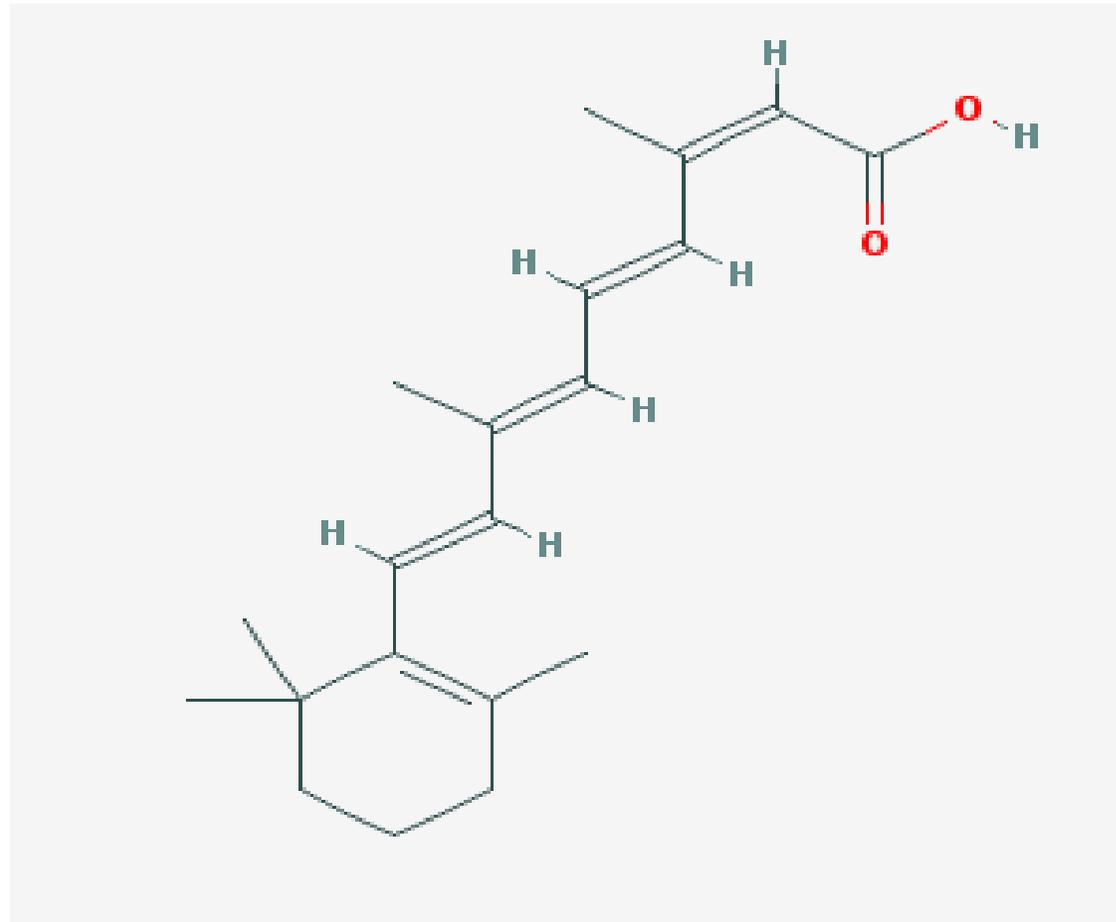


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Background and disclaimer

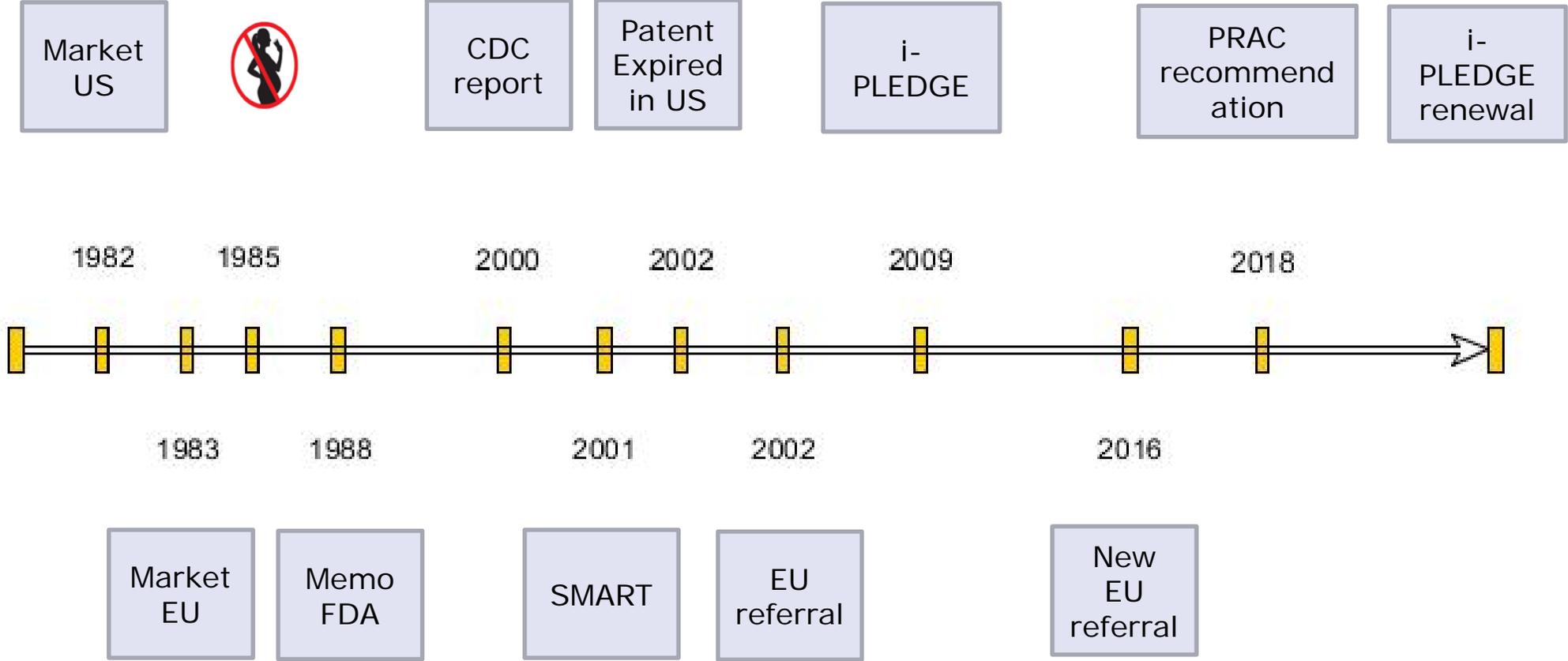
- **Background:** Results of CAST analysis conducted on UK pregnancy events for isotretinoin reported to the EudraVigilance database of the European Medicines Agency (EMA) from 2005-2017.
- Dissertation thesis for the MSc of Pharmacovigilance in the University of Hertfordshire, London, UK under the supervision of Dr Sherael Webley and topical supervision of Dr Ioannis Dokas, University of Thrace, Greece.
- Comments and advice provided by Dr Brian Edwards of NDA group, ACRES and ISoP
- Represents the opinions of the authors and does not express the official positions of EMA or MHRA or the Greek Agency.

ISOTRETINOIN



Chemical type of isotretinoin

HISTORY

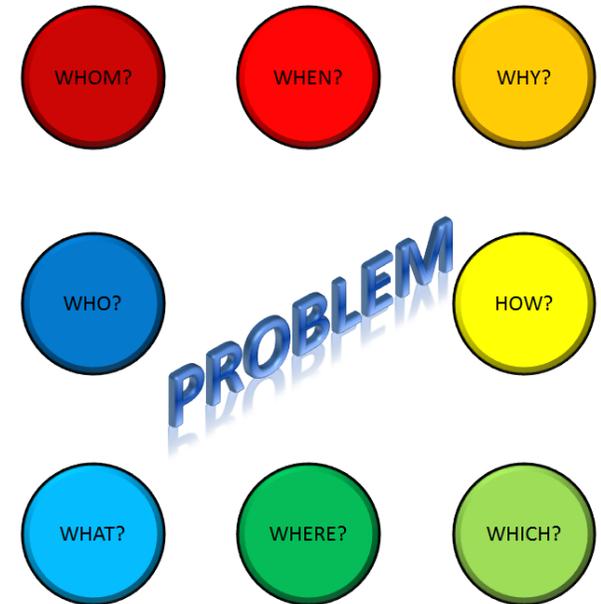


PROBLEM AND SCOPE

Problem: Pregnancies still occur even though risk minimizations were imposed (30 years).

Scope: Identify vulnerabilities in the current system and provide recommendations for their improvement.

Tool used: CAST

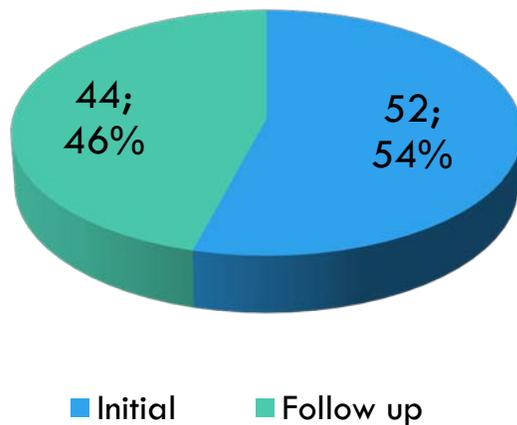


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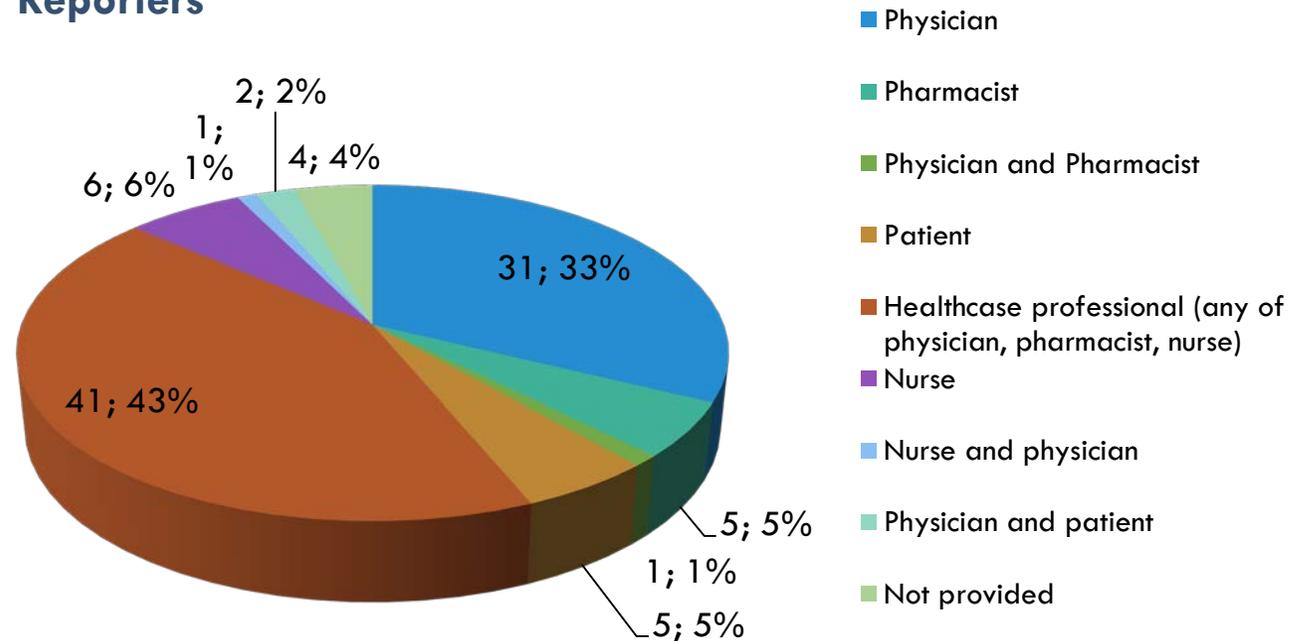
Methods

- CAST Analysis based on pregnancy reports in the UK
- 96 pregnancy reports retrieved and analyzed
- 52 initial cases (first time events) and 44 follow up cases (further action to obtain final outcome of pregnancy)

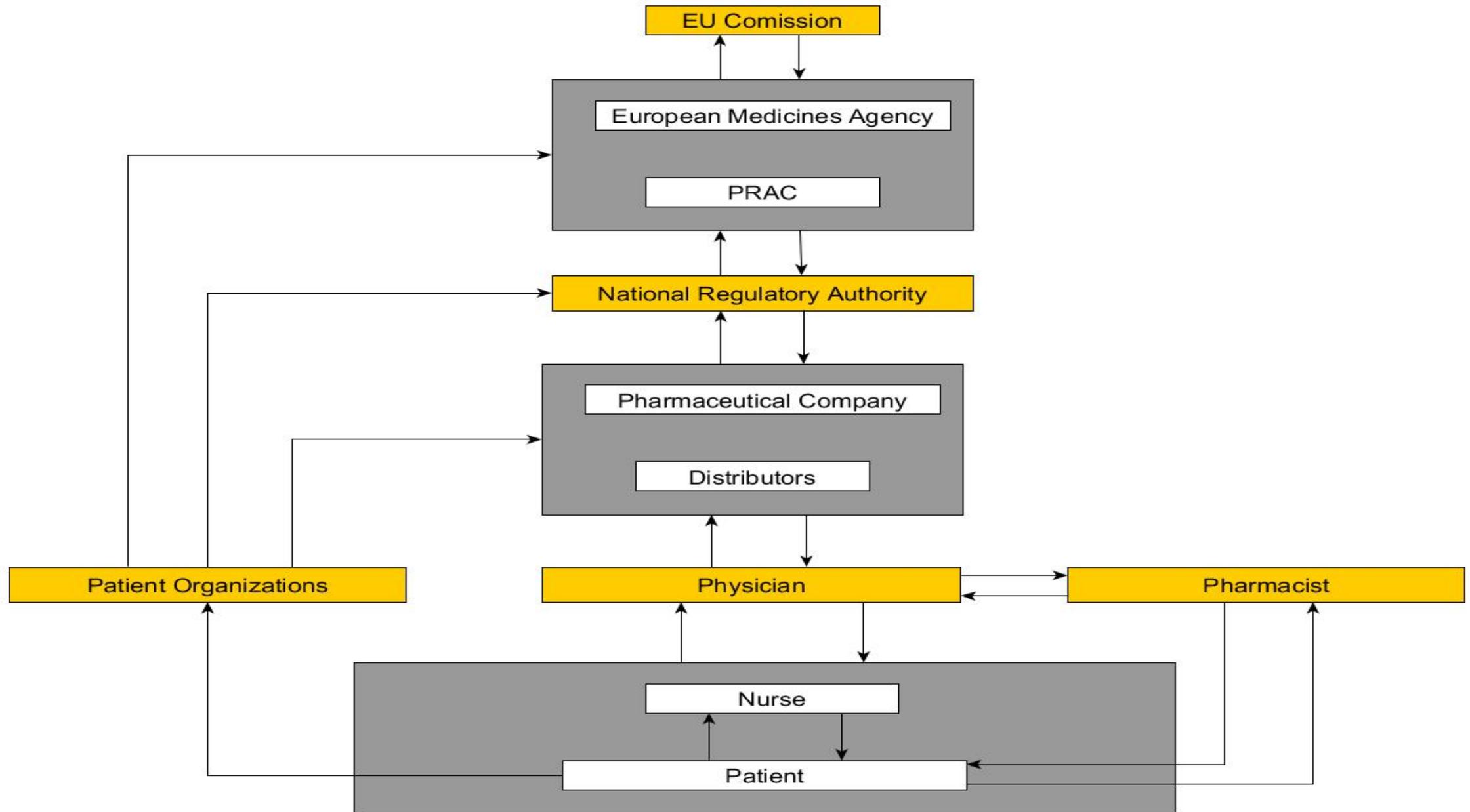
Report type



Reporters



Safety Control Structure



Cast analysis results

- System Hazard: 1
- Events associated with the problem: 11
- Questions raised: 38
- Unsafe Control Actions (UCAs) identified: 13
- Inadequate controls of the physical components: 3
- Recommendations in a two way manner (re-evaluation of some aspects of the Pregnancy Prevention Program and suggested improvements for some controllers)

CAST ANALYSIS

System Hazard: Pregnancy during or after the use of isotretinoin.

Safety constraints:

The patient must not become pregnant at least a month before starting, during or after the use of isotretinoin.

Measures must exist in order to prevent the event of pregnancy up to one month before, during or after the use of isotretinoin.

Specialist advice must be available in order to treat the patient in case pregnancy occurs.

CAST ANALYSIS- EVENTS INVOLVED IN THE ACCIDENT (PREGNANT while on ISOTRETINOIN)

ID	EVENT	QUESTIONS RAISED
1.	25 out of 26 cases from 2005 until 2011 were listed with MedDRA terms Pregnancy and outcome No adverse event . All the cases concerned the reference product of isotretinoin.	Why the adverse reaction is listed with outcome No Adverse Event although there is a second MedDRA term Pregnancy showing that the pregnancy has occurred? Why the pharmaceutical company listed the outcome of these cases as No Adverse Event cases? Is this meant to be no additional adverse event or adverse outcome? Do MedDRA coding conventions need examining?
5.	The companies inform the patients on risks and adverse reaction through Product Information.	What regulators do to check PILs of MAHs?
6.	Most of the Marketing Authorizations for isotretinoin are National and controlled by the Member States.	How do Member States control the National MAs? Is the process considered harmonized for all the Member States? What is the role of the EU Safety Committee (PRAC) in this process?

CAST ANALYSIS-EVENTS INVOLVED IN THE THE ACCIDENT (PREGNANT while on ISOTRETINOIN)

ID	EVENT	QUESTIONS RAISED
7	In the cases that were obtained there is a clear understanding that the contraception that was used during the administration of isotretinoin either failed or the patient didn't take at all the contraception or the patient was not compliant with the contraception that was used.	Why did the contraception failed? Why the patient was not taking contraception at all? Why the patient was not compliant with the means of contraception used? Is the advice for the method of contraception in the Pregnancy Prevention Program the right one? Is it a matter of religion in some Member States?
11	Considering the physician as controller, a dermatologist should be the one initiating the prescription and performs the pregnancy test alongside with a team of physicians led by him as the PPP informed.	Who should be the controller in this case? Only the dermatologist? Is this performed in practice or is control shared with GPs? Is the dermatologist the one that prescribes or in some way other persons take his place that are not responsible for the action i.e. nurses?

CAST ANALYSIS- ROLE OF PHYSICAL COMPONENTS

Family Planning Clinic

Missing or inadequate family planning clinic controls that might have prevented the cases of pregnancy:

- Women see General Practitioner after appointment. In case of an emergent situation the process lacks consultation about contraception.
- The nurse as actuator provides advice on possible next steps when a pregnancy occurs. The process lacks information on whether the advice is given directly by the nurse or after an appointment with the GP.
- Education of nurses on teratogenicity risks of isotretinoin.

Failures:

The advice that is sought in a family planning clinic is not always the appropriate one.

CAST ANALYSIS- ROLE OF PHYSICAL COMPONENTS

Unsafe inter

Example

➤ The appoi character	Oct. 2006	Pregnancy test performed prior to isotretinoin onset- Negative	ne emergent
➤ The advic needs adv	Oct. 2006	Onset of therapy with isotretinoin	ig the woman
	Dec. 2006	Stopped isotretinoin because of mood swings Contraceptive desorgestrel but unspecified dates of but resumed it on an unspecified	
<u>Contextua</u>	4 Jan. 2007	Second pregnancy test negative	
➤ Education	14-17 Jun 2007	Didn't take contraception but resumed it afterwards	
➤ Mental sta	14-17 Jun 2007	or between these dates: Intake of several pills of isotretinoin.	itutes of Family exist.
➤ Absence of planning of	27 Jul 2007	Confirmation of pregnancy (2-8 weeks pregnant)	
➤ Consisten	9 Sept. 2007	Spontaneous abortion	

CAST ANALYSIS-CONTROLLERS AND UNSAFE CONTROL ACTIONS

Physician

➤ Unsafe Control Actions (UCAs)

- UCA 1: The physician - consultant dermatologist - didn't perform any follow up with the patient.
- UCA 2: The physician didn't explain to the patient the risks of isotretinoin during pregnancy.



CAST ANALYSIS- UNSAFE CONTROL ACTIONS

Pharmacist

➤ Unsafe control actions (UCAs)

- **UCA 3:** The pharmacist didn't provide any information to the patient about the risks of isotretinoin during pregnancy.

(This is assumed in the CAST analysis as there are no information in the narrative but there was a case that a pharmacist reported that the patient seemed unaware of the risks of isotretinoin even though she was taking it, but no information is given whether the pharmacist provided counseling).



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CAST ANALYSIS- UNSAFE CONTROL ACTIONS

Distributor

➤ Unsafe control actions (UCAs)

- **UCA 4:** The Distributor didn't perform in local level the follow up on events of exposure to isotretinoin during pregnancy.

(This action is assumed in the CAST analysis as there are no data provided on the cases if the follow up was the action of the MAH or a local distributor.

This illustrates the lack of essential detail in many narratives).



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CAST ANALYSIS-UNSAFE CONTROL ACTIONS

Pharmaceutical company

➤ Unsafe control actions (UCAs)

- **UCA 5:**The Pharmaceutical Company didn't provide the appropriate MedDRA coding in the received adverse reactions.
- **UCA 6:**The Pharmaceutical Company didn't provide constructed narratives for serious cases that had to do with pregnancy cases.
- **UCA 7:**The Pharmaceutical Company didn't engage in follow up actions concerning cases of pregnancy in order to obtain the outcome.



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CAST ANALYSIS-UNSAFE CONTROL ACTIONS

MHRA/ Regulator

➤ Unsafe control actions (UCAs)

- **UCA 8:** The respective Regulator didn't inform the physicians about any changes to the PPP of isotretinoin or any risk minimization measure that concerned them (*This UCA is assumed as obstetrician provided information in one case*)
- **UCA 9:** MHRA/Regulator has not inspected and looked in depth processes of MAHs such as the changes in SmPC/ PIL, follow up activities, narratives and MedDRA coding.
- **UCA 10:** The collaboration between EMA, national Regulatory Authorities and PRAC was ineffective as the risk minimization measures of isotretinoin failed to fulfill their purpose.
- **UCA 11:** The different regulatory authorities in the EU Member States do not treat the national marketing authorizations of isotretinoin in a harmonized way.

Contextual factors:

Different factors of role of divergent nations when decision must be made

- Ethnicity
- Religion
- Economic state
- Compliance
- Behavior
- Living standards

More factors

- Change of the state of living
- Education
- Changes in technology
- Different tendencies (people tend to forget risks)

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CAST ANALYSIS-UNSAFE CONTROL ACTIONS

Pharmacovigilance Risk Assessment Committee- PRAC

➤ Unsafe Control Actions (UCAs)

- **UCA 12:** The collaboration between EMA, national Regulatory Authorities and the Committee was ineffective as the risk minimization measures of isotretinoin failed to fulfill their purpose.

This unsafe control action is considered a failure of three different controllers.

Contextual factors

Different factors of role of divergent nations when decision must be made	More factors
<ul style="list-style-type: none">• Ethnicity• Religion• Economic state• Compliance• Behavior• Living standards	<ul style="list-style-type: none">• Change of the state of living• Education• Changes in technology• Different tendencies (people tend to forget risks)

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CAST ANALYSIS-UNSAFE CONTROL ACTIONS

European Medicines Agency- EMA

➤ Unsafe Control Actions (UCAs)

- **UCA 13:** The collaboration between EMA, national Regulatory Authorities and PRAC was ineffective as the risk minimization measures of isotretinoin failed to fulfill their purpose.

This unsafe control action is considered a failure of three different controllers.

Contextual factors:

Different factors of role of divergent nations when decision must be made

- Ethnicity
- Religion
- Economic state
- Compliance
- Behavior
- Living standards

More factors

- Change of the state of living
- Education
- Changes in technology
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RECOMMENDATIONS

Two way recommendations:

1) **Concerning re-evaluation of certain aspects of the Pregnancy Prevention Program (PPP):**

- **Restriction in prescribing pharmacies trained to provide isotretinoin**
- **Preparation and education of the patient from the physician in mandatory face to face session**
- **Contraception methods:**
 - ✓ Use of patches, rings or diaphragms that limit the risk of pregnancy to 9% (6-12 pregnancies in 100 women/year) to barrier methods with possible risk of pregnancy to 18% (18 or more pregnancies in 100 women/year).
- **Pregnancy tests and the follow ups archived properly:**
 - ✓ Proof of performance by the appropriate staff/ team of the prescribing physician.
 - ✓ Use of paper records cards (such as with anticoagulants) or electronic solutions plus alert bracelets.
- **Family Planning Clinic:**
 - ✓ Better education of nurses into current, advanced and more safe contraceptive methods
 - ✓ Emergent appointments with physicians available in case of pregnancy event (24/7 phone line)
 - ✓ Dedicated educational materials through the Companies to the nurses of these Clinics or Medical centers.

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RECOMMENDATIONS

2) Concerning the controllers:

- **Better education of the patient regarding PPP and risks, including partner or close friend:**
 - ✓ Acknowledgement form that the risks have been understood,
 - ✓ Private sessions for discussion with the prescribing physician
 - ✓ Development of dedicated app or website for the risks of isotretinoin
- **Strengthening of communication between patient and physician:**
 - ✓ Appropriate monthly visits with the prescribing physician rather than the General practitioner. Sessions performed through Skype -patient must prove that participated in the sessions and understood (signed form)
- **Process of the physician being informed:**
 - ✓ Reminders through open access and free lessons or seminars from Regulators and Companies.
- **Strengthening of education of pharmacist:**
 - ✓ Key messages and short videos as “pop outs” in the electronic system of the pharmacy
- **Open participation of patient organizations in meetings with the Regulatory bodies** (conference organization on “hot” problems).
- **Outcome of pregnancy reports must be obtained in order to have the complete story:**
 - ✓ Efforts of follow up outcomes defined in the respective SOP and recorded.
 - ✓ Possible risk of systematic complacency that pregnancy cases are classified as expected and are ‘not serious’ because a plan is in place and ‘nothing else’ can be done.
- **Better education on an annual basis for the training of the Distributor from the MAH.**
 - ✓ Specific training for the recommendations of the PPP also from the MAH
 - ✓ Hypothetic scenarios on pregnancy cases and answers
 - ✓ Trained also to the relevant SOP of the MAH
- **PRAC Committee:**
 - ✓ Recommendation can be a change in the process of a referral and a re-evaluation of the measures taken at frequent times i.e. every 5 years.
 - ✓ A reinforce of the role of PRAC is considered effective.

STAKEHOLDERS' VIEWS AND SOME POINTS RAISED

▪ **Quality-controlled case processing activity:** MAH will follow up on cases (repeatedly when appropriate) and check that they have done so.

Published studies: Response rate for such follow-ups is very low.

▪ Pregnancy cases are considered "**Adverse Events of Special Interest**", which means that in many circumstances they are processed as if they were serious cases even though they do not meet the EMA definition of "serious". No plausible scenario in which the MAH would fail to give these cases the attention they deserve.

▪ Periodic reminders of drug risks are unlikely to be acceptable to regulators-concern that patients may discard them.

▪ Signed acknowledgement of risks by the patient is already part of the PPP in the US (human factor differs than actual risk).

▪ Role of the family planning clinic as a controller is perhaps one of the most important contributions of the analysis.

▪ Religion and economic state as factors: In some parts of the US and some other countries the entire subject of teenage sexuality is taboo.

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CONCLUSIONS

- 96 pregnancy cases based in the UK were retrieved and analysed, 13 UCAs identified
- **CAST revealed:** Important failures of the system and the systematic complacency



People focus on compliance and machine processing cases

Implication: Pregnancy cases after isotretinoin are managed '*just like any other case*'.

- Two sets of recommendations were provided
- CAST can be easily used for analysis of teratogenic substances.
- **Possible limitation of the research:** Interviews with reporters not performed due to long procedure for approval by UK Ethics Committee.

Awards and future plans

- Presentation on MIT, March 2018
- MSc award from Pharmaceutical Information and Pharmacovigilance Association (PIPA) for Outstanding Achievement
- ISoP Poster Presentation (14-17 November 2018, Geneva)
- Acceptance of abstract on Pharmacology 2018 conference, London, UK
- Upcoming paper with intention to submit in high-graded journal magazine
- Discussions on STAMP application on a medication error case with upcoming paper



Thank you for your attention!!!

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Thanks:

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