

CAST analysis of pregnancy adverse events DURING/AFTER isotretinoin administration

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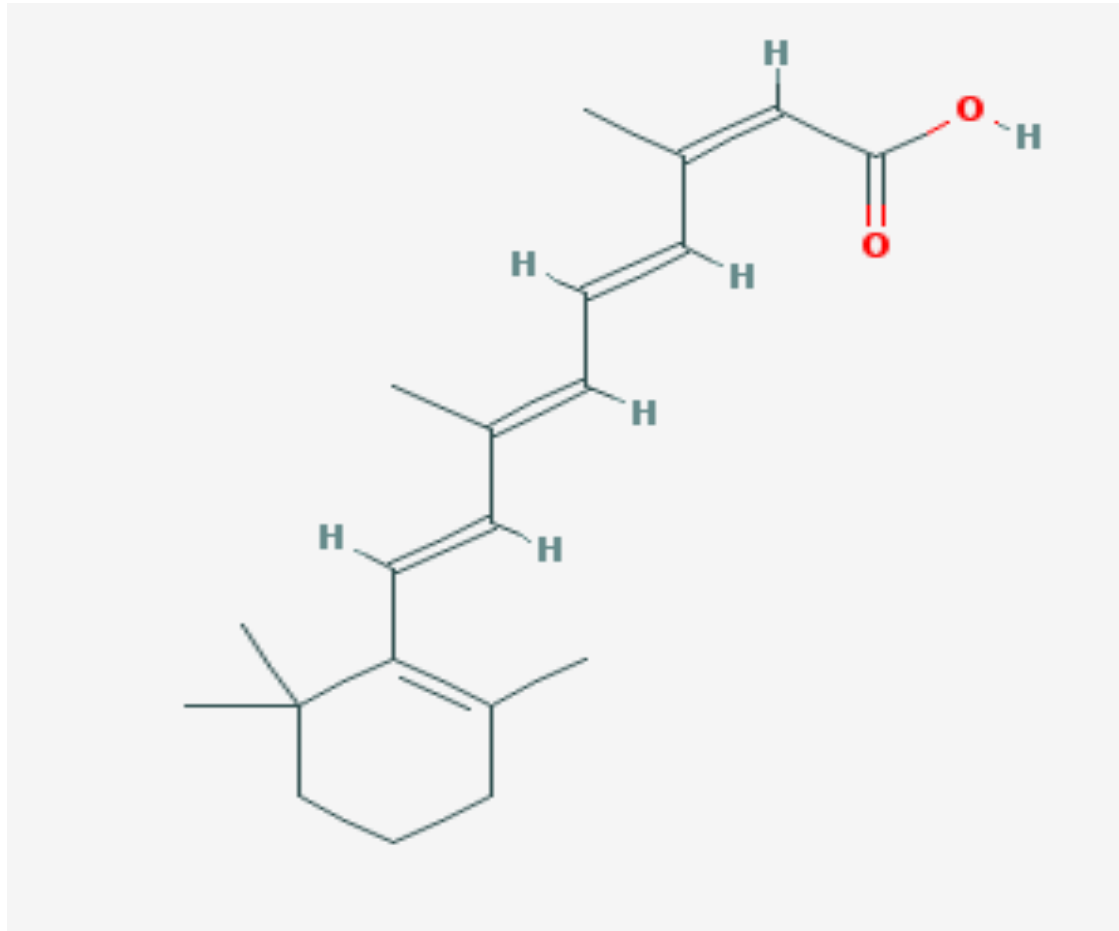


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Background and disclaimer

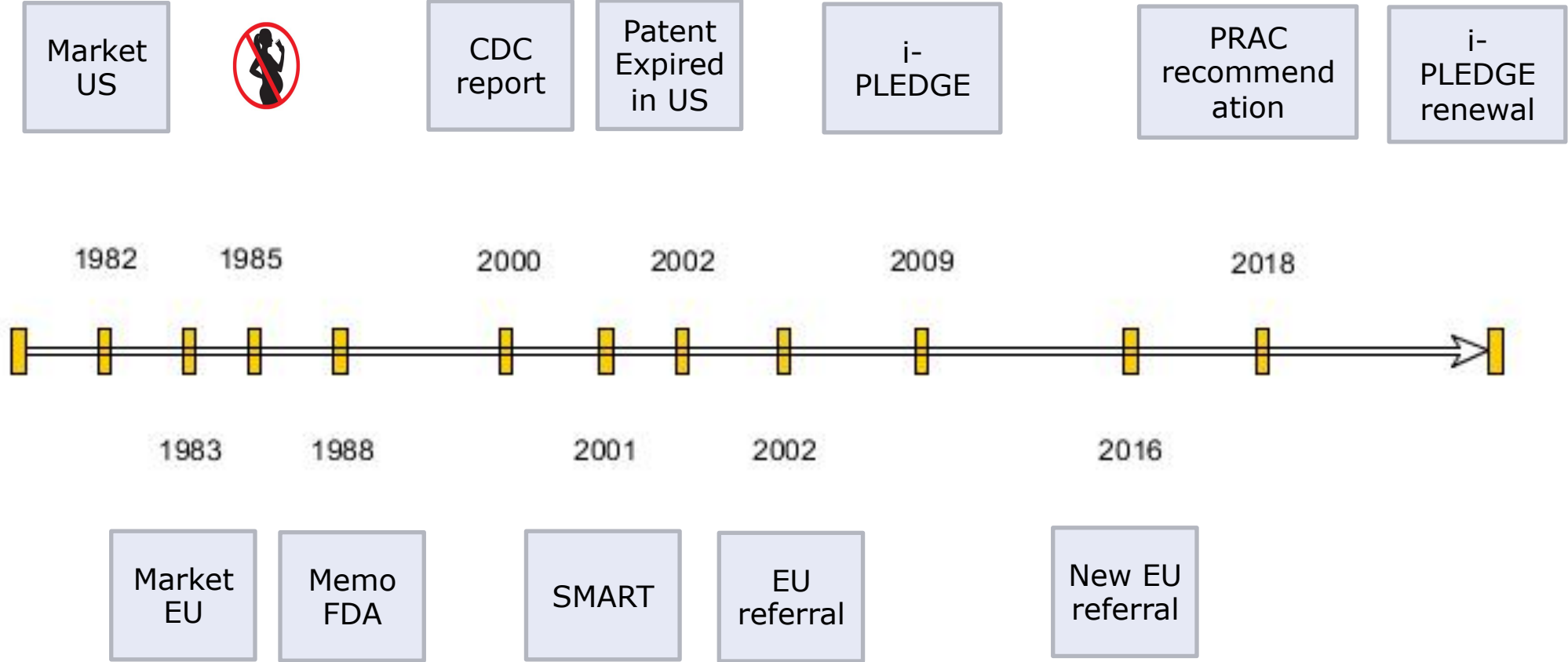
- **Background:** Results of CAST analysis conducted on UK pregnancy events for isotretinoin reported to the EudraVigilance database of the European Medicines Agency (EMA) from 2005-2017.
- Dissertation thesis for the MSc of Pharmacovigilance in the University of Hertfordshire, London, UK under the supervision 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

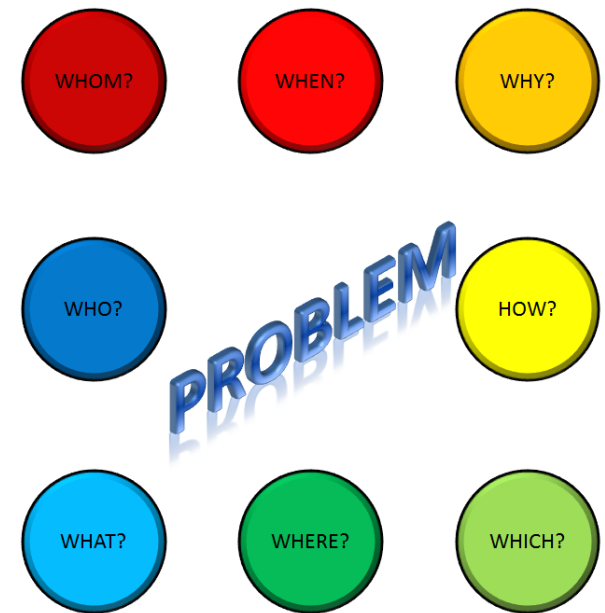


PROBLEM AND SCOPE

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

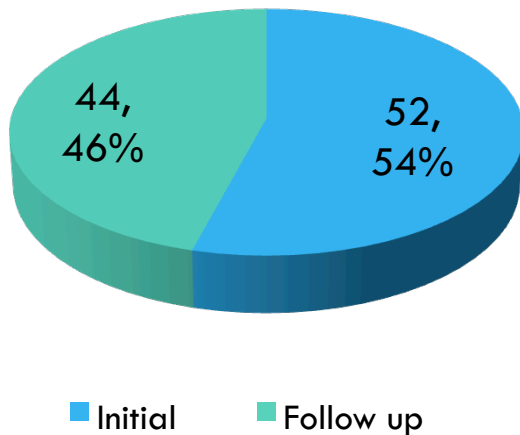


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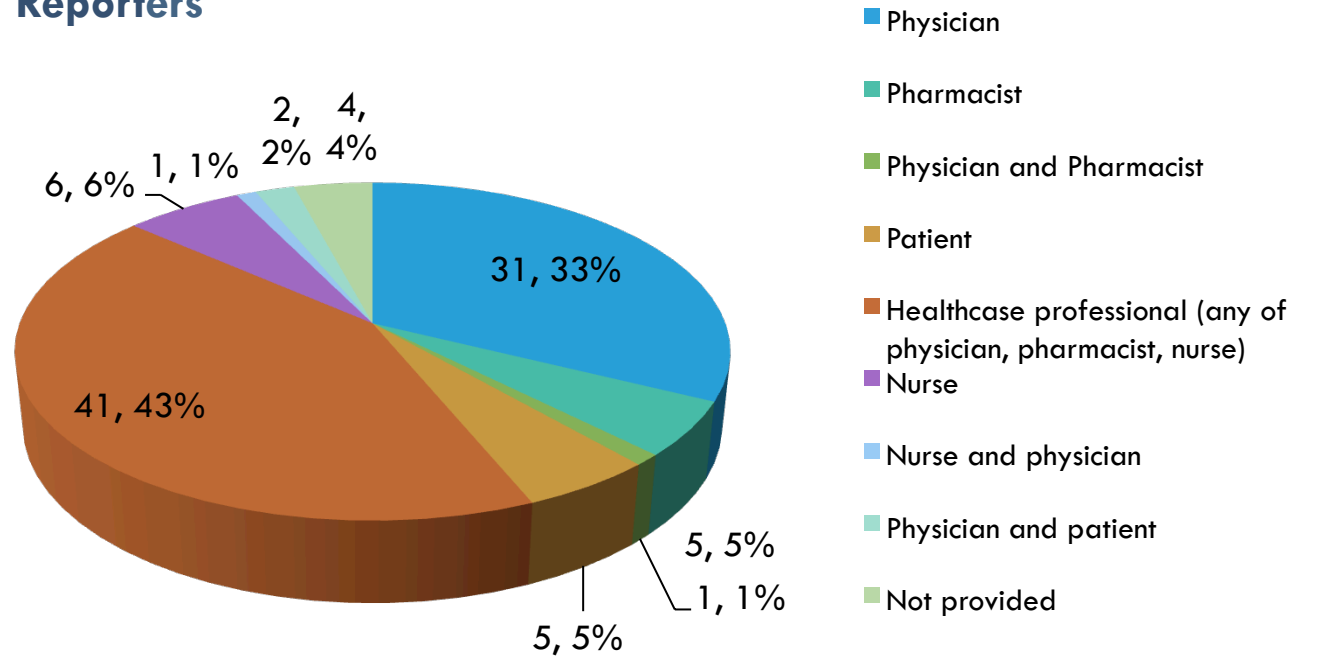
Methods

- 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



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 term Pregnancy and outcome No adverse event.	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
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
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~~7. In the cases that were obtained there is a clear understanding that the~~ ~~Why did the contraception failed? Why the patient was not taking~~

ID	EVENT	QUESTIONS RAISED
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7.	<p>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.</p>	<p>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?</p>
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Member States patients to consult a specialist in teratology?

11.	<p>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.</p>	<p>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?</p>
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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 interactions

Example

- | | | | |
|-------------------------------|----------------|--|---------------------------|
| ➤ The appointment character | Oct. 2006 | Pregnancy test performed prior to isotretinoin onset- Negative | the emergent |
| ➤ The advice from advice from | Oct. 2006 | Onset of therapy with isotretinoin | ing the woman needs |
| | Dec. 2006 | Stopped isotretinoin because of mood swings Contraceptive desorgestrel but unspecified dates of but resumed it on an unspecified | |
| Contextual | 4 Jan. 2007 | Second pregnancy test negative | |
| ➤ Education | 14-17 Jun 2007 | Didn't take contraception but resumed it afterwards | |
| ➤ Mental state | 14-17 Jun 2007 | or between these dates: Intake of several pills of isotretinoin. | stitutes of Family exist. |
| ➤ Absence of planning | 27 Jul 2007 | Confirmation of pregnancy (2-8 weeks pregnant) | |
| ➤ Consistent | 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

- Ethnicity
- Religion
- Economic state
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More factors

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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
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More factors

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RECOMMENDATIONS (proposed)

Based on the unsafe control actions 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 100 women per year) in relation to barrier methods with possible risk of pregnancy to 18% (18 or more pregnancies in 100 women per year).
- **Pregnancy tests and the follow ups archived properly:**
 - ✓ Proof that they are performed by the appropriate staff/ team of the prescribing physician.
 - ✓ Use of paper records cards (such as with anticoagulants) or electronic solutions plus alert bracelets

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RECOMMENDATIONS (proposed)

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 prior and during the use of isotretinoin.
 - ✓ Development of dedicated app or website for the risks of isotretinoin, suggested contraception methods and responsibilities.
- **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 on information on risks and safety recommendations can “pop out” in the electronic system of the pharmacy
- **Open participation of patient organizations in meetings with the Regulatory bodies** (conference organization on “hot” problems).
- **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 that must be given to patients and healthcare professionals (face to face or electronic means).
 - ✓ Trained also to the relevant SOP of the MAH (explaining how to conduct a follow up and the respected times for this).

RECOMMENDATIONS (proposed)

2) Concerning the controllers (cont.):

- **Constructed narrative in all pregnancy cases must exist**, irrespective of the data obtained- Narrative template
- **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.
- **Regulators must focus on actions and training of their staff in inspected areas like:**
 - ✓ Cases, narratives, MedDRA coding, PIL changes
 - ✓ Conduct the inspections combined with assessors or train the inspectors from assessors in the respected areas.
- **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.

CONCLUSIONS

- 96 pregnancy cases based in the UK were retrieved and analysed
- **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*'.

- 13 unsafe control actions were identified
- Two sets of recommendations are provided
- CAST can be easily used for analysis of teratogenic substances.

Future plans

- Application of CAST in other case studies such as sodium valproate and pregnancy reports.
- Discussions on PhD thesis for application of STAMP on a broader European level on medication errors.



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Thank you for your attention!!!

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Thank you to:

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