

Implementation of new EU Clinical Trial Regulation 536/2014

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Background

New regulation issued in July 2012



Published in draft 20 Dec 2013



CT regulation 536/2014 approved on 27 May 2014



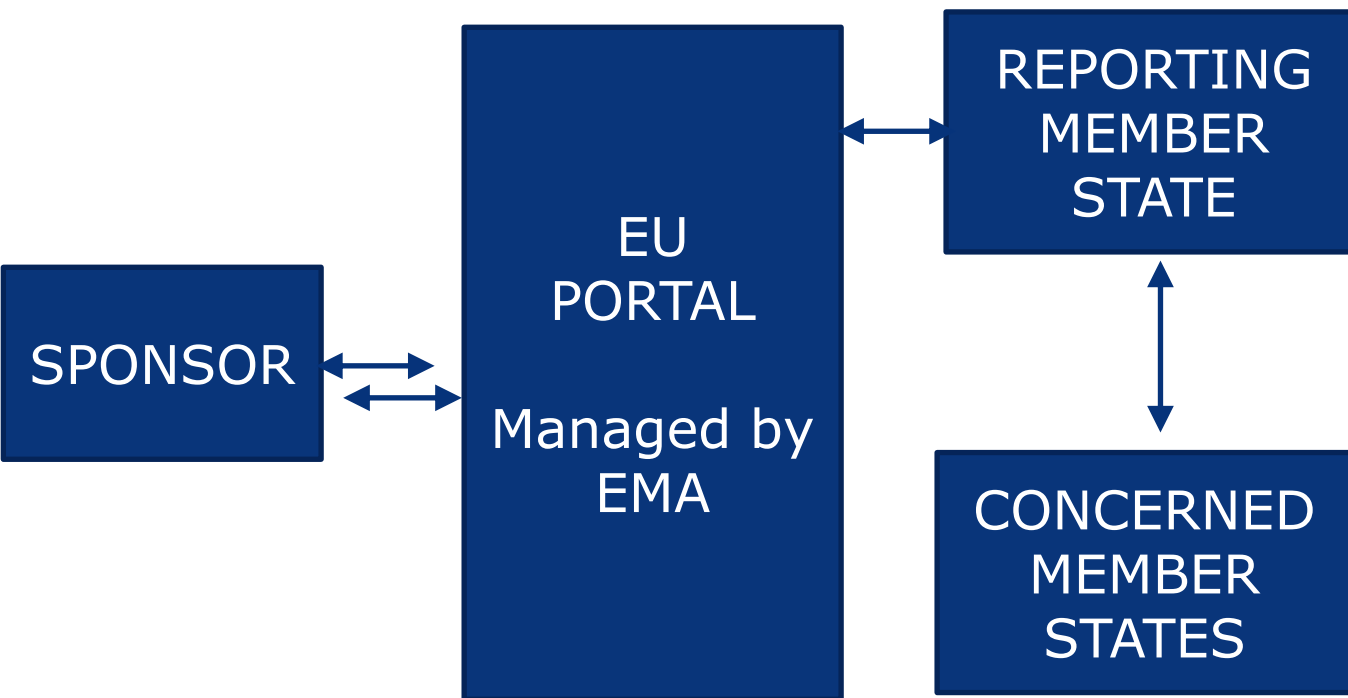
Will come into force by 28 May 2016
“unless the IT infrastructure...isn’t ready”

Regulation Not Directive

- No longer a Directive, therefore harmonisation is forced on Member States

- **Regulation is legally binding** - Rules for conducting clinical trials are identical throughout the EU.
- **Streamlined authorization procedure for clinical trials. A single application will be sufficient for conducting clinical trials in multiple member states.**

Submission, roles



1. In order to obtain an authorisation, **the sponsor** shall submit an application dossier to the intended **Member States concerned** through the portal referred to in Article 80 (the 'EU portal'). **The sponsor shall propose one of the Member States concerned as reporting Member State.**

(12) '**Member State concerned**' means the Member State where an application for authorisation of a clinical trial or of a substantial modification has been submitted under Chapters II or III of this Regulation respectively;

What's different / New

- Single EU Clinical Trials database to facilitate flow of information
- Single «ENTRY» point for CTA submission, emendments, informations
- Unique submission for ALL Concerned member states
- Simplified Single Unique evaluation procedure
- One final decision
- Reduced the Regulations diversity between member states (Harmonization)

Clinical labels – the details

ANNEX VI - UNAUTHORISED INVESTIGATIONAL MEDICINAL PRODUCTS

ANNEX VI - **C.** ADDITIONAL LABELLING FOR AUTHORISED INVESTIGATIONAL MEDICINAL PRODUCTS

Article 69: Language

The language of the information on the label shall be determined by the Member State concerned. The medicinal product may be labelled in several languages

Question: How will this be defined at the Member state level?

Annex 6 - UNAUTHORISED INVESTIGATIONAL MEDICINAL PRODUCTS

Paragraph	Label content	Inner and outer packaging label	Paragraph	Label content	Inner packaging label if 4 Immediate and outer packaging provided together or 5 Small immediate packaging
1(a)	name, address and telephone number of the main contact for information on the product, clinical trial and emergency unblinding; this may be the sponsor, contract research organisation or investigator (for the purpose of this Annex this is referred to as the 'main contact');	L/S	4(a) 5(a)	name of the main contact;	L/S
1(b)	the name of the substance and its strength or potency, and in the case of blind clinical trials the name of the substance is to appear with the name of the comparator or placebo on the packaging of both the unauthorised investigational medicinal product and the comparator or placebo;	L			
1(c)	pharmaceutical form, route of administration, quantity of dosage units;	L	4(b) 5(b)	pharmaceutical form, route of administration (may be excluded for oral solid dose forms), quantity of dosage units and, in the case of clinical trials which do not involve the blinding of the label, the name/ identifier and strength/potency; route of administration (may be excluded for oral solid dose forms) and, in the case of clinical trials which do not involve the blinding of the label, the name/identifier and strength/potency;	L
1(d)	the batch or code number identifying the contents and packaging operation;	L	4(c) 5(c)	batch and/or code number identifying the contents and packaging operation;	L
1(e)	a clinical trial reference code allowing identification of the trial, site, investigator and sponsor if not given elsewhere;	L/S	4(d) 5(d)	a clinical trial reference code allowing identification of the trial, site, investigator and sponsor if not given elsewhere;	L/S
1(f)	the subject identification number and/or the treatment number and, where relevant, the visit number;	L	4(e) 5(e)	the subject identification number and/or the treatment number and, where relevant, the visit number; and	L

L: Mandatory Label text

L/S: May be omitted from the label of a product and made available by other means, for example by use of a centralised electronic randomisation system, use of a centralised information system, provided that the safety of the subject and the reliability and robustness of data are not compromised. This shall be justified in the protocol.

Annex 6 - UNAUTHORISED INVESTIGATIONAL MEDICINAL PRODUCTS

Paragraph	Label content	Inner and/or outer packaging label	Paragraph	Label content	Inner packaging label / Immediate and/or outer packaging provided together or 5/5/5/1 immediate packaging
1(g)	the name of the investigator (if not included in (a) or (e));	L/S			
1(h)	directions for use (reference may be made to a leaflet or other explanatory document intended for the subject or person administering the product);	L/S			
1(i)	'For clinical trial use only' or similar wording;	L/S			
1(j)	the storage conditions;	L			
1(k)	period of use (expiry date or re-test date as applicable), in month and year format and in a manner that avoids any ambiguity; and	L	4(f) 5(f)	period of use (expiry date or re-test date as applicable), in month and year format and in a manner that avoids any ambiguity.	L
1(l)	'Keep out of reach of children', except when the product is for use in trials where the product is not taken home by subjects.	L/S			

L: Mandatory Label text

L/S: May be omitted from the label of a product and made available by other means, for example by use of a centralised electronic randomisation system, use of a centralised information system, provided that the safety of the subject and the reliability and robustness of data are not compromised. This shall be justified in the protocol.

UNAUTHORISED AUXILIARY MEDICINAL PRODUCTS AND ADDITIONAL LABELLING FOR AUTHORISED INVESTIGATIONAL MEDICINAL PRODUCTS

Paragraph	Label content	Inner and outer packaging label IF unauthorised auxiliary medicinal products	Paragraph	Label content	Inner and outer packaging label IF additional labelling for authorised IMP
6(a)	name of the main contact;	L/S	7(a)	name of the main contact;	L
6(b)	name of the medicinal product, followed by its strength and pharmaceutical form;	L			
6(c)	statement of the active substances expressed qualitatively and quantitatively per dosage unit;	L/S			
6(d)	batch or code number identifying the contents and packaging operation;	L			
6(e)	clinical trial reference code allowing identification of the clinical trial site, investigator and subject;	L	7(b)	clinical trial reference code allowing identification of the clinical trial site, investigator, sponsor and subject;	L
6(f)	directions for use (reference may be made to a leaflet or other explanatory document intended for the subject or person administering the product);	L/S			
6(g)	'For clinical trial use only' or similar wording;	L/S	7(c)	'For clinical trial use only' or similar wording.	L
6(h)	the storage conditions; and	L			
6(i)	period of use (expiry date or retest date as applicable).	L			

L: Mandatory Label text

L/S: May be omitted from the label of a product and made available by other means, for example by use of a centralised electronic randomisation system, use of a centralised information system, provided that the safety of the subject and the reliability and robustness of data are not compromised. This shall be justified in the protocol.

Requirements are broadly aligned with the current Annex 13, with the exception that the expiry date/re-test date information is required on the immediate packaging of small dosage units

Concern:

Update expiry date labeling when expiry date on inner packaging

Current process/practices

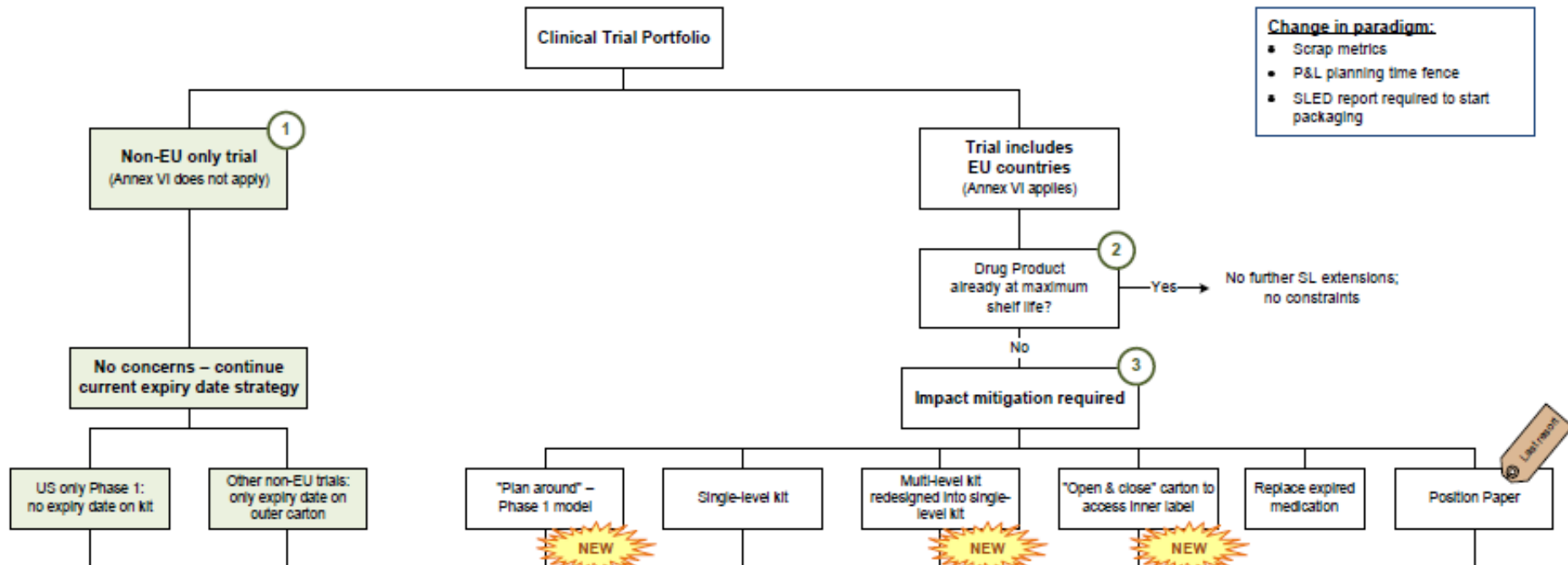
- Clinical trials can start with limited number of stability data and with a short expiry date.
- As a consequence many expiry date update labelings are performed
- Expiry update labeling can be done at the manufacturing site, at the depots and at the clinical sites by the pharmacist
- Update labeling protocol and labels sent to the clinical sites
- Currently only relabel outer carton; not open sealed kits (no expiry date on inside)

Janssen Workshop August 2015

- Make a *blue print* for expiry dating and expiry date update for a scenario when Annex VI becomes in force in its current restrictive wording
- Discuss practical ways for original labeling in order to avoid re-labeling
 - Innovative packaging/labeling
 - Discuss impact/potential of JIT
 - Differentiate between fase 1/fase 3 (depending on shelflife)

No 1 solution fits all

Decision tree



Question: How will this be managed by your companies?

Back-up

Transitional provision

- where the request for authorisation has been submitted **before the implementation date** that clinical trial shall continue to be governed by that Directive until three years from that date
- where the request for authorisation ... is submitted **between six months after the Portal implementation date and 18 months after that date** , or, if the publication of that notice occurs earlier than 28 November 2015, where that request is submitted between 28 May 2016 and 28 May 2017, **that clinical trial may be started in accordance with Articles 6, 7 and 9 of Directive 2001/20/EC.** That clinical trial shall continue to be governed by that Directive until 42 months after the date of publication of the notice referred to in Article 82(3) of this Regulation, or, if that publication occurs earlier than 28 November 2015, until 28 May 2019.

Technology solutions

- Flexible LCD display, that you update through the outer packaging
- Windows in outer packaging which can be opened and closed again, without breaking the integrity and sealing.
- Wrap which is put around the vial, and cannot come off again (origami solution) -> only label wrap
- Label around a syringe or vial, locked in a cardboard or pvc tray, with a part of the label sticking out of the tray (but in the outer box) where the update expiry date can be attached.

Planning solutions

- Set up intermediate stock with unlabeled inner vial?
- Not sure if this has advantage compared to just having vials in stock without secondary packaging.
- -Change mindset regarding planning of label activities: currently only possible to plan a campaign after availability of stab statement.
- This puts a lot of pressure on AD-TI (timely pulling samples for testing, analyzing data and providing approved stab statement).
- Also a lot of pressure on operations (when stab statement is finally available, rush to get everything packed and labeled)
- Pressure on QA, to get everything released on time for FPI.