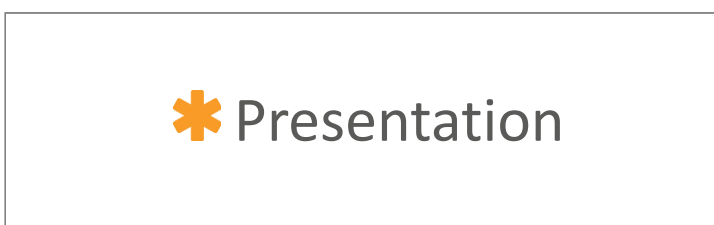
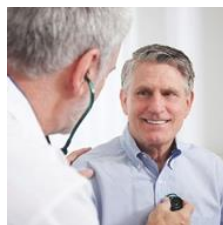


Annex VI Difficulties and Need for Change

Date: 18/02/2016 * Version: General use



Objectives of discussion



- 1) Promote mutual understanding for the need to change Annex VI for the good of patients in the EU;**
- 2) As far as practical, obtain mutual understanding of the technical reasons and concerns why the text of annex VI was changed;**
- 3) Understand the options and implications for the legal process in the Member States and how options can remain open for the future change of Annex VI;**
- 4) Understand the risks associated with Annex VI and the process of date extension at clinical sites where sponsors choose to make date extensions;**
- 5) Understand that trials will be lost to the EU because of the complexity that Annex VI brings and is counter to the intent of the CTR.**

The need to change Annex VI

1. EFPIA Position Paper 04 August 2014. (Attached 1)
2. EFPIA Video – (Can be played for those who have not seen it - [LINK to the video](#))
1. Annex VI EFPIA communication to the Commission Feb 2015. (Attached 2)
 - ✓ CTR can not be changed until it is effective
 - ✓ Can be changed for Annex VI after it is effective
2. More detailed understanding of the type of difficulties
 1. How often do date extensions take place
 - ✓ A real example
 2. Cost implications of Annex VI and expiry date

Types of difficulties

Difficulties with Annex VI	Difficulty sub types	Reason for problem
Immediate pack Expiry update	Blinded multiple containers e.g. double blind bottles or blisters in a dispensing pack	Risk of pack migration during up date and mix of treatment.
Immediate pack Expiry update	With a company's own product the Expiry Date data can be limited with up to 6 date extensions not uncommon.	Change of formulation own product. Product optimisation Pack optimisation Stability issue Early Phase to late phase change
Immediate pack Expiry update	Expiry date data limited with multiple updates of another company product	Comparator product needed in a blinded manner. Over-encapsulation
Immediate pack Expiry update	Not possible if device is to be used	If an additional label is required to be placed on the immediate container , this will no longer fit in the device

Types of difficulties continued

Difficulties with Annex VI	Difficulty sub types	Reason for problem
Immediate pack Expiry update	Environmental protection outer	Seal on an outer pack may give protection e.g. Nitrogen or inert gas flush or moisture protection
Immediate pack Expiry update	Security Seals	Must be broken during update on all packs
Immediate pack Expiry update	Storage conditions frozen – 70C	Label adhesion at -70 is very difficult. Inner packs typically are glass or plastic which makes this problem worse
Immediate pack Expiry update	Storage conditions frozen – 70C	Removal from outer packs gives high risk of thawing?
Immediate pack Expiry update	Storage conditions Cold 2-8C	Products are required to be taken out of cold storage thereby exposing them to temperature excursions that might affect stability.

Types of difficulties continued

Difficulties with Annex VI	Difficulty sub types	Reason for problem
Small pack update	Space on label	Space on the label is very limited Over labelling may be impractical
Small pack update	Sterility seal	Inner labelling may be inside seals to protect sterility e.g. pre filled syringes in blisters

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[illegible]

★ = Manufacture date

Cost implications of CTR Annex VI

- Highly variable from company to company depending on product, study and timing.
- Very few companies will have a clear measure as small changes can make a big difference and these changes only become apparent as development progresses per product.
- We have EU cost data from 20% of companies and have averaged this across the top 25 pharma companies.
 - The total cost of Annex VI is calculated at **162 million Euros per year**.
 - More than half the companies in data pool will have little or no additional costs due to their portfolio profile, bringing the average down.
 - One company not included in the data pool had a single study where Annex VI would have cost 1 Million Euros more.

Cost implications of CTR Annex VI

- This 162 million Euro is a significant proportion of the savings the CTR was intended to generate when proposed to the EU legislators.
- Large, innovative molecules will be disproportionately impacted – Against the intent of bringing more treatments for unmet medical needs to smaller EU patient populations.
- The quoted costs do not include any impact on lost sales that will occur at peak sales of new medications due to delays that will occur. 3 to 6 months delay in patient access is highly likely in some innovative medications due to the Annex VI burden. This could represent a billion Euro or more lost sales for a single product.

Understanding the reasons for late change

Member State possible reason	EFPIA response
Culture – “Even milk has an expiry”	IMPs have controlled distribution if correctly handled. If not correctly handled at the clinical site Expiry date is unlikely to make a difference. The increasing global emphasis on accountability at clinical site is a much better solution Milk does not have up to 6 date changes from cow to use.
Some countries have Expiry Date in their law	CTR will cause legal changes in any case. Reflection paper on IRT accepted by all countries after the change to Annex VI. All countries currently exempt inner / small packs as per GMP Annex 13 . In a number of public environments it has been expressed that some countries the EU follow the Annex VI provisions currently. No EU country does so currently in full i.e. including inner containers and small containers.
	Annex VI will be counter to the intent of accelerating products in the area of unmet medical need. Delays will occur that would not need to and is not in the interest of patients in the EU.

Understanding the reasons for late change

Member State possible reason	EFPIA response
IRT has caused problems	IRT is a range of solutions i.e. “a tool box not just a tool” IRT actively avoids problems when the correct tools are used well. Efpia would be happy to help generate guidance or Q&A that would deal with the different type of problems rather than create a larger problem with IMPs for patients as Annex VI has. The details from CA data has shown the potential for problems at an extremely low level when not used correctly. Probably many less problems created with IRT than have been avoided by the use of IRT. Industry has examples of where Expiry Dates have been on labels and medication was dispensed and taken after the date. In some cases Expired medication has been dispensed outside the IRT.

Legal changes for the CTR



- The CTR will be live October 2018 or before;
- Article 70 gives a basis for Annex VI to change once live;
- EFPIA would encourage Member States to keep the option for change open and to actively encourage it with the appropriate support of industry particularly around IRT;
- We would be interested in understanding the MS thoughts.

Date Extension at Clinical Site

- **The EFPIA concerns have been expressed that higher risk processes will be needed to date extend at clinical site.**
 - IRT, if allowed again under Annex VI, would reduce the risk when applied correctly
- **The delegated act Guideline consultation provides less clarity than Annex 13.**
 - EFPIA comments on this are available (line 355 to 362) (Attached 4).
 - What is the MS expectation for Clinical site relabelling by industry and academia (if ever needed).

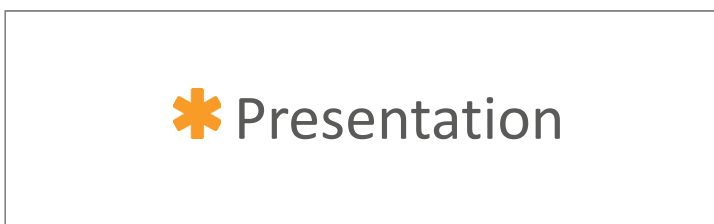
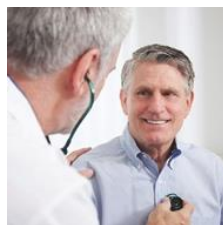
Attachments



1. EFPIA Position Paper 04 August 2014
2. Annex VI EFPIA Communication to the Commission Feb 2015
3. Difficulties with Annex VI Data capture template worked example
4. EFPIA Comments on GL on GMP for IMP Final 24nov2015

Annex VI Difficulties and mitigation potential

Date: 28/01/2016 * Version: General use



Objectives of paper

- **Recognise that CTR Annex VI will become effective approximately October 2018**
- **Recognise that many parts of the CTR environment want Annex VI to change as soon as it is legally possible.**
- **Promote the understanding that any study commenced under the CTR in late 2018 or 2019 will have to comply with Annex VI as it is now**
- **Share high level ideas on how the more unfortunate consequences of annex VI can be minimised. This recognises that these minimisation measures lead to increased costs of trials and make up a large portion of the costs of Annex VI estimated to be 162 Million euros a year.**

Draft ideas

- **Over-labelling Expiry Date at clinical sites.**
 - Guideline update clarification has been requested in November 2015 consultation
 - Outer carton only
 - Contract in place
- **Late stage labelling e.g. JIT – CMO's / Depots with a Licence only**
 - i.e. not at clinical sites
- **Reconsider if tamper evidence techniques are valid**
 - Do not tamper evidence at outer level
 - Tamper evidence at inner pack level only

Draft ideas

- **Have only one level of packing if possible**
 - **Potential implication on more dispensing of individual packs**
 - **Extra work for site staff**
 - **Dispensing**
 - **Accountability**
 - **Any risk of miss-dispensing is multiplied**
- **Package in smaller quantities with most recent Expiry Date**
 - **Increased set up**
 - **Increase QA / QP releases**
 - **Increased paperwork at all levels**

Draft ideas

- **Initial Date placed on all levels with date extension only on outer**
 - **With explanation in protocol**
 - **Deemed acceptable practice by all Part I and Part II reviews – Needs to be an accepted practice in advance of CTR implementation**
 - **Deemed acceptable practice by CGP inspectorate**
 - **Deemed acceptable by EC's**
 - **Explained to all site staff**
 - **Recommended in Patient facing material e.g. ICF and or Emergency Cards**

Draft ideas

- **Inner container Expiry Date relabelling**
 - High risk process performed only at licenced facility
 - Risk level specifically mitigated in procedures and documentation