EFPIA position paper

EU Clinical Trial Regulation Annex VI: Labelling of investigational medicinal products and auxiliary medicinal products - Impact on patient safety and validity of study data

1. Introduction

EFPIA contacted the European Commission on the 27 May 2014 to express significant concerns that some late stage edits to Annex VI of the EU-Clinical Trial Regulation (EU-CTR)[1], could risk product quality by increasing the handling required to effect shelf life extensions to investigational medicinal products (IMP), potentially increasing the risk to patients. The edits may also adversely impact EU competitiveness by limiting innovation and increasing administrative burden and cost. The current Good Manufacturing Practice (GMP) Annex 13 is well established, and well reflects evolving innovation and current practice. The new Regulation restricts existing flexibility, without improving quality and is therefore a step back. This position paper further substantiates the key concerns raised initially with additional facts and figures.

2. Inclusion of period of use on immediate packaging

The determination of 'period of use' (expiry or retest date) is complex, especially in early clinical development when clinical trial product shelf life is being characterised, and often extended, in parallel with trial conduct. For blinded trials, labelled 'period of use' can depend on other products used in the trials and multiple updates may be required[2].

To date, the requirement for providing, and updating 'period of use' information has been limited to the outer packaging of the IMP and could be performed at the clinical research site. We are not aware of any issues that have arisen from its omission on immediate packaging. The EU-CTR will require 'period of use' to be included on the immediate as well as the outer packaging; [3] and although the change was well intentioned, the unintended consequences of its implementation risk adversely impacting the following:

- ***Efficacy and quality:*** Storage conditions employed to maintain the quality of the IMP including freezer/ fridge, special atmospheric conditions and light protection; could be compromised when the outer packaging is opened so the immediate packaging of the product can be re-labelled for a shelf life extension.
- ***Risk of error/ tamper evidence:*** For each 'period of use' update, every outer pack in every site will need to be opened, out of direct Qualified Person control, often breaking (invalidating) tamper evidence as each primary container will need to be labelled. Treatments cannot be distinguished in blinded trials so the risk of error (mix-up of study medication) is high.[4] It also devalues tamper evidence, as patients may either be concerned if it is broken or may accept broken tamper evidence as standard.

[1] http://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=OJ:L:2014:158:FULL&from=EN

[2] Update frequency varies depending on the compound, its stage of development and the trial but a member company has an example of this occurring 5 times in one clinical trial.

[3] Annex VI references: for IMP: A.1 (1)(k); A.2.1 (4)(f); A.2.2 (5)(f); for AMP: B6(i)

[4] An EFPIA member company has already reported a SUSAR related to this process in a non-EU country.

- ***Legibility:*** Available space on primary containers is often limited; the additional information may adversely impact legibility, including that of other Annex VI mandated information, risking errors.
- **Wastage and environmental impact:** For small sized products like blister packs, ampoules or injectables, implementation of this requirement may cause significant compliance challenges and re-labelling may not be possible at all. This will result in product needing to be disposed and replaced with new stock rather than extension labelled. One member company has calculated that about 40% of the number of shelf life extension processes it performed in 2013 would not be possible in accordance with the new EU-CTR because of physical constraints like small vial size or blister pack surfaces. They estimated the material cost of IMP needlessly wasted as a result would have been about € 485,000, although for large trials of complex products the cost could be much greater. EFPIA members confirmed this to be a reasonable ballpark figure for this type of activity.[5]
- ***Continuity of supply:*** The additional processing as a result of further labelling is accentuated where additional transportation or replacement is required. This increases the risk of interruption of supplies to patients in trials, which could directly impact their health. It could also impact the conduct of the trial, potentially leading to delays in trial completion and knock-on delays to Marketing Authorisation Application submission and the availability of new licensed medicines to patients who need them.

3. Restrictions of electronic systems

Reducing the unnecessary cost and burden of the current EU Clinical Trials Directive (EU-CTD) and making the EU a more attractive location for performing clinical research were key drivers for the revision of the EU-CTD legislation, which resulted in the EU-CTR. The restrictions on use of electronic systems in Annex VI run counter to this in two ways, impacting both current operational efficiency and potential future innovation. At the same time, the use of electronic systems for managing 'period of use' has significantly advanced and its application in practice has proven to be positive for healthcare professionals and patients, which can be demonstrated in examples.

3.1. Prohibiting omission of the 'period of use' from labels via electronic systems[6]: A physical shelf life extension carries a high risk of error due to the level of manual intervention required (see previous section). It is also expensive and for a medium sized Phase III trial under the current EU-CTD framework, electronic systems could save an estimated € 443,100 in avoidable outer pack re-labelling cost.[7] Some companies have successfully managed both risk and cost using Interactive Response Technology (IRT) to control periods of use, eliminating the need for extension labelling activities. IRT allows fast access to important information such as 'period of use', and there are many examples of the approach being used successfully in numerous countries. Use of IRT in this setting would is prohibited in Annex VI.

The advantage of updating the IRT system is that it can be done instantly for all sites and no re-labelling is required. The system captures lot numbers and if the 'period of use' is

[5] Not including any processing or resupply costs
[6] EU-CTR Annex VI Section D8 and Section D9(a)(k), (b)(f), (c)(f) and (d)(i).
[7] Assume 300 sites, 3 re-labels during study and 100 kits per site = 443,100 Euros.

changed then an administrator can go in and update the whole batch irrespective of the location of the IMP from that particular lot. The IRT is set up so that investigators can access the system, enter the subject number who requires IMP to be dispensed and the system tells them which IMP to use. Any IMP that has reached the 'period of use' date, without an extension to that date, would not be available within the system to be allocated even if those kits were still at the investigator site. Taking away the option of using IRT for period of use is a backward step and a competitive disadvantage compared to countries, like the United States, which are in favour of more pragmatic approaches.

3.2. Prohibition of a range of other particulars being omitted from labels via electronic systems[8]: Section D8 of Annex VI requires that information omitted from labelling and made available by other means is justified in the protocol, which ensures appropriate use of electronic technology. In addition to the exclusion of 'period of use' from this approach, Section D9 of Annex VI excludes a range of additional information that cannot be omitted from labels. This restriction effectively blocks the future of innovative label solutions for use in the EU.

4. Next steps

In order to resolve the significant issues described in this paper, it will be necessary to revise Annex VI of the EU-CTR. An update to the implementing guidance for Annex VI may mitigate some impact in the interim and we would also like to discuss this possibility.

[8] EU-CTR Annex VI Section D9