Table 6: EU Clinical Trial Regulation and Impact to Clinical Trial Materials

Session 1:

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Session 2:

**Facilitator:** Melia Grim, *MedImmune, A member of the AstraZeneca Group*

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**SCOPE:**
The European Union has agreed to a new Clinical Trial Regulation (CTR) to harmonize clinical trials across EU member states. The goal of this regulation (536/2014) is to create an environment that is favorable to conducting clinical trials in the EU with the highest standards of safety for participants and increased transparency of trial information. It also includes a harmonized electronic submission and assessment process for clinical trials conducted in multiple member states. The agreement was first approved in council April 2014. The date of the application of the CTR has moved out until 2019. Implementation of this new regulation is slated to occur around Q2 2020 based on a successful validation of the portal/database.

Annex VI of this new regulation impacts the labeling of investigational products. The expiry date must now appear on the primary packaging as well as the outer carton. The use of Interactive Response Technology (IRT) to manage drug supply is no longer justified. This causes issues for biologic manufacturers who may have used IRT to manage clinical trial supplies especially for new compounds with short expiry dates.

While groups like EFPIA have presented sponsors concerns, there is no mechanism to change this regulation before it is adopted.

**QUESTIONS FOR DISCUSSION:**

1. Overall once implemented, do you believe this regulation will meet its goals?

2. If you are a sponsor company, are you aware of Annex VI?

3. Is your company proactively planning for the impact of Annex VI with respect to expiry dating?

4. What are some ways your company is looking to minimize the impact of this Annex?

5. Has your company come up with a workable solution?

6. If you are a regulator, what suggestions might you have for sponsors dealing with this Annex VI requirement?
DISCUSSION NOTES:

**Day 2:**
Will reg meet its goals?
How is having expiry on label versus a memo going to increase transparency?

Consequences:
- May result in delays to start of trials so that sponsor can generate more stability data and justify a longer expiry. This only delays inevitable need to relabel or discard material.
- Will QP review and approval further restrict stability claims (force compliance with Q1e, even though it does not apply strictly to clinical trial material)?
- Using documented notification of new expiry date, in lieu of over or re-labeling, allows clinical sites to confirm that material was within expiry at time of use. How is this less transparent than having date on label, or over-labeled/relabeled vial?
- Material at clinical sites will be difficult to relabel as they are not GMP facilities. This material will likely have to be discarded despite it being within updated extended expiry.
- Either incur material loses or more complicated and last minute supply chain to maintain supply at clinics.
- Will require a more minimal material inventory at sites to reduce risk of material disposal due to expiry, increasing risk of missed doses.
- Major process changes which reset expiry/stability will restart cycle of material loss and relabeling.

Minimize impact:
- Avoid Europe – not very practical. Ultimately EU sites will likely be included; but may delay drug availability.
- Do smaller fill lots, more frequently. Lose economies of scale, increase cost of clinical materials. This will have to be recouped at commercial phase.
- Could be managed through increasing complexity of supply chain. Just in time labelling at “local” depots, keep minimal supplies at clinical sites. Again, increased costs will have to be recouped at later date.
- Forecasting is going to have to get more accurate, otherwise losses will accumulate.

Questions:
- Labelling is a manufacturing step, will QP have to re-release material for clinical use?
- Does patient ever see vial, how will this increase transparency to patient if they only see dosed infusion bag?
- Unanswered questions on implementation.
- Will this apply to on-going trials where the label has already been approved?
- When is the subject information added (step A.1.f)? Not known at time of labelling…
- Who adds this? Clinician? Is it patient facing?
- f) the subject identification number and/or the treatment number and, where relevant, the visit number