Practical Considerations for EU Labeling Requirements of Investigational Drug Products following Annex VI Adoption and Amended CTR regulation No 536/2014

Lotte K. McNamara, PhD, Managing Director, BioProcess Technology Group, BDO USA

The biopharmaceutical industry has long wrestled with differences in labeling requirements for investigational drug products (DPs) intended for use in the United States (US) versus the European Union (EU). In late 2022, some relief came into sight for companies planning clinical trials in both geographies with the adoption of new regulations in the EU that seemed to be more aligned with the approach taken in the US. However, determining the labeling requirements for investigational DP can still be challenging depending on the reviewing health authority. This is particularly true for expiry labeling, which can have a significant impact on a sponsor's clinical supply chain management. Understanding the regulations is key to successfully labeling your product appropriately for use in clinical trials.

CTR REGULATION NO 536/2014 DETAILS LABELING REQUIREMENTS FOR INVESTIGATIONAL DRUG PRODUCTS

The Clinical Trials Regulation (EU) No 536/2014 of the European Parliament and of the Council (CTR)[i] entered into force on 16 June 2014; however, its implementation required the development of a fully functional clinical trials portal and database for the EU. This effort was completed in late 2021, enabling application of the CTR as of January 2022. The CTR ensures a greater level of harmonization of the rules for conducting clinical trials throughout the EU. It introduced an authorization procedure based on a single comprehensive submission via the centralized EU portal as well as an assessment procedure leading to a single regulatory decision applicable to all countries in the EU.

Upon adoption of the CTR, the directive for product labeling requirements in EU was changed from being part of the GMP requirements described in Annex 13 for Investigational Medicinal Products[ii] (sections 26-33) to being part of the legislative text of the CTR, Articles 66-70. Of note, Article 66 states that "The information which is to appear on the outer packaging and immediate packaging [of investigational medicinal (or auxillary) products] shall ensure subject safety and reliability and robustness of the data generated in the clinical trial, while taking account of the design of the clinical trial…" The specific requirements for investigational product labeling for EU clinical trials are detailed in Annex VI of the CTR and summarized herein in Table 1 for various clinical product configurations.

In contrast to the detailed requirements for labeling of investigational product intended for use in clinical trials in the EU, the US FDA requirements for investigational product labeling, as described in 21 CFR 312.6[iii], are quite minimal. In fact, the only stated requirement is "The immediate package of an investigational new drug intended for human use shall bear a label with the statement 'Caution: New Drug - Limited by Federal (or United States) law to investigational use.'" Despite the minimal requirements in the US, sponsors often include the majority of the content outlined in Table 1 on the label of investigational supply for US-based studies.

TABLE 1. SUMMARY OF EU LABELING REQUIREMENTS FOR INVESTIGATIONAL PRODUCTS AS DESCRIBED IN ANNEX VI

Label content	A.1. General rules	A.2 Limited labeling of immediate packaging: A.2.1: Immediate and outer packaging provided together	A.2 Limited labeling of immediate packaging: A.2.2: Small immediate packaging	B. Unauthorized auxiliary medicinal products	C. Authorized IMPs
Name, address and telephone number of the sponsor, contract research organization or investigator	(x)	(x)	(x)	(x)	x
Name of the substance and its strength or potency. Note, for blinded trials, the placebo or comparator shall also bear the same information as the IMP	x			x[1]	
Pharmaceutical dosage form, route of administration, quantity of dosage	x	x	x[2]		
The batch and/or code number	x	x	x	x	
A clinical trial reference code	(x)	(x)	(x)	x	x
The trial subject identification number/ treatment number and/or the visit number	x	x	x		
The name of the investigator (if not otherwise included)	(x)				
Directions for use (reference may be made to a package leaflet);	(x)			(x)	
"For Clinical Trial Use Only" or similar wording;	(x)			(x)	x
The storage conditions;	x			x	
Period of use (expiry date or retest date, as applicable), in month and year format;	x	(x)	(x)	(x)[3]	
"Keep out of reach of children" except when the product is for use in trials where the product is not taken home by subjects.	(x)				

Table keys:

- **x** means that the particulars must be included on label of the immediate/outer packaging of a product.
- **(x)** means that the particulars may be omitted from the label of the immediate packaging of a product and made available by other means, for example by use of a centralized electronic randomization system, use of a centralized information system, provided that the safety of the subject and the reliability and robustness of data are not compromised.
- **Gray box:** means that the particulars are not required to be included on the label.

1 Name of the medicinal product, followed by its strength and pharmaceutical form: Statement of the active substances expressed qualitatively and quantitatively per dosage unit (the latter is not required if using the centralized procedure)

2 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.

3 The period of use may be omitted from the immediate packaging, **IF**

- The immediate and outer packaging are intended to remain together and the outer package carry all the particulars listed for an auxiliary medicinal product.
- The immediate packaging takes the form of blister packs or small units such as ampoules, on which the particulars listed for an auxiliary medicinal product cannot be displayed, and the immediate packaging carry all the particulars listed for an auxiliary medicinal product.

AN AMENDMENT TO ANNEX VI OF CTR REGULATION 536/2014 ADDRESSES CONCERNS AROUND EXPIRY LABELING

Upon implementation of the CTR, concerns were raised related to the strict requirement regarding expiry labeling of *all* immediate packaging given the frequent need for re-labeling of clinical trial products that such a requirement would incur, which in turn could negatively impact the supply chain of an investigational product. The previous regulation governing EU-product labeling, Annex 13 (from the clinical trial directive[ii]), allowed for exceptions to expiry labeling of the immediate container when the product's primary and secondary packaging remained together, and the latter contained all the required information.

To understand the concerns related to expiry labeling, it is important to consider that limited stability data generally is available for product used in early phase clinical studies. To mitigate the limitations imposed by the limited stability data, it is allowable - and hence common practice - to extrapolate the shelf-life of clinical trial material beyond the period covered by real-time stability data when supportive data, including accelerated stability data and/or relevant stability data generated with representative material, is available. Per the EU guidance[iv]: "The maximum shelf-life after the extension should not be more than double, or more than twelve months longer than the period covered by real time stability data obtained with representative batch(es)." This extension principle allows the sponsor to apply an expiry beyond what is dictated by the available real-time stability data and is particularly helpful during the early months of a first-in-human trial when available stability data is often limited. However, careful tracking of investigational supply at depots and clinical sites is required to ensure material is either used prior to the labeled expiry or re-labeled in order to extend its shelf-life. Frequent re-labeling of the immediate container may increase risk to both the quality and safety of the product. Potential risks to product quality could arise during re-labeling of products that are light sensitive or that are stored under frozen conditions given that prolonged exposure out of the recommended storage environment and additional handling can impact to product stability. While re-labeling under frozen conditions and/or under low light exposure can be managed, it is considered challenging. Product safety could be impacted if re-labeling requires breaking of the tamper-proof seal of a secondary packaging and/or disassembly of a kit in order to re-label the primary packaging container.

Given these concerns, a new delegated act to amend Annex VI of the CTR regulation 536/2014 was adopted in September 2022 and made effective upon publication in the Official Journal of the European Union[iv] on 15 November 2022. The amended CTR eliminates the obligation to include expiry on the immediate packaging of some investigational and auxiliary medicinal products for clinical use allowing labeling of the secondary container only with the expiry date *under specific circumstances* where re-labeling can impact the quality and safety of the medicinal product. It is stated that "In those cases [i.e., where there is a potential risk to quality and safety of the product] it is appropriate and proportionate to the nature and the extent of the risk that the period of use is omitted from the immediate packaging". The circumstances in which the expiry is not required on the immediate packaging according to the amended Annex VI are detailed in Table 1. Briefly, the amended Annex VI states that labeling of the secondary container only may be allowable in the following two cases assuming appropriate justification is provided:

- The immediate and outer packaging is provided together.
- The immediate packaging is small.

CONCLUDING THOUGHTS

The amended CTR regulation is a tremendous move forward towards simplifying clinical trial logistics and labeling issues. "Real estate", the area of the investigational label on which text can be printed, is often limited for small volume liquid products. Additionally, shelf-life extensions require re-labeling which can be cumbersome and may increase risk to both the quality and safety of the product. The more flexible CTR requirements for expiry dating on primary packaging address both of these challenges. However, it is important to note that although the change in regulation has been adopted in the EU, interpretation of the regulations can vary from Qualified Person (QP) to QP. For instance, the phrase "potential risk to quality and safety of the product" is subjective and open to individual interpretation. It is therefore absolutely critical that any decisions with respect to labeling strategy are made in agreement between the product sponsor and the QP prior to the labeling operation. Not doing so could result in significant cost and timeline delays to a program.

The team in BDO's BioProcess Technology Group (BPTG) have a wealth of experience in ensuring that the labels of investigational products meet the requirements of the intended clinical study geographies. We look forward to working with you on your next labeling project.

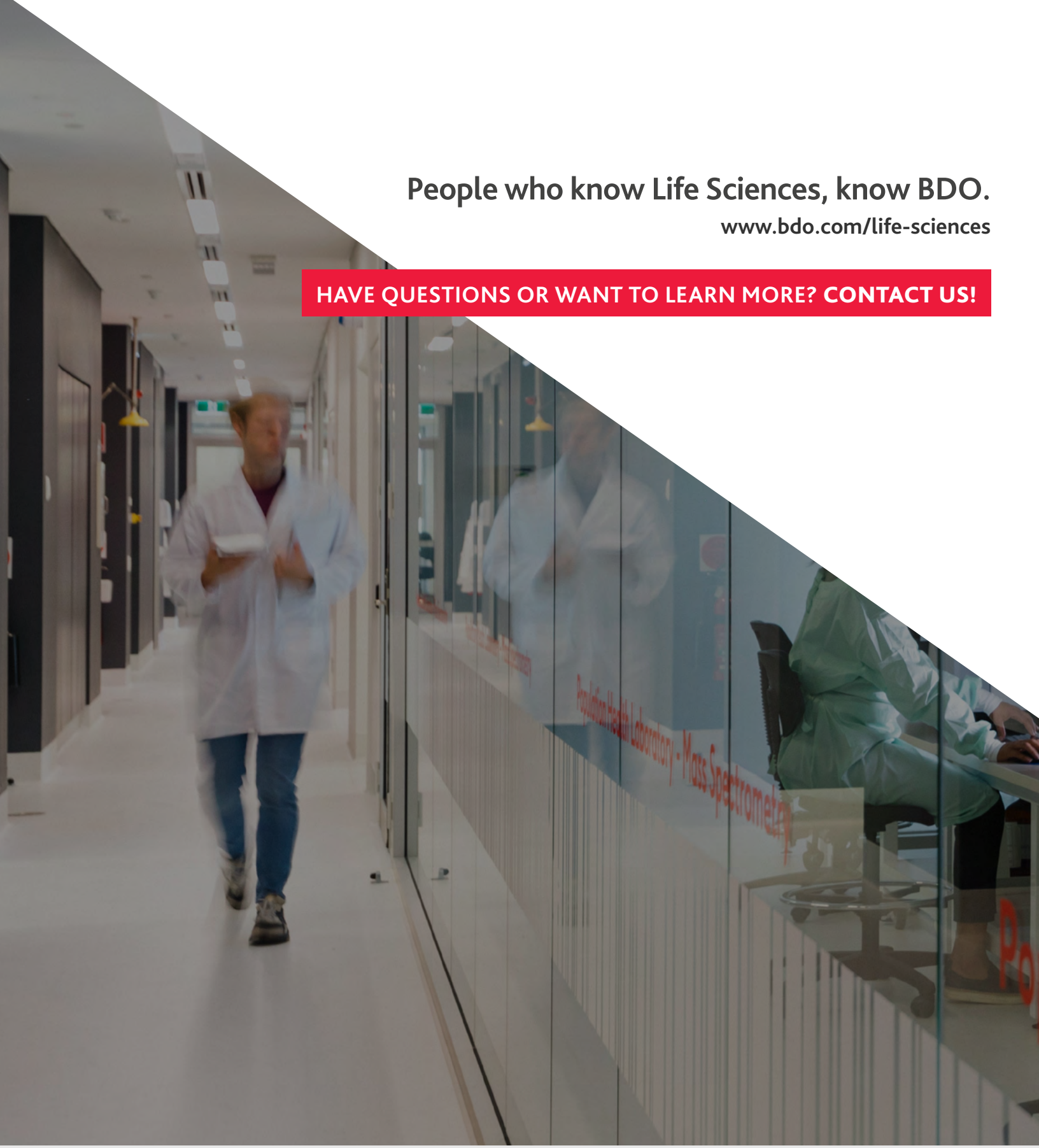
References

i https://health.ec.europa.eu/system/files/2016-11/reg_2014_536_en_0.pdf

ii https://health.ec.europa.eu/system/files/2016-11/2009_06_annex13_0.pdf

iii https://www.ecfr.gov/current/title-21/chapter-I/subchapter-D/part-312

iv https://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=CELEX:32022R2239



People who know Life Sciences, know BDO.

www.bdo.com/life-sciences

HAVE QUESTIONS OR WANT TO LEARN MORE? CONTACT US!

Our purpose is helping people thrive, every day. Together, we are focused on delivering exceptional and sustainable outcomes and value for our people, our clients and our communities. BDO is proud to be an ESOP company, reflecting a culture that puts people first. BDO professionals provide assurance, tax and advisory services for a diverse range of clients across the U.S. and in over 160 countries through our global organization.

BDO is the brand name for the BDO network and for each of the BDO Member Firms. BDO USA, P.C., a Virginia professional corporation, is the U.S. member of BDO International Limited, a UK company limited by guarantee, and forms part of the international BDO network of independent member firms. For more information, please visit: www.bdo.com.