



News bulletin for small and medium-sized enterprises

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This news bulletin is published four times a year by the SME Office of the European Medicines Agency.

The news bulletin aims to bring to the attention of SMEs, and their stakeholders, documents and activities related to the European regulatory environment.



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Pharmaceutical development guidance

A reflection paper on the pharmaceutical development of intravenous medicinal products containing active substances solubilised in micellar systems was finalised on 20 March 2012 ([EMA/CHMP/QWP/799402/2011](#)). It provides information on the development and characterisation of products such as:

- medicinal products for intravenous injection or infusion which contain active substances with a low aqueous solubility and solubilised in an aqueous micellar system;
- established small molecules, non-polymeric surfactants, which are sensitive to dilution effects during slow intravenous administration, quickly metabolised and which do not have a long half-life in plasma e.g. polysorbate 80.

A revised guideline on real-time release testing (RTRT) was published on 13 April 2012 ([EMA/CHMP/QWP/811210/2009-Rev1](#)). Compliance with release specifications can be demonstrated by performing a complete set of tests on the active substance and/or finished product, according to the approved specifications. Under certain conditions, an alternative strategy to systematic testing is possible. So far this concept was mainly applied to sterility testing (so called 'parametric' release approach). Recent ICH guidelines have made it possible to apply a similar approach to tests other than sterility, called Real Time Release Testing. The guidance applies to chemical and biological products.

A guideline on process validation was released on 13 April 2012 ([EMA/CHMP/CVMP/QWP/70278/2012-Rev1](#)). It was amended to bring it into line with recent ICH guidance which advises to use continuous process verification in addition or as an alternative to traditional process verification. It does not introduce new requirements but clarifies how companies can take advantage of the new possibilities given when applying enhanced process understanding coupled with risk management tools. The draft document applies to both human and veterinary medicines and is released for consultation until 31 October 2012.

Pharmaceutical development guidance continued

A revised guideline on the quality requirements of biosimilar medicines is open for comments ([EMA/CHMP/BWP/247713/2012](#)). It was updated to address issues relating to manufacturing and comparability. It is open for consultation until the end of November 2012.

A draft guideline on quality of biological active substances produced by transgene expression in animals was published on 31 May 2012 ([EMA/CHMP/BWP/159188/2012](#)). The document describes the approaches to be followed in order to achieve satisfactory quality for biological drug substances developed with this innovative technology. The deadline for providing comments is 30 November 2012.

Non-clinical and clinical guidance

A reflection paper on the non-clinical and clinical development of oral and topical HIV pre-exposure prophylaxis was published on 14 March 2012 ([EMA/171264/2012](#)). It focuses on the regulatory requirements relating to the development of agents with antiretroviral activity. Several aspects of the guidance may also be relevant to topical preparations (microbicides agents).

Two final scientific advice/qualification opinions on novel methodologies and biomarkers relating to drug development in Alzheimer's disease were adopted in April 2012:

- Use of cerebrospinal fluid amyloid beta 1-42 and t-tau signature and/or positron emission tomography amyloid imaging (positive/negative) qualified as biomarkers for enrichment in regulatory clinical trials in mild/moderate Alzheimer's disease ([EMA/CHMP/SAWP/893622/2011](#)).
- Positron emission tomography amyloid imaging (positive/negative) qualified as a biomarker for enrichment in predementia Alzheimer's disease clinical trials ([EMA/CHMP/SAWP/892998/2011](#)).

A draft reflection paper on the clinical development of tissue-engineered products was released on 17 April 2012 ([EMA/CAT/CPWP/573420/2009](#)). Tissue-engineered products are intended to regenerate, repair or replace human tissue. The document elaborates on how the nature of these products (e.g. surgical procedures, area/volume of missing tissue and compatibility of biomaterials with cells) impacts on the clinical requirements. The deadline for the public consultation is 31 July 2012.



A guideline on quality, non-clinical and clinical aspects of medicinal products containing genetically modified cells will come into effect on 1 November 2012 ([EMA/CAT/GTWP/671639/2008](#)). The document covers genetically modified cells intended for use in humans irrespective of the cell's origin (human autologous or allogeneic, xenogeneic) or whether the genetic modification was carried out for clinical purposes or not (e.g. for manufacturing). The requirements described in the guidance relate to market authorisation applications and its principles also apply to the product development.

The following ICH documents were published on 25 April 2012:

- 'ICH Q11 on the development and manufacture of drug substances (chemical entities and biotechnological/biological entities)' [EMA/CHMP/ICH/425213/2011](#). The document elaborates on the concepts of 'traditional' and 'enhanced' approaches to development and manufacturing. In a traditional approach, set points and ranges are defined and the control strategy is based on demonstration of process reproducibility and testing to meet established acceptance criteria. In an enhanced approach, risk management and scientific knowledge are used more extensively to identify process parameters that impact on critical quality attributes applicable over the lifecycle of the drug substance including. The enhanced approach provides the basis for more flexible regulatory requirements. The document will come into effect in November 2012.

Non-clinical and clinical guidance continued

- 'Questions and answers' on ICH E14 ('QT/QTc guidance'); [EMA/CHMP/ICH/310133/2008](#)
- 'Questions and answers' on M3 (R2) (guidance on non-clinical testing for clinical trials); [EMA/CHMP/ICH/507008/2011](#)

A draft guideline on the clinical investigation of medicinal products for the prevention of venous thromboembolism (VTE) in patients undergoing high VTE-risk surgery was published on 30 May 2012 ([EMA/CHMP/325170/2012](#)). It was updated to include revised definitions of major and minor bleeding and details on relevant secondary endpoints. The deadline for comments to the document is 30 November 2012.

Two guidelines on monoclonal antibodies will come into effect in December 2012:

- A guideline on the immunogenicity assessment of monoclonal antibodies intended for in-vivo clinical use ([EMA/CHMP/BMWP/86289/2010](#)). It elaborates on the major quality and clinical aspects to consider in the detection and systematic evaluation of immunogenicity against a therapeutic or in vivo diagnostic monoclonal antibody.
- A guideline on the non-clinical and clinical issues of similar biological medicinal products containing monoclonal antibodies ([EMA/CHMP/BMWP/403543/2010](#)). It complements the general guideline for biosimilar medicinal products (EMA/CHMP/42832/2005) and provides product-specific advice on comparability. The document may also apply to substances such as fusion proteins based on IgG Fc ('-cept' molecules).

Pharmacovigilance guidance



An ICH guideline '*E2C (R2): Periodic benefit-risk evaluation report (PBRER) (Step 3)*' was released on 21 May 2012 ([EMA/CHMP/ICH/544553/1998](#)). The Periodic Benefit-Risk Evaluation Report (PBRER) is a common standard for reporting on marketed products, including approved ones that are under further study. The document defines the recommended content and format of a PBRER and outlines points to be considered in its preparation and submission.

Two documents on the transitional measures for the implementation of the pharmacovigilance legislation were published:

- A 'Questions and answers' document ([EMA/228816/2012](#))
- Reporting requirements of individual case safety reports applicable to marketing-authorisation holders ([EMA/321386/2012 Revision 1](#)).

A draft position paper on '*potential medication errors in the context of benefit-risk balance and risk minimisation measures*' was announced on 1 June 2012 ([EMA/274183/2012](#)). It addresses the risk of medication error that arises where a newly introduced product could potentially be mistaken for an already established one containing the same active substance. It provides guidance on how the benefits and risks of such products should be weighed and how the risk of medication errors can be adequately addressed. The deadline for providing comments is 30 November 2012.

An e-learning course on the compliance with the requirements of Article 57(2) of the pharmacovigilance legislation (submission of information on medicines) was released on 16 May 2012. The modules can be streamed live or downloaded. Further information is available under [Link](#).

Clinical trials

A guideline on the quality documentation for biological investigational medicinal products in clinical trial applications came into effect on 15 April 2012 ([EMA/CHMP/BWP/534898/2008](#)). It elaborates on the specific documentation requirements of the quality section of the investigational medicinal product dossier. It applies to recombinant/non-recombinant/purified proteins and polypeptides, their derivatives, and products which they are components of (e.g. conjugates).



A reflection paper on the ethical and GCP standards in the conduct of clinical trials included in marketing authorisation applications submitted in the EU came into effect on 1 May 2012 ([EMA/121340/2011](#)). The document is part of the Agency's strategy to address the challenges arising from the globalisation of clinical research. It emphasises the role of independent local ethics committees in the oversight of clinical trials and stresses the importance of obtaining trial subjects' consent. It also discusses other key issues such as the use of active or placebo as comparator, or the access to treatment after a trial.

A 'Questions and answers' document on the guidance documents applying to clinical trials in Volume 10 of "Notice to Applicants" was released in April 2012 ([Link](#)). It was revised to include a section on safety reporting.

Regulatory guidance (Human and Veterinary medicines)

A guideline on the processing of renewals in the centralised procedure will enter into force on 2 July 2012 ([EMEA/CHMP/2990/00 Rev.4](#)). The document includes details about the date for renewals, the timetable for submitting the documentation and other procedural aspects.

EMA pre- and post-authorisation guidance for users of the centralised procedure were posted on:

- Biosimilar medicinal products ([EMA/940451/2011](#)).
- Post-authorisation guidance ([EMEA-H-19984/03 Rev 23](#)) which was updated to include information on: fees for a Type IA/ IA_{IN} variation, mock-ups and specimens post-authorisation requirements, paediatric requirements, and "61(3) Notification" i.e. change to Labelling/Package Leaflet (PL) unrelated to Summary of Product Characteristics.

Two documents on the electronic submissions of veterinary dossiers were published: a procedural announcement ([EMA/184958/2012](#)) on the acceptability of technically valid ('VNeS compliant') e-applications, and a related 'Questions and answers' document ([EMA/613295/2011](#)). In addition the veterinary electronic application forms for initial marketing authorisation applications for centralised, mutual recognition or decentralised procedures are now available under [Link](#).

A 'Questions and answers' document on *post-approval change-management protocols* was released on 13 April 2012 ([EMA/CHMP/CVMP/QWP/586330/2010](#)). Post approval change management protocols were introduced with the variations regulations. It is a step-wise approach in the assessment of changes (e.g. test methods, comparability, stability) which allows an early evaluation of the *strategy* for the change and a later separate evaluation of the data produced. Its expected benefits are a faster implementation of the changes as the strategy was agreed beforehand. It applies to all medicinal products for human and veterinary use including biotechnological or biological products, irrespective of whether a Quality by Design approach was used. Its use remains optional.

Public consultations

Two public consultations were released by the European Commission in June 2012 on:

- Fees for pharmacovigilance ([Link](#)). The document sets out the proposed new fees for pharmacovigilance activities and fee incentives for SMEs which are planned to be introduced in 2014. The consultation will contribute to the regulatory impact assessment and be used to amend the fees regulation. The pharmacovigilance fees will cover both centrally and non-centrally (mutual recognition/decentralised/national) authorised products. SMEs and particularly micro-sized enterprises (<10 staff; turnover or balance sheet total <2 million €) are advised to provide comments. The deadline for response is 15 September 2012.
- Categorisation of variations for human and veterinary products ([Link](#)). The guideline was updated to take into account scientific and technical progress and the pharmacovigilance legislation. The deadline for comments is 15 July 2012.

Initiatives supporting SMEs and meetings

The SME office would like to draw your attention to the following initiatives targeting SMEs:

- Enterprise Europe Network ([Link](#)). The Enterprise Europe Network is a key instrument in the EU's strategy to boost growth and jobs. Bringing together hundreds of business support organisations from more than 50 countries, it helps small businesses to develop business in new markets, source or license new technologies and help in accessing EU finance and EU funding.
- IPR Helpdesk ([Link](#)). It is a European initiative providing free advice and information on intellectual property rights, from legislation to model contracts.
- Pathfinder Awards. It is a technology transfer scheme intended to kick-start pilot projects that have significant potential to help develop innovative new products in orphan and neglected disease areas ([Link](#))

The report, presentations and media content of the following meetings were posted:

- Expert workshop on setting specifications for biotech products [Link](#)
- Workshop on medicines for the elderly [Link](#)
- Modelling and simulation workshop [Link](#)
- Workshop for micro, small and medium-sized enterprises (SMEs) – Focus on pharmacovigilance [Link](#)
- Workshop on biosimilar monoclonal antibodies [Link](#)

The following meeting has been announced:

- “Workshop on Pharmacogenomics: from science to clinical care” at the European Medicines Agency on 8-9 October 2012 [Link](#)

SME companies registered with the Agency

877 companies currently have SME status assigned by the Agency. The companies are published in the Agency's public SME registry at: <http://fmapps.emea.europa.eu/SME/>

Contact the SME Office

The SME Office has been set up within the Agency to address the particular needs of smaller companies. The Office aims to facilitate communication with SMEs through dedicated personnel who will respond to practical or procedural enquiries, monitor applications, and organise workshops and training sessions for SMEs. Any comments or queries on this news bulletin can be forwarded to the SME Office:

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