How Safe Are Biosimilars?

Implications of FDA and EMA Guidances and European Experience since 2006 – Part 2

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This two-part series provides insights into the new paradigm of biosimilar medicines based on approval and medical experience postapproval. It proposes a framework for the understanding, development and acceptance of a new generation of biologic medicines, biosimilars, in the US and worldwide.[1–3]

Currently, the knowledge gathered by regulators and industry permits a degree of confidence in biosimilars authorized in the EU after nearly six years of pharmacovigilance, providing reassurance in the regulatory approval process. Further safety aspects are explored in the following discussions, describing in depth the biosimilar development and regulatory approval criteria in Europe and the US.

At the same time, these articles attempt to dispel false perceptions contrary to the established safety and efficacy of biosimilars.

Level of Risk Taking a Biosimilar

Is there really a difference in risk in starting treatment with an originator biologic and then switching to an EU-approved biosimilar, or starting treatment with a biosimilar instead of the originator biologic medicine? Should the patient in the first case be maintained on the originator medicine, despite the fact that the biosimilar has been approved in Europe according to the highest standards by a regulatory body that represents 30 national Competent Authorities?

Any concerns regarding subpotency are allayed by the fact that the pivotal studies are all equivalence trials at present, or at a minimum are non-inferiority studies in line with the new US guidances.[4–6] Safety is established by a substantial battery of quality (chemistry, manufacturing and control—CMC) tests; nonclinical and clinical tests usually including a complex, 12-month clinical immunogenicity investigation using a variety of systematic antibody assay testing; and positive efficacy, in direct comparison with the European reference medicinal product (RMP).

Not only is the biosimilar medicinal product (BMP) thoroughly compared with the RMP for similarity, but every point of difference (every peak on the spectrum or any impurity) is carefully and critically assessed in the context of benefit: risk. Clearly, the degree of scrutiny of European regulators, led by the European Medicines Agency's (EMA) Committee for Medicinal Products for Human Use (CHMP), could not be more rigorous, and is informed by the combined experiences of the 27 EU Member States.

A monoclonal antibody (mAb), being costly, might not be used as an adjuvant in oncology in unsupported healthcare systems, but a biosimilar might. Even the use of a granulocyte colony-stimulating factor (G-CSF), filgrastim, as an adjuvant in oncology to reduce neutropenia, has increased greatly in some EU countries such as the UK due to cost savings, offering major advantages to patients.[7]

Surveys have shown a mAb biosimilar might be perceived as less risky in palliative treatment, or in an adjuvant setting compared with an acute life-saving scenario, or in a metastatic setting compared with the cost of an originator product.8 Hopefully, this attitude regarding the perceived risks of biosimilars will change as these compounds are better understood.

In some poorer European countries, biosimilars fulfill an unmet medical need. In developing countries worldwide, a biologic medicine might be affordable only on the introduction of the biosimilar, and in these circumstances the biosimilar would constitute a first entry into the market.

Pharmacovigilance

A European risk management plan (RMP_{PV}),[9] including a risk minimization and pharmacovigilance plan, is an essential part of a biologic Marketing Authorization Application (MAA) approval, and important throughout the lifecycles of both the biosimilars and the RMP to predict, mitigate and contain risk.[10,11] Risk can be affected by exposure, route of administration, indication and severity.

The RMPPV includes safety specifications consisting of a summary of important identified risks, including safety pharmacology and toxicology for important potential risks and missing information obtained from clinical studies; immunogenicity testing and evidence of its symptomology; spontaneous adverse event reporting; and scientific literature. It needs to be updated against changes in the risk management plan.

It can be assumed an US Food and Drug Administration (FDA) risk evaluation and mitigation strategy (REMS)[12] would only be relevant to a biosimilar where the originator product already had a REMS, although this is speculation and will depend on FDA's future experiences. Components of a typical FDA REMS are a Communication Plan, patient selection criteria, web-based materials, a medical scientific liaison, Elements to Assure Safe Use, an implementation system, a patient or physician survey and patient understanding of risk.

It is notable and unexpected that, according to the guidance, a biosimilar that does not qualify for interchangeability will be viewed as a "new active ingredient." As such it would be also be subject to the FDA's pediatric requirements.[13]

In fact, this would be triggered at the time of filing an investigational new drug (IND) and will require preparation of a pediatric plan. In the EU, a biosimilar is exempt from a pediatric investigational plan (PIP).

However, once approved, a biosimilar must follow changes in the approved RMP summarized in the product information (the EU summary of product characteristics (SmPC) and the US package insert (PI)). In Europe, it can additionally follow a separate lifecycle development pathway in principle, although there currently is nothing on this in the regulations or guidelines. This could mean new pharmaceutical forms, new indications or new target populations. This postapproval principle is present in the Canadian biosimilars guideline,[14] but not US or EU guidances.

The mAb guideline of November 2010 reflects four years of EMA and CHMP experience with biosimilars. It lays down the best principles and attempts to reduce the burden of nonclinical testing.[15]

It also explicitly requires the selection of the most sensitive and homogeneous populations (an aspect that allows extrapolation of indications). But justification that immunogenicity can be predicted in the other claimed populations based on the studies forming the basis of approval is an important condition.

Sensitive and homogeneous populations are repeatedly raised by EMA and CHMP when providing scientific advice. For instance, breast cancer is more homogeneous than head and neck cancer, or early stage cancer more homogeneous than late stage cancer with metastatic cancer or monotherapy over adjunct therapy.

FDA emphasizes sensitivity in its guidances, but does not directly mention homogeneity. Why this is omitted is not known, as homogeneity ensures a more reproducible and consistent response.

Clinical Efficacy

A decrease in potency or lack of efficacy in a medicine on the market is a pharmacovigilance issue; to date, there is no evidence of this, after five years of EU experience with marketed biosimilars.[16]

The most sensitive, homogeneous patient population and clinical endpoint are chosen in the preapproval studies to detect any product-related differences. This minimizes any confounding patient- and disease-related factors in order to increase precision of analysis and maximize response. It also reduces the variability and sample size needed to prove equivalence, and can simplify interpretation.

Patients with varying disease severity and disparate treatment histories might be expected to respond differently. It may remain uncertain whether such differences would be attributable to the consequence of patient- or disease-related factors rather than to discrepancies between the biosimilar and reference product. This is very relevant to mAbs.

FDA's guidance, like the EMA mAb guideline,[17] states that "A sponsor can use endpoints that are different from those in the reference product's clinical trials."[18]

FDA cautions about selecting the appropriate subjects, and against risking the inclusion of "patients (who) have different co-morbidities and disease states (e.g., immunocompetent or immuno-suppressed) and receive different concomitant medications."

"In general, using similar study populations is essential for supporting the constancy assumption that is critical to interpreting the non-inferiority finding in a one- or two-sided comparative test."[19]

It is worth noting FDA places a high degree of importance on clinical pharmacology studies as evidence of comparative efficacy and does not consider a need to prove benefit. This is exactly the same as EMA's opinion.

FDA places importance on safety determined by the immunogenicity study, and describes expectations very similar to those of EMA, among which is a minimum 12-month study. FDA does describe its expectation that an efficacy study would be conducted only when necessary, and describes some basic statistical criteria including the alternatives of equivalence and noninferiority designs.

Noninferiority with a primary variable of efficacy has not been allowed in the EU as a basis of any approval to date, as far as the author is aware. It may be acceptable for safety studies such as immunogenicity studies. However, FDA states both alternatives.

FDA recommends sponsors consider the use of population pharmacokinetics (PPK) to explain observed differences in safety and effectiveness that may occur due to variability in PK.[20] According to the guidance, "PPK methods are an efficient way to quantitate the influence of covariates (e.g., age or renal function) on PK and, in some cases, PD."

Pediatric assessment under the US Pediatric Research Equity Act (PREA) will be triggered for non-interchangeable biosimilars at the time of IND filing, although it may not be known to which of the two tiers of biosimilars the product will belong.

"Section 505B(n) of the FD&C Act, added by section 7002(d)(2) of the Affordable Care Act, provides that a biosimilar product that has not been determined to be interchangeable with the reference product is considered to have a 'new active ingredient' for purposes of PREA, and a pediatric assessment is required unless waived or deferred."[21]

An interchangeable biosimilar product is not considered to have a "new active ingredient" for the purposes of PREA, therefore a pediatric assessment of the interchangeable product is not required.

Clinical Safety Aspects

Selection of Subjects

Like efficacy, homogeneity and sensitivity aid in providing data that are easier to interpret. Also, selecting the most sensitive population is important in immunogenicity.

The inclusion of patients from non-European countries is generally acceptable for EU biosimilars so long as there are no ethnicity or other concerns in connection with intrinsic (genetics, metabolism, etc.) and extrinsic factors (diet, habitat, etc.). FDA allows non-US studies, but cites its guidances on foreign studies and ethnicity.[22] However, it is likely EU studies or studies conducted elsewhere in support of an EU biosimilar will be acceptable.

In Europe, knowledge of the RMP's efficacy and safety in a particular region may be necessary to prospectively define an equivalence margin. Stratification and appropriate subgroup analyses normally are expected in the EU if patients from different regions of the globe are included. Diagnostic and treatment strategies should be comparable to prevent the influence of extrinsic factors.

It is advisable to use the same safety parameter definitions as used for the RMP's original development program (if known) where no homogeneous definition exists (e.g., measurement of cardiotoxicity in the case of mAbs).

It is necessary to consider the normal clinical setting and how re-treatment of patients would be handled, and to systematically measure the safety of repeat patient exposure, e.g., oncological indications where patients undergo several treatment cycles.

Physicians' perceived risk of using a biosimilar was demonstrated in the EU by the reluctance of some to use Zarzio G-CSF in healthy subjects for stem cell mobilization, as the approval was based solely on healthy volunteer studies and not patients.[23] Medical uses of filgrastim G-CSF in the EU include dose intensification of chemotherapy (patients), prophylaxis of febrile neutropenia, treatment of febrile neutropenia and stem cell mobilization (healthy subjects), so some physicians felt the risk of subjecting healthy persons to a new treatment that is unproven in a Phase III clinical study was too high.

The pivotal clinical study (efficacy) or immunogenicity study (safety) can be extended as a postauthorization follow-up study to a full treatment cycle, where relevant and feasible. Where possible, patients previously treated with the RMP are excluded, to avoid

negatively influencing interpretation of the safety data, and also to decrease sensitivity for detecting differences. This can be particularly important in measuring meaningful antibody response to the biosimilar.

There is an EU postauthorization requirement for obtaining further indication-specific safety data for the RMP to capture data on safety across different licensed indications. The current mAbs being developed as biosimilars come in a range of pharmaceutical forms: powders for solutions or for concentrates, solution concentrates, ready-to-use solutions or alternative presentations such as vials, prefilled syringes, or cartridges (to fit pen devices). This variety of forms increases the risk of new chemical or biological impurities or bioburden through filtration or lyophilisation steps, and introducing new impurities through drug/packaging interaction. Most biosimilar developers try to follow the RMP profile and process to closely match up the excipients, packaging components and process to avoid such problems.

FDA is flexible on allowing new formulations and presentations of the biosimilar compared to the RMP, as noted earlier, as long as certain conditions are fulfilled, among which is the same pharmaceutical forms.[24]

Examples of mAb, Infusion Proteins

A biosimilar can be expressed from various yeast, E. coli, rodent or mammalian cell species that have different associated immunogenicities. For instance, process changes from chimeric (stem -iximab) to humanized (stem -zumab) to fully humanized mAbs (stem -umab) have progressively decreased risk of immunogenicity. Patients with human anti-mouse antibody (HAMA) or human anti-chimeric antibody (HACA) titers may experience allergic or hypersensitivity reactions when treated with other diagnostic or therapeutic mAbs.

The indications, doses and regimen of rituximab, infliximab and etanercept[25] illustrate the complexity of the use of the mAb and fusion proteins with particular clinical safety concerns, as well the challenge of selecting the appropriate patient populations for sensitivity and homogeneity for PK, PD and clinical efficacy and safety studies to support extrapolations to groups not investigated with the biosimilar.

Product-specific Examples:

- MabThera (rituximab): MabThera, an r-IgG1, is a rituximab concentrate for solution for infusion. It has three approved but diverse indications, each with different pharmacovigilance programs noted within section 4.8 of the EU SmPC: non-Hodgkin's lymphoma (NHL), chronic lymphocytic leukemia (CLL) and rheumatoid arthritis (RA). Only RA has an additional contraindication of cardiovascular disease. The size of the safety database depends on the condition treated and the nature of the biologic.

  The doses and regimens are different, e.g., for NHL, it is 375 mg/m2 body surface area per cycle, for up to eight cycles; for RA, it is 1,000 mg by intravenous (IV) infusion followed by a second 1,000 mg IV infusion two weeks later. The infusion rate can vary from 50–400 mg/h and influences adverse reactions. Infusion-related reactions are very common in RA patients given rituximab. Therefore, as this example shows, there are many variables in any biosimilar clinical development program that will impact not only efficacy but also safety.
- Remicade (infliximab): A Remicade vial contains 100 mg of infliximab powder for concentrate for solution for infusion. Remicade is indicated (second line treatment) for adults with active RA, Crohn's disease, ulcerative colitis in pediatric 6–17 year olds, psoriatic arthritis or plaque psoriasis (skin) in adults. Doses are either 3 mg/kg or 5mg/kg by IV infusion with diverse regimens. Therefore, distinctly different pharmacovigilance programs are involved.
- Enbrel (etanercept): This is a recombinant human tumor necrosis factor (TNF) inhibitor receptor p75 Fc fusion protein, a powder and solvent for solution for injection. Etanercept is, in principle, a "new generation" derivative of mAb infliximab maintaining the Fc moiety, but is a smaller molecule that represents the first fusion protein biosimilar candidate coming off patent, and has essentially the same indications as infliximab except for Crohn's or colitis. The recommended dose of Enbrel is 25 mg administered twice weekly or 50 mg administered once weekly by subcutaneous injection.

  The subcutaneous route raises the risk of dermally triggered serious hypersensitivity reactions compared to the IV infusion route, which in itself can induce "infusion reactions." The IV, however, represents higher exposure. So each route and pharmaceutical form has associated safety risks. FDA requires the subcutaneous route to be studied as it is associated with the highest risk of immunogenicity.

Reference Medicinal Product

The importance of choosing an acceptable RMP cannot be underestimated.

Impact of RMP

The RMP's safety profile is defined by the comparator's SmPC (EU) or PI (US), the RMP selected when more than one originator is marketed, which is the case with the r-somatropins or rhu-insulins, r-insulin analogues or LMWHs or r-interferons-alpha or r-interferons-beta.

Furthermore, the comprehensive battery of structural and analytical pharmaceutical comparability chemical, biophysical, biochemical and bioassay/bioidentity tests of the biosimilar versus the RMP not only defines the identity, integrity and potency connected with the product's efficacy, but also its impurity profile, stability, microbiology (sterility, endotoxins, preservative) and other safety aspects safety.

Selection of RMP

FDA has made some important concessions regarding the RMP. FDA's decision to accept an RMP from

another major regulated region[26] to "scientifically justify the relevance of these data to an assessment of biosimilarity"[27] is far-reaching. A product approved in the EU generally would qualify as an FDA-acceptable RMP as it complies with ICH regulatory standards.

FDA states in its Q&A guidance that one precondition is, "as a scientific matter, analytical studies and at least one clinical pharmacokinetic (PK) study and, if appropriate, at least one pharmacodynamic (PD) study, intended to support a demonstration of biosimilarity must include an adequate comparison of the proposed biosimilar product directly with the U.S.-licensed reference product."[28]

FDA would need bridging EU versus US RMP scientific data as proof of comparability, as well as all information that could be relevant on manufacturing sites and license holders.

Accepting a foreign RMP is a step beyond Europe, where the RMP must be purchased in the EU, according to the acquis communautaire legality, to render the studies pivotal. Otherwise, all the effort is wasted and the studies would be scientific findings that would only be supportive. Canada also has a provision allowing a non-Canadian RMP.[29]

As in Europe, where more than one RMP is available, comparability studies against a single product will suffice for approval.[30]

The US PI identifies a biosimilar this way, "Labeling of a proposed product should include all the information necessary for a health professional to make prescribing decisions, including a clear statement advising that: This product is approved as biosimilar to a reference product for stated indication(s) and route of administration(s). This product (has or has not) been determined to be interchangeable with the reference product."[31]

Being prepared to accept comparative data from a non-US RMP (such as the EU) is a significant advance and sets an excellent international precedent. This will allow an EU–US development program to be conducted, thereby saving time and resources. In cases where the biosimilar has already been approved in Europe, bridging studies can be agreed on with FDA.

Postapproval Reports

There is virtually no specific clinical European EPAR information on postapproval biosimilar clinical activities.[32]

A 2009 variation concerns an update of the SmPC following the completion of a class safety review by the Pharmacovigilance Working Party (PhVWP) and CHMP. As a result, CHMP requested an update to section 4.4 of the SmPC to include more information on pure red cell aplasia (PRCA) in patients with hepatitis C treated with interferon, ribavirin and epoetin, and section 5.1 to include additional data on the Cochrane meta-analysis and the effects of epoetins in cancer patients.

In 2010, there were updates to the Retacrit epoetin zeta label and the RMPPV version 8.0 concerning allogeneic blood transfusions in adult non-iron-deficient patients prior to major elective orthopedic surgery. The Marketing Authorization Holder (MAH) submitted data from a Phase III study comparing a subcutaneous test BMP's efficacy and safety (including immunogenicity) with an RMP in patients with renal anemia, to support an extension of the current indication to the product's use as an alternative to blood transfusions in adult patients about to undergo major orthopedic (bone) surgery where there is a potentially high risk from blood transfusion complication.

The original approval was for the IV route or administration, since the subcutaneous route was contraindicated in the EU at that time. The addition of a subcutaneous route of administration in the indication of "anaemia associated with CRF on haemodialysis and patients on peritoneal dialysis" and "severe anaemia of renal origin accompanied by clinical symptoms in adult patients with renal insufficiency not yet undergoing analysis" was recent.

In the case of G-CSF Zarzio and Filgrastim Hexal, the update of section 4.8 of the SmPC required the inclusion of the terms Graft versus Host Disease (GvHD) and pseudogout as undesirable effects and an update of section 4.4 to include a statement on traceability. The inclusion of GvHD was requested by CHMP following the assessment of PSUR 3, and the additional changes were proposed by the MAH to bring the product information in line with the RMP. There were also amendments to reflect a Core (class) SmPC change.

The Omnitrope Marketing Authorization was renewed based on the CHMP opinion this medicinal product's quality, safety and efficacy continues to be adequately and sufficiently demonstrated. Therefore, the benefit: risk profile of Omnitrope continues to be considered favorable. During the renewal procedure, changes were made to the Product Information to bring it in line with the RMP, Genotropin.

FDA Public Hearing

An FDA hearing on 11 May 2012 was chaired by Rachel Sherman, MD, MPH, associate director for medical policy at the agency's Center for Drug Research and Evaluation (CDER).[33]

The need for educational materials for patients and healthcare practitioners on biological and biosimilars, more clarity on interchangeability and the need for traceability and manufacturer accountability, among others, were raised by stakeholders. Although the issue of biosimilar and interchangeable naming conventions was raised, it was determined the combination of National Drug Codes, lot numbers and other potential unique identifiers in the US provide sufficient tracking capabilities to address safety concerns.

Dr. Sabine Straus from the Dutch Medicines Evaluation Board (MEB) revealed the results of a University of Utrecht/MEB study in Europe that explored the current status of traceability of biopharmaceuticals in the US and EU in spontaneous reporting systems in 2004–10.

Current research showed that batch information is available for approximately one in four suspected biopharmaceuticals. The study also revealed that biosimilar product identification is well ensured: 96.2% across three product classes, and especially for epoetin (98.9% of suspected epoetins).[34]

Concern was expressed that interchangeability being a "higher standard" than biosimilarity would create a public misconception that interchangeable products were "higher quality" than biosimilar products, reducing patient acceptance. Companies expressed their desire for FDA to harmonize its requirements with EMA's guidelines for biosimilars.

Conclusions

As increasing experience is gained with biosimilars approved under the scientific and regulatory rigor of the European Commission and EMA, it is hoped the medical community and patients will appreciate that biosimilars can be used safely in medicinal drug treatment strategies.

At present, the adoption of biosimilars is relatively slow due to various hurdles encountered after European approval, including Health Technology Assessment (HTA) body requirements, physician acceptance, patient acceptance and various lobbying interest groups. But, this situation must change because of escalating drug costs and many new biologic approvals, including therapeutic proteins fulfilling unique medical needs.

Many important considerations have been appraised and put forward in this twopart series. It is apparent the EU regulatory framework is ensuring equivalent biosimilar safety and effectiveness, although the data package forming the basis of approval is very demanding. FDA's system offers a scope that overlaps EMA requirements, although it is hoped FDA may relax some of EMA's study demands based on FDA's intended "stepwise" and risk-based "targeted" approach.[35]

This might affect future European biosimilar development by triggering a reconsideration of EMA's guidelines, as has been seen for anticoagulant low molecular weight heparins (LMWHs), each a complex mixture of oligosaccharides (e.g., enoxaparin, dalteparin and tinzaparin).[36] FDA surprisingly approved enoxaparin sodium in 2010 under an ANDA, a generic pathway.

FDA and EMA's cooperation in 2010–11 has been exceptional and covers MAA/NDA/BLA reviews, clinical safety, scientific advice, joint GMP/GCP inspections and all facets of drug development and approval.[37] It will be most interesting to see how the 2011 socalled "biosimilars cluster" consultation forum between the two regulatory agencies willprogress and affect international biosimilar development to the highest EU standards.

References

1. *Draft Guidance for Industry on Scientific Considerations in Demonstrating Biosimilarity to a Reference Product (issued jointly by FDA CDER and CBER, February 2012).*
2. *Draft Guidance for Industry, Quality Considerations in Demonstrating Biosimilarity to a Reference Protein Product (issued jointly by FDA CDER and CBER, February 2012).*
3. *Draft Guidance for Industry, Biosimilars: Questions and Answers Regarding Implementation of the Biologics Price Competition and Innovation Act of 2009 (issued jointly by FDA CDER and CBER, February 2012).*
4. *Op cit 1.*
5. *Op cit 2.*
6. *Op cit 3.*
7. *Private communications and presentations by companies marketing biosimilars at European Generic Association Annual conferences 2009–12.*
8. *Ibid.*
9. *Dowlat H. Regulatory Rapporteur. The Importance and Impact of the EU RMP and US REMS to risk–benefit assessments. Vol. 8, No 2, February 2011.*
10. *Ibid.*
11. *European Parliament and of the Council, Directive 2010/84/EU and Regulation 1235/2010/EU, Pharmacovigilance and The Rules Governing Medicinal Products in the European Union, Volume 9 Pharmacovigilance Guidelines.*
12. *Op cit 9.*
13. *Op cit 3.*
14. *Health Canada, Health Products and Food Branch. Guidance for sponsors: Information and Submission Requirements for Subsequent Entry Biologics (SEBs). Draft 5 March 2010.*
15. *Guideline on similar biological medicinal products containing monoclonal antibodies (Draft). EMA/CHMP/BMWP/403543/2010, (18 November 2010).*
16. *Op cit 7.*
17. *Op cit 15*
18. *Op cit 1.*
19. *Ibid.*
20. *Ibid.*
21. *Op cit 3.*
22. *Op cit 1.*
23. *Op cit 7.*
24. *Op cit 3.*
25. *European Medicines Agency. EPARS: Mabthera, Remicade, Enbrel.*
26. *Op cit 1.*
27. *Op cit 3.*
28. *Ibid.*
29. *Op cit 14.*
30. *Op cit 1.*
31. *Ibid.*
32. *European Medicines Agency. EPARS Postapproval. Retacrit Epoetin, G-CSF Zarzio, Filgrastim Hexal, Omnitrope.*
33. *US Food and Drug Administration. Draft Guidances Related to the Development of Biosimilar Products; Request for Comments at its White Oak Campus, 11 May 2012. www.fda.gov/Drugs/NewsEvents/ucm265628.htm. Accessed 30 June 2012.*
34. *European Medicines Agency, Fifth stakeholder forum on the implementation of the new pharmacovigilance legislation, Traceability of biopharmaceuticals in spontaneous reporting systems. 25 May 2012.*
35. *Kozlowski S, Woodcock J, Midthun K, Sherman RB. Developing the Nation's Biosimilars Program, New England Journal of Medicine. 2011, 365; 5, 385-8.*
36. *US Food and Drug Administration. US approval of anticoagulant Lovenox, Generic Enoxaparin, Questions and Answers, www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm220037.htm. Accessed 30 June 2012.*
37. *EMA/705027/2010 irectorate (June 2011). Interactions between EMA and FDA from September 2009 to September 2010.*