a more accurate and comprehensive clinical database and to ensure that any unexpected treatment issues are identified promptly. The EMEA guidelines will permit the use biosimilars for indications for which they have not been formally studied (ie, extrapolation) when proper justification is provided. While the EMEA guidelines are scientifically rigorous and provide a pathway for the approval of biosimilars, they do not fully address some important post-approval issues relevant to physicians, particularly in the oncology setting. These include automatic substitution with biosimilars, labeling so that physicians can make informed decisions, and nonproprietary naming for accurate prescribing and dispensing practices. Currently, the EMEA cannot guarantee the interchangeability of biosimilars with reference products, and because of the potential for differential clinical response it would appear prudent that automatic substitution should not be allowed for any biopharmaceutical – biosimilars or innovator products. Also, the use of biosimilars for indications based on extrapolation of data must be weighed against the possibility for differences in safety and efficacy. Such issues underscore the need for full disclosure in the product labeling of biosimilars so that physicians and patients can make informed decisions regarding product selection. A thorough knowledge of the issues surrounding biosimilars will ensure the appropriate use of biopharmaceuticals.

**16** INVITED

**Follow-on erythropoietins – Pros and cons**

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**Background:** Erythropoietin biosimilars are not generic equivalents of the innovator product and are likely to be approved in Europe soon.
**Material and Methods:** This report presents a review of present literature on biosimilar erythropoietins. Literature search included Medline and abstracts from ASCO, ESMO, ASH, EHA and ECCO meetings (2000-2007).
**Results:** Amino acid sequences of biosimilars of erythropoietin will most likely be similar to that of endogenous erythropoietin, but glycosylation patterns will differ. Differences in glycosylation may have a significant impact on the rate of plasma clearance, on receptor binding, and importantly on biological and on clinical activity. A recent study comparing 11 erythropoietin products from 4 different countries (Korea, Argentina, China, India), revealed significant variations in the distribution of erythropoietin isoforms. Further, in vivo bioactivity ranged from 71% to 226%, with 5 products failing to meet their own specifications.
Due to the differences in carbohydrate moiety and possibly immunogenicity and clinical activity, appropriate labelling of the drugs as unique molecules is mandatory. This is particularly important for identification of eventual late adverse effects during pharmacovigilance studies. Hence, switching or substitution between innovator products and biosimilars should not be enforced automatically, and must be viewed as a change in clinical management. Rigorous pharmacovigilance programs are needed to capture possible side effects and to build a database establishing the clinical use of each product.
On the positive side, biosimilars will increase the usage of drugs and benefit more patients. The introduction of biosimilars will motivate industry to increase its research efforts even further in order to develop new drugs, which will be protected by patent rights for a defined period.
**Conclusion:** Biosimilars are not identical to the innovator drug, cannot automatically be substituted and need careful pharmacovigilance programs. Their introduction will allow a greater number of patients to actually receive treatment, and will drive industry to further enhance its research efforts.

**17** INVITED

**G-CSF biosimilars – approval process, substitution and extrapolation**

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Two G-CSF products differing with respect to biological characteristics and approved indications are currently available in Europe. Comparative studies have demonstrated differences between these two products with regard to pharmacological properties and clinical outcomes and are not considered interchangeable. According to EMEA guidelines, G-CSF biosimilars have to demonstrate comparability in efficacy and safety to one of the two G-CSF products in the prophylaxis of severe cytotoxic chemotherapy-induced neutropenia. While a two-arm comparability study is recommended for chemotherapy regimens with known frequency and duration of severe neutropenia, a 3-arm study (including placebo arm) is required for other chemotherapy regimens.
Since limited clinical experience will be available at approval of biosimilars, substitution represents a major challenge. Automatic substitution may lead to the administration of multiple products and events would not be able to be linked to a specific product. Furthermore, the identification of biopharmaceutical products might not be possible if multiple products share one International Nonproprietary Name (INN).
Although data extrapolation has a rational basis, the process by which indications for a product were approved should be known. A potential concern with the concept of data extrapolation arises in particular for G-CSF biosimilars, since efficacy and risks may differ in patient populations depending on age, on disease (malignant or non-malignant) and immunosuppression. As an example non-immunosuppressed patients with chronic neutropenia may be more likely to develop antibodies to biopharmaceutical agents than immunosuppressed patients. Especially the use of G-CSF biosimilars for stem cell mobilization from healthy donors in allografting presents an ethical dilemma. Since healthy donors receive no therapeutic benefit from the receipt of CSFs for stem cell mobilization, ethical concerns dictate that drug safety be of paramount concern. Sufficient experience with the biosimilar product and adequate follow up should be required.
In summary, information is the key to mitigating the potential concerns regarding the use of biosimilars. Any change from one product to another should be considered as a change in clinical management. Extrapolation should be avoided for use of biosimilars in healthy stem cell donors as long as sufficient data from stem cell mobilization in patients are available.

## *Special session* (Mon, 24 Sep, 13:30−14:30)
## Retroperitoneal sarcoma

**18** INVITED

**Surgical standards of treatment**

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The specific problems of retroperitoneal soft tissue sarcoma relate to the proof of malignancy by biopsy and the heterogeneity of huge tumors with sometimes low grade and high grade compartments. Biopsy needs to prove that lymphoma, extragonadal germ cell tumors and lymph-node metastasis of tumors of the testicles do not hide behind a sarcomatous appearance. The future of defining molecular targets might also offer preoperative targeted therapy with new substances, for example in myxoid or round-cell liposarcoma.
The primary goal of surgery is an R0 resection – adjuvant chemotherapy has not proven to be of value. Thus, planning of the operative treatment must be made not to leave viable tumor tissue behind. At the first stage, an adequate imaging of the whole abdomen starting from the diaphragm down to the lower pelvis is required not to miss an extension of the tumor to the thorax, the lower pelvis, the adductors or paravertebrally. Usually retroperitoneal sarcoma is in close contact to one of the kidneys. If there is any risk that the kidney or the ureter will be involved in the resection, assessment of the function of the contralateral kidney is mandatory.
Concerning resectability the limits of resection are the spine, the neuroforamen, major involvement of the aorta, invasion or extension to the root of the mesentery with major small bowel resection as a consequence, bony structures as the ileo-sacral joint and extraabdominal extension. The retroperitoneal compartment, sarcoma usually originates in, offers a unique possibility for a radical resection. However, this means that tumor removal is a multivisceral resection by principle. Dissection of the aorta or vena cava, resection of the psoas muscle, removal of the internal oblique muscle, as well as keeping the sarcoma covered by large bowel resection and nephrectomy are the crucial steps. Extended resections include removal of parts of the vena cava and graft reconstruction, as well as partial resection of the aorta with graft or patch plasty and finally also autotransplantation of the kidney in case of involvement of the fatty capsule of the kidney only. Resection and reconstruction by diaphragm with a synthetic graft may complete the approach.
It must be born in mind that after removal of a huge retroperitoneal mass the small bowel will move to the former tumor bed and by this way makes postoperative adjuvant radiotherapy inefficient due to the limit of tissue radiation tolerability. Consequently, radiotherapy should be used prior to the operation. In high-grade soft tissue sarcoma, preoperative radio-/chemotherapy could be useful. Recently, in a randomized prospective trial, systemic chemotherapy combined with deep wave hyperthermia has proven effective, not only in the down-staging of tumors, but also in improving survival. This methodology might not be available at any center, but an experienced sarcoma center is required to offer the patient an optimum standard of care. A multistep explanation of the therapeutic