Biacore™ concentration and ligand-binding analyses in late-stage development and quality control of biotherapeutics
Biacore concentration and ligand-binding analyses in late-stage development and quality control of biotherapeutics

Biotherapeutic drugs including antibodies, cytokines, and hormones are used for treatment of a variety of diseases including arthritis, cancer, and diabetes. Compared to traditional small-molecule drugs, their structures are complex and they can assert their effects by binding with high specificity to more than one target molecule. During development and in quality control, a range of analytical technologies are used to characterize biotherapeutic drugs in terms of their structural integrity and activity. In this white paper, the use of Biacore for active concentration measurements, target binding, and Fc receptor (FcR) analysis is reviewed along with the use of these assays for assessment of drug potency and stability.

Introduction
The life cycle of a biotherapeutic product typically spans over thirty years as illustrated in Figure 1. Early development can exceed five years. Initial process development within the late-stage development is fairly rapid, approximately one year. The process is refined in parallel with the first clinical trials. Late-stage development can extend over three to five years depending on the duration of clinical trials. Once approved for an initial indication, a successful product can remain in manufacturing and quality control for over twenty years with additional indications added over time. Successful biotherapeutics such as Rituxan™, Herceptin™, Enbrel™, Remicade™, Humira™, Avastin™, and Lantus™, which were first approved between 1997 and 2004, all serve as examples of these timelines.

In the early phases of development, the focus is on the drug substance and the assumed mechanism of action (1). Early biotherapeutic development is typically target-based (2). For a therapeutic antibody, the mechanism of action includes target binding but can also include FcR and complement binding. For cytokines and hormones, receptor binding is essential. A lead substance should elicit the desired functional response of the target molecule, have adequate bioavailability and biodistribution, and should be evaluated from a safety perspective.

As the lead candidate enters late-stage development, several “critical quality attributes” (CQA), that is, properties that ensure clinical safety and efficacy (Fig 2), are established. Important process-related CQA such as protein integrity,

![Fig 1. Events in the life cycle of a biotherapeutic drug. Each development block and comparability study includes analysis for CQA.](image-url)
homogeneity, presence of host cell proteins, host cell DNA, and substances released from process or package material can be identified using risk assessments based on previous experience and knowledge and by control procedures. For each step in the process, critical process parameters (CPP) that can affect CQA are identified (3) and a control strategy is defined. In the bioprocess lab, analysis is focused on the control of cell culture (4) and purification (5) procedures. With CPP identified and a control strategy in place, the CQA should be secured and verification should be straightforward.

To support this process, requirements on test procedures and acceptance criteria have been described in regulatory guidelines (6) for biotechnological/biological products. Late-stage development includes process development, formulations, and clinical trials. This white paper focuses on development associated with chemical manufacturing and control, CMC (7). The assays discussed here are typically performed in core laboratories, which receive samples from process development, formulations, or production groups.

Development starts with setup and validation (8) of analytical methods and with securing reagents (9, 10) for the analytical program. A broad range (50 to 60 variants) of different analytical technologies may be used for CQA analysis (11). Mass spectrometry (MS) can be used to establish the identity of the drug (primary sequence) and for detection of size-distribution profiles linked to post-translational modifications such as glycosylation (12). MS is further used in combination with high-performance liquid chromatography (HPLC) and other chromatographic methods to detect and localize amino acid modifications (13). Chromatography techniques are broadly used for detection and isolation of charge and size variants (14). Sodium dodecyl sulfate-polyacrylamide gel electrophoresis (SDS-PAGE) and Western blotting demonstrate protein integrity, and in the case of antibodies, the presence of HHL-, HL- or L chains can easily be detected (15). Enzyme-linked immunosorbent assay (ELISA) and surface plasmon resonance (SPR) are commonly used for in vitro confirmation of biological activity by measuring interactions with antigen, receptor, FcR, or other binding proteins (11, 13).

Process development for CMC includes selection of the cell line for protein expression, development of the cell culture process, and purification of the drug substance, while formulation includes selection of excipients for the final drug product. During process development, the goals are to obtain high product yield and good process economy to ensure that properties related to initial CQA are maintained and to secure that the process itself is well controlled with low impurity levels. Formulations ensure that the final product has proper stability, administration properties, and pharmacokinetic profile. Throughout all steps of late-stage development, initial CQA are monitored and possible new CQA are evaluated. Before transfer to manufacturing, the complete list of CQA is established along with methods for their control. Manufacturing and quality control (QC) ensures a supply of product with consistent quality to the market. CQA are determined using state-of-the-art knowledge at a given time and might later have to be revised based on clinical data that accumulate over time.

Manufacturing timelines extending over decades constitute both challenges and opportunities. The challenge is to maintain a high and consistent product quality while manufacturing analytical technologies evolve and material and reagents become obsolete and have to be replaced. The opportunity lies in improvements that simplify processes and make them more reliable and/or more economic. The demonstration of comparability (16) does not necessarily mean that the quality attributes of the pre-change and post-change product are identical. However, based on results and existing product knowledge, it should be possible to predict that any differences in quality attributes have no adverse impact upon safety or efficacy of the drug product. Manufacturing changes can be frequent (17) and approval times for changed products can be lengthy.

While comparability studies put pressure on using modern analytical technologies, an even stronger push for extended and more detailed fingerprint analysis comes with the development of biosimilars (18, 19, 20). Biosimilars are generic products that are physically "identical" to an already approved drug and with the same safety and efficacy profile as that of the reference product. A biosimilar should mimic the reference product in terms of properties but the processes and technologies used for manufacturing and control can be different from that used for the reference product. The results from extensive analytical comparisons with the reference product may serve as an indication of the extent of clinical trials that have to be performed (18, 19, 21).
Biacore assays are based on ligand binding

Ligand-binding assays are key for characterization of biotherapeutic medicines. SPR and ELISA are extensively used ligand-binding assays. Biacore systems and ligand-binding assays from GE Healthcare’s Life Sciences business are based on SPR analysis and have been used for antibody characterization for more than twenty years.

The readout from a Biacore system is related to molecular mass and any binding event can be detected without the use of labels. The readout is continuous, which allows quality control of the entire binding event. This provides opportunities for data analysis based on binding responses obtained at one or several specific time points (report point analysis) or by comparing and even fitting entire binding curves for determination of kinetic and affinity parameters.

Biacore ligand-binding assays are truly direct-binding assays (22), are focused on relevant interactions (23), provide information on binding activities, and can detect even very weak interactions. This is in contrast to ELISA, which is an indirect method where detection is based on the use of a labeled secondary reagent, where the readout is obtained at a less well-defined time point, and where weak interactions might go undetected.

ELISA and Biacore assays can be used in direct and competitive formats in a variety of situations where binding data is required to confirm and quantitate the presence of an analyte or for characterization and confirmation of biological activity. Characterization of binding events is essential for confirmation of CQA as outlined in Figure 1 and is a vital part in forced degradation studies and a complement to—or even the basis for—potency assays. Assay setups are often similar between ELISA and Biacore systems although there is no guarantee that assay reagents are interchangeable from one platform to the other.

Biacore assays allow the researcher to plot data from several samples in overlay plots as illustrated in Figure 3. This effective data display makes data from Biacore assays relatively easy to interpret. Biacore data is often more precise than ELISA (24), presumably as Biacore assays involve fewer steps and are under strict time and temperature control.

Biacore systems measure active concentration with high precision

Concentration analysis is vital in several process development steps: to determine the yield in cell cultures over time; for identification of suitable chromatography conditions; for monitoring of final purification processes; and in formulation studies.

Concentration measurements can in their simplest form be based on values of absorbance measured at 280 nm wavelength ($A_{280}$ values), but this requires that interference from other UV-absorbing substances is ignored. $A_{280}$ values are often used in combination with HPLC studies. It can, however, be of more interest to produce concentration data that are related not only to total protein concentration but to the specific protein and even to the function/activity of the protein. Here, antibody- or receptor-based assays play an important role.

Figure 4 illustrates the dynamic range and precision in concentration analyses using Biacore systems. The assay readout is from a report point at the end of sample injection. In these examples, an antihuman Fc antibody is immobilized on the sensor surface. In Figure 4A, omalizumab at concentrations from 2 ng/ml to 1 mg/ml was injected for a 3 min period. The insert shows the response for the lowest (2 to 8 ng/ml) concentrations. This assay can be fine-tuned and, depending on the concentration range of interest, the analysis time can be adjusted. In Figure 4B, the sample injection time was reduced to 20 s and the concentration range of interest was from 0.5 to 50 μg/ml. The figure shows data obtained with repeated injections of standards, controls, and one selected sample over 1000 analytical cycles obtained on the same surface. Noticeably, standard and control samples were stable over time and the coefficient of variation for the repeat sample was 1.3%.

Clearly, Biacore assays are sensitive, have potential for a wide dynamic range, can be very rapid and, based on the Biacore system design, can be multiplexed with the possibility to run several assays in parallel.
Validation of a Biacore assay for antibody analysis considering immobilization and regeneration procedures, buffer conditions, sensor chip storage, interassay variability, limit of detection, and quantitation is described in reference 24, which additionally describes the use of a Biacore assay in a GMP environment.

**Biacore binding assays reflect the mechanism of action and can be developed into potency assays**

**Target binding**

Antibodies, cytokines, and hormones typically interact with their receptors. Cytokines and hormones typically retain their natural sequence but can be engineered for improved stability or half-life. Antibody therapeutics on the other hand are engineered to interact with relevant target molecules including antigens, FcR, and complement factors. Binding profiles presented in Figure 5 illustrate binding of a cytokine to its receptor and two antibodies binding to their targets. Clearly, binding properties vary considerably with estimated half-lives from 50 s (IFNα-2a) to 12 h (bevazizumab). Today there are several antibody formats in development with particular focus on bispecific antibodies where two distinct target functionalities are combined in one molecule. Examples where Biacore analysis has been used for characterization include: bispecifics that bridge Tcell and target-cell receptors (28); a bispecific antibody bridging FIXα and FX binding to mimic the natural function of factor FVIII (29); and a bispecific antibody that combines VEGF and Ang-2 functionalities to reduce the formation of blood vessels in cancer tissue (30).

Target binding is clearly an essential CQA and has to be controlled during development and later in QC for batch-to-batch consistency. While release assays are traditionally based on bioassays, ligand-binding assays (20, 31) can be considered when the mechanism(s) of action is/are defined provided that the assays reflect the mechanism of action (MOA). While kinetic data is useful for in-process characterization and batch-to-batch comparison, release assays require that the ligand-binding assays produce a product concentration that reflects the pharmacological activity (potency assay). Release assays are often based on relative comparisons and parallel line/parallel logistic analysis with defined conditions for equivalence (32).

**Fig 4.** Concentration data obtained with Biacore T200 system.

**Fig 5.** Binding of interferon alpha 2a (IFNα-2a) to (A) IFNAR2 (25), (B) CD20 to rituximab (26), and (C) vascular endothelial growth factor (VEGF) to bevazizumab (27). The plots are overlay plots of measured data and kinetic binding curves obtained with a 1:1 binding model. Reprinted (adapted) with permission from: (Fig 5A) Dhalluin, C. et al., Structural, kinetic, and thermodynamic analysis of the binding of the 40 kDa PEG-interferon-alpha2a and its individual positional isomers to the extracellular domain of the receptor IFNAR2, Bioconjug. Chem. 16, 518–527 (2005), reference 25; (Fig 5B) Ernst, J. A. et al., Isolation and characterization of the B-cell marker CD20, Biochem. 44, 15150–15158 (2005), reference 26; (Fig 5C) Papadopoulos, N. et al. Binding and neutralization of vascular endothelial growth factor (VEGF) and related ligands by VEGF Trap, ranibizumab and bevacizumab, Angiogenesis 15, 171–185 (2012), supplementary material from electronic article, reference 27. © 2015 American Chemical Society.
The dual-specificity assay for VEGF-Ang-2 antibodies described in (30) was later developed into a potency assay (23) as illustrated in Figure 6. VEGF was immobilized to the sensor surface. The bispecific Ang-2/VEGF CrossMAB (Roche) was injected followed by a second injection of angiotensin (Ang-2, Fig 6A). Two response values, R1 and R2, corresponding to VEGF and Ang-2 binding, respectively were obtained (Fig 6B). R2 values were further plotted versus the logarithm of the concentration of the CrossMAB (Fig 6C) and similar plots were obtained from experiments using deviating concentrations of the CrossMAB and stressed samples. Parallel line analysis, PLA, of these curves showed that the assay was applicable for potency estimates in the range from 60% to 140% of the nominal concentration.

**Fc receptor binding**

Fc receptors (FcγR) are expressed on different cell types and can be activating (FcγRI, FcγRIIa, and FcγRIIIa), inhibitory (FcγRIIb), or without effect (FcγRIIIb) in antibody-dependent cellular cytotoxicity, ADCC. The mechanism of action for several anticancer antibodies involves ADCC and here the interaction with FcγRIIIa present on natural killer cells might be of particular importance. Biacore analysis is widely used in research where antibodies are designed either for improved interaction with FcγR (33) or for elimination of immune effector functions when nonimmunostimulatory monoclonal antibodies (MAb) are developed (34).

The neonatal Fc receptor (FcRn) interacts with antibodies at a lower pH and is believed to be important for rescuing antibodies from lysozomal degradation and for prolonging the half-life of antibodies (35, 36). In late-stage development, the objective is to maintain the established FcyR and FcRn functions and in this context, Biacore assays are widely used in comparability studies (11).

Several assay formats have been used for studying the FcR-antibody interactions including: covalent coupling of FcR (37, 38, 39); capture of histidine-tagged FcR on immobilized antihistidine antibody (34, 40, 41); and capture of antibodies on protein L (42) and protein A (43). Capture formats combine the advantages of orientation of the captured molecule and common regeneration conditions across a range of interactions. Two capture formats used for FcγR analysis are illustrated in Figure 7A. Both these formats give stable capture and highly reproducible data and can be used across the entire range of FcγR with no change to the assay setup. Biacore analysis is widely used in research where antibodies are designed either for improved interaction with FcγR (33) or for elimination of immune effector functions when nonimmunostimulatory monoclonal antibodies (MAb) are developed (34).

Fig 6. Potency assay setup for VEGF-Ang-2 CrossMAB. [A] Interaction of Ang-2 and VEGF with bispecific CrossMAB analyzed by SPR using a Biacore system. (B) Overlay of sensograms recorded with CrossMAB concentrations of 0.35 to 30 g/ml (1:1.5 dilution series) with 1 g/ml Ang-2 binding. (C) Dose-response curve (Ang-2 binding response R2 vs CrossMAB concentration, log scale) of the CrossMAB binding signal. Reprinted from: J. Pharm. Biom. Anal., vol. 102, Gassner et al., Development and validation of a novel SPR-based assay principle for bispecific molecules, pages 144–149, © 2014, reference 23. With permission from Elsevier.
Histidine-tagged FcR

**Response range 120 to 200 RU**

**Time range 700 to 900 s**

**FcγRIa**

**FcγRIIa**

**FcγRIIIa**

Protein A

**Fig 8.** Binding and dissociation of antibody to FcRn at pH 6.0 (red) and dissociation of antibody as pH is shifted to 7.4 (blue).

While FcR assays with Biacore systems are essential for antibody characterization, this approach has also been proposed as a potency assay for antibodies where the interaction with FcγRIIIa contributes to the mechanism of action. Harrison and coworkers (41) used histidine-tagged receptor and alemtuzumab to develop a potency assay based on report points from several concentrations of the antibody. The potency assay used the 5PL algorithm and demonstrated good linearity and measured potencies were within 9% of the nominal values. The authors noted that the SPR assay showed greater internal precision and long-term reproducibility than a traditional cell-based, ADCC assay.

**Binding of complement cascade C1q to antibody**

The first step in the complement cascade is binding of C1q to the antibody (45). The C1q molecule has six heads connected by collagen-like stems to a central stalk. The isolated heads bind to the CH2 domain of the antibody. Blanquet-Grossard and coworkers (46) have demonstrated IgG binding to immobilized C1q. In Figure 9, the sensorgram is indicative of a slow on-rate and a slow off-rate. Note that the concentration of antibody is 1.5 µM and that the binding rate is low. Although these results indicate that C1q assays on Biacore systems are feasible, more public data on this assay would be helpful.

**Fig 9.** Binding of 1.5 µM rabbit IgG to immobilized C1q. Reprinted (adapted) with permission from Blanquet-Grossard, F. et al., Complement protein C1q recognizes a conformationally modified form of the prion protein. Biochem. 44, 4349–4356 (2005), reference 46. © 2015 American Chemical Society.
Biacore systems in stability and forced degradation studies
Changes in higher order structure can potentially alter the immunogenic profile of a biotherapeutic drug and thereby impact the safety of the drug. Amino acid modifications and changes in glycosylation can be identified by a combination of analytical techniques such as MS, electrophoresis, and chromatography and product variants can be isolated and characterized.

Methionine oxidation, glycation, and deamidation can be induced by protein stress. Whether such changes are actually accompanied by a change in conformation is uncertain. Interestingly, not only amino acid modifications but also 25% to 50% reduction in target binding, as determined by a Biacore assay, could be observed for stress conditions related to elevated temperature, elevated pH, and presence of hydrogen peroxide (47). Similarly, methionine oxidation of an IgG2 resulted in impaired binding to FcRn (48). Changes in target binding and FcRn binding for stressed samples thus indicate that interaction analysis may be used to detect small changes in antibody reactivity. Target and FcR interactions can therefore play an important role in stability and forced degradation studies.

To obtain more comprehensive fingerprints of antibody reactivity, we identified several domain-specific antibodies and bacterial proteins that are capable of binding IgG as well as differentiating between wild-type (WT) and stressed variants. In Figure 10, the stressed variant was subjected to treatment with 0.2% hydrogen peroxide for 18 h. MS analysis demonstrated a 20-fold increase in methionine oxidation increasing from 1% to 2.5% to between 20% and 50% depending on methionine position. Four common IgG binders directed towards Fc and hinge regions were able to differentiate between wild type (WT, red curves in Fig 10) and forced oxidized samples (blue curves). Similarly, three reagents identified changes from pH stress leading to deamidation and two reagents differentiated between WT and light-stressed antibodies. The latter were more prone to aggregation and compared to WT demonstrated differences in hydrophobic and charge profiles.

This data suggests that Biacore systems can be used for rapid analysis of changes in binding reactivity related to target-, FcR-, and IgG domain-specific functionalities and strengthens the use of Biacore analysis for screening of changes in reactivity in forced degradation studies and in regular stability testing.

Novel Biacore methods simplify and support comparability and biosimilar studies

Sensogram comparison for objective evaluation of Biacore binding curves
Kinetic and affinity analysis is very useful for comparison of interaction data. Nonconformance in kinetic and affinity parameters from one sample to another clearly signals that a change has occurred. However, kinetic and affinity analysis is based on the assumption that the interaction can be described by a binding mechanism and that a model can be fitted to observed data to obtain kinetic and affinity parameters. As illustrated by the excellent fits in Figure 5, this is often the case. However, the binding mechanism is not always known, interaction partners can be heterogeneous, or kinetic data can be uncertain. The interaction between rituximab and FcγRIIIaVal158 illustrated in Figure 11 is a good example.
When infliximab, omalizumab, and trastuzumab binding to FcγRIIIaVal158 was compared to that of rituximab, infliximab obtained a similarity score of 75% while the humanized antibodies (omalizumab and trastuzumab) obtained similarity scores close to 50%.

[Diagam: Fig 13. Similarity score for rituximab standard (blue bar), rituximab control (red bar), infliximab, omalizumab, and trastuzumab binding to FcγRIIIaVal158.]

With a robust assay, the sensorgram comparison approach provides a convenient alternative for comparison of binding data and can prove useful in batch-to-batch comparisons in comparability and biosimilar studies. An advantage of the sensorgram comparison approach is that calculations are rapid and that no fitting procedures have to be used. It is however important to carefully define the standard data that are used for calculation of the variation window as scoring is always with respect to the selected standard.

Calibration-free concentration analysis for rapid absolute and relative concentration measurements

Concentration analysis based on ligand binding typically requires a standard preparation with known active concentration. However, a standard preparation might not always be available, for example, when a protein is expressed for the first time or when concentration data for the standard reflects the total protein concentration and not the active concentration. In such circumstances, Biacore analysis can be used for direct assessment of the active concentration. This possibility was described already in 1993 (49) and has been refined with modern numerical integration tools for data analysis (50). The calibration-free concentration analysis (CFCA) method illustrated in Figure 14 provides a good estimate of the absolute concentration assuming that the diffusion coefficient of the analyte is known and that the observed binding rate is flow-rate dependent.
CFCA is an excellent tool for comparison of concentration data and is particularly useful for reagent characterization. CFCA is also a complement to kinetic analysis and sensorgram comparison methods when these indicate that changes in the interaction can be related to changes in active concentration. The use of CFCA for analysis of chromatography fractions and to guide purification efforts is described in reference 51.

Considering that relative concentration data is so easy to obtain with CFCA, it may also be used to complement and support potency assays.

**Biacore systems are tailored for work in a regulated environment**

Regulatory authorities impose increasing demands on pharmaceutical development and manufacturing companies to use quality-assured equipment and to follow detailed and carefully documented analytical and manufacturing procedures. The purpose of this control effort is to ensure consistent and reliable quality in pharmaceutical products that reach the market.

Biacore T200 GxP Package offers qualification services in connection with installation and service maintenance of Biacore T200, to provide the user with the necessary documentation for equipment qualification. Further, access rights in Biacore T200 GxP software are controlled through membership of Windows® users in the user groups BIAadministrator, BIAdeveloper, and BIAuser.

Within Biacore T200 software, the groups are permitted access as follows:

**BIAadministrator**: Full access to system operation and evaluation. Certain settings related to folder settings in the software are only accessible to BIAadministrators, who therefore have the responsibility of determining these settings for all other users.

**BIAdeveloper**: Access to all functions in system operation and evaluation with the exception of software preferences. BIAdevelopers are responsible for developing and publishing procedures for routine use. Published procedures consist of a run method and an evaluation method. This ensures that data is generated and evaluated according to defined protocols.

**BIAuser**: Access only to published procedures for system operation and data evaluation and to Control Software functions required for operation and maintenance of the instrument. BIAusers may only perform runs based on published procedures. In the Evaluation Software, BIAusers may only open result and evaluation files derived from published procedures. Some flexibility exists for the BIAuser, but changes made to the contents of result and evaluation files derived from published procedures are logged in in an operator-independent audit trail.

### Summary

The life cycle of a biotherapeutic agent can extend over twenty to thirty years. During this time, a manufacturer must develop and deliver a product with consistent quality. In support, regulatory authorities such as FDA and EMA issue guidelines aimed at ensuring efficacy of biotherapeutic medicines. Antibodies, cytokines, and hormones assert their actions through interactions with their target molecules and ligand-binding assays are highly relevant for characterization of the drug.

SPR using Biacore systems is used specifically in early development to define CQA. In late-stage development, SPR can be used for concentration analysis in cell culture, purification and formulation workflows, for kinetic analysis of drug-target interactions, for FcR analysis, and for assessment of changes in reactivity that can occur in stressed samples. Combined interaction data may be used for fingerprint analysis to provide a broader perspective of how a drug interacts with its partners and how stable it is under conditions of stress.

SPR is a direct-binding technique that can measure sequential binding events. This enables analysis of dual-target specificities in a bispecific antibody in a single assay setup. Potency assays for drug-target interactions and FcR interactions in QC are described in this white paper. Sensorgram comparison and CFCA methods introduce novel opportunities in comparability and biosimilar studies and have implications for potency assays.

Biacore systems have been developed to function in a regulated environment and come with installation and maintenance support and with software that combines flexibility in development with rigor in a QC environment. The product offering from GE includes Biacore systems and consumables in the form of sensor chips and kits for immobilization and capture. The use of receptor or antibody capture facilitates assay development and easy transfer from one site to another.
References


42. Mimoto, F. et al. Novel asymmetrically engineered antibody Fc variant with superior FcγR binding affinity and specificity compared with alucosylated Fc variant. mAbs 6(2), 1–8 (2013).


GE Healthcare UK Limited
Amersham Place
Little Chalfont
Buckinghamshire, HP7 9NA
UK

www.gelifesciences.com/biacore

GE and GE monogram are trademarks of General Electric Company. Amersham and Biacore are trademarks of General Electric Company or one of its subsidiaries. Avastin and Herceptin are trademarks of Genentech Inc. Enbrel is a trademark of Immunex Corporation. Humira is a trademark of AbbVie Biotechnology Ltd. Lantus is a trademark of Sanofi-Aventis GmbH. Remicade is a trademark of Janssen Biotech Inc. Rituxan is a trademark of Biogen Idec Inc. Windows is a registered trademark of Microsoft Corp.

All other third-party trademarks are the property of their respective owners.

© 2015 General Electric Company—All rights reserved. First published Jun. 2015
All goods and services are sold subject to the terms and conditions of sale of the company within GE Healthcare which supplies them. A copy of these terms and conditions is available on request. Contact your local GE Healthcare representative for the most current information.