

FILE BOUND JOURNALS

Clinical Pharmacokinetics

Review Articles

PopPK of Therapeutic mAbs
Pregabalin and Gabapentin: PK and PD

Original Research Articles

PopPK of Tapentadol IR
PopPK Study and Bayesian Estimation of Once-Daily Tacrolimus
PopPK of Atorvastatin

MEDICAL LIBRARY
CHILDREN'S
HOSP OF MI



LIBRARY
USE
ONLY



Adis

a Wolters Kluwer business

Amgen Exhibit 1041
Amgen v. BMS

Consulting Editor

Trevor M. Speight,
Auckland, New Zealand

International Editorial Board

G.D. Anderson, Seattle, WA, USA
F. Aweeka, San Francisco, CA, USA
J.H. Beijnen, Amsterdam, the Netherlands
D.J. Birkett, Sydney, NSW, Australia
A. Boddy, Newcastle upon Tyne, UK
A.M. Breckenridge, Liverpool, UK
D.D. Breimer, Leiden, the Netherlands
J. Brockmöller, Göttingen, Germany
H.R. Brunner, Lausanne, Switzerland
M.-L. Chen, Rockville, MD, USA
M.L. Dahl, Uppsala, Sweden
N.M. Davies, Pullman, WA, USA
H. Derendorf, Gainesville, FL, USA
C.L. DeVane, Charleston, SC, USA
S. Duffull, Dunedin, New Zealand
C.B. Eap, Lausanne, Switzerland
H. Echizen, Tokyo, Japan
E. Eliasson, Stockholm, Sweden
M.H. Ensom, Vancouver, BC, Canada
G. Geisslinger, Frankfurt, Germany
B. Green, Brisbane, QLD, Australia
R. Jelliffe, Los Angeles, CA, USA
U. Klotz, Stuttgart, Germany
F. Mentré, Paris, France
G.D. Morse, Amherst, NY, USA
P.J. Neuvonen, Helsinki, Finland
F. Pea, Udine, Italy
E. Perucca, Pavia, Italy
J.H. Proost, Groningen, the Netherlands
M.S. Roberts, Brisbane, QLD, Australia
A. Sánchez Navarro, Salamanca, Spain
J. Schentag, Buffalo, NY, USA
D. Sica, Richmond, VA, USA
S. Tett, Brisbane, QLD, Australia
M. Tod, Paris, France
D.J. Touw, The Hague, the Netherlands
C.J. van Boxtel, Nigtevecht, the Netherlands
J.N. van den Anker, Washington, DC, USA

Aim and Scope: *Clinical Pharmacokinetics* promotes the continuing development of clinical pharmacokinetics and pharmacodynamics for the improvement of drug therapy and to further postgraduate education in clinical pharmacology and therapeutics.

The Journal includes:

- leading/current opinion articles providing an overview of contentious or emerging issues;
- clinical pharmacokinetics and relevant pharmacodynamics of both single drugs and drug classes;
- pharmacokinetic principles behind effective drug treatment of particular diseases;
- new concepts and principles in pharmacokinetics;
- application of therapeutic drug monitoring to optimize therapy;
- prediction and avoidance of drug interactions;
- new methodology in drug development and advances in drug delivery systems;
- optimization of treatment for particular patient populations;
- regulatory aspects of pharmacokinetics and pharmacodynamics, with their practical implications.

Original research articles will also be considered for publication.

All manuscripts are subject to peer review by international experts. Letters to the Editor are welcomed and will be considered for publication.

Editor: Amitabh Prakash, MBChB, MD, FIPS, FIACS

Associate Editor: Jasbir Singh, MBChB, MS, PG Cert (PH)

Publication Manager: Anna Breckon, ELS

Editorial Office and Enquiries: Adis Journals, 41 Centorian Drive, Private Bag 65901, Mairangi Bay, North Shore 0754, Auckland, New Zealand. Information on the preparation of manuscripts will be provided to authors.

E-mail: journalCPK@adis.co.nz

<http://adisonline.com/pharmacokinetics>

Clinical Pharmacokinetics (print ISSN 0312-5963; online ISSN 1179-1926) is published annually as 1 volume with 12 issues by Adis, a Wolters Kluwer business. Subscription information is given at the back of each issue.

Policy Statement: Although great care has been taken in compiling the content of this publication, the publisher and its servants are not responsible or in any way liable for the currency of the information, for any errors, omissions or inaccuracies, or for any consequences arising therefrom. Inclusion or exclusion of any product does not imply that its use is either advocated or rejected. The use of trade names is for product identification purposes only and does not imply endorsement. Opinions expressed do not necessarily reflect the views of the Publisher, Editors or Editorial Board.

Copyright: © 2010 Adis Data Information BV. All rights reserved throughout the world and in all languages. No part of this publication may be reproduced, transmitted or stored in any form or by any means either mechanical or electronic, including photocopying, recording, or through an information storage and retrieval system, without the written permission of the copyright holder. The appearance of the code at the top of the first page of an article in this journal indicates the copyright owner's consent that copies of the article may be made for personal or internal use of specific clients. This consent is given provided that the fee of \$US49.95 per copy is paid directly to the Copyright Clearance Center Inc., 222 Rosewood Drive, Danvers, Massachusetts 01923, USA, for copying beyond that permitted by sections 107 or 108 of US Copyright Law. This consent does not extend to other kinds of copying such as copying for general distribution, for advertising or promotional purposes, for creating new collective works, or for resale.

Contents

Review Articles	Population Pharmacokinetics of Therapeutic Monoclonal Antibodies <i>NL Dirks, B Meibohm</i>	633-659
	A Comparison of the Pharmacokinetics and Pharmacodynamics of Pregabalin and Gabapentin <i>HN Bockbrader, D Wesche, R Miller, S Chapel, N Janiczek, P Burger</i>	661-669
Original Research Articles	Population Pharmacokinetics of Tapentadol Immediate Release (IR) in Healthy Subjects and Patients with Moderate or Severe Pain <i>XS Xu, JW Smit, R Lin, K Stuyckens, R Terlinden, P Nandy</i>	671-682
	Population Pharmacokinetics and Bayesian Estimation of Tacrolimus Exposure in Renal Transplant Recipients on a New Once-Daily Formulation <i>K Benkali, L Rostaing, A Premaud, J-B Woillard, F Saint-Marcoux, S Urien, N Kamar, P Marquet, A Rousseau</i>	683-692
	Development of a Population Pharmacokinetic Model for Atorvastatin Acid and Its Lactone Metabolite <i>R Narwal, F Akhlaghi, A Åsberg, M Hermann, SE Rosenbaum</i>	693-702

Register for the free Adis Electronic Table of Contents E-Mail Alert Service today at <http://adisonline.com>

Clinical Pharmacokinetics is indexed in the following biomedical databases: MEDLINE, EMBASE/Excerpta Medica, International Pharmaceutical Abstracts (IPA), BIOSIS Previews, BIOSIS Reviews Reports and Meetings, Current Contents/Clinical Medicine, Current Contents/Life Sciences, SciSearch, Science Citation Index, Journal Citation Reports/Science Edition, Proulx Science Integrity, PASCAL, Chemical Abstracts Service, Sociedad Iberoamericana de Información Científica (SIIC) and Journals@Ovid.

Population Pharmacokinetics of Therapeutic Monoclonal Antibodies

Nathanael L. Dirks and Bernd Meibohm

Department of Pharmaceutical Sciences, University of Tennessee Health Science Center, Memphis, Tennessee, USA

Contents

Abstract	633
1. Antibody Structure	634
2. Population Pharmacokinetics	636
2.1 Antibody Absorption	636
2.2 Antibody Distribution	638
2.3 Antibody Clearance	647
2.3.1 Fc-Receptor-Mediated Elimination	647
2.3.2 Target-Mediated Elimination	648
2.3.3 Clearance Models	648
2.3.4 Clearance Population Estimates	650
2.4 Covariates	651
2.4.1 Demographic and Anthropometric Measurements	651
2.4.2 Receptor Numbers and Disease-Related Factors	652
2.4.3 Pharmacokinetic Drug Interactions	653
2.4.4 The Dosage Level	653
2.4.5 Immunogenicity	654
2.4.6 Blood Chemistry	654
2.4.7 Disease and Co-Morbidities	655
2.5 Residual and Interoccasion Variability	655
3. Conclusions	655

Abstract

A growing number of population pharmacokinetic analyses of therapeutic monoclonal antibodies (mAbs) have been published in the scientific literature. The aims of this article are to summarize the findings from these studies and to relate the findings to the general pharmacokinetic and structural characteristics of therapeutic mAbs. A two-compartment model was used in the majority of the population analyses to describe the disposition of the mAb. Population estimates of the volumes of distribution in the central (V_1) and peripheral (V_2) compartments were typically small, with median (range) values of 3.1 (2.4–5.5) L and 2.8 (1.3–6.8) L, respectively. The estimated between-subject variability in the V_1 was usually moderate, with a median (range) coefficient of variation (CV) of 26% (12–84%). Between-subject variability in other distribution-related parameters such as the V_2 and intercompartmental clearance were often not estimated. Although the pharmacokinetic models used most frequently in the population analyses were models with linear clearance, other models with nonlinear, or parallel linear and nonlinear clearance pathways were also applied, as many therapeutic mAbs are eliminated via saturable target-mediated mechanisms. Population estimates of the maximum elimination rate ($V_{\max}$) and the mAb concentration at which elimination was at half maximum for Michaelis-Menten-type elimination pathways varied considerably among the different

therapeutic mAbs. However, estimates of the total clearance (CL) of mAbs with linear clearance characteristics and of the clearance of mAbs via the linear clearance pathway (CL_L) with parallel linear and nonlinear clearance were quite similar for the different mAbs and typically ranged from 0.2 to 0.5 L/day, which is relatively close to the estimated clearance of endogenous IgG of 0.21 L/day. The between-subject variability in the V_{max}, CL and CL_L was moderate to high, with estimated CVs ranging from 15% to 65%. Measures of body size were the covariates most commonly identified as influencing the pharmacokinetics of therapeutic mAbs.

In summary, many features of the population pharmacokinetics of currently used therapeutic mAbs are similar, despite differences in their pharmacological targets and studied patient populations.

Over the past two decades, there has been an increase in the research, development and therapeutic application of monoclonal antibodies (mAbs). Currently, there are over 20 mAb products (i.e. antibodies, antibody fragments or antibody conjugates) approved by the US FDA for therapeutic use in areas such as oncology, immunology, ophthalmology, cardiovascular disease and infectious disease. As most approved therapeutic mAb products are intact and unconjugated, this review focuses on this class of compounds.

It is estimated that half of all current projects in new drug development involve biologics, with mAbs being the predominant class of biologics under clinical investigation.^[1] In 2008, it was reported that there were over 200 mAbs undergoing clinical study.^[2] One likely reason for the continued success of the clinical development of mAbs is the application and integration of pharmacokinetic and pharmacodynamic concepts at all stages of preclinical and clinical drug development.^[3,4] Such implementation of pharmacokinetic/pharmacodynamic modelling and simulation in drug product development provides a rational, scientifically based framework for efficient decision making regarding the selection of potential drug candidates; for maximum information gain from the experiments and studies that are performed; and for conduct of fewer, more focused clinical trials with improved efficiency and cost effectiveness.^[5]

One application of pharmacokinetic/pharmacodynamic concepts in drug development is population pharmacokinetics, which attempts to quantify the typical disposition characteristics and sources of pharmacokinetic variability (such as between-subject or within-subject variability) within study populations. Population pharmacokinetics also attempts to identify and quantify the impact of covariates on systemic drug exposure, and to assess their potential implications for clinical dosing. Findings from population pharmacokinetic analyses are included in the drug labelling of over half of the approved therapeutic mAb products, and several mAb population pharmacokinetic studies have also been published in the scientific literature.

The aim of this article is to review the population pharmacokinetics of therapeutic intact mAbs, while highlighting important similarities/dissimilarities of different mAbs with respect to their drug disposition characteristics. The article is supplemented with discussions on the general pharmacokinetic behaviour of mAbs and their structural properties, which have partially been reviewed elsewhere in different contexts.^[6-9]

1. Antibody Structure

The basic structure of human antibodies or immunoglobulins consists of two identical heavy chains (H) and two identical light chains (L) joined together by a number of disulfide bridges. There are five classes (isotypes) of antibodies, termed IgG, IgA, IgM, IgE and IgD. They share the same basic structure but differ with regard to their heavy chains, termed γ , α , μ , ϵ and δ , respectively.^[10] In addition to the different heavy-chain structures, there are also two types of light chains (κ and λ). IgG is the most predominant of the five isotypes, with a serum concentration of approximately 12 mg/mL, and represents about 70–80% of total serum immunoglobulin.^[10] The IgG class can be further subdivided into four subclasses (or subisotypes) – IgG1, IgG2, IgG3 and IgG4 – based on structural differences in the γ heavy chain. This review focuses on IgG, as all of the population pharmacokinetic analyses included in the discussion were of therapeutic mAbs of the IgG type. All of the approved therapeutic intact mAbs are also of the IgG isotype.

The structure of IgG is depicted in figure 1a. The H and L chains of IgG are made up of variable (V) and constant (C) domains based on sequence similarities between different IgG molecules. The IgG molecule comprises three basic units: two identical antigen-binding fragments (Fabs) and the crystallizable fragment (Fc). The V_H, C_{H1}, V_L and C_L domains of the heavy and light chains make up the Fab, and the Fc is made up of the C_{H2} and C_{H3} heavy-chain domains. The whole IgG

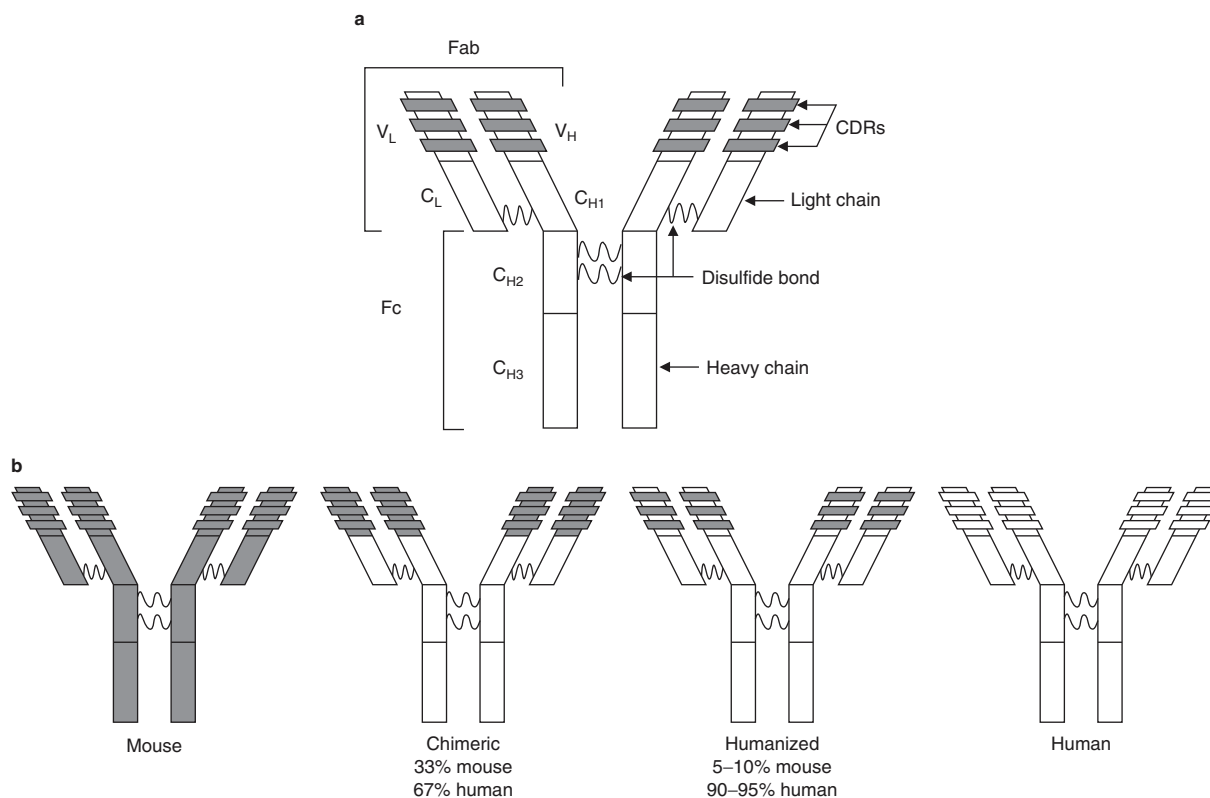


Fig. 1. Linear representation of (a) the structure of IgG and (b) the different classes of therapeutic monoclonal antibodies. The shaded areas in (b) depict molecule fractions of murine origin and the unshaded areas depict those of human origin. **CDR**=complementarity determining region; **C_H**=constant region of the heavy chain; **C_L**=constant region of the light chain; **Fab**=antigen-binding fragment; **Fc**=fragment crystallizable; **V_H**=variable region of the heavy chain; **V_L**=variable region of the light chain.

molecule has a molecular weight of around 150 kDa, and intact mAbs of the same isotype have an approximately similar molecular weight. Within the variable regions of both the heavy chain and the light chain, there are three sections called complementarity determining regions (CDRs). These hypervariable regions are associated with the affinity and specificity of the mAb for a given antigen. The structural diversity of the Fab allows different IgG molecules to recognize a wide variety of antigens, while the ability to trigger immune effector functions through interaction with Fcγ receptors and complement, such as antibody-dependent cellular cytotoxicity and complement-dependent cytotoxicity, are conferred by consistency in the Fc structure. The Fc region of the mAb also interacts with another important Fc receptor for IgG, the neonatal Fc receptor (FcRn), which acts in part as a salvage receptor protecting IgG from intracellular catabolism. Not only are the Fab and Fc regions important to antibody function, but they can also significantly influence the pharmacokinetic behaviour of mAbs.

Muromonab-CD3 (Orthoclone OKT3®) – a murine IgG2a antibody against CD3, which is indicated for the treatment of

acute organ rejection – became the first mAb approved for therapeutic use in 1986. However, the use of mAbs of murine origin in clinical practice has been limited by several factors, including their short elimination half-lives and significant immunogenic potential. To overcome these limitations of murine mAbs, advances in biotechnology, such as recombinant engineering, have facilitated the development of chimeric, humanized and fully human antibodies, which contain a larger content of human protein sequences.^[11] These three structural classes of mAbs are depicted in figure 1b. In chimeric mAbs, the antibody is constructed by transferring murine variable regions to constant regions of human origin. This reduces the murine content in chimeric mAbs to about one-third. In humanized or CDR-grafted mAbs, the CDRs (and possibly also parts of the framework regions surrounding the CDRs) are of murine origin, which makes up about 5–10% of the mAb. Although the immunogenic potential of a mAb is expected to decrease with decreasing murine content (murine > chimeric > humanized > human), all classes of therapeutic mAbs have the potential to trigger formation of human antibodies against the mAb.^[6] Such

anti-mAb antibodies can have a significant effect on both the pharmacokinetics and pharmacodynamics of the therapeutic mAb.^[7,9] The pharmacokinetic effect of the presence of antibodies against the therapeutic mAb can be assessed by including this as a covariate in the population model. Currently, most approved therapeutic mAbs are of the humanized type. Fully human mAbs that have been approved by the US FDA include adalimumab, golimumab, panitumumab and ustekinumab.

2. Population Pharmacokinetics

While a number of concepts related to population analysis are mentioned in this review (e.g. between-subject variability and residual variability), a discussion of the basic concepts and principles of population pharmacokinetic modelling is beyond the scope of this report. For readers who are not familiar with population pharmacokinetic modelling, there are a number of papers and books in the literature that provide an excellent review of the topic.^[12-16] Results from the population pharmacokinetic analyses are summarized in tables I–VI. The only non-therapeutic mAb included in the tables is mAb-CC49-I-125 (HuCC49ΔCH2), which was investigated in patients undergoing radioimmunoguided surgery.^[31] The structural characteristics and pharmacological target of the different mAbs are listed in table I, along with the patient population in which the study was conducted and the model used to describe the pharmacokinetics of the mAb. Population parameter estimates related to mAb absorption, distribution, elimination and identified covariate effects are presented in tables II–VI. Of note, all of the population pharmacokinetic analyses were of chimeric, humanized or fully human antibodies, except for the murine antibodies inolimomab and mAbF19 (table I). Differences in the population pharmacokinetics of murine mAbs and the other mAb types were observed and are discussed later in the review. While the patient populations in the studies covered a wide variety of clinical indications, all of the studies were conducted in adult patients. A few population pharmacokinetic analyses of mAbs have been conducted in paediatric patients, including analyses of daclizumab^[44] and felvizumab (SB 209 763),^[45] but these studies were not included in this review.

In the majority of the population pharmacokinetic studies, the nonlinear mixed-effects modelling was performed using NONMEM® software (Icon Development Solutions, Ellicott City, MD, USA) and the first-order conditional estimation method with or without the η - ϵ interaction option.^[46] Other software and methods used in a couple of studies^[27,47] included a conditional first-order method implemented in WinNonMix®

(Pharsight Corporation, Mountain View, CA, USA), and the Monte Carlo parametric expectation maximization (a method implemented in an augmented version of ADAPT II [Biomedical Simulations Resource, University of Southern California, Los Angeles, CA, USA]).

2.1 Antibody Absorption

Most mAbs that are approved or in development are administered intravenously, although some mAbs are administered subcutaneously (e.g. omalizumab, efalizumab, adalimumab) or intramuscularly (e.g. palivizumab). Oral administration of mAbs has been limited by their large molecular weight and polarity, as well as their susceptibility to denaturation and proteolytic degradation in the gastrointestinal tract.

While the mechanism of absorption following subcutaneous or intramuscular administration is not completely understood, it has been suggested that mAbs are absorbed primarily via the lymphatic system. This presumption is supported in part by a study in which the lymphatic absorption of floxuridine (5-fluoro-2'-deoxyuridine; molecular weight 0.246 kDa), inulin (5.2 kDa), cytochrome C (12.3 kDa) and human recombinant interferon alpha-2a (19 kDa) was investigated after subcutaneous administration in sheep.^[48] A positive linear relationship was observed between the molecular weight of the compound and the proportion of the dose absorbed via the lymphatic system. Molecules larger than 16 kDa predominantly underwent lymphatic absorption, while those smaller than 1 kDa were primarily absorbed by the blood capillaries. The molecular weights of the investigated compounds are much smaller than those of IgG and intact therapeutic mAbs of the IgG type (~150 kDa), thus extrapolation of the observed linear relationship to mAbs should be made with caution. A sheep model was also used in another study to investigate the contribution of the lymphatic system to the absorption and systemic availability of recombinant human erythropoietin alpha (30.4 kDa) following subcutaneous administration.^[49] This study reported 84% and 75% recovery of the administered dose in the peripheral and central lymph, respectively. In contrast to the results of the above studies in sheep, a study investigating lymphatic absorption of bovine insulin (5.6 kDa), bovine albumin (66 kDa) and recombinant human erythropoietin alpha (30.4 kDa) following subcutaneous administration in a rat model reported that for all three macromolecules, less than 3% of the administered subcutaneous dose was recovered in the lymph.^[50] The rat model used in this study may not be a good model for human subcutaneous absorption, thus extrapolation of the results to

Table 1. Published population pharmacokinetic (PK) analyses of therapeutic monoclonal antibodies (mAbs)

mAb	Structure/isotype	Target	Patient population	PK model
Alemtuzumab ^{[17] a}	CDR-grafted rat/human IgG1	CD52	B-cell chronic lymphocytic leukaemia	2C CL _{NL}
Denosumab (AMG162) ^{[18] a}	Human IgG2	RANKL	Healthy postmenopausal women	2C CL _{NL} + CL _L
ATM-027 ^{[19] a}	Humanized IgG1	Vβ 5.2/5.3 TCR	Multiple sclerosis	2C CL _L
Basiliximab ^[20]	Chimeric mouse/human IgG1	CD25	Renal transplant	2C CL _L
Basiliximab ^[21]	Chimeric mouse/human IgG1	CD25	Liver transplant	2C CL _L
Bevacizumab ^[22]	CDR-grafted mouse/human IgG1	VEGF	Various solid tumours and colorectal, non-small-cell lung and breast cancer	2C CL _L
Cetuximab ^[23]	Chimeric mouse/human IgG1	EGFR	Head and neck cancer	2C CL _{NL}
Clenoliximab ^{[24] a}	Chimeric macaque/human IgG4	CD4	Rheumatoid arthritis	2C CL _{NL}
Figitumumab (CP-751,871) ^[25]	Human IgG2	IGF-IR	Multiple myeloma and solid tumours	2C CL _{NL} + CL _L *
Denosumab ^{[26] a}	Human IgG2	RANKL	Healthy postmenopausal women and breast cancer	2C CL _{NL} + CL _L
Efalizumab ^{[27] a}	CDR-grafted mouse/human IgG1	CD11a	Psoriasis	2C CL _{NL} + CL _L
Efalizumab ^[28]	CDR-grafted mouse/human IgG1	CD11a	Psoriasis	1C CL _L
Golimumab ^[29]	Human IgG1	TNFα	Rheumatoid arthritis	2C CL _L
Efalizumab (hu1124) ^{[30] a}	CDR-grafted mouse/human IgG1	CD11a	Psoriasis	2C CL _{NL} + CL _L RMC
mAb-CC49-I-125 (HuCC49ΔCH2) ^[31]	CDR-grafted mouse/human IgG1-CH2 domain deletion	TAG-72	Colorectal cancer	2C CL _L
Infliximab ^[32]	Chimeric mouse/human IgG1	TNFα	Ankylosing spondylitis	2C CL _L
Infliximab ^[33]	Chimeric mouse/human IgG1	TNFα	Ulcerative colitis	2C CL _L
Inolimomab ^{[34] a}	Mouse IgG1	CD25	Acute graft-vs-host disease	2C CL _L
mAbF19 ^[35]	Mouse IgG	FAP	Colorectal cancer and soft tissue sarcoma	2C CL _L
Matuzumab ^[36]	CDR-grafted mouse/human IgG1	EGFR	Pancreatic and various cancers (primarily colorectal)	2C CL _{NL} + CL _L
Omalizumab ^{[37] a}	CDR-grafted mouse/human IgG1	IgE	Asthma, allergic rhinitis and healthy atopic subjects	TMDD
Panitumumab ^[38]	Human IgG2	EGFR	Various solid tumours and colorectal, non-small-cell lung and renal cancer	2C CL _{NL} + CL _L
Pertuzumab ^[39]	CDR-grafted mouse/human IgG1	HER2	Breast cancer, ovarian cancer and solid malignancies	2C CL _L
Rituximab ^[40]	Chimeric mouse/human IgG1	CD20	Rheumatoid arthritis	2C CL _L
Sibrotuzumab ^[41]	CDR-grafted mouse/human IgG1	FAP	Colorectal and non-small-cell lung cancer	2C CL _{NL} + CL _L
Trastuzumab ^[42]	CDR-grafted mouse/human IgG1	HER2	Breast cancer and solid tumours	2C CL _L
Ustekinumab ^[43]	Human IgG1	IL-12 and IL-23	Psoriasis	1C CL _L

a Population pharmacokinetic/pharmacodynamic analysis.

1C = 1-compartment model; **2C** = 2-compartment model; **CDR** = complementarity determining region; **CL_L** = linear clearance from the central compartment; **CL_{NL}** = nonlinear clearance from the central compartment; **CL_{NL} + CL_L** = parallel nonlinear and linear clearance pathways from the central compartment; **CL_{NL} + CL_L *** = nonlinear and linear clearance pathways from the central and peripheral compartments; **EGFR** = epidermal growth factor receptor; **FAP** = fibroblast activation protein; **HER2** = human EGFR-2; **IGF-IR** = insulin-like growth factor-I receptor; **IL** = interleukin; **RANKL** = receptor activator of nuclear factor-κB ligand; **RMC** = receptor-mediated clearance; **TAG** = tumour-associated glycoprotein; **TCR** = T-cell receptor; **TMDD** = target-mediated drug disposition; **TNFα** = tumour necrosis factor-α; **VEGF** = vascular endothelial growth factor.

humans should be done with discretion. Moreover, drawing any conclusions about the lymphatic absorption of IgG molecules on the basis of the results of the aforementioned studies should be done with caution because IgG molecules were not

specifically investigated. There is still a great deal of uncertainty regarding the physiological mechanisms involved in the absorption of IgG following subcutaneous or intramuscular administration and, in some aspects, these mechanisms may differ

from those for other macromolecules – for example, the potential involvement of FcRns in this process.^[9]

Lymphatic absorption is believed to occur via convection, a process in which the mAb is 'pulled' along by the flow of interstitial fluid into the highly permeable lymphatic capillaries, where it is eventually returned to the systemic circulation. Before the mAb reaches the systemic circulation, proteolytic degradation may occur at the injection site or during lymphatic transport, thereby reducing the bioavailable fraction of the antibody.^[9] The flow of lymph through the lymphatic vessels is relatively slow; for example, the lymph flow rate is approximately 1–2 mL/kg/h in the thoracic duct.^[51] As a result, absorption of the mAb can take place over several days. Typical values for the time to reach the maximal concentration following intramuscular or subcutaneous administration range from 1 to 8 days, and absolute bioavailability values generally range from 50% to 100%.^[6,7]

The majority of the population pharmacokinetic studies were performed using concentration data following intravenous administration, but subcutaneous data were available in a small number of studies. These studies are listed in table II along with population estimates and between-subject variabilities in absolute bioavailability and the absorption rate constant (k_a). The median (range) population estimate of the k_a was 0.217 (0.132–0.48) day⁻¹. Three different studies reported estimates of bioavailability, which included values of 49.1%,

56.4% and 74.7%. These population estimates of bioavailability and the k_a are in agreement with the general absorption characteristics of mAbs following intramuscular or subcutaneous administration. Estimates of between-subject variability in bioavailability and the k_a were high, with CVs ranging from 40% to 53% (table II), although the variability in these two parameters was not often estimated.

2.2 Antibody Distribution

The ability of mAbs to cross cell membranes is significantly hindered by their large molecular weight and hydrophilicity/polarity. Because of this, mAbs often have a small volume of distribution and are believed to be largely confined to the vascular and interstitial spaces. Other factors that influence the distribution characteristics of antibodies include the distribution and density of the antibody target and the morphology of the vascular capillaries (i.e. continuous, fenestrated or sinusoidal). The movement of mAbs across or between cell membranes may occur via transcellular or paracellular mechanisms, respectively.^[7,52,53]

The paracellular movement of mAbs occurs by means of convection, which is simply the transport of mAbs within the movement of fluid flow. This fluid flow is set up by the natural physiological exchange of fluids between the capillaries, the interstitial space and lymphatics. Convection is believed to be the primary mechanism responsible for the movement of mAbs from the vasculature to the interstitial space.^[9] Convection also plays a role in the distribution of mAbs within the interstitial fluid and facilitates the transport of mAbs out of the tissue as the interstitial fluid enters the lymphatic capillaries. Given that the paracellular pores of the lymphatic capillaries are much larger than those in the vascular endothelium, it is assumed that the convective clearance of mAbs from the tissue is much more efficient than the process of convective extravasation, thereby maintaining relatively low mAb concentrations in the interstitial fluid.^[7,9]

The transcellular movement of mAbs can occur via passive diffusion or endocytosis. However, given the physiochemical properties of mAbs, it is likely that passive diffusion does not play a significant role in their distribution. Endocytosis of mAbs can take place through three main processes: phagocytosis, fluid-phase pinocytosis and receptor-mediated endocytosis.^[6] Virtually all cells in the body have the ability to take up proteins and other macromolecules, including mAbs, from the surrounding fluid space via fluid-phase pinocytosis. Receptor-mediated endocytosis may take place following binding of mAbs to cell surface antigens or Fcγ receptors.^[7]

Table II. Population estimates of absorption-related parameters and their between-subject variability (BSV)^a

mAb	F ^{b,c}	F BSV (%CV) ^c	k_a (d ⁻¹) ^{b,c}	k_a BSV (%CV) ^c
Efalizumab ^[27]	0.564 [5.3]	51 [13]	0.242 [9.4]	44 [12]
Denosumab ^[18]	0.747 ^d		0.132 [4.9]	
Denosumab ^[26]	0.491 ^e		0.174 [5.1]	53
Omalizumab ^[37]			0.48 [5.7]	40
Efalizumab ^[28]			0.191 [0.095, 0.394] ^f	
Ustekinumab ^[43]			0.354 [0.277, 0.499] ^f	

a Blank cells indicate that estimates are not available or not estimated.

b Determined after subcutaneous administration.

c The numbers in square brackets are %RSEs unless specified otherwise.

d The θ_F was 2.96 [RSE 23%]; the CV of θ_F BSV was not estimated.

e The θ_F was 0.964 [RSE 7.9%] and the CV of θ_F BSV was 68%.

f 95% bootstrap CI.

θ_F = theta estimate for calculation of bioavailability; CV = coefficient of variation; F = absolute bioavailability; k_a = absorption rate constant; mAb = monoclonal antibody; RSE = relative standard error.

Table III. Population estimates of distribution-related parameters and their between-subject variability (BSV)^a

mAb	V ₁ (L) ^b	V ₁ BSV (%CV) ^b	V ₂ (L) ^b	V ₂ BSV (%CV) ^b	V _{ss} (L)	Q (L/d) ^b	Q BSV (%CV) ^b	k ₁₂ (d ⁻¹) ^b	k ₁₂ BSV (%CV) ^b	k ₂₁ (d ⁻¹) ^b	k ₂₁ BSV (%CV) ^b
Sibrotuzumab ^[41]	4.13 [3.7]	20 [52]	3.19 [8.8]	20 [52]	7.32 ^c	0.902 [9.6]		0.218 ^c		0.283 ^c	
Matuzumab ^[36]	3.72 [3.0]	22 [20] ^d	1.84 [9.0]	62 [28] ^d	5.56 ^c	0.919 [7.6]		0.247 ^c		0.499 ^c	
Efalizumab ^{[30] e}	5.14 [8.6] ^f	39 [33]	4.18 ^c		9.32 ^c	2.46 ^c		0.478 [24]	112 [53]	0.588 [11]	
Efalizumab ^[27]	4.50 [3.5] ^g	52 [9.0]	2.26 ^c		6.76 ^c	0.437 ^c		0.097 [21]	168 [6.1]	0.193 [13]	96 [7.7]
Denosumab ^[18]	2.38 [7.4]	16	1.59 ^c		3.97 ^c	0.533 ^c		0.224 [12]		0.336 [13]	
Denosumab ^[26]	2.42 [7.0]	37	1.27 [5.8]		3.69 ^c	0.629 [18]		0.260 ^c		0.495 ^c	
Figitumumab (CP-751,871) ^[25]	4.02 [4.0]	22 [50]	6.82 [24]	92 [49]	10.84 ^c	0.7 [14]	50 [56]				
Panitumumab ^[38]	3.95 [3.83, 4.10] ^h	34 ⁱ [28, 39] ^h	2.59 [2.30, 2.87] ^h	38 [27, 49] ^h	6.54 ^c	0.390 [0.323, 0.475] ^h		0.0987 ^c		0.151 ^c	
Cetuximab ^[23]	2.83 [2.69, 2.96] ^h	19 [13, 22] ^h	2.43 [1.95, 2.85] ^h	56 [18, 73] ^h	5.26 ^c	2.47 [1.49, 4.58] ^h	97 [40, 133] ^h	0.873 ^c		1.02 ^c	
Alemtuzumab ^[17]	11.3 [8.92, 16.4] ^j	84 [21]	41.5 [21.3, 73.2] ^j	179 [28]	52.8 ^c	25.2 [10.6, 51.1] ^j		2.23 ^c		0.607 ^c	
Clenoliximab ^[24]	3.58 [8.5]	37	5.35 ^c		8.93 ^c	0.877 ^c		0.245 [5.2]	12	0.164 [21]	28
Golimumab ^[29]	3.07 [2.63, 3.51] ^j	26 [28]	3.68 [2.71, 4.75] ^j	45 [40]	6.75 ^c	0.42 [0.31, 0.50] ^j	45 [52]	0.137 ^c		0.114 ^c	
Inolimomab ^[34]	2.76 [26]	68 [20]	2.25 [18] ^k		5.01 ^c	53.3 [52]	43 [425] ^k	19.3 ^c		23.7 ^c	
mAbF19 ^[35]	3.13 [11]	37 [49]	1.74 ^{c,i}		4.87 ^j	3.41 [18]		1.09 ^c		1.96 ^c	
mAb-CC49-I-125 (HuCC49ΔCH2) ^[31]	3.46 [3.09, 3.84] ^h	23 ^m [10, 34] ^h	2.50 [1.52, 3.69] ^h		5.96 ^c	0.154 [0.122, 0.191] ^h	39 [24, 54] ^h	0.0445 ^c		0.0616 ^c	
Rituximab ^[40]	2.98 [2.88, 3.08] ^j	12 [9.5, 14] ^j	3.64 ^c		6.62 ^c	0.656 ^c		0.22 [0.20, 0.25] ^j		0.18 [0.17, 0.19] ^j	
Trastuzumab ^[42]	2.95 [2.67, 3.27] ^j	29 [21, 38] ^j	4.79 ^c		7.74 ^c	0.484 ^c		0.164 [0.135, 0.191] ^j	54 [43, 62] ^j	0.101 [0.0826, 0.122] ^j	67 [57, 78] ^j
Pertuzumab ^[39]	2.74 [2.64, 2.84] ^j	16 [13, 19] ^j	2.16 ^c		4.9 ^c	0.556 ^c		0.203 [0.159, 0.416] ^j		0.258 [0.203, 0.480] ^j	25 [11, 34] ^j

Continued next page

Table III. Contd

mAb	V ₁ (L) ^b	V ₁ BSV (%CV) ^b	V ₂ (L) ^b	V ₂ BSV (%CV) ^b	V _{ss} (L)	Q (L/d) ^b	Q BSV (%CV) ^b	k ₁₂ (d ⁻¹) ^b	k ₁₂ BSV (%CV) ^b	k ₂₁ (d ⁻¹) ^b	k ₂₁ BSV (%CV) ^b
Bevacizumab ^[22]	2.66 [2.57, 2.76] ^j	17 [14, 20] ^j	2.76 ^c		5.42 ^c	0.593 ^c		0.223 [0.134, 0.501] ^j		0.215 [0.138, 0.416] ^j	
Infliximab ^[32]	3.06 [2.96, 3.16] ^j	18 ⁿ [16, 19] ^j	2.94 [2.63, 3.24] ^j		6.0 ^c	1.72 [1.14, 2.6] ^j		0.562 ^c		0.585 ^c	
Infliximab ^[33]	3.29 [3.02, 3.58] ^j	22 [18, 26] ^j	4.13 [3.65, 4.57] ^j		7.42 ^c	7.14 [3.67, 10.10] ^j		2.170 ^c			1.729 ^c
Basiliximab ^[20]	3.72 [1.2]	41 [18]	4.08 ^c		7.8 ^c	4.17 ^c		1.12 [14]		1.02 [31]	51 [29]
Basiliximab ^[21]	5.47 [7.4]	31 [32]	1.78 ^c		7.25 ^c	0.569 ^c		0.104 [38]	68 [45]	0.319 [25]	94 [33]
ATM-027 ^[19]	2.8 [6.9]	NE	3.1 [19]	25 [38]	5.9 ^c	2.18 [170]		0.779 ^c		0.703 ^c	
Omalizumab ^[37]	5.9 [1.8] ^o	13									
Efalizumab ^[28]	9.13 ^o [3.9, 11.7] ^j	29 [<10 ⁻³ , 44] ^j									
Ustekinumab ^[43]	15.7 ^{o,p} [15.1, 16.2] ^j	33 [28, 38] ^j									

a Blank cells indicate that estimates are not available or not estimated.

b The numbers in square brackets are %RSEs unless specified otherwise.

c Parameter derived from population estimates using the following equations: CL_L or $CL = k_{10} \times V_1$; $Q = k_{12} \times V_1 = k_{21} \times V_2$; $V_{ss} = V_1 + V_2$.

d Covariance of BSV estimated; correlation coefficients: V_1 , V_2 (0.777), V_1 , V_{max} (0.875), V_2 , V_{max} (0.875).

e Results reported for a 2-compartment CL_{NL} + CL_L model; a receptor-mediated clearance model was also investigated.

f Calculated for a 70 kg patient using the V_1 (73.4 mL/kg) and V_{max} (39 µg/kg/d) population estimates.

g Calculated for a 70 kg patient using the V_1 (64.3 mL/kg) and V_{max} (26.9 µg/kg/d) population estimates.

h 90% bootstrap CI.

i Covariance of BSV estimated; correlation coefficient: CL , V_1 (0.662; [90% {bootstrap} CI 0.396, 1.02]).

j 95% bootstrap CI.

k Covariance of BSV estimated; correlation coefficients: CL , V_1 (-0.05), CL , Q (-0.76), V_1 , Q (-0.62).

l The V_{ss} estimate was 4.87 L [RSE 9.2%] and the CV of the V_{ss} BSV estimate was 31% [RSE 45%].

m Covariance of BSV estimated; correlation coefficient: CL , V_1 (0.729; [90% {bootstrap} CI 0.335, 0.910]).

n Covariance of BSV estimated; correlation coefficient: CL , V_1 (0.342; [95% {bootstrap} CI 0.214, 0.456]).

o CL/F or V_d/F .

p Covariance of BSV estimated; correlation coefficient: CL/F , V_d/F (0.817).

CL = total clearance; **CL/F** = apparent total clearance after extravascular administration; **CL_L** = linear clearance from the central compartment; **CL_{NL}** = nonlinear clearance from the central compartment; **CL_{NL}** + **CL_L** = parallel nonlinear and linear clearance pathways from the central compartment; **CV** = coefficient of variation; **k₁₀** = elimination rate constant; **k₁₂** = transfer rate constant from the central compartment to the peripheral compartment; **k₂₁** = transfer rate constant from the peripheral compartment to the central compartment; **mAb** = monoclonal antibody; **Q** = intercompartmental clearance; **RSE** = relative standard error; **V₁** = volume of distribution in the central compartment; **V₂** = volume of distribution in the peripheral compartment; **V_d/F** = volume of distribution after extravascular administration; **V_{max}** = maximum elimination rate; **V_{ss}** = volume of distribution at steady state.

Table IV. Population estimates of clearance-related parameters and their between-subject variability (BSV)^a

mAb	V _{max} (mg/d) ^b	V _{max} BSV (%CV) ^b	K _m (mg/L) ^b	K _m BSV (%CV) ^b	CL _{int} (L/d) ^c	CL _L (L/d) ^b	CL _L BSV (%CV) ^b	CL (L/d) ^b	CL BSV (%CV) ^b	k ₁₀ (d ⁻¹) ^b	k ₁₀ BSV (%CV) ^b
Sibrotuzumab ^[41]	0.811 [25]	29 [50]	0.219 [57]	NE	3.70	0.530 [9.6]	57 [52]			0.128 ^c	
Matuzumab ^[36]	10.9 [14]	54 [38] ^d	4.0 [30]	NE	2.73	0.348 [4.1]	24 [21]			0.0935 ^c	
Efalizumab ^{[30] e}	2.73 [11] ^f	42 [51]	0.0973 [27]	122 [74]	28.1	0.535 ^c				0.104 [17]	21 [99]
Efalizumab ^[27]	1.88 [4.3] ^g	65 [8.1]	0.033 [21]	124 [6.8]	57.0	0.513 ^c				0.114 [5.8]	50 [9.5]
Denosumab ^[18]	0.0878 [7.5]	32	0.164 [11]	NE	0.54	0.066 [7.2]	25			0.0277 ^c	
Denosumab ^[26]	0.0895 [6.3]	46	0.192 [7.5]	NE	0.47	0.0710 [4.5]	32			0.0293 ^c	
Figitumumab (CP-751,871) ^[25]	2.42 [29]	34 [210]	1.22 [97]	69 [94]	1.98	0.243 [8.3]	59 [34]				
Panitumumab ^[38]	12.1 [11.4, 12.7] ^h	29 ⁱ [24, 33] ^h	0.426 [0.364, 0.586] ^h	80 ⁱ [59, 100] ^h	28.4	0.273 [0.258, 0.294] ^h	28 ^j [19, 37] ^h			0.0691 ^c	
Cetuximab ^[23]	105 [81.6, 159] ^h	15 [12, 19] ^h	74 [38.2, 163] ^h	NE	1.42						
Alentuzumab ^[17]	24.5 [15.6, 44.2] ^k	32 [32]	0.338 [0.226, 0.849] ^k	145 [37]	72.5						
Clenoliximab ^[24]	35.8 [4.2]	47	1.29 [23]	NE	27.8						
Golimumab ^[29]								0.40 [0.33, 0.49] ^k	44 [19]	0.130 ^c	
Inolimomab ^[34]								1.85 [19]	43 ⁱ [87]	0.670 ^c	
mAbF19 ^[35]								2.62 [15]	54 [31]	0.837 ^c	
mAb-CC49-I-125 (HuCC49ΔCH2) ^[31]								1.53 [1.36, 1.71] ^h	28 ^m [20, 35] ^h	0.442 ^c	
Rituximab ^[40]								0.257 [0.246, 0.271] ^k	28 [24, 32] ^k	0.0862 ^c	
Trastuzumab ^[42]								0.225 [0.213, 0.238] ^k	43 [39, 47] ^k	0.0763 ^c	
Pertuzumab ^[39]								0.214 [0.201, 0.228] ^k	31 [27, 34] ^k	0.0781 ^c	
Bevacizumab ^[22]								0.207 [0.188, 0.226] ^k	26 [23, 31] ^k	0.0778 ^c	

Continued next page

Table IV. Contd

mAb	$V_{\max}$ (mg/d) ^b	$V_{\max}$ BSV (%CV) ^b	K _m (mg/L) ^b	K _m BSV (%CV) ^b	CL _{int} (L/d) ^c	CL _L (L/d) ^b	CL _L BSV (%CV) ^b	CL (L/d) ^b	CL BSV (%CV) ^b	k ₁₀ (d ⁻¹) ^b	k ₁₀ BSV (%CV) ^b
Infliximab ^[32]								0.273 [0.259, 0.288] ^k	34 ⁿ [30, 37] ^k	0.0892 ^c	
Infliximab ^[33]								0.407 [0.388, 0.427] ^k	38 [35, 41] ^k	0.124 ^c	
Basiliximab ^[20]								0.882 ^c		0.237 [19]	35 [26]
Basiliximab ^[21]								1.33 ^c		0.243 [9.1]	42 [29]
ATM-027 ^[19]								0.190 [6.7]	28 [24]	0.0679 ^c	
Omalizumab ^[37]								0.176 ^c [2.1]	20		
Efalizumab ^[28]								1.29 ^o [1.17, 1.39] ^k	48 [45, 51] ^k		
Ustekinumab ^[43]								0.465 ^{o,p} [0.448, 0.480] ^k	41 [38, 44] ^k		

a Blank cells indicate that estimates are not available or not estimated.

b The numbers in square brackets are %RSEs unless specified otherwise.

c Parameter derived from population estimates using the following equations: CL_L or $CL = k_{10} \times V_1$; $Q = k_{12} \times V_1 = k_{21} \times V_2$; $V_{ss} = V_1 + V_2$.

d Covariance of BSV estimated; correlation coefficients: V_1 – V_2 (0.777), V_1 – $V_{\max}$ (0.875), V_2 – $V_{\max}$ (0.875).

e Results reported for a 2-compartment $CL_{NL} + CL_L$ model; a receptor-mediated clearance model was also investigated.

f Calculated for a 70 kg patient, using the V_1 (73.4 mL/kg) and $V_{\max}$ (39 µg/kg/d) population estimates.

g Calculated for a 70 kg patient, using the V_1 (64.3 mL/kg) and $V_{\max}$ (26.9 µg/kg/d) population estimates.

h 90% bootstrap CI.

i Covariance of BSV estimated; correlation coefficient [90% bootstrap CI]: $V_{\max}$ – K_m (0.461; [0.136, 0.746]).

j Covariance of BSV estimated; correlation coefficient [90% bootstrap CI]: CL_{NL} – V_1 (0.662; [0.396, 1.02]).

k 95% bootstrap CI.

l Covariance of BSV estimated; correlation coefficients: CL_{NL} – V_1 (–0.05), CL_{NL} – Q (–0.76), V_1 – Q (–0.62).

m Covariance of BSV estimated; correlation coefficient [90% {bootstrap} CI]: CL_{NL} – V_1 (0.729; [90% {bootstrap} CI 0.335, 0.910]).

n Covariance of BSV estimated; correlation coefficient [95% {bootstrap} CI]: CL_{NL} – V_1 (0.342; [95% {bootstrap} CI 0.214, 0.456]).

o CL/F or V_d/F .

p Covariance of BSV estimated; correlation coefficient: CL/F – V_d/F (0.817).

CL = total clearance; **CL/F** = apparent total clearance after extravascular administration; **CL_{int}** = intrinsic clearance (calculated as $V_{\max}/K_m$); **CL_L** = linear clearance from the central compartment; **CL_{NL}** = nonlinear clearance from the central compartment; **CL_{NL} + CL_L** = parallel nonlinear and linear clearance pathways from the central compartment; **CV** = coefficient of variation; **k₁₀** = elimination rate constant; **k₁₂** = transfer rate constant from the central compartment to the peripheral compartment; **k₂₁** = transfer rate constant from the peripheral compartment to the central compartment; **K_m** = concentration at which elimination is at half maximum (the Michaelis-Menten constant); **mAb** = monoclonal antibody; **NE** = not estimated; **Q** = intercompartmental clearance; **RSE** = relative standard error; **V₁** = volume of distribution in the central compartment; **V₂** = volume of distribution in the peripheral compartment; **V_d/F** = volume of distribution after extravascular administration; **V_{max}** = maximum elimination rate; **V_{ss}** = volume of distribution at steady state.

Table V. Identified covariates and their estimated effects on pharmacokinetic parameters^a

mAb	Covariate	Estimated covariate effects on pharmacokinetic parameters ^b					Notes
		V _{max}	CL _L	CL	V ₁	V ₂	
Sibrotuzumab ^[41]	BW ^c	0.00934 [49]	0.0182 [19]		0.0125 [21]	0.0105 [40]	
Matuzumab ^[36]	BW ^c		0.0087 [28]		0.0044 [35]		
Denosumab ^[18]	BW ^d	0.6 [27]	0.918 [28]		0.783 [30]		
Figitumumab (CP-751,871) ^[25]	BW ^d	1.11 [74]			0.630 [25]	2.21 [20]	
Panitumumab ^[38]	BW ^d	0.621 [0.488, 0.725] ^e	0.411 [0.261, 0.572] ^e		0.526 [0.415, 0.632] ^e		
	AGE ^d	-0.495 [-0.688, -0.297] ^e					
	SEX ^e		0.769 [0.721, 0.818] ^e		0.831 [0.792, 0.871] ^e		CL _L 23% slower and V ₁ 17% smaller in females
	LUNG ^f		0.861 [0.799, 0.937] ^e				CL _L faster in patients with colorectal or renal cancer vs non-small-cell lung cancer or other cancer types
	RENAL ^f		0.957 [0.873, 1.03] ^e				
	OTHER ^f		0.870 [0.792, 0.956] ^e				
Cetuximab ^[23]	IBW ^c	0.0108 [0.0077, 0.0139] ^e					
	WBCC ^c	0.0216 [0.0169, 0.0296] ^e					
	BW ^c				0.0083 [0.0057, 0.0115] ^e		
Alentuzumab ^[17]	WBCC ^d	0.194 [0.081, 0.382] ^g					
Golimumab ^[29]	BW ^d			0.75 fixed	0.86 [17]		
mAb-CC49-I-125 (HuCC49ΔCH2) ^[31]	BW ^h				1.0 fixed	1.0 fixed	0.75 fixed
Rituximab ^[40]	BSA ^d			1.02 [0.54, 1.64] ^g	0.73 [0.45, 1.05] ^g		
	SEX ⁱ			0.39 [0.17, 0.63] ^g	0.17 [0.08, 0.26] ^g		CL 39% faster and V ₁ 17% larger in males
Trastuzumab ^[42]	MET ^j			0.221 [0.0611, 0.429] ^g			CL 22% faster in patients with >4 metastatic sites
	ECD ^d			0.041 [0.013, 0.071] ^g	0.105 [0.0726, 0.146] ^g		
	BW ^d				0.556 [0.211, 0.824] ^g		
Pertuzumab ^[39]	BW ^d			0.587 [0.372, 0.826] ^g			

Continued next page

Table V. Contd

mAb	Covariate	Estimated covariate effects on pharmacokinetic parameters ^b					Notes
		V _{max}	CL _L	CL	V ₁	V ₂	
Bevacizumab ^[22]	ALB ^d			-1.01 [-1.42, -0.632] ^g			
	ALP ^d			0.169 [0.067, 0.258] ^g			
	BSA ^d				1.16 [0.890, 1.45] ^g		
	BW ^d			0.368 [0.088, 0.650] ^g	0.411 [0.284, 0.490] ^g		
	SEX ⁱ			0.264 [0.132, 0.398] ^g	0.221 [0.173, 0.285] ^g		CL 26% faster and V ₁ 22% larger in males
	ALB ^d			0.726 [0.472, 1.02] ^g	-0.333 [-0.461, -0.242] ^g		
	ALP ^d			0.133 [0.070, 0.206] ^g			
	AST ^d			0.0715 [0.002, 0.144] ^g			
	CHEM ⁱ			0.174 [0.096, 0.244] ^g			CL 17% slower when given with a bolus IFL regimen vs other concomitant chemotherapy regimens
	WBCC ^j			0.0106 [0.0051, 0.0162] ^g			
Infliximab ^[32]	IR ⁱ			0.419 [0.215, 0.662] ^g			CL 42% faster in patients with antibodies against infliximab
	BSA ^d			0.744 [0.510, 0.978] ^g			
	SEX ⁱ			0.100 [0.052, 0.146] ^g			V ₁ 10% larger in males
	ALB ^d			-1.54 [-1.94, -1.17] ^g			
	IR ⁱ			0.471 [0.28, 0.83] ^g			CL 47% faster in patients with antibodies against infliximab
	SEX ⁱ			-0.236 [-0.291, -0.181] ^g	-0.137 [-0.197, -0.072] ^g		CL 24% slower and V ₁ 14% smaller in females
	BW ^d				0.538 [0.394, 0.700] ^g		
	SEX ⁱ				0.250 [24]		V ₁ 25% larger in males
	BW ^d			0.911 [15]	0.658 [15]		
	BW ^d			0.754 [0.511, 0.956] ^g			CL/F 10% faster in obese patients (BMI ≥30)
ATM-027 ^[19] Omalizumab ^[37] Efalizumab ^[28]	AGE ^d			0.218 [0.091, 0.344] ^g			

Continued next page

Table V. Contd

mAb	Covariate	Estimated covariate effects on pharmacokinetic parameters ^b					Notes
		$V_{\max}$	CL_L	CL	V_1	V_2	
Ustekinumab ⁽⁴³⁾	L ^{YM} ^d			0.165 [0.065, 0.274] ^g			
	PAS ⁱ ^d			0.220 [0.132, 0.312] ^g			
	OBS ⁱ			0.0997 [0.015, 0.211] ^g			
	DOSE ⁱ			-0.240 [-0.292, -0.174] ^g			CL/F 24% slower in subjects given 2 mg/kg vs 1 mg/kg
	BW ^d			0.840 [0.731, 0.956] ^g	0.807 [0.707, 0.905] ^g		
	DM ⁱ			0.287 [0.189, 0.377] ^g	0.132 [0.045, 0.223] ^g		CL/F 28.7% faster and V_d/F 13.2% larger in patients with diabetes mellitus
	IR ⁱ			0.355 [0.172, 0.540] ^g			CL/F 35.5% faster in patients with antibodies against ustekinumab
	ALB ^d			-0.896 [-1.09, -0.673] ^g			
	CL _{CR} ^d			0.188 [0.128, 0.251] ^g			
	SEX ⁱ			0.059 [0.030, 0.093] ^g			CL/F 5.9% faster in females
	ALP ^d			0.113 [0.065, 0.161] ^g			
	RACE ⁱ			-0.111 [-0.154, -0.070] ^g			V_d/F 11.1% smaller in non-Caucasians vs Caucasians

a Blank cells indicate that estimates are not available or not estimated.

b The numbers in square brackets are %RSEs unless specified otherwise.

c Linear proportional (covariate centred) continuous covariate model; $P = \theta_1 \times (1 + \theta_{\text{COV}} \times (\text{COV} - \text{COV}_{\text{ref}}))$.

d Power (covariate normalized) continuous covariate model; $P = \theta_1 \times (\text{COV}/\text{COV}_{\text{ref}})^{\theta_{\text{COV}}}$.

e 90% bootstrap CI.

f Power categorical covariate model; $P = \theta_1 \times \theta_{\text{COV}}^{\text{COV}}$ where COV is 0 or 1, for example.

g 95% bootstrap CI.

h Allometric (covariate normalized) continuous covariate model; θ_{COV} in a power model fixed at 0.75 or 1.0.

i Linear proportional categorical covariate model; $P = \theta_1 \times (1 + \theta_{\text{COV}} \times \text{COV})$ where COV is 0 or 1, for example.

j Linear additive (covariate centred) continuous covariate model; $P = \theta_1 + \theta_{\text{COV}} \times (\text{COV} - \text{COV}_{\text{ref}})$.

θ = model parameter; **ALB** = albumin; **ALP** = alkaline phosphatase; **AST** = aspartate aminotransferase; **BMI** = body mass index; **BSA** = body surface area; **BW** = bodyweight; **CHEM** = concomitant chemotherapies; **CL** = total clearance; **CL/F** = apparent total clearance after subcutaneous administration; **CL_L** = linear clearance from the central compartment; **COV** = covariate; **COV_{ref}** = reference/typical covariate value; **CL_{CR}** = creatinine clearance; **DM** = diabetes mellitus co-morbidity; **DOSE** = dose group; **ECD** = serum level of shed human epidermal growth factor receptor-2 extracellular domain; **F** = female; **IBW** = ideal bodyweight; **IFL** = irinotecan/fluorouracil/leucovorin (folinic acid) regimen; **IR** = immune response with development of antibodies against the therapeutic mAb; **LUNG** = non-small-cell lung cancer; **LYM** = lymphocyte count; **M** = male; **mAb** = monoclonal antibody; **MET** = number of metastatic sites; **OBS** = obesity; **OTHER** = other cancer types (see referenced paper for details); **P** = typical value of a model parameter; **PASI** = Psoriasis Area and Severity Index score; **Q** = intercompartmental clearance; **RENAL** = renal cancer; **RSE** = relative standard error; **V₁** = volume of distribution in the central compartment; **V₂** = volume of distribution in the peripheral compartment; **V_d** = volume of distribution after subcutaneous administration; **V_{max}** = maximum elimination rate; **WBCC** = white blood cell count.

Table VI. Residual variability estimates^a

mAb	Proportional error (%CV) ^b	Additive error (mg/L) ^b
Sibrotuzumab ^[41]	9.3 [6.8]	0.0491 [19]
Matuzumab ^[36]	13.4 [1.5]	0.312 fixed
Efalizumab ^{[30] c}	11.7 [21]	
Efalizumab ^[27]	35.9 [1.5]	
Denosumab ^[18]	35.9	
Denosumab ^[26]		0.266 ng/mL
Figitumumab (CP-751,871) ^[25]	26 [6.9]	
Panitumumab ^[38]	42.0 [36.3, 48.4] ^d	0.03 [0.005, 0.05] ^d
Cetuximab ^[23]	14.6 ^e [12.3, 16.8] ^d 21.2 ^e [18.8, 23.7] ^d	
Alemtuzumab ^[17]	37.2 [31.0, 40.0] ^f	0.0647 [0.0372, 0.114] ^f
Clenoliximab ^[24]	8.8 [29]	
Golimumab ^[29]	15.0 [23]	
Inolimomab ^[34]	30.2 [7]	
mAbF19 ^[35]	12.5 [31]	
mAb-CC49-I-125 (HuCC49ΔCH2) ^[31]	15.1 [12.5, 17.6] ^d	19.1 dps/mL [12.7, 29.3] ^d
Rituximab ^[40]	19.0 [17.2, 21.3] ^f	0.54 [0.4, 0.64] ^f
Trastuzumab ^[42]	23 [21, 24] ^f	
Pertuzumab ^[39]	19.2 [17.3, 21.2] ^f	2.27 [0.002, 4.16] ^f
Bevacizumab ^[22]	17.2 [15.8, 19.0] ^f	7.2 [0.093, 10.3] ^f
Infliximab ^[32]	22.9 [21.8, 24.0] ^f	2.89 [2.48, 3.22] ^f
Infliximab ^[33]	40.3 [38.3, 42.2] ^f	0.0413 [0.0368, 0.0497] ^f
Basiliximab ^[20]	29.8 [35]	0.371 [51]
Basiliximab ^[21]	18.4 [18]	0.084 [23]
ATM-027 ^[19]	26.0 [9.3]	0.0084 [15]
Omalizumab ^[37]	16.7	
Efalizumab ^[28]	26.3 [22.2, 29.8] ^f	1.58 [1.01, 2.07] ^f
Ustekinumab ^[43]	25.6	0.085 fixed

a Blank cells indicate that estimates are not available or not estimated.

b The numbers in square brackets are %RSEs unless specified otherwise.

c Results are reported for a 2-compartment CL_{NL} + CL_L model; a receptor-mediated clearance model was also investigated.

d 90% bootstrap CI.

e Separate residual error models were used for each clinical trial.

f 95% bootstrap CI.

CL_{NL} + CL_L = parallel nonlinear and linear clearance pathways from the central compartment; CV = coefficient of variation; dps = decay per second; mAb = monoclonal antibody; RSE = relative standard error.

Another potential mechanism for extravasation of mAbs is transcytosis by vascular endothelial cells.^[7,52,54,55] Following fluid-phase pinocytosis by endothelial cells, mAbs within the intracellular vesicle may bind to FcRns. Not only does this protect the mAbs from degradation, but eventually the mAbs are recycled back into systemic circulation or transcytosed into the interstitial space.^[54] The FcRn-mediated transcytosis of IgG has been demonstrated in both endothelial and epithelial cells.^[56-62] However, the importance of FcRn-mediated transcytosis of IgG in the distribution of mAbs remains to be elucidated.

Following intravenous administration, the concentration-time profile of mAbs often follows a bi-exponential decline, which can be best described using a two-compartment pharmacokinetic model.^[11,63] Accordingly, a two-compartment model was used in the majority of the mAb population pharmacokinetic analyses (table I). In the few studies where a one-compartment pharmacokinetic model was used, concentration data were only available following subcutaneous administration. The distribution phase of the mAbs in these studies may have been masked by a slow absorption phase, which is often observed with mAbs following subcutaneous administration. An attempt was made in the population pharmacokinetic analyses of pertuzumab and inolimomab to fit a three-compartment model to the concentration data, but this resulted in an over-parameterized model and did not show a significant improvement in the fit versus a two-compartment model.^[34,39]

Population estimates and between-subject variabilities in distribution-related pharmacokinetic parameters are summarized in table III. Estimates of the volume of the central (V₁) and peripheral (V₂) compartments were similar for the different mAbs, with the exception of alemtuzumab. Compared with other mAbs, alemtuzumab not only had a much larger V₁ and V₂ (11.3 L and 41.5 L, respectively), but also had greater between-subject variability in both of these parameters (CVs 84% and 179%, respectively).^[17] It is unclear why these population parameter estimates for alemtuzumab are in stark contrast to those observed for many of the other therapeutic mAbs. The median (range) estimates of the V₁ and V₂, based on studies that used a two-compartment pharmacokinetic model (excluding alemtuzumab), were 3.1 (2.4–5.5) L and 2.8 (1.3–6.8) L, respectively. In general, the estimates of the V₁ were approximately equal to the plasma volume. Between-subject variability was quantified for the V₁ in all but one of the population pharmacokinetic studies (table III). The between-subject variability in the V₁ was usually moderate, as the median (range) CV across all of the studies was 26% (12–84%). The values of the volume of distribution at steady state (V_{ss} = V₁ + V₂) suggest

an apparently limited distribution outside the vascular space and are consistent with the behaviour of endogenous IgG. Based on data from early IgG metabolism studies in humans,^[64] the mean serum IgG concentration and the total body IgG pool were 12 g/L and 1.06 g/kg of bodyweight, respectively, which, for a 70 kg person, equates to a volume of distribution of around 6.2 L for IgG. Population estimates of the inter-compartmental clearance (Q) and the transfer rate constants from the central compartment to the peripheral compartment (k_{12}) and from the peripheral compartment to the central compartment (k_{21}) appeared to be less homogenous across the different mAbs, compared with population estimates of the V_1 and V_2 . In general, the estimates of the Q , k_{12} , and k_{21} suggested a slow transfer of mAb between the central and peripheral compartments. The median Q across all of the studies that used a two-compartment model was 0.79 L/day. Between-subject variability in the V_2 , Q , k_{12} , and k_{21} was often not estimated in the population pharmacokinetic models. When estimated, between-subject variability in these parameters was usually moderate to high. The volume of drug distribution corrected for subcutaneous bioavailability (V_d/F) was estimated in the population pharmacokinetic analyses of omalizumab, efalizumab and ustekinumab, which have bioavailability values following subcutaneous dosing of around 62%, 50% and 57%, respectively.^[28,37,43] After adjustment for bioavailability, the volumes of distribution of omalizumab, efalizumab and ustekinumab were approximately 3.7, 4.6 and 9.0 L, respectively, which is in line with the results for other mAbs.

When estimating the V_{ss} , using a noncompartmental analysis or by fitting a mammillary compartmental model to the data, the assumption is made that elimination of the drug occurs at a site(s) in rapid equilibrium with plasma or the central compartment.^[63,65] For some mAbs, this assumption may be valid. However, there may be instances when a mAb undergoes significant elimination in peripheral tissues (e.g. via receptor-mediated endocytosis). In these cases, the aforementioned methods of analysis can lead to errors in estimating the V_{ss} .^[63,65] Therefore, volumes of distribution reported in the literature for mAbs should be interpreted with caution.

2.3 Antibody Clearance

The two general pathways by which drugs are eliminated from the body are metabolism (e.g. catabolism) and excretion. However, the role of non-catabolic routes, such as renal and biliary excretion, in the clearance of mAbs is negligible. The glomerular filtration of mAbs is largely limited by their size, as the molecular cut-off weight for filtration is approximately

70 kDa.^[66] While biliary excretion has been reported for IgA, it does not appear to be a significant route for elimination of IgG.^[9,67] The primary route by which antibodies are eliminated is cellular uptake followed by proteolytic degradation. Therapeutic antibodies often exhibit two distinct catabolic pathways:^[8] (i) a non-specific, linear (first-order) clearance pathway mediated by interaction between the Fc region of the antibody and Fc receptors (i.e. FcRns and Fc γ receptors); and (ii) a nonlinear (target-mediated) clearance pathway mediated by the specific interaction between the Fab region of the antibody and its pharmacological target.

2.3.1 Fc-Receptor-Mediated Elimination

The use of the term 'non-specific' when referring to the linear clearance pathway reflects the notion that Fc-mediated elimination is a common pathway shared by both endogenous IgG and therapeutic IgG mAbs with a functional human Fc domain and that the pathway operates independently of the specific interaction between a mAb and its pharmacological target. Virtually all cells in the body have the ability to take up proteins and other macromolecules from the surrounding fluid space via endocytosis (e.g. fluid-phase pinocytosis). The formed endosome may subsequently be delivered to a lysosome, where its content undergoes enzymatic degradation. However, unlike most other proteins in the endosome, a significant portion of IgG can be salvaged from lysosomal catabolism by an FcRn-mediated mechanism in cells expressing the FcRn.^[68-70]

Following cellular uptake of IgG, the environment inside the early endosome becomes mildly acidic. IgG binds to FcRns in a pH-dependent manner, and the decrease in pH allows IgG to bind to FcRns expressed within the endosome. IgG that is bound to FcRns is redirected to the cell surface, while unbound IgG is delivered to the lysosome for degradation. This partitioning of IgG-FcRn complexes and unbound IgG into two different pathways appears to occur within the sorting endosome.^[70] Once the IgG-FcRn complex is transported to the cell surface, the affinity of IgG for FcRns decreases as a result of the physiological pH, and IgG is released into the extracellular fluid. This salvage pathway helps to explain the much longer elimination half-life of IgG (~21 days) compared with that of the other immunoglobulin classes, whose elimination half-lives range from 2 to 10 days.^[6] While the IgG1, IgG2 and IgG4 subclasses exhibit elimination half-lives of around 21 days, the elimination half-life of IgG3 is only 7 days. The shorter elimination half-life of IgG3, compared with those of the other IgG subclasses, has been attributed to differences in binding to FcRns.^[8] As the number of FcRns is limited, the salvage pathway can be expected to be capacity limited. This is

supported by findings from a study by Morell et al.,^[71] in which shorter IgG elimination half-lives were observed in patients who had elevated serum IgG concentrations compared with those who had normal IgG levels. However, the doses of therapeutic mAbs that are commonly administered are not likely to cause significant enough increases in serum IgG concentrations to result in saturation of the FcRn.^[72] Therapeutic mAbs are commonly administered at doses <10 mg/kg, which would increase the total body IgG by <1–2%, as humans typically possess 50–100 g of endogenous IgG.^[9] Furthermore, the estimates of total clearance of mAbs with linear clearance characteristics and the estimates of clearance via the linear clearance pathway of mAbs with parallel linear and nonlinear clearance are quite similar to the clearance of endogenous IgG. The FcRn is expressed in a wide variety of cells and tissues throughout the body, including the vascular endothelium, monocytes, macrophages, dendritic cells, hepatocytes and epithelial cells of the intestine, renal proximal convoluted tubules and upper airways.^[73,74]

The Fc γ receptors are another set of receptors that bind to the Fc portion of IgG. These receptors play a significant role in mediating various immune effector functions such as phagocytosis and antibody-dependent cellular cytotoxicity.^[75] There are three different classes of Fc γ receptors (i.e. Fc γ RI, -II and -III), and they differ with regard to their cellular distribution, specificity for the different IgG subclasses and affinity for monomeric or immune-complexed IgG.^[10] The Fc γ receptors are expressed on a wide variety of cells, including monocytes, macrophages, dendritic cells, neutrophils, natural killer cells, B cells and hepatocytes.^[10,73] Based on their innate roles in immune responses, Fc γ receptors may be involved in the clearance of soluble mAb-antigen immune complexes or cells opsonized by the mAb. However, the significance of Fc γ receptor-mediated catabolism of mAbs is not as well understood as the role of FcRns.

2.3.2 Target-Mediated Elimination

The interaction between a mAb and its pharmacological target can contribute to elimination of the mAb. A concept often applied to the pharmacokinetics of mAbs is target-mediated drug disposition, in which the interaction between a drug and its pharmacological target influences its pharmacokinetic characteristics.^[76,77] Receptor-mediated endocytosis, an example of target-mediated drug disposition, involves binding of the mAb to a receptor on the cell surface, which triggers internalization and subsequent lysosomal degradation of the mAb-receptor complex. The number of receptors within the distribution space of the mAb is limited, and the receptors may therefore become saturated at therapeutic doses of the mAb,

resulting in nonlinear clearance. The nonlinear clearance observed with many mAbs is believed to be due to saturation of target-mediated clearance pathways.^[8] The role that target-mediated clearance plays in total clearance of the mAb is dependent on a number of factors, including the concentration and distribution of the receptor, and the rates of receptor internalization and turnover.^[8]

Therapeutic mAbs that bind to soluble antigens may also undergo target-mediated elimination. One potential mechanism that has been suggested involves binding of the soluble mAb-antigen complex to Fc γ receptors on cells such as monocytes and macrophages, which subsequently triggers internalization and catabolism of the complex.^[9] If this elimination mechanism was present for a given therapeutic mAb, then it would be reasonable to anticipate that clearance of the soluble mAb-antigen complex would be faster than that of the unbound and free mAb. In a population pharmacokinetic/pharmacodynamic analysis of omalizumab (an anti-IgE mAb), the apparent clearance of the omalizumab-IgE complex was 0.32 L/day and that of free omalizumab was 0.18 L/day.^[37] The nonlinear pharmacokinetics observed with mAbs such as omalizumab and denosumab,^[18,78,79] which target soluble antigens, suggest that saturable target-mediated mechanisms of elimination are not limited to mAbs with membrane-bound antigens.^[9]

2.3.3 Clearance Models

The different pharmacokinetic models used in the population analyses are listed in table I. In most studies, compartmental pharmacokinetic models with linear, nonlinear, or parallel linear and nonlinear clearance pathways were used to describe the pharmacokinetics of the mAb. In the population pharmacokinetic/pharmacodynamic analyses of efalizumab^[30] and omalizumab,^[37] more complex, mechanistically based, target-mediated elimination models were applied.

A commonly used pharmacokinetic model that can be related to distinct physiological elimination pathways is a two-compartment model with parallel linear and nonlinear clearance from the central compartment, which is depicted in figure 2a. In this pharmacokinetic model, total clearance (CL) of the mAb consists of clearance via the nonlinear pathway (CL_{NL}) plus that via the linear pathway (CL_L). Physiologically, the nonlinear pathway is thought to be related to clearance of the mAb via saturable target-mediated mechanisms (e.g. receptor-mediated endocytosis), while the linear component represents clearance pathways, such as Fc-mediated elimination, that are not saturable at therapeutic mAb concentrations. The relationship between the clearance components of the model

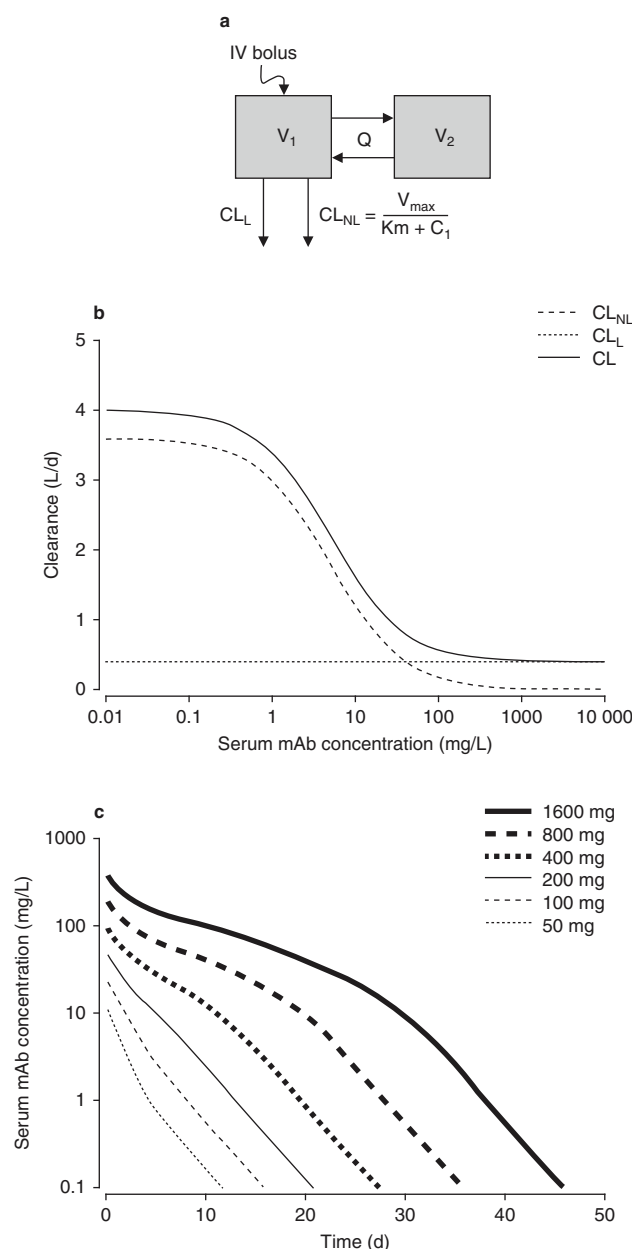


Fig. 2. Pharmacokinetic behaviour of a mAb with parallel CL_L and CL_{NL} pathways. **(a)** Schematic of a representative structural pharmacokinetic model with parallel clearance pathways. **(b)** Plot of the dependence of clearance on serum mAb concentrations. **(c)** Simulated serum mAb concentration-time profiles, using the pharmacokinetic model in **(a)** after single IV bolus doses of mAb 50, 100, 200, 400, 800 and 1600 mg. Parameter values of 18 mg/d (V_{max}), 5 mg/L (K_m), 0.4 L/d (CL_L), 4 L (V_1), 3 L (V_2) and 1.2 L/d (Q) were used for the simulation as well as for the clearance versus concentration plot. C_1 =concentration in the central compartment; CL =total clearance (calculated as $CL_{NL} + CL_L$); CL_L =linear clearance from the central compartment; CL_{NL} =nonlinear clearance from the central compartment (calculated as $V_{max}/(K_m + C_1)$); IV =intravenous; mAb =monoclonal antibody; K_m =concentration at which elimination is at half maximum (the Michaelis-Menten constant); Q =intercompartmental clearance; V_1 =volume of distribution in the central compartment; V_2 =volume of distribution in the peripheral compartment; V_{max} =maximum elimination rate.

(CL_L , CL_{NL} and CL) and the mAb concentration is described in figure 2b. At low mAb concentrations, the CL is relatively unaffected, and target-mediated elimination contributes a significant portion of the CL of the mAb (the CL_{NL} is approximately 7 times faster than the CL_L). With increasing mAb concentrations, the CL decreases dramatically as the target-mediated elimination pathway starts to become saturated. The mAb concentration range at which this significant decrease in the CL occurs is dependent on the dissociation constant (k_d) and/or the concentration of the drug producing 50% of the maximum effect of the mAb-receptor interaction, and for many mAbs this range lies between 0.1 and 100 mg/L. At high mAb concentrations, the CL approaches that of the first-order process (CL_L), while the contribution from the nonlinear pathway becomes negligible. Biphasic clearance versus the dose profile has been observed with several therapeutic mAbs, including cetuximab, trastuzumab and efalizumab.^[30,79-82] Another characteristic of this model is an S-shaped curve in the concentration-time profile (figure 2c). This may be observed at higher doses if mAb concentrations are sampled over a prolonged time period, and is due to an increase in CL secondary to an increase in CL_{NL} as mAb concentrations decrease. Given a two-compartment pharmacokinetic model with one linear and one nonlinear clearance pathway, there are different structural variations that can be conceived by varying the location (i.e. the central or peripheral compartment) of the two clearance pathways. Issues regarding the identifiability and indistinguishability of these different models have been investigated by Godfrey et al.^[83] In most studies that used a parallel elimination model, the configuration was one where both the linear and nonlinear clearance pathways originated from the central compartment. However, other structural variations were evaluated in the population pharmacokinetic analyses of matuzumab and figitumumab (CP-751,871).^[25,36]

The pharmacokinetic model most frequently used in the population analyses was a one- or two-compartment model with linear clearance (table I), which is inconsistent with the observation that many therapeutic mAbs exhibit nonlinear clearance.^[6,8] One reason for this discrepancy may have been related to the doses (concentrations) studied in the population pharmacokinetic analysis. Referring back to figure 2c, the dose of the mAb may result in concentrations that are high enough to saturate the target-mediated elimination pathway. A compartmental model with linear clearance may adequately describe the data at these high concentrations, as the nonsaturable Fc-mediated elimination pathway becomes the major determinant of mAb clearance. Nonlinear clearance has been observed with efalizumab and trastuzumab, and this was

attributed to saturation of target-mediated clearance pathways by their respective targets, CD11a and the human epidermal growth factor receptor (HER)-2.^[28,30,79,82] Contrary to these observations, two separate population pharmacokinetic analyses of efalizumab and trastuzumab found that their pharmacokinetics were adequately described using a compartmental model with linear clearance.^[28,42] Based on pharmacokinetic data from dose-escalation studies of efalizumab^[30] and trastuzumab,^[82] the doses of these mAbs investigated in the aforementioned population pharmacokinetic analyses may have resulted in steady-state concentrations where target-mediated clearance was saturated, and thus the use of a pharmacokinetic model with linear clearance was warranted.

In a population pharmacokinetic analysis of bevacizumab in patients with solid tumours, concentration data were pooled from a number of different clinical trials in which the dosing regimen for bevacizumab varied.^[22] The data from 10 patients who received bevacizumab doses of 0.1 and 0.3 mg/kg were excluded from the analysis, as the clearance at these doses was faster, and these doses were not evaluated in further clinical trials. The excluded set of patients represented a small fraction of the 491 patients who were included in the population pharmacokinetic study. The final population pharmacokinetic model for bevacizumab included a two-compartment model with linear clearance.^[22] The use of a pharmacokinetic model with linear clearance rather than nonlinear clearance seems reasonable in this case, since the population pharmacokinetic model was used to describe bevacizumab concentrations at clinically relevant doses and did not include the doses of 0.1 and 0.3 mg/kg.

The lowest-dose group was also excluded from a population pharmacokinetic analysis of golimumab, an antibody against tumour necrosis factor (TNF)- α , in patients with rheumatoid arthritis.^[29] The dataset that was used to build the population pharmacokinetic model included 21 patients who received single intravenous doses of golimumab ranging from 0.3 to 10 mg/kg; three patients who received 0.1 mg/kg were excluded from the analysis. The inclusion of data from the 0.1 mg/kg group resulted in convergence difficulties, and it was believed that this may have been due to a significant influence of TNF α -mediated disposition at the very low dose. The final population pharmacokinetic model for golimumab included a two-compartment model with linear clearance.^[29]

2.3.4 Clearance Population Estimates

Population estimates and their between-subject variability in clearance-related pharmacokinetic parameters are summarized in table IV. The estimates of the maximum elimination rate

($V_{\max}$) and the mAb concentration at which elimination was at half maximum (K_m ; the Michaelis-Menten constant) varied considerably among the different therapeutic mAbs. As nonlinear clearance is often attributed to target-mediated mechanisms, it can be expected that the $V_{\max}$ and K_m will be specific for a given mAb and its pharmacological target. The Michaelis-Menten-type parameters (the $V_{\max}$ and K_m) can be related to parameters of a full model of target-mediated drug disposition.^[84,85] While between-subject variability was always estimated for the $V_{\max}$, it was often not estimated for the K_m , thereby treating it as a fixed value across individuals. Given that the $V_{\max}$ is related to the number of pharmacological targets within the mAb distribution space and the K_m is related to the affinity of the mAb for its target, it is a reasonable approach to hypothesize that, physiologically, there is more between-subject variability in the $V_{\max}$ than there is in the K_m . Between-subject variability in the $V_{\max}$ was typically moderate to high, with a median (range) CV of 34% (15–65%) across the studies. When it was estimated, the variability in the K_m tended to be quite large, with most CV estimates being greater than 100%. For mAbs with population estimates of the $V_{\max}$ and K_m , their intrinsic clearance (CL_{int}) was calculated as $V_{\max}/K_m$, and is reported in table IV. All of the therapeutic mAbs listed in table IV for which the CL_{int} was calculated bind to a cell surface antigen. The pharmacological target of denosumab, receptor activator of nuclear factor- κB ligand (RANKL), is expressed not only in a membrane-bound form but also in a soluble form.^[86,87] An interesting observation was made regarding the relationship between CL_{int} and the location (i.e. blood or tissue) of the cell membrane target. Sibrotuzumab, matuzumab, cetuximab, denosumab and figitumumab all bind to cell membrane antigens that are primarily expressed in tissue, and their calculated CL_{int} values ranged from 0.47 to 3.70 L/day. On the other hand, efalizumab, alemtuzumab and clenoliximab target different CD antigens that are largely expressed on white blood cells (WBCs), and their CL_{int} values were much greater, ranging from 27.8 to 57.0 L/day. Mechanistically, the faster CL_{int} observed for mAbs that target blood cells, compared with that for mAbs that have membrane-bound targets in tissue, may be due to a larger number of antigens within the primary distribution space. Panitumumab, cetuximab and matuzumab are all anti-epidermal growth factor receptor (EGFR) mAbs, but the CL_{int} of panitumumab (28.4 L/day) was much faster than that of cetuximab (1.42 L/day) and matuzumab (2.73 L/day) [table IV]. It is uncertain as to why these differences in CL_{int} exist between the anti-EGFR mAbs, but one could hypothesize that the faster CL_{int} observed with panitumumab is in part due to its greater affinity for EGFR ($k_d = 5 \times 10^{-1}$ mol/L),

compared with cetuximab ($k_d = 39 \times 10^{-1}$ mol/L) and matuzumab ($k_d = 34 \times 10^{-1}$ mol/L).^[88-90]

Assuming a volume of distribution of 6.2 L and an elimination half-life of 21 days for IgG^[64] (with the exception of the IgG3 subclass), the clearance of endogenous IgG is approximately 0.21 L/day. The population estimates of the CL_L of mAbs were relatively close to the clearance of endogenous IgG, as the median (range) mAb CL_L estimate was 0.31 (0.066–0.535) L/day. The discrepancy between mAb CL_L values and the clearance of endogenous IgG may be due in part to the different affinities of the therapeutic mAbs, compared with IgG, for the FcRn and Fc γ receptor subtypes. The population clearance estimates for several of the mAbs were around 0.2 L/day and thus quite close to the clearance of endogenous IgG. This suggests that either these mAbs do not exhibit saturable, target-mediated clearance, or that clearance via this pathway was negligible at the concentrations studied in the population analysis.

The population clearance estimates for inolimomab, mAbF19, HuCC49 Δ CH2 and basiliximab were much greater than those for other mAbs. In the case of the first three mAbs that are listed, their increased clearance may have been due to impaired binding to FcRns, which protects IgG from proteolytic degradation.^[55] Both inolimomab and mAbF19 are murine IgG mAbs.^[34,35] The rapid elimination of murine mAbs in humans has been attributed to the lack of binding of murine IgG to the human FcRn.^[91] No indication was given in the population pharmacokinetic analyses of inolimomab and mAbF19 as to whether antibodies against these therapeutic mAbs were measured and/or detected.^[34,35] Considering that inolimomab and mAbF19 are murine mAbs, an immune response and formation of antibodies against the mAbs could be another potential reason for the greater clearance estimates of these mAbs, compared with those of other therapeutic mAbs. HuCC49 Δ CH2 is a humanized IgG1 mAb but is different in that it has a deletion in the CH2 domain to minimize immunogenicity.^[31] It has been suggested that the increased clearance of HuCC49 Δ CH2 may have been due to the CH2 domain deletion, which could have affected binding to the FcRn.^[31] This appears to be a valid argument, as the FcRn binds to a site on IgG that is formed between the CH2 and CH3 domains.^[10]

The population pharmacokinetics of basiliximab have been investigated in patients with kidney^[20] and liver^[21] transplants; the basiliximab clearance in liver recipients was found to be faster than that in kidney recipients. One likely explanation for the faster clearance of basiliximab in liver transplant patients is the additional route of basiliximab clearance through drained ascites fluid.^[21,92]

The apparent total clearance after subcutaneous administration (CL/F) was estimated in the population pharmacokinetic analyses of omalizumab, efalizumab and ustekinumab (table IV), which have bioavailability values following subcutaneous dosing of around 62%, 50% and 57%, respectively.^[28,37,43] After adjustment for bioavailability, the clearance rates of omalizumab, efalizumab and ustekinumab were approximately 0.11, 0.65 and 0.27 L/day, respectively. The between-subject variability in the CL_L and CL , much like the variability in the V_{max} , was moderate to large, with estimated CVs ranging from 20% to 59%.

2.4 Covariates

Covariates identified in population analyses of therapeutic mAbs and their estimated effects on pharmacokinetic parameters are presented in table V. Covariates were commonly identified for the pharmacokinetic parameters V_{max} , CL_L , CL and V_1 . As might be expected, no covariates were found to influence the K_m , which is not unexpected. As the K_m reflects the intrinsic affinity of the mAb for its target, commonly evaluated covariates, such as those related to demographics, body size measurements and blood chemistry/haematology, would not be expected to have an effect on the K_m . Polymorphic expression of the target could theoretically have an effect on the K_m , but this type of genetic information has not been incorporated into any population pharmacokinetic models for therapeutic mAbs published to date. Polymorphic expression in the gene that encodes the Fc γ IIIa receptor (*FCGR3A*) has been associated with better clinical and/or biological responses in non-Hodgkin's lymphoma patients treated with rituximab,^[93,94] Crohn's disease patients treated with infliximab^[95] and patients with breast cancer treated with trastuzumab.^[96]

2.4.1 Demographic and Anthropometric Measurements

Size covariates are probably the most frequently identified and clinically relevant covariates in population pharmacokinetic analyses, and are well established as predictors of systemic exposure to small-molecule drugs, as well as therapeutic mAbs.^[13] Based on the findings summarized in table V, measures of body size were clearly the most commonly identified covariates found to influence the pharmacokinetics of therapeutic mAbs. This is not surprising, since pharmacokinetic parameters such as clearance and volume are often functions of body size.^[97] Measures of body size that were frequently evaluated as covariates include bodyweight, ideal bodyweight and body surface area. A common practice in the mAb population pharmacokinetic analyses was to evaluate different size covariates during the covariate modelling process

to identify which, if any, were the most influential covariates and should remain in the model. Of the different measures of body size, bodyweight was the size covariate most commonly included in the final population pharmacokinetic model (table V). In most studies, the effect of body size on a pharmacokinetic parameter was modelled using a power function, and the exponent in the function was treated as an estimable parameter. However, in a population pharmacokinetic analysis of HuCC49 Δ CH2 in colorectal cancer patients, the exponent was fixed to commonly used allometric values of 0.75 for clearance terms and 1.0 for volume terms.^[31]

The use of fixed dosing versus body-size-based dosing of therapeutic mAbs in adults was recently addressed by Wang et al.^[98] A simulation study was carried out, using published population pharmacokinetic and/or pharmacodynamic models of 12 therapeutic mAbs, and the performance of the two dosing strategies in reducing pharmacokinetic and/or pharmacodynamic variability was investigated. The two dosing approaches performed similarly across the 12 mAbs that were investigated, with fixed dosing being better for some mAbs and body-size-based dosing being better for others. Based on the findings, the authors recommended using fixed dosing in first-in-human studies and, once sufficient data are available to assess the effect of body size on the pharmacokinetics/pharmacodynamics of the mAb, these findings can be used in part to determine the appropriate dosing strategy for subsequent phase III studies.^[98]

Besides body size, other demographic variables that were often evaluated as covariates included age, sex and race. Even after adjustment for body size, sex was identified as a predictor of the CL_L, CL and V₁ in a small number of studies (table V). The effect of sex on the pharmacokinetics of ustekinumab and infliximab was relatively small and not considered to be clinically relevant.^[32,43] In the population pharmacokinetic analyses of bevacizumab and rituximab, the evaluation of sex as a covariate showed that males had higher CL and V₁ values, ranging from 17% to 39% higher.^[22,40] However, according to the prescribing information of these two mAbs,^[99,100] no dose adjustments for sex are recommended. Contrary to the findings of the aforementioned population pharmacokinetic analysis of rituximab, which included 102 patients with rheumatoid arthritis,^[40] another analysis with over 2000 rheumatoid arthritis patients did not find an effect of sex on rituximab pharmacokinetics.^[100] Race was evaluated as a covariate in a number of population pharmacokinetic studies of bevacizumab,^[22] cetuximab,^[23] pertuzumab^[39] and alemtuzumab,^[17] but it was not found to influence the pharmacokinetics of any of these mAbs. The percentages of non-Caucasian patients were small in many studies and may have precluded the ability to identify any

possible differences between race groups. In population pharmacokinetic studies of infliximab^[32] and golimumab,^[29] race was not investigated as a covariate, because most patients were Caucasian. The only study where race was identified as a covariate was a population pharmacokinetic analysis of ustekinumab in psoriasis patients.^[43] The V_d/F of ustekinumab was found to be 11.1% smaller in non-Caucasian patients than in Caucasians, but this was not considered to be clinically relevant. Age was identified as a covariate only in the population pharmacokinetic analyses of efalizumab and panitumumab.^[28,38] Age was found to have an opposite effect in the two studies; age was positively correlated with CL/F in the efalizumab analysis but negatively correlated with the V_{max} in the panitumumab analysis.

2.4.2 Receptor Numbers and Disease-Related Factors

As many therapeutic mAbs undergo receptor-mediated endocytosis following binding to their target, it can be expected that the number of receptors within the distribution space of the mAb would affect its clearance. Covariates related to receptor numbers may include flow cytometry measurements (e.g. receptor density and receptor-positive cell counts) and analysis of biopsy samples (using immunohistochemistry or fluorescence *in situ* hybridization). Patient status and disease severity could also be related to receptor numbers, as one could hypothesize that in some conditions, a patient with more severe disease would have greater receptor expression. Time or the duration of treatment is another variable that may be related to receptor numbers if administration of the therapeutic mAb results in downmodulation of its target over time.

The population pharmacokinetic/pharmacodynamic analyses of omalizumab and efalizumab are excellent examples where the effect of target-mediated elimination has been accounted for with the use of a more complex mechanism-based model.^[30,37] Similarly, a population pharmacokinetic/pharmacodynamic analysis in patients with chronic B-cell lymphocytic leukemia found that alemtuzumab exhibited nonlinear clearance attributable to saturation of target-mediated clearance mechanisms.^[17] The only covariate found to influence the pharmacokinetics of alemtuzumab was the WBC count, which was a strong positive predictor of the V_{max}. This might be expected, as alemtuzumab targets CD52, an antigen present on the cell surface of WBCs (including lymphocytes and monocytes). The WBC count for each patient was updated over time when possible, and WBC counts were shown to generally decrease following repeated administration of alemtuzumab. Therefore, alemtuzumab exhibited both time- and concentration-dependent clearance.^[17]

An interesting use of time as a covariate was applied in a population pharmacokinetic analysis of rituximab in patients with non-Hodgkin's lymphoma.^[101] The authors hypothesized that an observed increase in the rituximab elimination half-life over time was due to a decrease in clearance as the B-cell (CD19+) count and/or the tumour burden also decreased. The pharmacokinetics of rituximab were described using a two-compartment model with two clearance pathways, where the clearance via one pathway remained constant, while the clearance decreased over time as a first-order process via the other pathway. A covariate analysis found that patients with higher CD19 counts or larger measurable tumour lesions at baseline had faster initial time-varying clearance.^[101]

Trastuzumab is a humanized IgG1 mAb, which targets HER2. The extracellular domain (ECD) of HER2 (a soluble antigen) can be shed from the cell surface into the systemic circulation, thereby providing an additional site for trastuzumab binding.^[42] In a population pharmacokinetic analysis of trastuzumab in patients with HER2-positive metastatic breast cancer, several variables were investigated as potential covariates, including HER2 overexpression (assessed by immunohistochemistry), the number of metastatic sites and serum concentrations of the ECD of HER2.^[42] All of the covariates were baseline values, hence no time-varying covariates were used. The number of metastatic sites was identified as the most influential covariate on trastuzumab CL, which was 22% faster in patients with four or more sites. The baseline concentration of ECD was found to positively influence both the trastuzumab CL and V_1 . Patients with ECD concentrations of 200 ng/mL or greater had 14% and 40% higher trastuzumab CL and V_1 values, respectively, compared with patients who had a median ECD concentration of 8.23 ng/mL. The impact of ECD levels on the CL of trastuzumab is in line with nonclinical studies, which suggested that the trastuzumab-ECD complex has a higher CL value than unbound trastuzumab.^[42] Potential reasons why ECD had an effect on the V_1 were not addressed in the publication. HER2 overexpression was not retained in the final model as a significant covariate.

According to the prescribing information for bevacizumab, a population pharmacokinetic analysis found that patients with a large tumour burden (at or above the median value of the tumour surface area) had a CL value of 0.249 L/day versus 0.199 L/day in patients with tumour burdens below the median.^[99] The tumour burden could not be evaluated as a covariate in a recently published population pharmacokinetic analysis of bevacizumab, because the relevant data were not available from all of the clinical trials included in the analysis.^[22] However, albumin and alkaline phosphatase were

found to positively influence clearance of bevacizumab, and both were correlated with the tumour burden in this study. Physical performance and disease severity scores (assessed using scoring systems such as the Karnofsky Performance Scale, the Psoriasis Area and Severity Index (PASI) and the Bath Ankylosing Spondylitis Disease Activity Index) are commonly evaluated as covariates in population pharmacokinetic studies of mAbs used in areas of oncology and immunology.^[23,32,36,42] The only study to identify one of these physical performance and disease severity scores as a covariate was a population pharmacokinetic analysis of efalizumab, which found that the PASI score had a modest effect on the CL/F.^[28]

2.4.3 Pharmacokinetic Drug Interactions

Pharmacokinetic drug-drug interactions between therapeutic mAbs and conventional small-molecule drugs are usually not expected, since mAbs are presumably not substrates for cytochrome P450 enzymes or drug transporters such as P-glycoprotein. In support of this expectation, many of the clinical pharmacokinetic drug interaction studies that have been conducted between therapeutic mAbs and small-molecule drugs did not identify any interaction.^[102] However, there have been a small number of clinical studies where small-molecule drugs had an effect on the pharmacokinetics of the mAb, or vice versa.^[102] Since therapeutic mAbs are often administered with other treatments, concomitant medication was evaluated as a potential covariate in several of the population pharmacokinetic analyses. In all but one of the studies, concomitant medication was found not to influence the pharmacokinetics of the mAb. Examples of mAbs for which concomitant medication was not identified as a covariate in the population pharmacokinetic analysis include cetuximab,^[23] rituximab,^[40] trastuzumab^[42] and infliximab.^[32] Concomitant chemotherapy was identified as a covariate in a population pharmacokinetic analysis of bevacizumab.^[22] When bevacizumab was administered with the bolus irinotecan/fluorouracil/leucovorin (IFL) regimen, its clearance was 17% slower than when it was used concomitantly with other chemotherapy regimens, but no different from that when it was used as monotherapy. The effect of the concomitant chemotherapy on the clearance of bevacizumab was minimal and probably does not necessitate any dosage adjustments.

2.4.4 The Dosage Level

Findings from prior pharmacokinetic studies may indicate that a therapeutic mAb exhibits complex pharmacokinetics with nonlinear clearance; however, the available concentration

data from a population pharmacokinetic analysis may not support such a complex model. If concentration data in the population analysis are available from multiple dose groups, the nonlinear clearance of the mAb could be accounted for in part by evaluating dose as a predictor of clearance. Such an approach was taken in a population pharmacokinetic analysis of efalizumab in psoriasis patients who received weekly subcutaneous doses of 1 mg/kg or 2 mg/kg.^[28] Efalizumab has been shown to exhibit nonlinear clearance, which is attributable to saturation of target-mediated elimination mechanisms;^[30] accordingly, various one-compartment models with linear, nonlinear, and parallel linear and nonlinear clearance pathways were evaluated in the study.^[28] A one-compartment model with linear clearance was found to adequately describe the pharmacokinetics of efalizumab, as the limited concentration data did not support the pharmacokinetic models with nonlinear clearance. Dose was investigated as a covariate on the CL/F, and it was found that patients in the 2 mg/kg group had 24% slower CL/F than patients in the 1 mg/kg group. The dose was also found to be a predictor of clearance in a population analysis of the mAb ING-1 in patients with advanced adenocarcinomas.^[103] The pharmacokinetics of ING-1 were investigated across four intravenous dose levels ranging from 0.03 to 1.0 mg/kg. The clearance of ING-1 was noted to decrease as the dose was increased, but the data did not support a pharmacokinetic model with nonlinear clearance. Therefore, a one-compartment model with linear clearance was selected, with dose included as a covariate on clearance. The clearance of ING-1 decreased from 56.7 to 21.8 mL/kg/day in the 0.03 mg/kg and 1.0 mg/kg dose groups, respectively.

For a therapeutic mAb that exhibits nonlinear pharmacokinetics due to saturable target-mediated mechanisms, the ability to detect and adequately characterize the nonlinearity in a population analysis is largely dependent on the availability of concentration-time data from a wide range of doses. However, as is often encountered in drug development, concentration-time data may only be available from clinical studies where the doses studied (which may be clinically and therapeutically relevant) are high enough to saturate the nonlinear target-mediated elimination of the therapeutic mAb, thereby making it difficult to detect and characterize the nonlinear pharmacokinetics. In such instances, if the population pharmacokinetic model is to be used for describing/predicting concentrations at doses where the nonlinear clearance pathway is at or near saturation, then use of a pharmacokinetic model with linear clearance would be a reasonable approach, as the Fc-mediated elimination pathway becomes the major determinant of mAb clearance (see figure 2b).

2.4.5 Immunogenicity

As therapeutic mAbs are exogenous proteins, they can elicit an immune response, resulting in formation of endogenous antibodies against the mAbs. The immunogenicity of a therapeutic mAb can be influenced by several factors, including the structure and murine content of the antibody, the immune status of the patient (e.g. immunocompetent or immunosuppressed), the dose level, the dosing frequency and the dosing route.^[104] Formation of antibodies as the result of an immune response can have a significant effect on the pharmacokinetics, efficacy and safety of a therapeutic mAb.^[104,105] A population pharmacokinetic analysis of infliximab in patients with ankylosing spondylitis found that patients who were positive for antibodies against infliximab had 42% faster clearance than the remaining patients.^[32] However, when concentrations below the lower limit of quantification (LLQ) were imputed as one-half of the LLQ (originally these values were removed from the dataset), patients who were positive for antibodies against infliximab had 77% faster clearance. The influence of antibody formation on clearance of infliximab was found to be much more pronounced in a population analysis conducted in patients with inflammatory bowel disease.^[47] In this study, patients with antibodies against infliximab had approximately 170% faster clearance than other patients. Another population pharmacokinetic analysis of infliximab in patients with ulcerative colitis found that patients who developed antibodies against infliximab had 47% faster clearance than those who did not.^[33] Formation of antibodies was also identified as an important covariate in a population pharmacokinetic analysis of ustekinumab, where psoriasis patients with a positive immune response had 36% faster CL/F.^[43]

2.4.6 Blood Chemistry

Blood chemistry tests related to hepatic and renal function were often evaluated as potential covariates in the population pharmacokinetic analyses but were rarely identified as covariates. In the population pharmacokinetic analyses of pertuzumab,^[39] bevacizumab^[22] and ustekinumab,^[43] blood chemistry was found to influence the pharmacokinetics of the mAb (table V). The effect of blood chemistry on the CL and V_1 in these studies was in general minimal and not likely to be clinically relevant. It should be noted that in many of the population pharmacokinetic analyses, the effect of marked hepatic and renal impairment could not be sufficiently evaluated, because the patients who were included in the studies typically had adequate hepatic and renal function. A population pharmacokinetic analysis of infliximab in patients with ulcerative colitis found that albumin was a negative predictor of CL.^[33] Similar observations were made in population pharmacokinetic studies of

pertuzumab and ustekinumab.^[39,43] In addition to IgG, the FcRn also binds and protects albumin from intracellular catabolism, thereby playing an important role in the homeostasis of both IgG and albumin.^[72,106] The authors of the infliximab analysis suggested that a higher albumin concentration could be an indicator of an increased number of FcRns and a related reduction in the rate of infliximab elimination.^[33]

2.4.7 Disease and Co-Morbidities

Only a few population pharmacokinetic studies have investigated the effect of disease or co-morbidities on the pharmacokinetics of the mAb.

The potential effect of disease on the pharmacokinetics of infliximab was investigated in a population analysis of patients being treated for either Crohn's disease or ulcerative colitis.^[47] No difference in the pharmacokinetics of infliximab was observed between patients with Crohn's disease ($n=30$) and those with ulcerative colitis ($n=3$), but the small number of patients with ulcerative colitis may have precluded the ability to detect a possible difference.

A number of co-morbidities, including diabetes mellitus, hypertension and hyperlipidaemia, were investigated as covariates in a population pharmacokinetic analysis of ustekinumab in psoriasis patients.^[43] This study found that patients with diabetes had 28.7% faster CL/F and a 13.2% larger V_d/F of ustekinumab. The reason behind the effect of diabetes on the pharmacokinetics of ustekinumab is uncertain, but the authors suggested that altered lymphatic flow and particle transport, altered capillary permeability, increased interstitial fluid volume and accelerated clearance of the antibody, resulting from increased glycation, could be potential mechanisms.^[43] Based on efficacy and safety data, the authors did not recommend that dose adjustments be made in patients with diabetes.

The potential effect of the cancer type was investigated in a population pharmacokinetic analysis of panitumumab in cancer patients with various solid tumours.^[38] Patients with non-small-cell lung cancer or other types of cancer had ~13–14% lower CL_L than patients with colorectal or renal cancer.^[38] The reason for the difference in CL_L between the different types of cancer is uncertain and was not addressed by the authors.

2.5 Residual and Interoccasion Variability

Residual variability in most of the population pharmacokinetic studies was modelled using either a proportional or a combined additive and proportional error model. In a few studies, an exponential error model was used to describe re-

sidual variability.^[23,25,30] Estimates of residual variability from the mAb population pharmacokinetic studies are summarized in table VI. Residual variability in the population pharmacokinetic analyses tended to be small to moderate. Based on the values in table VI, the median (range) CV of the proportional residual error across all of the studies was 21.2% (8.8–42%). The proportional residual errors were relatively comparable across the different studies, while the additive residual errors were notably different. The additive component of a residual variance model often corresponds to the LLQ of an assay. Therefore, the large differences in the additive residual errors may be due in part to the different analytical assays used for different mAbs.

Residual variability can be dependent on a number of patient- or study-related factors, and these can be incorporated into the residual variance model as covariates.^[13] In most of the mAb population pharmacokinetic analyses, a simple residual error model with no covariates was used. However, in a population pharmacokinetic analysis of cetuximab, separate residual error models were used for the two clinical studies that were included in the analysis.^[23] This was done because of the unbalanced sampling design of the two studies (i.e. extensive versus sparse sampling) and because the studies were conducted in different clinical settings.

In addition to between-subject and residual variability, another source of random variability that can be incorporated into the population pharmacokinetic model is interoccasion variability. The inclusion of interoccasion variability in model parameters was investigated for only a few mAbs. In a recent population pharmacokinetic analysis of matuzumab, interoccasion variability was included in the assessment of CL_L .^[36] Each infusion of matuzumab (up to the eighth infusion) was defined as one occasion. The CV of interoccasion variability in CL_L was 23%; however, this was very close to the estimated CV of between-subject variability in CL_L (24%). The incorporation of interoccasion variability was also found to improve the model in a population pharmacokinetic analysis of sibrotuzumab.^[41] Although sibrotuzumab was administered as an intravenous infusion, interoccasion variability was found to be best included in the disposition on 'bioavailability' in the central compartment (F_1). The CV of interoccasion variability in F_1 was 13% and was lower than the between-subject variability in the pharmacokinetic parameters, the CVs of which ranged from 20% to 52%.

3. Conclusions

A review of the literature has shown that the population pharmacokinetics of different therapeutic mAbs are similar despite differences in their pharmacological targets and despite

the fact that they were studied in different patient populations and disease states. A two-compartment model was used in the majority of the population analyses to describe the disposition of the mAb. Population estimates of the V_1 and V_2 were typically small with median (range) values of 3.1 (2.4–5.5) L and 2.8 (1.3–6.8) L, respectively. The estimated between-subject variability in the V_1 was usually moderate, with a median (range) CV of 26% (12–84%). Between-subject variability in other distribution-related parameters such as the V_2 and Q was often not estimated. Although the pharmacokinetic models most frequently used in the population analyses were models with linear clearance, other models with nonlinear or with parallel linear and nonlinear clearance pathways were also applied, as many therapeutic mAbs are eliminated via saturable, target-mediated mechanisms. Population estimates of the $V_{\max}$ and K_m , the parameters characterizing Michaelis-Menten-type saturable elimination pathways, varied considerably among the different therapeutic mAbs. However, estimates of CL in mAbs with linear clearance characteristics and CL_L in mAbs with parallel linear and nonlinear clearance were quite similar among the different mAbs and typically ranged from around 0.2 to 0.5 L/day, which is relatively close to the estimated clearance of endogenous IgG of 0.21 L/day. The between-subject variability in the $V_{\max}$, CL, and CL_L was moderate to large, with estimated CVs ranging from 15% to 65%. Measures of body size were the covariates most commonly found to influence the pharmacokinetics of therapeutic mAbs.

The similarities in the population pharmacokinetics of therapeutic mAbs are probably due in part to general structural features that are shared by most therapeutic mAbs as IgG molecules, such as a functional human Fc region. One could hypothesize that specific target-binding pharmacokinetic parameters such as the $V_{\max}$ and K_m are likely to be influenced by the interaction between a given therapeutic mAb and its target and thus show great variability among different mAbs, while the differences among parameters such as the CL_L , V_1 , V_2 and Q that are thought to be largely affected by the general structural features of mAbs are minimal. In fact, the biggest differences observed in the population pharmacokinetics of the considered mAbs were in population estimates of the $V_{\max}$ and K_m . For the most part, no significant differences were observed in the population pharmacokinetics of murine, chimeric, humanized and fully human therapeutic mAbs. The most notable difference observed between the different classes of mAbs was the larger population clearance estimates for the murine mAbs.

The pharmacokinetic characteristics of mAbs are very different to those of traditional small-molecule drugs^[11,79] and tend to be more complex, as mAbs often exhibit target-mediated

drug disposition and nonlinear pharmacokinetics,^[4] which are often species dependent and substantially complicate extrapolation of mAb pharmacokinetic characteristics from animal models to humans. When analysing the population pharmacokinetics of a mAb, it is therefore important not only to have a general understanding of the pharmacokinetics of mAbs but also to understand the biology and pharmacology of the system. The complex pharmacokinetic characteristics of mAbs pose a significant challenge to a pharmacometrician performing a population pharmacokinetic analysis, as complex models are often evaluated to describe the pharmacokinetics of the mAb, and the use of such models may be further complicated by limited concentration data. However, the similar population pharmacokinetic profiles of different therapeutic mAbs are an aspect of this class of biologics that can be used to the advantage of a more informed data analysis. The results of the studies summarized herein should be of value, as they provide a general concept of what to expect with regard to applicable structural pharmacokinetic models, commonly identified covariates and plausible estimates for typical population estimates, covariate effects, between-subject variability and residual variability, which could be used, for example, to aid in choosing initial estimates or setting parameter boundaries. The compiled results from the population pharmacokinetic studies could also serve a more practical purpose and be used to construct informative priors for a Bayesian data analysis or to construct parameter uncertainty distributions to simulate pharmacokinetic data for a prototypical therapeutic mAb. The ability to include prior information could prove to be particularly useful for mAbs, as they often exhibit complex pharmacokinetics, and the use of complex pharmacokinetic models (e.g. parallel linear and nonlinear clearance pathways) may not be fully supported by the available concentration data in datasets with sparse sampling and/or a limited number of dosage groups.

Acknowledgements

Dr Nathanael L. Dirks was partially supported by a fellowship from the American Foundation for Pharmaceutical Education (Rockville, MD, USA). No other source of funding was used to prepare this review. The authors have no conflicts of interest that are directly relevant to the content of this review.

References

1. Maggon K. Monoclonal antibody “gold rush”. *Curr Med Chem* 2007; 14 (18): 1978–87
2. Reichert JM. Monoclonal antibodies as innovative therapeutics. *Curr Pharm Biotechnol* 2008 Dec; 9 (6): 423–30

3. Galluppi GR, Rogge MC, Roskos LK, et al. Integration of pharmacokinetic and pharmacodynamic studies in the discovery, development, and review of protein therapeutic agents: a conference report. *Clin Pharmacol Ther* 2001 Jun; 69 (6): 387-99
4. Meibohm B. The role of pharmacokinetics and pharmacodynamics in the development of biotech drugs. In: Meibohm B, editor. *Pharmacokinetics and pharmacodynamics of biotech drugs: principles and case studies in drug development*. Weinheim: Wiley-VCH, 2006: 3-16
5. Meibohm B, Derendorf H. Pharmacokinetic/pharmacodynamic studies in drug product development. *J Pharm Sci* 2002 Jan; 91 (1): 18-31
6. Kuester K, Kloft C. Pharmacokinetics of monoclonal antibodies. In: Meibohm B, editor. *Pharmacokinetics and pharmacodynamics of biotech drugs: principles and case studies in drug development*. Weinheim: Wiley-VCH, 2006: 45-92
7. Lobo ED, Hansen RJ, Balthasar JP. Antibody pharmacokinetics and pharmacodynamics. *J Pharm Sci* 2004 Nov; 93 (11): 2645-68
8. Tabrizi MA, Tseng CM, Roskos LK. Elimination mechanisms of therapeutic monoclonal antibodies. *Drug Discov Today* 2006 Jan; 11 (1-2): 81-8
9. Wang W, Wang EQ, Balthasar JP. Monoclonal antibody pharmacokinetics and pharmacodynamics. *Clin Pharmacol Ther* 2008 Nov; 84 (5): 548-58
10. Roitt IM, Delves PJ, Martin SJ, et al. *Roitt's essential immunology*. 11th ed. Malden (MA): Blackwell Publishing, 2006
11. Mascelli MA, Zhou H, Sweet R, et al. Molecular, biologic, and pharmacokinetic properties of monoclonal antibodies: impact of these parameters on early clinical development. *J Clin Pharmacol* 2007 May; 47 (5): 553-65
12. Bonate PL. Recommended reading in population pharmacokinetic pharmacodynamics. *AAPS J* 2005; 7 (2): E363-73
13. Bonate PL. *Pharmacokinetic-pharmacodynamic modeling and simulation*. Boston (MA): Springer Science+ Business Media Inc., 2006
14. Ette EI, Williams PJ. Population pharmacokinetics I: background, concepts, and models. *Ann Pharmacother* 2004 Oct; 38 (10): 1702-6
15. Ette EI, Williams PJ. *Pharmacometrics: the science of quantitative pharmacology*. Hoboken (NJ): John Wiley & Sons, 2007
16. Sheiner LB, Ludden TM. Population pharmacokinetics/dynamics. *Annu Rev Pharmacol Toxicol* 1992; 32: 185-209
17. Mould DR, Baumann A, Kuhlmann J, et al. Population pharmacokinetics-pharmacodynamics of alemtuzumab (Campath) in patients with chronic lymphocytic leukaemia and its link to treatment response. *Br J Clin Pharmacol* 2007 Sep; 64 (3): 278-91
18. Peterson MC, Stouch BJ, Chen D, et al. A population PK/PD model describes the rapid, and sustained suppression of urinary N-telopeptide following administration of AMG 162, a fully human monoclonal antibody against RANKL, to healthy postmenopausal women. *AAPS J* 2004; 6 (S1) [online]. Available from URL: http://www.aaps.org/inside/focus_groups/poppk/imagespdfs/PopPKPD-2004Final.pdf [Accessed 2010 Jul 20]
19. Zingmark PH, Edenius C, Karlsson MO. Pharmacokinetic/pharmacodynamic models for the depletion of Vbeta5.2/5.3 T cells by the monoclonal antibody ATM-027 in patients with multiple sclerosis, as measured by FACS. *Br J Clin Pharmacol* 2004 Oct; 58 (4): 378-89
20. Mentré F, Kovarik J, Gerbeau C. Constructing a prediction interval for time to reach a threshold concentration based on a population pharmacokinetic analysis: an application to basiliximab in renal transplantation. *J Pharmacokinet Biopharm* 1999 Apr; 27 (2): 213-30
21. Kovarik JM, Nashan B, Neuhaus P, et al. A population pharmacokinetic screen to identify demographic-clinical covariates of basiliximab in liver transplantation. *Clin Pharmacol Ther* 2001 Apr; 69 (4): 201-9
22. Lu JF, Bruno R, Eppler S, et al. Clinical pharmacokinetics of bevacizumab in patients with solid tumors. *Cancer Chemother Pharmacol* 2008 Oct; 62 (5): 779-86
23. Dirks NL, Nolting A, Kovar A, et al. Population pharmacokinetics of cetuximab in patients with squamous cell carcinoma of the head and neck. *J Clin Pharmacol* 2008 Mar; 48 (3): 267-78
24. Mould DR, Davis CB, Minthorn EA, et al. A population pharmacokinetic-pharmacodynamic analysis of single doses of clenoliximab in patients with rheumatoid arthritis. *Clin Pharmacol Ther* 1999 Sep; 66 (3): 246-57
25. Yin D, Paccagnella ML, Lacy MQ, et al. Population pharmacokinetics of CP-751,871, a monoclonal antibody against IGF-I receptor, in patients with multiple myeloma or solid tumors [abstract no. 2524]. *J Clin Oncol* 2008 May 20; 26 (15 Suppl.) [online]. Available from URL: http://www.asco.org/ASCOv2/MultiMedia/Virtual+Meeting?vmview=vm_session_presentations_view&confID=55&sessionID=385 [Accessed 2010 Jul 20]
26. Peterson MC, Jang G, Kim W, et al. Selection of a phase 3 dose regimen for denosumab based on pharmacokinetic (PK), pharmacodynamic (PD), and safety data from multiple subcutaneous (SC) dosing regimens in breast cancer patients (pts) with bone metastases (BM) [abstract no. 3086]. *J Clin Oncol* 2006 Jun 20; 24 (18 Suppl.) [online]. Available from URL: http://www.asco.org/ASCOv2/MultiMedia/Virtual+Meeting?vmview=vm_session_presentations_view&confID=40&sessionID=395 [Accessed 2010 Jul 20]
27. Ng CM, Joshi A, Dedrick RL, et al. Pharmacokinetic-pharmacodynamic-efficacy analysis of efalizumab in patients with moderate to severe psoriasis. *Pharm Res* 2005 Jul; 22 (7): 1088-100
28. Sun YN, Lu JF, Joshi A, et al. Population pharmacokinetics of efalizumab (humanized monoclonal anti-CD11a antibody) following long-term subcutaneous weekly dosing in psoriasis subjects. *J Clin Pharmacol* 2005 Apr; 45 (4): 468-76
29. Zhou H, Jang H, Fleischmann RM, et al. Pharmacokinetics and safety of golimumab, a fully human anti-TNF-alpha monoclonal antibody, in subjects with rheumatoid arthritis. *J Clin Pharmacol* 2007 Mar; 47 (3): 383-96
30. Bauer RJ, Dedrick RL, White ML, et al. Population pharmacokinetics and pharmacodynamics of the anti-CD11a antibody hu1124 in human subjects with psoriasis. *J Pharmacokinet Biopharm* 1999 Aug; 27 (4): 397-420
31. Fang L, Holford NH, Hinkle G, et al. Population pharmacokinetics of humanized monoclonal antibody HuCC49deltaCH2 and murine antibody CC49 in colorectal cancer patients. *J Clin Pharmacol* 2007 Feb; 47 (2): 227-37
32. Xu Z, Seitz K, Fasanmade A, et al. Population pharmacokinetics of infliximab in patients with ankylosing spondylitis. *J Clin Pharmacol* 2008 Jun; 48 (6): 681-95
33. Fasanmade AA, Adedokun OJ, Ford J, et al. Population pharmacokinetic analysis of infliximab in patients with ulcerative colitis. *Eur J Clin Pharmacol* 2009; 65 (12): 1211-28
34. Dartois C, Freyer G, Michallet M, et al. Exposure-effect population model of inolimomab, a monoclonal antibody administered in first-line treatment for acute graft-versus-host disease. *Clin Pharmacokinet* 2007; 46 (5): 417-32
35. Tanswell P, Garin-Chesa P, Rettig WJ, et al. Population pharmacokinetics of antifibroblast activation protein monoclonal antibody F19 in cancer patients. *Br J Clin Pharmacol* 2001 Feb; 51 (2): 177-80
36. Kuester K, Kovar A, Lupfert C, et al. Population pharmacokinetic data analysis of three phase I studies of matuzumab, a humanised anti-EGFR monoclonal antibody in clinical cancer development. *Br J Cancer* 2008 Mar 11; 98 (5): 900-6
37. Hayashi N, Tsukamoto Y, Sallas WM, et al. A mechanism-based binding model for the population pharmacokinetics and pharmacodynamics of omalizumab. *Br J Clin Pharmacol* 2007 May; 63 (5): 548-61
38. Ma P, Yang BB, Wang YM, et al. Population pharmacokinetic analysis of panitumumab in patients with advanced solid tumors. *J Clin Pharmacol* 2009 Oct; 49 (10): 1142-56
39. Ng CM, Lum BL, Gimenez V, et al. Rationale for fixed dosing of pertuzumab in cancer patients based on population pharmacokinetic analysis. *Pharm Res* 2006 Jun; 23 (6): 1275-84
40. Ng CM, Bruno R, Combs D, et al. Population pharmacokinetics of rituximab (anti-CD20 monoclonal antibody) in rheumatoid arthritis patients during a phase II clinical trial. *J Clin Pharmacol* 2005 Jul; 45 (7): 792-801

41. Kloft C, Graefe EU, Tanswell P, et al. Population pharmacokinetics of si-brotuzumab, a novel therapeutic monoclonal antibody, in cancer patients. *Invest New Drugs* 2004 Jan; 22 (1): 39-52
42. Bruno R, Washington CB, Lu JF, et al. Population pharmacokinetics of trastuzumab in patients with HER2+ metastatic breast cancer. *Cancer Chemother Pharmacol* 2005 Oct; 56 (4): 361-9
43. Zhu Y, Hu C, Lu M, et al. Population pharmacokinetic modeling of ustekinumab, a human monoclonal antibody targeting IL-12/23p40, in patients with moderate to severe plaque psoriasis. *J Clin Pharmacol* 2009 Feb; 49 (2): 162-75
44. Pescovitz MD, Knechtel S, Alexander SR, et al. Safety and pharmacokinetics of daclizumab in pediatric renal transplant recipients. *Pediatr Transplant* 2008 Jun; 12 (4): 447-55
45. Meissner HC, Groothuis JR, Rodriguez WJ, et al. Safety and pharmacokinetics of an intramuscular monoclonal antibody (SB 209763) against respiratory syncytial virus (RSV) in infants and young children at risk for severe RSV disease. *Antimicrob Agents Chemother* 1999 May; 43 (5): 1183-8
46. Beal SL, Sheiner LB, Boeckmann AJ, editors. NONMEM users guides. Ellicott City (MD): Icon Development Solutions, 2006
47. Ternant D, Aubourg A, Magdelaine-Beuzelin C, et al. Infliximab pharmacokinetics in inflammatory bowel disease patients. *Ther Drug Monit* 2008 Aug; 30 (4): 523-9
48. Supersaxo A, Hein WR, Steffen H. Effect of molecular weight on the lymphatic absorption of water-soluble compounds following subcutaneous administration. *Pharm Res* 1990 Feb; 7 (2): 167-9
49. McLennan DN, Porter CJ, Edwards GA, et al. Lymphatic absorption is the primary contributor to the systemic availability of epoetin alfa following subcutaneous administration to sheep. *J Pharmacol Exp Ther* 2005 Apr; 313 (1): 345-51
50. Kagan L, Gershkovich P, Mendelman A, et al. The role of the lymphatic system in subcutaneous absorption of macromolecules in the rat model. *Eur J Pharm Biopharm* 2007 Nov; 67 (3): 759-65
51. O'Driscoll CM. Anatomy and physiology of the lymphatics. In: Charman WN, Stella VJ, editors. *Lymphatic transport of drugs*. Boca Raton (FL): CRC Press, 1992: 1-36
52. Garg A, Balthasar JP. Physiologically-based pharmacokinetic (PBPK) model to predict IgG tissue kinetics in wild-type and FcRn-knockout mice. *J Pharmacokinet Pharmacodyn* 2007 Oct; 34 (5): 687-709
53. Tabrizi M, Bornstein GG, Suria H. Biodistribution mechanisms of therapeutic monoclonal antibodies in health and disease. *AAPS J* 2010 Mar; 12 (1): 33-43
54. Ghetie V, Ward ES. FcRn: the MHC class I-related receptor that is more than an IgG transporter. *Immunol Today* 1997 Dec; 18 (12): 592-8
55. Ward ES, Zhou J, Ghetie V, et al. Evidence to support the cellular mechanism involved in serum IgG homeostasis in humans. *Int Immunol* 2003 Feb; 15 (2): 187-95
56. Antohe F, Radulescu L, Gafencu A, et al. Expression of functionally active FcRn and the differentiated bidirectional transport of IgG in human placental endothelial cells. *Hum Immunol* 2001 Feb; 62 (2): 93-105
57. Claypool SM, Dickinson BL, Yoshida M, et al. Functional reconstitution of human FcRn in Madin-Darby canine kidney cells requires co-expressed human beta 2-microglobulin. *J Biol Chem* 2002 Aug 2; 277 (31): 28038-50
58. Dickinson BL, Badizadegan K, Wu Z, et al. Bidirectional FcRn-dependent IgG transport in a polarized human intestinal epithelial cell line. *J Clin Invest* 1999 Oct; 104 (7): 903-11
59. Kobayashi N, Suzuki Y, Tsuge T, et al. FcRn-mediated transcytosis of immunoglobulin G in human renal proximal tubular epithelial cells. *Am J Physiol Renal Physiol* 2002 Feb; 282 (2): F358-65
60. McCarthy KM, Yoong Y, Simister NE. Bidirectional transcytosis of IgG by the rat neonatal Fc receptor expressed in a rat kidney cell line: a system to study protein transport across epithelia. *J Cell Sci* 2000 Apr; 113 (Pt 7): 1277-85
61. Praetor A, Ellinger I, Hunziker W. Intracellular traffic of the MHC class I-like IgG Fc receptor, FcRn, expressed in epithelial MDCK cells. *J Cell Sci* 1999 Jul; 112 (Pt 14): 2291-9
62. Tuma PL, Hubbard AL. Transcytosis: crossing cellular barriers. *Physiol Rev* 2003 Jul; 83 (3): 871-932
63. Tang L, Persky AM, Hochhaus G, et al. Pharmacokinetic aspects of biotechnology products. *J Pharm Sci* 2004 Sep; 93 (9): 2184-204
64. Waldmann TA, Strober W. Metabolism of immunoglobulins. *Prog Allergy* 1969; 13: 1-110
65. Straughn AB. Limitations of noncompartmental pharmacokinetic analysis of biotech drugs. In: Meibohm B, editor. *Pharmacokinetics and pharmacodynamics of biotech drugs: principles and case studies in drug development*. Weinheim: Wiley-VCH, 2006: 181-8
66. Lote CJ. Principles of renal physiology. 4th ed. Boston (MA): Kluwer Academic Publishers, 2000
67. Wu CT, Davis PA, Luketic VA, et al. A review of the physiological and immunological functions of biliary epithelial cells: targets for primary biliary cirrhosis, primary sclerosing cholangitis and drug-induced ductopenias. *Clin Dev Immunol* 2004 Sep-Dec; 11 (3-4): 205-13
68. Brambell FW. The transmission of immunity from mother to young and the catabolism of immunoglobulins. *Lancet* 1966 Nov 19; 2 (7473): 1087-93
69. Junghans RP. Finally! The Brambell receptor (FcRB). Mediator of transmission of immunity and protection from catabolism for IgG. *Immunol Res* 1997 Feb; 16 (1): 29-57
70. Ober RJ, Martinez C, Vaccaro C, et al. Visualizing the site and dynamics of IgG salvage by the MHC class I-related receptor, FcRn. *J Immunol* 2004 Feb 15; 172 (4): 2021-9
71. Morell A, Terry WD, Waldmann TA. Metabolic properties of IgG subclasses in man. *J Clin Invest* 1970 Apr; 49 (4): 673-80
72. Kim J, Hayton WL, Robinson JM, et al. Kinetics of FcRn-mediated recycling of IgG and albumin in human: pathophysiology and therapeutic implications using a simplified mechanism-based model. *Clin Immunol* 2007 Feb; 122 (2): 146-55
73. Daba MB. FcRn expression, ligands binding properties and its regulation in human immune cells and hepatocytes [thesis]. Oslo: University of Oslo, 2007
74. Roopenian DC, Akilesh S. FcRn: the neonatal Fc receptor comes of age. *Nat Rev Immunol* 2007 Sep; 7 (9): 715-25
75. Sigal LH. Basic science for the clinician 47: Fc gamma receptors [published erratum appears in *J Clin Rheumatol* 2008 Feb; 14 (1): 60]. *J Clin Rheumatol* 2007 Dec; 13 (6): 355-8
76. Levy G. Pharmacologic target-mediated drug disposition. *Clin Pharmacol Ther* 1994 Sep; 56 (3): 248-52
77. Mager DE. Target-mediated drug disposition and dynamics. *Biochem Pharmacol* 2006 Jun 28; 72 (1): 1-10
78. Marathe A, Peterson MC, Mager DE. Integrated cellular bone homeostasis model for denosumab pharmacodynamics in multiple myeloma patients. *J Pharmacol Exp Ther* 2008 Aug; 326 (2): 555-62
79. Tabrizi MA, Roskos LK. Exposure-response relationships for therapeutic biologic products. In: Meibohm B, editor. *Pharmacokinetics and pharmacodynamics of biotech drugs: principles and case studies in drug development*. Weinheim: Wiley-VCH, 2006: 295-330
80. Tan AR, Moore DF, Hidalgo M, et al. Pharmacokinetics of cetuximab after administration of escalating single dosing and weekly fixed dosing in patients with solid tumors. *Clin Cancer Res* 2006 Nov 1; 12 (21): 6517-22
81. Baselga J, Pfister D, Cooper MR, et al. Phase I studies of anti-epidermal growth factor receptor chimeric antibody C225 alone and in combination with cisplatin. *J Clin Oncol* 2000 Feb; 18 (4): 904-14

82. Tokuda Y, Watanabe T, Omuro Y, et al. Dose escalation and pharmacokinetic study of a humanized anti-HER2 monoclonal antibody in patients with HER2/neu-overexpressing metastatic breast cancer. *Br J Cancer* 1999 Dec; 81 (8): 1419-25
83. Godfrey KR, Chapman MJ, Vajda S. Identifiability and indistinguishability of nonlinear pharmacokinetic models. *J Pharmacokinet Biopharm* 1994 Jun; 22 (3): 229-51
84. Gibiansky L, Gibiansky E. Target-mediated drug disposition model: approximations, identifiability of model parameters and applications to the population pharmacokinetic-pharmacodynamic modeling of biologics. *Expert Opin Drug Metab Toxicol* 2009 Jul; 5 (7): 803-12
85. Gibiansky L, Gibiansky E, Kakkar T, et al. Approximations of the target-mediated drug disposition model and identifiability of model parameters. *J Pharmacokinet Pharmacodyn* 2008 Oct; 35 (5): 573-91
86. Khosla S. Minireview: the OPG/RANKL/RANK system. *Endocrinology* 2001 Dec; 142 (12): 5050-5
87. Lewiecki EM. Denosumab: an investigational drug for the management of postmenopausal osteoporosis. *Biologics* 2008 Dec; 2 (4): 645-53
88. Cohenuram M, Saif MW. Panitumumab the first fully human monoclonal antibody: from the bench to the clinic. *Anticancer Drugs* 2007 Jan; 18 (1): 7-15
89. Kim GP, Grothey A. Targeting colorectal cancer with human anti-EGFR monoclonal antibodies: focus on panitumumab. *Biologics* 2008 Jun; 2 (2): 223-8
90. Vanhoefler U, Tewes M, Rojo F, et al. Phase I study of the humanized anti-epidermal growth factor receptor monoclonal antibody EMD72000 in patients with advanced solid tumors that express the epidermal growth factor receptor. *J Clin Oncol* 2004 Jan 1; 22 (1): 175-84
91. Ober RJ, Radu CG, Ghetie V, et al. Differences in promiscuity for antibody-FcRn interactions across species: implications for therapeutic antibodies. *Int Immunol* 2001 Dec; 13 (12): 1551-9
92. Kovarik J, Breidenbach T, Gerbeau C, et al. Disposition and immunodynamics of basiliximab in liver allograft recipients. *Clin Pharmacol Ther* 1998 Jul; 64 (1): 66-72
93. Cartron G, Dacheux L, Salles G, et al. Therapeutic activity of humanized anti-CD20 monoclonal antibody and polymorphism in IgG Fc receptor FcγRIIIa gene. *Blood* 2002 Feb 1; 99 (3): 754-8
94. Weng WK, Levy R. Two immunoglobulin G fragment C receptor polymorphisms independently predict response to rituximab in patients with follicular lymphoma. *J Clin Oncol* 2003 Nov 1; 21 (21): 3940-7
95. Louis E, El Ghoul Z, Vermeire S, et al. Association between polymorphism in IgG Fc receptor IIIa coding gene and biological response to infliximab in Crohn's disease. *Aliment Pharmacol Ther* 2004 Mar 1; 19 (5): 511-9
96. Musolino A, Naldi N, Bortesi B, et al. Immunoglobulin G fragment C receptor polymorphisms and clinical efficacy of trastuzumab-based therapy in patients with HER-2/neu-positive metastatic breast cancer. *J Clin Oncol* 2008 Apr 10; 26 (11): 1789-96
97. Meibohm B, Laer S, Panetta JC, et al. Population pharmacokinetic studies in pediatrics: issues in design and analysis. *AAPS J* 2005; 7 (2): E475-87
98. Wang DD, Zhang S, Zhao H, et al. Fixed dosing versus body size-based dosing of monoclonal antibodies in adult clinical trials. *J Clin Pharmacol* 2009 Sep; 49 (9): 1012-24
99. Avastin® (bevacizumab): US prescribing information. South San Francisco (CA): Genentech, Inc., 2009 Jul [online]. Available from URL: <http://www.gene.com/gene/products/information/pdf/avastin-prescribing.pdf> [Accessed 2010 Jul 20]
100. Rituxan® (rituximab): US prescribing information. South San Francisco (CA): Genentech, 2010 Feb [online]. Available from URL: <http://www.gene.com/gene/products/information/pdf/rituxan-prescribing.pdf> [Accessed 2010 Jul 20]
101. Levi M, Li J, Frey N, et al. Characterization of the time-varying clearance of rituximab in non-Hodgkin's lymphoma patients using a population pharmacokinetic analysis [abstract no. 9]. American Conference on Pharmacometrics; 2008 Mar 9-12; Tucson (AZ) [online]. Available from URL: <http://tucson2008.go-acop.org/pdfs/Levi.pdf> [Accessed 2010 Jul 20]
102. Seitz K, Zhou H. Pharmacokinetic drug-drug interaction potentials for therapeutic monoclonal antibodies: reality check. *J Clin Pharmacol* 2007 Sep; 47 (9): 1104-18
103. de Bono JS, Tolcher AW, Forero A, et al. ING-1, a monoclonal antibody targeting Ep-CAM in patients with advanced adenocarcinomas. *Clin Cancer Res* 2004 Nov 15; 10 (22): 7555-65
104. Roskos LK, Kellermann SA, Foon KA. Human antiglobulin responses. In: Lotze MT, Thomson AW, editors. *Measuring immunity: basic science and clinical practice*. San Diego (CA): Elsevier Academic Press, 2005: 172-86
105. Mahmood I, Green MD. Pharmacokinetic and pharmacodynamic considerations in the development of therapeutic proteins. *Clin Pharmacokinet* 2005; 44 (4): 331-47
106. Anderson CL, Chaudhury C, Kim J, et al. Perspective: FcRn transports albumin: relevance to immunology and medicine. *Trends Immunol* 2006 Jul; 27 (7): 343-8

Correspondence: Dr Bernd Meibohm, Department of Pharmaceutical Sciences, College of Pharmacy, University of Tennessee Health Science Center, 874 Union Avenue, Suite 5P, Memphis, TN 38163, USA.
E-mail: bmeibohm@uthsc.edu