RHEUMATOLOGY

Rheumatology 2016;55:704–709
doi:10.1093/rheumatology/kev394
Advance Access publication 16 December 2015

Original article

# The majority of patients do not store their biologic disease-modifying antirheumatic drugs within the recommended temperature range

**Nicolaas D. Vlieland[1], Helga Gardarsdottir[1,2], Marcel L. Bouvy[2], Toine C. G. Egberts[1,2] and Bart J. F. van den Bemt[3,4]**

## Abstract

**Objective.** To monitor whether biologic DMARD (bDMARD) home storage temperatures comply with the manufacturers' Summary of Product Characteristics (SmPC) recommendations.

**Methods.** This observational study included consenting adult patients from eight Dutch pharmacies who received their bDMARDs with a validated temperature logger. Patients were instructed to store their packages according to standard label instructions and to return the temperature logger(s) after use. Primary outcome was defined as the proportion of patients that stored their bDMARDs within the SmPC recommended temperature range. In addition, the proportion of patients storing bDMARDs below 0°C or above 25°C for longer than two consecutive hours was estimated.

**Results.** A total of 255 (87.0%) patients (mean age 53.2 (S.D.; 13.1) years, 51.4% female) returned their temperature logger(s) to the pharmacy. Of these, 17 patients (6.7%) stored their bDMARD within the recommended temperature range. The proportion of the patients that stored their bDMARD for more than 2 h consecutive time below 0°C or above 25°C was respectively 24.3% (median duration: 3.7 h (IQR 2.2 h; range 2.0–1,097.1 h) and 2.0% (median duration: 11.8 h (IQR 44.3 h; range 2.0–381.9 h).

**Conclusion.** The majority of patients do not store their bDMARDs within the SmPC-recommended temperature range.

**Key words:** biologic DMARDs, rheumatoid arthritis, anti-TNF, epidemiology

CLINICAL SCIENCE

**Rheumatology key messages**

- The majority of patients do not store biologic DMARDs within the summary of product characteristics recommended temperature range.
- More research is required to investigate the relation between extreme storage temperatures and the effectiveness of biologic DMARD treatment.

## Introduction

The introduction of biologic DMARDs (bDMARDs) changed the treatment for patients with inflammatory rheumatic diseases dramatically. In 2013, etanercept and adalimumab were among the best-selling biologic drugs worldwide [1]. Although many patients benefit from using bDMARDs, results from clinical trials suggest that 13–25% of patients discontinue treatment with

[1]Department of Clinical Pharmacy, Division Laboratory and Pharmacy, University Medical Center Utrecht, [2]Division of Pharmacoepidemiology and Clinical Pharmacology, Utrecht Institute for Pharmaceutical Sciences, Utrecht University, Utrecht, [3]Department of Pharmacy, Sint Maartenskliniek and [4]Department of Pharmacy, Radboud Medical Center, Nijmegen, The Netherlands

Submitted 23 April 2015; revised version accepted 30 October 2015

Correspondence to: Bart J. F. van den Bemt, Department of Pharmacy, Sint Maartenskliniek, Hengstdal 3, NA Ubbergen 6574, The Netherlands. E-mail: b.vandenBemt@maartenskliniek.nl

bDMARDs within 1 year [2–5], which is slightly less than what has been reported in observational studies (15–43%) [6–8].

The formation of antidrug-antibodies (ADAs) to bDMARDs is considered to be one of the possible mechanisms underlying treatment failure [9]. bDMARDs are protein-based drugs and are generally more complex and less stable than traditional small molecule drugs. External factors such as vigorous shaking and extreme temperature conditions can lead to protein denaturation and may induce irreversible formation of protein aggregates [10]. Protein aggregation can increase the immunogenicity, lead to the formation of ADAs and may contribute to the risk of adverse drug reactions and decreasing effectiveness [11–13].

Proper storage and controlled distribution of bDMARDs are essential for ensuring the quality of these drugs. bDMARDs should, according to the summary of product characteristics (SmPC), ideally be stored between 2°C and 8°C [14–18]. In accordance with good distribution guidelines (GDP), drug transport between manufacturer, wholesaler and pharmacy is monitored to guarantee product quality until dispensing [19]. After the drug leaves the controlled environment of the pharmacy, drug transport and storage is taken over by the patient and the drug enters an environment that is often not equipped for storage of temperature-sensitive substances. Patients' home storage of temperature-sensitive drugs has been studied sparsely and only in studies with short follow-up (<30 days) [20, 21]. These observational studies showed that the home storage temperatures of bDMARDs often deviated from the recommended temperature range. None of these studies, however, have monitored home storage temperatures for the complete storage time. Therefore, the aim of this study was to monitor whether bDMARD home storage temperatures comply with SmPC recommendations for one complete dispense period.

## Methods

### Setting and study population

This prospective multicentre observational follow-up study was conducted in eight Dutch hospitals' (one academic hospital, six general hospitals and one specialized rheumatology clinic) outpatient pharmacies during December 2013 – January 2015. For reimbursement reasons, almost all bDMARDs are dispensed in the Netherlands by the outpatient pharmacy of the hospital where the patient has been treated by his/her rheumatologist. Patients were eligible for inclusion when treated with any of the following bDMARDs: etanercept, adalimumab, golimumab, certolizumab pegol or abatacept. Eligible patients received both written and verbal information and were asked for a written informed consent. This study was reviewed by the Medical Research and Ethics Committee University Medical Center Utrecht (protocol reference number 14-628/C), which concluded that the study did not fall under the scope of the Dutch Medical Research Involving Human Subjects Act and that ethical approval was therefore not required.

### Procedure

Patients who consented received their bDMARDs in the original manufacturer's packaging. Each package dispensed to the patient in a single delivery was put in a closed sealbag including a temperature logger (Supplementary Fig. S1, available at *Rheumatology* Online). Patients were instructed to store the medication according to label instructions and received care-as-usual, i.e. no additional storage advice was given in the context of this study. Patients were asked to return the temperature logger(s) to the pharmacy when the dispensed medicine had been used. Patients who did not return the temperature logger after three months received a reminder by post including a pre-stamped return envelope to return the temperature logger(s). If needed, second and third reminders were given by telephone at 2 and 4 weeks after the first reminder.

### Temperature loggers

The Safe-Rx temperature logger is a small (18 mm × 32 mm × 2 mm), temperature measurement device and is validated according to international standards [22]. The device can store up to 500 000 temperature measurements and was adjusted to measure temperature at least every 10 min. All temperature measurements were automatically stored in a protected online database.

### Outcomes

The primary outcome was the proportion of patients that stored bDMARDs within the SmPC-recommended storage range. SmPC-recommended temperature storage was defined as the total storage time between 2°C and 8°C without excursions outside this range for ⩾ 48 h in total or excursions below 0°C or above 25°C for ⩾ 2 h consecutive time. Deviations from the SmPC-recommended temperature storage conditions were defined as: proportion of patients storing bDMARDs below 0°C or above 25°C for ⩾2 h; the longest episode duration (consecutive time, hours) below 0°C or above 25°C; and the number of episodes ⩾2 h (consecutive time) below 0°C or above 25°C.

### Data analysis

Demographic data was presented using means (S.D.), medians [interquartile range (IQR)] or in percentages of the study population. Total measurement time was the time (in days) between the first and last temperature measurement, and total storage time was defined as the total measurement time minus the final 48 h of temperature measurements. In case the storage temperature changed from below 15°C to 15°C or higher for at least 12 h without subsequent cooling below 15°C for at least 48 h, the total measurement time was right-censored from the first 15°C excursion time point. This definition is further illustrated in Supplementary Figs S2–S4, available at *Rheumatology* Online). The proportion of total storage time within the

**Table 1** Patient characteristics (*N* = 293)

| | Patients included in analysis (N = 255) | | Patients lost to Follow up (N = 38) | | P values |
|---|---|---|---|---|---|
| Age, mean (s.d.) | 53.2 (13.1) | | 52.4 (14.5) | | 0.74 |
| Gender | N | % | N | % | |
| Female | 131 | 51.4 | 26 | 68.4 | 0.05 |
| Type of bDMARD | | | | | |
| Etanercept | 108 | 42.4 | 17 | 44.7 | 0.78 |
| Adalimumab | 135 | 52.9 | 19 | 50.0 | 0.74 |
| Golimumab | 7 | 2.7 | 1 | 2.6 | 0.88[a] |
| Certolizumab Pegol | 3 | 1.2 | 1 | 2.6 | |
| Abatacept | 2 | 0.8 | 0 | 0.0 | |

[a]Patients using Golimumab, Certolizumab Pegol and Abatacept tested as one group.

SmPC-recommended temperature range (2–8°C), below 0°C and above 25°C was calculated for all patients. Patient characteristics (gender, age and type of bDMARD) of patients lost to follow-up were compared with patient characteristics of those included in the analysis by using the t-test for normally distributed continuous variables and Pearson $\chi^2$ test for differences in proportions. Two-sided P-values $< 0.05$ were considered to indicate a significant difference. Patient characteristics of those storing bDMARDs within and not within the SmPC-recommended temperature range and of those who store their bDMARD below 0°C or above 25°C or not were also compared. All calculations were made with the statistical packages from SAS version 9.2 and SPSS version 21.

## Results

A total of 293 patients were included in the study, who received 882 temperature loggers. Of these, 255 patients (87.0%) returned 756 temperature loggers to the pharmacy and were included in our study population. The study population was 51.4% female, with a mean age of 53.2 (s.d.; 13.1) years (Table 1). More than 95% of patients received treatment with etanercept or adalimumab. The study population did not differ significantly from patients who did not return their temperature loggers to the pharmacy (68.4% female, mean age 52.4 (s.d.; 14.5) years).

The mean total measurement time was 105.7 days (s.d.; 45.9). The mean storage time was 82.2 days (s.d.; 42.6), with 54.8% of the total storage time falling within the SmPC-recommended storage temperature range (Fig. 1). The proportion of the total storage time below 0°C and above 25°C was 1.7% and 0.04%, respectively. Various patterns of storage temperatures were observed (Fig. 2). Only 6.7% of the patients stored all bDMARDs packages within the defined SmPC-recommended temperature range, whereas 24.3% of patients stored one or more bDMARD packages for more than 2 h below 0°C. The median duration of an episode where a bDMARD was stored at temperatures below 0°C was 3.7 h (IQR; 2.2 h, range; 2.0–1097.1 h), with a median frequency of 3 episodes (IQR; 14) lasting longer than 2 h. The percentage of patients who stored bDMARDs at above 25°C for episodes >2 h was 2.0%. The median frequency of episodes longer than 2 h with storage temperature above 25°C in these patients was 1 (IQR; 0.5), with a median duration of 11.8 h consecutive time (IQR; 44.3 h, range; 2.0–381.9 h). A total of 35 patients (13.7%) had three or more periods below 0°C for 2 h or longer (median frequency of episodes; 12.5, IQR; 29.3, range; 3.0–211.0). The proportion of patients who stored bDMARDs below 0°C for 24 h or longer consecutive time was 5.9%.

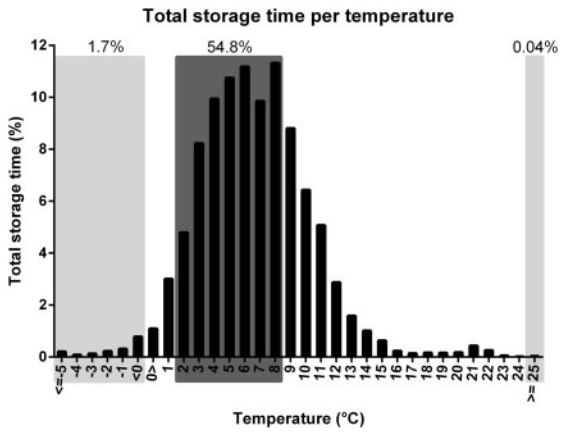
No statistically significant differences were found in gender, age and type of bDMARD of patients who stored bDMARDs within and not within the SmPC-recommended temperature range. The analysis also did not show any statistically significant difference in the gender, age and type of bDMARD in patients who did and did not store bDMARDs below 0°C or above 25°C.

## Discussion

This study demonstrates that the majority of patients with inflammatory rheumatic diseases do not store their bDMARDs within the manufacturer's recommended temperature range. In 26.3% of patients, bDMARDs were stored at home at temperatures below 0°C or above 25°C for longer than 2 h (consecutive time). Our findings were similar for males and females, across ages and across type of bDMARD.

Our results are in line with previous publications on home storage conditions for bDMARDs. These (short-term) studies demonstrated that 50–58% of the patients stored their bDMARDs outside the SmPC-recommended storage temperature range [20, 21]. The aforementioned studies report a slightly smaller proportion of patients storing biologics outside the SmPC-recommended storage temperatures than what is reported in our study. However, we used a more strict definition for storing conditions and had a longer follow-up period, which might partly explain the higher percentage of patients storing bDMARDs outside the recommended storage area.

**Fig. 1** Proportion of total storage time per temperature

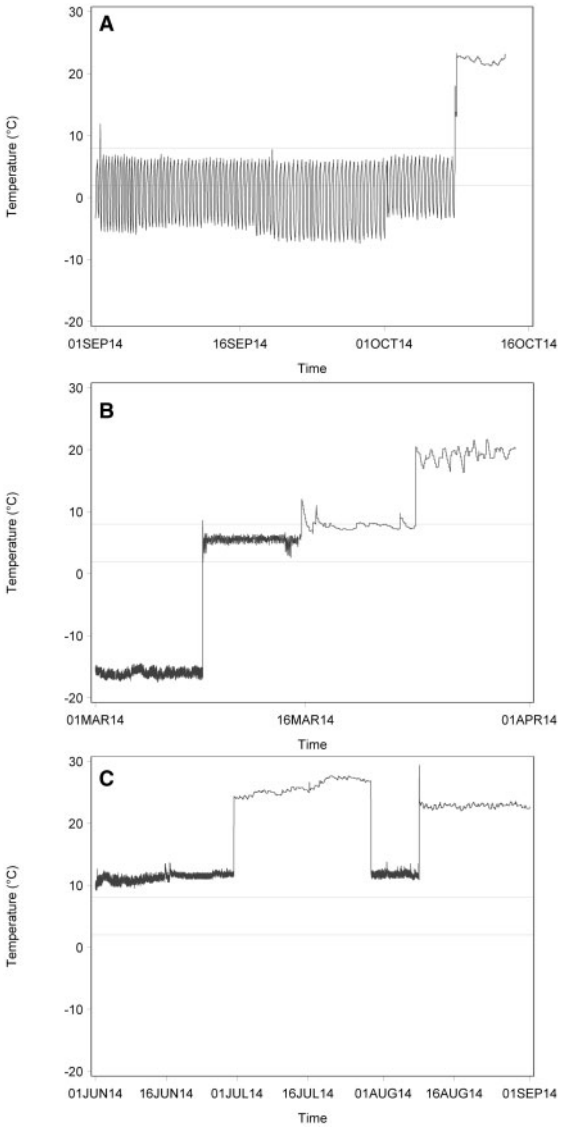



The proportion of total storage time between 2° and 8°C (54.8%) is indicated by dark grey and the proportion below 0°C (1.7%) and above 25°C (0.04%) by light grey.

Antibodies against bDMARDs have been found in adalimumab (6–28%) [23–25], but less data is available for the relatively newer bDMARDs abatacept, certolizumab pegol and golimumab [26, 27]. Antibodies against etanercept were all non-neutralizing and only detected in a small proportion of patients or not detected at all, suggesting that immunogenicity may be a less important issue for etanercept [28, 29]. ADAs in reaction to bDMARDs can reduce serum drug levels by directly inhibiting binding of the drug with the target or by formation of drug immune complexes that accelerate drug clearance. This may reduce its effectiveness and might induce adverse events, such as a severe allergic reaction or an immune response to the bDMARD that induces autoimmunity [11].

Storage outside the recommended temperature range could be due to a number of reasons. Patients can store their bDMARD in the refrigerator as instructed, but consumer refrigerators are usually not equipped with a temperature control alarm system and are not solely used for medication storage. Furthermore, older refrigerators or refrigerators with a less advanced cooling system and low airflow could have a greater variation in temperature control [30] (Fig. 2A). The bottom and upper shelf of the fridge might be cooler or warmer than other central parts of the refrigerator [31]. Our findings also suggest that bDMARDs are sometimes stored outside a refrigerator for short or longer periods (Fig. 2B and C), which is in line with what others have reported [32]. Information regarding the consequences of storage outside the SmPC-recommended temperature range for the product is limited and difficult to obtain for patients and caregivers [33]. It has been widely acknowledged that temperature fluctuations increase the formation of protein aggregates and affect the product quality [34]. We found that 24.3% of patients store bDMARDs below 0°C with a median duration of 3.7 h and with median number of excursions below 0°C of 3, which would expose bDMARDs to very low temperatures for a long time.

**Fig. 2** Storage temperature patterns among patients that stored bDMARDs at home




Examples of deviation patterns from the SmPC-recommended temperature range among patients who did not store bDMARDs within the SmPC-recommended temperature range (depicted by the horizontal lines). (A) A saw-tooth graph with multiple cycles of temperature rise and drop. This is in contrast with the examples B and C, which represent longer storage periods below 0°C (B) and at room temperature or above 25°C (C) before returning to storage temperatures close to or between 2°C and 8°C. bDMARD: biologic DMARD; SmPC: summary of product characteristics.

To our knowledge, this is the first study that monitors temperature-sensitive drugs for the complete storage time

of a single dispensing at home. Patients included were representative of the bDMARDs user population because bDMARDS are only dispensed from hospital-based pharmacies in the Netherlands, and only 13% of patients were lost to follow-up. Patient characteristics of those lost to follow-up did not differ from the study population. Limitations of this study were first the lack of information on patients' reasons for storing bDMARDs outside the recommended temperature range, such as due to travelling or accidental storage in the freezer. We also had no information on the exact moment of drug administration. The temperature logger was fixed to the secondary packaging and did not measure temperatures of each individual syringe or prefilled pen. Patients could have taken out one or more syringes or prefilled pens and had these stored elsewhere before injection. This would result in an underestimation of the number of patients who stored bDMARDs outside the SmPC-recommended temperature range. Further, storage time was defined as a period of the whole measurement time. Our definition allowed for less than 48 h outside the 2°C and 8°C temperature range without excursions of 2 h or longer below 0°C or above 25°C. This could have excluded actual storage time for a longer period than 12 h above 15°C. Our definition corrected for a subsequent period of cool storage of at least 48 h, which could have underestimated the duration of storage time outside the SmPC-recommended storage time. Last, the fact that measured temperature changes may not reflect the product temperature inside the package is a limitation. The insulation properties of the package, syringe and prefilled pen protect from short-term exposure to high and low temperatures. To account for possible delay in temperatures becoming equal between package and product, we applied the criterion that the bDMARD had to be stored for at least 2 h below 0°C or above 25°C.

In conclusion, storage conditions of bDMARDs outside the SmPC-recommended storage temperature range were observed in the majority of patients. To what extent moderate and extreme deviations in storage temperatures could affect product quality and influence efficacy and the occurrence of side-effects of the bDMARDs needs further investigation.

## Acknowledgements

We thank all participating pharmacies for their work and commitment during this study. We also thank the Confrérie Clinique B.V. in Eindhoven, The Netherlands, for technical assistance and use of the Mediccine technology for our investigations.

*Funding:* This work was supported by Achmea health insurances. Achmea was not involved in the design of the study, the data collection, analysing and interpreting of the results or writing of the manuscript and had no influence in the decision to submit the final paper.

*Disclosure statement:* The authors have declared no conflicts of interest.

## Supplementary data

Supplementary data are available at *Rheumatology* Online.

## References

1 Lawrence S, Lahteenmaki R. Public biotech 2013—the numbers. Nat Biotechnol 2014;32:1–8.

2 Weinblatt ME, Keystone EC, Furst DE *et al*. Long term efficacy and safety of adalimumab plus methotrexate in patients with rheumatoid arthritis: ARMADA 4 year extended study. Ann Rheum Dis 2006;65:753–9.

3 Pope JE, Haraoui B, Thorne JC *et al*. The Canadian methotrexate and etanercept outcome study: a randomised trial of discontinuing versus continuing methotrexate after 6 months of etanercept and methotrexate therapy in rheumatoid arthritis. Ann Rheum Dis 2014;73:2144–51.

4 van der Heijde D, Klareskog L, Rodriguez-Valverde V *et al*. Comparison of etanercept and methotrexate, alone and combined, in the treatment of rheumatoid arthritis: two-year clinical and radiographic results from the TEMPO study, a double-blind, randomized trial. Arthritis Rheum 2006;54:1063–74.

5 Kameda H, Kanbe K, Sato E *et al*. Continuation of methotrexate resulted in better clinical and radiographic outcomes than discontinuation upon starting etanercept in patients with rheumatoid arthritis: 52-week results from the JESMR study. J Rheumatol 2011;38:1585–92.

6 Strangfeld A, Hierse F, Kekow J *et al*. Comparative effectiveness of tumour necrosis factor alpha inhibitors in combination with either methotrexate or leflunomide. Ann Rheum Dis 2009;68:1856–62.

7 Neovius M, Arkema EV, Olsson H *et al*. Drug survival on TNF inhibitors in patients with rheumatoid arthritis comparison of adalimumab, etanercept and infliximab. Ann Rheum Dis 2013;74:354–60.

8 Hetland ML, Christensen IJ, Tarp U *et al*. Direct comparison of treatment responses, remission rates, and drug adherence in patients with rheumatoid arthritis treated with adalimumab, etanercept, or infliximab: results from eight years of surveillance of clinical practice in the nationwide Danish DANBIO registry. Arthritis Rheum 2010;62:22–32.

9 Vincent FB, Morand EF, Murphy K *et al*. Antidrug antibodies (ADAb) to tumour necrosis factor (TNF)-specific neutralising agents in chronic inflammatory diseases: a real issue, a clinical perspective. Ann Rheum Dis 2013;72:165–78.

10 Joubert MK, Luo Q, Nashed-Samuel Y, Wypych J, Narhi LO. Classification and characterization of therapeutic antibody aggregates. J Biol Chem 2011;286:25118–33.

11 van Schouwenburg PA, Rispens T, Wolbink GJ. Immunogenicity of anti-TNF biologic therapies for rheumatoid arthritis. Nat Rev Rheumatol 2013;9:164–72.

12 Garces S, Demengeot J, Benito-Garcia E. The immunogenicity of anti-TNF therapy in immune-mediated inflammatory diseases: a systematic review of the literature with a meta-analysis. Ann Rheum Dis 2012;72:1947–55.

13 Rosenberg AS. Effects of protein aggregates: an immunologic perspective. AAPS Journal 2006;8:E501–7.

14 Enbrel® SmPC, Pfizer Limited. http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/000262/WC500027361.pdf (14 May 2014, date last accessed).

15 Humira® SmPC, AbbVie Ltd. http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/000481/WC500050870.pdf (14 May 2014, date last accessed).

16 Simponi® SmPC, Janssen Biologics B.V. http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/000992/WC500052368.pdf (14 May 2014, date last accessed).

17 Cimzia® SmPC, UCB Pharma S.A. http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/001037/WC500069763.pdf (14 May 2014, date last accessed).

18 Orencia® SmPC, Bristol-Myers Squibb Pharma EEIG http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/000701/WC500048935.pdf (14 May 2014, date last accessed).

19 European Commission. Guidelines on Good Distribution Practice of Medicinal Products for Human Use, OJ C 343. 2013. http://ec.europa.eu/health/human-use/good_distribution_practice/index_en.htm (28 October 2014, date last accessed).

20 Cuellar MJ, Marco JL, Perez-Castello I, Castello Escriva A. Quality of storage of thermolabile drugs in patients' homes. Rev Calid Asist 2010;25:64–9.

21 Marco Garbayo JL, Cuellar Monreal MJ, Perez Castello I *et al*. Cold chain for the storage of heat-labile drugs in the home. Pharmaceutical Care Espana 2008;10:40–3.

22 Confrérie Clinique. SafeRx Temperature Logging System. 2015. http://www.confrerie-clinique.com/products/tempos/ (27 September 2014, date last accessed).

23 van de Putte LB, Atkins C, Malaise M *et al*. Efficacy and safety of adalimumab as monotherapy in patients with rheumatoid arthritis for whom previous disease modifying antirheumatic drug treatment has failed. Ann Rheum Dis 2004; 63:508–16.

24 Chen DY, Chen YM, Tsai WC *et al*. Significant associations of antidrug antibody levels with serum drug trough levels and therapeutic response of adalimumab and etanercept treatment in rheumatoid arthritis. Ann Rheum Dis 2013;74:e16.

25 Bartelds GM, Krieckaert CL, Nurmohamed MT *et al*. Development of antidrug antibodies against adalimumab and association with disease activity and treatment failure during long-term follow-up. JAMA 2011;305:1460–8.

26 Jani M, Barton A, Warren RB, Griffiths CE, Chinoy H. The role of DMARDs in reducing the immunogenicity of TNF inhibitors in chronic inflammatory diseases. Rheumatology 2014;53:213–22.

27 Nash P, Nayiager S, Genovese MC *et al*. Immunogenicity, safety, and efficacy of abatacept administered subcutaneously with or without background methotrexate in patients with rheumatoid arthritis: results from a phase III, international, multicenter, parallel-arm, open-label study. Arthritis Care Res 2013;65:718–28.

28 Dore RK, Mathews S, Schechtman J *et al*. The immunogenicity, safety, and efficacy of etanercept liquid administered once weekly in patients with rheumatoid arthritis. Clin Exp Rheumatol 2007;25:40–6.

29 Wolbink GJ, Aarden LA, Dijkmans BA. Dealing with immunogenicity of biologicals: assessment and clinical relevance. Curr Opin Rheumatol 2009;21:211–5.

30 Chojnacky M, Strouse G. Thermal analysis of refrigeration systems used for vaccine storage: report on pharmaceutical grade refrigerator and household refrigerator/freezer. NISTIR 7753 2010;1–59.

31 George RM, Burgess PJ, Thorn RD. Reducing food waste through the chill chain. Waste & Resources Action Programme (WRAP), 2010:1–95.

32 De Bolle L, Mehuys E, Adriaens E *et al*. Home medication cabinets and self-medication: a source of potential health threats? Ann Pharmacother 2008;42:572–9.

33 Cohen V, Jellinek SP, Teperikidis L, Berkovits E, Goldman WM. Room-temperature storage of medications labeled for refrigeration. Am J Health Syst Pharm 2007;64:1711–5.

34 Carpenter JF, Randolph TW, Jiskoot W *et al*. Overlooking subvisible particles in therapeutic protein products: gaps that may compromise product quality. J Pharm Sci 2009;98:1201–5.