



## Step forward in monitoring biological therapies

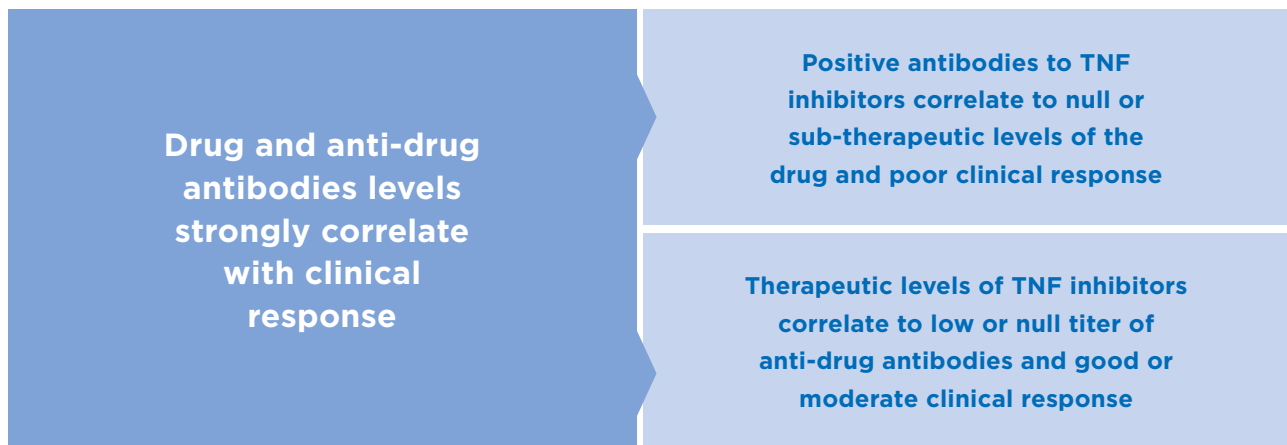
Efficient and high-quality testing for  
drug levels and immunogenicity

DRUG MONITORING

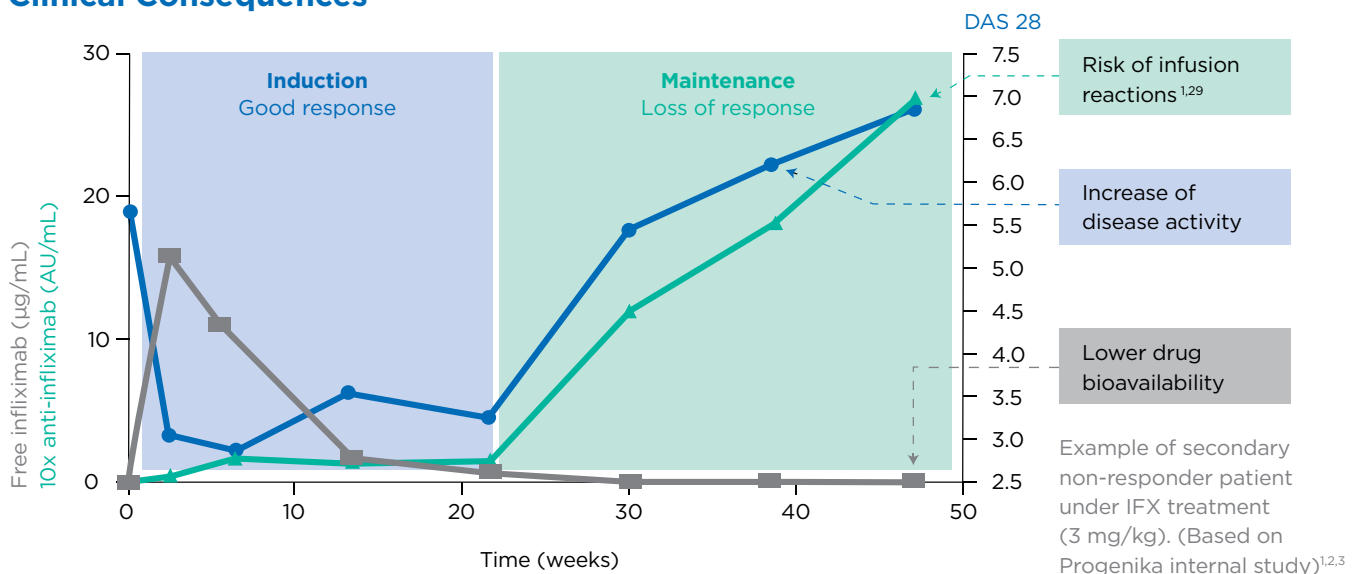
# Therapeutic drug monitoring: a real need

Therapeutic drug monitoring is being increasingly adopted to try to optimize patients outcomes, particularly during maintenance treatment.<sup>41</sup>

## Correlation between DL/ADA levels and clinical response<sup>3,27,28,33,37</sup>



## Clinical Consequences



# Testing for drug levels and immunogenicity

Easy-to-use ELISA kits for routine use in clinical laboratories.



**Quantitative determination of drug levels and anti-drug antibodies levels for the main biological treatments in different therapy areas**

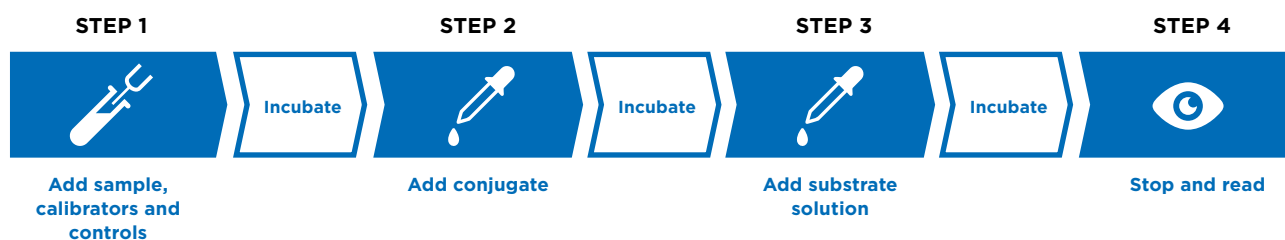
## Optimized methodology

- Multiple configurations. Removable strips
- Manual or automated mode
- Quick procedure: 2 hr 30 min
- Microplate precoated and ready-to-use reagents

## High quality for reliable results

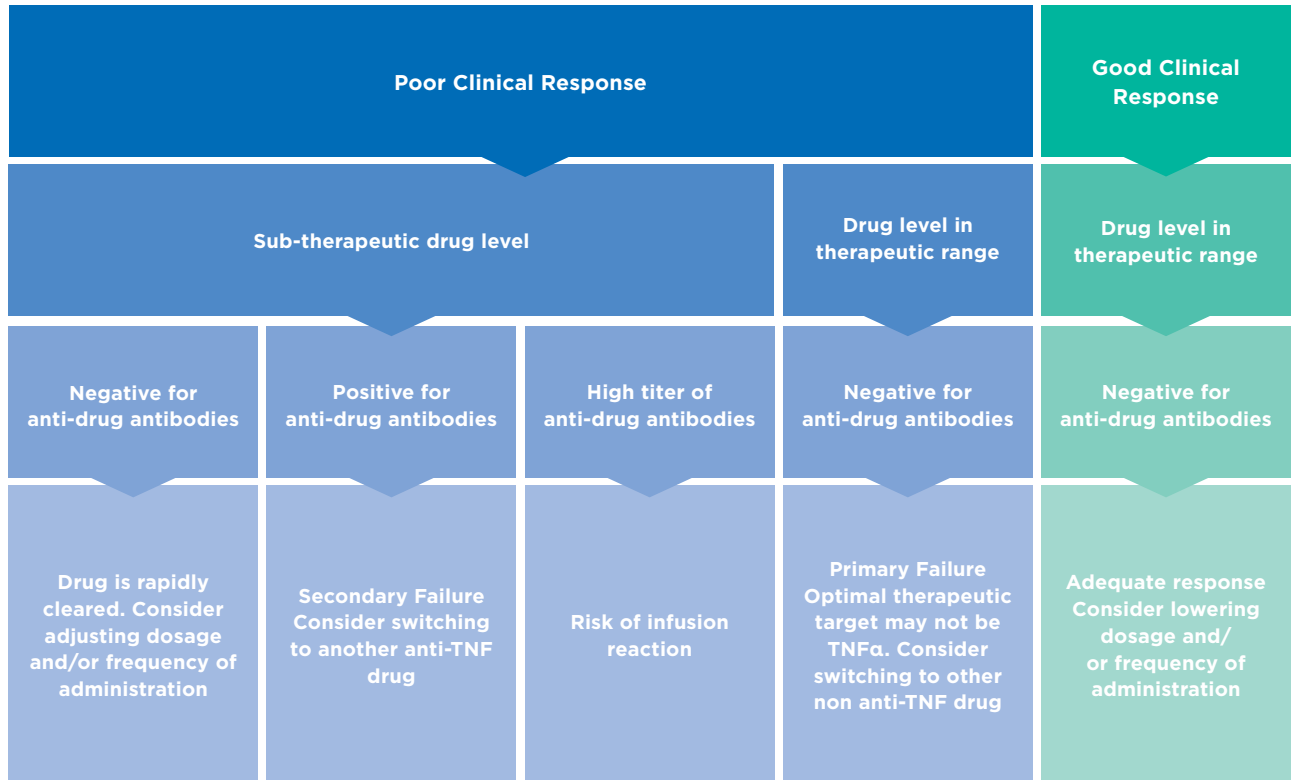
- Highly qualified professionals
- Supported by a large number of peer-reviewed articles
- High specificity and sensitivity
- Easy data interpretation

## Simple Procedure



**Quick procedure: 2 hours 30 minutes**  
**Hands-on time: 30 minutes**  
**4 simple steps**

## Algorithm for Patient Management



Illustrative internal algorithm for patient management using drug levels and immunogenicity testing. Not for use as sole input in clinical decisions. Based on published literature<sup>1,3,35,36,39</sup>

## Main benefits of therapeutic drug monitoring

**By providing TDM tools, clinicians may improve patient treatment strategy, reducing the risk of inadequate treatments, inappropriate dosages and side effects.**<sup>7,31,35,36,40,42</sup>

It is widely accepted that there is a correlation between drug levels and therapeutic response. In consequence, drug monitoring and, if appropriate, tests for antibodies, may provide a more accurate analysis and help to adjust dosage in a personalized therapy strategy.<sup>7,35,42</sup>

TDM may shed light on the main situations encountered in the clinical practice: primary treatment failure, inadequate treatment response, adverse reaction to the injection, or secondary loss of response.<sup>31,36,40,42</sup>

**Working together to administer the proper dose for the optimal treatment, resulting in efficient use of money**<sup>15,30,32,34,38</sup>

A lack of information about serum drug levels and ADA can lead to non-optimal clinical treatment decisions and lead to unnecessary costs.<sup>15</sup>

In consequence, a test-based strategy with TDM of anti-TNF is more cost-effective than an empirical strategy in both IBD and RA patients, with no negative impact on efficacy.<sup>30,34,38</sup>

TDM should be taken into consideration by physicians and healthcare authorities to guide decision-making in clinical practice and to reduce the costs of healthcare.<sup>38</sup>

### Main peer-reviewed articles using Promonitor kits

1. Pascual-Salcedo D, et al. Influence of immunogenicity on the efficacy of long-term treatment with infliximab in rheumatoid arthritis. *Rheumatology* 2011; 50:1445-1452.
2. Plasencia C, et al. Influence of immunogenicity on the efficacy of longterm treatment of spondyloarthritis with infliximab. *Ann Rheum Dis.* 2012;71(12):1955-60.
3. Rosas J, et al. Clinical relevance of monitoring serum levels of adalimumab in patients with rheumatoid arthritis in daily practice. *Clin Exp Rheumatol.* 2014;32(6):942-8.
4. Sanmarti R, et al. Towards optimal cut-off trough levels of adalimumab and etanercept for a good therapeutic response in rheumatoid arthritis. Results of the INMUNOREMAR study. *Ann Rheum Dis.* 2015;74(8):e42.
5. Jani M, et al. Clinical utility of random anti-tumour necrosis factor drug testing and measurement of anti-drug antibodies on long-term treatment response in rheumatoid arthritis. *Lancet.* 2015;385 Suppl 1:S48.
6. Chen DY, et al. Drug trough levels predict therapeutic responses to dose reduction of adalimumab for rheumatoid arthritis patients during 24 weeks of follow-up. *Rheumatology (Oxford).* 2016 ;55(1):143-8.
7. Chen DY, et al. Immunogenicity, drug trough levels and therapeutic response in patients with rheumatoid arthritis or ankylosing spondylitis after 24-week golimumab treatment. *Ann Rheum Dis.* 2015;74(12):2261-4.
8. Schmitz EM, et al. Therapeutic drug monitoring of infliximab: performance evaluation of three commercial ELISA kits. *Clin Chem Lab Med.* 2016;54(7):1211-9.
9. Llinares-Tello F, et al. Analytical and clinical evaluation of a new immunoassay for therapeutic drug monitoring of etanercept. *Clin Chem Lab Med.* 2015;53(10):e279-82.
10. Valor L, et al. Investigating the link between disease activity and infliximab serum levels in rheumatoid arthritis patients. *Clin Exp Rheumatol.* 2015;33(6):805-11.
11. Martin S, et al. Comparison study of two commercially available methods for the determination of golimumab and anti-golimumab antibody levels in patients with rheumatic diseases. *Clin Chem Lab Med.* 2015 ;53(11):e297-9.
12. Zisapel M, et al. Prevalence of TNF- $\alpha$  blocker immunogenicity in psoriatic arthritis. *J Rheumatol.* 2015;42(1):73-8.
13. Almirall M, et al. Drug levels, immunogenicity and assessment of active sacroiliitis in patients with axial spondyloarthritis under biologic tapering strategy. *Rheumatol Int.* 2016;36(4):575-8.
14. Siczekowska J, et al. Switching Between Infliximab Originator and Biosimilar in Paediatric Patients with Inflammatory Bowel Disease. Preliminary Observations. *J Crohns Colitis.* 2016;10(2):127-32.
15. Laine J, et al. Cost-effectiveness of routine measuring of serum drug concentrations and anti-drug antibodies in treatment of rheumatoid arthritis patients with TNF- $\alpha$  blockers. *Biologics.* 2016;10:67-73.
16. Elberdín L, et al. Positive correlation between etanercept concentration and the decrease in Psoriasis Area and Severity Index scale value. *Int J Clin Pharm.* 2016;38(5):1142-8.
17. Marini JC, et al. Comparisons of serum infliximab and antibodies-to-infliximab tests used in inflammatory bowel disease clinical trials of Remicade®. *AAPS J.* 2017;19(1):161-171.
18. Ghia C, et al. Analytical and Clinical Evaluation of an Immunoassay for Estimating Immunogenicity of Infliximab and Etanercept in Indian Population. *J Assoc Physicians India.* 2016;64(9):14-17.
19. Chimenti MS, et al. Long-term treatment with adalimumab in psoriatic arthritis: serum adalimumab concentration, immunogenicity and the link with clinical response. *J Int Med Res.* 2016;44(1 suppl):48-52.
20. Burmester GR, et al. Low immunogenicity of tocilizumab in patients with rheumatoid arthritis. *Ann Rheum Dis.* 2017;76(6):1078-1085.
21. Ruiz-Argüello MB, et al. Antibodies to infliximab in Remicade-treated rheumatic patients show identical reactivity towards biosimilars. *Ann Rheum Dis.* 2016;75(9):1693-6.
22. Cordero-Coma M, et al. Adalimumab for Treatment of Noninfectious Uveitis: Immunogenicity and Clinical Relevance of Measuring Serum Drug Levels and Antidrug Antibodies. *Ophthalmology.* 2016 ;123(12):2618-2625.
23. Manriquez J, et al. Determination of adalimumab and etanercept trough levels and drug antibodies in long-term psoriasis treatment: a single-centre cohort study. *Clin Exp Dermatol.* 2017;42(1):14-20.
24. Ruiz-Argüello MB, et al. Infliximab therapeutic drug monitoring test validated for measuring CT-P13 and SB2 biosimilars. *J Crohns Colitis* 2017. 2016;75:1693-6
25. Fiorino G, et al. Full interchangeability in regards to immunogenicity between the infliximab reference biologic and biosimilars CT-P13 and SB2 in inflammatory bowel disease. *Inflamm Bowel Dis.* 2017. 2018; 24:601-606
26. Fiorino G, et al. Letter: immunogenicity of infliximab originator vs. CT-P13 in IBD patients. *Aliment Pharmacol Ther.* 2017;46(9):903-905.
27. Balsa A, et al. Drug immunogenicity in patients with inflammatory arthritis and secondary failure to tumour necrosis factor inhibitor therapies: the REASON study. *Rheumatology (Oxford).* 2018. 2018;57:688-693

### Other peer-reviewed articles mentioned in this brochure

28. Radstake TR, et al. Formation of antibodies against infliximab and adalimumab strongly correlates with functional drug levels and clinical responses in rheumatoid arthritis. *Ann Rheum Dis.* 2009;68(11):1739-45.
29. Steenholdt C, et al. Severe infusion reactions to infliximab: aetiology, immunogenicity and risk factors in patients with inflammatory bowel disease. *Aliment Pharmacol Ther.* 2011;34(1):51-8.
30. Velayos FS, et al. A test-based strategy is more cost effective than empiric dose escalation for patients with Crohn's disease who lose responsiveness to infliximab. *Clin Gastroenterol Hepatol.* 2013 ;11(6):654-66.
31. Mulleman D, et al. Should anti-TNF- $\alpha$  drug levels and/or anti-drug antibodies be assayed in patients treated for rheumatoid arthritis? *Joint Bone Spine.* 2012;79(2):109-12.
32. Kriekaert CL, et al. Personalised treatment using serum drug levels of adalimumab in patients with rheumatoid arthritis: an evaluation of costs and effects. *Ann Rheum Dis.* 2015;74(2):361-8.
33. Nanda KS, et al. Impact of antibodies to infliximab on clinical outcomes and serum infliximab levels in patients with inflammatory bowel disease (IBD): a meta-analysis. *Am J Gastroenterol.* 2013;108(1):40-7.
34. Steenholdt C, et al. Individualised therapy is more cost-effective than dose intensification in patients with Crohn's disease who lose response to anti-TNF treatment: a randomised, controlled trial. *Gut.* 2014;63(6):919-27.
35. Wendling D, et al. Recommendations of the French Society for Rheumatology (SFR) on the everyday management of patients with spondyloarthritis. *Joint Bone Spine.* 2014;81(1):6-14.
36. Amiot A, et al. Therapeutic drug monitoring is predictive of loss of response after de-escalation of infliximab therapy in patients with inflammatory bowel disease in clinical remission. *Clin Res Hepatol Gastroenterol.* 2016;40(1):90-8.
37. Thomas SS, et al. Comparative Immunogenicity of TNF Inhibitors: Impact on Clinical Efficacy and Tolerability in the Management of Autoimmune Diseases. A Systematic Review and Meta-Analysis. *BioDrugs.* 2015;29(4):241-58.
38. Martelli L, et al. Cost-effectiveness of drug monitoring of anti-TNF therapy in inflammatory bowel disease and rheumatoid arthritis: a systematic review. *J Gastroenterol.* 2017;52(1):19-25.
39. Sandborn WJ. Crohn's disease evaluation and treatment: clinical decision tool. *Gastroenterology.* 2014;147(3):702-5.
40. Melmed GY, et al. Appropriateness of Testing for Anti-Tumor Necrosis Factor Agent and Antibody Concentrations, and Interpretation of Results. *Clin Gastroenterol Hepatol.* 2016;14(9):1302-9.
41. Harbord M, et al. Third European Evidence-based Consensus on Diagnosis and Management of Ulcerative Colitis. Part 2: Current Management. *J Crohns Colitis.* 2017;11(7):769-784.
42. Feuerstein JD, et al. American Gastroenterological Association Institute Guideline on Therapeutic Drug Monitoring in Inflammatory Bowel Disease. *Gastroenterology.* 2017;153(3):827-834.
43. Ruiz-Argüello MB, et al. Adalimumab therapeutic drug monitoring test validated for measuring ABP 501 biosimilar. *J Crohns Colitis.* 2019;13(1):S265-266.
44. Ruiz-Argüello MB, et al. Validation of a therapeutic drug monitoring test to measure the adalimumab biosimilar SB5 in comparison with the reference adalimumab. *J Crohns Colitis.* 2019;13(1):S324.

## Manual or Automated Mode

- Promonitor kits can be fully automated in any open ELISA processor, leading to an increase in productivity and reliability
- Grifols provides adapted protocols for Triturus and is continuously working on the adaptation to other instruments
- Tests can also be performed manually (2 hours 30 min or 1 hour 45 min) with minimal hands-on time (30 min) and the only platform required is a microplate reader

Tests can be fully automated in Triturus, SQII or any ELISA open processor

## Biosimilars

Evaluation studies have demonstrated that Promonitor kits are able to quantify the following biosimilars and the corresponding anti-biosimilar antibodies <sup>21, 24, 25, 26, 43, 44</sup> :

<b>Infliximab</b>	Remsima/Inflectra (CT-P13) Flixabi (SB2)	<b>Etanercept</b>	Benepali (SB4) Erelzi (GP 2015)
<b>Adalimumab</b>	Amgevita (ABP 501) Imraldi (SB5) Hyrimoz (GP 2017)	<b>Rituximab</b>	Truxima (CT-P10)

## Diagnostic Service

Grifols is offering TDM testing services in its facilities in Europe and North America. An easy-to-use sample collection and shipping service is provided (available in US). Physicians receive a complete report detailing results and reference values.



San Marcos, TX, US



Derio, Spain

## Current portfolio

Promonitor Infliximab  
 Promonitor anti-Infliximab  
 Promonitor Adalimumab  
 Promonitor anti-Adalimumab  
 Promonitor Etanercept  
 Promonitor anti-Etanercept  
 Promonitor Rituximab

Promonitor anti-Rituximab  
 Promonitor Golimumab  
 Promonitor anti-Golimumab  
 Promonitor Vedolizumab  
 Promonitor anti-Vedolizumab  
 Promonitor Ustekinumab  
 Promonitor anti-Ustekinumab

## Under development

Promonitor Tocilizumab\*  
 Promonitor anti-Tocilizumab\*

\*Already available for sale for RUO

Product registration and availability vary by country. Ask your local Grifols representative for more information.

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