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## INTRODUCTION

A growing number of medicines are based on biological molecules such as proteins and monoclonal antibodies. These novel drugs have resulted in new, more effective treatments for a number of serious conditions. Yet sometimes these medicines trigger a response from the patient's immune system, which can decrease the effectiveness of the drug or cause severe side effects.

The aim of the IMI-founded ABIRISK project **"Anti-Biopharmaceutical Immunization: Prediction and Analysis of Clinical Re to Minimize the Risk",** is to shed new light on the factors behind this immune response. The project, which represents the first concerted effort to solve this problem, officially kicked off March 1st, 2012. ABIRISK project will aid in the creation of new, safer **biopharmaceuticals (BPs)** and also generate tools to determine how individual patients are likely to respond to them both in clinical trials and after release to the market.

The ABIRISK consortium (presently made up of thirty-five partners, twenty-four of which are academic institutions, nine are EFPIA member companies and two are small and medium enterprises, with thirteen countries represented), has been designed to meet all of these requirements in order to target three types of disorders: **Hemophilia A, Multiple sclerosis and Inflammatory diseases: inflammatory rheumatisms (including rheumatoid arthritis) and inflammatory bowel diseases.**

ABIRISK Project will collect data both retrospectively from patients suffering from various types of diseases and treated with various BPs at European centers with a high level of experience in clinical research and will prospectively recruit additional patients in dedicated studies during the 5 years of this program. Guidelines and Standard Operating Protocols for the study of anti-drug immunization will be established and used to standardize the collection of prospective data from these patients.

ABIRISK Project thus represents a unique opportunity to create an interdisciplinary task force of clinical centers especially designed to study immune responses against biopharmaceuticals.

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# WELCOME

**Dear Reader,**

We would like to welcome you to the January 2017 issue of the **ABIRISK Scientific Newsletter**. The Scientific Newsletter gives you a monthly update on the most relevant literature related to ABIRISK topics published around the globe, both inside and outside ABIRISK consortium.

Each month we draw your attention to a selection of articles that we think make a difference in their respective fields.

In addition, you will find in this issue some regulatory news on biopharmaceuticals

We look forward to your visit on **ABIRISK** website for more information and updates on the program.

Enjoy reading !

Best wishes

***The ABIRISK management team***

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# LITERATURE

## This month's selected articles

Both papers demonstrate that the rate of immunogenicity is very low with tocilizumab, an anti-IL6R very broadly used in the treatment of RA: between 0 and 1.5%. It may explain that this drug is almost as efficient in monotherapy than in association with methotrexate. Interestingly, healthy donors show the same frequency of naive TCZ-specific and infliximab-specific CD4+ T cell precursors. Thus, the low prevalence of ADAs to TCZ might result from interleukin-6 blockade.

**Low immunogenicity of tocilizumab in patients with rheumatoid arthritis.**
Burmester GR, Choy E, Kivitz A, Ogata A, Bao M, Nomura A, Lacey S, Pei J, Reiss W, Pethoe-Schramm A, Mallalieu NL, Wallace T, Michalska M, Birnboeck H, Stubenrauch K, Genovese MC.
Ann Rheum Dis. 2016 Dec 22.

**Immunogenicity of tocilizumab in patients with rheumatoid arthritis.**
Sigaux J, Hamze M, Daien C, Morel J, Krzysiek R, Pallardy M, Maillere B, Mariette X, Miceli-Richard C.
Joint Bone Spine. 2017 Jan;84(1):39-45.

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## Immunogenicity

Non-neutralizing antibodies against factor VIII and risk of inhibitor development in patients with severe hemophilia A.
Cannavò A, Valsecchi C, Garagiola I, Palla R, Mannucci PM, Rosendaal FR, Peyvandi F.
Blood. 2016 Dec 29.

Immunogenicity of Human Interferon-Beta-Containing Pharmaceuticals.
Nazarov VD, Lapin SV, Mazing AV, Evdoshenko EP, Totolian AA.
Biochemistry (Mosc). 2016 Nov;81(11):1396-1400.

A Therapeutic Uricase with Reduced Immunogenicity Risk and Improved Development Properties.
Nyborg AC, Ward C, Zacco A, Chacko B, Grinberg L, Geoghegan JC, Bean R, Wendeler M, Bartnik F, O'Connor E, Gruia F, Iyer V, Feng H, Roy V, Berge M, Miner JN, Wilson DM, Zhou D, Nicholson S, Wilker C, Wu CY, Wilson S, Jermutus L, Wu H, Owen DA, Osbourn J, Coats S, Baca M.
PLoS One. 2016 Dec 21;11(12):e0167935.

Influence of anti-TNF immunogenicity on safety in rheumatic disease: a narrative review.
Matucci A, Cammelli D, Cantini F, Goletti D, Marino V, Milano GM, Scarpa R, Tocci G, Maggi E, Vultaggio A.
Expert Opin Drug Saf. 2016 Dec;15(sup1):3-10.

Influence of IL6R gene polymorphisms in the effectiveness to treatment with tocilizumab in rheumatoid arthritis.
Maldonado-Montoro M, Cañadas-Garre M, González-Utrilla A, Ángel Calleja-Hernández M.
Pharmacogenomics J. 2016 Dec 13.

Five-year Efficacy and Safety of Tocilizumab Monotherapy in Patients with Rheumatoid Arthritis Who Were Methotrexate- and Biologic-naive or Free of Methotrexate for 6 Months: the AMBITION Study.
Jones G, Wallace T, McIntosh MJ, Brockwell L, Gómez-Reino JJ, Sebba A.
J Rheumatol. 2016 Dec 1. pii: jrheum.160287.

## Methods

Development of Statistical Methods for Analytical Similarity Assessment.
Tsong Y, Dong X, Shen M.
J Biopharm Stat. 2016 Dec 15.

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Harmonization of Infliximab and Anti-Infliximab Assays Facilitates the Comparison Between Originators and Biosimilars in Clinical Samples.
Gils A, Van Stappen T, Dreesen E, Storme R, Vermeire S, Declerck PJ.
Inflamm Bowel Dis. 2016 Apr;22(4):969-75.

Rapid Test for Infliximab Drug Concentration Allows Immediate Dose Adaptation.
Van Stappen T, Bollen L, Vande Casteele N, Papamichael K, Van Assche G, Ferrante M, Vermeire S, Gils A.
Clin Transl Gastroenterol. 2016 Dec 8;7(12):e206.

## Biomarkers

Serum IL-33, a new marker predicting response to rituximab in rheumatoid arthritis.
Sellam J, Rivière E, Courties A, Rouzaire PO, Tolusso B, Vital EM, Emery P, Ferraciolli G, Soubrier M, Ly B, Hendel Chavez H, Taoufik Y, Dougados M, Mariette X.
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STAT6 and STAT1 Pathway Activation in Circulating Lymphocytes and Monocytes as Predictor of Treatment Response in Rheumatoid Arthritis.
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## Biosimilars

Infliximab Biosimilars in the Treatment of Inflammatory Bowel Diseases: A Systematic Review.
Radin M, Sciascia S, Roccatello D, Cuadrado MJ.
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The Role of Biosimilars in Inflammatory Bowel Disease.
Paramsothy S, Cleveland NK, Zmeter N, Rubin DT.
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Clinical Evaluation of Humira® Biosimilar ONS-3010 in Healthy Volunteers: Focus on Pharmacokinetics and Pharmacodynamics.
Dillingh MR, Reijers JA, Malone KE, Burggraaf J, Bahrt K, Yamashita L, Rehrig C, Moerland M.
Front Immunol. 2016 Nov 28;7:508.

## Rheumatoid Arthritis

Biological Agents In Rheumatoid Arthritis: A Cross-Link Between Immune Tolerance And Immune Surveillance.
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Risk of serious adverse effects of biological and targeted drugs in patients with rheumatoid arthritis: a systematic review meta-analysis.
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Rheumatology (Oxford). 2016 Dec 24.

A genetic risk score composed of rheumatoid arthritis risk alleles, HLA-DRB1 haplotypes, and response to TNFi therapy - results from a Swedish cohort study.
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Ceccarelli F, Massafra U, Perricone C, Idolazzi L, Giacomelli R, Tirri R, Russo R, Pistone G, Ruscitti P, Parisi S, Sainaghi PP, Cacciapaglia F, Zullo A, Marino V, Migliore A, Valesini G.
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Maintenance of efficacy and safety with subcutaneous golimumab in rheumatoid arthritis patients with low disease activity who previously received TNF inhibitors.
Wakabayashi H, Inada H, Nishioka Y, Hasegawa M, Sudo A, Nishioka K.
Clin Rheumatol. 2016 Dec 9.

IL-1 Inhibition in Systemic Juvenile Idiopathic Arthritis.
Giancane G, Minoia F, Davì S, Bracciolini G, Consolaro A, Ravelli A.
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Ombrello MJ, Arthur VL, Remmers EF, Hinks A, Tachmazidou I, Grom AA, Foell D, Martini A, Gattorno M, Özen S, Prahalad S, Zeft AS, Bohnsack JF, Ilowite NT, Mellins ED, Russo R, Len C, Hilario MO, Oliveira S, Yeung RS, Rosenberg AM, Wedderburn LR, Anton J, Haas JP, Rosen-Wolff A, Minden K, Tenbrock K, Demirkaya E, Cobb J, Baskin E, Signa S, Shuldiner E, Duerr RH, Achkar JP, Kamboh MI, Kaufman KM, Kottyan LC, Pinto D, Scherer SW, Alarcón-Riquelme ME, Docampo E, Estivill X, Gül A; British Society of Pediatric and Adolescent Rheumatology (BSPAR) Study Group, Inception Cohort of Newly Diagnosed Patients with Juvenile Idiopathic Arthritis (ICON-JIA) Study Group, Childhood Arthritis Prospective Study (CAPS) Group, Randomized Placebo Phase Study of Rilonacept in sJIA (RAPPORT) Investigators, Sparks-Childhood Arthritis Response to Medication Study (CHARMS) Group, Biologically Based Outcome Predictors in JIA (BBOP) Group., Langefeld CD, Thompson S, Zeggini E, Kastner DL, Woo P, Thomson W.
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Infection, malignancy, switching, biosimilars, antibody formation, drug survival and withdrawal, and dose reduction: what have we learned over the last year about tumor necrosis factor inhibitors in rheumatoid arthritis?
Ianculescu I, Weisman MH.
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Biological agents in polyarticular juvenile idiopathic arthritis: A meta-analysis of randomized withdrawal trials.
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## Inflammatory Bowel Disease

The biologics of ulcerative colitis.
Macaluso FS, Renna S, Orlando A, Cottone M.
Expert Opin Biol Ther. 2016 Dec 21:1-10.

Anti-Integrins in Ulcerative Colitis and Crohn's Disease: What Is Their Place?
Khanna R, Mosli MH, Feagan BG.
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Vedolizumab in the treatment of Crohn's disease.
Tarabar D, Hirsch A, Rubin DT.
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Editorial: adalimumab or infliximab as monotherapy, or in combination with an immunomodulator, in the treatment of Crohn's disease.
Christensen B, Sparrow MP.
Aliment Pharmacol Ther. 2017 Jan;45(1):178-179.

## Systemic lupus erythematosus

Targeting the interferon pathway with sifalimumab for the treatment of systemic lupus erythematosus.
Greth W, Robbie GJ, Brohawn P, Hultquist M, Yao B.
Immunotherapy. 2017 Jan;9(1):57-70.

## Multiple Sclerosis

Comparative effectiveness of interferons in relapsing-remitting multiple sclerosis: a meta-analysis of real-world studies.
Einarson TR, Bereza BG, Machado M.
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Natalizumab treatment of multiple sclerosis: new insights.
Delbue S, Comar M, Ferrante P.
Immunotherapy. 2016 Dec 22.

Depletion of CD52 positive cells inhibits the development of CNS autoimmune disease, but deletes an immune-tolerance promoting CD8 T cell population. Implications for secondary autoimmunity of alemtuzumab in multiple sclerosis.
von Kutzleben S, Pryce G, Giovannoni G, Baker D.
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Serum Lipid Profile Changes Predict Neurodegeneration in Interferon-B1a Treated Multiple Sclerosis Patients.
Uher T, Fellows K, Horakova D, Zivadinov R, Vaneckova M, Sobisek L, Tyblova M, Seidl Z, Krasensky J, Bergsland N, Weinstock-Guttman B, Havrdova E, Ramanathan M.
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Vitamin D supplementation reduces relapse rate in relapsing-remitting multiple sclerosis patients treated with natalizumab.
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New findings on inhibitor development: from registries to clinical studies.
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Giangrande P, Andreeva T, Chowdary P, Ehrenforth S, Hanabusa H, Leebeek FW, Lentz SR, Nemes L, Poulsen LH, Santagostino E, You CW, Clausen WH, Jönsson PG, Oldenburg J; Pathfinder™2 Investigators..
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## Opinions/Commentaries/ Across diseases reviews

Antibodies to watch in 2017.
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MAbs. 2016 Dec 14:0.

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Remarkable Pharmacokinetics of Monoclonal Antibodies: A Quest for an Explanation.
Reijers JA, Moerland M, Burggraaf J.
Clin Pharmacokinet. 2016 Dec 20

## REGULATION

### FDA

Guidance
Clinical Pharmacology Data to Support a Demonstration of Biosimilarity to a Reference Product

### EMA

Scientific guidance on post-authorisation efficacy studies - First version, adopted

Draft guideline on the clinical investigation of human normal immunoglobulin for intravenous administration (IVIg), draft: consultation open

Guideline on the principles of regulatory acceptance of 3Rs (replacement, reduction, refinement) testing approaches, adopted (updated)

Opinion/decision on a Paediatric investigation plan (PIP): Humira, Adalimumab
Therapeutic area: Dermatology/Immunology-Rheumatology-Transplantation/Ophthalmology/Gastroentology-Hepatology (updated)

Human medicines European public assessment report (EPAR): Simponi, golimumab
Revision: 26, Authorised

Biosimilar medicines (updated)

Clinical pharmacology and pharmacokinetics: questions and answers (updated)

Referral: Article 31 referrals, Factor VIII (updated)

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Workshop on qualification and reporting of physiologically-based pharmacokinetic (PBPK) modelling and simulation, European Medicines Agency, London, UK, From: 21-Nov-2016, To: 21-Nov-2016 (updated)

International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use guideline Q3C (R5) on impurities: guideline for residual solvents - Step 5, adopted (updated)

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