CURRENT OPINION

Drug Saf 2009; 32 (11): 995-1000
0114-5916/09/0011-0995/$49.95/0

Do Biological Medicinal Products Pose a Risk to the Environment?

A Current View on Ecopharmacovigilance

Thomas C. Kühler, Mikael Andersson, Gunnar Carlin, Ann Johnsson and *Lennart Åkerblom*

Medical Products Agency, Uppsala, Sweden

Abstract

The occurrence of active pharmaceutical substances in the environment is of growing concern. The vast majority of the compounds in question are of low molecular weight, intended for oral use and designed to tolerate, for example, the digestive enzymes in the upper alimentary tract, the harsh milieus found in the acidic stomach, or the microbe rich intestine. Accordingly, these xenobiotic compounds may, due to their inherent biological activity, constitute a risk to the environment.

Biological medicinal products, for example recombinant human insulin or monoclonal antibodies, however, are different. They are primarily made up of oligomers or polymers of amino acids, sugars or nucleotides and are thus readily metabolized. They are therefore generally not considered to pose any risk to the environment.

Certain classes of biological medicinal products, however, are associated with specific safety issues. Genetically modified organisms as vectors in vaccines or in gene therapy products have attracted much attention in this regard. Issues include the degree of attenuation of the live recombinant vaccine, replication restrictions of the vaccine vector, alteration of the host and tissue tropism of the vector, the possibility of reversion to virulence, and risk to the ecosystem.

In this review we discuss the fate and the potential environmental impact of biological medicinal products following clinical use from an ecopharmacovigilance point of view, and review relevant policy documents and regulatory statements.

The occurrence of active pharmaceutical ingredients and excipients, as well as their metabolites or conjugates, in the environment is of growing concern.[1-3] These compounds may reach different biotopes through sewage water either by sorption to sewage sludge, which is used as agricultural fertilizer, or by dilution into surface waters. Direct excretion onto grasslands by medicated animals held on pastures or spreading manure from medicated animals reared in-house constitute other major routes for distribution. Indeed, pharmaceuticals are found both in surface, ground and drinking water as well as in soil samples, albeit at low levels.

The vast majority of the compounds in question are of low molecular weight, approximately

500 Da, and designed for oral use. That is, they are intended to tolerate, for example, the digestive enzymes in the upper alimentary tract, the harsh milieus found in the acidic stomach, or the microbe-rich intestine. Accordingly, one would expect these compounds to have a chemical propensity to withstand other similar demanding settings outside the human or animal body.

For biological medicinal products, this does not necessarily hold true. Although there is no commonly accepted definition of biological medicinal products, we have used the criteria described in the EU pharmaceutical legislation.[4-6] Thus, in this review, we focus on high-molecular-weight compounds made up of oligomers or polymers of amino acids, sugars, nucleotides or combinations thereof. Individual building blocks are joined by amide, glucoside or phosphate ester bonds (figure 1), all of which are susceptible to chemical hydrolysis.

Examples of such compounds are recombinant human insulin for the treatment of diabetes mellitus or the humanized anti-tumor necrosis factor-α monoclonal antibodies for the treatment of rheumatoid arthritis and Crohn's disease. It is important to note that the definition of biological medicinal product used in this context excludes compounds such as antibiotics or steroid hormones.

Biological medicinal products are vulnerable to digestive enzymes and may serve as nutrient sources for micro-organisms. Hence, they are rarely, if at all, excreted and it is commonly accepted that they do not pose any obvious risks to the environment as reflected in the EU Environmental Risk Assessment guideline.[7] This guideline calls for the evaluation of environmental risk to be part of the market authorization application for medicinal products, but no such assessment is required for proteins or carbohydrates for example. For nucleic acid polymers, special considerations are needed whenever such products are carriers of genetic information, for example in the form of live vectors. These situations are dealt with in the EU guideline on Environmental Risk Assessment for Medicinal Products containing or consisting of genetically-modified organisms (GMOs).[8]

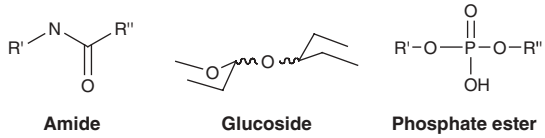

Fig. 1. Types of chemical bonds commonly found in biological medicinal products

While one could argue that the art of engineering associated with the production of drugs of low (classical) or high (biological) molecular weights may not necessarily differ, the consequences of accidental dissemination or intentional disposal of the latter into the environment may be substantial. This subject, however, is beyond the scope of the current review.

Ecopharmacovigilance[9] can be defined as the mapping of the route of entry of a pharmaceutical product into the distribution chain(s), including the spread, fate and biological impact on the ecosystem and human as well as animal health. This is a broader definition than that originally proposed by Keck.[10] Here, we discuss the fate and the potential environmental impact of biological medicinal products following clinical use from an ecopharmacovigilance point of view. We also present a review of pertinent policy documents and current regulatory statements relevant to the field.

1. Live Vector Vaccines and Safety Issues

Veterinary vaccines against infectious diseases containing live micro-organisms expressing an antigen of a heterologous infectious agent have been on the market in the EU since the beginning of year 2000. Several vaccines for human use are currently being evaluated in clinical trials but no marketing authorizations have as of yet (early 2009) been granted.

These veterinary vaccines are based on live recombinant canarypox or herpes viruses, and the European Medicines Agency (EMEA) has published a guideline for Live Recombinant Vector Vaccines for Veterinary Use.[11] In the development of live viral vaccines, different kinds of vectors are used, such as viral vectors with restricted replication in humans due to the species

barrier, e.g. avipox, and vectors that have been genetically engineered to be replication-incompetent such as adenoviral vectors.[12,13]

Specific safety issues for these vaccines include, for example, the level of attenuation of the live recombinant vaccine, the replication restriction of the vaccine vector and its design, the extent of immunity raised against the vector itself, alteration of the host and tissue tropism of the vector, the possibility of reversion to virulence, and the possibility of recombination with wild-type strains of the vector, to name but a few.[13] Other issues considered in the safety evaluation involve the method(s) of manufacturing, the containment principles, the technologies and practices that are implemented to prevent unintentional exposure to pathogens and toxins or their accidental release, as well as environmental risk(s). Additional requirements may be specified in the opinion preceding an approval of a GMO vector, e.g. test methods that can discriminate between wild-type virus and live recombinant vector vaccine, i.e. marker vaccines.

Replication-incompetent vector particles derived from lentiviruses can mediate transfer and expression of heterologous genes into a variety of cells. Unlike other retroviral vectors, lentiviral vectors can mediate gene transfer into non-dividing cells, such as lymphocytes, dendritic and nerve cells.[14] A new guideline describes quality aspects and non-clinical testing that may be relevant for lentiviral vectors that are intended for *ex vivo* or *in vivo* applications.[15] The biohazards associated with the contamination of the lentiviral vectors with a replication competent lentivirus are of concern as there remains a low risk of them contaminating lentiviral vector preparations. Therefore, tests should be used that can identify their presence.[15]

2. Environmental Risk Assessment

Current guidelines from the EMEA deal with the scientific principles and the methodologies to be used in the environmental risk assessment (ERA) of GMO-containing gene therapy medicinal products.[8,13] Guidance is given on how to apply the requirements given in the Directive 2001/18/EC regarding the deliberate release into the environment of GMOs.[16] The ERA should analyse whether there is a need for a risk management plan and if necessary devise appropriate risk mitigation methods.[8,16]

An ERA should be based both on documented evidence, including that derived from specific testing of the GMO-containing gene therapy product, and the 'precautionary principle'. The precautionary principle is defined in the Cartagena Protocol and aims at ensuring the safe transfer, handling and use of living modified organisms that may have an adverse effect on biodiversity and was adopted in Montreal in January 2000.[17,18] However, the EU Commission considers the precautionary principle to have a scope far wider than the environmental field and that it also covers the protection of human, animal and plant health. While it is also clear that it is a political prerogative to determine what an acceptable level of risk is, the EU Commission also states that the precautionary principle should not be a justification for ignoring scientific evidence.[8]

In the ERA, risks are identified and measures to reduce them defined and a conclusion on the acceptability of the (environmental) risk is made. The ERA should evaluate the characteristics of the GMO and its use in comparison with the corresponding wild-type counterpart present in the environment. The ERA should be current and any new information becoming available after a marketing authorization should be included in the monitoring plan. Depending on the outcome of the ERA, shedding data may also need to be included.

3. Shedding

Shedding is defined here as dissemination of a gene therapy product through excreta of the patient. A workshop was held in October 2007, on viral vector shedding, by the International Conference on Harmonisation Gene Therapy Discussion Group. The aim of the workshop was to provide a better understanding of the contribution of shedding studies to the benefit-risk assessment of gene therapy products. Points discussed in

relation to the design of non-clinical viral or vector shedding studies included relevance and selection of animal models, and advantages and disadvantages of assays used for detection of virus or vector shed into excreta. It was concluded that nucleic acid sequence-detecting and infectivity assays need to be developed.[19]

A calculation of environmental risk is based on the probability of transmission of the gene therapy medicinal product from the patient to third-party persons or animals. Therefore, shedding studies in a suitable animal model should be incorporated into the non-clinical medicinal product development programme.[8]

4. Determination of the Overall Risk of a Genetically-Modified Organism and Risk Management Plans

Adverse effects can occur directly or indirectly through mechanisms that may include the spread of the GMO in the environment, the transfer of the inserted genetic material to similar or dissimilar organisms whether genetically modified or not, phenotypic and genetic instability and interactions with other organisms.

Non-enveloped viruses are resistant and may be more difficult to inactivate using disinfectants and would persist longer in harsh environments outside the body, e.g. in sewage water or sludge. An assessment of the half-life of the GMO in the foreseen environment may therefore be necessary in order to address, for example, the persistence of a GMO.[7]

The final evaluation should be done as a summary of the overall risks that are connected to the specific gene therapy application. Also, a conclusion should be reached as to whether the overall environmental impact is acceptable or not.[7,8,16]

In the context of medicinal products, the environmental risk is the risk of transmission of the GMO to humans other than the intended person(s) or patient(s), to animals, or to the environment at large. Another risk may be posed by pathogens, which can arise by recombination with the original GMO.[8,13,16]

Scientific consideration should be given to identified or potential risks based on the ERA and virus shedding and its consequences.

The recent EU regulation on advanced therapies details post-authorization requirements.[20] This regulation covers cell and gene therapy and tissue-engineered products. It specifically requests the EMEA to draw up detailed guidelines relating to the post-authorization follow-up of efficacy and adverse reactions, as well as risk management.[21]

5. Discussion and Conclusion

EU pharmaceutical legislation requires drug developers to document the environmental consequences of the clinical use of a drug as part of the market authorization application. Such knowledge may then be used to arrive at informed and educated actions aimed at eliminating potential risks, if any. For example, the EU project KNAPPE (Knowledge and Need Assessment on Pharmaceutical Products in Environmental Waters) aims at identifying relevant priority actions to be taken in order to reduce the occurrence, impact and risk of medicinal products in the aquatic environment.[22]

Notwithstanding the above, it is important to stress that "… presence or absence …" (of an active pharmaceutical ingredient in the environment) should not be "… our litmus test … . Detection does not infer health risk and non-detection does not ensure safety."[23] We concur in that ecopharmacovigilance must not be driven by analytical capabilities but by scientific- and evidence-based risk assessments.

The average cost for developing a drug, whether it is a new chemical entity or a biological medicinal product, was recently estimated to be some $US160 million per year and the time from conception to fruition estimated to typically be 8 years, running the total cost to some $US1.3 billion.[24] The numbers take into account that seven or eight of ten drugs do fail during clinical development.[24,25] Hence, the drug discovery enterprise is an expensive high-risk venture with a high attrition rate. Considering that the current drug discovery pipeline does not meet society's

medical needs,[26,27] we note that striking the right balance between access to new medicines and the requirement for ecopharmacovigilance regulation will not be uncomplicated. On one side, society needs to cater for drugs for (unmet) medical needs; on the other side, society needs to protect the one and only habitat available to us as humans. Regarding the latter, the precautionary principle has been proposed as a means to safeguard the environment for present and future generations.[28]

When it comes to safeguarding the environment against the type of biological medicinal products discussed in this review, we argue that those in clinical use do not constitute a risk from an ecopharmacovigilance point of view. Compared with classical, low-molecular-weight drugs, they do not survive the passage through the human or animal body, and if they do, their chemical instability towards hydrolytic conditions and susceptibility to microbial breakdown render them harmless. The exception to the rule are GMOs for which ecopharmacovigilance measures are appropriate, as reflected in current legislation and by regulatory restrictions.

Acknowledgements

No sources of funding were used to assist in the preparation of this review. The authors have no conflicts of interest to declare that are directly relevant to the content of this review.

Dr Carlin's unexpected and sudden passing away during the final stages of preparation of this review is a sad loss to us and our workplace.

References

1. Carlsson C, Johansson A-K, Alvan G, et al. Are pharmaceuticals potent environmental pollutants? Part I: environmental risk assessments of selected active pharmaceutical ingredients. Sci Total Environ 2006; 364: 67-87
2. Carlsson C, Johansson A-K, Alvan G, et al. Are pharmaceuticals potent environmental pollutants? Part II: environmental risk assessments of selected pharmaceutical excipients. Sci Total Environ 2006; 364: 88-95
3. Jjemba PK. Pharma-ecology: the occurrence and fate of pharmaceuticals and personal care products in the environment. Hoboken (NJ): John Wiley & Sons, 2008
4. Directive 2001/83/EC of the European Parliament and of the Council of 6 November 2001 on the community code relating to medicinal products for human use [online]. Available from URL: http://ec.europa.eu/enterprise/pharmaceuticals/eudralex/vol1_en.htm [Accessed 2009 Aug 12]
5. Commission regulation (EC) no. 1084/2003 of 3 June 2003 concerning the examination of variations to the terms of a marketing authorisation for medicinal products for human use and veterinary medicinal products granted by a competent authority of a Member State [online]. Available from URL: http://ec.europa.eu/enterprise/pharmaceuticals/eudralex/vol1_en.htm [Accessed 2009 Aug 12]
6. Commission regulation (EC) no. 1085/2003 of 3 June 2003 concerning the examination of variations to the terms of a marketing authorisation for medicinal products for human use and veterinary medicinal products falling within the scope of Council regulation (EEC) no. 2309/93 [online]. Available from URL: http://ec.europa.eu/enterprise/pharmaceuticals/eudralex/vol1_en.htm [Accessed 2009 Aug 12]
7. Environmental risk assessment of medicinal product for human use. CHMP/SWP/4447/00 [online]. Available from URL: http://www.emea.europa.eu/pdfs/human/swp/444700en.pdf [Accessed 2009 Aug 12]
8. Guideline on environmental risk assessments for medicinal products consisting of, or containing, genetically modified organisms (GMOs). EMEA/CHMP/BWP/473191/2006 – Corr [online]. Available from URL: http://www.emea.europa.eu/pdfs/human/bwp/47319106en.pdf [Accessed 2009 Aug 12]
9. Daughton CG, Ruhoy IS. The afterlife of drugs and the role of pharmecovigilance. Drug Saf 2008; 31: 1069-82
10. Keck G. Teaching environmental toxicology for veterinary students and veterinarians: some new trends. J Vet Pharmacol Ther 2006; 29 Suppl. 1: 11-6
11. Guideline on live recombinant vector vaccines for veterinary use. EMEA/CVMP/004/04 [online]. Available from URL: http://www.emea.europa.eu/pdfs/vet/imp/000404en.pdf [Accessed 2009 Aug 12]
12. Concept paper on the development of a guideline on live recombinant vector vaccines. EMEA/CHMP/308139/2007 [online]. Available from URL: www.emea.europa.eu/pdfs/human/vwp/30813907en.pdf [Accessed 2009 Aug 12]
13. Guideline on scientific requirements for the environmental risk assessment of gene therapy medicinal products. EMEA/CHMP/GTWP/125491/2006 [online]. Available from URL: www.emea.europa.eu/pdfs/human/genetherapy/12549106en.pdf [Accessed 2009 Aug 12]
14. Naidini L, Blomer U, Gallay P, et al. In vivo gene delivery and stable transduction of nondividing cells by a lentiviral vector. Science 1996; 272: 263-7
15. Guideline on the development and manufacture of lentiviral vectors. CHMP/BWP/2458/03 [online]. Available from URL: http://www.emea.europa.eu/pdfs/human/bwp/245803en.pdf [Accessed 2009 Aug 12]
16. Directive 2001/18/EC of the European Parliament and of the Council on the deliberate release into the environment of genetically modified organisms [online]. Available from URL: http://eur-lex.europa.eu/ [Accessed 2009 Aug 12]
17. Communication from the Commission on the precautionary principle, COM (2000) 1 final, dated 2.02.2000 [online]. Available from URL: http://ec.europa.eu/environment/docum/20001_en.htm [Accessed 2009 Aug 12]

18. Convention on Biological Diversity. The Cartagena protocol on biosafety [online]. Available from URL: http://www.cbd.int/biosafety/ [Accessed 2009 Aug 12]
19. International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use. Communication paper: Gene Therapy Discussion Group meeting; Rotterdam, Oct 30-Nov 1, 2007. Addendum 1. Report: October 30, 2007 ICH workshop on viral/vector shedding [online]. Available from URL: http://www.ich.org/LOB/media/MEDIA4360.pdf [Accessed 2009 Aug 12]
20. The regulation on advanced therapies [online]. Available from URL: http://www.ec.europa.eu/enterprise/pharmaceuticals/advtherapies/index.htm [Accessed 2009 Aug 12]
21. European Medicines Agency, Committee for Medicinal Products for Human Use. Guideline on safety and efficacy follow-up: risk management of advanced therapy medicinal products [online]. Available from URL: http://www.emea.europa.eu/pdfs/human/advancedtherapies/14999508enfin.pdf [Accessed 2009 Aug 26]
22. KNAPPE homepage [online]. Available from URL: http://www.knappe-eu.org [Accessed 2009 Aug 12]
23. Halford B. Pharmaceutical pollution: pharmaceuticals have been finding their way into our environment for a long time, but just what are they doing there? Chem Eng News 2008; 86: 13-7
24. DiMasi JA, Grabowski HG. The cost of biopharmaceutical R&D: is biotech different? Manage Decis Econ 2007; 28: 469-79
25. DiMasi JA. Risks in new drug development: approval success rates for investigational drugs. Clin Pharmacol Ther 2001; 69: 297-307
26. Thomson Reuters. Thought leadership slides: clearly-presented data and analysis on recent trends and key aspects of the pharmaceutical industry you can use freely in your own presentations and reports [online]. Available from URL: http://scientific.thomsonreuters.com/pharma/slides/#regulatory [Accessed 2009 Aug 12]
27. European Commission DG Enterprise. Pharmaceutical sector inquiry: preliminary report [online]. Available from URL: http://ec.europa.eu/competition/sectors/pharmaceuticals/inquiry/preliminary_report.pdf [Accessed 2009 Aug 12]
28. Richmond RH. Environmental protection: applying the precautionary principle and proactive regulation to biotechnology. Trends Biotechnol 2008; 26 (8): 460-7

Correspondence: Dr *Thomas C. Kühler,* Medical Products Agency, P.O. Box 26, SE-751 03 Uppsala, Sweden.
E-mail: thomas.kuhler@mpa.se