# HEADS OF MEDICINES AGENCIES STRATEGY 2011-15

## BEUC contribution

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## Summary

To better address public health needs and optimize the safe use of medicines we encourage the National Competent Authorities to:

- Guarantee a strong, transparent and proactive pharmacovigilance system;
- Put in place and promote a consumer friendly direct reporting system for adverse drug reactions;
- Take appropriate measures to combat on line sales of counterfeit medicines;
- Make sure that the technologies used to trace medicines are safe and efficient;
- Establish a meaningful and transparent dialogue with all stakeholders, taking into account potential conflicts of interest;
- Continue the efforts of providing high quality information to the public;
- Proactively publish more information and documents, especially in relation to pharmacovigilance and clinical trials;
- Protect consumers from misleading advertising of health products and treatments;
- Monitor more closely promotional activities directed to health care professionals;
- Ensure that conditional marketing authorisations remain the exception and not the rule;
- Take immediate action in case of non compliance with the terms of the marketing authorisation;
- Maintain a clear distinction between the decisions regarding marketing authorisation and health technology assessment;
- Develop specific methodologies for the assessment of nanomedicines.




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## 1. Preliminary remarks

BEUC, the European Consumers' Organization, welcomes the strategy for the Heads of Medicines Agency 2011-2015. Due to the limited period of time available for the consultation ( 9-30 July) which also coincides with the summer holidays, our contribution is based on the submission we made to the European Medicines Agency Roadmap 2015 and on previous positions we expressed on the main issues identified in the consultation paper.

## 2. Pharmacovigilance

Medicines save lives but can also have serious adverse effects. According to the European Commission "it is estimated that 5% of all hospital admissions are due to an adverse drug reaction, 5% of all hospital patients suffer an adverse reaction and adverse reactions are the fifth most common cause of hospital death". A strong, transparent and proactive pharmacovigilance system is therefore vital to ensure consumer safety in relation to the use of medicines. Consumers are key stakeholders in relation to pharmacovigilance and can actively contribute through an integrated and efficient reporting system. Direct reporting is an essential tool to empower consumers and to improve their involvement in the management of their own health. With direct reporting, adverse drugs reactions (ADRs) can be detected earlier, more ADRs are reported (e.g. on non-prescription medicines), patients report ADRs that they are not willing to discuss with their health professionals (e.g. sexual or psychological ADR's) and health professionals do not act as a filter. This is particularly important as consumers are more involved in their own therapies (e.g. self-medication).

The evidence[1] indicates that patient reports which are unfiltered by professional interpretation can bring a new contribution to understanding ADRs, particularly those that have not previously been known and that they are of the same quality as those of health professionals. In addition patients may use vocabulary which is enlightening in understanding adverse drug reactions as the use of medical terminology by doctors sometimes leads to less detail and meaning. For example, when patients report "electric shock sensations" in the withdrawal of antidepressants, this has been "translated" as "paraesthesia", which communicates little of the disabling impact of withdrawal symptoms on users.

We welcome the Heads of Medicines Agencies (HMA) commitment outlined in the strategy (point 5.9) "to seek to promote consistently high standards of spontaneous reporting throughout the Network" and we encourage the National Competent Authorities (hereafter NCAs) to use all the levers identified to increase reporting rates (education, motivation, facilitation and promotion). In particular we consider essential that patient reporting is accompanied by appropriate information campaigns in all Member States.

In order to focus on the potential long-term effects of new medicines and to supplement companies' post-authorization safety studies and spontaneous reporting from consumers and healthcare professionals, the European Medicines Agency (EMA)

[1] a) Blenkinsopp et al. Patient reporting of suspected adverse drug reactions: a review of published literature and international experience. Br J Clin Pharmacol 2006; 63:148-56.
b) Report from the CHMP Pharmacovigilance Working Party (PhVWP) on Direct Reporting of adverse reactions by patients, 22 January 2008.



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and the NCAs should carry out additional independent research that follows a selected group of patients using specific medicines after they have been granted market authorization.
It is important that independent research is carried out inside and outside the agencies as part of the pharmacovigilance system and involves academia, centres of excellence and regional surveillance centres.

## 3. Counterfeit medicines

BEUC welcomes the actions to combat counterfeit medicines identified in the HMAs strategy paper but we think is important to address also internet sales.
Internet-based sales of pharmaceuticals are by far the major source of counterfeit medicines, threatening those who seek cheaper, stigmatized or unauthorized treatments.

Illegal internet pharmacies operate internationally and sell unapproved or counterfeit products that have an unknown origin[2].

BEUC members in different countries tested sales of medicines on the internet to verify the safety and reliability of this supply channel. They also made laboratory analyses to assess the quality of the products they purchased.

The results are worrying:

- in most cases they managed to buy prescription-only medicines without prescription;
- the laboratory tests revealed major quality problems, in addition to concerns regarding the storage and shipping of the products. A survey [3]published in October 2009 by the Dutch consumer association Consumentenbond, found that out of the 47 orders received, in 16 cases the dosage of active ingredient exceeded the standard dosage by more than 10% or fell short of it by more than 10%. In many cases the medicines contained the wrong substance or contamination of other substances;
- they received pills wrapped in newspaper sheets or loose bags;
- they didn't find any safety information on the web sites[4];
- the medicines were not accompanied by the patient leaflet or the leaflet was an inaccurate translation; the web sites didn't disclose the origin of the products and declined any responsibility[5];
- many of the web sites they used no longer existed two months afterwards.

On this basis we encourage the NCAs to launch ad hoc campaigns to warn consumers against the risk of buying medicines online from illegal sources as it has been done, e.g., in the Netherlands (http://www.internetpillen.nl), and in Portugal http://www.infarmed.pt/portal/page/portal/INFARMED/IMPRENSA/CAMPANHAS/INTERNET_2008 and in Belgium http://www.medicaments-par-internet.be/fr/.

2 Illegal y arriesgada, OCU n.75, January 2008.
3 Consumentenbond, October 2009.
4 Salutest, Altroconsumo n.210, December 2007.
5 Teste Saúde, DECO Proteste, n.70 December 2007.



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Consumers' organizations also have a role to play in informing the public (see footnotes 2, 3, 4, 5). Consumers should also be informed about how and to whom they can report suspected unlawful sale of medical products on the internet (for example to the competent health authorities or to their pharmacists). In the US the Food and Drug Administration (FDA) has a dedicated toll-free information line for these cases.

Another measure that could help to combat the phenomenon of illegal internet sales is to make companies that provide sponsored advertising services responsible and accountable for ensuring that the links they sponsor comply with the legislation and should not advertise illegal web sites selling medications.

A US study[6] conducted by research firms LegitScript.com and KnujOn.com.has found that over 80% of on-line advertisements for Internet pharmacies accepted by different search engines were fake or illegal Internet pharmacies and in violation of US federal and state law. The researchers were also able to purchase prescription drugs without a prescription and were sent counterfeit medications.

The liability of search engines that provide sponsored advertising needs to be carefully assessed in line with the existing Community legislation taking into account that, as pointed out by the Advocate General[7] of the European Court of Justice, sponsored advertising services provided for by Information Service Providers (ISPs) are not a neutral information vehicle as opposed to the natural results presented by search engines.

In those countries where on line sales of medicines are authorized, consumers should be provided with appropriate tools to identify legal sources such as a public register of legal internet pharmacies and a specific logo as it is already done in some member states.

In order to combat counterfeit, NCAs are exploring different technologies to track and trace medicines all along the supply chain and there are many pilot projects on going. From a consumer perspective, our major concern is that any technology used:

- fully ensures consumer safety;
- is reliable and applicable;
- improves the tracing mechanisms allowing identification and safe recall;
- safeguards consumer privacy;
- doesn't hinder competition;
- has no major impact on the final price of medicines.

Of all possible technologies, we do not currently support the use of RFID (radio frequency identification technology) because of the numerous privacy and security concerns it raises as well as the lack of information on the effects on health8. Other

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6 http://www.legitscript.com/blog/102

7 Opinion of the Advocate General Poiares Maduro delivered on 22 September 2009, Joined cases C-236/2008, C-237/08 and C-238/08 Google France Google Inc V Luis Vuitton Malletier.

8 It is expected that RFID technologies will significantly contribute to exposures to Extremely-Low-Frequency (ELF) components. Little or no data is currently available to assess the potential health hazards arising from the use of these technologies. Moreover, as recently stated by the European



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technologies, with lower safety, data protection and privacy implications should be exploited.

With the new track and trace system that will be introduced with the Directive to combat falsified medicines the pharmacists will scan the safety features and check them against the manufacturer electronic database. We are concerned that the collection of such sensitive information might raise significant privacy issues and potential abuses for commercial interests. First of all, consumers (e.g. those who use an electronic social security card when they buy a medicine) must be reassured that their personal data cannot be held within the system without their prior and expressed permission (opt-in). Second, the data regarding the number and the types of medicines sold by a single pharmacy should not be made available to the manufacturers who could use them to analyse prescribing trends in specific geographical areas and better target promotional activities towards health care professionals. At the moment pharmaceutical companies can purchase this information in the form of statistics but do not have detailed data for each pharmacy.

Last but not least, the issue of counterfeit should not be mixed with intellectual property rights arguments[9]. These arguments are based exclusively on commercial considerations and not on public health concerns.

## 4. Interaction with stakeholders

We question the choice of the HMA to focus exclusively on the interaction with industry stakeholders and we encourage them to outline in the strategy paper some key general principles for interaction with all stakeholders that can be applied to the network and to the NCAs. In particular, in relation to the interaction with patients and consumers organizations we encourage the HMA and all NCAs to take inspiration from the well established and well functioning framework adopted by the EMA. Over the years the patients and consumers working party (PCWP) has proven to have an important added value both for the Agency and for patients and consumers organizations.

BEUC values highly the cooperation with the European Medicine Agency and our members organizations are looking forward to being more involved in the activities of the national medicines agencies.

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Commission Scientific Committee on Emerging and Newly Identified Health Risks (SCENHIR), ELF magnetic fields are possibly carcinogenic, mostly based on occurrence of childhood leukaemia.
Regarding electromagnetic fields (EMF) exposure, ANEC and BEUC regret the lack of data for the risk analysis of RFID applications and pervasive computing applications. In particular, evaluation is needed if specific limits or extension to existing standards have to be added regarding on-body antennas (highly localised fields) or the combination of different sources operating at different frequencies or within different frequency bands.
We believe that new exposure assessment procedures for testing compliance with safety guidelines are necessary. Moreover, further research is needed in order to assess potential health risks of RFID technologies together with exposure assessment procedures.
In the meantime, we call on the Commission to apply the "principle of precaution" to the deployment of RFID technologies…However, in the case of RFID technology, the very technology used to protect IPRs can also be counterfeited, due to the very low or non-existent level of security of the tags used".
Consumers' scenarios for a RFID policy - Joint ANEC/BEUC Comments on the Communication on Radio Frequency Identification (RFID) in Europe: steps towards a policy framework, July 2007.

9 See for example: http://www.keionline.org/misc-docs/seizures/WHO_seizures_18feb.pdf

By including stakeholders regulators prove to be inclusive and responsive to societal needs and expectations. In this respect, it is vital to maintain a clear distinction between stakeholders and the representatives of the national authorities not only in terms of the interest they represent (the first ones partial interests, the second one general interest), but also in terms of the expertise they can provide.

When involving stakeholders, it is also essential to take into account that the people attending the meetings are not there in their individual capacity and that they represent an organisation.

A key element to take into account when involving all stakeholders – including experts and academics – is the conflict of interest. All those involved in the activities of a regulator should fully disclose all potential conflicts of interests. The competent authorities are then responsible for checking the accuracy of the conflict of interest declarations and for the consistent application of the rules.

## 5. Transparency

We welcome the HMA commitment for more targeted, timely and proactive communication via the network web site. What in the strategy paper is defined as "web presence", from a consumer perspective, it translates into "transparency". Transparency is an essential element in building consumers' trust and confidence in the HMA – and all agencies - and ultimately in medicines. The work of the HMA has a big impact on public health and on patients' safety.

The EMA, the HMA and the NCAs should ensure that all data related to the efficacy and safety of medicines, submitted to regulatory authorities (at national and supranational levels) is publicly available, including all pre-market clinical data and post-authorisation studies. We also believe that the Periodic Safety Update Reports (PSURs), and at least the assessment of PSURs, should be published. It is not the case at the moment and we hope this will change once the new EU legislation on pharmacovigilance will enter into force.

## 6. Information and advertising

The EMA and the NCAs should strive to become authoritative sources of information on medicines. BEUC doesn't support the current Commission proposal to relax the existing rules with regard to information that pharmaceutical companies can provide directly to consumers as we believe it falls short in making a clear distinction between information and advertising and it will give companies the possibility to choose on which disease and on which medicines to provide the information and to what extent. In addition we believe it opens the door to disease mongering giving rise to detrimental consequences, including a push towards high margin and life style medicines, an increase on health care costs, a bias against non-drug therapies and a pressure on the doctor/patient relationship.

Therefore, we ask the Commission and the Member States to develop a more comprehensive information strategy that truly responds to consumers' information needs and that fosters and promotes the existing sources of information starting with the valuable high quality information provided by the Medicines Agencies.



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We encourage the HMA to include in the paper a specific reference to the protection against misleading advertising of health products and treatments in line with the Council Conclusions on common values and principles in European Union health systems of 2006. We also ask the NCAs to ensure the correct application of the existing European legislation on advertising of medicinal products both for prescription medicines and for OTCs. We also ask for a closer monitoring of disease awareness campaigns, of promotional activities directed to health care professionals - according to the European Commission pharmaceutical companies spend 23% of their annual turnover in promotional activities and 17% on R&D – and also of the advertising of medical devices which is regulated at national level.

## 7. Independent, continued and proportionate risk-benefit assessment

Overall, BEUC supports the simplification of procedures as long as they ensure that pharmaceutical companies and competent authorities fully comply with safety requirements. Obviously we cannot accept that the simplification is done solely on the basis of saving costs and to remove the administrative burden if that will lead to lower quality standard of procedures.

In relation to the approval of new medicines we would like to raise a specific concern with regard to the conditional marketing authorization. In particular, BEUC strongly believes the conditional marketing authorisation should remain the exception and should not become the rule. With regard to post authorisation commitments, the experience[10] shows that in many cases where companies were required to conduct post-authorisation safety studies, they failed to do so. A report[11] of the United States Government Accountability Office (GAO) published in September 2009 revealed that "from 1992 through November, 2008, the Food and Drug Administration (FDA) asked pharmaceutical companies to complete 144 studies associated with 90 drug applications, and that companies had completed just two-thirds of the requested studies. 15 of the 52 uncompleted studies have been pending for more than five years, and several have been pending for more than eight years". The FDA has authority to speed a medicine's removal from the market if the sponsor fails to complete a required confirmatory study with due diligence or if such a study fails to confirm the medicine's benefit. But, the GAO report outlines that the agency has never exercised this authority, "even when such study requirements have gone unfulfilled for nearly 13 years," nor has it ever specified the conditions which would prompt it to take such action.

The report also adds that "weaknesses in FDA's monitoring and enforcement process hamper its ability to effectively oversee post marketing studies".

The result is that doctors and patients remain unsure whether some critical medicines used to treat illnesses like cancer and heart disease are actually beneficial. The experience of the US highlights that it is of upmost importance, not only to introduce stricter requirements for the conditional marketing authorisation, but also to provide the national medicine agencies with the powers and the appropriate tools to enforce the legislation.

10 Lexchin J "Notice of compliance with conditions: a policy limbo" Healthcare policy 2007; 2 (4):114-122.
11 FDA Needs to Enhance Its Oversight of Drugs Approved on the Basis of Surrogate Endpoints, United States government Accountability Office, September 2009. The full report is available at http://www.gao.gov/new.items/d09866.pdf



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The risk is to expose a large group of the population to unnecessary and avoidable risks especially if the medicine in question doesn't address unmet clinical needs and a safer alternative is already available. Evidence[12] shows that the already increasingly premature licensing of medicines, at the expense of proper evaluation, leads to more pharmacovigilance issues further down the line.

## 8. Health technology assessment (HTA)

HTA is a useful tool for decision makers in order to better ensure that consumers benefit from high quality, safe and efficient health care. HTA processes should be transparent and sensible. While it is vital that the medicines agencies provide HTA bodies with all the relevant information and data to corroborate their decisions, HTA bodies should not be bound by the medicines agencies decisions and vice versa. Finally we believe that HTA should not be used only to assess new medicines but also to remove the 'old' inefficient ones from the market.

## 9. New and emerging science

New and emerging technologies raise high expectations with regard to their potential in diagnostics, drug development and delivery (ex. personalised treatments), preventive methods and other health-related applications (ex. regenerative medicine). However a wide range of legal and ethical regulatory challenges need to be addressed, including the distinction between therapeutic and non-therapeutic use. There is therefore an urgent need to adapt the legal/regulatory framework but also to develop *ad hoc* methodology for the safety assessment of such technologies.

More specifically, on nanotechnologies, a major problem is the lack of a clear definition of nanomedicine and the consequent uncertainty as to which regulatory provisions are applicable, also in term of consent, confidentiality and data protection. For example, given that nanomedicinal products may combine different mechanisms of action (pharmacological, mechanical, chemical etc) the distinction between medical product and medical devices may be blurred[13]. We believe that in those complex cases the product should be regulated as a medicinal product to guarantee the highest level of safety for the patient (this principle is applied also in the Advanced Therapy Regulation[14]).

It is also important to make a distinction between risks for the patients undergoing an application of nanomedicine (for example risk of toxic effects in a person involved in clinical trials because of possible accumulation of cross-effect in tissues and organs) and health related risks associated with the toxicological effects of nano-pollution.

Medicinal products containing nanoparticles have already been authorised both in the EU and in the US under the existing legal framework and standard processes have been used to assess their risk for the patient.

12 Carpentier D et al. "Drug review deadlines and safety problems" N Engl J Med 2008; 358:1354-1361.
13 Opinion on the ethical aspects of nanomedicines, n.21, January 2007.
14 Regulation of the European Parliament and of the council on advanced therapy medicinal products and amending Directive 2001/83/EC and Regulation (EC) No 726/2004.



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General health related risk of nanoparticles have already been examined by several competent authorities including the Scientific Committee on Emerging and Newly Identified Risks (SCENIHR) and the Scientific Committee on Consumer Products (SCCP) on behalf of the EU, as well as the UK's Royal Society and Council for Science and Technology. According to these bodies, there is not only an alarming lack of data regarding the safety of nanomaterials, but also - and perhaps more importantly – the current risk assessment methodologies used for nanomaterials are inappropriate and need to be revised. Despite the above concerns of these leading scientific bodies, insufficient measures have been taken thus far regarding the management of the risks related to the use of nanomaterials.

Prospective technology studies should also be performed: scenarios need to be elaborated about possible adverse events related to the use of nanotechnologies in medicine and responses should be prepared to deal with these events.

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