RESPONSE TO: Commission Public Consultation: As Assessment of the Community System of Pharmacovigilance

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Type of stakeholder: **International Consumers' Advocacy Organisation**

Organisation: **Health Action International (Europe)**

Health Action International (Europe) (HAI-E) appreciates the European Commission's (DG Enterprise) decision to hold this consultation, and we credit their commissioning the "Fraunhofer report", an *Assessment of the European Community System of Pharmacovigilance*. In this submission, we draw on much evidence from that report in support of this submission. However, we also deprecate the narrowness of the Fraunhofer terms of reference.[1] The authors of the Fraunhofer report were positively *not* invited to address this key question: *What is the public health impact of all this Euro-activity on the health and welfare of European Citizens?*

In this submission, we argue that the present European system of pharmacovigilance is deeply flawed and probably not capable of ever developing from these foundations into the robust and responsive system that European citizens might expect, need and vote for. HAI-E believes that the existing system needs fundamental re-thinking; it is plainly insufficient, but not only because of the ill design of drug regulation: other factors[2] play a part, including the overwhelming complexity of European governmental systems.

[1] The European Commission's tender document for this assessment (General invitation to tender No ENTR/04/23. Title: *Assessment of the European Community System of Pharmacovigilance,* Specifications: 2004) specified the "Nature of the contract" as "to *document* the current system in terms of stakeholders' responsibilities, processes and resources" (emphasis added to distinguish between the requirement to document the system, rather than to evaluate it in terms of health impact). The assessors were asked to "consider the robustness of the present system, highlight its present strengths and weaknesses" – not in terms of human health, but "taking account of current environmental issues."

[2] Other factors include, notably, [a] the nature and scale of drug promotion and its influence on drug consumption; [b] extensive secrecy working to the advantage of commercial and regulatory interests; and therefore [c] the marginalisation of consumer, user and patient interests.

The European pharmacovigilance control system (EPCS) involves monitoring a mean of 5038 products[3] in each of 25 different countries, with scores of different manufacturers involved. There are, of course, huge differences in the resources available in different countries, some countries having over 20-times the pharmacovigilance staffing levels of others. Given the EU median figure – one pharmacovigilance (PhV) staff member per 1.3 million population it is not surprising that, "In some agencies the number of staff seems to be less than the minimum required to complete the necessary tasks." (Fraunhofer, p.6)

The suggestion is made in the Fraunhofer report (p. 6) that median staffing levels "might be used as a minimum value for all agencies", but this seems arbitrary and is unexplained. Moreover, this proposal points to an evolutionary model we believe to be inappropriate, not least because it would promote extensive duplication of effort. The emphasis should be on building an effective pharmacovigilance system for Europe, rather than on constructing some harmonised European system, dependent on substantive contributions from all players. This distinction seems critical, first, because systems based on parity of input may emerge no stronger than the weakest link; and secondly because this model will inevitably tend to be cumbersome and inefficient. In the meantime, consumers in Member States with limited resources and inadequate pharmacovigilance and drug safety systems[4] need to know where they stand – and we now formally request the Commission to publish the Fraunhofer data in Table 0.1 (page 6) to indicate the PhV financial and staffing resources available in each Member State.

We do not doubt that European initiatives might contribute very importantly to the welfare and safety of medicinal drug consumers, but believe they currently fail to do so: "The system is very difficult to oversee despite the existence of detailed guidelines" (Fraunhofer p. 6). But over and above these complexities of organisation, we believe there to be major deficits of conception, design and execution in the present European pharmacovigilance control system (EPCS), as follows.

[3] Fraunhofer, section 3.4
[4] "… the capability to assess safety issues does not exist in all agencies" (Fraunhofer p. 7)

1. Conflicts of Interest

The EPCS is marked by fundamental conflicts of interest, in two major respects. First there are major conflicts between health priorities and trade imperatives, and they are underlined by the responsibility for European drug regulation currently assumed by DG Enterprise. HAI-E concurs with the relevant conclusions and recommendations (16 and 48) of the recent UK Parliamentary enquiry[5] into 'The Influence of the Pharmaceutical Industry'. The enquiry recommended strongly against combining health responsibilities with sponsorship of the industry, as the European Commission attempts to do: "*These roles have not proved compatible. Health and trade priorities are not always identical and their combination leads to a lack of clarity of focus and commitment to health outcomes."* (Paragraph 392).

More specifically, this UK Parliamentary enquiry pointed to fundamental weaknesses in the Medicines and Healthcare Regulatory Agency (MHRA), some clearly resulting from attempts to balance two legitimate but competing interests. In the EU context, the Committee's criticism of the MHRA seem all the more worrying, since the MHRA is widely and no doubt rightly regarded as one of the very best European regulatory Agencies. The implication would be that most EU drug regulatory agencies perform no better, or worse:

> *During this long inquiry we became aware of serious weaknesses in the MHRA. Worryingly, in both its written and oral evidence the Agency seemed oblivious to the critical views of outsiders and unable to accept that it had any obvious shortcomings, except those that could be remedied by more*

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[5] House of Commons Health Committee: *The Influence of the Pharmaceutical Industry*, Fourth Report of Session 2004–05, *Volume I, 5 April 2005.*
http://www.publications.parliament.uk/pa/cm200405/cmselect/cmhealth/42/42.pdf
Recommendation 16. The interests of patients, the NHS and industry can be at odds and we have no confidence that the Department is capable of achieving the balance required. The 'cross-dressing' role of the Department in this regard does not serve the public as well as it should (Paragraph 335)
Recommendation 48. We recommend that responsibility for representing the interests of the pharmaceutical industry should move into the remit of the Department of Trade and Industry to enable the Department of Health to concentrate solely on medicines regulation and the promotion of health. (Paragraph 392)

> *transparency. The Agency's attitude to its public health responsibilities suggested some complacency and a lack of requisite competency, reducing our confidence in its ability to undertake the reforms needed to earn and deserve public trust. Nor did we conclude that the MHRA provides the discipline and leadership that this powerful industry needs. (Paragraph 376)*

Secondly, obvious conflicts of interest are involved when the same agency both approves drugs for marketing and takes responsibility for monitoring their safety in practice (pharmacovigilance). Conflicts arise because, when drug problems come to light after a drug has been licensed, questions will almost always arise about the adequacy of pre-marketing evaluation and the quality of regulatory scrutiny in the licence application process.

HAI-E therefore recommends that, in the immediate future, and while the European Commission continues to entrust DG Enterprise with drug safety regulation, DG Sanco (Health) should assume responsibility for overseeing pharmacovigilance activities. That would both help to soften the impact of conflict of interest, and bring badly-needed fresh thinking to what post-marketing drug safety appraisals should involve. However, we make this recommendation strictly on a 'stop-gap' basis. We emphatically believe that DG Enterprise should concern itself strictly with trade and commercial imperatives and play no primary part in medicines regulation that affects consumer health and safety. For reasons we would readily elaborate, we believe the dominant influence of DG Enterprise in medicines regulation seriously threatens health.

For the future, HAI-E envisages a European drug regulatory system in which *pre*-approval scrutiny and drug licensing evolve increasingly under centralised procedures, while *post*-marketing surveillance and pharmacovigilance activities are increasingly delegated to competent institutions and authorities in Member States. This would be more logical and more practical, because close contact and communication between patients, professionals and the authority are crucial. Nor would it necessarily distance DG Sanco too far from post-marketing surveillance – since this Directorate would need to play a key part in identifying priorities for investigation, coordinating the efforts of Member States, and avoiding duplication.

2. Role of pharmacovigilance in drug safety regulation

HAI-E considers *pre*- and *post*-marketing drug surveillance activities to be fundamentally out of balance. At present, the overwhelming emphasis in drug regulation is on pre-marketing drug assessment, despite abundant evidence that even the most careful assessments are often quite insufficient – yet they tend to be relied on as legal, if not holy grail, pretty much throughout the lifespan of patented drugs. Increasingly, the evidence shows that the clinical trials relied on for drug licensing purposes are often unrepresentative, biased, misinterpreted, over-promoted and otherwise seriously flawed - providing no adequate basis for predicting drug effectiveness, safety and clinical value. The evidence for this is now embarrassingly strong: for example, 50% of drugs regulated in the US have major ('black box') safety warnings added after licensing, and dosage recommendations need changing (almost always downwards) for one drug in every six.[6]

All this underlines the potential importance of post-marketing drug monitoring, yet pharmacovigilance has evolved very much as the 'poor relation' in drug control - an afterthought, add-on activity whose importance is largely lost on regulators, politicians and the public alike (Fraunhofer p. 154). The Fraunhofer survey records (p. 81) that, "the median proportion of PhV staff is only 5% of the total agency staff". Moreover, the emphasis in Pharmacovigilance (PhV) "strongly lies on the collection and analysis of spontaneous (suspected adverse drug reaction) reports" (p. 6), notwithstanding alarming levels of under-reporting. This seems highly inappropriate, as does the ritual tendency to value quantity of data over quality – to count and categorise the numbers of suspected ADR reports received, rather than to examine their meaning and significance.

And what of outcomes? The reality is that, "agencies have only weak means to influence the timing and content of communications" relating to drug safety, also that "the outcomes of regulatory action are only assessed in exceptional cases" (p. 161). It follows that: "There is very little information about what prescribers do with label

[6] For further information see pp 144-152 in Medawar C, Hardon A: Medicines out of Control? (published originally in Amsterdam by Aksant (2004).

information and label changes" (p. 162) and that "the agencies' influence on the prescription behaviour is weak" (Fraunhofer p. 154). HAI-E submits that the EPCS doesn't work, and needs fundamental re-thinking.

HAI-E shares the view that Marketing Authorisation Holders (MAHs) "are primarily responsible for the safety of their products, from the start of drug development and throughout the life cycle of a product" (Fraunhofer p. 51). This implies that regulators should not be doing the work that companies (MAHs) should be doing – or should be charging companies much larger fees if they need to do so. Under the present European system, producers are still permitted to externalise their costs, rather in the style of air polluting industries until the mid 20th century – when pollutants were simply blown up the chimney stacks. Typically, the harm was done so far downwind of the stacks, that it proved impossible to measure or to trace the damage to source.

The present drug regulatory posture involves abuse, by default, of both scientific and democratic first principles: drug regulators should seek and propagate the truth about drug benefit and harm. As it is, the regulators contribute profoundly to distorted public understanding, but typically go to great lengths to deny this. The leading European drug regulatory agencies continue to invite their downstream constituents to uncritically believe that new drugs bring health benefits and that 'no (approved) evidence of risk is evidence of no risk'. Neither is close enough to the truth.

So what is to be done, and by whom? HAI-E concedes that it may be too late – that the underlying ideals of Europe may already have been irresistibly and irreversibly overtaken. Perhaps trade priorities now rule, even to the extent of denying access to reliable information on drug benefits and risks/harms and the role of drugs in securing better health. We see much evidence of this and view with alarm some of the trends we see, but nevertheless suggest the following points for consideration:

- The present emphasis on gathering and pigeon-holing ever higher numbers of spontaneous ADR reports, and on number-crunching exercises, is badly misplaced. The Fraunhofer

enquiry made no real attempt to estimate levels of ADR under-reporting, though the report inadvertently hints at the nature of the problem, solemnly recording a WHO tabulation (Table 3.35, p.122) indicating that the relevant experts believe levels of drug-induced illness to be 173-times higher in Ireland than in Portugal. The figures in this table are otherwise incredible: to suggest that the incidence of ADR-relevant diseases in the EU-25 is 0.13 per 100,000 (UK, 0.05/100.000[7]) seems absurd. Far greater emphasis should be placed on the investigation of true levels of iatrogenic (drug-related) illness, including the role of prescribing behaviour in contributing to it.

- Statisticians and pharmacoepidemiologists have important roles to play, but their influence appears autocratic; they seem to be turning pharmacovigilance into something of a fiefdom. Such is the scale of drug use, the influence of drug promotion, poor reporting standards and the weakness of investigative tools, that failure to reach 'statistical significance' in official assessments of drug risks/harms may still materialise as hundreds of deaths and substantial suffering. Alongside highly orchestrated, overwhelming and often spurious evidence of drug benefit, these deficits in drug regulation seem potentially disastrous. HAI-E believes that far less emphasis should be placed on generating larger volumes of spontaneous reports, with much greater emphasis on scrutiny and follow-up of the most significant ADR reports received, certainly including reports from patients. At present, there appears to be virtually none.

- We believe the starting point in any good pharmacovigilance system is continuing and systematic enquiry into the level and cost of iatrogenic illness involving drug use. Such data as there are indicate that drug injury is a major problem, but the lack of hard evidence is worrying. The present situation might be compared, by analogy, to the attitude that the benefits of road transportation are so great as to obviate the need to conduct

[7] Official UK estimates propose that about 5% of all hospital admissions are wholly or partly attributable to ADRs, and that around 15% of patients admitted to hospital will also suffer ADRs. The best US estimates suggest that perhaps 100,000 people die from ADRs each year, but no convincing estimates yet exist of the extent of ADR-related illness in the communication.

systematic investigations of traffic accidents when they occur. Any worthwhile system of pharmacovigilance depends fundamentally on a capacity and willingness to learn from mistakes; hence the need for routine, independent investigations when major and unexpected drug problems arise. In practice such investigations hardly ever happen.

- Marketing Authorisation Holders (MAHs) may be considered "primarily responsible" for the safety of their products, but we believe this message gets lost – with companies tending to assume that their responsibilities amount to compliance with a vast and expanding range of national and European "pharmacovigilance system requirements". Since the median number of European regulatory inspections of MAHs on Pharmacovigilance matters is zero (Fraunhofer p.119) that commitment, in practice, seems slight: "it is questionable if the agencies can validly assess the compliance of MAHs with signal detection duties" (Fraunhofer, p. 129. See also p. 157[8], and p. 110, Fig 3.44)[9]. In place of much regulatory data gathering and analysis, we would wish to see a far greater regulatory emphasis on critical audit of MAHs' pharmacovigilance systems, properly funded by appropriate fees. We would also recommend, as a cornerstone of European PhV activities, formal and binding requirements on MAHs to conduct meaningful post-marketing investigations of possible problems.

- HAI-E shares the concerns expressed by the large majority of agencies surveyed about the influence of lack of transparency[10] (p. 116, Fig. 3.52) by MAHs. We further appreciate the need for "independence of the assessment from the MAH" as a critical success factor (p. 189, Table 4.1), while recognising also the considerable pressures that individual company employees

[8] "The compliance of MAHs with expedited reporting is routinely checked in only 41% of the cases", while compliance for provision of Periodic Safety Update Reports (PSURs) is checked in 56% of cases. The Fraunhofer report noted also (p. 156) that, "A small number of agencies have not even received a single PSUR report in 2004, which is an indicator of non-compliance of MAHs"

[9] Compliance of MAHs in analysis of signals from reports of suspected ADRs was rated 'Good' or 'Very Good' by only 37% of agencies, and 'Bad' or 'Very Bad' by 16%.

[10] "The transparency of the process of decision-making on safety issues … was only assessed as moderate, and in 27% of cases as bad or very bad".

may face if they draw attention to the limitations of company products. To address both problems, we suggest consideration might be given to the appointment of 'Compliance Officers' for PhV as, for example, in the financial services sector in the UK and elsewhere.

- It seems ironical that most agencies feel handicapped by lack of transparency on the part of MAHs, when high levels of regulatory secrecy have been a traditional source of complaint by the public. While HAI-E does recognise some improvements made over the past decade, it is also convinced that far greater transparency is needed, and fundamental to the attainment of any effective PhV and drug regulatory system. The reason is not simply to ensure proper accountability. It is to guarantee access to data relating to drug benefit and risk/harms, and to positively encourage others to analyse the available evidence. It is plainly unrealistic to expect drug regulatory agencies on their own to make timely and intelligent assessments of the vast and increasing amounts of data there are. Moreover, lack of transparency hinders the working of competition that would reward better drug products over others. There is a long way to go.

- HAI-E is also very concerned that drug benefits and harms, from a regulatory perspective, are perceived only in the narrowest terms. What thought have European regulators given to the problems of social and cultural iatrogenesis?[11] The answer appears to be none, but what will European citizens have to gain from greater collective wealth, if their fellow citizens fear chronically for their health and rely overwhelmingly on chemical solutions? Such concerns clearly fall within the scope of what pharmacovigilance is intended to be and do.[12]

  We should not be satisfied with the present focus on assessing system inputs rather than health outputs. The micro-examination of drug properties and effects is not sufficient as a

[11] See Medawar and Hardon, Op Cit., pp. 180-187

[12] HAI-E notes the official definition of 'pharmacovigilance' (PhV). It is "a key public health function", defined as "the processes and science of monitoring the safety of medicines and taking action to reduce risk and increase benefit" (Fraunhofer p.5).

measure of either drug impact or the attainment of health. See predictions on the risks of medicalisation by Ivan Illich (1974)[13], Lewis Thomas (1980)[14] and updates from Moynihan, Henry et al, 2006[15] on the risks and effects of disease mongering on community health.

In summary, citizens of Europe deserve much better than they get. The present European pharmacovigilance control system is not merely weak. The extent to which it helps to sustain the illusion that drug benefits to health hugely outweigh the harms, leads us to believe that its overall impact on health is positively dubious.

[13] Illich redefined the idea of 'iatrogenesis' and the thinking that went with it. He introduced two main ideas: that it was in the nature of medical practice to produce ill-health - "The medical establishment has become a major threat to health" - and that the damage done went much deeper than 'clinical iatrogenesis', the direct harm caused by treatment and medical intervention. Illich was also concerned about the 'social iatrogenesis' that resulted from the medicalisation of life. This promoted 'cultural iatrogenesis,' which implied general lack of confidence and loss of autonomy in achieving health and making sense of illness and death. See: Illich I., *Limits to Medicine - Medical Nemesis: the Expropriation of Health*, (London: Marion Boyars, 1976 (originally published in *Ideas in Progress*, January 1975).

[14] *"The trouble is, we are being taken in by the propaganda, and it is bad not only for the spirit of society; it will make any health-care system, no matter how large and efficient, unworkable. If people are educated to believe that they are fundamentally fragile, always on the verge of mortal disease, perpetually in need of support by health-care professionals at every side, always dependent on an imagined discipline of "preventive" medicine, there can be no limit to the numbers of doctors' offices, clinics, and hospitals required to meet the demand. In the end, we would all become doctors, spending our days screening each other for disease.*

We are, in real life., a reasonably healthy people. Far from being ineptly put together, we are amazingly tough, durable organisms, full of health, ready for most contingencies. The new danger to our well-being, if we continue to listen to all the talk, is in becoming a nation of healthy hypochondriacs, living gingerly, worrying ourselves half to death.

And we do not have time for this sort of thing any more, nor can we afford such a distraction from our, other, considerably more urgent problems. Indeed, we should be worrying that our preoccupation with personal health may be a symptom of copping out, an excuse for running upstairs to recline on a couch, sniffing the air for contaminants, spraying the room with deodorants, while just outside, the whole of society is coming undone." (Thomas L., The health-care system, in *The Medusa and the Snail* - more notes of a biology watcher, New York: Bantam, 1979).

[15] See: http://medicine.plosjournals.org/perlserv/?request=get-document&doi=10.1371/journal.pmed.0030191