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Benefit/risk communication by the European Medicines Agency: a study of influential stakeholders' expectations and attitudes

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Abstract

The objective of this project was to ***provide evidence based input that can be used to improve the Agency's communication of benefits and risks.*** This research project is a step towards using approaches from the risk communication discipline to improve the European Medicines Agency ("the Agency")[1] communication of benefits and risks in complex multi-stakeholder environments. This report presents a detailed analysis of influential stakeholders' expectations and attitudes. The research draws on behavioural and social psychology theories, which have been successfully applied in the past in a variety of contexts (nuclear technology, chemicals, food, etc.). The first finding is a confirmation that, similarly to other policy fields, health experts would be wrong to assume that top-down messages resonate among non-experts. Secondly, the study shows that effective risk communication becomes particularly challenging when several institutional actors – e.g. the Agency and National Competent Authorities (NCA) - interact with different publics simultaneously. The cases investigated demonstrate that multiple actors tend to maintain multiple and conflicting "voices"; that delays due to co-ordination may create information vacuums; and that specific national development (e.g. risk amplification by the media) may distort the entire communication process. The third result confirms that public involvement mechanism must be "managed" to make a positive impact on the benefit/risk communication outcome. In once case (Viracept) the active involvement of a patient representative by the Agency prevented an escalation of the incident. In another case (Gardasil), scientific advice from independent experts helped to mitigate the public scare. The reports formulates four recommendations to improve benefit/risk communication: 1- establishing an external risk communication advisory board; 2- Forming a strategic view on transparency; 3- Making patients' active involvement a routine; 4-Reviewing the format and timing of communication vehicles. The external risk communication advisory board should have the mandate to bridge medical and communication expertise in order to develop situation-specific two-way communication models that meet the expectations and needs of the various publics.

[1] The Agency was still called "EMEA" during the first phase of the study. The term EMEA therefore appears in some of the quotes.

1. Introduction: Risk communication on medicines in the post-trust society

The nature of risk communication is changing (Löfstedt et al. 2010a). At the level of national and European authorities, new communication practices have been introduced in many sectors as a response to the emergence of a new regulatory model based on transparency, public participation and social and environmental values (Löfstedt 2004). These developments have affected a number of policy areas, including the medical sector (Löfstedt and Bouder 2010). Under the previous style of regulation, often referred to as the consensual style of regulation, policy makers met behind closed doors and made regulatory decisions. The need for external communication was not acutely felt, as consultation took place with a number of 'elite groups' including heads of industry, senior regulators and trade union representatives. The general public usually accepted the outcome of these arrangements, they did not expect to be included (Ashby and Anderson 1981) and, as a consequence, regulators did not have to face major challenges about the communication of benefits and risks to the public.

Towards the end of the 20th century, regulatory crises have changed this environment durably. Events such as transfusions with HIV-infected blood supplies in France, Bovine Spongiform Encephalopathy (BSE) in the United Kingdom and beyond, and dioxins in Belgian chickens have challenged the consensual model of regulation (Majone and Everson 2001). The main effect has been a sharp decline of public trust in regulators and the emergence of a "post-trust" environment (Lofstedt 2005) where citizens and the media have become more critical about governments and scientists. The general features of the model are shared to varying degrees throughout Europe, with important effects on benefit/risk decisions:

- The first trend is to allocate benefit and risks in a more inclusive fashion, to encourage greater public and stakeholder participation in the policy process;
- Regulators are also urged to make their strategies more transparent to meet demands for more accountable decisions; and
- Finally, the status and role of science are challenged, as scientists are seen by society as just one of many voices.

The consequences of the post-trust context have also been felt in the field of medicines. Since the late 1990s, increased public debates about safety concerns (hepatitis B vaccine, MMR vaccine, Vioxx, Avandia, etc.) has highlighted that, in addition to traditional voices -e.g. government officials, scientists and industry representatives- new opinion leaders such as journalists, 'alternative' scientists and members of advocacy groups have a key influence in shaping the risk debates. For instance the challenging nature of this new environment has had a major impact on the management of the MMR vaccine scare in the United Kingdom and the hepatitis B vaccine debate in France (Bouder 2006). Open dissent between sources of information and/or power, has also proved to jeopardise confidence in the regulatory process, as shown in the debate about the risks of Cox2 inhibitors (Löfstedt 2007). The public may question the scientific robustness of risk decisions when influential players disagree, when competent authorities communicate differently, or when they seem to collude with each other (Löfstedt 2005). The need to maintain a scientific

approach to the management of risks requires to better manage the circulation of scientific and non-scientific viewpoints. At the same time, the quality of the interactions between influential players becomes critical, as patients and the general population will not rely on a unique source of expertise to accept or run away from risks. The necessity to better understand perceptions, anticipate worries and respond to concerns effectively demands, as a precondition, to improve the quality of risk communication practices in complex multi-stakeholder environments.

2. Research agenda: connecting risk communication research to policy priorities

At the beginning of the study, it was noted that policy-makers have shown a sustained interest in re-thinking the risk communication of medicines. Examples include WHO initiatives on risk communication and the Erice declaration of 1997 (Hugman 2006) that called for 'independent expertise to ensure that safety information on all available medicines is adequately collected, impartially evaluated, and made accessible to all'; a communication chapter in the EU pharmacovigilance guidelines[2] the European Commission's Communication of 10 December 2008 and the related legislative package on safe, innovative and accessible medicines, which aims to make pharmaceutical information more transparent; the Agency Road Map to 2010[3] ; the Agency/ Committee for Medicinal Products for Human Use (CHMP) Working Group with Patients Organisations[4]. Outside Europe the creation of a new Food and Drug Administration (FDA) Risk Communication Advisory Committee (2007)[5] reflects similar priorities.

Yet, traditional research on medical communication may be of limited value to achieve these policy goals. The main reason is that research on the communication of medical risks does not typically encompass the changing relationship between risk and society. Historically, the medical research community has concentrated its efforts on psychology and the relationship between patients and healthcare professionals. There has been much written on the topic of the communication of risk from the perspectives of medical psychology and sociology over recent years, including the work of Berry, Bennett, Calman, Edelman, Kaplan, Morris, O'Connor, Payne, Raynor, Rosenstock, and Sutton (e.g. Berry 2004; Calman 1996; Bennett et al. 2010). Communication to patients constitutes the key area where the medical sector has traditionally sought external risk expertise (Merz et al. 1993; Fischhoff 1999). In 2003, a special issue of the British Medical Journal (BMJ) stressed the need to better communicate risks to patients (Bellaby 2003; Godolphin 2003; Sedgwick and Hall 2003; Smith 2003). Although risk scholars were involved in the exercise the main focus remained primarily about doctor-to-patient communication (Alaszewski and Horlick-Jones 2003). There has been until recently little discussion of pharmaceutical risk communication.

[2] Volume 9A of the Rules Governing Medicinal Product in the European Union accessed at http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/document_listing/document_listing_000199.jsp&murl=menus/regulations/regulations.jsp&mid=WC0b01ac05800250b3.

[3] Accessed at: http://www.ema.europa.eu/pdfs/general/direct/directory/3416303enF.pdf

[4] EMA/CHMP Working Group with Patients Organisations Outcome of Discussions: Recommendations and Proposals for Action 9, EMA/149479/2004 Final, 17 March 2005)

[5] http://www.fda.gov/bbs/topics/NEWS/2007/NEW01648.html

3. Methodology

The study was developed over a period of twelve months by an academic expert with a strong background in risk and policy research. The researcher was imbedded within the Agency, under the "National Expert" programme. An *ad hoc* Steering Committee was established to facilitate the project management. This group was composed of 13 members of Agency staff engaged in critical activities (pharmacovigilance, risk management, patients' information, external communication, regulatory affairs, etc.). The researcher completed the project following a detailed research protocol. This section presents the research path, including a summary of the theories and methods used, as well as critical aspects of the research design.

3.1 Theoretical framework

Historically risk studies were initiated in relevant areas as a rational attempt to forecast and mitigate possible harmful events (hazards) (Bernstein 1998), which explains why the initial stage of risk communication has been about conveying technical evidence to non-technical audiences. At its core, probabilistic thinking relies on the assumption that decisions about risks are rational, should be geared towards the maximisation of benefits and the minimisation of risks, and are best informed by probabilistic calculations of the likelihood and magnitude of possible harmful events (Jaeger et al. 2001). Toxicology and epidemiology are no exception (Lave 1987; National Research Council 1991; WHO 1977).

Risk communication emerged from research in risk perception showing that public or lay concerns about hazards did not correspond with the quantitative assessments of experts (Jaeger et al. 2001). Baruch Fischhoff (1995) and William Leiss (1996) have highlighted the evolutionary process that risk communication has undergone. Leiss (1996) has identified three phases in the evolution of risk communication practice:

- The first phase focused on the necessity of conveying probabilistic thinking to the general public and to educated lay audiences;
- The second phase focused on the persuasion of audiences and the management of public relations to convince people that some of their behaviour is inappropriate;
- In the third phase, the aim has been to develop a two-way communication process in which scientists, risk managers, and various laypersons engage in a social learning process.

Contemporary scholars treat risk communication as a two-way process that entails "multiple messages about the nature of risk and other messages, not strictly about risk, that express concerns, opinions or reactions to risk messages or to legal or institutional arrangements" (NRC 1989, p.21). This two-way process is more efficient when it is "proactive", i.e. when institutions engage in effective interactions with other stakeholders and avoid information vacuums (Lofstedt 2005).

In addition to replication experiments about how individuals perceive various situations, including attention to their heuristics and biases (Slovic et al. 2002), risk communication has also benefited from the analysis of the societal dynamics affecting decision (e.g. Löfstedt 2005; Rayner and Cantor 1987; Renn and Levine 1991). In the

past decades new research advancements in *social psychology* have improved our understanding of collective behaviour in the face of uncertainty. Specific attention has been paid to the social mechanisms that may affect perceptions, acceptance and ultimately decisions. For instance, a theory of the social amplification of risk has been developed (Kasperson et al. 1988; Pidgeon et al. 2003) to "*explain why the specific risks and risk events undergo more or less amplification or attenuation*" of perceived risks (Kasperson and Kasperson 2005, p. 107). Another critical advancement has been the study of the mechanisms that lead to trusting or distrusting institutions (Renn and Levine 1991; Löfstedt 2005).

One commonality between these theories is that the views and actions of influential stakeholders have a key impact on risk amplification, lay perceptions and trust. Influential stakeholders may vary from issue to issue, but usually include the news media, scientific experts and other opinion leaders (e.g. among healthcare practitioners), networks of peer and reference groups, industry, government officials, vocal activists within or outside organised Non-Governmental Organisations (NGOs).

Risk communication research and medicines

A small -however highly relevant- number of studies about pharmaceutical risk have been developed most notably by Bostrom, Fischhoff and Slovic (see Bostrom 1999; Fischhoff 1999; Slovic et al. 2007). These studies concentrate on the perception of pharmaceutical risks. It has conveyed useful insights into cognitive factors. The comparisons of the perceptions of eighty one hazards by Slovic et al. (1985) suggested, for example, that, besides DNA technology, classic pharmaceutical products such as Valium, antibiotics, Aspirin and vaccines ranked low in the scale of potential "dread" factors"[6], much lower than the concerns for nuclear or chemical risks.

In Europe, small-scale exploratory case studies have been conducted on specific events, such as vaccines scares (Bouder 2006), pain killers (Lofstedt 2007) and anti-diabetes drugs (Lofstedt 2010). Yet, the only systematic review of trust in the regulator undertaken in Europe, has focused on the USA Food and Drug Administration (FDA) (Lofstedt et al. 2010).

3.2 Research questions

The overarching objective of this project was to ***provide evidence based input that can be used to improve the Agency's communication to ensure safer and more effective use of medicinal products[7] and provide adequate information that balances benefits and risks of medicines appropriately[8]***.

[6] Risk perception studies have been developed by means of factor analysis and have indicated that the broader domain of characteristics of various hazards can be condensed to a small set of higher-order characteristics or factors. Factor 1, labelled "dread risk," is defined at its high end of perceived lack of control, dread, catastrophic potential, fatal consequences, and the inequitable distribution of risks and benefits. Nuclear weapons and nuclear power score highest on the characteristics that make up this factor.

[7] Art. 57(c) of Regulation (EC) No. 726/2004

[8] EMA Road Map to 2010

Risk events may affect the regulator's view of the balance between benefits and risks. The main goal of this project was to explore[9] and analyse stakeholders' views in the specific context of risk events to clarify what benefit/risk communication practice[10] would be the most effective. The project focused on answering the following research questions:

- What are the views and expectations of stakeholders?
- Do current communication channels build or undermine trust?
- How could the risk communication practice be improved?
- How could the communication process bridge the gap between opposite views and expectations to maximise the opportunities for consensus on benefits and risks?

3.3 Research design

This report offers an analysis and recommendations backed by widely used social science concepts and methods. As a preliminary step the project involved the preliminary review of the state-of-the art body of risk communication literature (see section 2.1). As a result, this study is framed by concepts that combine the conventional sender-receiver model of communication (Laswell 1948, Shannon and Weaver 1949) with social amplification of risks by the media (Kasperson et al. 1988; Pidgeon et al. 2003) and trust theories (Löfstedt 2005). Therefore, the researcher shaped the study's analytical framework according to theoretically and empirically tested criteria of risk communication "successes". Success in this context is defined as a meaningful and constructive exchange of information between the parties involved (Bostrom et al. 1994). Two criteria were considered essential to appraise the performance of the risk communication process:

- The communication of risks leads to a more effective system of information exchange, which impacts positively on behaviour and leads to measurable positive outcomes (e.g. less adverse reactions).

- The communication of risks leads to more satisfaction of the parties involved and reduces conflicts among the stakeholders, therefore conducive to higher levels of trust.

In environments where trust for the regulator is high, a top-down communication model lead by medical experts may be sufficient to achieve success. In low trust environments, on the other hand, an active engagement of the involved parties in a two-way communication process would achieve better results[11]. The experience of

[9] The exploration approach must be understood in the context of social science research categories (i.e. *explanation, description, illustration, exploration and meta-evaluation*) (Yin 2003, p.15).
[10] The author of this report defines "risk communication practice" as the arrangements, processes and mechanisms that structure the interactions between the various actors involved in exchanging information on the benefits and risks.
[11] A two-way risk communication process is "an interactive process of exchange of information and opinion among individuals, groups and institutions. It involves multiple messages about the nature of risk and other messages, not strictly about risk, that express concerns, opinions or reactions to risk messages or to legal or institutional arrangements" (NRC 1989, p. 21).

high-profile controversies (e.g. Vioxx, MMR vaccine in the United Kingdom, Hepatitis B vaccine in France) allowed the formulation of a **critical hypothesis**:

> The European regulator is confronted to post-trust environments, and, as a consequence, stakeholders are likely to expect a two-way communication model rather than old-style top-down messages.

This study adapts Löfstedt (2005) key variables of trust. Three key variables have been defined:

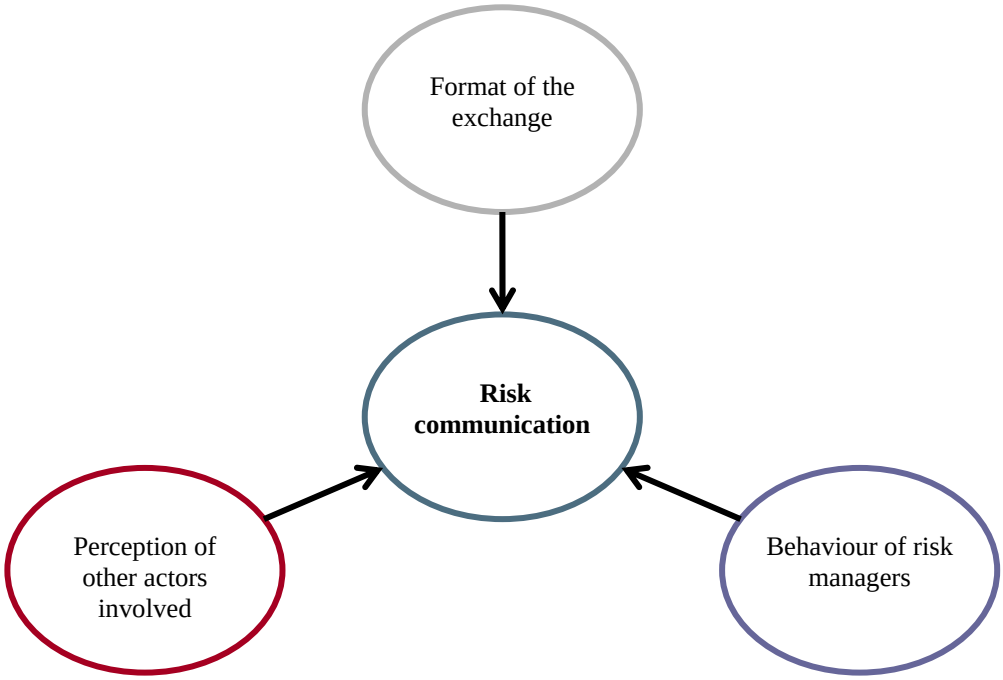
The first variable is about the *format of the exchange*. In a high public trust, high/low uncertainty risk situation, public information can be top down and deliberative risk management strategies are therefore not required. In a low public trust environment effective risk communication requires to implement a risk management strategy selected after the reasons for the distrust. Deliberative techniques can help create public trust regarding a contentious issue, if public distrust has to do with partiality, but are expensive and time consuming.

The second variable concerns the *behaviour of risk managers*. The regulator has to test and see whether there is public trust. Proactive regulators, who act before a crisis, are more likely to gain trust. In low trust situations, charismatic individuals are extremely helpful in negotiating successful deliberative outcomes. When different levels of government are concerned, all levels need to support the final outcome.

The third variable relates to the perception of the non-regulatory actors involved. Industry and interest groups may in many cases try to enhance the trust vested in them at the expense of regulators, which in turn can lead to failures of the risk management process. When the regulator is not seen as impartial it will benefit from co-operating with highly trusted institutions and individuals.

Figure 1 presents a simple representation of the key variables that influence the risk communication outcome.

Figure 1- Inputs to risk communication: key variables



3.4 Study population

The researcher explored the views and representations of **influential stakeholders** independently of their level of expertise. 'Influential' stakeholders were defined as the key voices that have a direct influence on the formulation and communication of policy decisions. Healthcare professionals were not included in the selection, as their communication to patients is already well-studied, and their impact on policy is less direct. For the same reason, it was not necessary to include randomised samples of 'patients' or 'the general public'. The identification of a critical mass of over 100 influential stakeholders (from government, industry, journalists, patients groups, scientists, etc.) was closely linked to concrete investigation cases (see *Topics*). The study population included public sector (regulators), private sector and third parties:

- "Regulators" :
    - Members of the Agency scientific committees, especially those individuals who played a key role (e.g. Rapporteurs)
    - Regulators in national agencies
    - The Agency's staff (including Product Team Leaders) and experts
    - Elected Officials (MP, MEP)
- "Industry":
    - Marketing authorisation holders (MAHs)
    - Industry bodies
- "Third parties":
    - Patients" organisations
    - Other third parties (e.g. consumers organisations)
    - Scientific opinion leaders
    - Medical and non-medical journalists and editors.

3.5 Inclusion criteria

The key selection criterion was "influence", understood as high-impact communications that frame the public debate, e.g. CHMP drafting of a specific communication or influential patients' organisations taking a public stance. Selected participants, whether recognised as 'experts' or not, were meant to have played an active role in the selected topics. In a number of cases this implied going beyond the usual pool of institutional interlocutors. Some interlocutors of the Agency with only little influence were excluded. Respondents came from Member States and beyond. Individual respondents were selected on the basis of established social science techniques used to capture the views of a 'milieu' (Gaskell 2000):

- Background research was conducted on archival documents, media reporting and other topic-related information.
- The so-called 'snow ball technique' was also used, whereby respondents designate other critical respondents.
- Interviewees were then approached by email and telephone.

To avoid bias, this selection was cross-checked and discussed with members of the Steering Committee and external experts. Specific attention was paid to ensuring a fair geographical balance between Member States, within the limitations of the topics chosen.

3.6 Topics

Because of its exploratory nature, and to ensure accessibility to relevant and manageable information this research has adopted a case study strategy (Yin 2003). In addition to general selection concerns about feasibility and opportunity, the case selection process reflected the many facets of views on benefit/risk in the pharmaceutical area (EMA 2009a). Tensions exist around the notion of benefit/risk. The objective was to capture and explore possible variations that may have an impact on expectations. Four specific criteria were used to select relevant cases:

- Theoretical relevance;

- Medical significance;
- Policy relevance;
- Societal concern.

Theoretical relevance is about the key factors uncovered by risk theories that help clarify how individuals make benefit/risk judgements. Risk research has shown that, although the basic levels of worries about medicines are generally lower than for other risks (e.g. nuclear or chemical risks), perceptions vary significantly (see Table 1). People also views the benefits and risk of vaccines through specific *heuristics* (Ball et al. 1998; Bostrom 1999; Slovic et al. 1985; Slovic 1987; Slovic et al. 2007).

Table 1- What kind of medicines worry people?

Product / Perception	Low	Moderate	High	Dread
Vitamin pills	X			
Acupuncture	X			
Aspirin		X		
Valium		X		
Antibiotics		X		
Cancer chemotherapy			X	
Diet medicines			X	
Depression and anxiety medicines			X	
AIDS therapies			X	
DNA technology				X

Source: Adapted from Slovic et al. 1985; Slovic 1987; Slovic et al. 2007

Medical significance is about conventional definitions of benefits and risks in the medical area. For instance, the European pharmaceutical legislation defines a risk-benefit balance as an evaluation of the positive therapeutic effects of a medicinal product in relation to any risk relating to the quality, safety and efficacy of this product as regards to patients' health or public health[12]. Policy relevance is about the concerns that have prompted the regulator to step in -for example to withdraw a product- or that have triggered sustained discussions among decision makers, for example at CHMP meetings. Policy relevance is also about selecting the appropriate level of competence and responsibilities: only centrally authorised products or at least products where the Agency has played a significant regulatory role should be included in the selection. Societal concerns are about areas where there is tangible proof that influential stakeholders take the issue seriously for example through media coverage.

To ease the selection process, the 13 members of the Steering Committee were interviewed in March 2009. This process was particularly important. The Agency was the main focus of the study and it was essential to investigate both the commonalities and the differences of perception within the organisation. The interview process lasted from 30 minutes to one hour and fifteen minutes. Interviewees were introduced to the research project as well as the dynamic of the selection process. Then, they were

[12] Article 1 point 28 or Directive 2001/83/EC as amended

invited to highlight a few possible cases. Finally, they were asked to provide their views on alternatives suggested by other interviewees.

The researcher anticipated that Committee members' suggestions may exhibit significant variations. Yet, despite differences in background, suggestions showed a remarkable degree of convergence around three major issues:

- high profile drug recalls on safety grounds;
- vaccines scares;
- contamination / quality issues.

The application of the selection criteria led to the selection of three cases: Viracept, Acomplia and Gardasil.

Then, in order to reduce the chance of an Agency's self-selection bias, the researcher appraised the relevance of these specific issues against known risk perception factors. HIV, for example, is a source of anxiety, and the HIV treatments have been reported to score high on the scale of apprehensions (see Table 1). Since the outbreak of the 1980, patients' organisations have been actively involved (Permamand 2006). The case of a contamination issue linked to an anti-HIV drug, Viracept offered a very topical case. This case was particularly interesting from the perspective of the emotional factors linked to HIV and the subsequent media interest. It is also interesting from the perspective of introducing a more formal involvement of patients' organisations in the Agency's decision and communication processes.

Among high profile recalls on safety grounds, two products, Acomplia and Raptiva came top of the list. When the two were compared Acomplia appeared to be the favourite choice. Acomplia was also of higher relevance from a risk perception/communication perspective. It was centrally authorised. Finally, it has attracted far more media attention and draws on two major public concerns for obesity (on the positive side) and for suicide (on the negative side). Suicide was also an unfocused concern of four of the respondents, which strengthened the case.

Although most participants suggested that the study should somehow reflect the specific issue of vaccines, they have expressed more diverse views on possible cases. Suggestions that came highest on the list were Gardasil and Hexavac. Gardasil was found particularly interesting from a societal perspective because of the public health objective to prevent human papillomavirus (HPV) infections. The issue has also received a lot of media attention, both on the positive (cervical cancer prevention) and negative side (sexual behaviour and cost of the vaccination). The product presents a case of hypothetical risk comparable to the MMR case.

During the interview process, respondents were also asked whether other cases could have been selected. Despite much more diverse backgrounds, their answers confirmed the high relevance of the selection, which points towards the existence of a "social milieu" (Gaskell 2000) when it comes to medical risks.

3.7 Data collection and analysis

The research process has been pursued through:

- A content analysis of critical primary sources (archival documents, press articles) and, to a lesser extent, secondary sources (relevant literature).
- Interviews of key stakeholders. The interview material collected to address the first objective will also support an analysis of the respondents' discourses.

The analysis of critical sources was used at early stages of the research to provide robust contextual information and at later stages to allow the robust triangulation of the data. Data triangulation refers to the collection of information from multiple sources aimed at corroborating the same fact or phenomenon. In this case it involved systematic desktop research to triangulate information prior to and after the interview. Main sources included:

- Numerous internal and external communications from the Agency, e.g.:

- CHMP's European Public Assessment Reports (EPAR) of the product
- Other reports from the CHMP, its working parties, etc.
- Press releases
- Questions and Answers (Q&As) documents
- "Lines to take"
- "Lessons learnt";

- Other critical sources:

- Websites and press releases of the institutions involved (governments, industry, patients and consumers' organisations) involved
- Specific information to healthcare professionals (Dear Doctor letters, etc.)
- Related articles in peer-reviewed journals (Lancet, NEJM, BMJ, etc.)
- Media as appropriate (e.g. El Mundo, El Pais, Wall Street Journal)
- Other public discussions (e.g. vaccine opponents[13]).

The interview process was inspired by innovative investigation methods introduced by psychologists. Cognitive scientists have uncovered and analysed the limitations of most communications. Many communicators tend to repeat standardised messages - that reflect their priorities rather than those of the targeted audience (Bok and Morales 1998)- regardless of their impact on behaviour (Crosby and Yarber 2001). They often ignore common gaps in knowledge and misconceptions (Halperin 1999). Scholars from Carnegie Mellon University have developed the "mental model" approach that avoids these shortcomings. The main objective of the approach is to learn from the mental representations of experts and lay people to develop communications that bridge gaps and misconceptions (Bostrom et al. 1994). This approach implies[14] to:

1- Design an integrated assessment using information from topic experts;
2- Gather information from target audience;
3- Identify gaps, misconceptions and critical problems in audience's comprehension;
4- Develop intervention to correct problems;

[13] For example the Spanish "Victims of the HPV vaccines", which also contains a discussion forum: http://www.aavp.es/
[14] See http://dels-old.nas.edu/emergingissues/docs/Downs.pdf

5- Evaluate the communication.

The mental model approach, as a distinct methodology, concentrates on the relationship between the views of scientists and those of lay audiences. As such, it does not formally apply to the exploration of the views of more diverse and partly organised interests. Yet, the innovative nature of the model, both in terms of approach and methods became a conceptual framework to guide this study. It helped confront the traditional weaknesses of communication. The main constraint of the mental model stems from its thoroughness. Open-ended interviews last for about an hour and their time-consuming nature limits the size of the sample compared to other approaches (e.g. surveys). Yet, results from the Carnegie Mellon team who have conducted the largest number of mental model studies indicate that in-depth interviewing and analysis of a small convenient sample produce much better and more useful results than randomised conventional quantitative questionnaires (e.g. Bostrom et al. 1992).

This study used the following data collection process, inspired by the mental model approach:

- One hour individual face-to-face interviews of the influential stakeholders;
- Open-ended questionnaires with very simple questions that do not frame the answer;
- Going from the general to the specific. A set of general questions, common to the three cases, helped to guide the discussion (e.g. "what may have triggered risk-related concerns in your organisation"). Specific questions also reflected the distinct attributes of each case, to ensure contextual relevance.
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The interviews:

- Did not intend to control the behaviour of the study population;
- Relied on relevant data management methods, which collect and analyse stakeholders' rather than projecting the researcher's concepts and categories.

The study collected in-depth information from 102 respondents. 77 formal interviews were conducted in the United Kingdom, France, Spain and Switzerland. The researcher conducted additional interviews through teleconference in the same counties, as well as Belgium, Bulgaria, Germany, Ireland, Italy, the Netherlands, USA, and Sweden. Table 1 introduces the profile of the respondents involved. The relative over-representation of regulators is due to the distinct populations of European and national regulators (in the EU, Switzerland and North America) introduced in Table 2[15]. The nature of the risk, a contamination issue involving a more complex risk assessment process, required a larger pool of interviewees in the Viracept case (Table 3). Most of the individuals contacted agreed to take part. There were 4.32% passive refusals (people who did not return calls and emails) and no active refusals. The level of detail of the information disclosed varied. Cross-validation of the information suggested that the trustworthiness of the responses was generally high, although the researcher uncovered distinct nuances about how the same information was presented. Yet, the guidance offered by the researcher, the

[15] The last two categories are captured under "others".

large amount of data involved (i.e. size and diversity of the cohort), combined with strong triangulation helped to fill gaps and verify information.

Table 1- Interviewees by origin

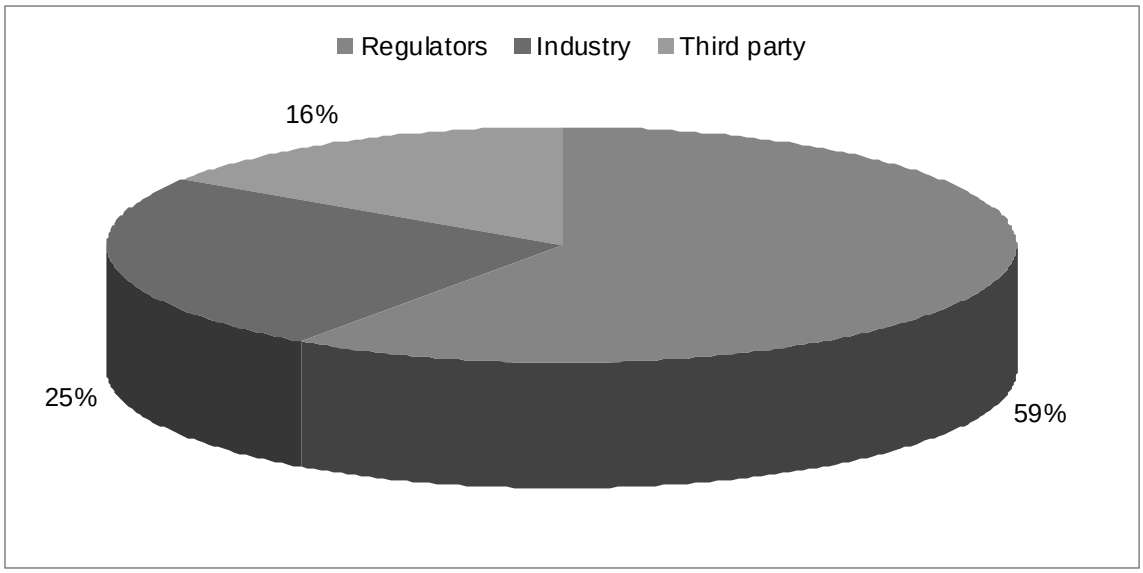


Table 2- Population of regulators

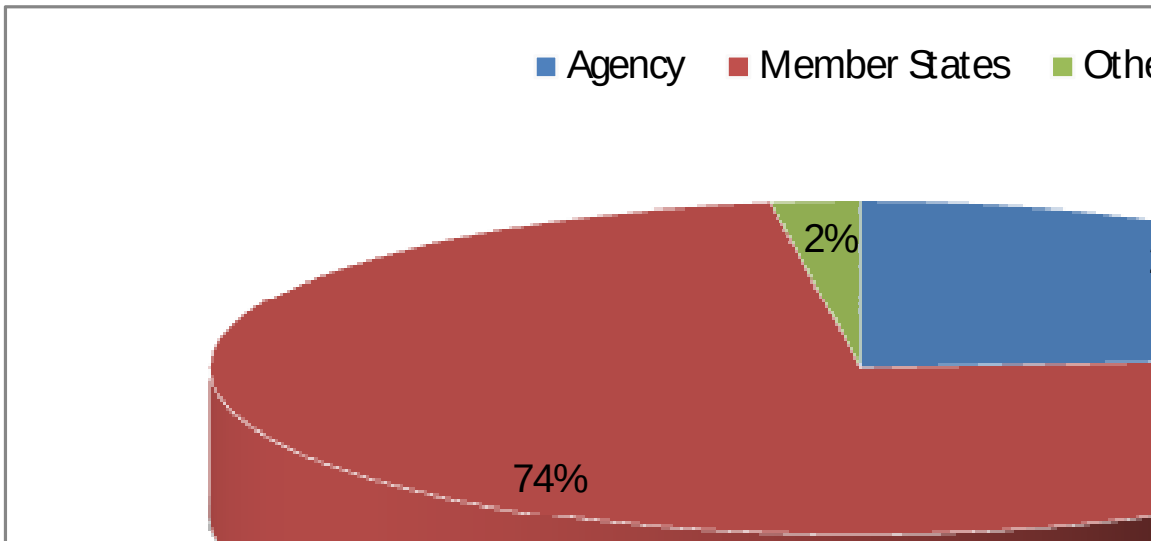
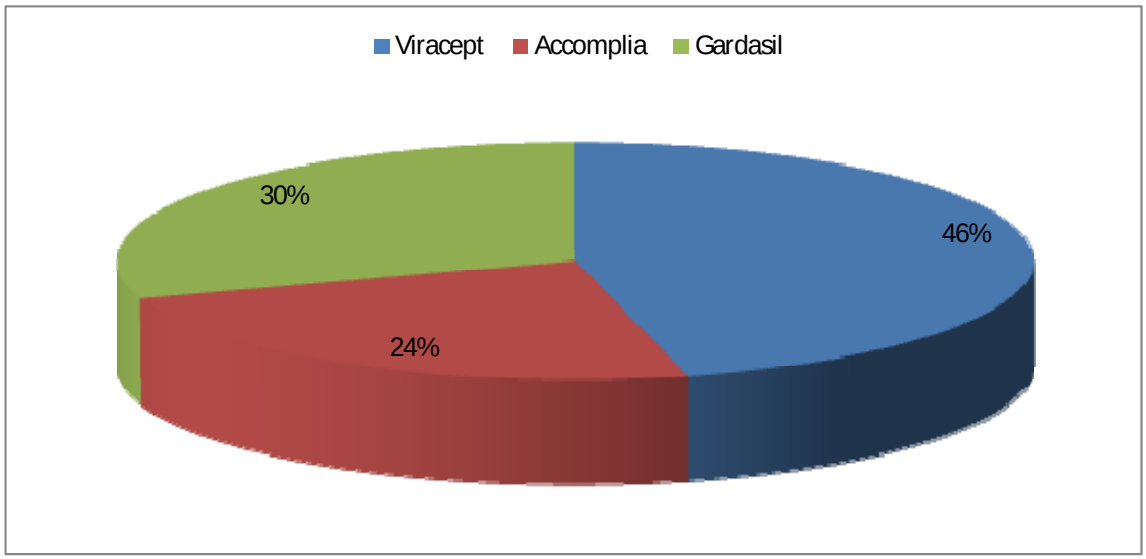


Table 3- Interviewees by case



The researcher followed a standardised process to deal with the interviews material:

1- Background review and characterisation of the scientifically known factors presented in the Agency's internal sources about the nature and characteristics of the benefits and risks involved.
2- Elicitation of individual beliefs on the basis of a structured analysis of the open-ended interviews. The traditional 'cut and paste' technique was preferred to the use of automated software packages, which support "*data administration and archiving*" rather than "*data analysis*" and are usually based on "*code and retrieve*" rather than "*cross-referencing*" techniques (Kelle 2000, p. 285). In the present case the main challenge was precisely analysis and cross-comparisons rather than the classification of a large amount of information.

3.8 Format

The report presents three monographs, one for each case, followed by a cross-case analysis. It does so using a standardised reporting structure, which follows the conventional categories of risk management (NRC 1983; Renn 2007) (see Table 2).

Table 2: Case reporting structure

Risk characterisation	**Benefit/risk judgement**	**Reassessment of the benefit/risk judgement**
Benefit and risks of the product prior to alert (introductory paragraph)		
1. Initial alert		
	2. Handling of uncertainty	
	2.1 Response	

	2.2 Risk evaluation	
		3. Reassessment of the risk (if relevant)

Some aspects of the reporting format may be unfamiliar to medical professionals and natural scientists, e.g. the use of quotes. Quoted words and phrases from research participants are a common feature of qualitative research reports. Quotes are used to support researcher claims, illustrate ideas, illuminate experience, evoke emotion, and provoke response (Sandelowski 1994). In qualitative research quotes are used routinely to strengthen the presentation of data and make prevalent discourses clearer for the reader. They are therefore demonstrative or illustrative, not decorative or arbitrary.

For ethical reasons, the researcher guaranteed anonymous responses. Quotes have been anonymised, a standard practice in social science.

4. VIRACEPT

Viracept is an antiviral medicine, which contains nelfinavir (as nelfinavir mesilate) as its active substance. It is used in combination with other antiviral medicines to treat adults, adolescents and children over three years of age who are infected with HIV-1. Viracept was first introduced on the market in 1998. In the year 2000 Viracept was prescribed mostly to pregnant women and children because of it high tolerability. It was recalled from the European market on 6 June 2007. The recall was due to the presence of an impurity known as ethyl mesylate (EMS), also called methane sulfonic acid ethylester.

4.1 Initial alert

During the last months of 2006 and at the beginning of 2007 Roche had detected some impurity formation at the manufacturing stage. In May 2007 patients reported an unpleasant smell (Lutz 2009). According to a respondent from the company "Some nausea and vomiting were also reported. We realised that the problem was likely to be serious". In June 2007 Roche informed the European Commission of the contamination. Although the company had been able to identify the impurity formation, Roche scientists still needed to identify the root causes:

> "*It meant that we had to work backward to find out what had happened. In practice it meant 24 hours a day of testing of 4-5 months of production*".

EMS is a known to be genotoxic, i.e. it is harmful to DNA, the genetic material in cells. At sufficient levels it may trigger cancer. A large population had been exposed, which, arguably, heightened worries of the regulators and the company. The contaminated batches of Viracept tablets were distributed around the world to a total of 29 countries including six within the European Union (France, Germany, Italy, Portugal, Spain and the United Kingdom). In North Western Europe the medicine was less prescribed, while most patients were found in developing countries and Eastern Europe. In all, an estimated 20,000 to 25,000 patients had being exposed to EMS. It

was argued that in the worst cases, patients may have taken highly contaminated Viracept for months (at least from March-June 2007).

4.2 Handling of uncertainty

The course of events may be divided into three phases, i.e. precautionary decision, risk evaluation and re-assessment of the precautionary decision. Each phase has influenced risk communication.

4.2.1 Response

On 6 June 2007, Roche and the Agency announced that, in agreement with the Swiss medicines agency (Swissmedic)[16], Viracept was recalled in Europe and some other world regions. The USA, Canada and Japan were not affected because it is Pfizer and not Roche that manufactures and markets Viracept in these countries. Interviewees from Roche have indicated that the company was very supportive of the recall. A respondent indicated that:

> "*It is better to be "super-precautionary" than too lax. We will never be blamed for doing too much while we could be blamed for doing not enough*".

Roche immediately recalled all batches of Viracept from the European market and informed prescribing doctors about the incident. The recall was more difficult to enforce in other parts of the world, especially developing countries where Viracept was usually distributed by NGOs and where doctors and patients were more difficult to identify. In this respect many respondents from industry, regulatory and patient sides have complained about the lack of positive involvement of international mechanisms, including WHO, to help with the global recall.

On the same day, the Agency published a press release, while Roche issued an "Investor Update" to inform their respective networks as well as the general public. Both documents may be accessed online. The regulator and the industry shed different lights on the event. While Roche only mentioned higher than normal levels of impurity, the European agency, using expert rather than lay language, highlighted the presence of a risk requiring some evaluation:

> **Roche Investor Update[17]:**
> **"Roche recalls Viracept due to chemical impurity".**
> "A detailed chemical analysis of the affected tablets showed they contain higher than normal levels of methane sulfonic acid ethylester".

> **Press Release** (Ref. EMEA/251718/2007)[18]**:**
> "Ethyl mesylate is a **known genotoxic substance** (…). The level of risk to patients resulting from this contamination **is difficult to measure,** and is currently **under further evaluation.** The company is performing a complete

[16] Swissmedic announced the recall the following day, on 7 June 2007
[17] http://www.roche.com/investors/ir_update/inv-update-2007-06-06b.htm
[18] http://www.ema.europa.eu/humandocs/PDFs/EPAR/Viracept/25171807en.pdf

> recall of the medicinal product. (…) Patients receiving Viracept should therefore contact their doctor immediately (...)"

What impacts did these communications have on patients? Parallel messages on the risk may have confused healthcare professional and patients, with the likely outcome of alarming them. However, HIV-AIDS organisations were directly involved by the European regulator, national regulator and Roche, with the effect of 'smoothing' subsequent discussions about the risk. The Agency involved a known and well-respected member of the European AIDS Treatment Group, who then became the interface between the organisation and the patient community. He described the first contact as follows:

> "*I received a phone call out of the blue: we have a safety issue, there are some impurities in tablets we would like to involve you."*

Member States also mobilised their network of HIV/AIDS organisations. In France they were especially proactive, which is not surprising because the French regulators had a very difficult relationship with HIV/AIDS groups in the 1990s when the transfusion of haemophiliacs with HIV-contaminated blood products (1984-1984) was made public. As a result, anything related to HIV is taken very seriously. The French agency, AFSSAPS, involved TRT-5, a coalition of 8 leading organisations, including Act Up Paris and AIDES[19]. Their involvement also started with a phone call:

> *"It all started with a phone call from AFSSAPS telling us that some batches needed to be recalled."*

TRT-5 and AFSSAPS meet 2 to 3 times a year to review and update information issues. TRT-5 members have indicated that they feel "privileged" about the role they play in the policy process.

In this context of mounting concern about the risk the Agency went a step further. On 21 June, it announced that, because the quality and safety could not be ensured it was recommending to the European Commission to suspend the marketing authorisation for Viracept.

On 18 July 2007, TRT-5 wrote a letter to the Agency, AFSSAPS and two EC Commissioners expressing their worries, using strong statements such as:

> "[this raises] *Important questions regarding the quality of drugs authorised by the EMEA"*.
> *"We do not accept that such crisis should happen again"*.

The Agency did not involve TRT-5, which on the other hand remained in close contact with AFSSAPS. They also held separate conversations with Roche France. The patient representative involved by the Agency acted as a facilitator within the patient community. He also acted as the interface with healthcare professionals.

[19] Accessed at http://www.trt-5.org/

According to one respondent: "*Knowing that a patients' advocate was involved reassured everybody*".

By the end of July, although the recall was still effective and Viracept was therefore unavailable for patients, the European Commission's decision on market withdrawal was still pending. The Agency published further Q&As on 26 July 2007 (Ref. EMEA/337440/2007) where it reinforced its view that "The EMEA's recommendation to the European Commission that Viracept's marketing authorisation be suspended still applies"[20]. The Q&As document also heightened its message about the seriousness of the risk:

"Recent batches of nelfinavir mesylate, the active substance in Viracept, have been contaminated with **high levels** of ethyl mesylate".

The marketing authorisation for Viracept was finally suspended on 7 August 2007, almost seven weeks after the Agency's call for suspension.

The initial alert was strong enough to generate high concerns in industry and regulatory circles, and the recall reinforced this message. On the other hand, some patient representatives wondered whether the delays in the decision to suspend meant that regulators were having second thoughts about the seriousness of the risk.

4.2.2 Risk evaluation

A popular view of the precautionary principle is that after a precautionary ban has been imposed, more evidence should be found to reach an informed decision (Klinke and Renn 2002; Sunstein 2003). The Agency was concerned with two main issues. The first issue had to do with the contamination process. Was it incidental or was it systemic? As soon as the contamination was known, the Agency launched an investigation to identify the causes of the contamination. Swissmedic, in collaboration with the Agency, organised an inspection of the Basel active substance manufacturing site on 11 June 2007. The results were presented to the Agency on 19 June 2007. Experts found out that the risk was systemic and resulted from "*the cleaning of a tank with the wrong type of alcohol*" to use the words of one respondent. Roche was asked to adapt its manufacturing process and a re-inspection of the site was envisaged to check on Roche's compliance.

The second issue was the health impact. At the same time of the recall levels of uncertainty remained high with respect to the potential consequences for patients. The Agency held a meeting of toxicology experts on 13 June 2007 and its scientific body, the CHMP[21], which meets on a monthly basis, looked into the issue the following week. The conclusion of this assessment, published in the Agency's Q&As of 21 June 2007 (Ref. EMEA/276379/2007)[22], was that there was "currently insufficient data to

[20] http://www.ema.europa.eu/humandocs/PDFs/EPAR/Viracept/33744007en.pdf
[21] The European Medicines Evaluation Agency (EMEA) was established in 1995 by the European Commission. Scientific opinions are provided by the Committee for Human Medicinal Products (CHMP) (formerly the Committee for Proprietary Medicinal Products, CPMP) of the European Medicines Agency, as the Agency is now called.
[22] http://www.ema.europa.eu/humandocs/PDFs/EPAR/Viracept/27637907en.pdf

establish which dose of ethyl mesylate may be toxic to humans." The CHMP requested Roche to:

- Identify the group of patients who had been exposed to contaminated batches of Viracept in order to establish registries;
- Carry out toxicological studies.

In order to establish registries, the CHMP recommended the following patients:

- Exposed to high levels of contaminant in the batches of Viracept released since March 2007;
- All pregnant women who have ever been exposed to Viracept;
- All children who have ever been exposed to Viracept, including those exposed *in utero*.

Some countries were in favour of registries, including France and the United Kingdom, while others were more sceptical. Respondents from Roche, on the other hand, argued that it was neither realistic nor feasible. As the Agency later revised its view on the subject (see below), the debate about the feasibility of the registries remained largely theoretical.

The toxicological studies have been described as "in-depth studies into the effects of EMS". The studies were conducted in mice, as existing toxicology data on EMS did not permit an adequate patient risk assessment (Pozniak et al. 2009).

4.3 Re-assessment of the risk

The positive results of a re-inspection of the Basel site as well as reassuring toxicological studies changed the regulator's perspective.

A joint EU-Swissmedic re-inspection was organised at the Basel active substance manufacturing site from 5 to 7 September 2007. Roche had met the requirements of the action plan defined in June, which reassured the regulators. The results were presented to the CHMP on 17 September 2007.

Toxicology studies took almost a year to bring results. The process involved back and fourth interactions between the Agency and Roche, experts' panel meetings and public meetings where third parties were also involved. On 17 June 2008 Roche provided the Agency with an updated risk assessment (Müller et al. 2009; Müller and Singer 2009). It was considered that, based on extrapolation of mice to humans, the levels of EMS were too low to present a serious health risk. On 24 July 2008, the CHMP issued a follow up "Question and Answers" document (Ref. EMEA/CHMP/375807/2008), where it validated the studies:

> "Company experts have used special models that allow results from animal studies to be 'extrapolated' to humans. This has allowed them to calculate the threshold value for patients who have been exposed to ethyl mesilate (2 mg per kilogram and per day)."

> "These animal studies have shown that 'there is a threshold level below which ethyl mesilate does not have a harmful effect on the DNA (25 mg per kilogram and per day in the mouse).' " [23]

Some patient representatives interviewed for this study have complained about the technical nature of the data conveyed, which hampered their capacity to assess the methodology and the data. Generally, however, they had sufficient levels of confidence in the process -led by the Agency and carried by Roche- to buy into the robustness of the research.

These developments changed CHMP and the Agency's opinion on the usefulness of registries. A respondent from the Agency declared:

> "*Finally we decided that there should be no registries, thanks to the work of people from toxicology and pre-clinical studies who came to reassuring conclusions*".

On 20 September 2007 the Agency informed the public that:

> "The Committee was satisfied by the actions taken by the company and by the outcome of the inspection, which confirmed that the necessary measures had been put in place";

The crisis was officially over and Roche informed the public on 20 September 2007 that Viracept was recommended for re-instalment and on 19 October 2007 that the European licence was re-established by the European Commission. The Agency did not announce these decisions, but published some follow up Q&As nine month later, on 24 July 2008.

> "Patients who took Viracept tablets at the highest level of contamination were exposed to levels of ethyl mesilate of about 0.05 mg per kilogram per day.As these levels are below the threshold, the CHMP concluded that patients exposed to contaminated Viracept are not at an increased risk of developing cancer, and that they do not need to be followed up as was previously planned" (Doc. Ref. EMEA/CHMP/375807/2008)[23].

Respondents from Roche have expressed some relief over the final resolution of this crisis, despite the large amount of resources mobilised. Reactions of regulators in Member States have been more diverse. Some were satisfied. Others were of the opinion that the complete set of data from toxicology studies came too late. This case also demonstrates that regulators may disagree on the risk, even after a formal position has been taken. For instance some national regulators still argue that registries should not have been abandoned. One Member State even tried to set up patients' registries after the idea was ruled out by CHMP. One respondent from Roche suggested, for example, that a Member State:

> "*[a Member State] did not accept the CHMP's decision. They still wanted to monitor, through their AIDS centres, patients who had taken over*

[23] http://www.ema.europa.eu/humandocs/PDFs/EPAR/Viracept/Q&A_Viracept_37580708en.pdf

100ppm. Roche wrote a letter to the country's authorities saying that it was the EMEA's decision for Europe. Then discussions involved us, the EMEA and the country's national competent authority. The national authority had difficulties accepting the CHMP's decision."

Patients' organisations did not present a unified view of the management of the crisis. Although they were generally satisfied with their degree of their involvement, some expressed concerns about the "strain on resource" on them for what turned out to be a negligible risk.

5. ACOMPLIA

Obesity is defined as the accumulation of dangerous levels of fat into the body[24]. It presents a long term-risk of high magnitude and significance for society. According to the WHO it has now reached epidemic proportions globally[25], among children, adolescents and adults (Paxton et al. 2006).

Acomplia (rimonabant) is an anti-obesity medicine manufactured by Sanofi-aventis. It was approved for marketing in the European Union in June 2006. Rimonabant is the first member of a new class of molecules that target a newly recognised physiological system, the endocannabinoid system. It is a cannabinoid receptor antagonist, which acts by blocking a specific type of receptors, the cannabinoid type 1 (CB1) receptor. Rimonabant was licensed as an adjunct to diet and exercise in the management of obese patients (BMI 30 kg/m2), or overweight patients (BMI > 27 kg/m2) with associated risk factors, such as type 2 diabetes (who may be taking oral anti-diabetes medication or insulin) or dyslipidaemia.

Expectations were high. Respondents described Acomplia as a one in a decade blockbuster. Although this was presented with irony, an article by Jacob Goldstein, published on the WSJ's blog on health and the business of health spoke of:

> "The buzz machine for Sanofi-Aventis' Acomplia, the much-hyped, long-awaited cure-all of modern ills, got rolling three years ago, after the company presented astonishing clinical data at a meeting of heart specialists. The drug appeared able to help patients shed pounds, stop smoking and manage their cholesterol problems". (Goldstein 2007)

Prior to its approval, the medicine was also seen as potentially capable of treating depression and helping people stop smoking. These arguments were developed in the EPAR (European Public Assessment Report)[26], which may still be accessed online[27],

[24] The World Health Organization (WHO) defines it as "condition of abnormal or excessive fat accumulation in adipose tissue, to the extent that health may be impaired" *WHO (2000) (PDF). Technical report series 894: Obesity: Preventing and managing the global epidemic. Geneva: World Health Organization.* ISBN 92-4-120894-5. http://whqlibdoc.who.int/trs/WHO_TRS_894_(part1).pdf.

[25] http://www.who.int/dietphysicalactivity/publications/facts/obesity/en/

[26] The Agency publishes information on the products assessed by the CHMP. Any positive opinion given by the Committee is published in the first instance as a Summary of Opinion. More detailed information is published later, following the granting of a Marketing Authorisation by the European Commission as EPAR. The EPAR reflects the scientific conclusion reached by CHMP at the end of the centralised evaluation process. The legal basis for its creation and availability is contained in Article

as well as non-regulatory material, such as health magazines and "online pharmacy" websites[28]. Respondents from Sanofi-aventis also suggested that Acomplia may also prevent cardiovascular risks, including clogged arteries and heart disease. Acomplia was also considered for type 2 diabetes, as it may reduce glycated haemoglobin (HbA1c) levels, thereby helping to reduce risk of long-term microvascular complications. This would be expected in addition to reductions in weight and waist circumference.

On the downside, initial concerns were rather moderate. The EPAR for Acomplia (2006) suggested that "depressive disorders reported with rimonabant 20 mg were usually mild or moderate in severity" (p. 33). The CHMP's assessment also highlighted that these adverse events were dose dependent and that most of the cases were resolved with the corrective measures undertaken, either discontinuation or anti-depressant treatment.

5.1 Initial alert

Acomplia was marketed in 18 Member States (Austria, Belgium, Cyprus, Denmark, Estonia, Finland, France, Germany, Greece, Ireland, Italy, Lithuania, Malta, the Netherlands, Slovakia, Spain, Sweden and the United Kingdom). In the USA, where Rimonabant is known as Zimulti, concerns developed at the pre-authorisation stage over the potential effect that the compound may have on mental health. Suicidal thoughts were reported in patients in clinical trials. In June 2007, FDA's concerns were strong enough to refuse approving Rimonabant for use in the United States. Respondents from patients' organisations highlighted that, in the past decade, the risk of suicide has become one of the regulators' top worries:

> *"Regulators worried about cardiovascular risks ten years ago, psychiatric effects are today's concern."*

5.2 Handling of uncertainty

On 13 June 2007, the FDA independent advisory committee unanimously voted against recommending regulatory approval after hearing evidence that Acomplia increases the risk of suicidal behaviour. Acomplia was already on the European market. After the decision, the product became subject to a number of restrictions, before being finally suspended from the European market in 2008. Respondents disagreed about how much the FDA's position may have influenced the Agency's assessment of benefits and risks. One respondent from the industry side suggested that "*EMEA did not want to seem weaker than its American counterpart*" but staff at the Agency's and CHMP members have highlighted that their decisions were based on a thorough review of the evidence. The assessment procedures announced in the

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13(3) of Regulation (EC) No 726/2004. It is made available by the Agency for information to the public, after deletion of commercially confidential information.

[27] http://www.ema.europa.eu/humandocs/PDFs/EPAR/acomplia/H-666-en6.pdf

[28] For example: "Lose Weight and Quit Smoking With New Drug" http://www.webmd.com/diet/news/20040217/lose-weight-quit-smoking-with-new-drug ; "Acomplia's potential resides in its promising therapeutic profile in two vast and highly underserved markets: obesity management and smoking cessation." http://www.acompliareport.com/News/news-011505.htm

Agency's external communications and described to the investigator indicate that Sanofi-aventis was asked to carry out further scientific assessments. But would they have been requested had the product been approved in the USA?

5.2.1 Response

The milestones of the Agency communication were as follows:

- On 19 July 2007, the Agency issued a Q&A document (EMEA/330598/2007) where it restricted prescriptions away from susceptible patients. The Agency's wording was that "Acomplia must not be used in patients on antidepressants or with major depression". This message was reinforced on 25 July 2007 (EMEA/318931/2007).
- In May 2008, the CHMP recommended updating the product information to "reflect the fact that depression may occur as a side effect of Acomplia in patients who have no obvious risk factors apart from obesity itself", and "to advise prescribers to monitor patients for signs and symptoms of psychiatric disorders, particularly depression, after the start of treatment".
- After more studies, the Agency suspended the product , which was announced by a press release on 23 October 2008.

After almost a year, the Agency came to the conclusion that "the benefits of Acomplia no longer outweigh its risks and the marketing authorisation should be suspended across the European Union (EU)." The press release issued on 23 October also indicated that

> "The CHMP considered that the new data from post-marketing experience and ongoing clinical trials indicated that serious psychiatric disorders may be more common than in the clinical trials used in the initial assessment of the medicine. The CHMP was also of the opinion that these psychiatric side effects could not be adequately addressed by further risk minimisation measures".

In the Agency's view, the new data from post-marketing experience and the ongoing clinical trials indicated that serious psychiatric disorders may be more common that in the initial assessment. The Agency presented its decision to suspend as a "precautionary measure". In this case the review of the Agency's decisions and communications suggests that several years of risk assessments and at least a year of risk minimisation measures pre-ceded the decision to suspend. One participant opposed the "precautionary" nature of the USA decision to the "risk minimisation" nature of the European approach. As a consequence, the term "precaution" ought to be interpreted in a loose way, mostly in relation to the Agency's expressed willingness to revisit its decision on the basis of new information.

The quality of the risk assessment has been disputed. On the regulatory side some NCAs members of expressed their satisfaction about the approach. In their view, the communication reflected each step of a thorough investigation. Other regulators - sometimes within the same national authority- disagreed. Some believed that the assessment took too long, or that conclusions were reached too quickly. On the industry side, the Agency's position was described as follows:

> *"[The] EMEA reasoning was that there is an approximate doubling of the risk of psychiatric disorders in obese or overweight patients taking Acomplia compared to those taking placebo."*

The issue was of course whether the "doubling of the risk" represented a significant risk in absolute terms, or not, which has direct implications for its communication. Industry voices also suggested that, when it requested more evidence and when it reviewed this evidence, the Agency:

> "*was only interested in the risks, not the benefits.*"

Most respondents from the regulatory side, at both European and national level did not share this view. Yet, when they described the communication of the risk assessment, they usually spoke of the risks and did not detail how these may relate to benefits. For example, the risk assessment suggested that patients generally take Acomplia for a short period, which reduces the benefits. In the course of the interviews, however, respondents from the regulatory side preferred to talk about the risks rather than detail this type of arguments. Members of patients' organisations did not comment the benefit/risk assessment, some making the point that they did not have sufficient information to do so.

5.2.2 Risk evaluation

Interviewees from the industry side usually suggested that the evaluation of the risk was biased, that the risks had not been properly weighed against Acomplia's benefits, especially so with respect to the wide range of potentials that this innovative product may bring. In their view Rimonabant "*was not given a proper chance*" with the effect of jeopardising an entire new class of products. Some regulators took the opposite views that the evaluation was balanced. A member of the CHMP suggested that his reading of the adverse reports suggested that "*frightening things had happened*", which implied that only much stronger benefits would be worth taking such risks. The view that something had to be done and that Acomplia could not stay longer on the market was heightened by the very critical media reporting that surrounded the restrictions (Benkimoun 2008) and suspension (Goldstein 2008).

However, the interviews conducted for this study suggest that regulators' and patients' judgements about the benefit/risk balance are still far from consensual. On the one hand staff members from competent authorities backed the decision on the basis that "the benefit/risk balance had become negative" and patients even asked "*why EMEA kept it for so long"*. Some regulators also wondered why Sanofi-aventis had invested so much in this medicine, which, in their view was bound to fail. Yet, other staff members of NCAs suggested that this product was useful to the specific population of obese patients, and that they received a number of complaints after the withdrawal. Others also suggested that the mental health profile of the target population was maybe not representative of the general population. Judgments about the risk may not fully reflect this fact, which led to neglect possible mitigation measures.

The absence of consensus within the regulatory community challenged the consistency of benefit/risk communication on one critical point: the decision to stop or continue clinical trials. Clinical trials are not under European responsibility. CHMP may discuss the issue but has no authority over the decision, which rests at Member States level. At the time of the suspension, a number of countries supported the continuation of the trials, while others were opposed to it. The message to patients, on the other hand, conveyed a blurred picture of the level of concern, which the MRHA, for example, translated into:

> *"Prescribers should not issue any prescriptions for Acomplia and should review the treatment of patients currently taking the medicine. Patients who are currently taking Acomplia should consult their doctor or pharmacist at a convenient time to discuss their treatment. There is no need for patients to stop treatment with Acomplia immediately, but patients who wish to stop can do so at any time. Patients currently included in clinical trials with Acomplia should contact the investigator, who will be able to provide more information".*[29]

It was critical therefore to conduct a high quality debate within each Member States, about the benefits and risks of Acomplia to inform critical decisions about the trials. For instance Swedish regulators highlighted the quality of the reporting by Läkemedelvärlden (LmV.), a health journal directed to pharmacists and doctors.

When interviewed, individual regulators disagreed about whether the trials should have continued or not. Most regulators suggested that it would have been impossible to communicate and would have run the risk of appearing like "double standards". A minority, however, expressed sympathy for Sanofi-aventis' position, that, with strong safeguards on prescription the potential of this product could have been further explored. After some discussion, Member States finally reached an agreement to discontinue the trials.

5.3 Re-assessment of the risk

The Agency's press release of 23 October 2008 indicated that "the lifting of the suspension is conditional on the marketing authorisation holder resolving the issues identified by the Agency". In practice, however, no respondent suggested that Acomplia may make its way back to the European market.

6. GARDASIL

Gardasil, manufactured by Sanofi Pasteur MSD SNC, is a vaccine for the prevention of high-grade cervical dysplasia (CIN 2/3), cervical carcinoma, high-grade vulvar dysplastic lesions (VIN 2/3), and external genital warts (condyloma acuminata) causally related to Human Papillomavirus (HPV) types 6, 11, 16 and 18. In other

[29] Europe wide suspension of Marketing Authorisation for Acomplia (rimonabant) , MHRA, Accessed at:
http://www.mhra.gov.uk/Safetyinformation/Safetywarningsalertsandrecalls/Safetywarningsandmessagesformedicines/CON028547

words, Gardasil is administered to prevent cervical cancers and other pre-cervical cancers triggered by these sexually transmissible diseases. Gardasil and Cervarix, another HPV vaccine produced GlaxoSmithKline, are administered to teenage girls. The indication is based on the demonstration of efficacy in adult females of 16 to 26 years of age and on the demonstration of immunogenicity in 9- to 15-year-old children and adolescents. Protective efficacy has not been evaluated in males.

Gardasil and Cervarix produced "outstanding efficacy against primary and secondary endpoints associated with the vaccine type HPVs and were highly and consistently immunogenic" (Schiller et al. 2008). Gardasil was authorised in the European Union (EU) in September 2006. Gardasil (and Cervarix) created high hopes in many circles including industry, regulators and some physicians who wanted to prescribe as soon as possible. In January 2009, around three million girls in Europe had been vaccinated. A member of an HIV/AIDS patient organisation highlighted:

> "*It is a real breakthrough in medical history. The first vaccine that works against cancer"*.

6.1 Initial alert

When the marketing authorisation was granted, Gardasil presented no major concerns for side effects, e.g. immunological reactions and disorders typical of vaccines such as Guillain-Barré syndrome. The Agency received reports of deaths in women who had previously received Gardasil, including in January 2008 two reports concerning the sudden and unexpected deaths of two young women in Germany and Austria. By this date, however, 1.5 million persons had been vaccinated. The absence of any causal relationship suggested only a sad coincidence. The Agency issued a press release on 24 January 2008 to reassure the public30. Cases of multiple sclerosis were also reported. They are usually reported when large populations are vaccinated and have triggered concerns in the past for example in the case of the Hepatitis B vaccine (Hernan et al. 2004). Many scientists, however, tend to refute causation (Sadovnick & Scheifele 2000; Ascherio et al 2001; De Stefano et al 2003).

On Friday 6 February 2009 two girls from the Spanish province of Valencia were admitted in hospital. Both girls came from the same area and had been vaccinated with the same batch of Gardasil. They were put into the same room. They were very agitated and in both cases repeated and prolonged seizures and loss of consciousness were observed. Doctors were alarmed, they diagnosed *Status Epilepticus* (SE) and decided to induce coma to put their brains to sleep. SE is a life-threatening condition in which the brain is in a state of persistent seizure.

6.2 Handling of uncertainty

The event caught the media's attention and was immediately followed by extensive coverage (El Mundo 2009a and b; El Pais 2009). The dominant view was that this event was a serious 'outbreak'. The crisis was handled through precautionary measures, followed by a reassessment of the risk in the light of evidence.

[30] Accessed at :
http://www.ema.europa.eu/humandocs/PDFs/EPAR/gardasil/Gardasil_press_release.pdf

6.2.1 Response

The Valencia province's health authorities alerted the Spanish Ministry of Health (*Ministerio de Sanidad y Consumo*) without delay. Although staff members of the Spanish medicine agency AEMPS (*Agencia Espanola del Medicamento y Productos Sanitarios*)[31] were convinced that a safety issue was very unlikely, the provincial and central health authorities agreed to stop distribution of the batch. The immobilisation of the batch in Spain, which represented 75 582 doses, became effective from 10 a.m. on Monday 9 February 2009. In a press release, the General Directorate of the Spanish Ministry of Health in charge of pharmaceuticals presented the Minister's decision as an enforcement of "the precautionary principle" [32].

AEMPS staff members have indicated that the recall in the Valencia province strengthened the idea that the vaccine was responsible for what happened. Media coverage intensified, with detailed account of the girls' health, and various testimonies mostly hostile to the vaccine (El Mundo 2009 c, d and e; Ferrado and Prats 2009; Gallardo 2009). As soon as it was announced, the issue spread outside Spain and other European countries started to worry about the batch. Italian authorities stopped the batch. The following day (10 February), Sanofi Pasteur stopped the entire batch. The USA market remained unaffected, where Gardasil is a registered trademark of Merck.

6.2.2 Risk Evaluation

Similarly to their colleagues of AEMPS, CHMP members did not consider that the vaccine was to blame. The Agency's involvement remained both limited and supportive of AEMPS' views. Ten days after the 'outbreak', on 19 February 2009, the CHMP issued a reassuring press release:

> "Based on the current data, [CHMP] has concluded that the cases are unlikely to be related to vaccination with Gardasil and that the benefits of Gardasil continue to outweigh its risks. Therefore the Committee is recommending that vaccination with Gardasil should continue in accordance with national vaccination programmes in Member States."

The same document, however, did not rule out the risk:

> "The CHMP and its Pharmacovigilance Working Party are investigating this situation further. The marketing authorisation holder has been requested to provide a full analysis of the batch, as well as further information on the vaccine's side effects, any similar cases, and possible ways in which Gardasil

[31] The Agency operates under the authority of the Ministry of Health

[32] Suspensión temporal de la administración de un lote de una de las vacunas frente al virus del papiloma humano Suspensión temporal . 9 de febrero de 2009

could be linked to the cases seen in Spain. Following assessment of all of the available data, the CHMP will determine whether further action is needed. "

"As part of its continuous monitoring of medicines, the CHMP recommended an update of the Product Information for Gardasil in January 2009, to reinforce information on syncope (fainting) as a side effect of vaccination with Gardasil, indicating that it is sometimes accompanied by tonic-clonic movements (movements resembling a seizure). This opinion has been forwarded to the European Commission, for the adoption of an EU-wide decision."

Sanofi Pasteur conducted its investigation. The batch involved was manufactured in the Netherlands (Haarlem). The laboratory in charge of giving the "batch release certificate" was the United Kingdom National Institute for Biological Standards and Control. As expected, negative results followed. Reassuring information also came from the Centre for Disease Control and Prevention. CDC was in contact with the Public Spanish Health Directory General, including John Iskander, Associate Director for Science, Inmunization Safety Office, Division of Healthcare Quality Promotion, (CDC). One respondent from the Spanish Ministry of Health stated:

"John provided us with information (which actually was in the public domain) on the comparative rates of syncopes and convulsions of Gardasil as compared to other vaccines used in adolescents".

Spanish authorities on the other hand, were still criticised for having exposed the teenage girls to a risk and not having banned the vaccine. They launched their own initiative to put an end to the controversy. They chose to establish an ad hoc expert committee to look into the issue. One Spanish regulator explained:

"We have successfully used such experts committees in the past".

The process involved meetings in Valencia and Madrid. The Committee came to the conclusion -signed unanimously by its members- that there was "*a close relationship with the vaccination but no evidence of a biological relationship*". In their conclusions the Committee members carefully avoided to mention the diagnoses of the episodes presented by the two girls. It was considered that such mention could violate their privacy. The full report, never published, was presented to the health authorities.

After the release of the conclusions of the investigation committee the media controversy stopped overnight. On 24 April AEMPS officially released the immobilised batch of Gardasil NH52670 and announced in a press release that:

"Batch NH52670 of the said medicine does not present any quality defect, and the benefit-risk ratio of the vaccine for human papilloma virus has not suffered any variation, and continues being favourable (…)"

In the end this crisis involved weeks of discussions, publications, papers, articles, and heated television and radio coverage[33]. The parents of the girls decided to sue the manufacturer and the legal cases are still in dispute.

7. Discussion

The above cases, similarly to other reviews of pharmaceutical issues (Bouder 2006; Löfstedt 2007 and 2008) suggest that the medical field is moving rapidly towards a "post-trust" environment where the media may amplify relatively minor safety issues, where trust in "big pharma" is low, and where the regulator's authority is not necessarily taken for granted. Patients, who have taken an active role since the 1980s, especially in the HIV/AIDS field, have been involved in the debate. In a post-trust environment they are likely to be more trusted than traditional authorities. This section:

- Characterises the prevalent views and expectations of influential stakeholders;
- Analysis the impact of the current communication practices on trust;
- Suggests steps to improve the current communication model.

7.1 Stakeholders views and expectations

European regulators increasingly support a model of risk communication that relies on more transparency and public participation (RRAC 2009; Löfstedt et al. 2010a) including in the medical field (Löfstedt and Bouder 2010). The three cases illustrate the specificities of the pharmaceutical regulatory environment. Although top-down mechanisms to release information are relatively well-developed (it has been called "fishbowl transparency": OECD 1996, Coglianese 2009), the risk dialogue remains less participatory than in other areas of regulation. This study therefore confirms earlier observations about the "bi-partite" nature of the communication model (Bouder 2007). Pharmaceutical regulators and industry have established deliberative channels, while third parties (e.g. patients and consumers organisations) were involved on a non-systematic and ad hoc basis at the time of the events. In this respect the involvement of a patient representative throughout the Viracept case constitutes an innovation and a precedent for the Agency, and was described as such by several respondents. Patient and consumer involvement has since increased, e.g. via the PCWP EMA human scientific committees working party with patients' and consumers' organisations established in 2006, the Patient Observers to PhVWP (pilot in 2009, regular as of May 2010). Patients/consumers representatives are also involved for:

[33] See for example the online article files published by mainstream newspapers such as El Mundo http://ariadna.elmundo.es/buscador/archivo.html?q=http%3a%2f%2fwww.elmundo.es%2felmundosalud%2f2007%2f11%2f12%2foncologia%2f1194890027.html&t=3&w=45&s=1; and El Pais: http://www.elpais.com/buscar/gardasil

- All EPAR summaries;
- All package leaflets;
- All safety communications.

In addition they may be involved on an ad hoc basis for other issues such as major safety variations at working party level or class reviews.

Agency's Q&A documents and critical information about the risk and benefits of medicines are well-established transparency mechanisms. "Fishbowl transparency" (OECD 1996; Coglianese 2009) implies that information is made available to everyone, yet without providing context and details. As part of its Transparency Policy (EMA 2009b; EMA 2010) the Agency is likely to significantly increase the amount of data and evaluation disclosed. For instance, the Agency already publicly announced the initiation of referral procedures[34]. This trend is also supported by key aspects of the new pharmacovigilance, in particular the introduction of public hearings and national medicines web-portals (Directive 2010/84/EU). These initiatives will address people's right to know but do not involve a two-way communication process. From a risk communication's perspective, the downside of "fishbowl transparency" is that websites and other media are likely to become saturated with information that patients are unable to interpret. Increased transparency will only work if decision makers are clear about what they expect publics/patients to do with the information provided and whether it will support expected outcomes (Löftsedt and Bouder forthcoming).

How do views and expectations inform these evolutions, which are likely to shape future risk communications? Regulators put more information online, but are they ready to answer the questions from patients, journalists and other members of the public in a meaningful way? Table 3 presents a matrix designed to capture the diversity of the respondents' expressed views. In order to allow meaningful generalisations to be drawn, only the most recurring wishes have been included. Rows indicate what stakeholders wish and columns whom they would wish it from. Some expectations are directed towards people's own organisations and colleagues. This information is also included.

Table 3: What do stakeholders expect of other stakeholders?

Who expects what / *From whom*	*National authorities*	*Patients*	*Industry*	*Agency*
National authorities	Internal/international co-ordination	Co-operation	Transparency	Co-ordination, speediness
Patients	Access	Internal co-ordination	Access	Access

[34] The EMEA uses the procedure defined as 'referrals' in community law to resolve disagreements and address various concerns. Under the referral procedure, a medicine, or the class or medicines, is 'referred' to the CHMP, so that the Committee can make a recommendation for a harmonised position across the European Union.

Industry	Access, clarity, speediness	Co-operation	Co-ordination and speediness within company	Access, clarity, speediness
Agency	Co-ordination across levels of government	Co-operation	Transparency	Internal co-ordination

The analysis of the three concrete cases suggests that the current evolution of transparency mechanisms, such as web portals and press releases are not necessarily central to influential stakeholders' expectations.

Patients' organisations are calling for access rather than raw information. The Agency's website was often described as one among other sources and probably not the most critical source of information that patients' organisation use to make judgements about benefits and risks. Access, on the other hand, means having more frequent dialogues with the Agency. Concrete suggestions included seating around the discussion table (CHMP, working parties, etc.) and providing feedback on important matters.

Respondents from the industry praised co-operation with the Agency on the Viracept case and wished more co-operation when they felt it was not sufficient, for example in the Gardasil case. Their wishes potentially contradict the patients' expectations that regulators and national authorities should remain strictly separated from industry. Again passive transparency mechanisms were not seen as the most critical communication vehicle.

Both members of NCAs and representatives of the industry wished for more transparent channels of decision, better co-ordination across levels of government (regional, national and European). The time factor was also presented as a critical dimension. An overwhelming majority of respondents from outside and within the Agency suggested that only a strong co-ordination between CHMP, the Agency's secretariat and the European Commission could speed up the communication process to ensure prompt and timely communications.

7.2 Impact of current communication practices on trust

The Gardasil and Viracept cases confirm that risk scares may have dramatic consequences for public health objectives. Similarly to the MMR vaccine in the United Kingdom or the Hepatitis B vaccine in France (Bouder 2006) the Gardasil scare resulted in a significant drop in Gardasil vaccination rates in Spain, especially in the province of Valencia. Other provinces were less affected, especially those provinces where Cervarix was the preferred alternative. Figures from the health authorities in Valencia, show that the HPV vaccine coverage in the province went down by more than 10% as a result of the crisis. The crisis originated when the cohort of girls were being vaccinated with the second dose and the major impact was noted with the third dose:

First dose: 85.23 %;
Second dose: 81.10%;
Third dose: 70.99%.

A known effect of precautionary measures is that it tends to stigmatise the products and technologies in question and reduces their lifespan (Sunstein 2003). When the contamination took place, Viracept was a maturing drug whose patent would expire in 2014. Many alternatives were prescribed to patients, especially in Western Europe. Some respondents suggested that these facts had an impact on the regulator and Roche's tough approach. They argued that Roche would have been more reluctant to give up high a profile blockbuster and that the regulator's risk/benefit assessment would have been different in the case of an indispensable drug. Valid or not, this argument does not account for the impact of Viracept's withdrawal outside Europe. When it was recalled, Viracept was still prescribed to a significant number of patients in Eastern Europe (including those countries joining the EU in 2004 and 2007), in Russia and in many developing countries. Many respondents highlighted that the complexity of opacity of the supply chain outside Europe -batches are usually purchased by NGOs and then are difficult to track- as well as the weak role played by international co-ordinators proved to be very disruptive. It was for example reported that some Russian doctors stopped prescribing the medicine without offering any alternatives.

Assessing current practices against cognitive factors

The three cases confirm the key advantages that regulators and manufacturers could receive from a better integration of cognitive research into their communication approach. For instance, it could have helped the regulators to gauge the sensitivities around the Viracept and Gardasil cases.

In France, the contamination of haemophiliacs from HIV-contaminated blood products in the 1980s has had long term effects on the perception of HIV/AIDS-related risks (Baud 1999; Bouder 2006). Well-organised HIV/AIDS organisations are active and able to mobilise quickly (Baud 1999). The press and patients groups were also putting significant pressure in other parts of Europe. When it organised the recall the Agency did not have a thorough assessment of these sensitivities at hand. The result was some unnecessary pressure on the European regulators and Roche. The fact that Viracept was an "old" drug with a limited number of patients concerned helped to contain the crisis.

In the case of Gardasil, there is similar evidence that the vaccination campaign was planed with little consideration for public perception issues. In many countries, discernible resistance to vaccination has been observed, leading to a decline in vaccination levels. People tend to think that immunity acquired after natural infection is preferable to vaccines (Howe and Johnston 1996), while a number of parents refuse vaccination because they feel that they are in control and able to prevent the dramatic consequences of the disease (Meszaros et al. 1996). Some people feel a higher sense of responsibility for the death of their child after a vaccination than after a vaccine-preventable disease (Asch et al. 1994; Ritov and Baron 1990).

When compared to drugs, vaccines bear an additional factor of involuntariness (Ball et al. 1998; Bostrom 1996). For example, laws mandating vaccination for school entry render vaccination an involuntary risk affecting children (Evans et al. 1997). It has also been observed that vaccine acceptance is a particular challenge when the prevalence of a disease is low (Ritvo et al. 2005). Ball et al. 1998 have suggested that

compression (overestimating the frequency of rare risks and underestimating the frequency of common risks), *availability* (of negative information reported by the media), *omission bias* (actions are perceived as more harmful than omission), risk *ambiguity*, and *freeloading* (people rely on high vaccination rates and herd immunity to protect their unvaccinated child) may contribute to anti-vaccine *decision heuristics*. On the other hand, *bandwagoning (*'I do it because everyone else is doing it') and *altruism* may work in favour of vaccination. These factors requires from the regulator to invest more resource into a scientifically sound communication of the risk (Bostrom 1999).

In the case of Gardasil the key factor of *altruism* was less powerful than for other vaccines because the target population are teenagers and not young children, who are seen as more vulnerable. Other specific factors also played against the public acceptance of Gardasil. On the one hand, the strength of the pricing controversy was likely to heighten the resistance to the vaccination campaign. In addition, the risk is much less likely to materialise than, for example small pox. The risk may also be prevented through sexual abstinence and education, which therefore requires a trade-off between the vaccine and other preventive approaches. The vaccine is not an obvious choice for parents because it requires accepting that their daughters may become sexually active very soon. We know from research on unwanted pregnancies that 'taboos' are powerful in this area (Bok and Morales 1998; Crosby and Yarber 2001), which constitutes a limitation to behavioural change.

7.3 Improving the current communication model

What systematic advice could help the Agency improve its communication of benefits and risks? Although there are no simple formulas to overcome the constraints of new models of communication characterised by higher demands for "active transparency" including access to decision-making, a number of guiding principles have been formulated that may help to overcome the teething problems of risk communication in post-trust environment. Key aspects include (Löfstedt 2005; Löfstedt et al. 2010b in print):

- Developing frequent dialogues between regulators, industry, media and key politicians are key to successful risk communication as this is building relationships based on trust. This trust building can best occur prior to a crisis occurring.

- Confrontations between the key parties in any dispute will not only destroy public trust in the key actors involved, but will also in more cases than not be socially amplified by the media.

- Do not involve lawyers in risk communication disputes unless it is absolutely necessary. When it comes to disputes, lawyers by their very nature attempt to inject more distrust in the process rather than less.

- Risk communication will always be easier if the parties involved in a dispute are both competent and base their decisions on the best available science.

- Involving highly trusted individuals as early as possible can help in solving risk communication disputes amicably.

- NGOs, in the post trust era of, can significantly shape policy outcomes.

- The opinions of local policy makers are important particularly in areas where decisions are taken across levels of government.

- The issue of responsibility can also be important. It is also about who is seen as responsible in the eyes of the public.

In the Viracept case, one major trust-building action by the Agency has been to involve a highly respected patient representative. This person acted as a mediator between the regulator, the industry and other patients' organisations. This is consistent with the risk communication finding that "involving highly trusted individuals as early as possible can help in solving risk communication disputes amicably". Given the sensitivity of the issue in some Member States, including France, this help proved to be precious.

Although public worries were clearly more limited, the Agency adopted a proactive communication approach in the Viracept case. On the other hand it developed minimal communication for the resolution of the Gardasil case. This imbalance suggests that the Agency tends to follow a "deficit model" of risk communication where its own priorities about benefits and risks shape its communication. The Agency communicates risks to the outside world when its secretariat and the CHMP are worried. A post-trust risk communication model suggests that it should communicate proactively when societal worries are high. The European regulator did not take into account the potential for media amplification that resulted from the Spanish situation.

A number of factors may have helped the regulators to better anticipate the Gardasil scare. First of all, Gardasil is expensive. Each vaccination costs several hundred Euros. Prior to the scare, the price aspect already generated considerable opposition from different corners of Spanish society. Grassroots organisations involved in sexual health prevention argued that the vaccine was a waste of public resource and that conventional prevention measures would be as effective. In Spain, provincial governments are responsible for healthcare, while the central government makes crucial decisions about public health policies, including vaccination policy. Provincial governments, who are responsible for financing the vaccination programme, were also concerned about the financial implication. Finally, regulators and industry could not rely on influential third parties to speak out for the vaccine. Consumers and patients organisations were highly critical of the aggressive vaccination campaign. For example, the 250,000 members strong consumers' organisation OCU supported the vaccination campaign in principle, but opposed what they perceived as an aggressive marketing campaign. One member of the organisation declared:

> *"The message on the benefits was much too simplistic, basically get vaccinated and you will deal with cancer".*

In its publication *OCU Compra Maestra 336* of April 2009, OCU explained (page 8) its position on the alert generated by the 2 suspicious cases (¿Respetan los derechos del paciente?). At that moment, OCU requested:

- "To inform the patients before the vaccination about the balance between benefit/risk of Gardasil.
- To inform the patients that Gardasil was a new drug and that it is of most importance to declare any possible risks associated to it.
- To defend the importance of informing the patients and their right to a free choice."

The Gardasil case reinforced a significant conclusion of risk communication theory and empirical research, which is that risk amplification/ attenuation takes place in the national context, and is linked to national debates. It is therefore not very surprising that the death of the girl just vaccinated with Cervarix in the United Kingdom has almost not had any media impact in Spain (despite the fact that it is also marketed there).

Communicating evidence and precaution

In Europe, the new model that emerged in response to the regulatory failures of the 1990s has changed the relationship between scientific knowledge and decisions. As such, it has also affected the status of scientific evidence in policy making. The direct consequence has been the success of new regulatory approaches most prominently the precautionary principle (Löfstedt 2004). The consequence is that the role of science is less important as scientists are often seen as just one of many stakeholders. Therefore, a crucial question for improving future communication of benefits and risks is whether the regulator needs to emphasise precaution or evidence. The balance between evidence and precaution has been central to the academic debates about risk regulation and communication (Kempton and Craig 1993, Löfstedt and Vogel 2001; Wiener and Rogers 2002; Sunstein 2003). There are at least 19 definitions of the precautionary principle (Sandin 1999), but it may be broadly described as the attempt to act in the face of uncertainty in order to be 'safe rather than sorry'. Governments chose frequently to err on the side of caution, to avoid or reduce particular risks that many citizens regard as unacceptable, even if the available scientific evidence does not or cannot prove evidence of harm (Vogel 2003, p. 2).The precautionary principle is usually invoked in situations bearing a high level of uncertainty. The magnitude of a risk, and its irreversibility are usually the key arguments in favour of this principle (Klinke and Renn 2002). Most respondents, however, appeared to be unaware of these tensions.

Most respondents highlighted the need to respond to *uncertainty*. But what is "uncertainty"? Interviewees did not suggest a clear definition. Klinke and Renn (2002) have argued that contemporary risks usually express four types of challenges: *seriousness*, *uncertainty*, *complexity* and *ambiguity*. *Uncertainty* refers to the scope of the knowns and unknows. It is mostly quantitative. *Seriousness* is rather qualitative. It usually refers to major -sometimes collective- threats to the environment or human health, irrespective of exposure, dose-response relationships or intake quantity. In the pharmaceutical area, the bio-accumulation of slowly-degradable substances in the environment or the body could fall into this category. *Complexity* refers to the

difficulty in dealing with multiple causes and consequences. In many cases, the existence of an obvious relationship between a medicine or a vaccine and related side effects tends to diminish the importance of the complexity challenge. The combination of side effects resulting from the simultaneous intake of medicines, though, may increase the level of complexity, as does the conjunction with other factors (e.g. genetics, etc.). *Ambiguity* refers to the variability of interpretations arising from a fixed set of data. For example better detection methods may lead to scientific discussions about the meaning of a specific set of information. If we detect cancer better, for example, does it necessarily mean that the risk of cancer is statistically higher than before?

In the present case a category on benefit *confidence* may be added to reflect the level uncertainty in relation to the efficacy of the product (seen by most respondents as equalling "benefit"). Table 4 adapts and applies these criteria to the three cases.

Table 4: Defining the scope of uncertainty

	Benefit confidence	Risk uncertainty	Risk Seriousness	Ambiguity of data	Complexity Of data
Viracept	High	High	Medium	Medium	Low
Acomplia	Controversial	Controversial	High	High	High
Gardasil	High	Low	Low	Low	Low

In theory only Acomplia presented a high uncertainty situation, while in the Gardasil case most stakeholders had high confidence about the data. The Viracept case presented an intermediary situation. Tenants of the precautionary principle would suggest that Acomplia and Viracept were good reasons to invoke the precautionary principle and develop risk communication accordingly. Tenants of evidence-based models, on the other hand, would have advised to gather more evidence on the Acomplia and Viracept cases. In practice, the Agency took the following steps:

- In the Acomplia case, the communication of benefits and risks was centred around risk minimisation.
- In the Gardasil case, there was a dichotomy between the precautionary communication of the national and sub-national authorities and the more evidence-based communication of the Agency.
- Viracept presented a more classic example of precautionary measures.

This suggests that both evidence and precaution played a distinct role. This role, however, remained implicit rather than explicit. The choices between evidence and precaution were not clearly defined and communicated. Most respondents from the regulatory side -at both national and European level- implicitly contradicted the facts by holding the view that their response was always "precautionary". Several respondents suggested explicitly that "precaution" is the best way to deal with uncertainty. Among regulatory circles, a positive value was implicitly attached to the concept. Among industry circles the view was more nuanced. For example, respondents from the quality side within Roche praised the "precautionary" management of the Viracept case; a respondent from Sanofi Pasteur, on the other

hand, suggested that regulators should show more courage when they deal with inexistent risks. They should have defended Gardasil with more strength.

In the current environment, reflection on the nature of the communication model that the Agency wishes to follow would help to achieve a more balanced communication of "benefits and risks". This paradox illustrates the difficult context in which most regulatory decisions take place. Although this study was clearly and explicitly interested in understanding how stakeholders consider the balancing of benefits and risks, the bulk of the responses concentrated on the downside of the risk. When they spoke of benefits, participants only mentioned the efficacy of the product as its "benefit". They did not mention other benefits. In the Acomplia case, one may have expected that the difference that weight loss or gain makes in everyday life may be considered as one crucial element informing the regulatory discussion. Yet, the current regulatory approach essentially treats it as a matter for patients. The effect is that regulatory discussions about the tradeoffs between expected benefits and expected risks do not sufficiently reflect the wider social context. In a more open environment where regulatory decisions are publicly discussed the media may amplify the gap between regulators and patients.

8. Recommendations

This report presents a detailed analysis of influential stakeholders' expectations and attitudes. The research draws on behavioural and social psychology theories, which have been successfully applied in the past in a variety of contexts (nuclear technology, chemicals, food, etc.). The first finding is a confirmation that, similarly to other policy field, health experts would be wrong to assume that top-down messages resonate among non-experts. Secondly, the study shows that effective risk communication becomes particularly challenging when several institutional actors e.g. the Agency and NCAs interact with different publics simultaneously. Multiple actors tend to maintain multiple and conflicting "voices"; delays due to co-ordination may create information vacuums; specific national development (e.g. risk amplification by the media) may distort the entire communication process. The final result is a confirmation that systems of transparency and involvement need to be reasoned. The fishbowl transparency model cannot translate complex scientific information into meaningful messages towards lay audiences. An approach to transparency that combines openness with proactive risk communication will have a decisive impact on the benefit/risk communication outcome. In one case (Viracept) the active involvement of a patient representative by the Agency prevented an escalation of the incident. In another case (Gardasil), scientific advice from independent experts helped to mitigate the public scare. One crucial improvement will come from increased networking mechanisms at EU level and between the EU and Member States. The EMA has already moved in this direction, through soliciting information about situations in Member States and supporting coordination at European level (EMA 2010) The author of this report wishes to formulate four recommendations to improve the Agency's future benefit/risk communication:

1- Establishing an external risk communication advisory board

An external risk communication advisory board, composed of experts from the risk communication and medical field would help integrate risk communication research into everyday processes. It should have the mandate to bridge medical and communication expertise in order to develop situation-specific two-way communication models that meet the expectations and needs of the various publics. It would help to draw and implement lessons from cognitive science to build more robust risk communications. Similar boards have already been established in Europe, for example the risk communications' group of the European Food Safety Agency. The format, membership and role of the new group would need to be adapted to the needs of the pharmaceutical field. To be effective, the set up should maintain a strong link with the risk communication discipline.

2- Forming a strategic view on transparency

A strategic view of what transparency means for benefit/risk communication would help better respond to stakeholders' expectations. It would help the Agency to define the "active transparency" mechanisms that will supplement traditional and increasingly web-based information to healthcare professionals and patients. These tools could for example include science fora, where people from medical and non-medical backgrounds will meet around key topics. The dynamic nature of the process would also help to improve these traditional methods as they would become more interactive.

3- Making patients' active involvement a routine

A standard lesson from risk communication in post-trust environments is that regulators should be proactive. Patients' organisations should be more systematically involved on sensitive issues early in the assessment phase. This involvement should become a routine in distinct areas where patients' organisations have expressed concerns, where risk perceptions are negative or where intense media coverage is likely to trigger risk amplification.

4- Reviewing the format and timing of communication vehicles

Communication to the outside world should target audiences and reflect their needs. Standard one-size-fits-all documents, e.g. Q&A and press releases, are neither adapted to experts nor the general public. To some extent they miss both targets. The drafting process and timing should reflect these priorities and avoid the "deficit model".

Glossary

Hazard – a hazard is something that is dangerous and likely to cause damage if it occurs.

Risk – a risk is a danger that *may* occur – risks are often considered as a combination of a hazard and the chance that it happens.

Stakeholder – an individual or group who engages with a risk and who influences others' approach to, or understanding of, the risk.

Two-way communication – a process that does more than well-crafted one-way messages on risk and develops a dialogue with key stakeholders and the public.

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