STAKEHOLDER ENGAGEMENT IN PHARMACEUTICAL REGULATION: CONNECTING TECHNICAL EXPERTISE AND LAY KNOWLEDGE IN RISK MONITORING

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The exclusive position of scientific expertise in pharmaceutical regulation is being increasingly challenged. Several authors suggest that lay knowledge could play a role in governing risks. We use the literature to develop ideal-typical regulatory arrangements with low and high lay stakeholder involvement: a technocratic and a democratic arrangement. We propose that a more technocratic arrangement will yield a better process and output performance while a more democratic arrangement will result in more stakeholder satisfaction. These propositions are explored through two case studies of pharmaceutical regulation in the Netherlands: in pandemic influenza and in HIV. Our study shows equivalent process and output performances but we found indications that the democratic approach results in more stakeholder satisfaction. We conclude that in pharmaceutical regulation, there is no a priori reason to limit involvement to experts: in situations of fundamental uncertainty, democratic monitoring of pharmaceutical risks can contribute to the system's robustness.

DAHL'S DEMOCRATIC DILEMMA

New approaches to regulation such as 'better regulation' (Baldwin 2010; Radaelli and Meuwese 2009) and 'new regulatory decision-making' (Löfstedt 2004) aim to improve regulation. But, while government regulators aim to base their regulation work on an evidence base of scientific knowledge, both lay and professional stakeholders also produce knowledge (Lowes *et al.* 2010). The value of this knowledge is heavily debated. De Francesco and Radaelli (2010, p. viii) argue that experts working for government regulators should play a pivotal role, but Weimer (2010) counters that lay stakeholders may have valuable (tacit) knowledge to contribute to regulatory decision-making. In the context of this debate, Löfstedt (2004, p. 343) raises the following rather controversial question: 'Should scientists have only equal weight with local knowledge or stakeholders' intuitions?' Abels (2004) sees this as a manifestation of Dahl's (1994) democratic dilemma: the idea that democratic participation and system effectiveness are irreconcilable.

Dahl's democratic dilemma becomes poignant in the governance of topics that are complex and inherently uncertain, such as the field of modern medicine with inherent complex benefit–risk profiles. In the European context of pharmaceutical regulation, risk-aversion in society has increased and many questions have been raised concerning the trustworthiness of pharmaceutical regulation. Recent cases of drug withdrawals from the market (e.g. the statin Baycol in 2001 and the widely used anti-inflammatory drug Vioxx in 2004) and concerns about safety of particular pharmaceutical products (e.g. the antidiabetic product Avandia in 2010) have fomented this aversion. The fatal consequences of Vioxx have resulted in public attention on drug regulation and efforts to counter commercial interests by bringing more stakeholders into the regulatory process (Zwillich 2005).

A specific strand of literature on pharmaceutical risk regulation has criticized the closed and secretive nature of the regulatory process for some time (Abraham 1995, 2002) and highlights the large influence of companies on clinical testing and regulatory

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decision-making (Williams *et al.* 2008, p. 817). As a remedy, several authors suggest opening up the regulatory process, at the same time making sure that stakeholders are not captured by industry as well (for an overview, see Williams *et al.* 2008, p. 818). These publications present an interesting and important position but hardly answer the question whether lay stakeholder engagement actually improves pharmaceutical regulation.

Empirical research is used to enhance our scientific understanding of the contribution of stakeholder engagement to the governance of pharmaceutical risks. Regulatory arrangements are studied in a specific institutional setting: post-marketing surveillance of conditional approvals of pharmaceuticals in the European Union (Boon *et al.* 2010). This is an institutional regime that enables early access to pharmaceuticals when there is a direct and immediate need and alternatives are lacking, under the condition of strict monitoring of pharmaceutical risks. We have formulated the following research question: Do regulatory arrangements with lay stakeholder involvement improve the governance of pharmaceutical risks?

TWO ARRANGEMENTS FOR STAKEHOLDER ENGAGEMENT IN MONITORING RISKS

How do government regulators deal with lay stakeholders? Building upon Hood *et al.*'s (2004) work – and with its roots in Douglas and Wildavsky's (1982) cultural approach – we have developed an *ideal-typical distinction* between two approaches: the technocratic approach and the democratic approach.

The *technocratic approach* assumes that regulation should be based on judgments of established experts. The complexity of regulating high-tech risks is conceptualized as a problem of uncertainty: better knowledge can help to reduce the complexity and minimize risks. The ideal is an evidence-based approach to regulation (Nutley *et al.* 2007; Radaelli and Meuwese 2009, p. 649): regulatory decisions are made on the basis of established evidence provided by medical professionals, the government, independent scientists, and scientists working in the pharmaceutical industry. Lay stakeholders are regarded as sources of information for scientific analyses and not as participants.

The *democratic approach* – referred to by Radaelli and Meuwese (2009, p. 650) as the 'civil republican model', whereas Börzel and Risse (2010) label this model as 'non-hierarchical' – builds upon the idea that regulation needs to be constructed in interactions between various (professional and lay) stakeholders. Different types of knowledge are deemed to be relevant and important to the process of regulation. The complexity of regulating high-tech risks is seen as an issue of ambiguity: values and norms influence knowledge claims and cannot be separated from them. Ambiguity cannot be reduced but needs to be dealt with through processes of negotiation and learning. Scientists play an important role but are also seen as (professional) stakeholders (Löfstedt 2004, p. 338).

These ideal-types have ancient roots and represent basic perspectives on public administration. Regulatory arrangements are a specific type of governance arrangement: an arrangement for regulating risk. To give more content to these ideal-types and to enable empirical analyses of regulatory arrangements, we propose the following five (interrelated) dimensions (Hancher and Moran 1989; Hood *et al.* 2004; Hutter and Jones 2007; Kim 2006; Kooiman 1993; Koppenjan and Klijn 2004; Rhodes and Marsh 1992):

(1) Contacts between government regulators, companies, client groups, intermediaries, professionals, and so on can be analyzed in terms of *interaction patterns*. Technocratic

arrangements will show a high degree of 'network centrality' (Ibarra 1993): the regulator is the central actor and only interacts with experts. Information exchanges predominantly concern information flows from the various (professional) stakeholders to the government regulator. Democratic regulatory arrangements will show frequent interactions between all actors and hence a lower degree of network centrality. Information exchanges between (professional and lay) stakeholders are crucial to the arrangement and create more 'collective intelligence'.

(2) The interactions between regulators and stakeholders are guided by *formal and informal rules* (Hood *et al.* 2004, p. 9). Formal rules will stipulate the kind of information that companies and medical professionals will have to provide to regulators and also how clients can send information to these regulators. Codified, legal frameworks play a key role in determining formal rules. Conversely, informal rules are developed in interactions between stakeholders. They are constructed in these interactions and lead to role perceptions. Technocratic approaches tend to be based on formal rules, whereas informal rules play a more important role in democratic arrangements.

(3) The interaction patterns between the regulator and stakeholders can be characterized in terms of *openness and participation*. In an open arrangement, stakeholders are provided with information about regulation and stakeholders can easily participate. An open arrangement is to be expected in regulation with a high level of stakeholder involvement. A technocratic approach is expected to be accompanied by a closed arrangement: little information is provided to the environment and few opportunities for participation are created. Openness also refers to risk perceptions that are regarded as valid. Democratic approaches recognize that stakeholders have different risk perceptions and different assessments of benefits associated with technologies (Ravetz 2006, p. 100), whereas technocratic approaches have developed sophisticated risk analyses but these will only be open to 'proven' risks or risks that are recognized in and validated by the scientific community.

(4) Various forms of *power* (e.g. formal mandate, publicity, legal threats) are used to dominate network interactions and steer these into the direction of specific interests at the expense of the interests of other actors. Actors may also find ways to create win–win games and converge *interests*. These converging interests are to be expected in a democratic arrangement when stakeholders are not dominated but are allowed to participate since all actors need *to negotiate common interests* to create legitimacy. Diverging interests can be expected in a technocratic arrangement since government regulators have the (formal) power *to impose certain interests*, defined by the regulator on the basis of an analysis of the field and interactions with certain actors (Permanand 2006), which may easily trigger resistance from other actors who have conflicting agendas.

(5) In a technocratic approach, *knowledge* is thought to be concentrated within a small group of *experts*. In this approach actors rely on established knowledge as created and certified by recognized institutions (Ravetz 2006, p. 115). These experts inform regulation and transfer knowledge to stakeholders and the public. In a democratic model of stakeholder involvement, knowledge is thought to be distributed over various actors. Knowledge is also conceptualized as richer because it includes not only formal but also local and experiential knowledge (Ravetz 2006, p. 115). Knowledge is not being transferred from experts to the public but is constructed in interactive processes between various stakeholders.

These dimensions can be used to analyze regulatory arrangements in terms of their technocratic or democratic nature.

PERFORMANCE OF REGULATORY ARRANGEMENTS

To evaluate the performance of different regulatory arrangements, we need to develop a 'yardstick'. Koppenjan and Klijn (2004, p. 124) highlight that objective criteria cannot be defined in a multi-actor perspective because there is no substantive yardstick, no central objective and goal-seeking behaviour. Other authors argue that an exclusive emphasis on subjective criteria may lead to incomplete or unreliable evaluation (Sorensen and Torfing 2009, p. 241). The emerging consensus seems to be that researchers should strive for a multifactor evaluation in the form of a combination of process and output criteria and stakeholder satisfaction (De Francesco and Radaelli 2010; Koppenjan and Klijn 2004; Provan and Milward 2001; Sorensen and Torfing 2009).

For pharmaceutical regulation, *output criteria* include use of pharmaceuticals, measured through the adherence to therapy, and the safety of pharmaceuticals, measured through the adherence to post-marketing monitoring. The *process criteria* are assessed in terms of the quality and quantity of the performance in different stages of producing 'signals', i.e. reports for which the causal relationship between drug use and adverse drug reactions (ADRs) is validated. These stages include signal detection, signal processing, and decision-making based on the signals produced (Bührlen *et al.* 2006). Specific indicators include the quality and quantity of safety reports, signals, and outcomes of regulatory actions. The *level of satisfaction* of the various stakeholders with pharmaceutical regulation can be assessed quantitatively and qualitatively by evaluating their reactions to regulatory efforts. Are key stakeholders satisfied or do we see signals of dissatisfaction? Do the media report on a lack of satisfaction among patient groups? Have regulators received signals that indicate limited satisfaction among stakeholder groups?

Process, output, and satisfaction criteria need to be interpreted together. A multifactor evaluation calls for interpreting the various indicators within the context of other indicators. An indicator such as the number of signals is ambivalent: it could mean that there are relatively many problems with the pharmaceuticals but it could also mean that the system for signal detection functions relatively well. Many signals and high satisfaction, for example, seems to indicate that signal processing functions well, whereas many signals and low satisfaction indicates that there are relatively many problems with the pharmaceuticals.

When comparing the technocratic and democratic approaches to monitoring the effects of pharmaceuticals, one can detect a difference in the assumed relation between process and output criteria on the one hand, and stakeholder satisfaction on the other. The technocratic approach assumes that stakeholder satisfaction results from strong process and output performance (Abels 2004; Scharpf 1999). If the regulator performs well and communicates the results to stakeholders, satisfaction will be high. However, good results may not suffice. Various authors have highlighted that, besides good results, engagement from stakeholders in regulatory processes is needed to produce stakeholder satisfaction (Durant 1999; Fischer 1999; Joss 2002). One can expect that a more technocratic approach will produce strong process and output results but fall short on stakeholder satisfaction.

The democratic approach assumes that system effectiveness is not sufficient for securing stakeholder satisfaction (Abels 2004, p. 1). The relation between process performance and stakeholder satisfaction is reversed: satisfaction with the regulator is expected to result in better collaboration with stakeholders and therefore to better risk management.

The democratic approach has been criticized for endangering the performance of risk monitoring systems by building decisions and practices on non-scientific knowledge (Abels 2004). One can formulate the expectation that a more democratic approach will result in high stakeholder satisfaction, but it may show shortcomings in terms of the (scientific) quality of the regulatory process and its output.

RESEARCH DESIGN

This research focuses on the regulation of pharmaceuticals that are conditionally approved by the European Medicines Agency (EMA). The specific features of this regulatory arrangement are that pharmaceuticals can be marketed even though they have not been fully tested under the condition that their effects are monitored and evaluated rigorously through post-marketing surveillance. This institutional regime has been designed to enable the development of pharmaceuticals for seriously debilitating or life-threatening diseases (e.g. cancer and HIV), medicines used in emergency situations (e.g. pandemic influenza), and orphan drugs (i.e. pharmaceuticals specifically developed for treating rare medical conditions also referred to as 'orphan diseases').

Within the domain of conditional approvals, we have selected illustrative cases of pharmaceutical regulation in the Netherlands with varying degrees of lay stakeholder involvement to explore these expectations. The governance of pharmaceutical risks associated with vaccination against pandemic influenza has been implemented without direct forms of lay stakeholder involvement, whereas the risk governance of anti-HIV products is associated with strong forms of lay stakeholder involvement. There are important similarities between these cases, such as the great sense of emergency and imminent pandemic, early access to therapies, and the fact that both cases concern the field of virology. Furthermore, the regulatory challenges are similar, as the viral products needed European market approval (via EMA) and both Dutch cases are exposed to the same post-marketing surveillance system (being regulated/organized at the national level). There are also substantial differences in the nature of the diseases and the time regulatory arrangements were set up. In our analysis, we take into account that the differences between the cases are substantial and could influence the governance of pharmaceutical risks. The research design should be understood as an exploration through two different cases rather than as a rigorous case comparison.

The cases are studied on the basis of interviews, expert workshops, and extensive desk research. Forty-one in-depth interviews with representatives of all relevant parties for the two cases were conducted. They were involved in HIV and/or pandemic influenza vaccine innovations. Since the range of potential interview respondents is confined, for example the number of HIV patient organizations is limited, we aimed to contact and interview a complete set of stakeholders in the field.

The respective *numbers of interviews* and *participants in expert meetings* were as follows: Dutch medicines evaluation board (3, 1); Healthcare Inspectorate (1, 0); pharmaceutical companies (8, 1); industry representative organization (1, 1); patient organizations (5, 4); groups that are critical of vaccination (2, 1); national reimbursement agency (1, 0); medical specialists who also lead research groups (5, 1); organization that represents nurse practitioners (1, 0); umbrella organization for municipal health services (1, 0); Dutch representative organization of pharmacists (1, 0); Dutch health ministry (1, 1); scientists studying the pharmaceutical sector (excluding the authors) (2, 3); Dutch reimbursement agency (1, 0); ethicists (2, 1); representatives of post-marketing surveillance centres (6, 2); and the research funding organization (0, 2). For five groups, there was an overlap

between interviews and participation in expert meetings. Respondents ranged from director-level to people specifically responsible for and experts in the post-marketing dossier in their organizations.

The interviews were semi-structured and focused on the respondents' roles in the regulatory process. While doing this, special attention was paid to the five dimensions mentioned in the previous section, i.e. interaction patterns, (in)formal rules, openness and participation, power and interests, and expert knowledge. The level of satisfaction with pharmaceutical regulation was measured by asking about the respondents' perception of regulatory efforts. The interviews were audiotaped and transcribed for further analysis and axially coded. The interview data were substantiated and triangulated by three multi-stakeholder workshops involving a wide array of stakeholders in the field of drug registration and post-marketing surveillance in the Netherlands. While describing the two case studies, the respondents are rendered anonymous and coded as R1, R2, etc.

The desk research used literature from the following sources: (1) data on the output and process performance criteria using literature on treatment adherence and results of post-marketing surveillance; (2) policy documents, scientific articles, etc. which the interview respondents recommended; and (3) a literature search of the Scopus bibliographic database using (a combination of) the keywords 'conditional approval', 'approval under exceptional circumstances', 'early access', 'pharmacovigilance', and 'post-marketing surveillance'. All searches were carried out in combination with keywords that restricted search results to the disease areas under study and the related pharmaceutical products. The documents were used to obtain information about the process of regulation and the resulting output, and these performance measures were assessed through expert opinions and comparison with other countries (HIV), and by comparison with official government targets and other cases of the same disease (pandemic influenza).

CASE 1: PANDEMIC INFLUENZA

Pandemic influenza seemed to be a health risk of the past but this proved to be an illusion after the avian influenza outbreaks in Asia at the end of the 1990s (Stephenson *et al.* 2004). In 2001, a conference on 'Pandemic Preparedness in the Community' marked the start of planning for the next pandemic by the EU, and in 2004, the EMA produced a guideline for the regulation of influenza vaccines. In April 2009 the first cases of the influenza A virus subtype H1N1 were discovered in Mexico. The virus rapidly spread and in June of that year the World Health Organization (WHO) declared the influenza type pandemic. This set a process in motion: the EMA and pharmaceutical companies prepared the mock-up vaccine with the present virus strain for the accelerated approval of pandemic influenza vaccines and the first mock-up vaccines were approved in 2008. In the Netherlands, the health ministry decided to set up a large-scale vaccination programme for children and for higher-risk groups. During weekly crisis meetings, representatives of the ministry met with the National Institute for Public Health and the Environment (RIVM) and the umbrella organization for municipal health services (GGD Nederland). The minister decided that the Dutch Pharmacovigilance Centre Lareb would be responsible for collecting and analyzing safety reports on pandemic influenza vaccinations.

Analyzing the regulatory arrangement

The health ministry coordinated the vaccination and Lareb was the major player in safety reporting. The *interaction pattern* had a high degree of network centrality since the

interactions with 'critical' stakeholders groups were limited and hardly friendly in nature (R13, R10, R9, R2). These stakeholders were critical about the vaccination because they wanted to choose autonomously about vaccination, they distrusted the motives of the government and companies involved, and they had a view of life (religious or holistic healing) that refused vaccination (R3, R1). Some of these groups were well organized but others were only formed by a few people who used the internet for disseminating their views. This internet dynamic was not connected to the efforts of regulators: there was hardly any interaction between the critical voices and government regulators.

The risk monitoring practices largely followed formal legal *rules* of post-marketing surveillance. Pharmaceutical companies were obliged to report any (serious) safety concerns to the regulatory agencies (R11, R14), and medical professionals and municipal health services were obliged to report adverse drug reactions (Bührlen *et al.* 2006; R29). An informal rule in this arrangement was that non-experts were to stay quiet. The dominating experts perceived the role played by critical consumers as 'detrimental and unreasonable' and were of the opinion that the critical groups should not confuse the public (R2). The critical groups perceived the informal rules as top-down decisions: 'These executive actors have no reservations and they oversimplify this message in their communication: vaccines are always safe and effective' (R3).

The degree of *openness and participation* is perceived differently. The regular set of stakeholders formed a rather closed clique (R2, R9) but they perceived the safety monitoring as being open to everyone. Every individual was allowed to report to Lareb and the aggregated results of the reporting were published (R9). The critical stakeholders valued the opportunity for all people to report side-effects to Lareb (R3) but, at the same time, they thought that 'not all reports are registered' (R1) and that 'only the tip of the iceberg is reported' (R3). They claimed that elements of safety monitoring were ignored, such as co-vaccination, following cohorts of vaccinated people over time, experiential stories of vaccination, and proposing hypotheses that verify instead of falsify the existence of causality between vaccination and side-effects (R3, R1). The critical groups complained about the lack of transparency of governmental agencies (R3) while the regular stakeholders saw themselves as communicating transparently: ' . . . we do not have any reasons to cover up any side-effects' (R2).

The health ministry and government regulators had a certain degree of *power* to design the vaccination programme and the related safety monitoring according to their own interests. The power the critical groups had was to discourage vaccination (which they did). These critical groups derived their power from, as they claim it, 'feelings that had been shimmering and prevalent in society for a long time' (R3). They also pointed to the use of the internet as a way to organize their efforts on a low profile and as a way to collect support and arguments (R1, R3).

Knowledge about the disease, vaccination, and related risks and benefits resulted from discussions between influenza experts. Communication was regarded as an integral and important aspect of the vaccination programme (R12, R2). The information was provided through handout leaflets, mass media, and the internet. The patient reporting venue on the Lareb website was emphasized, and Lareb approached those who reported with follow-up questions (R9). The critical stakeholders could not participate in processes of knowledge production and they complained about the fact that the regular stakeholders 'did not take them seriously at all and think their remarks not sound enough' (R1). The regular side accused the critical groups of causing confusion, 'being unapproachable' (R2), and being critical just as a knee-jerk reaction to the government.

Evaluating regulatory performance

The analysis of the *process performance* indicated that the number of signals that were being processed by the regulatory arrangement is considerably higher than with seasonal influenza vaccine (Van Puijenbroek *et al.* 2010). The quality of the signals can be considered to be high because the profile of the reported adverse events is comparable with side-effects known from clinical trials (Van Puijenbroek *et al.* 2010). With a time lag of one day from signal to file, the arrangement works fast. Signal processing is perceived to be reliable due to cross-checking and personal case review. The speed of processing these signals is high, with on average 2.8 days for serious reports which allows for real-time safety monitoring (Van Puijenbroek *et al.* 2010). The speed of implementing decisions is high and communications from official, regular stakeholders went through one channel.

The analysis of the *output performance* started with the vaccination coverage levels. These levels range from 68 per cent of people at risk in care institutions, to 62 per cent of children, to 43 per cent of healthcare professionals (VWS 2010). The government was reasonably satisfied with attendance because it was higher than the coverage of the seasonal influenza (VWS 2010) and HPV vaccines. However, it remains much lower than the coverage of the vaccination schedule for small children for diseases such as diphtheria, pertussis, tetanus, and poliomyelitis. It is unknown whether all side-effects were reported but, still, the number of consumer reports is higher than with other diseases.

Were stakeholders *satisfied*? There is much discussion in the media, and amongst users and critical groups, but also amongst medical specialists and scientists about the benefit–cost ratio of the vaccination. Vocal groups expressed publicly their dissatisfaction with the regulatory arrangement. The involuntary factor is relevant here: critical groups underlined that there was no free choice in receiving the vaccine and that they were even coerced into receiving it: 'We aim at making vaccination an individual choice. Now, however, in their communication (at least) the government emphasizes the necessity of vaccination' (R3). Some of the experts indicated that the media attempted to show the full range of arguments and in their efforts may have overemphasized the importance of minority groups (R3).

CASE 2: HIV

AIDS was first detected in California and New York in 1981. Since then the prevalence has grown rapidly, as well as the attention paid to this disease because of its seriously debilitating, progressive, and untreatable character and because there was little knowledge about the disease. Scientists in public research institutes and companies began to work on medicines for AIDS and at the end of the 1980s this began to bear fruit. With the introduction of novel drugs other issues began to arise, such as how to ensure fast access for patients and how to monitor safety issues. From the 1990s on, several informal and formal post-marketing arrangements were set up in collaborations between patients and medical professionals.

Analyzing the regulatory arrangement

In the early days of AIDS in the Netherlands, the homogeneity of the AIDS patient groups and the medical professionals, and their concentration in the Amsterdam area, facilitated an intensive *pattern of interactions*. There was little knowledge about the disease and virologists frequently contacted public healthcare professionals, medical specialists, and company experts. In treatments, contacts between care professionals and patients were frequent and constructive. Post-marketing surveillance was organized through

new, informal arrangements (R17, R6, R18, R19, De Mooij 2004). Later, interactions between scientists, doctors, and companies became more formalized, while contacts between medical specialists, nurses, and patients remained frequent and patients stayed knowledgeable. Some of the informal practices of HIV monitoring were later formalized by creating institutions such as the Stichting HIV Monitoring (R17, R26, R25).

The formal *rules* about post-marketing surveillance stipulated that stakeholders such as medical professionals should report ADRs and companies should collect reports and pass them on to the regulatory agencies. In the HIV/AIDS field these formal rules were also applied (R22, R23), but part of the post-marketing surveillance arrangements were specifically designed to be bottom-up, and co-evolved with the development of knowledge about the disease and the way it could be treated. These novel approaches were introduced in a rather homogeneous, small, and closed community of all relevant stakeholders (R17, R15, R20). The informal rule that patients needed to be involved in the development of monitoring practices emerged from these early interactions and was not disputed by scientists or medical professionals.

The homosexual group was dominating the scene, even to such an extent that other patient groups were not heard, either because their voice was not strong enough (e.g. intravenous drug abusers, immigrants from low-income countries, and seropositives who had slightly different interests in disease communication and prevention) or they were too singular (haemophiliac patients) (R4, De Mooij 2004). Hence, the *openness* of the arrangement was not limited to experts but it was limited to certain patient groups. Although gradually the concentration in Amsterdam ceased to exist and more stakeholders became involved in the care and safety monitoring of HIV/AIDS, the community remained homogeneous and closed to other patient groups (R20, R21, R25, R15).

The bottom-up nature of the post-marketing surveillance arrangements of HIV/AIDS, and the inclusion of a wide range of stakeholders, meant that there was no central *powerful* stakeholder. Government agencies were following rather than leading in setting up activities and institutions, and they mostly supported initiatives by patients and medical professionals. In particular, homosexual patients obtained leverage because of their strong cognitive resource position, their electoral significance, and their access to powerful political networks. The interests of patients, scientists, companies, and medical professionals were mostly pointing in the same direction (R19). That is, their activities were aimed at quick advancement of science and therapy. One should notice, however, that the power of other patient groups and the power of taxpayers was limited. Power was concentrated in homogeneous networks.

Since *knowledge* about the disease and the way to deal with treatment and side-effects co-evolved, a wide range of stakeholders, including patients, could be regarded as laymen and experts at the same time (R17, R6, R24). Both patients and medical professionals had a high degree of expertise, which was the result of scarce and growing knowledge about the disease and what the interview respondents perceived to be the well-educated, well-resourced character of the patients (R17, R6, R18, R24). The lack of knowledge about the disease led to frequent interactions between the medical specialists involved and patient groups and hence collective knowledge production.

Evaluating regulatory performance
To assess the *process performance* we looked at the processing of signals. Signals are picked up by various stakeholders, such as doctors and patients, but side-effects are generally only reported to the company (R20, R21, R22, R23). Post-marketing surveillance goes

through large-scale company systems, medical professional networks, and discussion forums of patient organizations. The speed and quality of this signalling is regarded as good. Signal processing in company post-marketing surveillance systems proceeds via formalized schemes and is reliable and fast (R22, R23, R11). More academic and large-scale questions, such as the hypothesis regarding the causal relationship between antiviral drug use and cardiovascular disease, are picked up by ad-hoc consortia of scientists, doctors, and companies (R17, R6, R7). Dissemination of knowledge about (potential) side-effects and the results of these studies happens extremely quickly, for example through patient groups, communication bureaus attached to conference organizations, and the medical community (R6). In the early days, the quality of these signals communicated by patients may not have been high, which the unsubstantiated safety scares around the drug AZT showed, but this certainly improved as a result of professionalization and self-reflection of patients.

In terms of *output performance*, adherence is important in order to suppress viral replication. In the Netherlands studies showed complete adherence of a mere 43 per cent (Hugen *et al.* 2002) to 47 per cent (Nieuwkerk *et al.* 2001) for Highly Active Anti-Retroviral Therapy in the long run. This level of adherence seems low, but these results are quite similar to other countries (Chesney *et al.* 2000). In addition, the adherence to post-marketing surveillance efforts is high. It is perceived that patients, nurse practitioners, and medical specialists are reporting side-effects quite well to each other and to the companies. Reporting to spontaneous reporting schemes is regarded as limited and hence reports cannot easily be scaled to larger populations. Overall, it took some time to develop adequate responses, but these responses resulted in high adherence to post-marketing surveillance efforts with some difficulties of scaling these to the population level and registering adverse drug reactions (ADRs) in public information systems.

The stakeholders that were included in the close-knit community were *satisfied* with the post-marketing surveillance schemes, which could (partially) be explained because they largely set these up themselves. Companies complain that the specific obligations they need to comply with are not feasible or clear enough (R22, R23). Patients and scientists perceive side-effects related to long-term drug use and 'small, forgotten' side-effects to be increasingly important. Little information is available about the level of satisfaction of the stakeholders outside these close-knit communities since these patient groups – intravenous drug abusers, immigrants, and haemophiliac patients – were not able to bring attention to their position.

ANALYSIS AND CASE COMPARISON

The case studies show that pharmaceuticals within the same institutional regime of conditional approvals were regulated in different regulatory arrangements. The results of the two case studies are summarized and presented in table 1.

In the pandemic influenza case there was a fairly technocratic approach to monitoring the effects of drugs. Institutionally, this approach is inherited from newborn and seasonal influenza vaccination practices and the programmes that react to emergencies such as SARS. These practices favour speed and efficiency over deliberation and interactions. The scale on which the vaccination needed to be deployed called for a 'military' campaign. Access to networks was restricted to industry, selected experts, and government organizations. Patient groups and opponents of this vaccination were kept outside these networks. There was an emphasis on formal expertise and formal rules for interactions,

TABLE 1 *Comparing regulatory arrangements of two cases*

Dimension	Pandemic influenza	HIV
1. Interaction patterns	High network centrality – Government agencies, scientific experts, and pharmaceutical industry interact frequently and exclusively – Critical groups organize their own interactions on the internet	Continuing low network centrality – 1990s: frequent, informal interactions between patient groups, professionals, and the pharmaceutical industry – Later: more formal interactions but still frequent patient involvement
2. Formal and informal rules	Formal arrangement – Existing rules emphasized formal reporting by companies, professionals, and municipal health services – Informal rule: non-experts are supposed to stay quiet since this would confuse the public	From informal to formal arrangement – Bottom-up surveillance arrangements – Arrangement co-evolved with knowledge about the disease – Formal arrangement still stipulated patient involvement
3. Openness and participation	Closed arrangement – Clique of government regulators, scientific experts, and pharmaceutical industry – Individual patients can send in reports to reporting agency (Lareb)	Semi-open arrangement – Forced open to patient involvement by mainly gay patient communities – Closed to other patient communities (e.g. haemophiliac patients, intravenous drug users)
4. Power and interests	Diverging interests – Focus on public health: variety of patient interests is not acknowledged – Concentrated formal government power in designing the vaccination programme – Critical groups develop countervailing power through the internet	Converging interests – Patient groups, professionals, and the pharmaceutical industry had converging interests and produced powerful networks – Power of 'outsiders' such as other patient groups but also taxpayers was limited
5. Role of knowledge and expertise	Knowledge transfer – Knowledge is concentrated in the hands of formal experts and transferred to the public – Arguments of critical groups were labelled as non-scientific and therefore irrelevant	Knowledge creation – 1990s: nobody was an expert – Learning networks of patients and experts: coproduction of knowledge – Later: both patients and medical professionals had a high degree of expertise

and knowledge sharing with the public was limited to targeted campaigns. One should notice that individual patients were not excluded altogether: they were invited to send their reports about ADRs to the national post-marketing surveillance centre Lareb.

The HIV case shows a more democratic approach. Patients were connected to regulators, industry, and professionals in several ways. Power was distributed, knowledge was shared, and interactions were guided by informal rules. Collective learning was the common goal in this arrangement and relevant knowledge was deemed to exist with both professionals and patients. One should notice that the network seems rather open, but access was restricted to vocal gay communities and engagement from other patient groups was limited. In contrast with the pandemic influenza case, at the early stage the experts did not have scientific knowledge about the disease and possible treatments and they invited lay stakeholders to engage in processes of knowledge production to improve regulation. Institutionally, the governance structures of post-marketing surveillance co-evolved with knowledge about the disease and treatment itself. The small scale and concentration of

TABLE 2 *Evaluating the regulatory performance of the two cases*

Evaluative dimension	Pandemic influenza	HIV
1. Process performance	High. Many high-quality signals from professionals and patients are collected by Lareb and processed adequately	High. Many high-quality signals are collected and processed adequately through a variety of (patient) systems
2. Output performance	Reasonable. The coverage was higher than for HPV but lower than for regular vaccinations for small children	Reasonable. Developing new approaches took some time. Local systems are not always scaled to population level
3. Satisfaction	Limited. Various groups in society were not satisfied with the arrangement	High. (Vocal) patients, medical professionals, and companies are satisfied with the arrangement

patients, together with a high degree of involvement of patients and medical specialists, meant that post-marketing surveillance was organized bottom-up and only later became formalized. This left ample room for stakeholders to shape the surveillance practices.

A crucial difference between the two cases is that the arrangement for monitoring the risks associated with vaccinations against pandemic influenza does not result in enlightening people (Dahl 1994, p. 30) or a public understanding of science (Durant 1999). People are being told that they should receive the vaccination, but government organizations don't really make an effort to raise their level of consciousness about the risks and benefits. The government does not engage in a debate with the opponents of these inoculations and hence people are left in doubt. In contrast, the arrangement for HIV results in processes of collective learning and enhanced knowledge on both sides: patients learn from medical professionals and vice versa. The democratic ideal of empowering patients – albeit a specific group of patients – is a crucial element in this arrangement. Ravetz (2006, p. 115) highlights that the biggest hurdle that needs to be overcome for carrying out participatory science is the prejudice that no one can handle science unless they have a university degree in the specific subject. The arrangement for HIV has overcome this hurdle; the arrangement for pandemic influenza has not.

How do these two arrangements perform in terms of output and process performance and stakeholder satisfaction? The results from the case studies are presented in table 2.

The table shows that the process and output performance of the arrangement for monitoring the effects of pandemic influenza score, respectively, 'high' and 'reasonable', but the degree of stakeholder satisfaction is 'limited'. A strong element of the performance is the collection of a high number of signals from professionals and patients while a weaker element is the relatively low coverage of the vaccination. A qualitative assessment of these findings showed that a vocal group of opponents finds that government has been captured by specific (business and institutional) interests. This critical group has managed to attract much media attention and has reached significant groups of patients. This indicates that the regulatory arrangement succeeds in managing to deliver quickly and on a large scale, but fails to produce stakeholder satisfaction. In line with Abels' (2004) argument, the lack of engagement results in limited stakeholder satisfaction.

The scores for the arrangement for monitoring the effects of HIV pharmaceuticals are 'high' and 'reasonable', respectively, on process and output performance, and also 'high' on stakeholder satisfaction. Although the development of new approaches took much time

and the resulting system is still rather fragmented, this model has enabled collective learning in a community of experts and a selected group of lay stakeholders and, hence, good performance. One should notice that the groups that were kept outside this arrangement – drug addicts, prostitutes, and haemophiliacs – are less vocal and embedded in political networks, and therefore have a limited effect on public perceptions of performance.

On the basis of this analysis we can now evaluate our expectations. We found little empirical support for the expectation that the technocratic approach would be superior in terms of process and output performance since both the technocratic approach to pandemic influenza and the democratic approach to HIV showed strengths and weaknesses. The more technocratic approach for pandemic influenza scored well in terms of scaling signals to the level of the whole population and speed of developing a post-marketing surveillance approach, but the lack of adherence due to doubts about the vaccination is a challenge to regulatory effectiveness. The more democratic approach for HIV scored well in terms of adherence due to broad support in the gay community, but learning and knowledge production took place within a limited community and took a considerable amount of time in terms of scaling up monitoring initiatives. The focus on specific patient groups and informal contacts creates information that is not necessarily useful to population-wide pharmaceutical regulation.

We did find some support for the expectation that the democratic arrangement performs better in terms of stakeholder satisfaction than the technocratic arrangement. We found that the patients directly involved in the regulatory arrangement in the HIV case were satisfied with the regulatory performance, whereas the critical patients in the pandemic influenza case were not involved and were not satisfied with the regulatory performance. This difference can be understood as a difference in the role of vocal patient groups in regulation: these vocal groups were engaged in the HIV case and not engaged in the pandemic influenza case.

The cases show differences in their level of lay stakeholder engagement but one should be careful in attributing differences in performance and satisfaction to the make-up of these regulatory arrangements. A crucial difference between the cases is the nature of the disease. Patients with HIV suffer from the consequences of their disease and benefit more from the potential effectiveness of a treatment. Since the medicines are a patient's only treatment option, they are much more likely to accept ADRs and they have a certain sense of responsibility for the regulatory monitoring arrangement. People who receive a preventive vaccination against pandemic influenza because they run a certain risk of being contaminated with the disease and to protect public health might have a smaller tolerance for ADRs and might not feel any responsibility for the monitoring arrangement.

There are many other differences between the disease areas that influence the performance of regulatory arrangements such as the role of the media, the political climate, and the interests of pharmaceutical companies, and we do not claim that the outcomes are the sole result of differences in regulatory arrangements. Still, earlier work on government policies for HIV seems to support our analysis. Bovens *et al.* (2001) made a comparison of how governments dealt with the issue of preventing HIV contamination through blood transfusions and studied countries with more technocratic arrangements (e.g. France) and more democratic arrangements (e.g. the Netherlands). Their findings pointed in the same direction as our research: there was no difference in process and output performance, and a higher score on stakeholder satisfaction for the democratic arrangement.

BEYOND DAHL'S DEMOCRATIC DILEMMA

Do regulatory arrangements with lay stakeholder involvement improve the governance of pharmaceutical risks? Our research shows that more lay stakeholder engagement does not result in a stronger process and or better output performance but it does result in a higher stakeholder satisfaction. In the case of pharmaceutical regulation, the long-term willingness to use pharmaceuticals may diminish if citizens are not satisfied with the system of pharmaceutical regulation (cf. Harris *et al.* 2010, p. 2184; Löfstedt 2004, p. 337). This approach echoes – although in a considerably less radical manner – the work of Illich (1973) about challenging the monopoly of experts and revaluing the practical wisdom of laymen. On the basis of our empirical findings we suggest that in times when expertise is increasingly questioned, experts will need to find ways to connect their knowledge to the knowledge of stakeholders even if they consider them to be laymen.

Connecting to lay knowledge may not always be easy for experts: they need to have the communicative skills to discuss scientific issues in an accessible manner. Experts will also be open to new forms of critique and they will need to discuss their opinions not only in scientific but also in societal terms (Kitcher 2001; Ravetz 2006). They should also take into account the heterogeneous nature of these interactions. The connection between experts and lay stakeholders is not straightforward in the sense that scientists only produce formal knowledge and laymen keep to lay knowledge. Building new regulatory networks means including a wide range of stakeholders and taking into account different types of (formal, tacit, and lay) knowledge.

This article focuses on the *outcomes* of different regulatory arrangements and it does not specifically answer the question why different arrangements emerged for HIV and pandemic influenza. The empirical material provides some indications, but an analysis of *causes* for different arrangements requires additional work. On the basis of our case descriptions, the relatively weak position of the technocratic arrangement – the medical profession has no clear answer to the threat of AIDS – and the relatively strong position of stakeholders – the patient groups were highly vocal and organized – seem to explain the resulting democratic arrangement in the case of HIV. The literature highlights that collective knowledge creation is important specifically when there is much uncertainty about the risks associated with pharmaceuticals (Ebbers *et al.* 2011).

While a rich diversity of partly overlapping mechanisms may be considered to be less efficient since it may lead to redundancies in post-marketing surveillance, it increases the flexibility and adaptability of the risk arrangement and provides opportunities for various forms of lay stakeholder involvement. When more certainty about the disease and treatments is created, less variety may be needed since the chances of unlikely events are reduced. This type of development is already taking place in the field of HIV pharmaceuticals and the arrangement seems to be evolving into a more technocratic one.

Follow-up research needs to delve into the role of institutional, cultural, and technological differences. The patterns we found may hold in a fairly egalitarian society such as the Netherlands, but we need to study whether engaging stakeholders can also enhance trust in pharmaceutical regulation in more hierarchical societies. In addition, we need to find out to what extent stakeholder engagement influences the effectiveness of and satisfaction with regulation in knowledge-intensive domains that are more distant from individual experiences. Is stakeholder engagement in regulation important for new technologies that do not trigger tangible individual risks? More empirical research in different countries and different technological domains is needed to come to a comprehensive understanding

of the role of lay stakeholder engagement in risk regulation of controversial new technologies.

Let us return to Dahl's dilemma: are democratic participation and system effectiveness irreconcilable? Rose (2008) emphasized that, in view of the process of co-evolution of regulation and technology, practitioners and laymen can play an important role in societal surveillance over new technologies. Ravetz (2006, p. 122) highlights that medical knowledge has become increasingly challenged and that the internet is further transforming this field into a contested domain. In the field of pharmaceutical regulation, this means that formal and informal connections between patient groups, pharmaceutical companies, medical professionals, and government authorities may be crucial to the robustness of risk regulation. Such an opening up of the regulatory decision-making to extensive public access requires overcoming traditional power relations in the pharmaceutical sector (Abraham 2003). Löfstedt (2004, p. 340) suggests that there may be a contradiction between an open process and the scientific level of the process, but we found no empirical support for this claim. Our research confirms Abels' (2004, p. 4) conclusion that there is no necessary dilemma between citizen participation and system effectiveness: in situations of fundamental uncertainty, democratic monitoring of pharmaceutical risks can contribute to the system's robustness.

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