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Divergence and convergence of commercial and scientific priorities in drug development: The case of Zelmid, the first SSRI antidepressant



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ABSTRACT

Based on a realist conceptualization of interests, this paper explores how commercial and scientific priorities appear to have converged and diverged during the development of the antidepressant Zelmid. The drug represents the first of the selective serotonin reuptake inhibitors (SSRIs) to reach the market. Zelmid was synthesized in 1971 and launched by the Swedish firm Astra in 1982, but subsequently withdrawn the next year because of adverse neurological effects. This paper draws on in-depth interviews with scientists representing both industry and academia who had high-level involvement in various phases of the project (experimental, pre-clinical and clinical), as well as on textual sources such as scientific articles and memoirs. Zelmid was a product of mechanism-based or “rational” drug discovery from the early 1960s and the associated intermingling of science and commerce. It is argued that both scientists and the pharmaceutical company shared an interest in embracing mechanism-based drug discovery because it simultaneously promised medico-scientific advances and profits. However, the intermingling of science and commerce also strained the relationship between scientific and commercial priorities further along the trajectory of the drug; for example, concerning issues such as dosage strategy and drug use in primary care, where corporate management allegedly took decisions contrary to the recommendations of both academic and company scientists. On such occasions the asymmetry in power became apparent in scientists' narratives: commercial considerations trumped those of science since, ultimately, decisions rest with management, not with scientists. In addition, temporality appears to be associated with the divergence of commercial and scientific priorities. While rare during experimental and pre-clinical phases, divergence was concentrated downstream to the clinical testing and post-marketing phases. It is hypothesized that a similar pattern of convergence and divergence of commercial and scientific priorities may exist in the trajectory of other drugs.

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1. Introduction

For the social sciences a fascinating property of pharmaceuticals is how they connect multiple social groups within our highly technological societies. This includes the various professionals involved in drug discovery and evaluation, the companies responsible for production and marketing, the authorities responsible for regulation, as well as the doctors who prescribe these drugs and the patients who take them (Gaudillière, 2005). This paper brings together two partially overlapping strands of social science

research on pharmaceuticals. One is concerned with the values and priorities in drug research and development (R&D) (Sismondo, 2004); the other with the historical trajectory of specific drugs (Gaudillière, 2005). Regarding the first strand, one major concern rests with the intermingling of science and commerce (Rasmussen, 2004), including the resultant possibilities and perils, especially related to pharmaceuticals innovation (Achilladelis and Antonakis, 2001) and the public health repercussions of prioritizing the interests of commerce over science (Abraham, 2008). Regarding the latter, the focus has been on detailing drug histories and viewing these histories in a broader scientific, industrial, and medical context, such as in relation to the ideas and practices that have guided R&D (Green, 2007; Quirke, 2014). Informed by these research strands, this paper explores how commercial and scientific priorities appear to have converged and diverged during the

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trajectory of the antidepressant Zeldid, launched by the Swedish firm Astra in 1982, but withdrawn the subsequent year because of adverse neurological effects.

Zeldid represents the first of the so-called selective serotonin reuptake inhibitors (SSRIs) to reach the market, years before competing products such as blockbusters Prozac (fluoxetine) and Zoloft (sertraline) were marketed from the late 1980s. The remarkable success of the SSRIs was followed by controversies about efficacy, safety and overtreatment (Healy, 2004). In turn, these developments have sparked special interest in the history of SSRIs (Healy, 1997; Moncrieff, 2008; Herzberg, 2010), and indeed of antidepressants and depression in general (Rasmussen, 2008; Shorter, 2009; Mulinari, 2012). However, from a social science perspective, the history of Zeldid is interesting to scrutinize not only because the drug happened to be the first in a long series of serotonin- (and profit-) boosting antidepressants. Although it is interesting to note how development of this drug was propelled by a convergence of commercial and scientific interests that stimulated the intermingling of industry and university research, perhaps even more interesting is how such intermingling is said to have resulted in tensions and outright conflict between commercial and scientific priorities further along the trajectory of the drug.

In the following, this point is brought to the fore through micro-level examination of the trajectory of Zeldid from the perspective of the academic and industry scientists involved in its R&D. The relevance of this analysis extends beyond the present case because, as earlier research suggests, convergence as well as divergence of scientific and commercial priorities may be general characteristics of the current pharmaceutical innovation regime (Abraham, 2008).

2. Data source and research methods

Theoretically and methodologically, this paper builds on a realist conceptualization of interests (Abraham, 2008). Thus even though the industry, as Vivian Quirke (2014; p.656) points out, “is neither monolithic nor static, but – just as modern medicine – flexible and diverse” pharmaceutical companies are, as John Abraham (2008) argues, still hierarchical organizations that have an objective, though not always over-riding, commercial interest in profit maximization. By contrast, scientists – even those in the industry – do not necessarily have commercial interests in R&D, and their actions are likely influenced by intellectual, disciplinary and professional motives. This is in part why the idea of managing or prohibiting “conflict of interests” to minimize corporate bias makes sense, as well as polices to increase or maintain the autonomy of scientists, regulatory agencies and academic institutions vis-à-vis industry (Thompson, 1993). Such a realist framework of interests does not, however, assume that interests – and hence priorities – always diverge between pharmaceutical companies and scientists (or other actors). Nor does it assume that pharmaceutical companies and scientists are *solely* motivated by commercial and scientific interests, respectively. In fact because the relationship between interests, actors and actions is not straightforward an ongoing empirical challenge is to explore how various interests converge and diverge in pharmaceutical R&D and how this impacts on micro-level knowledge-claims, practices and controversies pertaining to pharmaceuticals (e.g. Abraham, 2008).

Based on such a framework, the present paper represents an effort to document the course of events in relation to Zeldid. To that end, between 2010 and 2012 the author conducted ten semi-structured interviews lasting from one to three hours with academic and industry scientists and management involved in its R&D during various phases (experimental, pre-clinical and clinical). All participants were informed beforehand that they would not remain anonymous and were asked to provide written informed consent,

which everyone did. The study was approved by the Ethical Committee at Lund University, Sweden (no. 2010/274). Interviews were tape recorded and transcribed. Transcripts were read comprehensively and coded systematically according to relevance to the research question: how commercial and scientific priorities converged or diverged. In some cases, ambiguities were clarified via written correspondence. Oral reports have proved highly valuable for investigating the history of psychopharmacology (Healy, 1997, 2002), but a well-known challenge facing oral reports is accuracy. Multiple sources were therefore used to cross-check facts and reconstruct the course of events. Besides interviews this includes textual sources, such as scientific articles, memoirs and other written accounts by involved individuals (Ross, 1998; Agurell, 2009), some of whom are now deceased (Östholm, 1995). It should be noted however that with respect to the motives of the corporate leadership the evidence was mainly gathered from texts by the late Lars Werkö (2000, 2003), a long-time member of Astra's Board of Directors (1965–1985) and Executive Vice President and Research Director of the company (1978–1985). Attempts to query the Marketing Director responsible for Zeldid to get confirmation or alternative interpretations of events proved unsuccessful. Consequently, the story is told from the perspective of key academic and industry scientists.

3. Background: synthesis of selective serotonin-boosting antidepressants

By the mid-to-late 1960s, many psychopharmacologists had come to consider *noradrenaline* as the critical neurotransmitter to target for pharmacological treatment of depression (Mulinari, 2012). This belief was underpinned by findings that tricyclic antidepressants (TCA) block neuronal uptake of noradrenaline, and that various other compounds that increase brain noradrenaline have an antidepressant effect (Schildkraut and Kety, 1967). However, in 1968, pharmacology professor and subsequent Nobel laureate Arvid Carlsson of Gothenburg University, Sweden, together with colleagues from Karolinska Institutet in Stockholm, published a seminal paper proposing that the TCA imipramine may alleviate depression in part by blocking reuptake of the neurotransmitter *serotonin* (Carlsson et al., 1968). In many ways, this proposal that serotonin may be involved in the mood-elevating effect of TCAs set the stage for the ensuing development of SSRIs in the 1970s and 1980s by almost every major pharmaceutical firm worldwide (Healy, 1997).

Inspired by this original idea, Carlsson suggested first to the Swiss firm Geigy, the owners of clomipramine, the most serotonin-selective TCAs tested, and then to the Astra subsidiary Hässle that they develop selective serotonin reuptake inhibitors – subsequently SSRIs – for the treatment of depression. According to Carlsson (2010; interview), only Astra Hässle showed immediate interest and had already involved Carlsson in a partnership to work on other projects, which entailed close collaboration between Carlsson and the Hässle chemist Hans Corrodi (Östholm, 1995). The continuing partnership would benefit both parties: Astra would own exclusive rights to any resultant compounds; Carlsson would receive support to further develop the serotonin project and was also guaranteed royalties from future sales (Carlsson, 2010; interview).

At the time Astra's R&D operations were organized into four independent subsidiaries (Sundling and Brennan, 2004). Three subsidiaries were strategically located in proximity to Swedish universities: Hässle in Mölndal outside of Gothenburg, Astra's Research Laboratory (subsequently Astra Pharmaceuticals) in Södertälje outside of Stockholm (where Astra headquarters was also located), and Draco in Lund in southern Sweden. The fourth –

Astra USA – was located abroad. Each subsidiary had its own pre-clinical research laboratories, and devised its own product policy, clinical trials and marketing strategy. However, the company executive board supervised activities and set the budgetary frameworks.

It was together with two Astra Hässle chemists — Hans Corrodi and Peter Berntsson — that Carlsson proceeded to develop what would become the first marketed SSRI, Z-1-(4-bromophenyl)-1-(3-pyridyl)-3-dimethylaminopropen, internally referred to as H102/09 (later zimelidine and then zimeldine, and marketed as Zelmid) in his Gothenburg laboratory in 1971. Carlsson, Corrodi and Berntsson began their work on a group of antihistamines (pheniramines) that they found could block both serotonin and noradrenaline reuptake. Among the pheniramines, they identified brompheniramine as the most potent serotonin reuptake blocker, which they therefore selected as the starting point for their synthesis program (Carlsson, 2010; interview). After a series of chemical modifications, the new compound, H102/09, was created with selective and potent serotonin reuptake blocking properties *in vitro*.

At this juncture, it is important to point out that Carlsson was not alone in pushing for an SSRI in the late 1960s. Remarkably, in Södertälje just outside Stockholm, less than 500 km from Gothenburg, Astra's Research Laboratory under the auspices of chief psychopharmacologist Svante Ross had largely independently been working on a similar project.

The origin of this project can be traced back to a 1967 publication where, in fact, Ross' team first demonstrated the presence of a serotonin reuptake mechanism in brain tissue (Ross and Renyi, 1967). The Astra researchers assessed serotonin reuptake by exposing slices of mouse brain to radioactive (tritiated) serotonin and then measuring how much radioactivity was incorporated. Using this technique, they demonstrated the serotonin reuptake blocking effect of various compounds, including a weak effect of the TCA desipramine. Shortly thereafter, researchers from the much larger US company Pfizer corroborated these findings (Blackburn et al., 1967). Ross (2012; interview) explained to me: “Our discovery was in itself not very remarkable, but it was important because it showed that it was possible to develop SSRIs.”

To that end, they chose another chemical route for synthesizing SSRIs than the route designed by Carlsson's team. They created so-called rigid spiro compounds that were structurally related to the TCA drug amitriptyline and that, based on previous experience, they believed could be selective for one neurotransmitter reuptake mechanism. However, because these compounds were difficult to synthesize, they also made biphenyl derivatives of these compounds (Ross, 2012; interview). It turned out that the spiro compounds were selective noradrenaline reuptake inhibitors, while the biphenyl derivatives were somewhat selective for serotonin. Among all these compounds, Ross and colleagues eventually decided to conduct extensive tests on what they perceived as the best candidate – PUB105 (compound no. 3a in (Carnmalm et al., 1975)).

4. H102/09 and PUB105: results of a paradigm shift in drug development

Thus around 1969–1970, both Ross' and Carlsson's teams had initiated synthesis programs aimed at making a more serotonin-selective antidepressant. Notably, both programs embodied the idea that drug development should be directed by hypotheses about how the targeting of a specific biological mechanism (e.g. serotonin reuptake) may produce therapeutic value (e.g. antidepressant effect) – later referred to as rational drug discovery (Adam, 2005). In psychopharmacology, such ideas were enabled by the scientific advances of previous years regarding chemical

neurotransmission and the pharmacological effects of psychotropics, as well as by developments in laboratory techniques, including those based on radioactivity used by Ross and colleagues (Healy, 2002; Mulinari, 2012). However, as will be argued here, the implementation of this more deductive approach to drug discovery at Astra was also underpinned by converging scientific and commercial interests in drug R&D, owing to the simultaneous promise of profits and medico-scientific advances.

Critically, the idea of synthesizing molecules that would affect a predefined biochemical target diverged from the principles previously employed by Astra and many other companies. In his memoirs the late Ivan Östholm, Research Director at Astra Hässle between 1959 and 1977, describes the old approach to drug discovery:

“Each successful medicine developed in the laboratories of these companies resulted from the synthesis by chemists of thousands of new chemical compounds, followed by tests known as screening. Following large standard programs, pharmacologists observed the effects of these chemicals in animal experiments to see whether they were worth testing as medicines. Between 5000 and 8000 substances could be tested before a useful medicine was found (Östholm, 1995, p.32).”

The problem with this approach, Östholm claimed in retrospect, was first that it required vast economic and technological resources, and second that the drugs developed were often derivatives of existing drugs and were therefore unlikely to represent major therapeutic advances. Because Astra was a small enterprise in the 1950s and 1960s, it lacked the resources to compete efficiently using this method of drug development. For Astra, Östholm says, this situation created an incentive to embrace “rational” drug discovery when the opportunity emerged i.e. when investigation of pharmacological mechanisms at the cellular and molecular level became possible (Östholm, 1995).

In Södertälje, Svante Ross played a central role in this paradigm shift. Ross, who had recently earned a degree in physiology, began to take an interest in mechanism-based drug discovery shortly after being recruited in 1957 to Astra's brand new Södertälje research laboratory during a research expansion phase (Ross, 1998). At Astra, Ross was tasked with developing rodent tests to screen for psychotropic effects of molecules synthesized by in-house chemists. The results were quite discouraging; many molecules were synthesized, but none seemed to have a behavioral profile that warranted clinical testing. Faced with such disheartening results, Ross (2012; interview) says, he proposed implementing novel ideas of “mechanism-based drug development”. This suggestion allegedly gained support from the laboratory leadership, which was searching for ways to improve the drug discovery process.

In Södertälje, the first study directed by Ross to follow this outline dates back to the early 1960s (Ross, 1998). It aimed at identifying an inhibitor of the enzyme catechol-O-methyl transferase (COMT). Based on the work of Julius Axelrod (1957) in the US, it was believed that COMT promoted inactivation of catecholamines such as noradrenaline. Because the enzyme monoamine oxidase (MAO) has a similar function, and because MAO inhibitors were known antidepressants, Ross and colleagues decided to test whether a COMT inhibitor would also be an antidepressant. It was in this context that intra-company collaboration was first established between Ross in Södertälje and Corrodi in Gothenburg, the Astra Hässle chemist working with Arvid Carlsson. However, despite shared interest in mechanism-based drug development, they agreed to pursue research independently. This, Ross explained, was largely because he wanted the freedom to use his industry work in an academic context for his doctoral thesis (personal

communication), underscoring the salience of intellectual/disciplinary interests even among industry scientists.

The COMT inhibitor project was soon abandoned because it turned out that COMT inhibition did not have the pharmacological effect that researchers were looking for. Moreover, Axelrod had shown that, actually, neuronal reuptake was the vital mechanism regulating synaptic noradrenaline levels (Axelrod et al., 1961), for which he later received the Nobel Prize. However, adhering to the “rational” drug discovery paradigm, Ross' team immediately began to focus on finding molecules that would influence noradrenaline reuptake (Ross, 2012; interview). For this, they used a technique to measure uptake of radioactively labeled noradrenaline into brain slices.

Then, during this work, an idea emerged that perhaps reuptake of serotonin in the brain could be measured, too – a concept not yet described in the literature (although serotonin reuptake in non-neuronal tissue was described by Axelrod in 1963). The availability of highly active radioactive serotonin enabled Ross and colleagues to test this idea, and they found that, indeed, there was active reuptake of serotonin in the brain (Ross and Renyi, 1967). Inspired by this finding and by suggestions from others – notably that serotonin may be involved in the mood-elevating effect of TCAs (Carlsson et al., 1968), or even in the pathophysiology of depression (Coppin, 1967) – they began to synthesize molecules that may act as selective serotonin reuptake inhibitors as described above.

While in Södertälje the shift toward mechanism-based drug discovery thus seems to have been an endogenous process that started sometime in the early 1960s, at Astra Hässle the former Research Manager Östholm (1995) has related that this line of research was established in 1961 after a meeting with Arvid Carlsson during which Carlsson suggested that Hässle should develop drugs targeting known biological mechanisms. According to Östholm, Carlsson's recommendations and his subsequent involvement with Hässle became the turning point for the Astra subsidiary, which now shifted its R&D approach from a chemical to a biological pathway. Thus, in the coming years, a number of original compounds were created at the nexus of industry and academia based on this philosophy; in addition to zimelidine, the best-sellers metoprolol to treat cardiovascular disorders and omeprazole to treat peptic ulcer that transformed Astra into a highly profitable global company in the early 1990s.

It is important to point out that Astra was not alone in pursuing the new paradigm of mechanism-based drug discovery in the 1960s. Rather, as Ross explained to me, prominent psychopharmacology researchers, such as Axelrod and Carlsson, had advanced such ideas beginning in the latter half of the 1950s and similar ideas were informing research in other disease areas (Adam, 2005). Nonetheless, as late as the early 1980s, some major pharmaceutical companies still relied on large synthesis and screening programs. This is evident from the following *British Medical Journal* excerpt from a 1982 symposium report – *Decision Making in Drug Research* – with representatives of major drug companies, universities and government institutions:

“One stimulating concept advanced at the meeting was an attempt to create new drugs by starting from a biological hypothesis and making use of new chemical substances to elucidate pharmacological or biological mechanisms. Such an integration of pathophysiological and pharmacological approaches may lead to new types of drugs (Gross, 1982, p.1444).”

Arguably, the implementation of mechanism-based drug discovery from the early 1960s portrayed above, which led up to the attempt to develop SSRIs from the late 1960s by both Ross' and

Carlsson's teams, was enabled by the convergence of commercial and scientific interests. Consistent with this, Astra Hässle's Research Director Östholm claims that the recognition that Astra needed new avenues for drug discovery drove him to seek help from, and embrace the ideas of university researchers specialized in pharmacology and experimental medicine, most notably Arvid Carlsson (Östholm, 1995). Conversely, according to Carlsson (2010; interview), the curiosity about creating and testing the effect of an SSRI (and other “rationally” designed drugs) drove him to seek help from drug companies despite being generally skeptical of the industry's scientific conduct. Similarly, the Astra scientists in Södertälje say they chose to develop an SSRI not for personal or corporate financial gain, but because the creation of an SSRI was appealing from a scientific perspective. Indeed, according to Ross, a principal impetus for the Astra scientists was to contribute to the advancement of psychopharmacology and, probably also, to propel their own scientific status, which entailed publishing findings in traditional academic fora.

5. The metabolite norzimelidine: tensions between scientific and commercial priorities

In the early 1970s, Astra still had two antidepressant projects running in parallel. However, the company realized that it lacked the resources to simultaneously push two antidepressants through the testing required by authorities for approval (Werkö, 2003). Therefore, a decision was taken to carry out a comparison of PUB105 and H102/09 with the aim of discarding one of them. The results were presented at a big meeting in 1971 with representatives from both project teams where it was decided to discard PUB105 (Ross, 1998). According to Sven Ove Ögren (2011; interview) – who was recruited to Astra in Södertälje in 1968 to test candidate psychopharmacological substances in animal models, and who one year later assumed responsibility for the PUB105 project (when Ross left to pursue academic work in the US for one year, including six months in Axelrod's lab) – one major reason for selecting H102/09 was that it appeared to be less toxic. Moreover, H102/09 was much more serotonin selective. As Ross (1998) later explained, this decision was therefore rational from a scientific standpoint insofar as the whole idea was to create a selective serotonin reuptake blocker.

Around this time, the perceived need to concentrate resources also underpinned major company-wide organizational changes (Werkö, 2003; Sundling and Brennan, 2004). Notably, this included concentrating all brain research to Astra Pharmaceuticals in Södertälje including the H102/09 project – now formally zimelidine. In the mid-1970s, following completion of pre-clinical studies in Södertälje, as well as initial testing on healthy volunteers (Ross, 1998), Astra Pharmaceuticals commissioned clinicians to test zimelidine on patients (Benkert et al., 1977). In one trial, organized by clinical pharmacologist Folke Sjöqvist at Karolinska Institutet, the drug was given to 6 depressed patients in doses of 25–150 mg twice daily for about 3 weeks (Sifers et al., 1977). The scientists verified that zimelidine was a selective serotonin reuptake inhibitor. However, they also noted that zimelidine metabolized to norzimelidine, which prompted Sjöqvist to suggest to Astra Pharmaceuticals that they assess the therapeutic value of norzimelidine – a suggestion, he says, to which researchers at the subsidiary never responded (Sjöqvist, 2011; interview).

The finding that zimelidine metabolized into norzimelidine was far from unexpected, however. Shortly after the project's transfer to Södertälje, Astra Pharmaceuticals' preclinical team realized that zimelidine was a pro-drug (i.e. it had to be metabolized to be therapeutically active) and that norzimelidine explained much of the drug's effect in animal models (Ross and Renyi, 1977). However,

norzimelidine seemed to have no apparent advantages versus zimelidine, when comparing their overall pharmacological properties (Ögren et al., 1981). Both compounds are serotonin reuptake blockers, and after oral administration of the same doses to rats, zimelidine and norzimelidine did not differ significantly in their ability to block serotonin uptake (Ross and Renyi, 1977). Sven Ove Ögren – who took command of the project in 1974 after the death of the previous project supervisor, the Zelmid co-inventor Hans Corrodi – explained retrospectively:

“The metabolism of zimelidine resulted in a molecule [norzimelidine] which was serotonin selective, but with higher plasma and brain concentrations than zimelidine. This differs from the TCAs, in which the main metabolites are noradrenaline selective ... so that selectivity was maintained after metabolism.” (Ögren, 2011; interview)

However, from a pharmacokinetic perspective norzimelidine may still be preferable to zimelidine because patients may vary in their ability to metabolize zimelidine (Sjöqvist, 2011; interview). Moreover, Ögren (2011; interview) notes that the toxicological profiles of the two compounds may differ; but this was never properly tested, in part due to lack of support from corporate management, Ögren claims.

For Ross this decision was at least partly motivated by commercial considerations: “It was considered to be too late to replace zimelidine since several other pharmaceutical companies were nipping at our heels” (personal communication). This was consistent with the explanation of Lars Werkö (2003) – Executive Vice President and Research Director of the Astra Group 1978–1985 – that Astra felt that the norzimelidine patent was far too close to expiration to justify further studies, which Sjöqvist (2011; interview) stressed would have been sensible from a strictly scientific perspective. However, from a financial perspective, focusing efforts on getting zimelidine to market was considered the better option, Werkö (2003) claims.

6. Indication and dose: clashes between commercial and scientific priorities

After encouraging results in small clinical trials, zimelidine advanced to controlled studies for final evaluation in endogenous depressions. From 1977 onward, trials were conducted in various European countries, as well as in Australia and Canada (Sundling and Brennan, 2004). Psychiatrist Jan Wälinder in Gothenburg conducted one of the trials in collaboration with Arvid Carlsson. At the time, Wälinder (2011; interview) explained to me, endogenous depression (as opposed to reactive) was conceptualized as a severe psychiatric disorder without apparent external cause, characterized not only by depressed mood, but also by a diurnal pattern in which symptoms predominate late at night and in the mornings. In addition, elements of psychomotor retardation should be present. However, the disorder was so rare that investigators were only able to recruit about twelve new patients per year to the trial. Indeed, recalled Stig Agurell (2011; interview) – Research Director of Astra Pharmaceuticals during this time and later President of Astra Pharmaceuticals – the difficulties in recruiting sufficient numbers of suitable patients with endogenous depression was a major problem across the board.

Notwithstanding such problems, the overall results from the clinical studies suggested that zimelidine was at least as effective as comparator drugs, but better tolerated by patients (e.g. (Wälinder et al., 1981; Loudon et al., 1981; Montgomery et al., 1981)). On this basis, Astra decided to register the drug for endogenous depression. But here something contentious happened that would

become the epicenter of subsequent controversies. Astra decided to seek approval for a *uniform daily dose of 200 mg*. The company also decided *no step-wise dose increment* was to be suggested, which was routine for antidepressants on the market (Werkö, 2003). In other words, all patients would receive the 200 mg dose from the first day of treatment. This dosage strategy was employed in some trials (Montgomery et al., 1981). However, in general practice trials, researchers were often more cautious and administered a lower 100 mg dose throughout the entire trial (Delia et al., 1981), or during the first two weeks, and only then stepped up to the full dose (Loudon et al., 1981). Similarly, in the Gothenburg trial directed by Wälinder, patients were started on 100 mg daily, which was increased after three days to 200 mg divided into two equal doses (Wälinder et al., 1981).

According to Ögren, the idea of uniform dosing was strongly promoted by marketing executives – despite resistance from company scientists, who stressed that this was inconsistent with current practice. As Ögren (2011; interview) recalls, “the message came down that if the full dose could not be given from day one, they would not be interested in launching the product.” Moreover, Ögren says, company management was not open to the possibility of making a proper dose–response curve for the drug’s clinical effect, which meant that the optimal dose remained unknown. However, based on available animal data, the optimal clinical dose of Zelmid was predicted to be lower than 200 mg (Ögren, 2011; interview).

Astra presented the idea of the uniform 200 mg dose at a conference held in Greece in April of 1980 (Carlsson et al., 1981). Most delegates seemed to respond favorably to Astra’s proposal (Agurell, 2011; interview). But not everyone was satisfied: Arvid Carlsson, Stuart Montgomery, and Jan Wälinder, all of whom had been involved in key trials, felt that Astra had set the dose too high (Carlsson, 2010; Wälinder, 2011; interview). The underlying reason was some evidence that the therapeutic effect was compromised when plasma levels of zimelidine and norzimelidine reached a certain threshold (Montgomery et al., 1981; Wälinder et al., 1981). For Wälinder et al. (1981), this indicated that the “daily dose chosen in the present study, i.e. the recommended 200 mg, may be somewhat too high.” Montgomery et al. (1981), however, restricted their recommendation of a lower dose to older patients. Several years later Stig Agurell (2009), the Research Director of Astra Pharmaceuticals, also pointed to some evidence that adverse drug reactions were less frequent when the dose was reduced to 100 mg daily, increased in a step-wise manner, or administered in two separate doses of 100 mg each. But according to Carlsson (2010; interview) and Wälinder (2011; interview), discussions centered less on the risk of adverse effects than on the risk of losing therapeutic efficacy. In light of the available data, they claim to have recommended that Astra sort out the existing dose-related uncertainties, just as Ögren had allegedly done earlier. This position is supported by the written account provided by Werkö (2003). Wälinder (2011; interview) explained:

“We soon became aware that Astra had recommended doses that were not at all consistent with what we had seen. If one were to be critical, you could say that it was a way to recoup invested research money. Arvid and I went up and met with the Astra Board of Directors and said that they have to calm things down. This was after the Corfu conference, where we began to suspect that they were being too aggressive in their marketing.”

According to Wälinder (2011; interview), they also requested that the company defer promotion of the drug to general practitioners until proper testing had been completed.

“From the onset, we were highly committed to the idea that before we have enough experience, this substance should be limited to use by psychiatrists. Should we accumulate evidence over time that this works, we will gradually shuttle it into primary care. But until such time, it stays within the realm of the psychiatric specialist. And this is where Astra was unable to resist and ventured out into primary care.”

The Astra leadership apparently disregarded such opinions (but seemingly accepted the suggestion of a lower dose for the elderly). For some reason, so did the pharmaceutical authorities – Astra’s application was given the green light.

But why was a single, higher dose of such importance to Astra? [Werkö \(2003\)](#) – who was part of the Astra management – gives the following answer: company management believed that a simple dosage scheme was the key to the large and profitable primary care market. To achieve this goal it was important to “not complicate treatment” (p.104). In his memoirs [Werkö \(2000\)](#) wrote: “The important question of dose and treatment initiation was not a medical issue, but came to be determined by those who would convince the market (or the prescribing doctors) of treatment excellence” (p.364).

Astra is also said to have rejected requests from scientists for additional clinical trials ([Werkö, 2003](#); [Carlsson, 2010](#); interview). The Astra leadership might have felt that producing more data only meant losing time. Another factor was a newly signed agreement with drug giant Merck, at that point the world’s largest pharmaceutical corporation, which wanted to sell Zelmid in the US ([Werkö, 2003](#)). Licensing the drug to Merck opened a new financial panorama for Astra, which at that time was a peripheral drug firm on the global scene ([Sundling and Brennan, 2004](#)). It is difficult to say whether things would have been different had Astra taken the criticism seriously. In any case, they did not. In 1982, Zelmid was introduced in Sweden and several other countries, including the UK and Germany.

7. The rise and fall of Zelmid

Already a few months post-launch, Zelmid became associated with a few cases of hypersensitivity reactions resulting in fever and muscle pain ([Agurell, 2009](#)). This was not unexpected. The drug information sheet contained the following statement: “Cases of hypersensitivity reactions (1%) including symptoms such as fever, muscle and joint pain ... have been reported” ([Astra, 1983](#)). However, within about one year, reports of potentially fatal side effects surfaced ([Agurell, 2009](#)). By the spring of 1983, reports of a flu-like condition began to arrive, sometimes accompanied by muscle cramps, liver dysfunction and a few cases of Guillain–Barré, a potentially fatal neurological disorder. In May of 1983, Swedish pharmaceutical authorities issued a warning regarding potentially serious adverse effects. Among an estimated 25 000 patients treated with Zelmid, authorities affirmed 80 likely cases of this influenza-like syndrome, sometimes with neurological complications, but believed the true figure could be much higher because of reporting bias ([Anonymous, 1983](#)). Given the seriousness of the situation, they raised concerns that “in just a short period, based on various indications a large number of patients had been exposed to this new chemical compound” (p.2034). They required doctors to immediately report suspected cases of Zelmid-induced hypersensitivity reactions, and to desist from off-label prescribing: “Zelmid should primarily be prescribed by psychiatric specialists based on strict indications” ([Anonymous, 1983](#), p.2034).

The Swedish pharmaceutical authorities were not alone in raising concerns. A month later, in June of 1983, British authorities

informed Astra that they intended to withdraw the drug because of its side effects ([Sundling and Brennan, 2004](#)). But despite the anxiety of authorities, Astra’s executive management at first seemed not to want the drug to be recalled ([Sundling and Brennan, 2004](#)). However, when additional cases of Guillain–Barré surfaced, on September 15, 1983, following an internal investigation, Astra decided to withdraw the drug globally before Merck had the chance to release it in the US ([Agurell, 2009](#)). According to [Stig Agurell \(2009\)](#) – who attended the meeting where the withdrawal decision was taken – the President of the Astra Group asked everyone present to lay any commercial considerations aside, which resulted in unanimous support for withdrawal. Possibly, under threats of forced withdrawal and with mounting medical concerns, resisting withdrawal could have been perceived as a risky commercial strategy that could have severely damaged the company’s reputation.

At the time of withdrawal Zelmid had been prescribed to more than 200 000 patients, which in 1983 represented an astonishing figure for an antidepressant produced by a minor player. In Sweden alone, the figure was about 75 000 patients, representing 40 percent of the antidepressant market ([Sundling and Brennan, 2004](#)). It was later estimated that at least 1 in 10 000 treated with zimelidine would develop Guillain–Barré, compared with a “spontaneous” occurrence rate of 1 in 50 000. To this day how the drug causes such effects remains unclear, although an immunological process unrelated to the drug’s serotonin reuptake blocking effect seems likely ([Bengtsson, 1992](#)). Some evidence also suggests that such severe adverse reactions are dose-dependent, which has naturally triggered discussions about whether they could have been avoided ([Werkö, 2003](#)). However, of the 80 cases reported to Swedish pharmaceutical authorities in 1982, 17 had received a daily dose of 100 mg ([Anonymous, 1983](#)), suggesting that although administration of the lower dose could perhaps have reduced the number of such serious adverse events, they would not have been completely avoided.

Still, how could Zelmid have become so widely prescribed in such a short period of time? According to [Jan Wälinder \(2011](#); interview) and [Marie Åsberg \(2010](#); interview) – two of Sweden’s most influential psychiatrists at the time – part of the explanation is that doctors perceived Zelmid to be convenient, safe and effective compared with existing medications. However, Åsberg and Wälinder also hold that aggressive marketing influenced doctors to prescribe the drug. For example, [Åsberg \(2010](#); interview) recollected how sales representatives promoted the drug to general practice physicians by stressing the limited side effect profile and that, unlike TCAs, patients could not commit suicide by overdosing. This sentiment is supported by other accounts; [Werkö \(2003\)](#) retrospectively portrayed Astra’s marketing as “overwhelming” (p.105), while journalist [Ingrid Carlberg \(2008\)](#) described some of the marketing strategies, including free lunches, trips, and gifts to doctors. In this respect the Zelmid story previewed subsequent SSRI marketing strategies, albeit in milder form ([Healy, 2004](#); [Zetterqvist and Mulinari, 2013](#)). Indeed, commentators have noted how Zelmid’s extraordinary yet brief success became an eye-opener for many larger companies with similar drugs in the pipeline ([Healy, 2004](#); [Shorter, 2009](#)). Insofar as that is correct, this study suggests that Astra may have paved the way by showing competitors how intense marketing and a simple dosage scheme opened the golden gates to the vast primary care market.

8. Conclusion

The development of Zelmid over almost a 15-year period was contingent on dynamic interactions between academic scientists, industry scientists and research management. As the above account

suggests, those interactions were characterized by both convergence and divergence between commercial and scientific priorities at distinct points along the drug's trajectory. Arguably, the convergence of commercial and scientific priorities underpinned the push toward mechanism-based drug discovery from the early 1960s following important innovations in laboratory techniques and the simultaneous promises of medico-scientific advances and profits. However, the Zelmid story also suggests that the intermingling of science and commerce was far from unproblematic. Thus, along Zelmid's trajectory, scientific and commercial priorities also appear to have diverged at various points, sometimes even resulting in conflict. On such occasions it is pertinent to note that a *power asymmetry* is apparent in the narratives of scientists: commercial considerations appear to have trumped those of science since the power to decide ultimately rests with corporate management, not with scientists. Accordingly, corporate concerns with patent expiration were said to have underpinned the decision not to pursue thorough investigation into the metabolite norzimeclidine despite scientists' interests. However, perhaps this is most apparent concerning the issues related to dosage and to drug use in primary care, where corporate management allegedly took decisions contrary to the recommendations of both academic and company scientists.

A striking feature of this story is how such still-lingering scientific doubts had seemingly little impact on Zelmid's reception among health care professionals; physicians even prescribed Zelmid off-label (i.e. for non-endogenous depression). Although Astra supported a wide use of the drug by hefty marketing it would be unwise to reduce physicians' behavior to an outcome of marketing. As pointed out by Green (2007) physicians often make pragmatic treatment choices, and like subsequent SSRIs Zelmid was more convenient than existing antidepressants due to its simple dosage and the low risk for suicide by overdosing.

A limitation in the present analysis is that the emphasis on interests may have resulted in the downplaying of other factors that possibly contributed to disagreements, for example communication gaps or the various technical, legal, regulatory, organizational or financial constraints that actors faced. Indeed, interest explanations should not be considered exhaustive (Abraham, 2008), although they may be particularly apt for studies of corporate science (Sismondo, 2011). Moreover, by relying heavily on interviews many years after the fact there is a risk that scientists' intellectual concerns are being idealized and commercial pressures and incentives downplayed. Arvid Carlsson, for example, was entitled to royalties from Zelmid sales, but when queried about this responded that his motivation was always scientific as opposed to commercial, citing the dosage controversy to support this. As studies of conflict of interests in medical research emphasize, researchers in both industry and academia may be influenced by multiple and sometimes conflicting interests, including intellectual and commercial interests (Thompson, 1993). This study does not question the relevance of such potentially conflicting interests within single actors; rather it highlights how priorities converge and diverge also between actors.

The notion of converging or diverging priorities between actors is not new. Such ideas have, for example, emerged from and informed previous historical analyses of pharmaceutical innovation (e.g. Green, 2007; Quirke, 2014) and regulation (e.g. Abraham, 2008; Tobbell, 2012). What this study adds to this literature is to suggest a *temporality* in the divergence of commercial and scientific priorities. Divergence was rare during the experimental and pre-clinical phases (although there may have been some tension, as the norzimeclidine example suggests), but became concentrated downstream during clinical testing and post-marketing. This may partly reflect the fact that experimental and preclinical research at

Astra at that time was decentralized where, Ross (1998) writes, "initiatives were still at the laboratory level" (p.7) and where local research management, Östholm (1995) submits, was not "dependent on support from the company's marketing experts when choosing projects and deciding which compounds should be used for clinical trials" (p.152), as was, he argues, common practice in other companies.

This alignment of R&D and marketing (e.g. Green, 2007; Dumit, 2012) together with some recent changes in the research organization of companies (e.g. outsourcing and offshoring) (Petryna, 2009) could admittedly challenge the present-day relevance of this case study. On the other hand, drug developers of today face some of the same scientific and regulatory challenges as did Astra in the 1970s and 1980s, such as a need to investigate drugs' pharmacological and toxicological profiles and organize a sequence of pre-clinical and clinical studies to gain market access. Moreover, as in the 1970s and 1980s, corporate financial investment and profit prospects grow intensely along a drug's trajectory, meaning that awareness and involvement by higher levels of management will typically be greatest in the late project phases. Also, the current market incentive structure, as conditioned for example by patent rules, ensure that it is in the firm's interest to swiftly increase the size of the potential market, for example through heavy marketing (OECD, 2009), which provides fertile ground for mismatches between scientific and (especially short-term) commercial priorities. Therefore, it may be possible to discern a similar pattern of convergence and divergence of priorities in the trajectory of other drugs. Consistent with this idea, the literature on the conduct of drug companies is densely packed with examples of companies that ignore scientific concerns during the clinical and post-marketing phases (e.g. Dukes et al., 2014), whereas examples from the experimental and preclinical phases are far less common (however see, Abraham and Ballinger (2012)). This may not only be because the experimental and preclinical phases are less open to scrutiny, but may also reflect the actual nature of drug R&D. Specifically, ignoring scientific concerns in the experimental and pre-clinical phases may come at a high cost, since a company that heavily invests in a project with inherent scientific flaws is likely to pay dearly downstream during the R&D process. In stark contrast, too much credence given to scientific concerns during the clinical testing and post-marketing phases may also pose financial risk since it could delay, restrict or even hinder market access.

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