To: European Medicines Agency (EMA)
Copy: The Committee for Medicinal Products for Human Use (CHMP)

The disapproval of the ADHD drug Concerta and Janssen's- "sophisticated strategies" for marketing in Sweden

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The pharmaceutical company Janssen-Cilag's application to get Concerta approved for adults was DISAPPROVED by the European drug regulatory authorities in May 2011. Janssen-Cilag (now just Janssen) committed itself *not to* market Concerta for adults – the drug was not to be prescribed to that target group.

But the pharmaceutical company did the opposite. It *increased* its sales of Concerta for adults in Sweden from 112 million SEK (14 million EUR) to 142 million SEK (17 million EUR) in 2011. This meant that the company has sold the, for adults, not authorized drug (methylphenidate) for 420 million (51 million EUR) since 2006.

This report takes up the "sophisticated strategies and tactics to disseminate misrepresentations" about Concerta that the drug company made use of in Sweden. The report compares these with the advanced criminal practices that drug companies made use of in the U.S., resulting in *multibillion-dollar fines* for the drug companies, most recently, 3 billion U.S. dollars for GlaxoSmithKline (GSK).

The case in point is Sweden. However it can be assumed that the circumstances are similar in other European countries. What is written in this report is therefore of extreme importance for the European Medicines Agency (EMA).

We have a situation where an important European investigation, leading to the *disapproval* of Concerta for adults, has not been made public. The investigation has been concealed – together with the serious harmful effects that emerged in the studies. The only reason the data below can be presented is that the Swedish Medical Products Agency (probably) made a mistake and sent out the documents in an FOI request.

We have a situation where a pharmaceutical company has been allowed to continue to profit from a disapproved drug – and even, as in Sweden, increased its sales with 25% *after* the disapproval.

We have a situation similar to the Mediator scandal in France, where an already disapproved drug was allowed to stay on the market causing death and harmful events.

I expect that the European Medicines Agency acts to handle the medical scandal described in this report.

U.S. authorities have in recent years initiated extensive investigations to handle the advanced criminality that brought the pharmaceutical industry to the absolute top in the fraud league. **[1]**.

In one of the most recent cases GlaxoSmithKline (GSK) has been ordered to pay **3 billion U.S. dollars** "to resolve Fraud Allegations and Failure to Report Safety Data". **[2]** At the press conference where the decision was announced, one could find senior representatives of the Department of Justice, Department of Health and Human Services, "Deputy Commissioner for Global Regulatory Operations and Policy" from the U.S. Food Drug Administration FDA, representatives of the FBI. In his speech at the conference Deputy Attorney General James M. Cole emphasized that the decision "underscores the Administration's firm commitment to protecting the American people and holding accountable those who commit health care fraud". He also said that the Department of Justice in just three years, since 2009, "restored" 10.2 billion U.S. dollars in the field of health care fraud! In conclusion, he had this to say: "Let me be clear: we will not tolerate health care fraud. And, in every instance where we uncover it, we will use all available tools to hold those responsible to account." **[3]**

Below I will present evidence of the "sophisticated strategies" for marketing that Janssen made use of in Sweden to increase the sales of Concerta for adults. The company marketed the drug to adults although it had never been approved for adults, and despite the fact that the company got its application disapproved. I will compare the behavior in Sweden with data in the American legal cases.

We can summarize the situation by saying that the pharmaceutical company Janssen in 2007-2011 has sold Concerta to adults in Sweden to a value of 420 million SEK. [4] In 2011, the year when the application to get Concerta approved for adults was *DISAPPROVED,* and when the drug was declared to have a "negative benefit/risk balance" for adults, the company increased its sales of the drug for adults from 112 million SEK to 142 million SEK.

How could this happen?

We will look at specific examples of the "**sophisticated strategies and tactics to disseminate misrepresentations" *** that the company made use of in Sweden to get Concerta placed on the adult market, and compare these with what has emerged in legal cases in the United States. We will look at **"a variety of marketing tools disguised as medical education, scientific research and patient advocacy literature"** that the pharmaceutical company used, and how the company "**concealed and failed to disclose information about safety," and about the effects** of Concerta. How it acquired **"key opinion leaders", "advisors"** and **"experts",** and how the company provided inducements including **"research funding", "consulting fees"** and **"enhanced professional reputation"** to these **"**experts", to get **"biased research in favor"** of Janssen's drug. (*****The quotes in the paragraphs are from the Complaint against Janssen in Texas.)

As for the American legal cases, we will compare the methods with the case in Texas **[5]** http://jannel.se/texas-janssen-complaint.pdf , where Janssen in early 2012 had to pay 158 million U.S. dollar **[6]**, and the case against GlaxoSmithKline (GSK) recently completed. In the latter

case GSK had to pay 3 billion U.S. dollar. **[2]** We will also compare it with the case against the pharmaceutical company Forest Labs, in which Forest agreed to pay 313 million U.S. dollar, primarily for its illegal marketing of Cipramil (Celexa) for children. **[7]** http://jannel.se/celexa-complaint.pdf The case is of particular interest from a European point of view, as it involved the cover-up of the results of a European study of Cipramil on children, led by the Swedish Professor in Psychiatry Anne-Liis von Knorring (also Scientific Advisor to the Swedish Medical Products Agency, MPA).

Janssen disseminated false information about the effects of Concerta for adults via a sponsored "expert group"

Janssen paid for all meetings of the psychiatrist group "The European Network Adult ADHD", to produce one for Concerta (methylphenidate) positive *consensus document,* which the pharmaceutical company could then use in their marketing of Concerta for adults. **[8]** The group wrote in the document: "We thank Janssen-Cilag who provided support for meeting costs of the European Network Adult ADHD."

Although Janssen (July 2010) had knowledge of *the **disapproval*** of Concerta in the European study, the company permitted publication of completely opposite data about the good effects and mild adverse effects of Concerta in adults in the group's *consensus document* (September 2010).

A comparison of the data that emerged in the European study of Concerta, and what was stated in the consensus document:

Consensus document: "stimulants are by far the best studied and most effective treatment for ADHD." "Stimulants are effective in about 70% of [adult] patients with ADHD in controlled trials."
The European study: "B/R [Benefit/Risk] of Concerta in the proposed indication is negative". Overall, the conclusion of Janssen´s submitted studies were "failed", the company could not demonstrate a beneficial effect even short-term (after seven or thirteen weeks).

Consensus document: "Stimulants … improves ... anger outbursts, mood swings."
The European study: "A causal relationship with Concerta was established for aggression, tics and depression."

Consensus document: "Side effects are usually mild and transitory ..."
The European study: "The lack of demonstrated efficacy coupled with the safety issues, especially cardiovascular safety (potential long-term effects of increase in BP [blood pressure]) abuse potential, and psychiatric/aggression AEs [Adverse Events] render the BR [Benefit/Risk] negative for the proposed indication."

Consensus document: "Importantly, both clinical studies and clinical experience support the view that methylphenidate does not lead to stimulant or drug addiction. On the contrary, it has been shown to have a neutral or reducing impact on substance abuse and the risk of relapse."
The European study: "It is assessed there is a significant abuse and diversion risk with Concerta."
"... the misuse/abuse potential of methylphenidate is considered a major safety concern: in combination with the concerns regarding the reliability of the diagnosis, adults may try to get diagnosed for ADHD to retrieve methylphenidate in a legalised manner."

Janssen's experts concluded that Concerta (methylphenidate) is the **"first choice medication treatment"** for adults with ADHD **"based on an extensive and still growing body of data on efficacy and safety".** Janssen knew at the time of publication that neither efficacy nor safety was considered to exist for Concerta for adults. Despite that, the company allowed the above false marketing messages to be disseminated to doctors and authorities.
Swedish representatives in the psychiatrist group, "The European Network Adult ADHD" were: **Ylva Ginsberg, Susanne Bejerot, Dan Edvinsson** and **Maria Råstam** .

In the group we could also find prominent European psychiatrists like **Philip Asherson** (U.K.), **Sandra JJ Kooij** (the Netherlands), **Miquel Casas-Brugue** (Spain) and **Josep A Ramos Quiroga** (Spain), the last three heavily involved also in the manipulated studies described below (Study 3013, Study 3002).

We can compare the above with what the Department of Justice wrote in its case against GlaxoSmithKline (which led to the company having to pay 3 billion U.S. dollars). The Department of Justice describes (p. 2) that GSK's fraudulent marketing of Paxil (Seroxat) included the following: The company marketed Paxil as safe and effective (for children), although the FDA had not given approval for use in children, and although GSK's own clinical trials had failed to show Paxil's efficacy, and instead found that the drug could induce suicidal tendencies in children. **[9]** http://jannel.se/DOJ.GSK.Complaint.pdf

In the case with Janssen's expert group, we have a similar activity but now for Concerta for adults, where the company claimed that Concerta (methylphenidate) was "safe and effective" for adults, "first choice", even though the drug was not only *not approved*, but also *disapproved,* that the company had failed to show a positive effect in the combined results of their studies, and that new serious adverse effects had emerged.

Janssen misled doctors and authorities about the effects and adverse effects of Concerta in its own clinical trials

Janssen published false and misleading articles about the results in their three double-blind placebo-controlled trials of Concerta in adults (submitted as part of the application). They thereby misled doctors and authorities about *the effects and harmful effects*, and thus got the drug prescribed to a target group for which it never had been authorized. The *actual* results only emerged in the, yet unpublished, European investigation of Janssen's application to get Concerta approved for adults.

Study 3013

Study 3013 was the longest of the three double-blind studies Janssen submitted to European regulatory authorities, in support of its application to get Concerta approved for adults. It was 13 weeks long and included 279 subjects. Four of the 10 authors of the study were employees of the pharmaceutical company, one was a former employee and the other five authors had been consulting for the pharmaceutical company or had worked in the company's Advisory Board. Janssen had full control of the study in all its phases from design through to the final statistical analysis and interpretation of the results.

Interesting for Sweden is that one of the lead authors was psychiatrist **Ylva Ginsberg** . Two other Swedish investigators were psychiatrists **Dan Edvinsson** and **Per Woxler**.

The study ended in April 2009 and was selected by Janssen as one of the studies that would lead to an approval of Concerta for adults. But assessors at the U.K. Medicines and Healthcare products Regulatory Agency, MHRA (leading the European investigation) did not accept the data Janssen submitted and requested clarification. The conclusion in the European study became finally very clear: **Study 3013 was "clearly a failed study". [10]** (See page 3, Final Variation Assessment Report, Concerta Day 90, 26 April 2011)

This did not prevent Janssen, who most likely expected that the findings and conclusions in the European study would never be made public, to publish other, opposite information about the study in an article in the World Journal of Biological Psychiatry, November 22, 2011. **[11]** In the article Janssen said the following about the effects of Concerta found in the study signed by, among others, psychiatrists **Ylva Ginsberg**, **Sandra JJ Kooij**, **Miquel Casas-Brugue** and **Josep A Ramos Quiroga**): **"[Concerta] provided overall benefits in the treatment of adults with ADHD"**. In the article Janssen came to the following conclusion about the *harmful effects* that had emerged: **"Concerta] was well tolerated in the study."** A conclusion that must be considered false given that the MHRA's study emphasized that **19 percent of the subjects (34 of 182) receiving Concerta *discontinued* the study (compared to 2 percent in the placebo group) due to adverse effects.** (More about Janssen's cover-up of harmful effects later.)

Study 02-159

Study 02-159 was the 7-week study that Janssen submitted in support of their request. It included 236 subjects. Five of the seven authors of the published article were employees of Janssen, two sat in the company's Advisory Board. The study had quite some *impact* for Janssen as one of the authors, **Thomas Spencer**, professor of psychiatry at Harvard Medical School, was a "key opinion leader" in world-class. (Spencer has recently, together with his colleagues Joseph Biederman and Timothy Wilens, been the subject of extensive investigations by the U.S. Congress.) **[12]** The study ended on 21 November 2006 and was published in June 2009 (i.e. *before* Janssen submitted its application for approval of Concerta for adults). **[13]**

Janssen's data and analysis in study 02-159 was challenged *very strongly* in the European investigation. When the important issues eventually were answered by Janssen, the following assessment of the study was done: **"In the strictest interpretation this could be seen as a failed trial", or in *best* case, a "borderline failed study". [10]** (See page 5, Final Variation Assessment Report, Concerta Day 90, 26 April 2011)

One of the Swedish authorities that was misled by Janssen's fraudulent presentation of data in Study 02-159 was The Swedish Council on Health Technology Assessment (SBU). In its report on ADHD to the Government in January this year **[14]** SBU, to a considerable degree, based its conclusions about "efficacy" of methylphenidate (Concerta, Ritalin) on the data *published by Janssen* and its acquired "key opinion leaders" in Study 02-159. For example SBU took up the subject of "response rate" of Concerta in the study (p. 115), and wrote that it was 36.9% for Concerta against 20.9% for placebo. Forming *the basis* for the latter conclusion about the effects of methylphenidate in adults were two studies, one by the

above mentioned Biederman, and Study 02-159: **"These studies showed a significantly higher proportion who responded to treatment during treatment with methylphenidate than with placebo"** (p. 82). Upon request, the Director of SBU Måns Rosén and the leader of the ADHD project Professor Lars Jakobsson admitted that they, when the above conclusions were presented, did not have access to the European regulatory authorities' investigation, but only to Janssen's published data. They did not want to change the report to the Government despite it being based on manipulated data.

In the European study, the following conclusion was made about Study 02-159 (April 2011): **"In the strictest interpretation this could be seen as a failed trial", or at best a "borderline failed study."** But in Janssen's published article about the study (June 2009), the article that SBU built its positions on, it was written that the results **"support the use of [Concerta] as an effective and safe treatment for the management of ADHD in adults". [13]**

Janssen had used several fraudulent methods to arrive at the conclusion that Concerta was an "effective and safe treatment". One of these methods was what is called the LOCF (Last Observation Carried Forward). This means that if a person at *one* assessment point in the study showed a positive result (on a rating scale) but, for example, shortly afterwards suffered such a serious damage that the person had to end the study, the positive result was anyway counted at the end – the person became a so-called responder. The European regulatory authorities did not accept – as opposed to the psychiatric journal – this deceptive way to count. They demanded that the persons who had to end the trial were deducted (and not considered "responders"). And then Janssen did not get any positive results for Concerta compared with placebo.

Another fraudulent method Janssen made use of to get a positive result in Study 02-159, was to, to a large extent, include study participants who had received methylphenidate (the drug class of Concerta) – and who thought it was a positive experience. At the same time they excluded persons found to be "non responders" to methylphenidate, i.e. persons who had been deemed not to have had any positive effect of methylphenidate, and those *whose children* (!) got methylphenidate but had no positive effect of the drug. **In Study 02-159, 35 percent of the participants had received "ADHD medication".** In other words Janssen included a very high proportion of persons in the study who had received drugs of the same type as Concerta, and who thought it was a positive experience. Despite these fraudulent "inclusion criteria" the company did not succeed to produce a clear positive effect of Concerta (in comparison with placebo).

Study 3002

Study 3002 was the shortest of the placebo-controlled studies Janssen submitted in support of its application. Two of the eight authors of the published article were employees of Janssen and five of the other six had been consulting for the pharmaceutical company or worked in the company's Advisory Board. In this short five weeks study Janssen had, also according to the European drug regulatory authorities' investigation, showed that Concerta had "a better effect" than placebo, but in the articles about this, as well as in the articles about the other studies (3013 and 02-159), the pharmaceutical company had disseminated false and misleading statements about the harmful effects shown in the studies.

Janssen's false and misleading information about the harmful effects in the studies

The Janssen-sponsored psychiatrist group "The European Network Adult ADHD" wrote in its consensus document from September 2010 that **"Stimulants … improve ... anger outbursts, mood swings."** (See earlier). Janssen allowed dissemination of this false information even though the company knew that the European regulatory authorities came to the following conclusion: **"A *causal* relationship with Concerta was established for aggression, tics and depression."** [Italic added.]

The European study showed that in the three Janssen-submitted, double-blind studies (3013, 02-159 and 3002) "13 of the 596 subjects receiving Concerta … were withdrawn for aggression-related adverse events (vs. none receiving placebo)". [10] (See page 65, Preliminary Variation Assessment Report, Concerta, July 2010, see also FVAR, p.12, 26 April 2011.)

These 13 persons suffered so ***severe*** aggression that they had to be taken out of the trials. *None* of those on placebo suffered such serious aggression that they had to end the trials.

The European study also showed that a total of **71 out of 596 subjects (11.9%) from the Concerta group had suffered aggression (compared to 17 persons, 5.5%, from the placebo group). [10]** In the combined studies of Concerta in adults (placebo-controlled, and others) **202 of a total of 1369 subjects, 14.8%, suffered aggression. [10]** (See FVAR, p.12, 26 April 2011.)

Although it was known that Concerta CAUSED and augmented aggression in adults Janssen disseminated, via its psychiatrist group, the false information that Concerta *improves* problems as anger outbursts.

About 23 000 adults received methylphenidate (Concerta, Ritalin) in Sweden last year. Based on the above results we can for them to do the following calculations: **Around 500 of these individuals suffered *severe* aggression CAUSED by the treatment.** It should be noted that this is a *low* estimate since many of the adults receiving Concerta, according to other surveys, take the drug together with alcohol and other (illegal and psychiatric) drugs.

Based on the fact that 11.9% of the CONCERTA group (compared to 5.5% in the placebo group) suffered aggression or increased aggression, we can say the following about what happened in Sweden in 2011: **Around 1500 persons (the difference Concerta group-placebo group, 6.4%) who were treated with methylphenidate experienced aggression or increased aggression CAUSED by methylphenidate (again, a low estimate).**

But in the articles Janssen sent for publication in psychiatric journals the company failed to inform about the findings on aggression and hostility in the studies – just **one** report about aggression in the three published articles. Not a word was written on the findings of aggression in the article about Study 02-159 **[13]**, not a word about aggression in the article about Study 3013 **[11]**, **one** word about aggression in the article about Study 3002. **[15]**

Instead Janssen, in the three articles, announced that **"[Concerta] was well tolerated in the study"** (Study 3013), an **"effective and safe treatment"** (Study 02-159), an **"effective treatment ... with a safe profile"** (Study 3002). In contrast the European study found (in addition to what has already been said):

The risk was three times higher, in those taking Concerta in the short-term studies, to suffer from manic/psychotic disorders compared with those receiving placebo. The reasons persons had to end the studies **"included Thinking abnormal (severe), Delusions of reference (severe) and Abnormal behavior (severe), and all these events resolved following discontinuation." [10]** (See Preliminary Variation Assessment Report, page 64.) In other words, there was a ***causal relationship*** between Concerta and the psychotic/manic states.

In close connection with this, it emerged in the studies clear evidence that Concerta can ***cause*** **anxiety and agitated conditions in adults** ("evidence for the risk of new-onset anxiety, tension and agitation"). **"**Adult studies have identified anxiety as a very common risk in adults." **[10]** (See Preliminary Variation Assessment Report, page 117.)

In the European investigation it was concluded: **"The main new safety concern from the study data is around the frequency of psychiatric adverse events and that this is often de novo [new]. Of note is the incidence of anxiety but also rates of depression and aggressive and hostile behavior are raised." [10]** (See Preliminary Variation Assessment Report, p.66.)

Janssen's presentation of adverse events (such as the rewriting of Concerta caused aggression to "irritation") can be compared with how GSK renamed the harmful effects of the antidepressant Paxil (Seroxat). GSK's fraudulent presentation is shown in the U.S. Justice Department's indictment against the company (which led to 3 billion U.S. dollars in fines). Paxil induced suicidality in several of the children who were part of GSK's studies. GSK did not tell that, but instead used the term **"'emotional lability' to describe the five patients who attempted to commit suicide or exhibited other self-injurious behavior".** GSK's actions in this area can be found on pages 4-13. **[9]**

Janssen acquired the following Swedish psychiatrists for the above studies: **Ylva Ginsberg (Study 3013, Study 3002), Dan Edvinsson (3013, 3002), Per Woxler (3013, 3002), Eva Lindström (3002), Gunnar Jakobsson (3002), Niels Guldberg (3002), Sten Levander (3002), Eija Maahr (3002).** These psychiatrists had confidentiality agreements with Janssen about not revealing anything about what had emerged in the trials without the pharmaceutical company's written consent. **[16, 17]** It is unclear to what extent these psychiatrists have been involved in the fraudulent presentations in the published articles. **Ylva Ginsberg** is the only one of these investigators who is indicated by Janssen as main author (study 3013).

Janssen spread false information and concealed known data about the abuse potential of Concerta

Janssen spread – directly and through the acquired "key opinion leaders" and "experts" – false information about ***the abuse potential*** of Concerta. In order to transform the drug to *something else* than a narcotic drug the "small dose" was continually stressed – the "therapeutic effect" was said to be quite different from the "euphoric effect" that addicts got at doses, that were said to be, 100 times higher than the ones psychiatrist prescribed. False information was disseminated that the potential for abuse of Concerta was

nonexistent or small. Misleading information was spread that Concerta decreased the risk of abuse.

This was done despite the fact that Janssen knew that Concerta was placed in the same drug class as amphetamines and cocaine, *substances with high abuse potential* and largely with the same effects as methylphenidate (Concerta, Ritalin). **[18]** This was done despite the fact that Janssen knew that the European investigation found **"a significant abuse and diversion risk with Concerta". [10]**

Janssen spread in their marketing publications – *aimed directly at adults* – this type of information about the abuse potential of Concerta: **"Medication will also reduce the risk of abuse." "There are no known studies that indicate any risk to develop addiction as a result of treatment with stimulants." [19]** In Janssen's information film *Myths and Facts about ADHD* the pharmaceutical company with a large check kills the "myth" that methylphenidate would be addictive (!) **[20]** (See illustration.) In Janssen's written *Information about ADHD and Concerta* we get to know "the truth" under the headline *Myths and truths about stimulants*: **"Medication with the doses recommended for ADHD does not give any experience of 'being high' and propensity for addiction has not been found."** As stated above, it is also said: **"An addict takes a dose approximately hundred times higher." [21]** *Nowhere* in the publication can we find information that Concerta is classified as a drug with high abuse potential. This is the fraudulent information that Janssen is spreading, even though, in a just completed matter, Janssen ensured the Swedish Medical Products Agency (MPA): **"We will [in] all information ensure that information on the narcotic drug classification for Concerta always will be included." [22]**

Janssen's acquired "key opinion leaders" and other "experts" helped to spread the false information about the abuse potential for Concerta to authorities, public and media. In the application to the Ethical Review Board to do Janssen's aforementioned study in adults – Study 3002 – psychiatrist Eva Lindstrom at Uppsala University Hospital wrote: **"We believe that the potential for abuse is virtually nonexistent." [23]** Already in 2002, Björn Kadesjö wrote in the official guideline *ADHD in children and adults,* from the National Board of Health and Welfare: **"It is important to know that the medication in the doses used *does not* give a euphoric experience."** [Emphasized here.] In the application to the Ethical Review Board, to give prisoners Concerta in a trial, psychiatrists Nils Lindefors and the aforementioned Ylva Ginsberg wrote: **"The doses of methylphenidate used to treat ADHD have no euphoric effect."** For Concerta they wrote that *it is not even possible to obtain a euphoric effect at higher doses*: **"Would you still manage to take a higher amount you do not get a euphoric effect at higher doses." [24]**

Unlike the above myths and marketing messages, the following was found in the European study of Concerta: **"It is assessed there is a significant abuse and diversion risk with Concerta." [10]**

Before we proceed with what has emerged in the European study of Concerta, it may be appropriate to give some "anecdotal evidence" – specifically 103 pages with stories from Swedish patients about the "euphoric effect" of Concerta and Ritalin. Here we have lots of data about how Concerta and Ritalin in "therapeutic doses" provide a euphoric effect -

which is greatly enhanced if you crush, snort and inject the drugs. **[25]** (In Swedish) http://jannel.se/concrit.Apr2010.pdf

Among the scientific studies that Janssen submitted, as part of the application to get Concerta approved for adults, were three so-called Abuse Potential Studies. These were studies conducted *specifically* to determine the abuse potential of Concerta.

The first of these studies (Study 12-005) [10] (See Preliminary Variation Assessment Report, Concerta) was a double-blind, placebo-controlled study where the subjects (n=49, 18-48 years) were "healthy volunteers with a history of recreational use of stimulants". The subjects had previously used cocaine (88%) and methamphetamine (25%). The study compared placebo with Ritalin (IR, Immediate Release) 60 mg and Concerta, 108 mg. It used the questionnaire Drug Rating Questionnaire, Subject (DRQS-VAS), which primarily measured the degree of "Liking", as answer to the question: "Do you like the drug effect you are feeling now?"

The conclusion of the assessment was: "The results clearly suggest that even when Concerta is not crushed (a more likely scenario of abuse), that this imparts a pleasant effect in this population of recreational drug users." Ritalin IR gave, as expected, also this "pleasant effect", but there was no significant difference between the drugs.

The second of these studies (Study 12-007) was a double-blind, placebo-controlled, randomized study, where the subjects (n=49) were "healthy subjects with a history of occasional recreational stimulant use", in which one compared placebo with Ritalin (IR) 50 mg, 90 mg and Concerta 54 mg, 108 mg.

The MHRA wrote that Concerta probably would be crushed if persons wanted to abuse the pill, *but* that this study had also demonstrated the "addiction potential" of the usual doses (54 mg and 108 mg.)

The conclusion from the evaluation (MHRA) was that Concerta "confer a positive effect on the 'Liking' element of the DRQS [Drug Rating Questionnaire Subject] ... If the tablets are crushed then the effects are likely to be heightened. The effect of augmentation of the effects of other drugs of misuse is not known and it is known diversion is a significant problem. "

The third of these studies (Study 12-1302) was on *active* drug abusers [persons with a diagnosis of "substance abuse"] and the assessment (MHRA) was that in this group it "is unlikely that anyone would take Concerta in this fashion should they wish to abuse it." These users would, in other words, take other drugs if they had a choice, and would probably crush or take Concerta in another fashion, if they wished to abuse Concerta.

In summary, Janssen's submitted studies showed a considerable abuse potential for Concerta in the usual dose, 54 mg, that psychiatrists prescribe. The medical authority was apparently surprised by the "pleasant effect" that these "therapeutic doses" gave the subjects. The "drug effect" that emerged got the MHRA to question what the *real* outcome was all about in the other short-term studies when adults "with ADHD" got Concerta.

The MHRA raised the very pertinent question of the trial of Concerta 54 mg and 108 mg, and that it **"demonstrated ... pleasurable effects which raises the question of how much of the action seen in [other] randomized controlled trials is due to the euphoric effects of Concerta."** (See Preliminary Variation Assessment Report, page 21.)

The pharmaceutical company proved, in the submitted "Abuse Potential Studies", the abuse potential of Concerta in *normal* doses. One also got the investigating authorities to question if the "positive effects", as demonstrated in the other placebo-controlled short-term studies of persons "with ADHD", was not in fact the familiar *euphoric effect* of Concerta – in other words the narcotic drug effect.

The conclusion became: "It is assessed there is a significant abuse and diversion risk with Concerta."

The Dutch Medicines Agency wrote in its comments: **"the misuse/abuse potential of methylphenidate is considered a major safety concern: in combination with concerns regarding the reliability of the diagnosis, adults may try to get diagnosed for ADHD to retrieve methylphenidate in a legalised way." [10]**

Janssen used "key opinion leaders", "advisors" and "experts" to promote Concerta for adults

By providing **"research grants", "consulting fees"** and **"high professional reputation"** to **"key opinion leaders", "advisors"** and **"experts"** Janssen got these to lead **"medical education", to speak in other forums and to participate in the design of "treatment guidelines", thus spreading false information concerning the drug's "safety" and "efficacy", and thus promoting Concerta for adults.** Janssen made use of sponsored patient groups of to put pressure on politicians and government officials so that they provided financial support for the prescription of Concerta to adults.

Foremost among these "key opinion leaders" in Sweden was psychiatrist **Ylva Ginsberg** at the Karolinska University Hospital. Ginsberg wrote already 2004 a confidentiality agreement with Janssen **[17]** and was the principal investigator in Study 3002 and Study 3013. She was also one of the authors of the fraudulent publication of the results of Study 3013. (See above.) At the same time Ginsberg was responsible for the Stockholm County Council's and the Swedish Prison and Probation Service's "independent" study in the Norrtälje Prison, which was ultimately aimed at making Concerta (methylphenidate) a "standard treatment" in many of the country's prisons. Ginsberg was, as said earlier, a member of the Janssen-sponsored psychiatrist group, "The European Network Adult ADHD", and was appointed to the company's Scientific Committee at the marketing meeting Nordic Psychiatry Academy ADHD in 2009. **[26]** Ginsberg lectured (along with the aforementioned psychiatrists Per Woxler and Dan Edvinsson) in the Janssen organized medical education "News and established practice in the treatment of ADHD, bipolar disorder and addiction". **[27]** Ginsberg has, as an "independent investigator", appeared in countless magazine articles, radio and television programs, where the value of treating adults with Concerta has been

emphasized. In none of these appearances Ginsberg has conveyed the information described in the European study on Concerta.

Psychiatry Professor **Johan Franck** had in his expert assignments for government agencies, as the Medical Products Agency (MPA), "forgot" to tell that his department received 100 000 SEK in research funding by Janssen. **[28]** Franck has for many years helped Janssen to market Concerta for adults. In autumn 2011, six months *after* the European authorities gave a final *disapproval* of Janssen's application **[10]**, Stockholm Drug Therapeutic Committee published the journal *Evidence,* which on the front page had a picture of Franck, together with the text: **"Strong evidence for the use of methylphenidate".** In the journal Franck lets us know: **The evidence for prescribing methylphenidate for ADHD in children and adults is strong**, and that criticism of the treatment is inappropriate. We are further told: **"Individuals with ADHD have since long been successfully treated with stimulant medications, earlier with amphetamine and now with methylphenidate."** This message is sent by Franck to 8,000 readers in the Stockholm County Council, six months after the European regulatory authorities gave final *disapproval* of the application to get Concerta approved for adults, and announced that the drug had a negative benefit/risk balance for the target group. None of this was conveyed by Franck to readers.

The same message, only even more deceptive, was put forward in the journal *Independent* 2007. Franck said: **"When you are taking CNS stimulants something happens and streamline traffic in the brain. Suddenly you can read a book, listen, talk, communicate. You can sit quietly and wait for your turn. We have treated children for 50 years with good results. We have treated adults for ten years with good results. There is much research about it."[30]** We should compare the previously described European analysis of the research on Concerta for adults with Franck's claim that stimulants "streamline traffic in the brain." Franck also describes his prescription of Concerta and Ritalin to drug abusers. Swedish authorities already know that the picture of "low doses" and good results presented by Franck in the article has no basis in reality, although the prescription business has been allowed to continue. (In Swedish) **[31]**

A seminar arranged by the Swedish Association of Local Authorities and Regions (SALAR), with the strange name "ADHD - We must do what we think is right", September 2009, gathered most of the "key opinion leaders," "advisers" and "experts" who, together with Janssen, have got the prescriptions of Concerta for adults to skyrocket over the last few years. **[32]** Here they gathered under the motto "***dare to* let people with criminality and substance abuse get treatment".** [Italic added.] Johan Franck let the audience know: **"For short-term treatment of adults there is clear evidence [for the prescription of methylphenidate]."** And with good evidence Franck means: **"that there are scientific studies that are published and are quality controlled by the authorities, as MPA and SBU and the like."**

The "key opinion leader" who did not receive direct funding for research by Janssen, but still had a key to the development of Janssen's profits on the prescription of Concerta, is the owner of the lobbying firm ISAK, **Anders Milton**. **[33]** Milton completed his assignment as the Swedish national psychiatry coordinator 2006, after, among other things, having started several projects that led to a substantial increase in the prescribing of methylphenidate to

adults. He went, in connection with the termination of his government assignments, directly to the pharmaceutical industry (then as Pfizer's Swedish CEO's right hand). Milton has in a number of statements announced that the prescribing of methylphenidate to adults is "evidence based" and that those who stand opposed to this prescription, base their view on "ideological reasons". Milton has had a significant role in Janssen's promotional seminars. From Milton's strong commitment to Janssen's business it can be assumed that the pharmaceutical company is one of the clients the PR firm ISAK is taking care of (further investigation is necessary).

The above are just some examples of how seemingly independent "experts" have made it possible for Janssen in medical education, in medical journals, the media and in government relations and relations with politicians, to promote Concerta for adults.

The examples given above (and as set out below) should be compared with the expert statement from the prosecutor in the case against Janssen (Johnson & Johnson, "J & J") in Texas, where the company had to pay 158 million U.S. dollars. **[6]** In the statement, we can (p. 12) read how the pharmaceutical company **"exerted improper influence over potential payors and prescribers." [34]** http://jannel.se/Rothman.Report.pdf We can read about the **"activities that it funded in medical education, research, and publishing were, in fact, thinly disguised marketing activities."** The Pharmaceutical Company's various activities had **"the goal of establishing relationships that would advance marketing"** (in Texas for the company's antipsychotic drug Risperdal)**.**

The report states (p. 14) that Janssen defined their **"customers"** as follows: **"any individual or company that has the ability to prescribe or influence the use of Janssen's products."** This view on "customers" also covered **"advocacy groups, researchers, state officials and decision-makers".** We can (pp. 14-20) read the exciting story of how Janssen, via eminent psychiatrists, in a project propelled "Treatment Guidelines" that put the company's drug as "first choice"; the project's purpose was not to create one on scientific grounds formulated document, but to develop a marketing tool for Janssen's product. Very relevant for Swedish conditions are the description (pp. 30-32) about how the pharmaceutical company was working with Dr. Joseph Biederman at Harvard University and Massachusetts General Hospital; Biederman's research is what SBU, the MPA and the National Board of Health and Welfare *usually* refer to as support for the prescription of methylphenidate to children and adults. The detailed descriptions (pages 44-77) of the company sponsored research are an alarming reading. We find the conclusion: **"the message of the article was consistently favorable to the J & J product"**. At the end of the statement (pp. 77-86) it is described how the drug company uses patient organizations for marketing purposes. The report concludes (p. 86): **"To use an organization that presents itself as the public voice of the mentally ill in order to enhance marketing strategies is an egregious example of the exercise of undue influence."**

Janssen made use of sponsored patient groups, in Sweden of the group *Attention.* Together they issued a press release about the company's studies of Concerta in adults, *before* these studies even begun. **[35]** In the press release Janssen, Attention and researcher, psychiatrist Niels Guldberg, said that 240 000 adult Swedes "had ADHD." About Janssen's study they said: **"Hopefully it can lead to that many thousands of adult Swedes will finally have access**

to medication that can improve their lives tremendously." Now we know that *the real result* of Janssen's combined studies showed that Concerta was both ineffective and harmful for adults, and that the drug had a high potential for abuse, with a high diversion risk. No press release has been sent out about this. When the area of Gothenburg did not finance methylphenidate for adults the advocacy group Attention intervened on behalf of the pharmaceutical company, to ensure the **"start-up of treatment with stimulants".** Attention put pressure on politicians and officials so that Janssen's Concerta (and other methylphenidate drugs) would be financed and prescribed for adults, even though no drug was approved for the group. **[36]** Janssen's profits on the prescription of Concerta for adults in Gothenburg soared.

In Texas Janssen succeeded in the above manner to create "Treatment Guidelines" that set the company's product Risperdal as "first choice", and thus greatly increased sales. We can compare this with how Janssen in Sweden has succeeded in placing its, for adults *disapproved* drug, Concerta as **"first choice"** in treatment guidelines. In the previously mentioned publication, *Evidence* from the Stockholm County Council (drug committee), from autumn 2011, we can read the chapter (p. 5): "Recommended interventions for ADHD in adults." We are told: **"stimulant drugs in the form of methylphenidate in the first place" ["first choice"]**. **[29]**

In the guidelines for the Stockholm County Council, Regional Care programs in 2010 **[37]**, we get again (p. 103) to hear the false information that **"approximately 70% [of adults] have good effect [of methylphenidate] in shorter-term studies"** (compare with the above descriptions of Janssen's submitted, short-term studies). We are told **that methylphenidate has an effect on "easily-induced irritability"** (compare the European study, which found that Concerta *causes* aggression and hostility in adults). We are told (p. 103) that psychiatrist Susanne Bejerot (in Janssen's psychiatrist group "The European Network Adult ADHD"), found that **80% of adults with methylphenidate "reported good or very good effect"**.

That's how the pharmaceutical company Janssen put Concerta on "the adult market" in Sweden and increased its sales with 25% for 2011 – the year when the drug got its final *disapproval* for adults in Europe.

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References

[1] Public Citizen, "Rapidly Increasing Criminal and Civil Monetary Penalties Against the Pharmaceutical Industry: 1991 to 2010";December 16, 2010, http://www.citizen.org/hrg1924
[2] Department of Justice, "Documents and Resources from the July 2, 2012 GlaxoSmithKline (GSK) Press Conference", http://jannel.se/DOJ.GSK.Resources.pdf
[3] Department of Justice, "Deputy Attorney General James M. Cole Speaks at the GSK Press Conference " http://jannel.se/DOJ.GSK.Cole.pdf

[4] Pharmacy Service AB, prescription of ADHD drugs in Sweden 2007-2011, http://jannel.se/ADHD.droger2007-2011.pdf
[5] State Prosecutor Greg Abbott, "Plaintiff's Second Amended Petition," December 12, 2008, http://jannel.se/texas-janssen-complaint.pdf
[6] The New York Times, "J. & J. to Pay $ 158 Million to End Suit Filed by Texas" January 19 2012, http://www.nytimes.com/2012/01/20/business/johnson-johnson-settles-risperdal-claim-in-texas.html
[7] Department of Justice , United States of America v Forest Laboratories and Forest Pharmaceuticals, 13 February 2009, http://jannel.se/celexa-complaint.pdf
[8] Kooij et al, "European consensus statement on diagnosis and treatment of adult ADHD: The European Network Adult ADHD", *BMC Psychiatry,* September 3, 2010, http://www.biomedcentral.com/1471-244X/10/67
[9] Department of Justice, "Complaint", 26 October 2011, http://jannel.se/DOJ.GSK.Complaint.pdf
[10] MHRA, *Preliminary Variation Assessment Report,* Concerta, July 2010 http://jannel.se/PVAR.Concerta140710.pdf , MHRA, *Final Variation Assessment Report,* Concerta Day 90, April 26, 2011 http://jannel.se/ FVAR.Concerta.Day90.260411.pdf , MHRA, *Final Variation Assessment Report* , Concerta, 26 May 2011, http://jannel.se/FVAR.Concerta260511.pdf
[11] Casas, Rösler, Kooij, Ginsberg, Ramos-Quiroga, Heger, Berwaerts, Dejonckheere, van der Vorst, Schäuble. "Efficacy and safety of prolonged-release OROS methylphenidate in adults with attention deficit/hyperactivity disorder: A 13-week, randomized, double-blind, placebo-controlled, fixed-dose study." *The World Journal of Biological Psychiatry* , 2011, Early Online, 1-14. http://informahealthcare.com/doi/abs/10.3109/15622975.2011.600333
[12] New York Times, "Researchers Fail to Reveal Full Drug Pay", 8 June 2008, http://www.nytimes.com/2008/06/08/us/08conflict.html?pagewanted=all
[13] Adler, Zimmerman, Starr, Silber, Palumbo, Orman, Spencer. "Efficacy and Safety of OROS Methylphenidate in Adults With Attention-Deficit/Hyperactivity Disorder A Randomized, Placebo-Controlled, Double-Blind, Parallel Group, Dose-Escalation Study," *Journal of Clinical Psychopharmacology*, 2009, 29, 239-247. http://journals.lww.com/psychopharmacology/Abstract/2009/06000/Efficacy_and_Safety_of_OROS_Methylphenidate_in.8.aspx
[14] SBU, Chapter 3, Diagnostics and treatment of ADHD and autism spectrum condition, 9 January 2012; http://www.sbu.se/upload/psykiatrirapport_regeringen120111/Diagnostik%20och%20behandling%20av%20ADHD%20och%20autismspektrumtillstånd.pdf
[15] Medori R, J Ramos-Quiroga A, Casas M, Kooij JJS, Niemela A, Trott GE, Lee E, Buitelaar JK. "A randomized, placebo-controlled trial of three fixed dosages of prolonged-release OROS methylphenidate in adults with Attention-Deficit/Hyperactivity Disorder". *Biol Psychiatry* 2008, 63 (10): 981-989. http://www.sciencedirect.com/science/article/pii/S000632230701102X
[16] Janssen/Karolinska-Ginsberg, *Agreements,* 15 December 2004, http://jannel.se/janssen/ginsberg.avtal.PDF
[17] Ginsberg/Janssen, *Confidentiality Agreement*, December 12, 2004, http://jannel.se/janssen/ginsberg.confidentialityagreeement.PDF
[18] The U.S. DEA, *Drug Information*, http://www.usdoj.gov/dea/concern/m.html
[19] Janssen-Cilag, "ADHD - when life as an adult does not work", published around 2005. (In a later version of the publication, from 2007, the company had been forced to remove those grossly misleading claims.)
[20] Janssen, "Myths and Facts about ADHD," (2012), drug company information site Living with ADHD. http://jannel.se/janssen.film.metylfenidat.pdf
[21] Janssen-Cilag, "Information about ADHD and Concerta", 2011.
[22] Janssen, "About Marketing of Concerta in the newsletter Living with ADHD / Reg 25:2012 / 502 875", 13 March 2012.
[23] Lindstrom, "Application for Ethics Review", Dnr 2004: M-405, was added to the Ethical Review Board in Uppsala, 26 October 2004.
[24] Ginsberg / Lindefors, "Side Letter re Application for Ethics Review", 3 October 2006.
[25] A compilation of stories from the Swedish "users" on the Internet, from 2007-2009, http://jannel.se/concrit.Apr2010.pdf
[26] Janssen-Cilag, presentation of the Scientific Committee, for the Nordic Academy Psychiatry ADHD, 2009.
[27] Education Directory, the "Psychopharmacological training for psychiatrists",(2010), http://edu.ipuls.se/www/_public/pub_course.cfm?CourseId=5884&FromSearch=1
[28] Aftonbladet, "Have been wrong", 30 September 2011, http://www.aftonbladet.se/nyheter/article13706369.ab

[29] Stockholm County Council, Evidence, No. 4 2011,
http://www.janusinfo.se/Global/SLK/Evidens/evidens_4_2011.pdf
[30] Independent, ”Who dares to prescribe drugs to an addict”, 1/2007,
http://rfhl.se/rfhl15/images/rfhl/oberoende/arkiv/oberoende1-07.pdf
[31] Larsson, “Amphetamine to abusers “with ADHD” - Report on a business in open conflict with science and proven experience”, March 2011, http://jannel.se/missbrukADHD.pdf
[32] The Swedish Association of Local Authorities and Regions, Web TV, “ADHD - We must do what we think is right”, 1 September 2009;
http://web22.abiliteam.com/ability/program/livepro/admin/bthfront.asp?FOLDERNAME=20090901_0956_norralatin&PRODUCER_ID=xaimkwdkn
[33] Resumé,”Anders Milton becomes PR consultant with ISAK”, 5 February 2008,
http://www.resume.se/nyheter/pr/2008/02/05/anders-milton-blir-pr-kons/
[34] Rothman, “Expert Witness Report”, 15 October 2010, http://jannel.se/Rothman.Report.pdf
[35] Janssen-Cilag, “No treatment for adults with ADHD”, press release, June 8, 2005
http://www.euroinvestor.se/news/story.aspx?id=8916950
[36] GT Debate: “ADHD sufferers receive no treatment”, 10 September 2007,
http://www.expressen.se/gt/ledare/debatt-adhd-sjuka-far-ingen-vard/
[37] Stockholm County Council, “Regional Care programs” (ADHD), 2010,
http://www.vardsamordning.sll.se/Global/Vardsamordning/Dokument/Publikationer/Vardprogram/RV_ADHD_webbversion.pdf