Open Letter II, to Dr. Ian Hudson, Chief Executive of the MHRA

14 February 2014

ADHD drugs – MHRA and the Concerta scandal

Thank you for the answer (below) on behalf of Dr. Ian Hudson, CEO of the MHRA.

It seems as if my important information is not coming across, so I will try to be a bit more clear in my response.

As you know Johnson & Johnson (and its subsidiary Janssen) in November 2013 agreed with the U.S. Department of Justice to pay 2.2 billion USD, mainly for the illegal marketing of the psychiatric drug Risperdal. The Attorney General of the United States, Eric Holder, said at the press conference presenting the agreement, "these are not victimless crimes" [1].

Let's also look at the case in Texas, where Janssen in early 2012 had to pay 158 million USD [2]. In that case we can, with the words from the State Prosecutor, look at specific examples of *"sophisticated strategies and tactics to disseminate misrepresentations"*, *"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"* of the drug (Risperdal); 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 from the Complaint against Janssen in Texas [3].)

Let's compare this with Janssen's actions to market and sell Concerta to adults in Europe, despite the agreement with the MHRA and other European drug regulatory agencies *not* to do this.

I refer in my letter below to the secret internal MHRA documents about the Concerta investigation; the documents revealing that Concerta was found to have "negative benefit/risk balance" for adults. I am glad that MHRA now has made the most important of these documents available to the public, even if it is *very* hard to find it. But here it is:
http://www.mhra.gov.uk/home/groups/l-unit1/documents/websiteresources/con2033483.pdf

The MHRA assessment document about Concerta to adult is dated **14 July 2010**. Janssen had the information that the Concerta application for adults "is not approvable" and "should be refused" (page 18 in the document) in July. But at the same time Janssen sponsored "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 [4]. The group wrote in the document: "We thank Janssen-Cilag who provided support for meeting costs of the European Network Adult ADHD."

So despite knowing about the ***disapproval*** of the Concerta application, 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.* The publication of the wide spread document about the good effects of methylphenidate (Concerta, Ritalin) for adults,

was done **3 September 2010,** 2 month after MHRA informed the company that the Concerta application "should be refused".

Here is 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 that 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.

In the group we could also find prominent European psychiatrists, among them **Professor Philip Asherson** (U.K.), advisor to the National Institute for Health and Clinical Excellence (NICE), and a member of the group writing the guidelines for treatment of adults with ADHD in U.K.

The investigation by MHRA and other European agencies showed:

- The combined studies showed that Concerta had no significant positive effects for adults and that the drug caused a number of serious adverse effects, Concerta had a "negative benefit/risk balance" for adults;

- The submitted studies gave clear evidence that Concerta could ***cause*** anxiety and agitated conditions in adults ("evidence for the risk of new-onset anxiety, tension and agitation");

- The submitted studies gave clear evidence of the abuse potential and of the risk of diversion of Concerta;

- A ***causal*** relationship was established for Concerta for aggression, tics, and depression;

- No warnings were to be issued about the fact that it had been proven that Concerta could cause anxiety, agitated conditions and aggression in adults, ***for the simple reason that Concerta should not be prescribed to adults***;

- Concerta could ***only*** be prescribed to adults who before the age of 18 had received methylphenidate (Concerta, Ritalin) and who were judged to have had an "adequate response and acceptable tolerance", ***and*** for which a withdrawal of the drug had been tried without success. The pharmaceutical company Janssen-Cilag declared that it agreed to the following conditions: **"those patients with ADHD who would be considered for continuation of treatment into adulthood *must* have previously been treated with methylphenidate and continue to show adequate response and acceptable tolerability."** [Emphasis here.] No other adults could be considered.

In other words MHRA agreed with Janssen that the company did not need to issue warnings about what emerged in the clinical studies on adults. The company did not need to issue data about the lack of positive effects and the harmful effects proved in Janssen's own studies. MHRA said basically that Janssen did not need to tell this:

Table 59. Number (%) of Subjects With an Important Adverse Event by Adverse Event Category of Special Interest and by Treatment Group
(CONCERTA EU SCS: All Treated Subjects Analysis Set)

Adverse Event Categories of Special Interest	Placebo (N=309) n (%)	DB CONCERTA (N=596) n (%)	Total CONCERTA (N=1369) n (%)
Total no. subjects with Adverse Events	87 (28.2)	307 (51.5)	815 (59.5)
Hypertension	12 (3.9)	32 (5.4)	136 (9.9)
Tachycardia	0	36 (6.0)	81 (5.9)
Raynaud's phenomenon	2 (0.6)	3 (0.5)	6 (0.4)
Psychosis/mania	3 (1.0)	17 (2.9)	45 (3.3)
Anorexia	23 (7.4)	174 (29.2)	394 (28.8)
Migraine	6 (1.9)	7 (1.2)	25 (1.8)
Repetitive behaviours	0	1 (0.2)	1 (0.1)
QT prolongation	1 (0.3)	0	4 (0.3)
Arrhythmias	11 (3.6)	80 (13.4)	240 (17.5)
Cerebrovascular disorders	0	1 (0.2)	1 (0.1)
Aggression	17 (5.5)	71 (11.9)	202 (14.8)
Hostility	0	3 (0.5)	11 (0.8)
Depression	32 (10.4)	100 (16.8)	270 (19.7)
Suicidality	0	1 (0.2)	3 (0.2)
Tics/tourette's syndrome/dystonias	4 (1.3)	25 (4.2)	72 (5.3)
Carcinogenicity	0	0	5 (0.4)
Withdrawal syndrome	0	1 (0.2)	1 (0.1)

From Janssen's "Response Document" (page 84) to the MHRA, 11 January 2011.

In the Company's three best (!) studies of Concerta on adults, the ones chosen for Janssen's application, the following harmful events emerged in the short-term studies (up to 13 weeks), where Concerta was compared to placebo:

- **The persons who received Concerta had a 270% increased risk for heart disorders in form of Arrhythmias;**
- **The persons who received Concerta had a 116% increased risk for Aggression;**
- **The persons who received Concerta had a 62% increased risk for Depression;**
- **The persons who received Concerta had a 225% increased risk for neurological disorders in form of Tics/Dystonias;**
- **The persons who received Concerta had a 190% increased risk for Psychosis/Mania;**
- **The persons who received Concerta had a 295% increased risk for Anorexia;**

And what happened?

After the initial assessment from MHRA (14 July 2010), that Concerta was to be *disapproved* for adults, Janssen and its sponsored psychiatrists issued the misleading data in the Consensus document (2 September 2010).

In January 2011 Janssen declared that the company will withdraw its application – and made the agreement with MHRA *not to* issue warnings about the proven harmful effects.

MHRA agreed with Janssen that Concerta was *not* to be prescribed to adults in Europe. The Agency made the following clear in the Final Variation Assessment Report (FVAR p. 9) from May 2011: (for the period October 2010-October 2011): "The usage [of Concerta] may not increase in this time period." [5]

And Janssen just continued to market and sell Concerta to adults in Europe as if the assessment by MHRA had never been done. In Sweden the company increased its sales of Concerta for adults from 112 million SEK (10.5 million GBP) in 2010 to 180 million SEK (17.0 GBP) in 2013; an increase with 60% (!!) since the drug was disapproved for adults [6].

MHRA is handling the Periodic Safety Update Reports (PSURs) for Concerta in Europe. These reports show that *no effective actions* have been taken by the Agency to enforce the agreements in the years after the disapproval.

***Tens of thousands* of adult patients in Sweden and the rest of Europe have been misinformed and misled about the effects and harmful effects of the drug. MHRA has done nothing to make the real results of Janssen's studies (as written above) known to the patients, while allowing the company and its sponsored psychiatrists to use *"a variety of marketing tools"* to push the drug out on "the adult market".**

So there you have the Concerta scandal. What is MHRA going to do about it?

Yours sincerely,

Janne Larsson
Reporter
Sweden
janne.olov.larsson@telia.com

[1] Department of Justice, Comments by Attorney General, Eric Holder, 4 November 2013, http://www.justice.gov/iso/opa/ag/speeches/2013/ag-speech-131104.html
[2] 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
[3] State Prosecutor Greg Abbott, "Plaintiff's Second Amended Petition," December 12, 2008, http://jannel.se/texas-janssen-complaint.pdf
[4] 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
[5] MHRA, Final Variation Assessment Report, FVAR, 26 May 2011, http://jannel.se/FVAR.Concerta260511.pdf
[6] e-Hälsomyndigheten, Prescriptions of ADHD drugs in Sweden 2008-2013, http://jannel.se/N06BA.pdf

From: MHRA Customer Services
Sent: Thursday, February 13, 2014 4:31 PM
To: jan.olov.larsson@telia.com
Subject: Fw: ADHD drugs - Will MHRA handle the Concerta scandal by approving Ritalin for adults?

Dear Mr Larsson,

Thank you for your letter in relation to ADHD drugs with reference to Concerta and Ritalin. With regard to Concerta XL, the MHRA has responded to your previous enquiry on the variation procedure to extend the indication into adults drawing to your attention that the Summary of Product Characteristics (SPC) for Concerta XL contains a clear statement that it is not appropriate to commence methylphenidate treatment in adults. Any adverse events continue to be monitored as part of Pharmacovigilance processes and there are extensive warnings in the SPC already on psychiatric adverse events. Further information on this can be found within the Public Assessment Report for Concerta XL which can be accessed via the link below:

http://www.mhra.gov.uk/home/groups/l-unit1/documents/websiteresources/con2033483.pdf

With regards to your reference to a Novartis application for use of Ritalin in adults the MHRA has not approved an application such as the one referred to in the Swedish press release from January 2013. For further information in relation to that specific application we would suggest you contact Novartis or the Swedish Medical Products Agency directly.

Kindest Regards,

Yvonne Smith
Customer Services
External Relations
Medicines and Healthcare products Regulatory Agency
Tel: 020 3080 6000

Your views matter. Tell us what you think of the service you have received from us by following the link below:
https://www.surveymonkey.com/s/MHRACustomerServicesFeedback

From: Jan Larsson [mailto:jan.olov.larsson@telia.com]
Sent: 02 February 2014 19:43
To: MHRA Customer Services
Cc: Hudson, Dr Ian; DOH - DHMail (ISD4); nice@nice.org.uk
Subject: Fw: ADHD drugs - Will MHRA handle the Concerta scandal by approving Ritalin for adults?

Open Letter to Dr. Ian Hudson, Chief Executive of the MHRA

(The text below in PDF http://jannel.se/MHRA.Concerta.Ritalin2.pdf)

2 February 2014

ADHD drugs - Will MHRA handle the Concerta scandal by approving Ritalin for adults?

In the beginning of 2011 secret internal MHRA documents revealed: The application to get the ADHD drug Concerta approved for adults was **refused**; Concerta was found to have "negative benefit/risk balance" for adults.

The disapproval of the drug for adults has been a well-kept secret: NO information whatsoever has been issued by the MHRA or the other European medical agencies about the disastrous results.

Let's look on what was hidden for doctors and the public.

This is the not published table over the Adverse Events of Concerta in clinical trials. It is part of the manufacturer Janssen's "Response Document" (page 84) to the MHRA, from 11 January 2011.

Table 59. Number (%) of Subjects With an Important Adverse Event by Adverse Event Category of Special Interest and by Treatment Group
(CONCERTA EU SCS: All Treated Subjects Analysis Set)

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The combined studies showed that Concerta had no significant positive effects for adults and that the drug caused a number of serious adverse event – the most important ones described in the table above. Some countries like Holland and France were very negative to the presented evidence from Janssen, while others, like Sweden, wanted to *in some way* get the application through anyway (despite the disastrous results in the trials).

The assessor at the MHRA requested the following in July 2010: "The risks of anxiety/anxiety disorders, depression, aggression, agitation restlessness, suicide related events, psychosis, mania/delusions, decreased appetite, clinically important decreased weight, cardiac arrhythmias, tics/worsening of tics or tourette's syndrome should be added to the Safety Specification as Important Identified Risks."

Janssen had to back down and said: "The Company no longer seeks an extension of the indication to include adults with ADHD." Janssen repeats this statement 29 times (!) in the "Response Document" to the MHRA. And so, no new warnings were issued to other authorities, doctors or patients.

The disapproval was a shock to the ADHD industry and to some medical agencies in Europe. In Sweden the Medical Products Agency (MPA) had for years allowed an explosion in the "off label" prescription of Concerta to adults, with the assumption that the drug was soon to be approved.

And the agency had been assisted by the current Chairman of the **Committee for Medicinal Products for Human Use (CHMP) at the European Medical Agency (EMA), Tomas Salmonson, in his position at the MPA.**

However Concerta was disapproved, found to be harmful and without any significant positive effects for adults. This did not stop the marketing in Sweden.

The prescription of Concerta to adults in Sweden increased with 60% (!!) from 2010 to 2013. Janssen sold the ***disapproved*** drug Concerta to adults in Sweden for 488 million SEK (45 million GBP) in these three years. (See updated figures from Apotekens Service AB **http://jannel.se/N06BA.pdf**) The highest sales figures for 2013 for methylphenidate in Sweden are for the disapproved drug Concerta to adults.

But now a fantastic "solution" to handle the problem has been presented, having the potential to save the drug manufacturer and all the officials involved in this medical scandal.

And the help for MHRA, MPA and Janssen to handle the scandal comes from an unexpected player – the pharmaceutical company Novartis. The manufacturer of **Ritalin** – **basically the same drug as Concerta** – has announced its application to get Ritalin approved for adults in Europe. (Swedish press release from 30 January 2013, **http://www.cisionwire.se/novartis/r/novartis-ansoker-om-godkannande-for-ritalin-for-behandling-av-vuxna-patienter-med-adhd,c9362988**)

Novartis has sought "scientific advice" from some of the more positive countries in Europe, about how to get the drug approved. The company has also chosen to only submit this application for Ritalin approval in *some* countries – the more positive ones. Meaning that the

company can avoid the negative statements from the same assessors handling the Concerta application.

A spokesperson from the Swedish Medical Products Agency, Bengt Andrée, announced (!) that Novartis´ application about Ritalin for adults will soon be approved. Andrée said in media: "Everything indicates that treatment for adults will be approved" and that "a statement [about Ritalin] is expected in early summer" (2013).

I am sure Novartis has learned from the failed Concerta submission and that there is a big interest from the officials mentioned above to push through the approval of Ritalin for adults. We can expect that the submitted studies will get a positive assessment this time – no embarrassing questions – and suddenly the concealed and alarming Concerta results can be expected to no longer exist! Janssen will also be saved; no criminal actions will be taken.

But it's hard to see how the above can fit with the MHRA declaration: "We protect and improve the health of millions of people every day through the effective regulation of medicines and medical devices, underpinned by science and research."

So Mr Hudson, will the MHRA take part in this dirty game of approving Ritalin, so that we can forget about the Concerta scandal?

Yours sincerely,

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