

Risk: In the sixties the drug DUOGYNON was an innovation. But did it cause malformations in children? And was the manufacturer aware of it? The files are now in the hand of TAZ. And form a lesson about guilt and morality.

ONE SINGLE TABLET

by Heike Haarhoff

On an early summer's day in 2015 a pensioner from the UK and a primary school teacher from Bavaria are meeting up to look through a stack of old yellowed papers in order to find evidence. It is the case of their lives.

Marie Lyon, 69, gave birth in 1970 to her daughter. Sarah's left forearm is missing, fingers grow from the elbow. Andre Sommer, 39, was born in 1975 with a deformed penis and his bladder grew outside of his abdomen.

A tiny room in the red brick building of the Berlin State Archive, ten square meters, almost a cell. Clear light falls through the transom windows, on the wall an office rack, in front a table, four chairs, nothing else. On the shelves are open cardboard boxes full of documents, written with a type writer in dusty document files.

There are more than 7,000 pages with confidential correspondences and company headed paper of the once mighty Berlin-based pharmaceutical company SCHERING from the sixties and seventies. Documents related to a pharmaceutical product, which no longer exists, but which Marie Lyon and Andre Sommer are holding responsible for the suffering of thousands of people. Its name: DUOGYNON.

Marie Lyon gazes over the cartons with the files. "Our treasure", she whispers, "...with explosive potential." That she certainly hopes

for. For ten years they are both been looking for these files. Five years ago they met through their mutual search [for these files].

The public are not allowed to access these files but Lyon and Sommer have access to them. The reason for the special permission is due to personal circumstances. As private investigators in their own interest.

Marie Lyon, blonde coloured hair, with subtle make-up looks towards Andre Sommer, very short haircut, and hoodie. "Where do we start?"

In 1970, Marie Lyon had taken a tablet, in order to determine whether she was pregnant. Just like Andre Sommer's mother. In the UK you would find the name PRIMODOS on the package and in Germany DUOGYNON, but the drug was the same.

DUOGYNON, that was, to put it simply, a combination product on the basis of the female hormones Oestrogens and Progestogens. In 1950 SCHERING launched it on the German market and other European countries, in form of capsules and injections – and under different names. Until 1978 doctors prescribed it to female patients if their menstrual cycle was irregular and the menstruation was missing, but also as a pregnancy test. Only in the 1980s urine tests took over. If the strong hormone dose didn't trigger the menstruation, it

What did they know behind those windows? The SCHERING Head Office in Berlin in the seventies.

was ruled that the woman was pregnant.

A drug suitable to initiate the menstruation – and precisely such a pill should diagnose [a pregnancy] in women who wanted babies and who didn't want after all to lose the fertilized egg.

The suspicion: Europe-wide the drug supposedly damaged thousands of children so severely in the womb that they were born with open backs, heart defects, brain damage, with shortened or missing limbs, deformed intestines, bladders or genitals. Some babies died shortly after the birth. Probably some miscarriages as well.

"DUOGYNON," says Andre Sommer, might be a second CONTERGAN (THALIDOMIDE)."

Maybe. Maybe the sleeping pill CONTERGAN (THALIDOMIDE), the biggest pharmaceutical scandal of the 20th century, wasn't the only drug with the most severe side effects for unborn babies. Andre

Sommer and Marie Lyon want to collect evidence on the basis of these files. And hundreds of other allegedly affected people to which they keep contact via self-help groups in Germany and the UK are waiting for answers.

When was the first time that SCHERING had information that the drug could cause embryonic deformities? And if it was available [the information]: Why hasn't the corporation withdrawn it earlier from the market? Why didn't they ban the use as a pregnancy test? Out of unscrupulousness? Out of negligence? Out of fear of loss of sales and loss of image?

There is still no answer to these questions from the manufacturer to date; and there is no legal basis to force them to do so. It seems undisputed: the company hasn't violated current law. That this is the case is due to the fact that the majority of regulations, which protect patients nowadays against risks of drugs, didn't exist then. The present

Medicines Act came into force in 1978. Prior to this, no studies were required to demonstrate that a drug is secure, safe and effective, before it has been approved. If at all, manufacturer tested drugs on rodents. Even package leaflets weren't compulsory. In 1950, as DUOGYNON was launched in Germany, you could buy new substances - hardly tested - without prescription in the pharmacy.

Recognizing that mothers are not to blame

Is the only question we can ask during this process was it against the law? Where does it start, where does the moral responsibility of a company whose business is the health of human beings end? Drugs can cause damage. Sometimes, still today, they are only discovered when the drugs are already launched. It would be an important step, if the company would help to clarify the facts involved, if they would open their archives, and if they would put all the cards on the table. So far however,

SCHERING which BAYER took over in 2006 refuses to cooperate.

Andre Sommer said: "It is this not knowing that is so hard to endure. Not to know whether the company really didn't know or whether they are only pretending to have not known."

Because that will dictate whether you can still hold them to account. Probably not legally. Probably not in a materialistic way. But perhaps morally. That the company recognizes that the deformities are no coincidence. By officially putting on record those mothers are not to blame. Although, they were the ones putting the tablet into their mouth and swallowing it with a glass of water.

The BAYER-Group reacts only in writing to questions on this topic: "BAYER still rules out that the drug is the cause for embryonic deformities." Extensive research and reports of "renowned experts" had already shown this in the 1970s and 1980s. Really?

1961

The Federal Government established the Federal

Ministry of Health. Source: Federal Ministry of Health

Andre Sommers search began when he discovered his mother's letters.

And one word stood out: DUOGYNON

"Look," says Marie Lyon. A piece of paper puzzles her. The protocol of an animal test. It is the 6th December 1965, 15 years after the launch [of DUOGYNON], as SCHERING AG presents a study on mice and rabbits: Do the active ingredients of the drug create deformities in the offspring? It is that period of time after the discovery of the CONTERGAN (THALIDOMIDE) scandal, the pharmaceutical industry is alarmed, and many manufacturers intensify their research.

The result of the tests: No detectable deformities. But then it read: "As expected, in high doses only the resorption rate increases." "The term resorptions mean dead foetuses [...]", it says in the appendix.

If DUOGYNON is deadly for unborn mice and rabbits – how likely is it that the drug is harmless for human embryos?

Marie Lyon was 23, when she realized that she was pregnant. "Very young and so happy", she says today, she laughs, and she still knows how exactly she felt, at that time, at the beginning of 1970. Proud of herself and her body in which now a baby would grow, a planned child. And how she went to the gynaecologist, and he said in order to be sure, she should better do a test, only one tablet, and if she didn't get a menstruation, then you will certainly be pregnant. "I have not once asked what ingredients are in the tablet", says Marie Lyon. She took it [the tablet].

It is a worry-free pregnancy and a birth with no complication. The shock hits her only when the midwife presented her her daughter: The tiny creature, the most beautiful child under the

sun, Sarah - but what, please, is this? An arm which stops on the elbow. Fingers, growing out of the elbow. Operations. Prostheses. Tears. And always the feeling of guilt. To be guilty that Sarah will be bullied in the kindergarten.

Risks and [side] effects:

■ **The drug:** *In 1950 the pharmaceutical company SCHERING introduces injections and capsules with the name "DUOGYNON". The hormone preparation is recommended among other things as the pregnancy test. If you don't get a menstruation after taking [DUOGYNON], the woman would be pregnant. In England it is sold as "PRIMODOS".*

■ **The suspicion:** *In 1967 a British paediatrician writes in an scientific paper for the first time about a possible link between the drug and malformations in the unborn. Amongst other things shortened limbs and deformed genitals were mentioned. Estimates speak today of thousands of possibly affected people.*

■ **The process of coming to terms with the past:** *In 2012 claims for inspection of the record are rejected due to statute of limitations. Since the autumn of 2015 there is an investigation committee in the UK concerning this issue.*

To be guilty that she will cycle, will swim and will learn how to ride,- obviously a disabled child will learn how to cycle, how to swim and ride, but only if this child has a mother who is as strong as Marie Lyon -, but much later than other children. To be responsible for this flaw. Until years later - Sarah is perhaps eight or nine - she takes a genetic test and finds out: that the disability has nothing to do with her, so much is certain,

but was caused 'outside' of her body. But where?

That was the time, says Marie Lyon, when her feelings of guilt grew gradually into anger. And her quest began. With mothers whose children were born with similar deformities. With doctors whose pregnant patients were given the drug: PRIMODOS, the English version of DUOGYNON.

Andre Sommer doesn't know the name DUOGYNON. Not until by chance he came across a box, about ten years ago, when he was clearing up the house of his parents - filled with old newspaper reports from the 1970s and 1980 on DUOGYNON and correspondence between his mother and other mothers with disabled children and with doctors.

Maybe she wanted to protect him from the emotional vortex, in which you will be sucked, if you start looking for the WHY and to be met with disapproval by authorities, politicians and industries and shrugging of shoulders, disinterest and rejection. But at this time his mother is in a vegetative state, he can still ask her questions, but doesn't get any more answers.

Up to date Andre Sommer had endured over 15 operations just because of the artificial urinary outlet on the stomach which nobody knows how long it will last. His penis is reconstructed.

"I owe it to my mother to find out what really happened." he says.

The quest for the truth about DUOGYNON is above all a fight of mothers. Marie Lyon says Sarah, her daughter, wants nothing to do with it. She is now 45 years old, she wants to live

1976

The pharmaceutical manufacturers are bound to

accompany every medicinal product/drug with a package leaflet. Source: Medicines Act

her life, go to work and spend time with friends. She came to terms with her [deformed] arm; she doesn't want to be constantly reminded that she is different. But her mother still asks herself the question WHY. Andre Sommer will ask the question for his mother.

Andre Sommer sued twice BAYER AG to have access to the files. He lost both times due to statute of limitations.

Now, in the Berlin State Archive, he holds for the first time documents in his hand which were never written to be made public: Exchange of letters between the legal department of SCHERING and concerned doctors. Scientists specialized in the study of causal embryonic malformations. As well as: Internal thoughts of strategies of the corporation towards sales and market shares.

State attorneys of Berlin seized the files at the end of the seventies in a preliminary investigation. Several mothers with deformed babies brought criminal charges [against SCHERING] due to bodily harm. Also Andre Sommer's mother, Lydia Sommer, who was given DUOGYNON by her GP in 1975, supported this group. In December 1980 the investigations were stopped. The confidential files were locked up in the State Archive until the protection

period for individuals will expired. This may take years, if not decades.

Via a detour, copies of the confidential documents which were stored at the State Archive reached the TAZ. Without the cooperation of BAYER AG we cannot say whether and how complete they [the files] are. No one knows what additional material is stored in the corporate archives.

"I owe my mother to find out what really happened".

Andre Sommer

But in any case the files show a profile of one of the once most powerful companies in the Federal Republic of Germany which had doubts about their product latest since the mid-1960s. And which they followed up on these doubts, in their own way. But nevertheless refused to draw consequences, in form of a recall of the drug or otherwise, and [to do] in-depth studies – perhaps as they were certain to conform to the law.

The first public reference that there could be a problem with DUOGYNON came in October 1967 from the British paediatrician Isabel Gal. Mothers would bring their deformed babies to her to the hospital in Surrey. Until Gal wants to find out more and starts asking the women about their medication during

[their] pregnancy.

In an article for the magazine NATURE Gal writes that that there could be a correlation between female sex steroids and malformations of the neural tube in foetuses – she calls the SCHERING product PRIMODOS a risk.

In the years up to 1973, the files show that SCHERING conducted further experiments of embryo toxic effects of DUOGYNON but only in mice, rabbits and rats. The basic view: DUOGYNON is not harmless. In April 1973, for instance, a study with rats concludes: "A relationship between the detected anomalies and substance application cannot be ruled out with certainty."

In addition, also in 1973 Photographs of deformed rabbits, a chamber of horror in black and white: "Deformity of the head", you can read under a photo, you can see the gaps in the skull through which parts of the brain protrude.

DUOGYNON is still used in Germany as a pregnancy test.

"They already have talked years before my birth about my future and health risks but didn't react," says Andre Sommer.

1978

The new Medicines Act comes into effect. It

includes for the first time an authorisation procedure for medication. Source: Medicines Act

Why, Andre Sommer and Marie Lyon ask themselves today, why did no one step in?

In order to understand this, you need to bring to mind the sixties and early seventies of the Federal Republic of Germany. The careless handling of drugs, the uncritical faith in progress of the post-war generation which - latest since the success of the contraceptive pill - had won the prerogative above all that hormones aren't proper medication, all this contributed to the fact that the public outcry against DUOGYNON failed to materialize over the years. In Germany the gynaecologists still prescribed DUOGYNON as a pregnancy test albeit the warning of the Drug Commission in the *Deutschen Ärzteblatt* (German Medical Journal).

And although the drug was finally withdrawn in 1978 in England - after Finland and Holland - from the market due to the risk of malformation, very little changed in Germany. There was no mechanism to prohibit a drug legally. SCHERING only stopped recommending DUOGYNON as a pregnancy test and only changed the name of the drug. Only in 1981 the corporation withdrew the follow-up product from the market - on the grounds that the treatment of menstrual

problems with this medication is outdated.

The criminal law punishes individual proven violations of the law. But above all are there ways to negotiate moral responsibility? In the CONTERGAN (THALIDOMIDE) trial the foundation, from which injured parties still receive money, wasn't established due to a criminal conviction but due to a civil law settlement.

A foundation that is also the hope of many DUOGYNON-parents. They want to make sure that their children are [financially] secure, in case they need help or due to consequential health problems have to leave their jobs prematurely.

"A Study could draw more than ever attention to the suspicion", warn employees.

In the UK the Parliament is by now involved with this case. Since October 2015, an investigating committee examines medical scientific findings about PRIMODOS.

That the foundation exists is the merit of Marie Lyons. She waited sometimes for hours in front of offices of British Members of the Parliament in order to talk directly to them about her request.

Were not regulatory authorities and politicians

responsible to monitor the pharmaceutical industry and to protect the general public? Was it not their responsibility?

That as well should be checked by the committee. Results are only expected in a few years. In Germany politicians reject the 'historical process of coming to terms with the past' so far. "What if one day the British Government pays damages?" wonders Andre Sommer. Would this make a difference in Germany? Is it allowed to treat injured parties differently?

Also in the sixties it was the UK that drew consequences. The pharmaceutical manufacturer in 1967 was alarmed by the publication of the paediatrician Isabel Gal. SCHERING Chemicals Limited, the UK subsidiary, set up a crisis unit. An external statistician is responsible to check the report of the scientist. "Gals' report in itself", he assessed "seems to be correct". He advises further investigations. But the research department declined: "There would be danger that such an extensive study would only draw attention to the suspicion and therefore leading to unwanted attention."

Inside the corporation the anxiety grows: "SCHERING..", the leader

1990

In radio and TV advertisements (for drugs) the

note "Risks and side effects..." are implemented.

Source: Medicines Act

Marie Lyons' daughter was born disabled. Guilt turned into anger.

of the clinical research team from the UK warns, "...should 'keep in mind' that we are dealing here with a product that is able to change the chemical environment of a foetus. We should be extremely careful in this matter."

Meanwhile the paediatrician Isabel Gal doesn't rest. She explained that she wants to publish her explosive findings in her dissertation.

Two British SCHERING employees take an unusual step. On 6th June 1968 they contact Karlheinz Friebe, head of the Medical Research Department of SCHERING AG in Berlin, with a "Strictly confidential" letter. They don't tolerate any longer the inaction of the parent company. "It is our moral duty as a manufacturer to do everything possible to ensure that the products on the market are harmless" they demand. "It is up to us to show that the product is safe to use and not up to the outside parties to show us it is not." The letter culminates in an appeal to the conscience of the company: "From the ethical point of view we are not satisfied with what has been done."

Karlheinz Friebe, the manager from Berlin, reacts. One week later he gives green light for a prospective study on 5,000 women as well as for other animal experiments.

But the British health authorities voice concerns. Such a large study appears too time-consuming.

Also first analyses of the public authorities with PRIMODOS revealed that there hadn't been more deformities but

rather "a significantly higher" miscarriage rate.

After this study the Berlin headquarter of the corporation decided not to do anything. Should such studies come to light, it would threaten the company with 'negative publicity with all the negative commercial consequences' feared the Senior SCHERING employees.

The two British Schering employees are in despair. They press again towards animal experiments. The rat is "no suitable animal", they write in February 1969, the studies should at least be repeated on baboons, since these are similar to humans. And under these circumstances PRIMODOS 'lost the right' as a pregnancy test. It would be better if SCHERING would withdraw the product from the market on its own initiative. "If we were forced to recall [the product] it would lead to considerable publicity at home and abroad."

Damage instead of cure

■ The CONTERGAN scandal: The sleeping pill CONTERGAN (THALIDOMIDE) was launched in 1957. It was also prescribed to pregnant women. In Germany approx. 5,000 children with severe malformations were born. The manufacturer Grünenthal paid 100 Mio DM as a settlement (ca. 51 million Euro). The CONTERGAN foundation was only founded in 1972 due to the decision of the German Parliament. ■ The Hemophilia scandal: In the eighties haemophiliacs were administered "factor VIII", it had been produced from blood plasma. In 1983 the drug was already contaminated with viruses, but it was still administered for many more years. Thousands were

infected with HIV, Hepatitis B and hepatitis C. In 1995 a foundation was set up, but only for the HIV infected. 100 Mio. DM came from the Federal Government, 90.8 Mio. DM was paid by six pharmaceutical companies.

Six years later, in 1975, one of the colleagues writes once again to Berlin. In the 'last five years', he refers to figures from the British Health Authority, 'the surveillance of medicinal products on pregnant women' has shown that of those who had had a hormonal test, a relative risk of 5:1 exists to give birth to a deformed child.

Were the two Britons something like the conscience of the company? Did they have supporters, possibly from the Berlin headquarter, which the British subsidiary was subordinated to? The more time passes, the more difficult it will be to hear contemporary witnesses from the past. One of the two employees is already deceased, the paediatrician Isabel Gal suffers from severe dementia. The TAZ didn't succeed during a week long search to locate the high-ranking SCHERING employees from Berlin who translated the large part of the reports into German. The BAYER AG is unable to help you. Karlheinz Friebe, the former head of the Department of Medical Science, lives today as a pensioner in Berlin, a friendly man with a weak voice, who doesn't remember. "There were legal conflicts," he says one afternoon in December 2015 during a phone conversation. "But more I do not know." He cannot remember his correspondence with the British colleagues - maybe a misunderstanding?

1994 The pharmacopoeia was implemented. It contains regulations for quality, testing and designation of pharmaceuticals. Source: Medicines Act

Andre Sommer says: "For them it was only profit and to save their own skin." When in 1977 the mother of a suspected disabled child – through medication – sues SCHERING, the corporation in Berlin weighs up what is less harmful for the profit: Shall we allow a trial? Or reach a settlement with the mother beforehand? The legal department noted: "The profit of PRIMODOS is apparently declining in England. There were already considerations to withdraw the product from the English market. "The question of 'image' remains. "However we would probably lose a bit of credibility if our own subsidiary in England always has had the opinion that we should have done more."

Schering has not done enough, says the professor

At the end of the seventies there is growing criticism towards SCHERING - in Germany as well. Mothers of disabled children make these malformations public; Headlines of Der Stern in 1978: "Thousands of children accuse". In Berlin, the criminal charges against SCHERING were filed. The company is now considering carrying out the study, which was discussed for more than 10 years, on great apes. In March 1978 an employee from the department of medical science travels to the USA, to the University of California. After his return he tells his superiors: "Dr. H. said that studies with primates are useful because primates are the closest to people. This is also important for experiments that were carried out due to exculpation." Reasons for exculpation. Reasons for the absolution of guilt. Andre Sommer lifts his gaze from the paper and looks to Marie Lyon. "They wanted

to subsequently clear their name." But this study wasn't carried out either. SCHERING is terrified of the length of the investigation period and the high costs.

On the 16th February 1978 three high level SCHERING employees travel to Herbert Tuchmann- Duplessis to Paris. The Professor is a renowned embryo toxicologist; he was already an official expert in the CONTERGAN (Thalidomide) trial. Now SCHERING wants to hire him – with a positive report of an expert for the company in mind. But the professor hesitates to get along with it. "Prof. TD's view is that SCHERING hasn't done enough."

It became late afternoon whilst still in the National Archives. Marie Lyon and Andre Sommer didn't have any break during the day and they look exhausted. But also satisfied. The files could be a first and next step to greater public pressure.

In 2009, when the money of the CONTERGAN (Thalidomide) Foundation was long used up, the CONTERGAN (Thalidomide) manufacturer Grünenthal transferred again 50 Mio. Euro. Many say that this happened was due to a broadcast of a film about the scandal and the subsequent public debate. Also, a moral damage can be the start of a company to act if courts can't do it any longer. This is a different kind of negotiation. A trial in which the judgment can still be passed.

Marie Lyon scrolls once again through one of the last entries. It is the advice that the scientists from Paris gave in 1978 to the people of SCHERING about DUOGYNON: They could

only argue the question of causality i.e. the causal link between taking [the tablet] and the malformations. However, in the question of guilt they wouldn't be able to win. The problem is a moral one, it was now important to save the honour of the company. Just as you can read it on the yellowed paper in Marie Lyons hand: "save the honour of the company."

■ **Heike Haarhoff**, 46, health editor of the newspaper taz. In November 2010 she wrote her first article on the obligation towards DUOGYNON

2006 it is mandatory to have the braille on pharmaceutical packaging. Source: Medicines Act

Duty The pharmaceutical manufacturers live from the trust of patients – therefore they should also provide information, says Bettina Schöne-Seifert

"It is about integrity"

A SCHERING laboratory in Berlin in the fifties.

Interview HEIKE HAARHOFF

taz. am wochenende: Mrs. Schöne-Seifert, despite all the research opportunities pharmaceutical products are launched on the market and then after years of using them you find out that they can cause extreme damage. Do pharmaceutical manufacturers have a different responsibility than for example furniture manufacturers?

Bettina Schöne-Seifert: Yes, because damage to body and soul have existential value for the affected. Furthermore, the pharmaceutical industry with their research departments is part of the scientific community and therefore subject to their standards. These standards require honesty, transparency and care, as well as dealing with side effects and suspicious reports. Of course, this applies to other sectors, such as aircraft manufacturers as well. But it is precisely the pharma-

ceutical manufacturers which always emphasize their special responsibility to service the patient and receive -regulatory authority or not - also a significant trust in advance.

Does this ethical responsibility also apply to medicines that were launched at a time where there were no registration procedures, let alone defined medicinal legal requirements? Of course, you have to be careful not to project current information about causal relations or ideas on appropriate regulations to ensure the safety of medicines on earlier times.

Duty of care, coming to terms, and obligation to inform can always only be orientated on each case of available or acquired knowledge. But that does not relativize the obligations itself.

In the case of the pregnancy test DUOGYNON it is very difficult to prove the existence of a causal link between taking [DUOGYNON] and the embryonic malformations

as the drug at that time was neither tested on humans nor on apes. How should the manufacturer now behave?

On a moral level this is not a question: The manufacturer has to give information, has to give information of the handling at that time of risk reporting and at that time the basis for security clearance. All files in the company's archive should be checked by an independent expert committee and the results should be made public. If the allegations of misconduct and its cover-up are really substantiated, BAYER as a successor of SCHERING should react in different ways, humane as well as financially.

After admission of guilt usually claims of damages follow. Which interest therefore would a pharmaceutical cooperation have to throw light on this matter? Honesty and Transparency are – at least retrospectively – also better for the manufacturer as measures to cut themselves off. And for the ones, who think it is possible that their own deformities or rather the deformities of their children are related to the use of DUOGYNON, above all, transparency is important. Even if no moral guilt can be proved and no causality is confirmed. Besides, it is however, once more, a question of integrity and credibility of the pharmaceutical industry as a whole.

Bettina Schöne-Seifert

■ 59, is professor of medical ethics at the University of Münster and a member of the advisory board for the 'coming to terms' of the behaviour of North Rhine-Westphalia in the CONTERGAN scandal.