Annual Report 2017

octapharma

Winner of 11 Communication Awards 2018

From donor...

From donor to patient

At the heart of our business is a journey from plasma donor to patient. This journey is made possible by the people working throughout Octapharma. Around the clock, around the world, our employees play their part in changing and saving the lives of millions of patients worldwide.

Who we are

Octapharma is one of the largest human protein product manufacturers in the world, developing and producing human proteins from human plasma and human cell lines. As a family-owned company, Octapharma believes in investing to make a difference in people's lives and has been doing so since 1983; because it's in our blood.

Our vision

Our passion drives us to provide new health solutions advancing human life.

Our mission

For the safe and optimal use of human proteins.

Time stamps throughout the report show that employees are working around the clock to make a difference in patients' lives. We follow the donor to patient journey shown below.

1 Donor

Our donors transform lives by giving their plasma so our patients can be treated with life-changing medicine.

Pages 04–13

2 Single donation control

Inspection of individual plasma donations.

Pages 16–17

3 Quality

Performing quality analytics throughout all processes.

Pages 18–23

4 Fractionation

Separating plasma into its various components to capture the desired proteins.

Pages 28–33

Revenue

€1.72bn

+8% 2016: €1.6bn

Operating income

€349m

-9% 2016: €383m

Capital expenditures

€201m

+21% 2016: €166m

Employees

7,674

+8% 2016: 7,094

Plasma donation centres

95

Manufacturing sites

6

R&D sites

7

Countries in which patients are treated with our products

113

Contents

Experience more:
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5 Purification

Removal and inactivation of contaminants and pathogens.

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6 Filling/finish

Filling of medical product under aseptic conditions.

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7 Visual inspection

Inspection and approval of finished product based on authority requirements.

Pages 46–47

8 Patient

Millions of patients all around the world are empowered to go further in their life adventure.

Pages 48–53

Chairman & CEO's introduction

Octapharma reports another record-breaking year for 2017 with revenue in excess of 1.7 billion Euro and operating profit similar to recent years.

These results were made possible by a good performance across our three therapy areas, with particularly strong contributions from octanate®, octanine®F, octaplex® and Nuwiq®.

Our commitment to discovering innovative solutions to treat rare diseases is evidenced by the exciting milestones we have reached. Our newly developed Fibrinogen concentrate, fibryga®, represents an important addition to our bleeding-management portfolio. We received regulatory approval in the USA, Canada and the EU. Two important clinical studies are ongoing to expand the indication of fibryga® to include acquired fibrinogen deficiencies.

Our human cell line recombinant Factor VIII, Nuwiq®, has been shown to address the most serious issue facing haemophilia A patients, inhibitor development. The interim data from the NuProtect study was published in the journal *Haemophilia*, demonstrating a rate of only 12.8% of high-titre clinically relevant inhibitors in previously untreated patients (PUPs).

> The year 2018 marks the 35th anniversary of Octapharma and today I am happy to lead such a successful global family business.

Following completion of the clinical programme in primary immune deficiency patients, our new subcutaneous immunoglobulin, cutaquig®, has been submitted for registration in the USA, Canada and the EU.

Plasma collection is the foundation of our business. As we rely on this scarce raw material from our plasma donors, we have the obligation to ensure we are utilising every drop optimally. We continued the significant investments of recent years into expanding our fleet of plasma collection centres to secure the volume of plasma required to meet the growing demand for plasma-derived products. We also successfully in-sourced plasma testing to our new state-of-the-art US Food and Drug Administration (FDA) approved laboratory, and received FDA approval for our new plasma storage warehouse.

In collaboration with the humanitarian programme Project SHARE, Octapharma donated 30.5 million international units of Nuwiq® for distribution in 16 countries where these medicines are scarce or still unavailable.

I am excited about our partnership with the inspirational haemophilia patient Chris Bombardier who, with the support of grants from Octapharma, became the first person with haemophilia to summit Mount Everest in Nepal and Mount Vinson in Antarctica. Chris has now completed his quest of climbing the highest mountains on each of the seven continents of the world.

Octapharma now employs almost 8,000 people, each of whom play their individual role in changing and improving the lives of millions of patients in 113 countries. The theme of annual report 2017 is the relationship from donor to patient with a focus on the people who make it possible. This report, and the 16 new films, offer a glimpse of what is involved in creating plasma derived medicines. Follow a 24 hour tour through Octapharma and meet the father Zoran, one of our plasma donors, with his son, Simon, who relies on gammanorm® to live a normal life.

Let me conclude my 2017 review with the promise that our five company values Ownership, Integrity, Leadership, Sustainability and Entrepreneurship remain the foundation of all of our decisions and behaviour every day to support our vision of providing new health solutions advancing human life.

Wolfgang Marguerre
Chairman & CEO, Octapharma Group

Above, left to right:

Frederic Marguerre
Shareholders' Representative
President, Octapharma Plasma Inc. USA

Wolfgang Marguerre
Chairman & CEO,
Octapharma Group

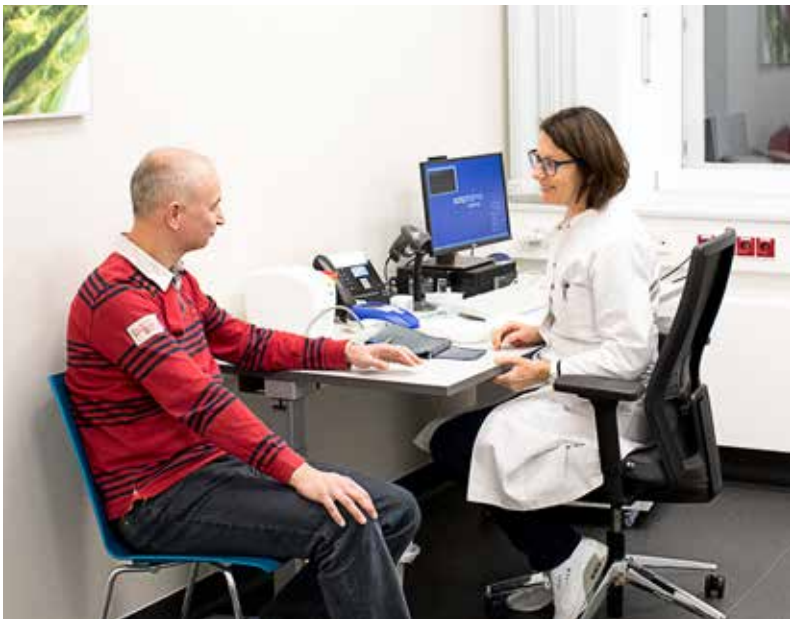
Tobias Marguerre
Managing Director,
Octapharma Nordic AB

7,674
Employees

€1.72bn
Revenue

Donating plasma to save lives – including my son's

"It was just perfect for me to donate plasma with the company which makes my son's medicine". Zoran, Verena and their three children – Laura (13), Simon (11) and Lisanna (8) – live in Berlin-Spandau. Simon was diagnosed with a rare immune disease as a baby and has been using gammanorm®, a plasma-derived subcutaneous immunoglobulin (SCIG), for 10 years.



Left Zoran during a medical examination and health talk with the physician in the plasma donation centre.

300+

immune diseases are treated with our products

Top Zoran during his donation.

Bottom Plasma donation bottles.

Zoran says: "Many sick people wouldn't be able to survive without plasma-derived medicine. Simon wouldn't be able to live without gammanorm®. He would surely get infected somehow and that would have devastating consequences. And that's why it's important to raise awareness: if you donate plasma, you're essentially saving lives."

Simon had his first serious infection when he was eight months old. He had inflammation in his blood and it was difficult for his body to cope. At first, he was treated with antibiotics and was in the hospital for almost two weeks. Simon had an extremely severe infection when he was 11 months old. He had a sudden fever and his joints were inflamed. He couldn't move. Simon screamed whenever he was touched, which was very stressful for his parents. Simon spent 15 days in hospital. Multiple examinations were performed to ascertain the cause, and one of the doctors suspected that Simon's infection had something to do with his immune system. Simon was diagnosed with a rare genetic disorder – X-linked agammaglobulinemia (XLA), also known as Bruton's Agammaglobulinemia. The white blood cell formation process does not generate mature B cells, which manifests in a complete lack of gamma globulins, including antibodies which

Watch Zoran and Simon's story
annualreport.octapharma.com

Donating plasma to save lives – including my son's continued

are needed to defend the body against infection. The diagnosis was a relief for Simon's parents because they now knew he had an immunodeficiency which, although not curable, was treatable with immunoglobulin products derived from human plasma.

The diagnosis was not the end of the family's struggles. Being very young, Simon's baby fat made it extremely hard to locate the veins to insert an intravenous drip for the immunoglobulin treatment. His mother, Verena, recalls: "Simon screamed really loudly as if he were being tortured. The doctors were drenched in sweat. I had to hold him down. The whole process was a real horror for everybody."

Simon's parents were happy to find out that they could soon begin treatment at home with gammanorm® and administer it subcutaneously. Zoran remembers when the doctors explained how the medication is produced: "When we realised that hundreds of donors were required for the amount of medicine our baby needed, we were absolutely astonished. It was shocking to learn how many people have to donate plasma in order to take care of one sick baby. We were also – to be perfectly honest – a little bit scared to think that so many donors were needed just to produce the amount that is essential for our son.

"I'm healthy so I decided to donate plasma myself. When I first started to donate, I tried to go every week. However, it was pretty far to the plasma centre and I had to set aside a lot of time, so I stopped for a while. But last year, while reading the local paper, I saw that an Octapharma plasma donation centre had opened in Berlin-Spandau, very near to our home. I thought, man that is great! I started donating again in January 2017.

"I donate plasma once a week and dedicate an hour and a half to that in my schedule. After I get home from work, I cycle to the plasma centre. I sign in and complete the survey which you need to fill in every time you attend the centre. Then my blood pressure is checked, they take my temperature and I'm weighed. If you are given the green light by the doctor, you go to the plasma collection area to donate. Once you're connected to the plasmapheresis machine, you get a jab in the arm, and then that's it. You're able to read a book, listen to music or just relax.

"From the very first moment when you register everything is well explained and you are always treated extremely well. There are always enough people around to help and you're in good hands and feel very secure. The atmosphere is really great.

"I am happy to be giving something that will help others. And you don't have to do much. You only have to endure a small needle prick and give up a bit of your time. Every now and then, the thought will occur to me: 'My son is now receiving a medicine that so many people made possible through their plasma donations.' That's a really good feeling."

Simon's parents want to encourage others to donate plasma because they know what it's like to depend on life-saving plasma-derived products. Verena says: "it's important that more people donate plasma, because the drugs that are made from it are critical for many people. For Simon, this is definitely the case, and it's so important that these medicines are always available. I've heard that there are more and more medical conditions that are being treated with this kind of medication. The demand is increasing and that's why the number of donors needs to increase as well."

> We were absolutely astonished when we realised that hundreds of donors were required for the amount of medicine our baby needed.

Zoran
Berlin, Germany

Find out more about Zoran's son Simon on p50.

Above Zoran cycling to the donor centre near his home after work.

Right Verena, Simon's mother, encourages others to donate plasma.

Saving lives starts with our donors

It all starts in our donation centres. We ensure life-saving plasma is collected in a safe, clean, and friendly environment.

We are open seven days a week from 7am–7pm for our valued customers. As Centre Director, I arrive at 6am to perform morning quality controls with my staff and get our centre ready for daily operations. We welcome our donors throughout the day, and work to ensure they have the best possible experience in our centre. I believe it is important to build a strong rapport with each of our donors through mutual respect and excellent customer service so that the centre feels like more of a family environment to them, and not just a business.

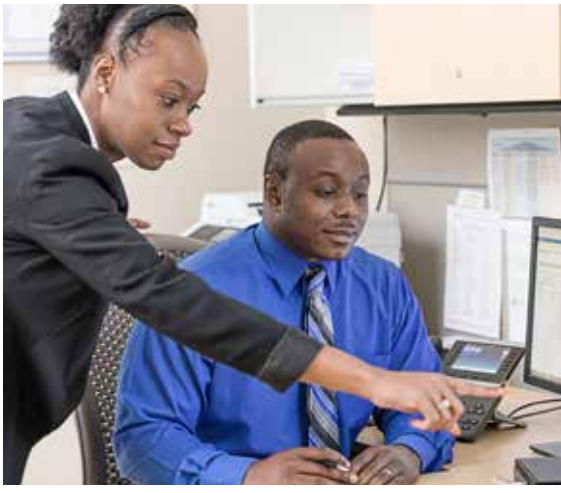
We keep the patient in mind with everything we do. Because we collect plasma for life-saving medicines, we operate in a highly regulated environment. We have multiple standard operating procedures and checks in place to ensure the safety of our donors and the quality of the plasma we collect. We explain our procedures to donors to make sure they understand how our processes benefit both our donors and patients. In everything we do, we think about the final product and the millions of patients who rely on plasma-based medicines.

We are the very beginning of the process, and without our donors there would be no finished product. Our donors express many different reasons for donating – and their motivations vary. Some of our donors give plasma to earn supplemental income, others donate to save a life, and still more donate because they have either been a patient, or know someone who benefited from the medicines we help make. We also have donors who enjoy coming to our centre and spending time with our staff and donors because they like the social interaction. For our donors and centre staff, we are all part of a larger plasma community.

> We are the very beginning of the process, and without our donors there would be no finished product.

I have worked in the plasma industry since 2005. I started as a donor during college. I began working in a plasma donation centre as a plasma processor, then was promoted to training coordinator before leaving to study public health. I came back and opened the Houston centre in the spring of 2016. I consider myself an ambassador of the plasma industry, and I want our company to be the face of the industry. To me, Octapharma Plasma is the standard because our focus on training, operations and customer experience drive our success.

As a leader, I'm a coach at heart. I enjoy watching employees grow into the next phases of their careers. Assisting in their journeys is the most enjoyable part of my job. If I can build a cohesive team and help my staff fulfil their highest potential, that's wonderful. I'm proud to be part of a company that develops professional employees while contributing to the wellbeing of our donors, patients, and communities.



Above Centre management collaborate to ensure quality and traceability of plasma collected.

Right Our valued donors provide life-saving plasma for the medicines we create.

Hurricane Harvey

Hurricane Harvey made landfall in Texas as a category 4 hurricane on the evening of 25 August 2017. Over a four-day period, Houston, the fourth most populous city in the USA, with 2.3 million people, faced historic flooding after intense rainfall. A year's worth of rain (more than 50 inches) fell in Houston in a matter of days. Everyone in the area, including donors and employees, was affected one way or another. The Octapharma Plasma corporate office created a fundraiser page for our 80+ US donation centres to join together and raise more than $10,000 dollars to help centre staff affected by the flooding.

Donor Centre Director Willy Felton said, "Hurricane Harvey was a tough, eye-opening experience for everyone. My entire neighbourhood was surrounded by water, so I was living on an island for two weeks. People were even trapped on the roofs of buildings. Members of our staff and donor community lost everything, including cars and clothes. It was a devastating loss for a lot of people."

Of Hurricane Harvey's aftermath, Willy said, "We still have some donors that have not returned, have been displaced, or have lost everything. The Houston centre's donors and staff received an outpouring of support and have been as positive as possible throughout this experience. After all, material items can be replaced, but no lives were lost, and that's what's most important. In our recovery efforts, we've found that Hurricane Harvey actually reinforced the importance of donating plasma. Our donors are more motivated than ever to donate life-saving plasma that enriches the lives of others."

Willy Felton
Donor Centre Director, Houston, Texas

Saving lives starts with our donors continued

Our donation process takes care to fully support our donors and their needs.

1

Donor arrives at the centre and is welcomed by staff.

Donors must be **+18 years old, +50kg** in weight and **healthy**

Industry-wide figures*

61%
of source plasma donors are male

30%
of total donations are given by donors aged 25–35

55%
by donors +35 years old

17.5
donations per donor on average

2

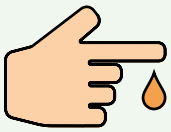
Donor's identity is verified; details are managed in our donor registry system.

First-time plasma donors are required to bring a current, valid photo ID, proof of a Social Security number, and proof of their current address. Return donors are required to verify their identity with a valid photo ID before each plasma donation.

Donating fits around my full-time job, and is a way to make money while making a difference.

Amber
Plasma donor

3



Donor completes a health questionnaire, physical screening, and blood sample testing.

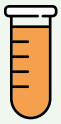
As soon as I learned how much plasma helps others, I knew I was going to donate as much as I could.

Shelby
Octapharma employee and plasma donor

*An industry-wide collection of donor demographic data for 2012. Source Plasma Donors: A Snapshot. (2017) Schreiber, G. B., Kimber, M. C., Plasma Protein Therapeutics Association.

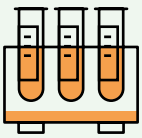
4

The donation process takes **45 to 90 minutes**



300 to 880ml of plasma is taken each time

5



Donations are labeled with a barcode, so at any point in the process the plasma can be traced.

Every plasma unit collected is traceable. If a unit does not pass rigorous testing, the donor is notified that they will not be permitted to donate again, their name is added to a national deferral registry, and their plasma donation is pulled from production.

6

Each plasma sample is extensively tested to ensure only safe, quality plasma is used in the manufacture of medicines.

Donating lets me contribute to my family's budget while still focusing on my children. Knowing real patients makes donating extremely meaningful for me.

Angie
Plasma donor

Ensuring safety and suitability of donors and quality and traceability of plasma

A donation centre's Quality Assurance (QA) team ensures a standardised plasma collection environment for staff, donors and patients.

Above Plasma samples are collected and prepared to be sent to the laboratory for viral marker testing.

Our daily work includes observing and instructing staff, reviewing records and documentation, and supporting internal audits that check systems in place at each centre. QA ensures a standardised plasma collection environment for staff, donors and patients.

Our donor management system (DMS) supports centre systems in place for quality, safety and traceability, and when standard operating procedures change, DMS also updates with current processes.

When we register a potential donor in DMS, we record their full name, address, social security number, allergies, distinguishing characteristics, medical history and more. Each potential donor is given an in-depth health screening and medical questionnaire to assure suitability. If any of a donor's responses indicate a concern, a medical professional questions the donor further, which may result in deferring the donor if his or her answers do not meet strict donor eligibility requirements. To become qualified, a donor must donate two times and have acceptable test results for each donation. All donors undergo a screening before each donation to ensure they meet safety requirements defined by the Food and Drug Administration (FDA) and other regulatory agencies.

> "For me, getting to know donors on a first-name basis is important in order to give great customer service and ensure donor wellbeing."

In QA, we stress the importance of accurately entering data and recording results in DMS. For example, it is important to enter a donor's temperature, blood pressure and weight correctly during the donor registration. This is for donor safety. If a donor is not within acceptable limits, a temporary deferral will be applied for a minimum of 24 hours. Accuracy in data entry is vital for donor safety, and ensures deferrals are applied appropriately.

People in the USA can donate twice within a seven-day period, with at least 48 hours in between donations. The Plasma Protein Therapeutics Association created a nationwide cross donation check system (CDCS) to protect donors' health by minimising the risk of cross donations. Each time a donor attempts to donate at an Octapharma Plasma location, the system confirms they have not donated at another centre within the last seven days.

After a donor completes his or her donation, plasma samples are collected and frozen in an on-site freezer. Our technicians collect a minimum of three samples, including viral marker testing samples. Every day, samples are collected and sent to a laboratory for viral marker testing. Sample testing time can range from five to 14 days. Once test results confirm donor health and plasma safety, we ship the plasma donation to our production sites. If plasma is not deemed suitable for manufacture, it is pulled and destroyed as medical waste.

Donors who receive an unsuitable test result, e.g. a positive viral marker, are entered into the National Donor Deferral Registry, which is a database of permanently deferred US plasma donors. The donor's name and social security number are flagged, preventing donation at any US plasma centre.

I have a bachelor's degree in social work and studied psychology, which gives me a good understanding of all different types of staff and donors. My background helps me relate to others, because I appreciate that everyone is different. For me, getting to know donors on a first-name basis is important in order to give great customer service and ensure donor wellbeing while they are in our centre. There are still some stigmas attached to the plasma industry, but we're educating our community to show that plasma donors are regular people – they are moms and dads, workers and students. Donors have multiple reasons for donating – everything from supplementing their income to helping save lives. Without our loyal donors, we cannot complete our job, which is to provide safe, quality plasma for life-saving medications used by patients.

I moved to Texas to help open the Houston centre in 2016. Opening a new centre is a very demanding process that requires dedication and commitment to your job. Once you see it all come together, it is very rewarding. I am now starting a new role as Centre Director in our donation centre in Garland, Texas and am looking forward to continuing my good work with Octapharma Plasma.

Tiffani Chiles
former Quality Assurance Supervisor, Houston, Texas, now Centre Director, Garland

40
staff work in the centre

72
donor beds

350
donors per day

Centre hours:
7am–7pm, seven days a week

Research that helps people

The molecular biochemistry department conducts analysis and develops assays to look at the functions of different proteins.

I completed my master's thesis and doctoral thesis at Octapharma. Both theses focused on the molecular structure of von Willebrand Factor (VWF) protein and the structure-function relationship of VWF.

The molecular biochemistry department supports other departments by conducting analysis and developing assays to look at the functions of different proteins. For example, we have developed assays to look at fibrinogen fibres under a microscope; used a flow chamber model to investigate VWF under flow; and developed glycan assays to analyse post-translational modifications. We support our colleagues in production by analysing samples and identifying proteins by their molecular weight. We use a mass spectrometer for this, which also enables us to identify unknown proteins. We have also developed cell-based assays to understand the immunological properties of plasma proteins in general.

We play an important role in basic research for new product development, most recently in the development of a new subcutaneous recombinant FVIII product. It all started with a discussion and an idea of Christoph Kannicht, General Manager of Octapharma Biopharmaceuticals, to administer FVIII subcutaneously. When you inject small molecules, like peptides, they can go directly into the blood vessels, however large proteins like FVIII and VWF need to enter the circulation via the lymphatic system. The major challenge in the case of FVIII is to transport it into the blood. Because it is so "sticky", when injected subcutaneously, FVIII adheres to membranes in the epidermis. When administered alone, FVIII has almost zero bioavailability, because it binds to cell membranes. Our idea was to administer FVIII with VWF because VWF blocks this binding, so allowing the FVIII to reach the patient's bloodstream.

> "Sometimes you can become entirely absorbed in the laboratory or in your research, but we should never forget the real people we are helping."

Since I have worked extensively on VWF, we discussed what would be the perfect VWF part for this product. The VWF molecule contains different binding domains, one of which is the FVIII binding domain. You can make this domain longer or shorter and, depending on its size, its efficiency at blocking FVIII phospholipid binding domains is changed. We tested a number of fragments and discovered one to be especially good. This most dutiful fragment was tested in the first experiments for the proof of concept. In our R&D facility in Heidelberg, we produced recombinant fragments and tested them again. With recombinant production, you have the benefit of being able to improve your fragment. We modified the structure of the final fragment so that it has better properties; it is released slowly into the circulation and has prolonged half-life, meaning it circulates longer in the body, which in turn leads to half-life prolongation of the FVIII molecule.

Today, several parts of the development are running in parallel: the pharmacology and toxicology studies, upstream process development, development of purification, formulation development and R&D production batches.

Our work is never routine. I enjoy new challenges and working on new products. We have different fields of our research and co-operate and publish studies with excellent scientists outside of our company. Seeing the stories of the children whose lives are determined from the beginning by their illness, is very powerful. As a relatively new mother myself, this was a powerful reminder of the importance of our work. Sometimes you can become entirely absorbed in the laboratory or in your research, but we should never forget the real people we are helping. It's amazing to do what you love, research and science, and help other people – it's the ideal combination for me.

Dr Barbara Solecka-Witulska
Senior Scientist – Molecular Biochemistry, Berlin, Germany

Far left Sample preparation.

Left Preparations for mass spectrometry.

Watch Barbara's video:
annualreport.octapharma.com

Controlling the plasma which enters production

Single donation control (SDC) is the foundation of traceability of all our individual plasma donations.

My main task is to perform the single donation control (SDC) which means scanning each individual bottle of plasma donation in order to check if it fulfils the quality requirements, and to reject the ones which do not.

SDC is the foundation of traceability of all our individual plasma donations. This traceability is important for the safe and efficient production of our products; because we must be able to go through the whole production chain in both directions: from final medical product to the plasma donation used to produce the batch, and vice versa. SDC removes rejected donations to guarantee that the donations which will be used in production fulfil all the quality criteria. We only send the good plasma donations to production.

A typical day starts with the control file preparation for the plasma donation batches which will be controlled that day, and to check that everything is prepared to allow the SDC to be performed. The scan of each individual plasma donation allows us to make the link between the physical donation and the data supplied by the plasma collection centre.

Once scanned, if a donation is good, it is accepted. The donation is put into a plasma box labelled as "Accepted". When the box is full with good donations, it is weighed, closed and put in cold room storage before being used in production.

A donation may be rejected by visual rejection criteria, e.g. donation bottle integrity (to avoid a risk of contamination); red cells (which block the filters in the process); or insufficient donation volume. If any of these criteria is met after scanning, we manually enter it into the system, adding all the required data (e.g. carton number).

There are also rejection criteria given directly by our manufacturing execution system, OctaMES. In this case, the virus tests have been uploaded in the system and the corporate quality plasma department entered all relevant data given by the plasma collection centre. When I scan the donation, the system makes a specific noise and the screen colour changes. This is unmistakable so cannot be accidentally ignored. For positive donations or look backs, specific documentation must be completed to prove that the donations have been removed. All rejected donations are put in a box labelled "Rejected", put "in jail" in the cold room and then destroyed as biological waste.

> We must respect the donors and their plasma because they take the time to save lives, and do so by giving a part of themselves.

In some cases, we control the donations without having all the necessary data. These donations are put in "On hold" boxes. This is the case for plasma with missing polymerase chain reaction (PCR) test results or plasma for which the quarantine date has not been reached. Such boxes are blocked until all the missing data comes in and the inspection can be completed.

After the SDC step, the corporate quality plasma department must approve the plasma for use in production. Then it is transferred to the production site by the transport department. Basic fractionation then begins the process of thawing and pooling the plasma.

We must respect the donors and their plasma because they take the time to save lives, and do so by giving a part of themselves. When I think about our patients, I am always conscious of the importance of our job to improve and save patients' lives. I also appreciate how lucky I am to have good health.

Annabelle de Crignis
Single Donation Control – Technician, Lingolsheim, France

600
plasma bottles processed per day

0.8 litres
in a bottle of plasma

Far right Single donation control with each individual donation visually checked and scanned into the donation management system (OctaMES).

Right Checking documentation and preparing team activities.

1

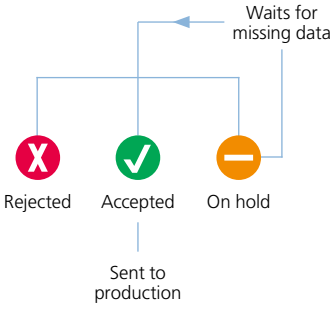
Visually inspected

2

Barcode scanned

3

Quality check



4

Stored in a freezer at -25°C

Watch Annabelle's video:
annualreport.octapharma.com

Detecting viruses early by targeting DNA and RNA

PCR (polymerase chain reaction) methods detect viral nucleic acids directly, and therefore can identify recently infected donors who have not yet produced antibodies.

Top Prior to preparation of the minipools, the plasma samples are placed in racks to enable automated de-capping and pooling.

Bottom The barcodes of all plasma samples are scanned before the minipooling process starts, and the identities are handled within the LIMS-PCR system where the connection between the individual sample and corresponding minipool is made.

Hepatitis C (HCV), for example, is detectable by PCR around 1–2 weeks after the time of infection, whereas the levels of HCV antibodies, which is the immune system's response to the infection, are not detectable until up to two months after the time of infection. This is called the window period, in which recently infected donors are not detected by conventional antibody-based assays.

Polymerase Chain Reaction (PCR) is a NAT-type of method, which is short for nucleic acid amplification technique, in which specific genetic material is amplified to reach detectable levels. In PCR, a certain kind of reagent (primers) is used to target a small but specific part of the virus-genome (deoxyribonucleic acid (DNA) or ribonucleic acid (RNA)) in question, and with the help of an enzyme, this small genomic area is amplified over and over again if the target is present. As soon as the small target is amplified, a third component of the PCR reaction (the probe), emits a signal that can be detected by the PCR instrumentation.

All plasma units are tested using antibody/antigen-based methods for the detection of human immunodeficiency virus (HIV), hepatitis C (HCV), and hepatitis B (HBV) at the time of donation. After that, all donations are PCR screened in minipools for detection of HIV, HCV, HBV, HAV, parvovirus B19 (B19V), and on occasion hepatitis E (HEV). Plasma from the USA is PCR tested in the USA due to FDA regulations. All untested plasma of non-USA origin is PCR tested in Stockholm. Our corporate PCR laboratory in Stockholm supplies all Octapharma production sites with individual donation level PCR results. The lab performs minipool testing of all plasma, unless it has been fully PCR-tested elsewhere. Manufacturing plasma pool scale testing is done either in Stockholm or at the Octapharma PCR laboratory in Frankfurt.

> We are at the centre of many interesting questions. There is a fundamental curiosity which makes it enjoyable to explore methods and find ways to optimise them.

Minipool testing is not a regulatory requirement, but is rather an internal strategy to minimise the risk of contaminating a whole plasma pool for production, which would be a tremendous waste of raw material and loss of final product for patients. Minipool testing minimises the number of samples required to be analysed. Instead of testing 480 plasma samples individually, a 480-donation-pool is prepared that contains a small volume from each of the 480 samples. The 480-pool is analysed for detection of viruses by PCR and if a positive PCR result is obtained, the samples are resolved so that the individual, virus-containing plasma unit can be identified. The virus-containing plasma units are then removed prior to production.

Our PCR laboratory in Stockholm consists of three groups, namely the PCR pooling team that performs the minipooling of samples from plasma units, the PCR analysis team that performs routine PCR analyses of minipool samples as well as plasma pool samples, and my team, the PCR R&D and support section that develops, validates, implements, and supports the PCR methods used in Stockholm. These three teams work both in parallel and as part of one workflow.

PCR pooling lab

A normal day in the PCR pooling lab starts with taking the PCR samples that arrived the day before out of the refrigerated room where they have been thawing. The sample tubes are put into racks, de-capped, and put into the minipooling robots, 480 samples at a time. The robot then aspirates a small volume from each sample, distributes it to 96 well microtiter plates and to another tube, the 96-pool tube. Small volumes from all of the 480 samples are thereby distributed in five 96-pools and corresponding microtiter plates. After that, yet another pooling is made from mixing a small volume from each of the five 96-pool samples into one tube, and a minipool containing a contribution from all the original 480 samples, a 480-pool, is made. The barcoded identities of all tubes and microtiter plates are hierarchically organised in the laboratory information management system (LIMS)-PCR system, which is a specialised LIMS platform designed to handle the complexity of minipools. Approximately 10–20 minipool runs are

performed per day, which corresponds to the same number of 480-pools containing 5,000–10,000 individual plasma samples.

PCR analysis laboratory

Meanwhile, the PCR analysis laboratory performs nucleic acid extraction and PCR analysis of HIV, hepatitis C (HCV), hepatitis B (HBV), hepatitis A (HAV), parvovirus B19 (B19V), and on occasion also hepatitis E (HEV), on samples either from minipools or plasma pools. On a daily basis, 10–60 minipool samples, including 480- and 96-pools, are fully analysed with 5–6 PCR methods, and on a weekly basis 10–15 plasma pool samples are analysed with 4–5 PCR methods.

PCR R&D and support

The PCR R&D and support team provides the PCR analysis team with support related to the methods, interpretation of complex results, scientific advice, providing input on issues regarding virus safety and contamination, and also the reporting of PCR results. The R&D activities in my team consist mainly of developing new PCR methods for detection of various pathogens, both in plasma, serum, and other samples. The analytical methods must be re-developed from time to time e.g. to comply with regulatory demands, to allow for utilisation of new generations of instruments, to allow for a higher grade of automation etc. After a new method has been developed, it is validated according to current guidelines, meaning that several pre-defined parameters of the method are tested in a stringent manner, such as the determination of analytical sensitivity, evaluation of the method robustness, that all relevant genotypes are detected etc. If the method performance fulfils the pre-defined demands, the validation is approved. Before the method can be implemented, any possible regulatory impact is assessed by international drug regulatory affairs (IDRA). If this is the case, we prepare the documentation for authority submission, and then await regulatory clearance. Once authority approval is obtained, usually within a year, we implement the method in the PCR analysis group for routine testing of minipools and plasma pool samples. All these actions are handled in the change control system, to ensure proper documentation, assessment, responsibilities, and traceability.

The R&D and support team's work is creative and often not routine, with many lively discussions. The very same curiosity that led me to my career in science, is what drives me here now at work. There is a fundamental curiosity which makes it enjoyable to explore methods and to find ways to optimise them. I enjoy the versatility of my role: one day I am discussing the most intrinsic genomic details of HCV with my team, the next day I am involved in a multi-site discussion on how HIV serology can be interpreted.

Working in our PCR laboratory, we are at the centre of many interesting questions, and it's great to lead and be part of a team that delivers input to the regulatory aspects of PCR testing. My philosophy is: honour the donor and honour the patient. Every donated plasma unit counts, and thanks to a continuous, high-quality plasma supply and a strong quality organisation, we can provide safe and efficient life-saving treatments to patients around the world.

Dr Elisabet Ekvärn
Head of PCR R&D and Support,
Plasma Quality, Stockholm, Sweden

Watch Elisabet's video:
annualreport.octapharma.com

Performing analytical methods to test quality

Our daily work in Quality Control Analytics is the testing of final containers, intermediates, in-process samples, and stability samples.

I joined Octapharma as an apprentice in 2004. In Quality Control (QC) Analytics, our daily work is the testing of final containers, intermediates, in-process samples and stability samples to ensure that all tested parameters are in their specified limits to guarantee the good quality of our products.

We receive samples from throughout the production process and test certain parameters. Some of the in-process samples are time critical, so we need to have an efficient schedule for testing to ensure production can continue in good time. Our results of the time-critical in-process samples allow the various production units to proceed with further production steps – in some cases the results confirm that the production steps were done correctly and they can continue the production process. So we have to work very precisely and reliably.

In Analytics 1, we have about 50 different analyses (the combined analytics teams in Vienna use more than 100 test methods). Ten to 15 different methods are performed on average per day. Some methods are used to test ten to 15 samples per day, others up to 50 samples per day. We use our laboratory information management system (LIMS) to manage the samples, analysis and the results. We have flexible working times which must comply with the incoming in-process samples. At 6am, the first samples arrive so some employees are scheduled for the "morning shift" from 6am–2.30pm. Some analysts also do optional evening shifts from 2pm–10pm. We have staff on-call duty for samples which come during the night, or late in the evening, as the testing times for some in-process samples can shift for various reasons.

Before we start the routine analysis, we print a working list from the LIMS system to see all the samples we have to prepare. We prepare the reagents and the devices used for the method. If we get completely fresh in-process samples, they are usually in liquid state, though they can come in frozen (if they have been stored for a few hours). Our final container samples are stored in a cooling or freezing room. For samples and reagents that must be stored at minus 70 degrees, there are special deep freezers. For lower temperatures, we have liquid nitrogen containers.

If we are testing final container samples of lyophilised (freeze-dried) products, we have to reconstitute them. So for the final container testing of coagulation factor concentrate, like octanine®F or octaplex®, we dissolve the lyophilised product with water to get the liquid product. For some methods, the products have to be further diluted with a special buffer.

I enjoy the versatility of my work. My position involves a combination of performing tests, a lot of office work (writing standard operating procedures, for example) and interesting activities such as instrument qualification, employee training and support. And I occasionally represent my group leader in organisational lab matters.

> In coagulation testing we recreate the process of blood clotting in the laboratory environment. This is my real passion.

Coagulation testing is my real passion, because I am also responsible for the automated coagulation analyser, called STA-R. In coagulation testing, we recreate the process of blood clotting in the laboratory environment. For example, we test the concentration of coagulation factor IX (FIX) in octaplex® and octanine®F. Coagulation cannot occur with the FIX product alone, we also need reagents with other coagulation factors naturally present inside the human body and an activator and calcium to start the coagulation. We load the reagents into the instrument, then perform a calibration. The instrument measures the clotting time of samples relative to the standard. The sample and the special reagents are pipetted into a cuvette, in which the movement of a small metal ball indicates the progress of clotting. When and if the samples clot, the ball will not roll, so the instrument detects that clotting has occurred. With a high FIX content, for example, the clotting time will be short.

For octagam®, we test amongst others the protein content performing protein determination using the Biuret method. In the presence of protein, a special blue-coloured reagent changes to violet and the intensity of the colour is measured by a photometer.

Electrophoresis is applied to separate the proteins. An electric current is used to separate the proteins applied on a gel. The protein components have a different size and electrical charge and move from one side to another. The bigger the protein component, the less it will move. This separation of possible contained protein components allows us to ensure the purity of a product, such as octagam® or albunorm®.

Plasma is a scarce and precious raw material. Sometimes, when it is your routine daily business, you can forget that. It is important to remember that our raw material comes from humans and that our products are used by humans. Our patients rely on us not only for effective products, but safe products. Every minute, every hour, every action of all staff is very important and makes a difference to the whole system working well. I watched the patient films and to see real patients is a great reminder of the importance of our work. I am proud to work here and feel honoured to be part of the system.

Bernhard Süss
Senior Technician QC Analytics 1,
Vienna, Austria

Every batch of final product is tested for compliance and patient safety

1. 100% testing of all specified parameters.
2. 100% review of all process parameters.
3. Compliance with all requirements leads to internal release of the batch.
4. Samples of every plasma pool are re-verified for absence of viral markers as well as for virus DNA/RNA.
5. Batches are also tested externally and released by an Official Medicine Control Laboratory (OMCL).
6. To release the batch of final product, an external control of all defined criteria is required. After this, the medicines can be used by patients.

Top Locating samples for testing in the cooling room.

Bottom The Biuret method. In the presence of protein, a special blue-coloured reagent changes to violet.

Watch Bernhard's video:
annualreport.octapharma.com

Documenting the complete history of every production batch

Each and every step is captured in the batch record. We ensure good manufacturing practice (GMP) compliance, conformity and completeness of process documentation.

Left Batch record check in the control station of the Basic Fractionation department during a GMP walk.

Above Training of staff on good manufacturing practice (GMP).

I'm actually a veterinarian and worked with horses before I decided to change career and moved into pharmaceutical production, joining Octapharma as a trainee in 2004.

Our department is responsible for the process documentation of the whole of production, from the moment we receive the plasma from our warehouse, right through to final product packaging. Each little step in our processes is captured in the so-called batch record. We have different products in different concentrations, and for each product we have different process steps. Production operators have to make manual records to demonstrate that all the steps are defined and were taken correctly. All the temperatures and parameters must be documented, and who did what and when. We have to have those records to have the complete, fully traceable history of each and every production batch.

Good manufacturing practice (GMP) is the minimum manufacturing requirement to ensure safe, high quality products for patients. There are various guidelines from different countries, but all guidelines follow the same basic principles: manufacturing facilities have to be clean and hygienic with controlled environmental conditions and manufacturing processes must be clearly defined. Also, all processes have to be validated and the instructions and procedures have to be written in clear language. Work instructions provide step by step directions for what to do for each process, e.g. raise the temperature in the tank from 2 to 5°C.

In addition, our operators have to be trained to carry out and document procedures. Part of my role is to conduct the training of all new production operators. I take them on a tour through our production floors, so they can see and understand all the different steps and departments, not just the one in which they will be working. I also explain to them the clean room procedures and give them a general GMP training to make them aware of how important it is. And when the standard operating procedures are updated, the staff are trained on these changes, too.

Our products aren't transformed from plasma to final product in a single process. Our intermediate products are frozen and stored for further processing at a later stage. This means that for each product, we have more than one batch record. In one week, we have more than 100 batch records to review. A preliminary check of the batch records is done by the head of the respective department. I then conduct the batch record review, checking all the batch records for GMP compliance, conformity and completeness. This includes checking that all the information is contained in the batch record, checking that all the fields are filled in, that the stamps are legible, if all the times are documented and that all the records for the different machines are included. The closer we come to the final product, the more automated the steps, so some of our processes produce electronic files or records, like the chromatography systems, which are used in purification.

> The batch record gives us the complete, fully traceable history of each and every production batch.

I also conduct "GMP walks" in the production area, to check that everything is as it should be, e.g. that operators are correctly dressed, that operating procedures are present, clear and up to date, and that all the log books have been filled in correctly. Each month we have a couple of inspections from regulatory authorities during which inspectors check what kind of control systems we have in place and that all our actions and processes are compliant.

There is of course a lot of routine work with batch record reviews, but I also support projects, e.g. the extension of basic fractionation in Vienna. I am supporting the planning by providing information about the different process steps. We have a really great team as well as a lot of interaction with other departments. I enjoy working directly with the production staff, not just sitting in my office doing documentation work. Everyone in the production chain contributes to ensure safe final products. We have great products that really save lives, which motivates me to come to work every day and to make my contribution.

Dr Barbara Hierweck
GMP and Compliance
Production Manager, Vienna, Austria

Watch Barbara's video:
annualreport.octapharma.com

Around-the-clock production of virus-inactivated pooled plasma

The manufacture of octaplasLG®, our virus inactivated and prion-reduced pooled plasma, is a 24-hour process; production has to be done within a day to preserve the plasma proteins.

Top Each frozen bag of octaplasLG® has a unique identity and is scanned individually during final packaging.

Bottom Discussing a chromatography column with a colleague.

I joined Octapharma in 2012 as a process operator, later becoming first operator on the night shift, which developed into my current role as process specialist. My main responsibilities are to make sure that the processes are running, that the equipment is working and, ultimately, that the product is made.

The most important steps in the production of octaplasLG® are the pooling and the virus inactivation. We pool 600–1,500 individual plasma donations in an 800-litre stainless steel vessel. From that, we produce an average of 3,600 bags of octaplasLG®, which is 780kg of plasma. Pooling plasma gives us a standardised product. Pooling levels out individual heterogeneity of single plasma donations and reduces the variability of plasma components, resulting in consistent product quality.

Here in Stockholm we produce octaplasLG®, which is named because of the use of affinity ligand gel (LG) chromatography in the prion-reduction step. There are 27 of us working on octaplasLG® production in Stockholm and we operate in three shifts – day, afternoon and night. Everyone who works on octaplasLG® production has an impact on producing that batch. We currently run four batches a week, which is planned to increase to five.

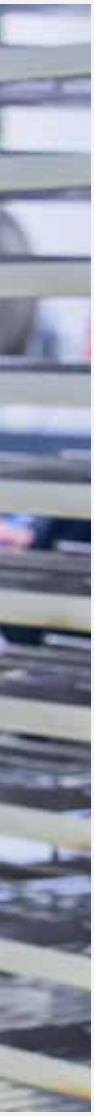
Working on the production of octaplasLG®, we get to see the whole process from start to finish. Our process involves the pooling of individual donations; filtration; virus inactivation; purification; prion reduction; sterile filtration and aseptic filling. Our job is to preserve the proteins: to do so, we regulate the temperature and pH (acidity level). Throughout the process, the ingredients are stirred continually to ensure a homogenous product. We do everything, from thawing the plasma, right through to the point when it is frozen and packaged as a final product, ready for patients.

OctaplasLG® is used during major operations and for major blood loss. There are also long-term patients who need regular plasma exchange. Without our plasma donors, we don't have any product, so the act of donation is one of the most important contributions for patients. Knowing that the raw material we use is from plasma donors makes me feel more motivated to take care of it, and find new ways of improving production efficiency.

We recently underwent a major change by switching from one large chromatography column to small, parallel columns. This is more efficient both for maintaining the columns and for the process operators. There was a lot of planning leading up to the scheduled annual summer shutdown. I helped out with the installation, running the tests, and assisting in the cleaning validation. The validation batches, the first three batches we made after the change, demonstrate that the new process fulfils the requirements and product specifications.

I like the variety of my job most. One day I can be assisting with packaging, the next day I might be packing a column and on another day I may be abroad, doing a factory acceptance test (FAT) for a new machine. It's a great mix between administrative and practical assignments. I enjoy finding new ways to improve efficiency using the principles of lean production. In my spare time, I am studying for a degree in technical engineering.

Ali Difoullous
Process Specialist – octaplasLG®,
Stockholm, Sweden



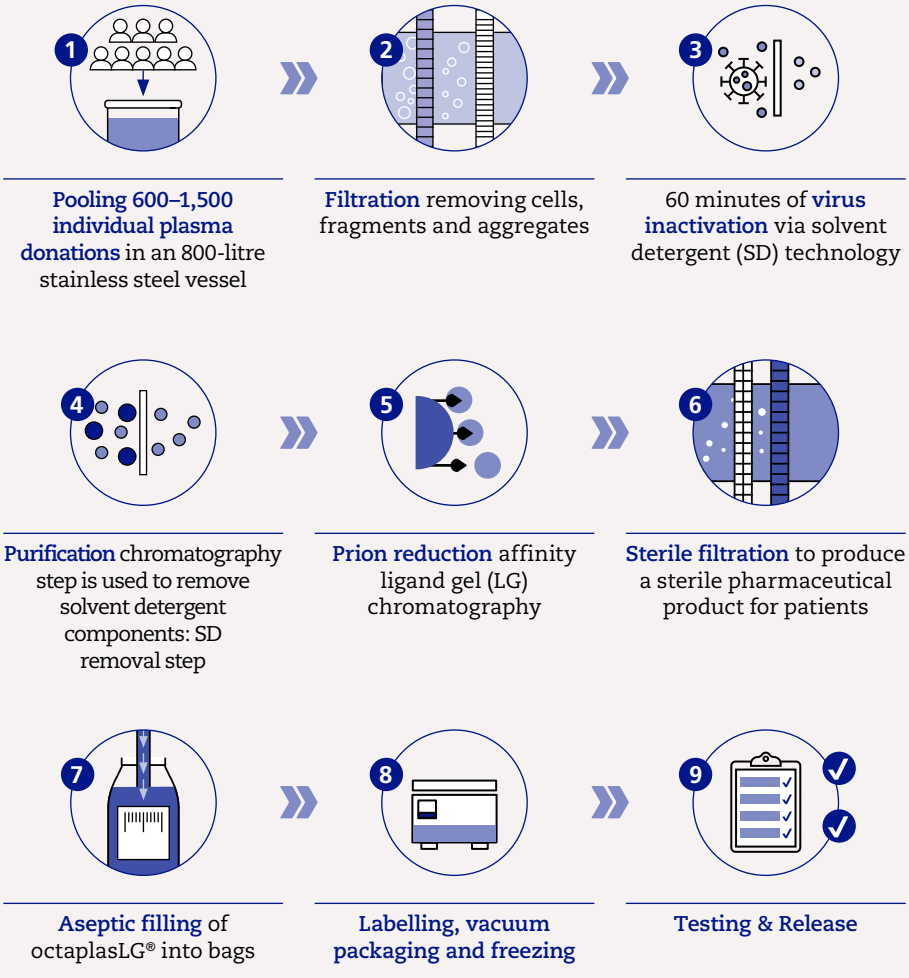
24 hours
to manufacture

600–1,500
single donations are pooled

60 minutes
of viral inactivation

3,600 bags
of plasma in a batch

The manufacture of octaplasLG®



Watch Ali's video:
annualreport.octapharma.com

Maintaining the cold chain

Ensuring refrigeration and optimal temperature control throughout the process.

Right Freeze drier cooling units.

Bottom Monitoring of freeze-drier cooling units.

I am responsible for the cold chain throughout production – from the raw materials to the storage of intermediates and finished products. My role is to ensure that all refrigeration equipment remains available and in optimal operating condition. As cold temperatures are ubiquitous in our manufacturing processes, I can be found almost everywhere around the manufacturing site. There is no place for errors in our industry and every day the equipment for which I have responsibility is under constant surveillance by recordings, alarms, preventive visits and predictive analyses. The control and mastery of temperature at all steps of the process is essential to ensure product quality.

We have a multitude of equipment which is often complex and increasingly regulated, especially in relation to environmental impact. All of our installations use the mechanical compression of a refrigerant gas, generally a hydrofluorocarbon (HFC), which produces cold by expansion or evaporation, similar to what happens when you agitate a spray can. The principle is basically the same as that used by the air conditioning of your car or your refrigerator at home, but due to the power and application needed, the installation quickly becomes akin to a gas plant.

There are many temperature requirements for the storage of plasma, cryoprecipitate, intermediates, finished products, as well as during the transformation phases themselves (centrifugation, fractionation, stirring, filtration, cryoprecipitate-freezing and lyophilisation). There are so called "cold groups" of small, medium and higher power for very diverse applications, from air conditioning offices to maintaining temperatures of storage rooms and freezers. For example, -5°C for the air conditioning of the production premises; -25°C for fractionation tanks; -65°C for lyophilisers; -70°C for the freezing of some finished products, and for the storage of cryoprecipitate. All temperatures are continuously monitored and recorded digitally. The temperature sensors are calibrated and checked according to a schedule established by the maintenance plans.

> The control and mastery of temperature at all steps of the process is essential to ensure product quality.

My role also involves following maintenance contracts in place on certain equipment, anticipating possible problems and settling them as quickly as possible so that there is no impact on maintaining the required cold chain. Such an interruption would in some cases have serious consequences for ongoing processes, intermediates or finished products in cold rooms. My typical daily activities are the control of the equipment, its operation, being able to observe a drift which can announce a future problem and follow-up of the suppliers as part of preventive maintenance. I also perform investigations during deviations to find the cause of malfunctions. The computerised maintenance management system

(CMMS) is a tool that allows us to ensure the operational and regulatory monitoring of equipment (breakdowns, curative maintenance, preventive maintenance, leak detection, hydraulic testing). We inform the CMMS with each intervention. The system constitutes the electronic logbook of each piece of equipment.

During a potential power outage, all the technical resources of the plant are mobilised to restart everything as soon as possible and check that the outage had no impact on work in progress. Fortunately, this is very rare.

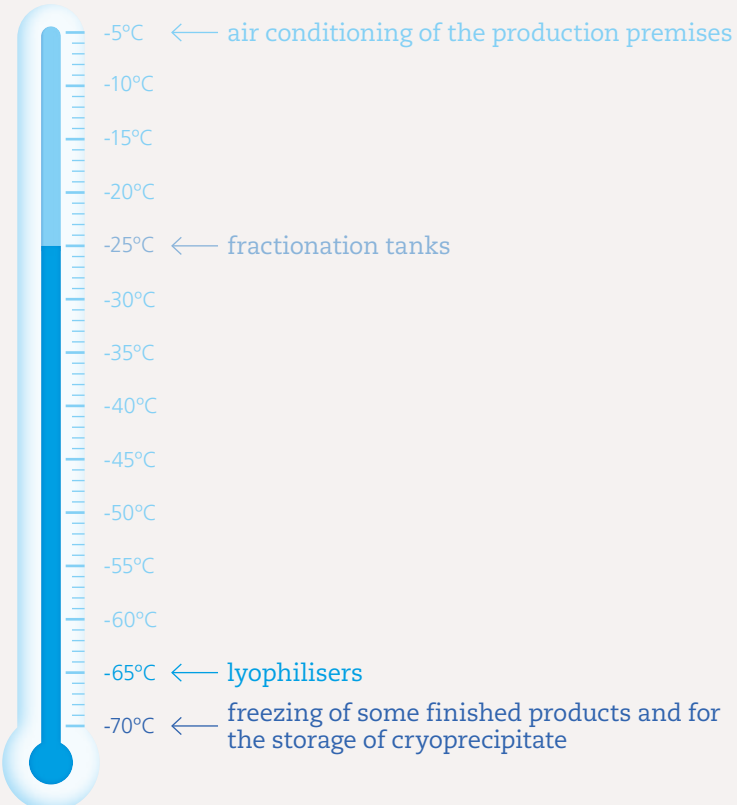
What fascinates me the most is the operation of the cold groups and the production of heat or cold by the change of state of the HFCs. I love to control the various parameters of an installation, to optimise them and thus be able to observe my impact on the efficiency of the installations. I also enjoy researching the cause of any deviations or the source of recurring problems.

I never miss an opportunity to laugh with my colleagues and friends. I like being active. I like sports in general, swimming, mountain biking, football and the outdoors.

Sébastien Fritsch
Maintenance Technician,
Facilities & Utilities, Lingolsheim, France

Watch Sébastien's video:
annualreport.octapharma.com

Temperature control



Separating plasma proteins

Fractionation is the separation of plasma proteins by influencing their solubility. By changing the ethanol concentration, pH-value and temperature, different proteins are separated at different settings.

Here in Springe we manufacture intermediate pastes: cryoprecipitate, and pastes I + II + III, paste II & paste V. The term intermediate refers to the fact that we do not manufacture the end product at this site (with the exception of paste V to albunorm®), but rather the intermediates which are further processed into finished products at other production sites.

We work 365 days a year, 24 hours around the clock. There are 100 fractionation employees in Springe, working in nine shift groups. The early shift starts at 6am, the late shift at 2pm, and the night shift at 10pm. There is no such thing as a typical working day. I start around 7.30am, the production team starts with our "pulse" meeting which department heads, foremen, and various process operators attend and discuss what happened during the night shift.

The material we are working with is very precious. If some part of the paste is contaminated, it can no longer be utilised and must be discarded. It doesn't matter in which part of the process you work, whether we are cleaning, paste-harvesting, producing or pooling, if something goes wrong somewhere it is always very expensive.

> "I most enjoy cooperation with other departments, exchanging information, collaborating on joint projects and validation activities."

We currently have three plasma poolings per day. A pool contains between 1,630kg and 1,770kg of plasma. On average that corresponds to 1,662 litres. We need between 2,000 and 6,000 individual donations for one pool (depending on the type of donation – source or recovered). In one day, we process approximately 5,250kg of plasma at our site, which equates to 6,000 to 18,000 single donations.

If our plasma donors didn't exist, we wouldn't be here. We, as the producer, must, of course, maintain a consistently high standard in the manufacture of intermediates in order to make the product safe for the patient.

Hygiene is imperative and we operate in a clean room class D environment. To access the production area, every employee has to pass through a personnel lock, a process which includes disinfection. Special clean room clothing must be worn.

We have a manufacturing protocol for each process, which documents everything, additions, extractions and the process itself. For example, the addition of filter aids, salts, or buffer solutions, whether added manually or automatically, are always noted in the manufacturing protocols. Here four-eye (that is to say, two people) inspections are always stipulated in the manufacturing protocols. Four-eye inspections are stipulated for the process steps that are immensely important, where absolutely no errors should happen, otherwise there will be losses or deviations.

I enjoy the variety of my work. There is not much of a routine because there's always something new going on. In my role, I prepare and review the manufacturing protocols, design and create standard operating procedures, train, guide, instruct and lead employees. There are times when there is a tight window, when something is changed, or a new project arises and you have to be able to react quickly, which is one of the things that I enjoy. In recent years, our automation standard has been increased a lot for the systems. What used to be done manually has now been partially or largely automated to increase efficiency. "Program 2019" aims to double production capacity while significantly increasing the overall efficiency of

manufacturing operations. In recent years, we increased capacity from 1.2 to 1.8 million litres of plasma. This will further double to 3.5 million litres once our new fractionation department (Annexe B) is finished.

It is always nice to deal with other employees. I most enjoy cooperation with other departments, exchanging information, collaborating on joint projects and validation activities.

We also work a lot with operations support and the technical department, mainly about maintenance, repairs and scheduling when work can be performed on which systems. If there are any problems with the systems or the cleaning systems (malfunctions, pump failures etc.), the schedules have to be set accordingly with the technical department so that there is as little delay in the production process as possible.

Patients rely on us to ensure that what they receive is of consistently high quality. I enjoy being a part of improving the lives of seriously ill patients. People who get our products are very sick and if you can help them somehow, it's a nice feeling.

Knuth Litke
Fractionation Manager, Springe, Germany

Far left In-process control: pH measurement.

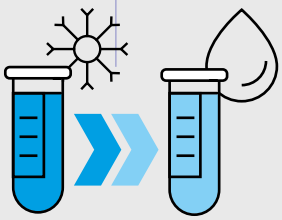
Left Pooling process – cutting of plasma bags.

Watch Knuth's video:
annualreport.octapharma.com

Biochemical processes to separate plasma

Fractionation is the separation of plasma proteins by influencing their solubility. By changing the ethanol concentration, pH-value and temperature, different proteins are separated at different settings.

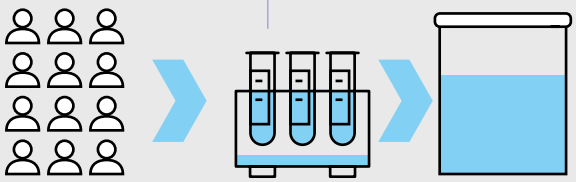
1



Thawing

The plasma is deep-frozen at -25° to -30°C. The cool rooms are warmed slowly up to -5°C to thaw the plasma. The plasma remains in the cool room for about 16 hours, then it is driven to pooling.

2



Pooling

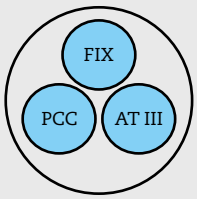
There are three poolings per day.

A pool contains between 1,630kg and 1,770kg of plasma. On average, that corresponds to 1,662 litres.

Between 2,000 and 6,000 individual donations (depending on if the plasma was donated via plasmapheresis or as a whole blood donation) are needed for one pool.

In one day, approximately 5,250kg of plasma are processed, which equates to 6,000–18,000 single donations.

Mass capture after pooling

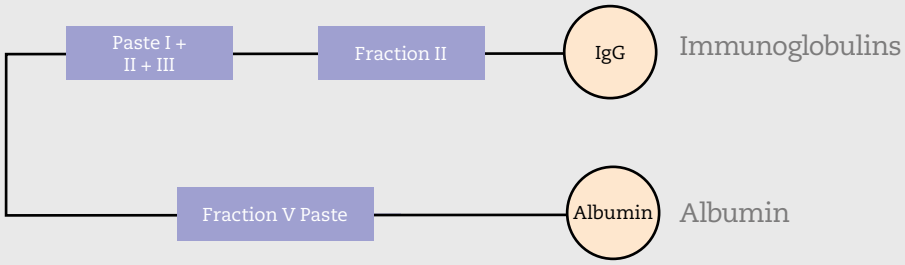


Factor IX

Prothrombin Complex Concentrate

Antithrombin III

Precipitation



Precipitation
Fractionation makes use of the fact that proteins precipitate depending on temperature and alcohol concentrations. During precipitation I+II+III, different additives are added – Acetate buffer to adjust the pH value and ethanol to precipitate the Paste I + II + III. Then this solution is filtered to separate Paste I + II + III, the gamma globulin paste.

As before, a supernatant is obtained and processed in the next production step – precipitation IV. The process is similar to precipitation I + II + III: a certain amount of ethanol is added and the temperature lowered to -7°C. The more progressive the process, the higher the ethanol concentration in the suspension, because a certain amount of ethanol is added time and again to precipitate different proteins. After precipitation IV, the paste is separated. This is paste IV, which is disposed of. And then we have another supernatant, our filtrate IV. Adding an Acetic acid /Ethanol mixture over 19 hours and lowering the temperature to -9°C, the pH value is adjusted again and that's the last product produced in the Springe fractionation department. That's where we get paste V, the albumin paste.

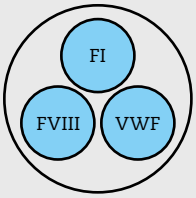
3a

4

Chromatography
The supernatant is pumped over the chromatography column to remove the factor XI and is subsequently transferred into a vessel for the next production step.

3b

Cryoprecipitate



Fibrinogen

Factor VIII

Von Willebrand Factor

Centrifugation
The first intermediate product, i.e. the cryoprecipitate, is created by cold precipitation. The cryoprecipitate is harvested from the centrifuge. It's a yellowish mass that has a pudding-like consistency. It is then shock-frozen with nitrogen at approximately -200°C. It is taken out of the nitrogen in the form of cubes of about 5cm. These cryo cubes are bagged in 15–20kg batches. The cryo is then poured into them, packaged, and put into crates, and then temporarily stored in our deep-freeze warehouse until delivery. The other pastes (I + II + III, II & V) are similar.

Getting the right material to production at the right time

The groundwork for production starts with us. It is our role to ensure that the production department gets the right material, of the right quality, in the right amount, at the right time.

Above Meeting with colleagues, agreeing on the allocation of tasks.

Left Stock control in the warehouse. Control of the actual balance according to OctaMES.

My main responsibilities include receiving the materials, storing them and commissioning them so that they are available to production when needed.

We have a daily recurring delivery for the fractionation department, which is our main recipient. They receive a specific amount of various materials every day without having to place a separate order each time. We prepare material throughout the day and the "tunnel transport", which runs in three shifts, 24/7, drives everything over to production at specified times – 4pm and 8pm.

When we get to work in the morning, around 7am, we have orders waiting in our email inbox. The foremen who are working the night shift process the orders. They might do the orders at 11pm, but we don't see the orders until the morning. If the ordered substance is needed by 2pm, we plan to drive it out to Production by then. We know about our orders a maximum of one day ahead of time, but it could also be as little as five minutes. We have one ongoing order delivered daily to fractionation, but it also happens that someone calls and says, "I urgently need X" because they need a replacement material quickly so that production can proceed.

We have approximately 400 different materials in storage. This includes raw materials, such as gloves, bottles, plugs, waste containers, cardboard boxes, bin liners, paper, office materials, tryptophane and octanoic acid (two important components for stabilising albumin). We handle additives needed for production, including salts, filter aids, filtering candles, filter beds and sampling containers. The material regularly needed by production includes filter aids, acetic acid, disodium phosphate, trisodium citrate, sodium chloride, sodium hydroxide, filter beds, filtering paper, filtering candles, clean room Polyethylene (PE) packs for rubbish and PE bags for packing the intermediates. Space is our biggest challenge. We have a high-bay shelf warehouse with 1,429 spaces for pallets. We use a very narrow aisle (VNA) forklift which is electronically secured so we can put things on the shelves and take them away without risking injury.

> I'm proud when evening time rolls around and all the work orders have been processed and the warehouse is clean.

In the morning, we get all the package deliveries that have to be processed (goods received or deliveries). We have to process what's there as quickly as possible and ensure it gets to the right department. We enter it into our manufacturing execution systems and deliver it, and that's how things continue the whole day, as new orders keep coming in. At the end of the day, the biggest order for the fractionation department has to be ready so that it can be driven over at 8pm.

I most enjoy driving the big industrial trucks, and the contact with colleagues, drivers and suppliers. I'm proud when evening time rolls around and all the work orders have been processed and the warehouse is clean and everything has been picked up. You are taught during your advanced training courses that our work has to be thorough because our medications are given to people who are quite ill. But when you see that there are people who are really getting on well and are in control of their life because of the medication, of course that makes you especially proud.

Klaus Kolewe
Storage Specialist, Springe, Germany

Watch Klaus's video:
annualreport.octapharma.com

Validating cleaning methods used for production equipment

As part of the international regulatory framework in which Octapharma operates, the Cleaning Validation department contributes to patient safety by validating the cleaning methods of all equipment in production.

I am proud to be part of the cleaning validation department which my colleague and I built from the ground up. I was the first member of the team, which was established as part of attaining the US Food and Drug Administration (FDA) licence. It's my "baby". As part of the international regulatory framework in which Octapharma operates, our department contributes to patient safety by validating the cleaning methods used for production equipment.

We ensure that the cleaning methods applied reduce the risk of cross contamination between production batches in line with the regulations. Our role is to demonstrate that the cleaning methods effectively reduce product residue from the equipment surfaces, e.g. from vessels, chromatography columns, filter presses and filling machines.

Two cleaning methods are applied: automatic cleaning (cleaning in place – CIP – for vessels, pipes, filling and washing machines for production equipment, etc.) and manual cleaning (for small parts used in the production process).

> We ensure that the cleaning methods applied reduce the risk of cross-contamination between production batches in line with the regulations.

Due to the substantial extension plans currently realised in Vienna, my main activity is the cleaning validation of new equipment. For example, the new pilot plant will have 24 new vessels (from 100 litres capacity up to 1,100 litres), two new washing machines and one new filter press. We must validate the cleaning methods of all of this equipment. I attend planning meetings and thus am able to evaluate any potential issues in terms of cleaning validation activities from the very beginning.

When new equipment is purchased, Octapharma performs factory acceptance tests (FATs) at the vendor's site to check the quality. For example, in the case of a new vessel, the FAT includes a spray pattern test during which the vessel's inner surface is investigated for spray shades. After installation of the tank at Octapharma, installation qualification and operation qualification tests are performed and the spray pattern test is repeated.

Prior to release to routine production, three surrogate runs are performed: the vessel is soiled with a surrogate solution and, after a drying period (i.e. dirty hold time), the CIP cycle is started. If a vessel is big enough, we climb into it and take swab samples from the inner surfaces to check for any product residue after each completed cleaning cycle.

Safety regulations prohibit entering vessels without colleagues in attendance (staff safety is our priority when anyone climbs into a vessel). Therefore, my colleagues and I perform the cleaning validation of such equipment together. The person climbing into the vessel wears a helmet and harness with a security belt. This is necessary because a large vessel is three or four metres high and can be slippery.

In the next validation step, the cleaned vessel has to be kept for a defined period in the status "cleaned" (i.e. clean hold time). After the period has passed, contact samples are drawn

from the inside of the vessel. The samples are sent to our colleagues in the microbiological laboratory to analyse for microbiological growth.

Due to the complexity of the cleaning validation process, the validation of equipment can take up to 30 days.

After this qualification, the vessel is ready to be used in routine production. Nonetheless, additional cleaning validation runs are performed after use of the vessel with each product by taking swab samples again, since each product matrix has individual characteristics that might potentially affect cleaning. For each cleaning validation acceptance criteria, such as visually clean and no detectable product residues, are defined upfront. In case a cleaning validation is not successful the root cause for failure is investigated. After implementation of corrective and preventive measures, the procedure for cleaning validation is repeated.

There is no education offered by any type of school to train you in cleaning validation. The only chance to acquire knowledge is to learn by doing it. The longer you stay in this job, the more you will see, learn and enhance your experience. This all helps to solve cleaning validation issues if equipment, for example, does not get thoroughly cleaned by the applied cleaning procedures.

I enjoy my job in the cleaning validation department because I am in contact with different departments – production, engineering, QC etc. – as well as with my colleagues at other Octapharma production sites, with whom I share knowledge and find solutions. My work is varied and interesting, I really never have the same work every day. Every day is different to the day before.

Werner Swoboda
Cleaning Validation, Vienna, Austria

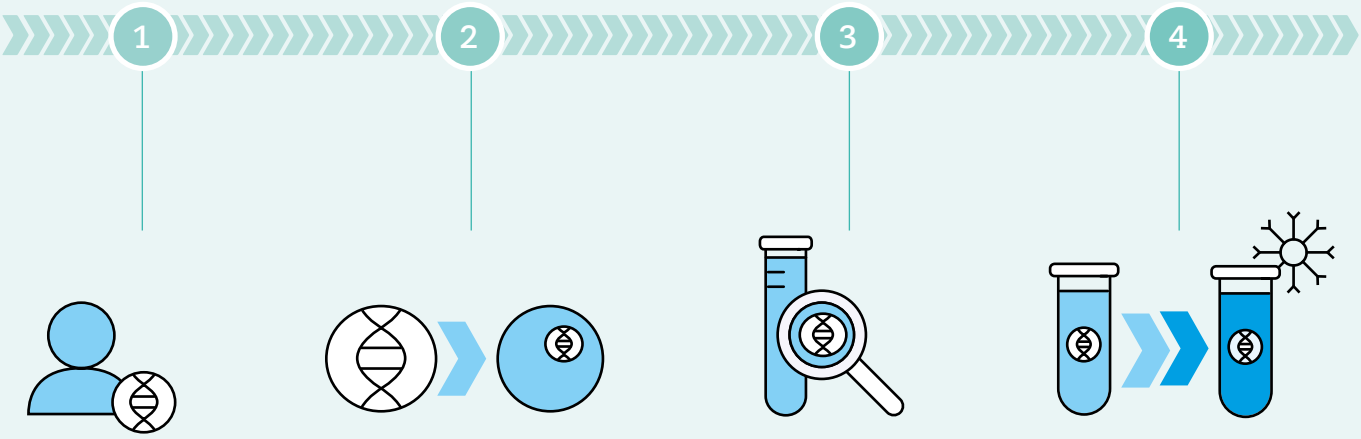
Far left Validation of the cleaning process of production tanks using spray patterns and UV light.

Left Performing a Micro Bicinchoninic Acid (BCA) assay in the Operations Support laboratory.

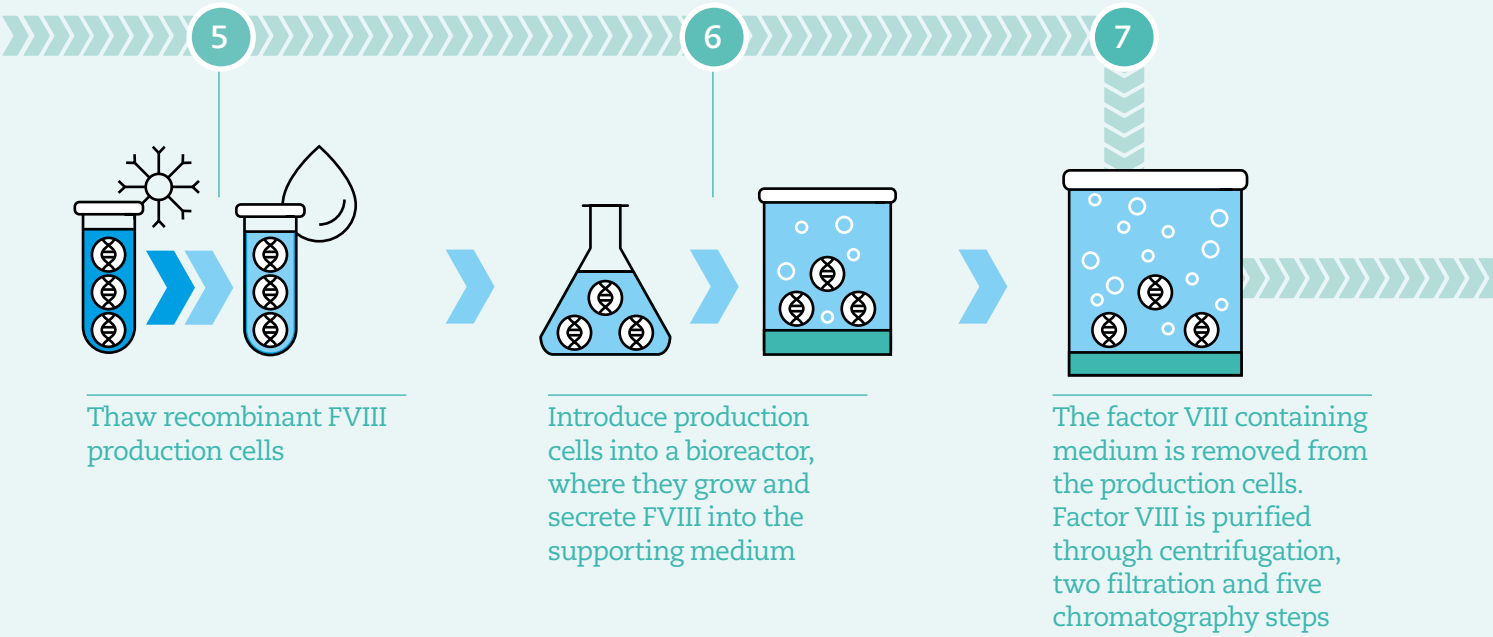
Watch Werner's video:
annualreport.octapharma.com

Inserting the gene to produce FVIII

Initial steps using recombinant DNA technology to create Nuwiq® production cells



Ongoing steps to produce Nuwiq®



Introduction

With plasma-derived products, the desired protein, e.g. factor VIII (FVIII), is separated from other human plasma proteins by fractionation. In recombinant production, however, Octapharma produces FVIII by inserting the gene which produces FVIII into a human cell line and cultivating the cells. While the purification steps are similar, it is the cultivation steps and the technology behind the production of FVIII in a human cell line that really differentiates recombinant products from plasma-derived products. Our recombinant FVIII (rhFVIII) protein product is called Nuwiq®. From the thawing of a working cell bank to a final drug substance batch ready for filling and freeze-drying, Nuwiq® takes about eight weeks to produce.

Cell cultivation (seven weeks)

During cultivation, the recombinant FVIII cells are continuously supplied with nutrients (sugar, oxygen, salts, etc.) for growing and producing FVIII. Bioreactors (an apparatus in which a chemical process is carried out involving biochemically active substances) are used for inoculation and expansion of cells and the production of the FVIII protein. The cells are grown in progressively larger bioreactors, beginning with a 20-litre reactor. All bioreactors are operated in conjunction with systems which control the cultivation parameters, such as temperature, pH, dissolved oxygen and carbon dioxide. All steps in the cell cultivation process are performed in sterile conditions to avoid contamination.

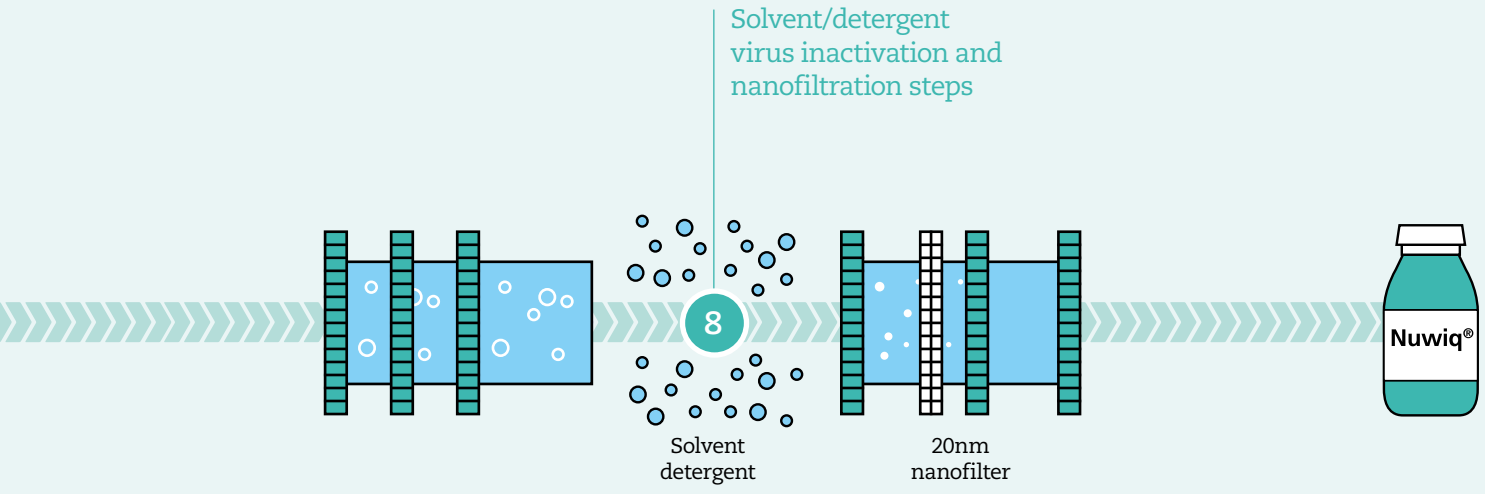
Firstly, the cells are stored in a nitrogen freezer, in 1ml vials as a "working cell bank". When the cells are thawed, they then have to be expanded in incremental steps. This is done in shaker flasks which are incubated in shaker incubators. The medium exchange and expansion is done manually and occurs every second and third day. It is important to keep the cells in their exponential growth phase during expansion, and the volume must be increased in proportion to the cell density. When a sufficient quantity of cells is reached, they can be transferred from the shaker flasks to the bioreactors.

The transfer from the shaker flasks to the bioreactors is done aseptically by connecting a sterile flask of concentrated cell suspension to the small inoculation 20-litre bioreactor. It takes approximately four weeks from the thawing and expansion in shaker flasks to inoculation and expansion in the 20-litre bioreactor. In this bioreactor, the cells are grown to inoculate the next bioreactor, of 100 litres capacity. The cells are cultivated in this larger bioreactor until they have reached a sufficient quantity to inoculate the 500-litre production bioreactor. This takes approximately a week.

The 500-litre bioreactor is the production bioreactor, in which the FVIII is produced. Production of one 500-litre batch takes two weeks. The cells are then harvested and transferred to continue with purification of the FVIII protein.

Purification (one week)

Purification removes unwanted proteins, cell residuals, DNA and potential viruses. This is done by several filtration and chromatography steps which give a solution of pure and concentrated FVIII protein.



Cultivating Factor VIII from a human cell line

We receive batches of cultivated recombinant Factor VIII (rhFVIII) cells and our objective is to obtain the purified FVIII which has been produced inside the cells.

Top Working on inventory raw material with OctaMES.

Bottom In discussion with colleagues in front of the bioreactor equipment.

Purification removes unwanted proteins, cell residuals, DNA and potential viruses. This is done by several filtration and chromatography steps which give a solution of pure and concentrated FVIII protein.

We first extract the FVIII from the cells and then remove all the cells by centrifugation and filtration. The FVIII is concentrated and purified by five different chromatography steps and two pathogen clearance steps, including virus inactivation by solvent detergent (SD) chemicals and DNA removal by nano-filtration, before formulation and polishing.

When we receive batches from cultivation, several steps have to be done by the purification group simultaneously. Luckily, our team helps one another and our great mix of competencies is used to approach all challenges. I have 30 years of experience working in pharmaceutical production but had, until 2014, only been working in "the last steps" of production. When packaging and visual inspection was moved to Germany in 2014, I joined biopharmaceutical production. I saw it as a great opportunity and challenge to move into recombinant production. It was especially interesting for me to learn about this new and innovative technology with a human cell line. While I do not have any academic background within biotechnology, luckily I work in a team which has a lot of this knowledge and experience. It feels great to work in an environment where everyone works together and contributes with their individual strengths.

> There are new projects in the pipeline, and I look forward to learning new things. I enjoy being involved in an area that is always developing.

I arrive at work at 7am every weekday. I usually start my day by checking and calibrating all the instruments and equipment. Then I have to prepare different buffers, e.g. a buffer which we run through all the equipment to clean it, and a salt-buffer used to release cells from aggregation.

Recombinant production is a delicate and sensitive process. The cells must be carefully handled to avoid contamination and having to reject the batch. The cells are very sensitive to changes in temperature and pH and these parameters have to be monitored carefully. Recombinant production, compared with plasma fractionation, is on a much smaller scale, as we handle, at most, some hundreds of litres, whereas in fractionation they are working with several tons of plasma per day.

The process steps of purification are always the same since they are executed according to regulated and pre-defined standard operating procedures. It is rewarding when, time after time, we produce a product that fulfils all specifications and is approved.

I believe that Octapharma is a company that considers the long term aspects and puts the patients in focus. There are new projects in the pipeline, and I look forward to learning new things and I enjoy being involved in an area that is always developing. I am here to make sure patients receive quality-controlled products that really help them in everyday life.

Mei Chuan Chiang
Biopharmaceutical Production – Process Technician (Bio100 line 1 – Nuwiq®), Stockholm, Sweden

Watch Mei's video:
annualreport.octapharma.com

8
weeks to produce Nuwiq®

30.5m
international units of Nuwiq® donated to 16 developing countries

Purifying products during the night shift

In fine fractionation, we take the intermediates we receive from basic fractionation and purify them into final products.

I start work at 9.30pm and when I finish at 6.25am I go home and have breakfast with my children, drive them to school and, after sleeping, I pick them up.

When we start our shift, the evening shift explain everything that's happened so we are up to speed. As first operator, I am responsible for the schedule, so everyone on the shift knows which product they will be working on that night. On the night shift we spread out the competencies so that we are all flexible and can potentially work on any one of the products we produce, namely – octanate®, octagam® and gammanorm®.

In fine fractionation, we take the intermediates we receive from basic fractionation and purify them into final products. Cryoprecipitate is the intermediate which we use to produce octanate®, and fraction II is the intermediate which we use to produce octagam® and gammanorm®.

First we take our intermediates and put them in a solution of either water or water/ethanol, depending on the product. The separation of the proteins begins in the next steps with chromatography.

The process continues with pH-adjustments and cleaning processes. We wash the product, with either water or salt solutions. We have steps in the process, called filtration, where we use different kinds of filters depending on the size of the molecule we wish to capture. When we are approaching the end of the process, we have a step called ultrafiltration which is a variety of membrane filtration in which forces like pressure or concentration gradients lead to a separation through a semi-permeable membrane.

Virus inactivation is one of the most critical stages of our process. The plasma is tested for viruses throughout the process, from the point of donation through to the finished products. Even if there would theoretically be any viruses, they would be deactivated at the solvent detergent (SD) step during purification. During this critical step, the temperature and stirring speed are tightly controlled and monitored. The solution is stirred using a propeller-driven motor. The tank has a set temperature point which is the ideal temperature for both the desired product and the solvent detergent chemical. In the case of octanate®, we stir the mixture for eight hours and ten minutes at 25–26°C. The control system registers all the temperatures and confirms that the solution has been stirred for the correct amount of time. We also manually look in the tank every hour to check that it is still stirring. We print out a graph showing the temperature line confirming that the solution has remained within the prescribed temperature range.

> Working the night shift suits me well because I get to be with my children longer than most other people.

We always have an end filtration into a sterile vessel that we deliver to the pharmaceutical department for filling, and in the case of octanate®, freeze-drying.

In general, the fine fractionation steps for all products are similar. However, there are differences. In the case of octagam®, for example, we have two viral inactivation steps and a phase of sedimentation, during which the product must lie still for 24 hours. And in the case of octagam®, instead of washing the product three times as with octanate®, it is washed once, during which the bigger particles are captured.

Every step of Octapharma's production process is interdependent. Without our donors, we wouldn't have plasma. Without basic fractionation, we wouldn't have intermediates. Without product documentation, we can't ensure and prove to the authorities that our work is done the correct way. Without the pharmaceutical department, we can't prepare the products to be ready for patients.

Some years ago, we had a Christmas party and there was a speaker who said we should be proud because when someone asks what we do, we can say we save lives every day. That was a turning point for me. What we do is much more than just work. We take pride in what we do because we know it has an impact on people's lives. You have to be at your best all the time, because that's what we promised the regulatory authorities and, of course, our patients. It's very easy to go to work when you know you are helping people to have the life that most of us take for granted.

I love spending time with my family. Every third week I have a free week and that's when I work on our house, which is right beside a forest and a lake in the countryside. It was built in 1800 – our aim is to return it to its former glory and give the house its soul back.

Thomas Linfors
Process Operator, Fine Fractionation – night shift, Stockholm, Sweden

Top Writing on the pulse board for the pulse meeting before the next shift arrives.

Bottom Talking with a colleague about the gammanorm® column (right).

Watch Thomas's video:
annualreport.octapharma.com

Removal and inactivation of contaminants and pathogens

Purification processes to filter out contaminants and pathogens
Precipitation
Ultra/diafiltration
Chromatography

Virus removal/inactivation
Solvent detergent is added to destroy viruses
Nanofiltration to filter out viruses

Investing to increase capacity and automation

Octapharma is investing in new state-of-the-art filling lines for our production sites. The aim is that fully automated lines will increase filling capacity, which ultimately means we can produce more products for patients.

Top Executing the Project Pulse meeting reporting safety/environment, delivery, resources and quality.

Bottom Using intervention gloves to access the isolator to assemble the filling set at the new LVP filling line.

In Stockholm, the new large volume parenterals (LVP) line will be used for our liquid products: octagam®, gammanorm® and albunorm®. The new small volume parenterals (SVP) line is already in operation with octanate® and Nuwiq®, which are freeze-dried products.

The significance of the new LVP installation for patients is that, being a fully automated line with an isolator, it eliminates human contact from the filling process. With the new line, our liquid products will be filled in different-sized vials within the isolator, before the machine stoppers the vials and capsules them. After that, the vials will be taken out of the isolator to resume their journey in the whole process.

When we talk of "the LVP line", we are actually referring to many specialised, precision machines, from the vial washing machine to the isolator, combined together. This line was designed specifically for us and tailor-made to our requirements. I am proud that I was involved in the factory acceptance test (FAT) of the new machine at the vendor's facilities – I learned a lot during that time. The experience allowed me to evolve into my current role as sub project manager for the site acceptance test (SAT). We installed the new line in the first quarter of 2017. This required one part of the building to be shut down in order to rebuild the area. Now that the LVP filling line has been delivered and installed, we are at the site acceptance phase. This stage is to determine that the new machines work according to our user requirement specifications (URS).

> The new installation is a fully automated line with an isolator which eliminates human contact from the filling process.

The SAT is performed with experts from the manufacturer and our LVP line operators. We perform a large series of tests, to see that the installation performs to our expectations. We run different test formats every day on the different

stations of the line, from vial washing to the printing of the ink jet number. They include checking that the machine is putting the stoppers on the vials correctly, which assures vial integrity. This is important because if the stopper is not put on correctly, one cannot cap the vial. After the SAT has been successfully completed, the next steps are the installation qualification (IQ) and the operational qualification (OQ). We aim to hand over the equipment to production in 2019, when the plan is to operate 24 hours per day, seven days per week.

The new filling lines represent a significant investment of time and money. One cannot order such complex machines from a catalogue, and it takes many months of detailed tests and calibrations before one can manufacture our products to the desired quality. Every little detail is vital and important.

I started with Octapharma in 2012, as an operator in the pharmaceutical department of our Stockholm site, and became responsible for writing standard operating procedures (SOPs) for production processes. Today, as an inter-site team member, I work closely with other Octapharma production sites, building relationships and sharing experiences with colleagues. Our shared goal is to have standardised procedures. The corporate filling lines and freeze driers (FLFD) project installed similar filling lines in Stockholm and Springe. My role now is to standardise the working routines and create SOPs in the local languages, with the aim to have the same routines at both sites. An SOP is like a recipe: if you follow its instructions, you should always get the same result. It is rewarding to work with the other sites to develop standardised procedures. Our efforts will also have a positive impact on future installations at other sites.

I love working in the pharmaceutical industry because I learn new things every day and our daily work is for patients who really need our products. You maybe don't think you have achieved something significant in one day but, actually, a small thing can have a big impact. When I think of our patients, I want to give them the best. You know that the work you do is helping people in need.

Sara Mahzoon
Inter-site Team Member,
Stockholm, Sweden

Watch Sara's video:
annualreport.octapharma.com

Preserving human proteins by freeze-drying

The small volume parenterals (SVP) department is mainly responsible for our lyophilised (freeze-dried) products: fibryga®, octanate®, octanine®F, octaplex® and wilate®.

Above Discussing the monitoring framework conditions (MFC) system.

Right Operators preparing the vial washing machine for the filling process.

Freeze-drying is a preservation process in which heat-sensitive substances are rapidly frozen before being dried in a vacuum.

The products we work with are finished, formulated products. During filling and freeze-drying, the product is always open and this, of course, presents a certain risk of contamination, which must be avoided. A human being is the greatest risk factor when making sterile products. We receive the product from the purification department.

Clean rooms

Our work is very complex. Everyone has to work extremely precisely and be constantly alert. The fewer direct human interventions, the lower the risk of contamination. We work with a lot of machines and different processes in 15 rooms with different levels of clean room classification. A clean room is a controlled environment with a specified maximum number of particles per cubic metre at a specified particle size, which is measured by a particle counter. We operate in class D, C, AB and A. When moving between the different levels of clean room, you must have a complete change of clothes, including overalls, mouth protection, glasses, gloves and protective overshoes. Such rules are set by the regulatory authorities, and our staff members are thoroughly trained in the necessary procedures. We use personnel monitoring which means that every operator has to make a copy of his or her gloveprints and also from different places on their sterile overalls. This monitoring allows us to confirm that an operator has not contaminated his or her work.

Filling

Our monitoring framework conditions (MFC) system is used to monitor the whole of the filling process. There are four main parameters: air velocity, differential pressure or room pressure, temperature and humidity. If any of these parameters are exceeded, an alarm is sounded. When this occurs, our work is halted, filling is stopped and we have to investigate and report on what has happened. It could be that there has been a drop in pressure or that the room temperature is too high.

Freeze-drying/lyophilisation

One of my main tasks is preparing the freeze-drying machines, or lyophilisers ("lyos", for short), for production. We use automated processes ("chains") to clean the lyophilisers, including "sterilisation in place" and we perform various filter tests, leakage tests and endurance tests before using the lyos in production.

We have six lyos at our Vienna manufacturing site, four of which are completely automated. The automated machines are able to load and unload the freeze dryer in what we call an isolator, a closed system. The isolator is a sealed clean-room system, independent of the environment and free of any human influence.

Loading temperature is important. We load at 20°C, but there are products, such as wilate®, that we load at lower temperatures. In this latter case, the equipment's loading shelf is pre-cooled to match the specified loading temperature.

> Our patients count on us. Everything has to be absolutely right, from start to finish.

Freeze-drying stabilises and preserves the product's proteins. The product begins in liquid form, and is then frozen, causing crystals to form. Next, the product is dried in a vacuum before the temperature is increased. The product of the freeze-drying process is a white powder we informally refer to as "lyo cakes".

At the end of the freeze-drying process, the product bottles are sealed, but the risk of contamination remains for as long as the bottle doesn't have a bottle cap. That's why we carry out vacuum checks to ensure all vials are vacuum sealed.

Once the product has been freeze-dried, it is unloaded with robots, i.e. fully automatically, without any human intervention. The injection number and the lead number are printed which means that each product and batch can be easily identified. With wilate®, for example, we have to test every bottle for residual moisture and vacuum. After a period of up to 14 days, we carry out the 100°C terminal dry heat step, which inactivates enveloped and non-enveloped viruses.

We work a four-shift model – four days working from 6am to 6pm, followed by four days off. Then we work the night shift from 6pm to 6am, again followed by four days off. When you are working with machines and computers, technical problems can and do happen, which can be frustrating. On the other hand, everyone is pleased when we have freeze-dried our products, taking them one step closer to patients.

I'm happy to be a member of this big family that is Octapharma. I've been here for 21 years and I've watched how we have grown. I'm proud of our company and of the fact that we produce more products every day and bring new products to market to help more patients. My colleagues and I are life savers. We make absolutely certain that we work in accordance with all standards, in a clean environment, and that we follow all regulations. Our patients count on us for these vital medicines. Everything has to be absolutely right, from start to finish.

Zoran Mitric
Shift Supervisor – Small Volume Parenterals (SVP), Vienna, Austria

Inspecting finished products with intense concentration

We are one of the last steps before our products are delivered to our customers. Therefore, it is of great importance that the bottles are carefully inspected and that the labelling and packaging is done accurately.

Top Technician, operator and shift leader discussing the next packaging steps.

Bottom Semi-automatic visual inspection using a magnifying glass.

We should always keep in mind that the products that we inspect and pack will reach our patients. Our products are injected intravenously, which means that foreign substances in the product could be harmful. During visual inspection (VI), we scrutinise our products. We check the vials to determine if there are any deviations. The responsibility for our patients' health is in our hands.

Visual inspection requires a lot of concentration, which I define as the conscious increase of attention on to a certain thing. I focus my concentration specifically on my task. What is important to me is that the concentration is connected with a certain motivation and interest in the product. This is a vital product, and of course, I always keep in mind our patients.

In the first VI cabin you look for defects, in the second cabin you look for turbidity or opaqueness. The sequence is always 1) defects and 2) turbidity, it is never in the reverse order because if you look at the turbidity first, the magnifying glass makes your eyes tired. The inspectors change after 15 minutes so that their eyes can recover. We have at least a 15 minute period to rest our eyes, during which we do other activities that are not that strenuous for the eyes.

When I check each bottle, I look at the individual points that I have to check in a particular sequence. You can briefly stop the line if you think you see something, which makes the bottle turn and the product swirl within it. Liquid products are checked for turbidity and foreign particles, as well as a missing inkjet number, while freeze-dried products are examined for colour differences, as well as missing vacuum, faulty stoppers, defects in the glass, etc. If we find an error, the quality in operations department is informed.

> We scrutinise each bottle looking for deviations. The responsibility for our patients' health is in our hands.

It takes almost a whole shift to visually inspect a big batch of 15–16,000 bottles. In one minute, we can inspect 48 50ml bottles. If the batches are smaller, we can complete two or even three batches a day. Our biggest challenge is not to complete as many orders as possible in one day, but to be completely accurate and thorough in the execution of our orders. It doesn't matter how great the stress is, we must never lose concentration and accuracy. The most important thing we always have to keep in mind is the fact that we are solely responsible for our actions and our way of working.

When I hear some of our patient stories, on the one hand I am very sad and sympathetic to the patients. On the other hand, I am happy that we make products that help patients by giving them the opportunity to lead a better life. Our products save the lives of many people.

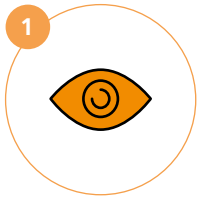
48 bottles
inspected in 60 seconds

15–16,000
bottles inspected in one shift

Teamwork plays a major role in packaging, and that togetherness makes our work easier and has a positive effect on our success. What I like about my work is that we are always confronted with challenges. I am curious, and although I have been working in this company since 2002, I am still learning every day. That is the most beautiful thing, to always be curious. I am proud that I can be part of Octapharma. It is a wonderful feeling to come to work every day knowing that I'm doing something good again. I feel the greatest joy. I love my work.

Roza Kirovakov
Visual Inspection and Packaging Operator, Vienna, Austria

The finished product is inspected and approved based on authority requirements



Visual inspection
Inspection of product for defects and turbidity.

Packaging
Product packed into boxes and stored in cold rooms or freezers at required temperatures.

Bringing new optimal therapies to patients in need

The purpose of clinical R&D (CRD) is to prove, through clinical studies, that our products are efficacious and have a favourable safety profile in the treatment of certain diseases. I have been involved in clinical trials with octanate®, wilate®, Nuwiq® and fibryga®.

We build a bridge between pre-clinical R&D, during which products are developed and characterised, and bringing new optimal therapies to patients in need. I joined the Moscow office of Octapharma in 2010 as Clinical Research Associate, monitoring clinical studies with octanate® and Nuwiq®. In 2012, I moved to Octapharma's headquarters in Switzerland.

Rare diseases

As Octapharma develops many products for rare diseases, we keep in close contact with the clinical trial sites specialised in the treatment of these diseases. We are updated on everything that happens to each patient within the study. The size of the studies and the close interaction with the study sites (investigators, nurses, study coordinators) ensures fruitful, long-term cooperation. It also creates a vault of information for identifying patients for future studies, while providing early insights into the clinical efficacy and safety profile of the drug under development.

It can be challenging to secure timely patient enrolment due to specific limitations inherent to rare therapeutic areas, such as the low overall number of patients, competitive recruitment and geographic distribution of patients. On the other hand, working in rare diseases provides us with the opportunity to bring life-saving therapies to patients for whom there are limited diagnostics and therapeutic options locally.

Study planning

In the study planning phase, as clinical trial manager, I work with various stakeholders, including alignment with the international business unit (IBU) and the international drug regulatory affairs (IDRA) team, which is ensured by core project team (CPT) meetings. I have very close alignment with my management in terms of strategic content and scientific expertise in the study concept. We also discuss the study design with the investigators. My responsibilities during the study planning phase include preparation of the study protocol with feedback loops internally within the CRD and corporate drug safety unit (CDSU); or externally with the principal investigator. Documents are prepared, including investigators' brochure; informed consent (IC) master version, as well as country-specific versions; and statistical analysis, monitoring, safety reporting and risk analysis planning documents.

Regulatory authorities and ethics committees

Once all the study documents are prepared, they are submitted to the ethics committees (EC) and regulatory authorities (RA) in each participating country. If the studies are not approved with the first submission, questions from the authorities must be addressed in a timely manner to avoid delaying the study.

Ethical principles related to the rights, safety and wellbeing of patients taking part in studies are built into our CRD activities. Clinical trials should be conducted in accordance with ethical principles that have their origin in the World Medical Association's Declaration of Helsinki, and that are consistent with good clinical practice (GCP) and the applicable regulatory requirements. Before the study is initiated, foreseeable risks and inconveniences should be weighed against the anticipated benefit for the individual trial subject and society. A trial should be initiated and continued only if the anticipated benefits justify the risks. The rights, safety and wellbeing of the patients taking part in the trial are the most important considerations and should prevail over the interests of science and society.

Investigational sites

Once a study is approved by the regulatory authorities and ethics committees, and the contract with the institutions is fully executed, investigational medicinal product (IMP) is shipped to the sites and the study initiation visit (SIV) is planned. This is a very important part of the study, during which the site's personnel are trained on GCP, the study design, study procedures, IMP handling procedures; administration of the IMP, the laboratory tests, completion of Sponsor's documentation; and discussion of monitoring visit frequency for performing source data verification (SDV). Throughout the study, regular monitoring visits are conducted at the site to ensure that the study is conducted according to GCP and local requirements.

Clinical study report

The study is clinically completed once the last patient has had the last visit within the study. With the data management team, we begin the "data cleaning" process. We review the data and any queries generated are sent to the site, where the investigator checks the data and provides the requested clarifications. Once the data is ready, the clinical study report is prepared with the medical writer.

Working on our new fibrinogen concentrate

I value being a part of the core project team for our fibrinogen concentrate, fibryga®, which allows for alignment and insights into different aspects of the product's life. It is rewarding to see the product I have been working on for five years now approved for clinical use in various countries. I am currently the clinical trial manager of two clinical studies with fibryga®: FORMA-04 and FORMA-05.

The FORMA-04 paediatric study in patients with congenital hypofibrinogenemia is a prospective, open-label, uncontrolled, phase III clinical study, with patients from birth to 11 years old. These patients bleed spontaneously or after trauma, which can become life-threatening if not treated. However bleeding is less frequent than in haemophilia patients. Clinical trials in children are challenging and filled with important ethical considerations. For this paediatric study, there is a clear benefit of providing therapy with a double-virus inactivated fibrinogen concentrate to the patients who present to the centre with bleeding. The challenge is to actually have the bleeding episode documented within the study. Sometimes, the 'waiting for the bleed' period is rather long; secondly, in the countries participating in the study, patients often live quite remotely from the hospitals which are the investigator sites in the study. Despite these challenges, the study has already recruited all but one patient and is most likely to be completed ahead of schedule.

FORMA-05 is a phase II study of pseudomyxoma peritonei (PMP) surgery. FORMA-05 aims to investigate the efficacy and safety of fibryga® and cryoprecipitate for fibrinogen supplementation during the course of surgical intervention. Despite the complex clinical setting, a smooth collaboration with the study team was established, and the study has shown satisfactory progress so far.

Every study has its own journey of interactions with internal and external peers, including clinical research organisations, central laboratories, data management groups, independent data monitoring committees, experts and consultants. Overall, the most enjoyable part of my job is working with the investigators, the study nurses and coordinators of our investigator sites. I love to hear that the patients participating in a study are satisfied, happy and perhaps would like to participate in another Octapharma study in the future.

Dr Irina Kruzhkova MD
Clinical Trial Manager,
Lachen, Switzerland

Donors, like my father, strengthen my body's defences

Simon is 11 and has been using gammanorm®, a subcutaneous immunoglobulin (SCIG), for 10 years. As a baby, Simon was diagnosed with a rare immune disease called Bruton's Agammaglobulinemia, which means that he has a complete lack of antibodies which are needed to defend his body against infection.

Left Simon has been playing classical guitar for four years.

Bottom Simon chooses what to watch while receiving his gammanorm® infusions.

Since Simon has been on immunoglobulin (IgG) replacement therapy, he has never had to go back to the hospital due to infection. His mother, Verena, says: "We do not take much for granted. I am grateful that Simon is still alive. If we had lived 100 years ago, he would not have reached his first birthday. And every time he celebrates another birthday, I am just grateful that he is still here."

Gammanorm® gives the family self-reliance and independence. Being able to treat Simon at home means that they can remain independent in terms of their timetable. They don't have to go to the hospital, they can administer the treatment at home and make it a part of their everyday lives. When the family go on holiday, they just take all the equipment with them.

Simon explains: "The subcutaneous treatment is not unusual for me. I've been doing it for 10 years now and it has one downside, which is that you have to sit for two hours. But it also has an advantage – I can watch movies and that's just great."

> I have already told some of my friends that I have a disease and that I need to take medication.

While he was getting his infusions as a little boy, Simon would look at picture books, and later his parents would read stories to him. Today, Simon occasionally does homework during the infusion, but often he chooses to watch a film on the family tablet. As the family don't have a television, this is a real treat for the children, and his sisters are sometimes envious because Simon gets to choose what to watch. The fact that the children are allowed to watch a film makes it a popular activity and something of a highlight. Sometimes his sisters will ask, "When will we do the infusion?"

Today, Simon's parents take turns to do his infusion. Simon is responsible for making the preparations. He gets the medicine from the fridge in advance, he gets out all the equipment – the pump, the syringes, and sanitary items. The spots for the infusions on his thighs are disinfected. The medicine is drawn up into the syringe and the needles are connected. Simon gets one infusion on his left thigh and one on his

Donors, like my father, strengthen my body's defences continued

right. His immunologist says that soon he should learn to do the infusions on his own, which will make the routine smoother when he reaches puberty. Simon's parents hope that he will be able to master his treatment as soon as possible. The infusion needs to become a matter of routine, like brushing his teeth.

"How you communicate to others always depends on how you communicate it to yourself," reflects Verena. "We are always trying really hard not to dramatise Simon's condition at all. You can talk about it quite factually, and at some point people start to open their eyes because they realise, 'Oh, that's pretty intense what they're telling me'. But the reaction would certainly be different if you were to dramatise it in a totally emotional way. We deliberately don't do that. We don't want Simon to be treated differently from other children. We just want him to grow up normally. And I think that's how his self-perception is. He doesn't see himself as sick." One of Verena's biggest concerns is that eventually there will be bacteria that are resistant to antibiotics, and if they spread that would be a huge threat to Simon. Another big concern she says, is "that one day there won't be enough medicine for whatever reason, whether political or economic. These are two worst case scenarios".

Zoran says, "It's important to us that people understand that Simon's disease is treatable and also how his medicine is produced. To produce his medication there is only one way: through blood plasma donations."

"I have already told some of my friends that I have a disease and that I need to take medication," explains Simon. "I always explain it like this: I always used to get sick and the doctors realised that my immune system was not functioning correctly and I have to have medicine infused once a week."

Simon makes stop-motion films (produced by taking many individual photographs of static characters that appear to move when the photographs are played back at high speed) of scenes built out of Lego blocks. At school, Simon likes English and music. He is very interested in electronics and technology and wants to learn more about it later and probably have a job in this field. Simon is very active, he plays football and basketball, competes in athletics and sprinting, and enjoys the trampoline. For the past four years he has been playing classical guitar, which he says calms him down when he is stressed. "I play guitar not just because I have to practice, but because I really enjoy it."

Simon
Berlin, Germany

Find out more about Simon's father, Zoran, on page 4.

Left The family at dinner. Left to right: Lisanna, Verena, Laura, Zoran and Simon.

Below Simon and his father Zoran enjoy playing football together.

Watch Simon and Zoran's story:
annualreport.octapharma.com

Diseases and therapies

Transforming patients' lives since 1983, Octapharma is dedicated to empowering more patients to go further in their life adventure.

Haematology

In people with bleeding disorders, the clotting process doesn't work properly. In haemophilia A, haemophilia B and von Willebrand disease (VWD) factor VIII, factor IX or von Willebrand factor (VWF) respectively are missing or don't work as they should.

This causes these patients to bleed for a longer time than those whose blood factor levels are normal. Most bleeding occurs internally, into the joints or muscles. Repeated bleeding without prompt treatment can damage the cartilage and the bone in a joint, leading to chronic arthritis and disability. Early on demand or prophylactic therapy that replaces the missing coagulation factor is able to effectively control or prevent acute bleeding in this group of patients.

Tadeo

Salta, Argentina

Tadeo has severe haemophilia A and wants to be a superhero. He loves to swim and play football with his father. His parents have peace of mind knowing that our product protects their son from bleeds.

Watch Tadeo's video:
annualreport.octapharma.com

Immunotherapy

People with immune deficiencies are prone to severe infections due to a lack of naturally occurring protective antibodies (immunoglobulins). These patients need replacement of the missing immunoglobulins in order to protect them against infections and ensure they can lead a normal life.

Conditions where the immune system is out of balance are generally referred to as immune-mediated diseases, of which auto-immune diseases are a well-known subgroup. Immunotherapy treats immune diseases and deficiencies by inducing, enhancing, or suppressing an immune response through immunomodulation or immunoglobulin replacement therapy.

Critical care

Patients in intensive care and emergency care often require immediate medical attention to prevent shock and quickly restore the body's natural balance – such as normal blood volume and clotting (coagulation) function.

Plasma and plasma derived products are used by emergency medicine physicians and paramedics around the world in life threatening and severe medical situations.

Ed Carlos

Diadema, Brazil

Ed Carlos is a Street Dance teacher who lost one of his lungs due to an undiagnosed immune deficiency. Since starting treatment with our product Ed Carlos sees himself as living as a true human.

Watch Ed Carlos's video:
annualreport.octapharma.com

Lisa

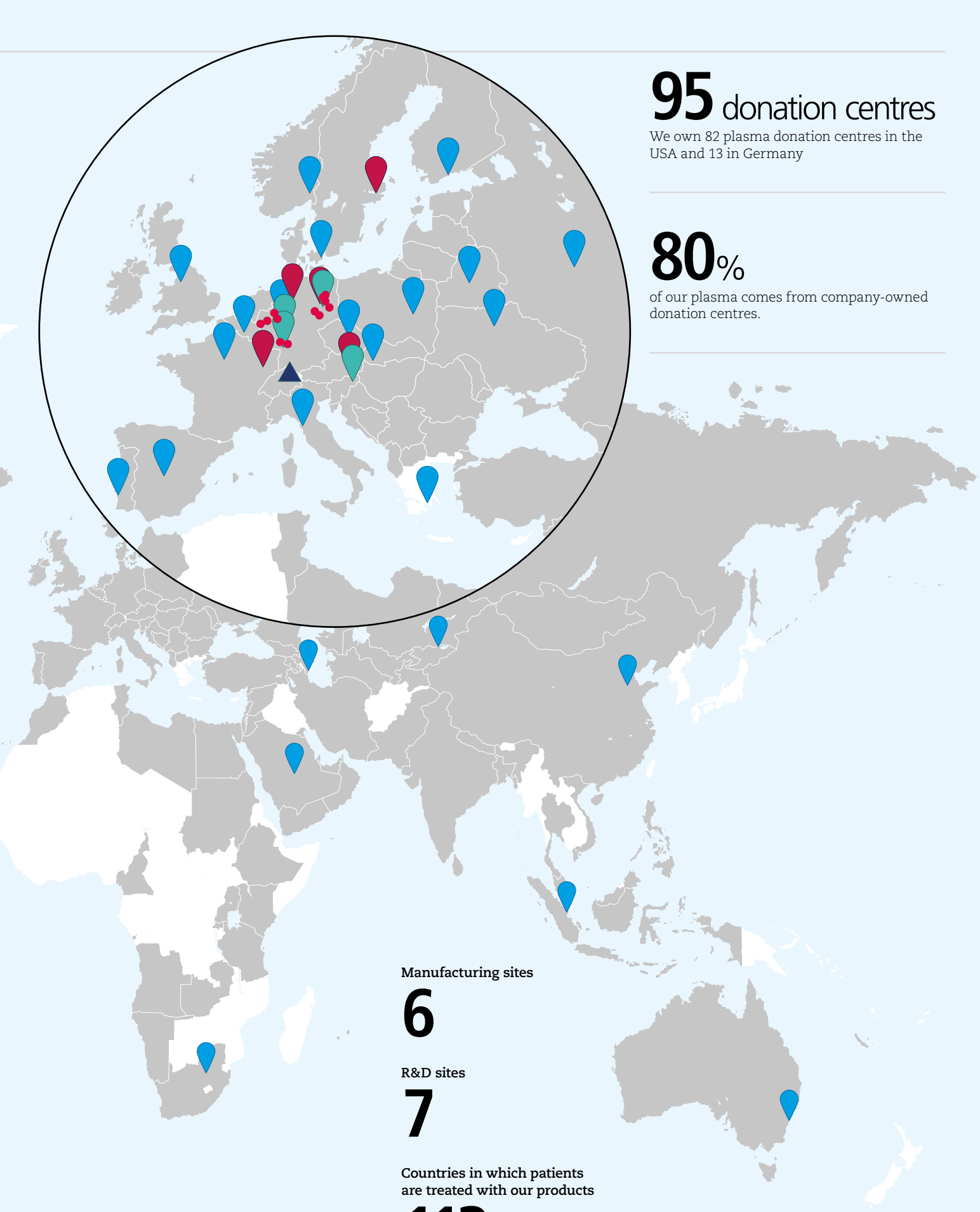
Mersea Island, UK

Lisa has an ultra-rare, life threatening blood disorder. She became ill very suddenly and was rushed to the hospital's critical care unit. Lisa was given plasma exchange with our product. She feels lucky to be alive.

Watch Lisa's video:
annualreport.octapharma.com

Transforming plasma into life-changing medicines

Patients and healthcare professionals in 113 countries rely on the expertise of our passionate employees. Our interconnected organisation masters the complex journey of plasma, starting with our donors, to develop and manufacture human protein products.



95 donation centres

We own 82 plasma donation centres in the USA and 13 in Germany

80%

of our plasma comes from company-owned donation centres.

Manufacturing sites

6

R&D sites

7

Countries in which patients are treated with our products

113

Board of Directors

Standing, left to right:

Flemming Nielsen
President,
Octapharma USA, Inc.

Norbert Müller
Board Member

Frederic Marguerre
Shareholders' Representative
President, Octapharma
Plasma Inc. USA

Wolfgang Marguerre
Chairman & CEO,
Octapharma Group

Tobias Marguerre
Managing Director,
Octapharma Nordic AB

Wolfgang Frenzel
Research and Development

Josef Weinberger
Corporate Quality and
Compliance Officer

Seated, left to right:

Olaf Walter
Board Member

Gerold Rempeters
Corporate Production Officer

Matt Riordan
Board Member

Roger Mächler
Chief Financial Officer

Our Board of Directors' decisions are guided by our five company values. **Ownership** means that we take responsibility and are fully accountable for our conduct. Our **Integrity** guides us to live by high ethical standards and care less about being right than about doing the right thing.

The cornerstones of great **Leadership** are always leading by example and striving to be the best at what we do. **Sustainability** reminds all of us to focus on the long term and of meeting the needs of patients not only for today but also for tomorrow. Our **Entrepreneurship** honours our roots while encouraging innovative thinking to inspire progress.

Financial review

Strong performance and continued investments in research and infrastructure to provide more medicines to patients in need.

Over the last six years, the Octapharma Group has accomplished a remarkable compound annual growth rate of 15% and reports another record-breaking result for 2017, with sales of €1.72 billion – €120 million (7.5%) more than 2016's figure (on a constant currency basis, the growth rate is 9.4%). All our products performed well, especially wilate® and Nuwiq®. The company's continued strong and balanced sales growth would not be possible without effective collaboration across all divisions and regions, and the focus and commitment of all its employees and business partners.

€1.72bn
Revenue

€349m
Operating income

Gross profit in 2017 is €592 million, €2 million higher than in 2016. Despite the €120 million increase in revenue, the 34.4% gross margin is 2.5 percentage points lower than last year. The relatively small growth in absolute gross profit is a result of foreign exchange movements and investment in production capacity to fulfil the growing global need for plasma-derived products.

It is in the nature of the plasma protein industry that increasing production capacity does not result in linear profit growth. To ensure each litre of plasma is used to best effect, the company will continue to expand its product portfolio with innovative new products and services, and enter new markets.

Operating income is €349 million. Net cash from operating activities is €353 million (20.5% of revenue). Trade receivables have remained stable despite the significant sales growth and our net inventory has increased by €57 million, to a comfortable holding of raw plasma.

Our total operating expenses were €243 million, which includes significant investment in our future product portfolio: €87 million was invested in research and development (R&D) and €201 million in the extension of our production capacity and infrastructure. Much of this fulfils the aims of Program 2019, our development

> Over the last six years, the Octapharma Group has accomplished a remarkable compound annual growth rate of 15% and reports another record-breaking result for 2017.

initiative, launched in 2014, to double production capacity and significantly increase the overall efficiency of our manufacturing operations. Investments in people, equipment and property prepare the company for the demands of the future.

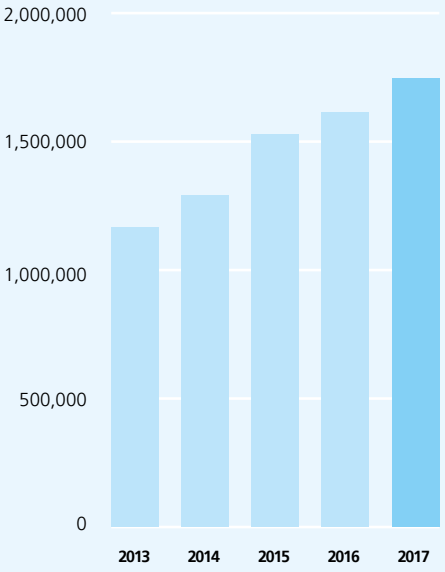
In 2018, our target is to achieve a high single-digit sales growth percentage and an absolute operating profit result comparable to 2017.

The significant investment made in research and infrastructure strongly positions Octapharma to fulfil the needs of more healthcare professionals and patients around the world.

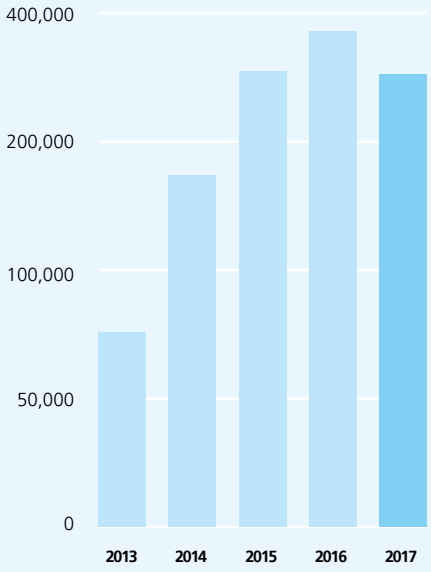
Roger Mächler
Chief Financial Officer

Key Figures of the Octapharma Group

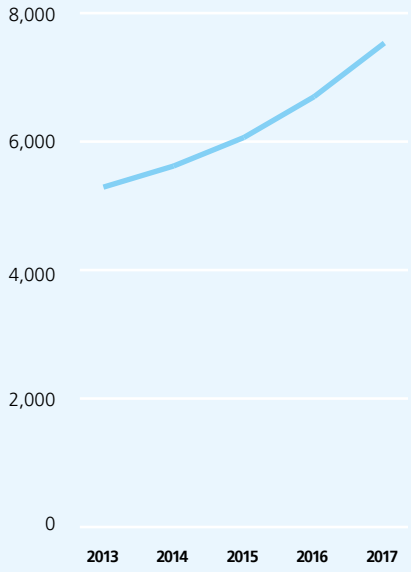
Revenue in 1,000 EUR



Operating income in 1,000 EUR



Average Headcount



(Monetary figures are in 1,000 EUR)	**2017**	2016	2015	2014	2013
Operating income	**348,861**	382,776	351,239	271,192	149,924
Net profit of the year	**252,116**	345,450	330,267	236,136	124,398
Year-end headcount	**7,674**	7,094	6,213	5,683	5,514
Return on investment	**10.2%**	15.3%	17.0%	14.2%	8.5%
Profit from operations per employee	**47**	58	58	49	28
Cash ratio	**187%**	180%	174%	122%	79%
Days of sales in receivables	**126**	137	123	135	123
Days of purchases in inventory	**217**	218	227	249	274
Cash flow from operations	**353,090**	287,966	382,437	274,541	205,558
Expenditures to ensure future prosperity	**287,197**	249,611	242,383	168,265	111,236
Research and development	**86,508**	83,500	72,825	41,792	45,780
Capital expenditures and investments in activities	**200,689**	166,111	169,558	126,473	65,456

Financial Statements of the Octapharma Group*

Consolidated Income Statement of the Octapharma Group

(All figures in 1,000 EUR)	**2017**	2016
Revenue	**1,720,350**	1,600,057
Cost of sales	**-1,128,068**	-1,010,219
Gross profit	**592,282**	589,838
Research and development	**-86,508**	-83,500
Selling and marketing	**-99,151**	-94,659
Regulatory affairs	**-15,640**	-14,213
General and administration	**-49,959**	-51,525
Other income	**11,073**	38,023
Other expenses	**-3,236**	-1,188
Total operating expenses	**-243,421**	-207,062
Operating income	**348,861**	382,776
Non-operating income and expenses	**-35,028**	5,368
Profit before taxes	**313,833**	388,144
Income tax	**-61,717**	-42,694
Net profit of the year	**252,116**	345,450

*The following summary financial statements are derived from the consolidated financial statements of Octapharma Nordic AB, Stockholm and comprise the summary income statement for the period from January 1 to December 31, 2017, the summary balance sheet and the summary cash flow statement for the year then ended, aggregating non-material financial statement captions.

Consolidated Statement of Financial Position of the Octapharma Group

(All figures in 1,000 EUR)	**2017**	2016
Assets		
Cash and cash equivalents	**485,600**	445,467
Trade receivables	**595,865**	601,850
Other receivables	**23,536**	27,240
Loans granted	**30,353**	139
Derivative financial instruments	**477**	403
Inventories	**655,048**	597,955
Other current assets	**30,991**	51,858
Total current assets	**1,821,870**	1,724,912
Financial investments	**2,559**	15,256
Deferred tax assets	**53,156**	77,872
Loans granted	**691**	821
Investments in associates	**8,270**	11,058
Property, plant and equipment	**655,311**	565,677
Intangible assets	**4,729**	14,729
Total non-current assets	**724,716**	685,413
Total assets	**2,546,586**	2,410,325

(All figures in 1,000 EUR)	2017	2016
Liabilities and equity		
Trade payables and other payables	**98,739**	96,698
Derivative financial instruments	**1,222**	3,333
Income tax payables	**24,292**	30,100
Accruals	**93,273**	90,493
Current provisions	**42,198**	26,688
Total current liabilities	**259,724**	247,312
Deferred income	**2,312**	2,593
Provisions	**82,489**	92,869
Deferred tax liabilities	**28,929**	25,846
Other non-current liabilities	**542**	215
Total non-current liabilities	**114,272**	121,523
Total liabilities	**373,996**	368,835
Share capital	**100**	100
Retained earnings	**2,180,532**	2,009,836
Currency translation adjustments	**-8,042**	31,554
Total equity attributable to owners of the company	**2,172,590**	2,041,490
Total liabilities and equity	**2,546,586**	2,410,325

Consolidated Statement of Cash Flows of the Octapharma Group

(All figures in 1,000 EUR)	**2017**	2016
Net profit for the year	**252,116**	345,450
Depreciation of property, plant and equipment	**88,180**	77,759
Amortisation and Impairment of intangible assets	**10,000**	20,632
Change in fair value of non-current assets	**22,850**	9,724
(Profit) loss on sale of property, plant and equipment	**1,775**	542
Changes in long-term liabilities and provisions	**3,438**	8,476
Unrealised foreign exchange (gain) loss	**20,988**	1,810
Cash flow before changes in working capital	**399,347**	464,393
(Increase) decrease of working capital	**-46,257**	-176,427
Net cash from operating activities	**353,090**	287,966
Acquisition of property, plant and equipment	**-200,689**	-166,111
Change of financial investments	**1,579**	93
Proceeds from sales of property, plant and equipment	**563**	339
Net cash used in investing activities	**-198,547**	-165,679
Financing activities	**-110,000**	-70,000
Net cash used for financing activities	**-110,000**	-70,000
Net change in cash and cash equivalents	**44,543**	52,287
Cash and cash equivalents beginning of period	**445,467**	392,658
Effect of exchange fluctuation on cash held	**-4,410**	522
Cash and cash equivalents end of period	**485,600**	445,467

Report of the Independent Auditor on the summary financial statements

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REPORT OF THE INDEPENDENT AUDITOR ON THE SUMMARY FINANCIAL STATEMENTS

Octapharma Nordic AB, Stockholm

Opinion

The accompanying summary financial statements on pages 63 to 66, which comprise the summary balance sheet as at December 31, 2017, the summary income statement and summary cash flow statement for the year then ended, and related notes, are derived from the audited financial statements of Octapharma Nordic AB, Stockholm, for the year ended December 31, 2017.

In our opinion, the accompanying summary financial statements are a fair summary of the audited financial statements, on the basis described on page 63 of the annual report 2017.

Summary Financial Statements

The summary financial statements do not contain all the disclosures required by International Financial Reporting Standards (IFRS). Reading the summary financial statements and the auditor`s report thereon, therefore, is not a substitute for reading the audited financial statements and the auditor`s report thereon.

The Audited Financial Statements and Our Report Thereon

We expressed an unmodified audit opinion on the audited financial statements in our report dated February 23, 2018.

Management`s Responsibility for the Summary Financial Statements

Management is responsible for the preparation of the summary financial statements on the basis described on page 63 of the annual report 2017.

Auditor's Responsibility

Our responsibility is to express an opinion on whether the summary financial statements are a fair summary of the audited financial statements based on our procedures, which were conducted in accordance with International Standard on Auditing (ISA) 810 (Revised), *Engagements to Report on Summary Financial Statements*.

KPMG AG

Orlando Lanfranchi
Zurich, 23 February 2018

Anna Pohle

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