PreviPharma

Innovative drugs for patients with unmet medical need

Management of donors using IgG levels based eligibility criteria

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Development of Regulations in Germany

- 1991 TP on every donation, IgG every 15th donation
- 1997 ARGE Plasmapheresis was founded
- 1999-2003 The ARGE carried out the SIPLA study
- 2012-2013 SIPLA II Study (includes First time donors)

The importance of IgG as the leading protein regarding donor safety (as well as product quality) as well as differentiated collection volumes were recognized.

In 2005, IgG testing frequency was therefore increased to every 5th donation

- 2017 60 donation per year

Schulzki et al.: SIPLA I 2006
Kiessig et al. SIPLA II. ISBT 2013

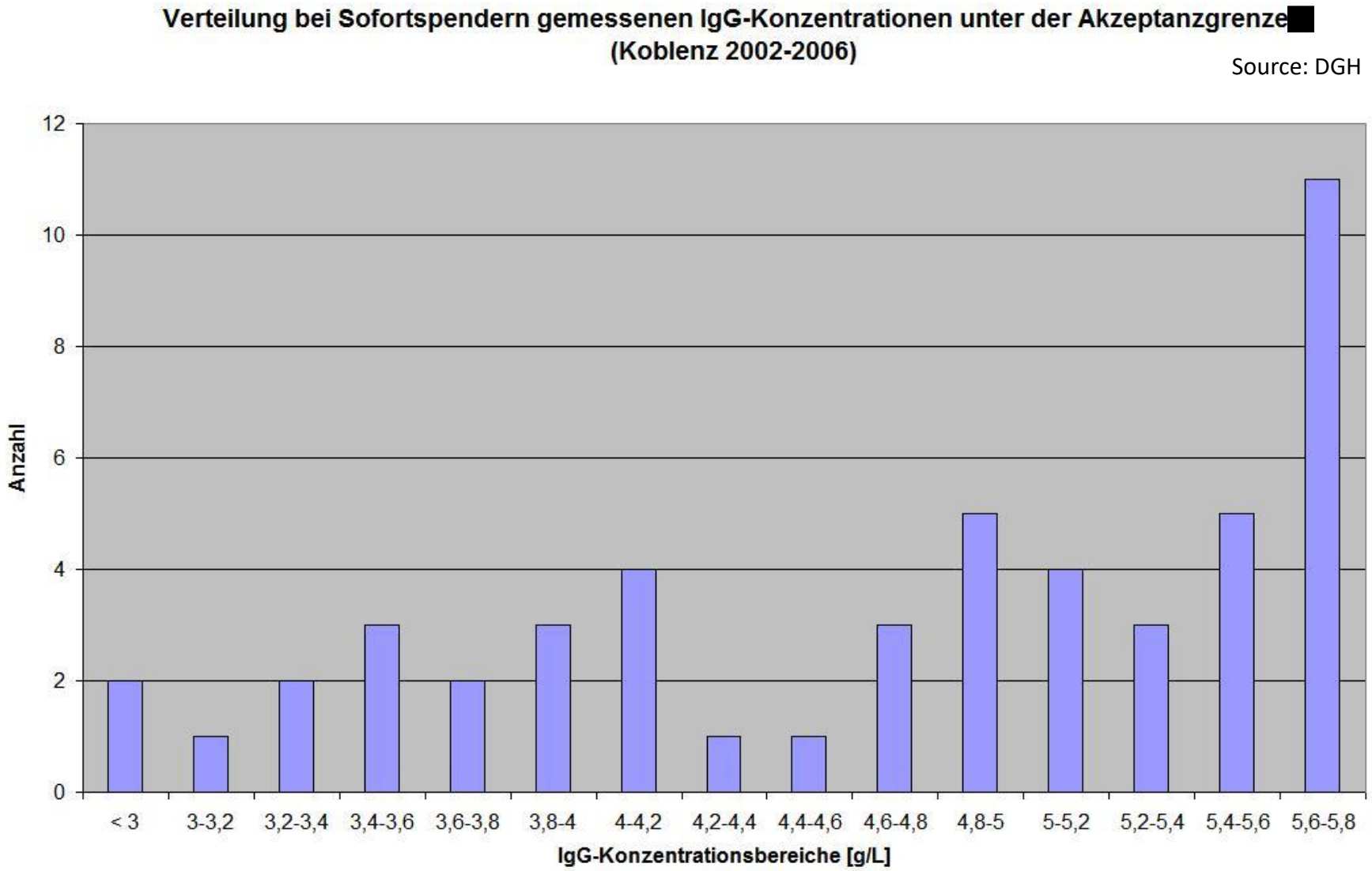
Introduction

- Donor health is a top priority for the plasma collection industry.
  - Globally, the industry has collected over 130,000,000 plasma donations over the past 5 years with an extraordinary safety record.
- The Dublin Consensus Statement 2011 … , O'Mahony & Turner: 2.11 The health of the donor should not be compromised by their donation.
- Data-driven, scientific rationale to help inform and guide policy decisions.
- In this presentation: several key points and highlighted outcomes from several studies involving our sector.

What is the Recipe?

- IgG levels are highly variable from donor to donor. They depend on gender, age, childhood exposure to antigens, immunizations, recent infections suffered, ethnicity and individual factors
- We see IgG‘s of first-time potential plasma donors from 0 to 28 g/L.
- Persons with an IgG of <6 g/L or >19 g/L at the first time are sent for further investigation.
- TP is mostly tested in combination with IgG to see the complete picture and observe the donor‘s protein metabolism over a longer period of time.
- Both proteins are easily tested from the product (plasma anticoagulated with 4% citrate) and can be reconverted to serum values with a validated conversion factor. We so avoid unnecessary blood sampling.

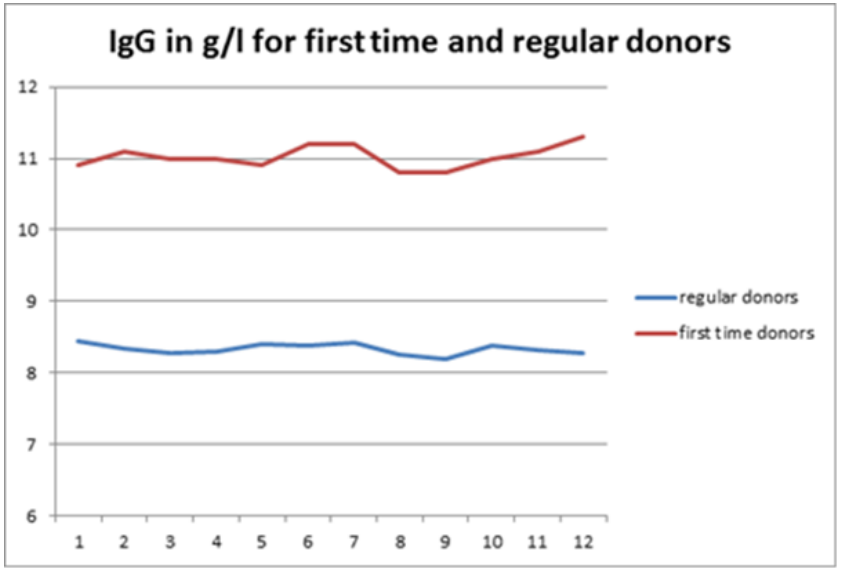
Distribution of IgG Levels of Potential First-Time-Donors



Source: DGH

The Art of Keeping Donors above IgG Levels of 6 g/L

- IgG levels drop by 2-3 g/L with regular donation and take approx. 2 to 3 weeks to recover to original levels.
- TP drops by approx. 8 g/L with regular donation
- Recovery rate to original levels varies significantly and needs individual donation patterns.



Other Parameters Detected →

Germany / SIPLA I & II

TP: Bredford / Biuret

IgG: Nephelometry / Turbidometry

Both: every 5th donation

Both: has to follow nat. Lab Med Guidelines (precision, recovery, … validated ICH Q2R)

Other regions

- TP: Polarimetry (at each procedure)
- IgG: by Electrophoresis or (4 monthly)**
- Both: not state of the art***
- Inacceptable precision, recovery, …
- Too infrequent

Results: up to 24% more IgG in Regions with regular IgG observations*

*Laub et al.: Specific protein content of pools of plasma for fractionation from different sources: impact of frequency of donations. Vox Sanguinis (2010) 99, 220–231

: CFR **§640.65: https://www.ecfr.gov/cgi-bin/text-idx?SID=7d14143c40b0a1459c073878caea3c01&mc=true&node=pt21.7.640&rgn=div5#se21.7.640_165t

***: Weichselbaum TE.: An accurate and Rapid Method for the Determination of Protein in small Amounts of Blood Serum and Plasma. AmJClinPathol (1946) 16, 40-49

All Parameters Detected

Influenced by plasmapheresis

- IgG
  - Longer recovery
- TP
  - Short recovery

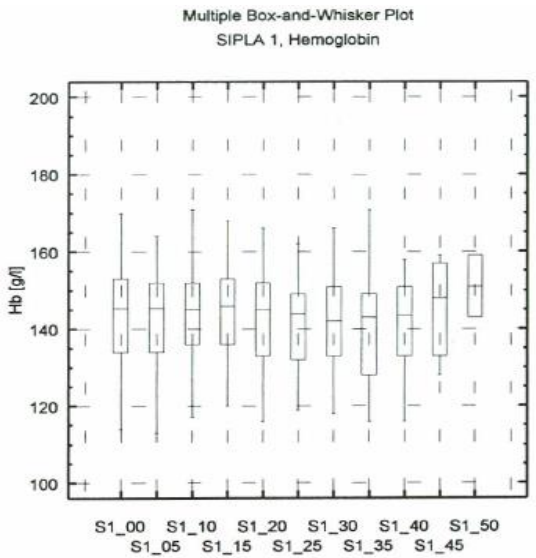
- Regulations needed for
  - Donor safety and
  - Plasma quality

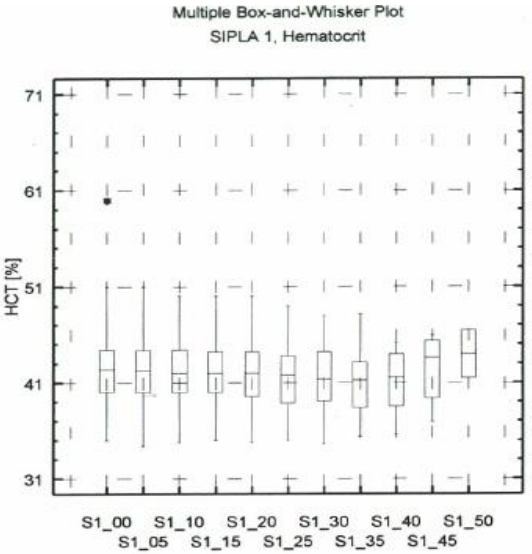
Not influenced by plasmapheresis

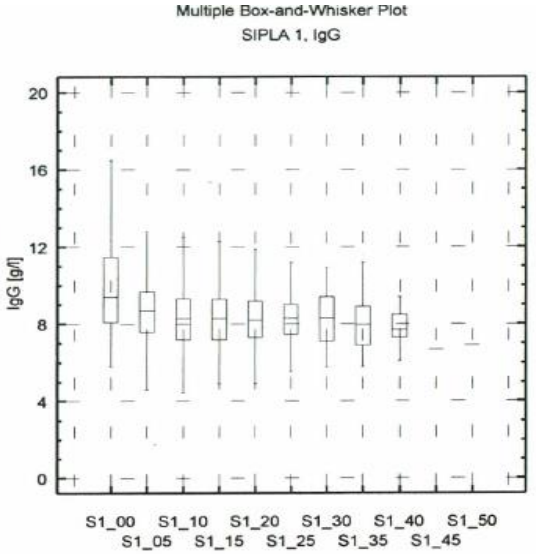
- Hemoglobin
- HCT

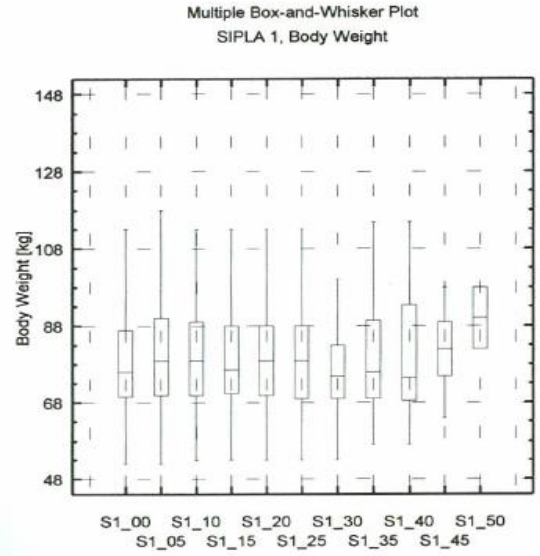
- No need for regulations

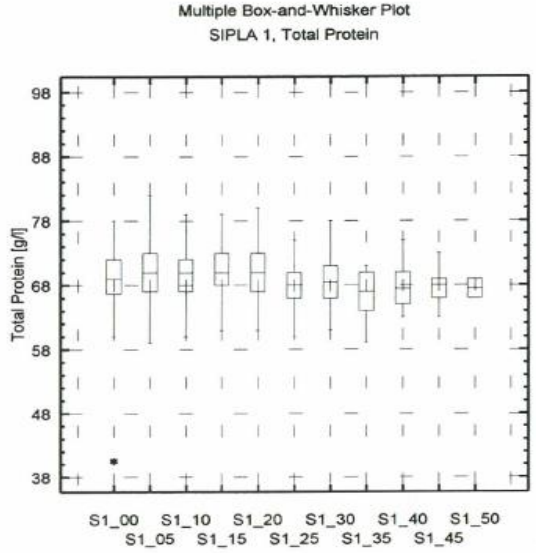
Other Parameters Detected











Legend to the figures:

S1 = SIPLA 1

- S1_00: Data at starting point
- S1_05: Data at the 5th donation
- S1_10: 10th donation
- S1_15: 15th donation
- S1_20: 20th donation
- S1_25: 25th donation
- S1_30: 30th donation
- S1_35: 35th donation
- S1_40: 40th donation
- S1_45: 45th donation
- S1_50: 50th donation
- S1_55: 55th donation

How to Keep Donors IgG Levels > 6 g/L

Fixpoints: either donor's **last** / **first** IgG

Therefore, in order to achieve sufficient quantities to meet the demand, plasma collectors developed a system to guide donors regarding their donation frequency.

- Manually, according to donor's last/first IgG
- With a fixed donation interval, according to donor's last/first IgG (donation programs with fixed intervals)
- With an electronic system, that increases IgG/TP testing frequency, when levels drop, and reduces donation frequency accordingly, to **avoid dropping at**

  IgG < 6 or

  TP < 60 g/L.

Analysis of Donor Loss after Initial Deferrals

Determination of donor recurrence rates after protein and IgG blocking.

Period 01.01.2015 until 31.03.2017

	Male [n= 5979]	Female [n= 6778]	Return rate[%] Male	Return rate[%] Female
Deferral b Total Protein (initially)	2475	4395		
Of which combined TP / IgG-Deferrals	516	858		
1. Follow-up analysis	2342	4093	94	93
2. Follow-up analysis	2101	3585	84	81
3. Follow-up analysis	1909	3245	77	73
IgG-Deferrals (initially)	4020	3244		
1. Follow-up analysis	3573	2859	88	88
2. Follow-up analysis	2972	2350	73	72
3. Follow-up analysis	2525	1972	62	60

Source: Haema AG

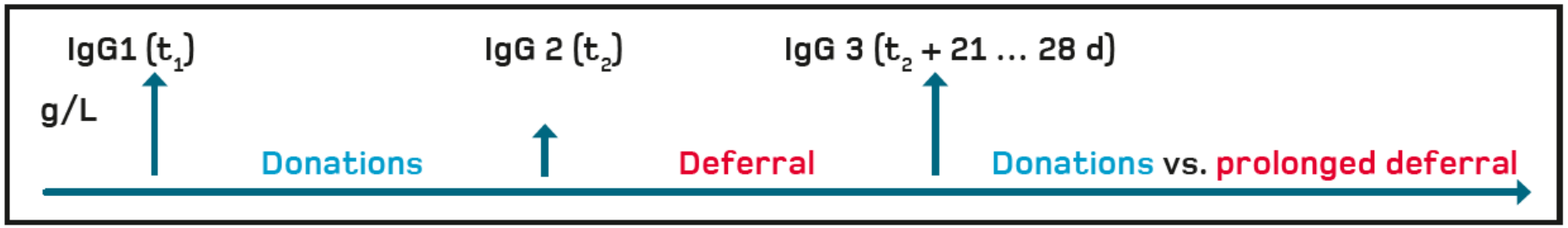
Donation Frequency Management Systems

There are advantages and disadvantages the starting point (First vs last IgG):

- **First time IgG**
  - Clear definition of possible donation frequencies from the very beginning
  - Also donors active in more than one center are recognized and therefore thwarted
  - Avoid cross donations

- **Last IgG**
  - Continuous adaption to the donors capabilities
  - Avoid cross donations

Example: Timelines



Möller et al.: ISBT 2010

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Summary Statistics: IgG1, IgG2 and IgG3

	IgG1	IgG2	IgG3
Sample size (n)	6667	6667	6667
Lowest value (g/L)	1.9400	1.9400	2.8900
Highest value (g/L)	16.3000	5.9900	15.4800
Arithmetic mean (g/L)	8.8030	5.5073	6.8547
95% CI for the mean (g/L)	8.7610 to 8.8450	5.4966 to 5.5180	6.8207 to 6.8886
Median (g/L)	8.7000	5.6100	6.6300
95% CI for the median (g/L)	8.6500 to 8.8000	5.6000 to 5.6500	6.6000 to 6.7000
Variance	3.0575	0.1981	2.0003
Standard deviation (g/L)	1.7486	0.4451	1.4143

Beware: Target in the treatment of immunodeficient patients:

IgG > 6 g/L (according to current guidelines)

Example: Regeneration / Synthesis Rates

Male		Female	
TP	IgG	TP	IgG
• **0,211 ±** 0,285 **g/L/Day**	• **0,033 ±** 0,0409 **g/L/Day**	• **0,217 ±** 0,326 **g/L/Day**	• **0,04 ±** 0,044 **g/L/Day**

Highly individual differences

Ulrich et al.: DGTI 2017

Donation Frequency Management Systems

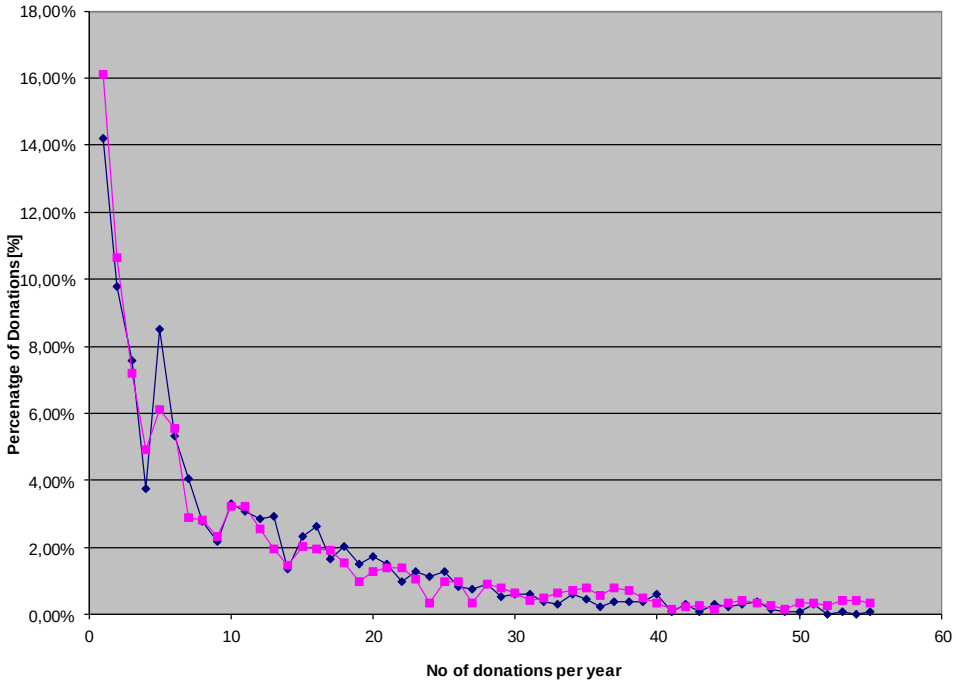
There are advantages and disadvantages to all systems:

- **Manual systems:** time consuming, too much room for individual decisions by health professionals and frequency being changed at every visit, loss of potential plasma, insufficient reduction of IgG-deferrals
- **Algorithm system:** might be inflexible, donor is in a fixed donation pattern, loss of potential plasma, sufficient reduction of IgG-deferrals
- **Electronic system:** needs to be programmed in the donor software, but is the ideal system to guide donors and health professionals.

- With this system, a maximum individual donation frequency can be achieved, with deferrals for IgG of less than 2%

Donation Frequency

As a result of **guiding** and **individualizing** donors‘ donation frequency,
(and of course personal reasons) numbers of donations vary greatly:



Average number of donations per year

• 1-5	36%
• 6-10	16%
• 11-20	18%
• 21-30	12%
• 31-45	11%
• 46-55	4%
• 55-60	3%

Individualized Plasma Donation

With any of the systems collectors get a good overview over that specific donor‘s protein recovery rate and can act accordingly and reduce donation frequency, if necessary or encourage higher donation frequency, if protein levels are very high.

We achieve higher donation frequencies than with a rigid interval and still **maintain donor safety** and **adequate plasma protein levels**.

We have collected data on millions of plasma donors over the last 20 years, and have seen an enormous variance in protein loss and recovery among individual donors.

Individualized Plasma Donation

- Accordingly, regulatory maximum number of donations are completely arbitrary, be it 33, 60 or 104.
- Likewise, annual volume limitations are senseless. Plasma is not an issue of „volumes“. **We collect life-saving proteins**, with IgG as the most sought after being the most important one for an increasing number of therapies.
- … without impacting the donors safety!
- If an IgG/TP monitoring system is in place, requirements to limit number of donations or annual donation volume can be waived.
- **Any limits should be evidence-based ad should include the donor safety!**

Individualized Plasma Donation

- Achieving as many donations as possible for that specific donor‘s protein recovery rate with as little deferrals for low IgG as possible and keeping him long-term healthy and happy as a donor, is a proven way to a sufficient plasma supply on a national or European level
- **Increasing the donation frequency**

  = product safety
- **Optimizing the donation frequencies to the donor capabilities**

  = donor safety

  IgG 6 … 8 g/L = 26 donations per year, every 2nd week

  IgG 8 … 10 g/L = 52 donations, one per week

  IgG > 10 g/L = up to 104 donations (two per week)

  = increases IgG yield in the fractionation process
- **This allows a better patient supply**

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Laub et al.: Specific protein content of pools of plasma for fractionation from different sources: impact of frequency of donations. Vox Sanguinis (2010) 99, 220–231

- Group I: EU plasma
- Group IV: Other plasma

Table 3 Comparison of total protein and specific plasma protein contents in plasma pools collected from Group I and Group IV donors (mean ± SD)

	Content in g/l in donations			
	Group I n = 51	Group IV n = 41	%	P-value
Protein (g/l)	A	B	Variation[a] C	D
Total protein	60·46 ± 3·46[b]	55·20 ± 2·60	−9	< 0·0001
Albumin	34·05 ± 2·24	29·05 ± 3·08	−15	< 0·0001
Total IgG	8·48 ± 0·61	6·49 ± 0·51	−24	< 0·0001
IgM	0·96 ± 0·13	0·69 ± 0·09	−28	< 0·0001
IgA	1·64 ± 0·22	1·54 ± 0·18	−6	< 0·05
Transferrin	2·23 ± 0·18	2·06 ± 0·15	−7	< 0·0001
Haemopexin	0·70 ± 0·05	0·62 ± 0·06	−11	< 0·0001
α_1 glycoprotein	0·67 ± 0·04	0·65 ± 0·07	−2	> 0·05
Retinol-binding protein	0·03 ± 0·01	0·03 ± 0·01	−10	< 0·05
C_1 inhibitor	0·21 ± 0·01	0·232 ± 0·02	+12	< 0·0001
Prealbumin	0·19 ± 0·03	0·21 ± 0·02	+9	< 0·0001
C-reactive protein	1·72 ± 0·29	2·08 ± 0·67	+21	< 0·05

Sources

- Comparison of safety of experienced and first-time-donors in intensified plasmapheresis (Kießig et al. ISBT, 2013)
- A prospective multicenter study on the safety of long-term intensive plasmapheresis in donors (Schulzki et al. 2006):
  - Total drop-outs: 2.860 (75,6% of donors)
  - Reasons: Socioeconomic: 49,2%, Medical unrelated to plasmapheresis: 10,4%, Plasmapheresis-related: 16%
    - Low IgG: 12,4% (no diff. re. 750 – 850ml or gender)
    - Total protein: 2,0% (no relevant diff. between gender)
    - Hb: 1,5% (female sign. more often, p <0,0001)
    - Other: 0,1%
- Burkhardt et. al (2015) evaluated DRK North-Ost‘s safety records for the years 2011-2013
- The impact of different intensities of regular donor plasmapheresis … , Tran-Mi et al. (2004)
- Diekamp et al. (2014) analysed UEs in a database of 1.107846 plasmapheresis donations (2008-2011)