Initial comments on the technical content of the Assessment Report from CSL Behring UK Ltd (17th Jan 2008)

Comments were made on the following pages of the assessment report:

I) Page 37 section 3.3:
1500 IU of Rhophylac neutralises 15ml of foetal red blood cells as per Summary of Product Characteristics, this figure differs from the WinRho figure of 17ml.

Although the current BCSH "Guidelines for the use of prophylactic anti-D immunoglobulin" recommend a two-dose regimen (as per summary given in Table 1 of the document), the guideline is based on the NICE 2002 guidelines, and both guideline documents note that a single-dose regimen may be an effective alternative, subject to further evidence. Furthermore, it may be worth adding that the BCSH guidelines are due to be updated in June 2008, presumably following the update of the present NICE guidelines.

II) Page 42, 1st paragraph:
The pool size of Rhophylac is 300 litres.

III) Page 88, under "cost":
The single-dose regimen should read Rhophylac. (Partobulin SDF is a two-dose regimen).

IV) Page 88, sub-section "compliance": In response to the RCN's concern:

Local procedures would need to be developed for a RAADP programme regardless of whether a one or two-dose regimen is used. The procedure should provide details on when RAADP is offered and how to manage women who miss their dose.

The targeted week(s) of RAADP presented on the manufacturers' Summary of Product Characteristics (SPC) are the weeks for RAADP administration rather than an opportunity to offer the RAADP and related advice. Typically, RAADP is offered early in pregnancy and well before week 28 with eligible women scheduled to have the RAADP injection at, for example, week 28. Offering RAADP at week 28 allows little time for decision making.

Therefore, there is no difference in the number of opportunities for offering RAADP to eligible women whether it is a one- or two-dose regimen.

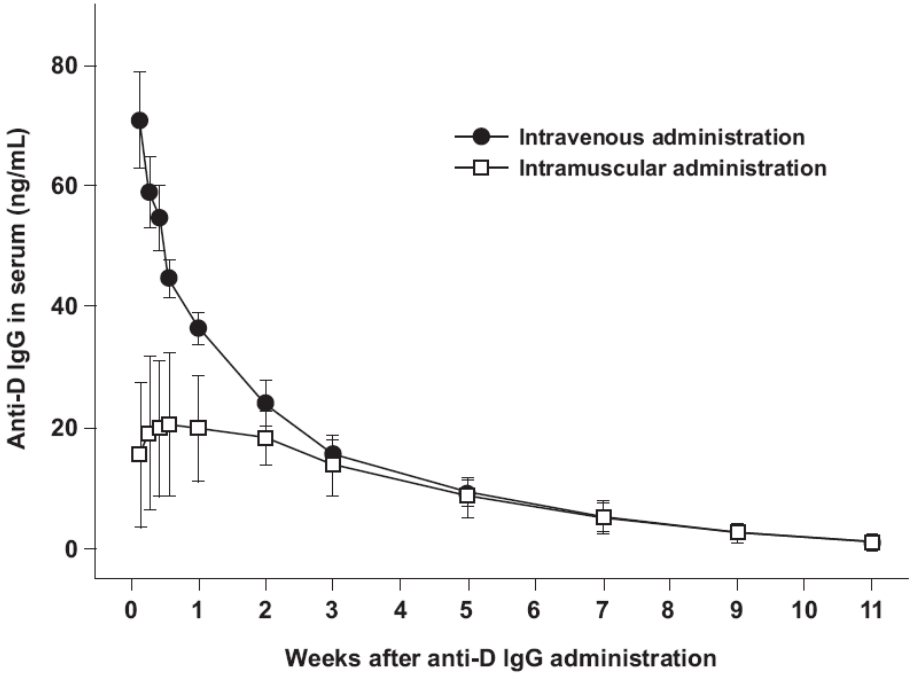
Sensitisation may occur when women miss the first dose of the two-dose regimen or the single dose of the one-dose regimen. Any missed dose or delay in the administration of either of the regimens contributes to the risk of sensitisation.

V) Page 87 (section "One-dose versus two-dose regimen",1st paragraph) and 128 (section 8.1, 3rd paragraph): In response to the comments from the RCN over concern that a single dose does not provide enough protection:

No head to head studies have been undertaken which compare one- and two-dose regimens of RAADP and there is no evidence to suggest that two doses of 500IU or 1250IU are more or less effective than a single dose of 1500IU at 28 weeks as stated in the assessment report.

The following is included in the CSL Behring submission:
One study has shown that Rhophylac 1500 IU, when used as a one-dose regimen at 28 weeks' gestation, provides measurable serum anti-D IgG levels up to at least nine weeks after administration (Bichler et al 2003) [Figure 1]. Measurable serum anti-D IgG levels were also reported at, and beyond, 11 weeks post-Rhophylac administration. Another study reported that a one-dose regimen of Rhophylac 1500 IU at 28 weeks' gestation (with a further dose within 72 hours after delivery to a Rh D-positive child) resulted in no cases of Rh D sensitisation (MacKenzie 2004).

Figure 1 Mean (SD) anti-D IgG serum concentrations after intravenous and intramuscular administration of one-dose Rhophylac 1500 IU at 28 weeks' gestation (Bichler et al 2003)



Three studies have shown that one-dose regimens of RAADP 1500 IU at 28 weeks' gestation are effective in reducing Rh D sensitisation rates, which ranged from 0-0.3% with RAADP, compared with 1.7-1.8% with no RAADP (Table 1) (Bowman and Pollock 1978; Bowman and Pollock 1987; Trolle 1989). In addition, two separate studies of one-dose regimens of RAADP 1500 IU at 28 weeks' gestation reported that 44% and 35.6% of women had detectable anti-D IgG at delivery (Kennedy et al 1998; Witter et al 1990).

These data demonstrate that one-dose RAADP 1500 IU regimens, including Rhophylac, are effective in preventing allo-immunisation during pregnancy.

Table 1. RAADP studies using one-dose regimens

Source	Anti-D prophylaxis group		Control group (No RAADP)	
	N	**% Sensitised**	**N**	**% Sensitised**
Bowman et al (Bowman and Pollock 1978)	1804	0.3	3533	1.8
Bowman and Pollack (Bowman and Pollock 1987)	9303	0.3	3533	1.8
Trolle (Trolle 1989)	346	0.0	354	1.7

National guidelines outside UK

One-dose regimen is widely accepted in countries outside the UK, please see information below taken from CSL Behring submission.

National guidelines outside the UK

Practice guidelines and one-dose RAADP practice outside the UK

One-dose 1500 IU RAADP regimens are recommended in guidelines for RAADP in the United States, Canada, France, Switzerland and Germany, demonstrating that one-dose RAADP 1500 IU is widely accepted (Table 9).

Table 9. Practice guidelines recommending one-dose regimens for RAADP outside the UK

Country	Society	Specific guideline	Strength of recommendation
United States	American College of Obstetricians and Gynaecologists (ACOG 1999)	Rh D-negative women who are not Rh D-alloimmunised should receive anti-D IgG 1500 IU at approximately 28 weeks of gestation, unless the father of the baby is also known to be Rh D-negative	A
United States	American Society of Clinical Pathologists (Hartwell 1998)	Antepartum administration of a standard 1500 IU dose (intravenous or intramuscular) anti-D IgG is indicated between 28 and 30 weeks of gestation in all pregnant Rh D-negative women who have not already developed anti-D	Not reported
Canada	Society of Obstetricians and Gynaecologists of Canada (SOGC 2003)	Anti-D IgG 1500 IU (intravenous or intramuscular) should be given routinely to all Rh D-negative nonsensitised women at 28 weeks gestation when foetal blood type is unknown or known to be Rh D-positive	IA

France	Collège National des Gynécologues et Obstétriciens Français (CNGOF 2005)	Any Rh D-negative pregnant woman, not immunised against antigen D and whose foetus is known or suspected to be Rh D-positive, will be offered an intramuscular anti-D immunoglobulin injection of 1500 IU at 28 weeks' gestation (+/- 1 week)	A
Switzerland	Akademie Feto-Maternale Medizin (Akademie Feto-Maternale Medizin 2005)	Anti-D should be administered between 28 and 30 weeks of gestation	Not reported
Germany	Des Bundesausschusses der Ärzte und Krankenkassen (des Bundesausschusses der Ärzte und Krankenkassen 2003)	If in an Rh D-negative pregnant woman, no anti-D antibodies are detectable, then in Week 28 to 30 of pregnancy, a standard dose (about 300 µg) of anti-D immunoglobulin should be injected to prevent a sensitization before birth	Not reported

Level A evidence: recommendation is based on good and consistent evidence; Level of evidence I: evidence obtained from at least one properly randomised, controlled trial; Not reported: the strength of the evidence in the recommendation was not provided.

VI) Page 124 – Compliance and one versus two doses 6.2.3.3

Compliance
We feel that the assumption of 100% compliance for the two dose regimens used in the model is an over-estimation. Mackenzie *et al* found that, of a sample of eligible women in Oxford, only 76% received both doses and only 29% received both doses at the correct gestation (page 80 of the assessment report). Although compliance was seen to have increased at a later period, it did not reach 100%.

An audit report by Brian Robertson provided by King's College hospital, received following our original submission, found that over a 3-month period the number of antenatal women who did not attend for the second dose of 500 IU prophylactic anti-D was 32 out of the 190 who received the first dose. This equates to 16.8% of women who were not covered for the 3rd trimester.

For logistic reasons, a one-dose regimen offers greater compliance than a two-dose regimen.

In response to the RCN's "opportunity to provide RAADP" statement:
As mentioned in IV) above, there is no difference in the number of opportunities for offering RAADP to eligible women whether it is a one- or two-dose regimen.