MEDICAL ASSESSMENT REPORT

1. INTRODUCTION

1.1 Therapeutic Class

Vaccine for prophylaxis
Viral attenuated vaccine ATC code J07B D52

1.2 Background

Measles, mumps and rubella combined vaccination is widely used as part of national immunisation schedules to achieve long term immunity to these potentially serious viral diseases. In developed countries with a low incidence of measles the combined vaccine is usually administered after the age of 1 year to ensure the previous disappearance of significant levels of maternally derived antibody.

1.3 Regulatory Status

The strains used in this vaccine are Schwartz (measles), RIT4385, derived from Jeryl Lynn (mumps), and Wistar RA 27/3 (rubella). The measles and rubella components are licensed in the following products: Rimevax (measles), Ervevax (rubella) and Eolarix (measles, rubella). The novelty of the present application is therefore the previously unlicensed mumps strain. This was chosen after a comparative feasibility study from one of two strains isolated from the Jeryl Lynn vaccine, which is the mumps component of the principal comparator vaccine M-M-RII.
The Applicant's previously licensed combined measles, mumps, rubella vaccine was withdrawn following reports of aseptic meningitis associated with the Urabe AM 9 mumps strain.

1.4 Indications

Active immunisation against measles, mumps and rubella.

1.5 Dosage and Dosage Schedules

'A single 0.5 ml dose of the reconstituted vaccine is recommended.
Priorix is recommended for immunisation of children over 12 months of age. It should be given according to the recommended schedule, and may be used for both primary and booster doses.'

2. EFFICACY

4.1 Overview of Clinical Trials

12 clinical studies have been performed, including 8124 children, of whom 5976 received Priorix. A feasibility study formed the basis for the choice of strain of mumps virus to include in the vaccine. Nine consistency studies compared several lots of the vaccine with existing measles, mumps, rubella vaccines to demonstrate consistency of the lots and comparability of the vaccine for immunogenicity and safety. One study evaluated the effect of simultaneous varicella immunisation and one study examined the use of the vaccine as a booster.

4.2 Feasibility Study

Assessment of the safety, reactogenicity and immunogenicity of two SmithKline Beecham Biologicals' live attenuated Measles (Schwarz strain) Mumps (RIT 4385 strain or RIT 4386 strain) Rubella (RA 27/3 strain) candidate vaccines. A single blind, randomised, controlled clinical study in healthy 15- 18-month old children. Study 102

180 children age 14 to 21 months, 88 female and 92 male were randomised to be immunised with one of the two candidate vaccines or with Merck, Sharp & Dohme's M-M-RII vaccine. For the immunogenicity assessment one 21 month old boy (older than specified age), two children in whom the post immunisation sample was collected too early and one child with pre-immunisation sample unavailable were excluded from the analysis. All children in the analysis were found to be seronegative for measles, mumps, and rubella prior to immunisation. Seroconversion rates and geometric mean titres (GMT) at 42 days post immunisation were as follows:

	RIT 4385 strain	**RIT 4386 strain**	**M-M-RII**
n	57	59	60
Measles			
Seroconversion	56 (98%)	58 (98%)	60 (100%)
95% CI	91, 100	91, 100	94, 100
GMT	2430	2693	2770
95% CI	2107, 2803	2340, 3099	2450, 3131
Mumps			
Seroconversion	55 (96%)	48 (81%)	60 (100%)
95% CI	88, 100	69, 90	94, 100
GMT	2450	921	1660
95% CI	2037, 2946	728, 1164	1385, 1990
Rubella			
Seroconversion	57 (100%)	59 (100%)	60 (100%)
95% CI	94, 100	94, 100	94, 100
GMT	67	76	77
95% CI	58, 77	63, 93	65, 91

At 12 months of age seroconversion rates and geometric mean titres were available only for subsets of the first and third groups as follows:

	RIT 4385 strain	**M-M-RII**
n	37	43
Measles		
Seroconversion	36 (97%)	43 (100%)
GMT	2274	2840
Mumps		
Seroconversion	31 (84%)	40 (93%)
GMT	751	954
Rubella		
Seroconversion	37 (100%)	43 (100%)
GMT	90	77

The RIT4385 strain was selected as the candidate vaccine.

4.3 Consistency Studies

4.3.1. Comparative assessment of the immunogenicity and reactogenicity of three consecutive lots of SmithKline Beecham Biologicals' live attenuated Measles (Schwarz strain) Mumps (RIT 4385 strain) Rubella (RA 27/3 strain) vaccine and of Merck, Sharp & Dohme's M-M-RVax. A multicentre, single-blind randomised, controlled clinical study in healthy 12 to 18 month old children. Study 106

574 children age 11 to 16 months, 296 female and 278 male were randomised to be immunised with one of the two candidate vaccines or with Merck, Sharp & Dohme's M-M-RII vaccine. For the immunogenicity assessment 62 children were excluded from the analysis because of failure to meet demographic eligibility criteria, unknown preimmunisation antibody status and unknown or incorrect sampling dates. Two children in the analysis were found to be seropositive for measles, 4 for mumps, and 3 for rubella prior to immunisation. Seroconversion rates and geometric mean titres (GMT) in the initially seronegative children at 42 days post immunisation were as follows:

	Priorix MJR114A43	**Priorix MJR115A43**	**Priorix MJR116A43**	**M-M-RVax**
Measles -n	126	125	128	123
Seroconversion	126 (100%)	125 (100%)	125 (98%)	120 (98%)
95% CI	97, 100	97, 100	93, 99	93, 99
GMT	3210	3222	3495	3918
95% CI	2872, 3587	2902, 3576	3187, 3833	3622, 4239
Mumps -n	125	125	128	122
Seroconversion	121 (97%)	125 (100%)	124 (97%)	121 (99%)
95% CI	92, 99	97, 100	92, 99	95, 100
GMT	2081	1974	1669	2108
95% CI	1833, 2362	1730, 2251	1467, 1898	1872, 2372
Rubella - n	125	125	128	123
Seroconversion	125 (100%)	125 (100%)	128 (100%)	123 (100%)
95% CI	97, 100	97, 100	97, 100	97, 100
GMT	69	69	68	71
95% CI	62, 77	61, 77	60, 77	64, 79

No statistically significant differences were seen between the Priorix groups or between the pooled results for the Priorix children and the results for the M-M-RVax children for measles or for rubella. For mumps there was a statistically significant difference between the Priorix groups ($p = 0.045$) and because of this no comparison was made with M-M-RVax.

At one year all but two in the third group were seropositive for measles and all were seropositive for rubella. Seropositivity rates for each group for mumps were 82%, 90% 87% and 86% respectively.

4.3.2. Comparative assessment of the immunogenicity and reactogenicity of three consecutive lots of SmithKline Beecham Biologicals' live attenuated Measles (Schwarz strain) Mumps (RIT 4385 strain) Rubella (RA 27/3 strain) vaccine and of Merck, Sharp & Dohme's M-M-RVax. A multicentre, single-blind randomised, controlled clinical study in healthy 15 to 18 month old children. Study 107

500 children were enrolled in the study; 488 received vaccine according to the protocol. 462 age 10 to 22 months, 197 female and 265 male were included in the reactogenicity assessment and a subset of 225 children had samples available which enabled them to be included in the immunogenicity analysis. 171 children in the analysis were found to be seropositive for measles, 4 for mumps, and 2 for rubella prior to immunisation. Seroconversion rates and geometric mean titres (GMT) in the initially seronegative children at 60 days post immunisation were as follows:

	Priorix MJR114A43	**Priorix MJR115A43**	**Priorix MJR116A43**	**M-M-RVax**
Measles -n	7	8	18	16
Seroconversion	7 (100%)	8 (100%)	18 (100%)	16 (100%)
95% CI	59, 100	63, 100	82, 100	79, 100
GMT	2273	2939	2143	2549
95% CI	1186, 4356	1713, 5044	1471, 3120	1702, 3816
Mumps -n	51	56	46	47
Seroconversion	46 (90%)	53 (95%)	44 (96%)	46 (98%)
95% CI	77, 97	85, 99	85, 99	89, 100
GMT	994	1064	634	1097
95% CI	840, 1176	886, 1279	527, 764	883, 1363
Rubella - n	52	57	46	47
Seroconversion	52 (100%)	57 (100%)	46 (100%)	47 (100%)
95% CI	93, 100	94, 100	92, 100	93, 100
GMT	124	132	130	140
95% CI	111, 139	118, 149	112, 150	123, 161

No statistically significant differences were seen between the Priorix groups or between the pooled results for the Priorix children and the results for the M-M-RVax children for measles, mumps, or rubella.

At one year all but one, in the first group, were seropositive for measles and all were seropositive for rubella. Seropositivity rates for each group for mumps were 77%, 80%, 82% and 92% respectively.

4.3.3. Blinded, randomized, multicentre study to compare the safety, reactogenicity and immunogenicity of three lots of SmithKline Beecham Biologicals' live attenuated Measles (Schwarz strain) Mumps (RIT 4385 strain) Rubella (RA 27/3 strain) vaccine and of Merck, Sharp & Dohme's M-M-RII vaccine given to healthy children at the age of 12 to 24 months. Study 109

This study was divided into two parts with different lots of vaccine in the two parts.
332 children were enrolled in the first part of the study and vaccinated; 254 age 12 to 24 months, 120 female and 134 male, were included in the immunogenicity analysis. 3 children in the analysis were found to be seropositive for measles, 3 for mumps, and 6 for rubella prior to immunisation. Seroconversion rates and geometric mean titres (GMT) in the initially seronegative children at 42 days post immunisation were as follows:

	Priorix MJR114A43	**Priorix MJR115A43**	**Priorix MJR116A43**	**M-M-RII**
Measles -n	61	59	63	68
Seroconversion	58 (95%)	57 (97%)	63 (100%)	63 (93%)
95% CI	86, 99	88, 100	94, 100	84, 98
GMT	1947	2355	2176	2701
95% CI	1571, 2412	1948, 2848	1771, 2674	2292, 3183
Mumps -n	60	59	63	69
Seroconversion	56 (94%)	58 (98%)	58 (92%)	66 (99%)
95% CI	84, 98	91, 100	82, 97	88, 99
GMT	1064	1268	1371	1431
95% CI	896, 1263	1046, 1536	1123, 1675	1237, 1655
Rubella - n	60	59	62	67
Seroconversion	58 (97%)	59 (100%)	62 (100%)	65 (97%)
95% CI	89, 100	94, 100	94, 100	90, 100
GMT	71	70	74	77
95% CI	60, 84	59, 82	63, 86	68, 88

No statistically significant differences were seen between the Priorix groups or between the pooled results for the Priorix children and the results for the M-M-RVax children for measles, mumps, or rubella.
In the second part of the study the Priorix strains used were MJR124A42, MJR125A42 and MJR126A. 70 children were included in the immunogenicity analysis and similar results were obtained.

4.3.4. Blinded, randomized, multicentre study to compare the safety, reactogenicity and immunogenicity of three lots of SmithKline Beecham Biologicals' live attenuated Measles (Schwarz strain) Mumps (RIT 4385 strain) Rubella (RA 27/3 strain) vaccine and of Berna's Triviraten, given to healthy children 12 to 24 months old. Study 110

This study was divided into two parts with different lots of vaccine in the two parts.
1779 children were enrolled in the first part of the study. 385 age 12 to 24 months, 185 female and 200 male were included in the immunogenicity analysis. 3 children in the analysis were found to be seropositive for measles, 16 for mumps, and 7 for rubella prior to immunisation. Seroconversion rates and geometric mean titres (GMT) in the initially seronegative children at 60 days post immunisation were as follows:

	Priorix MJR114A43	**Priorix MJR115A43**	**Priorix MJR116A43**	**Triviraten**
Measles -n	97	94	104	87
Seroconversion	96 (99%)	94 (100%)	104 (100%)	84 (97%)
95% CI	94, 100	96, 100	97, 100	90, 99
GMT	2842	2850	2759	677
95% CI	2475, 3263	2498, 3253	2384, 3194	596, 770
Mumps -n	97	90	99	83
Seroconversion	93 (96%)	88 (98%)	98 (99%)	24 (29%)
95% CI	90, 99	92, 100	94, 100	20, 40
GMT	1903	1575	1457	470
95% CI	1636, 2212	1349, 1838	1254, 1693	375, 589
Rubella - n	95	94	104	86
Seroconversion	95 (100%)	94 (100%)	104 (100%)	86 (100%)
95% CI	96, 100	96, 100	96, 100	96, 100
GMT	98	95	108	131
95% CI	87, 110	84, 107	98, 118	119, 143

No statistically significant differences were seen between the Priorix groups or between the pooled results for the Priorix children and the results for the Triviraten children for measles or rubella. For mumps no statistically significant differences were seen between the Priorix groups, but the pooled immune response results for the Priorix children were statistically significantly greater than for the Triviraten children ($p \leq 0.001$).
1116 children were enrolled in the second part of the study. 292 age 12 to 23 months, 139 female and 153 male, were included in the immunogenicity analysis. 5 children in the analysis were found to be seropositive for measles, 21 for mumps, and 10 for rubella prior to immunisation. Seroconversion rates and geometric mean titres (GMT) in the initially seronegative children at 60 days post immunisation were as follows:

	Priorix MJR124A43	Priorix MJR125A43	Priorix MJR126A43	Triviraten
Measles -n	79	68	65	75
Seroconversion	75 (95%)	68 (100%)	63 (97%)	74 (99%)
95% CI	87, 99	95, 100	89, 100	93, 100
GMT	2989	3759	3340	572
95% CI	2499, 3576	3338, 4233	2802, 3982	500, 656
Mumps -n	78	65	61	67
Seroconversion	74 (95%)	64 (98%)	59 (97%)	25 (37%)
95% CI	87, 99	92, 100	89, 100	26, 50
GMT	1612	1325	1430	671
95% CI	1355, 1916	1129, 1554	1147, 1782	471, 957
Rubella - n	79	65	64	74
Seroconversion	78 (99%)	65 (100%)	64 (100%)	74 (100%)
95% CI	93, 100	94, 100	94, 100	95, 100
GMT	112	127	118	148
95% CI	97, 129	114, 142	103, 136	136, 162

No statistically significant differences were seen between the Priorix groups or between the pooled results for the Priorix children and the results for the Triviraten children for measles or rubella. For mumps no statistically significant differences were seen between the Priorix groups, but the pooled immune response results for the Priorix children were statistically significantly greater than for the Triviraten children ($p \leq 0.001$).

4.3.5. Comparative assessment of the immunogenicity and reactogenicity of three consecutive lots of SmithKline Beecham Biologicals' live attenuated Measles (Schwarz strain) Mumps (RIT 4385 strain) Rubella (RA 27/3 strain) vaccine and of Merck, Sharp & Dohme's M-M-RVax. A single-blind randomised, controlled clinical study in healthy 15 to 18 month old children. Study 112

336 children were enrolled in the study and received vaccine. 67 age 15 to 17 months, 35 female and 32 male were included in the immunogenicity analysis. One child included in the analysis were found to be seropositive for measles, none for mumps, and none for rubella prior to immunisation. Seroconversion rates and geometric mean titres (GMT) in the initially seronegative children at 60 days post immunisation were as follows

	Priorix MJR114A43	**Priorix MJR115A43**	**Priorix MJR116A43**	**M-M-RVax**
Measles -n	15	17	17	17
Seroconversion	15 (100%)	17 (100%)	17 (100%)	17 (100%)
95% CI	78, 100	80, 100	80, 100	80, 100
GMT	2671	2489	2291	2772
95% CI	2051, 3478	2036, 3042	1753, 2996	2114, 3634
Mumps -n	15	18	17	17
Seroconversion	15 (100%)	18 (100%)	17 (100%)	16 (94%)
95% CI	78, 100	81, 100	80, 100	71, 100
GMT	963	1674	1266	1550
95% CI	669, 1386	1139, 2460	909, 1762	1131, 2123
Rubella - n	15	18	17	17
Seroconversion	15 (100%)	18 (100%)	17 (100%)	17 (100%)
95% CI	78, 100	81, 100	80, 100	80, 100
GMT	59	67	61	52
95% CI	45, 78	51, 87	40, 91	38, 71

No statistically significant differences were seen between the Priorix groups or between the pooled results for the Priorix children and the results for the M-M-RVax children for measles, mumps, or rubella.

4.3.6. Blinded, randomized, multicentre study to compare/assess the safety and reactogenicity and to compare immunogenicity of three lots of SmithKline Beecham Biologicals' live attenuated Measles (Schwarz strain) Mumps (RIT 4385 strain) Rubella (RA 27/3 strain) vaccine and of Merck, Sharp & Dohme's M-M-RII, given to healthy children at the age of 12 to 24 months. Study 117

499 children were enrolled in the study and received vaccine. 96 age 12 to 20 months, 48 female and 48 male were included in the immunogenicity analysis. One child included in the analysis was found to be seropositive for mumps, four for mumps, and none for measles prior to immunisation. Seroconversion rates and geometric mean titres (GMT) in the initially seronegative children at 42 days post immunisation were as follows

	Priorix MJR114A43	**Priorix MJR115A43**	**Priorix MJR116A43**	**M-M-RII**
Measles -n	23	25	25	23
Seroconversion	23 (100%)	25 (100%)	25 (100%)	22 (96%)
95% CI	85, 100	86, 100	86, 100	78, 100
GMT	3524	3151	3120	3397
95% CI	3042, 4082	2705, 3675	2504, 3886	2777, 4156
Mumps -n	22	25	25	23
Seroconversion	20 (91%)	25 (100%)	19 (76%)	22 (96%)
95% CI	78, 100	81, 100	80, 100	71, 100
GMT	1630	1277	828	1111
95% CI	1232, 2156	1009, 1616	604, 1135	800, 1543
Rubella - n	23	23	23	23
Seroconversion	23 (100%)	23 (100%)	23 (100%)	23 (100%)
95% CI	85, 100	85, 100	85, 100	85, 100
GMT	78	65	54	67
95% CI	62, 97	50, 84	42, 71	59, 81

No statistically significant differences were reported between the Priorix groups or between the pooled results for the Priorix children and the results for the M-M-RII children for measles, mumps, or rubella.

4.3.7. Blinded, randomized, multicentre study to assess the safety, reactogenicity and immunogenicity of three lots of SmithKline Beecham Biologicals' live attenuated Measles (Schwarz strain) Mumps (RIT 4385 strain) Rubella (RA 27/3 strain) vaccine and of Merck, Sharp & Dohme's M-M-RII, given to healthy children at the age of 12 to 24 months. Study 118

This study was divided into two parts with different lots of vaccine in the two parts. 248 children were enrolled in the first part of the study. 101 age 12 to 23 months, 43 female and 58 male were included in the immunogenicity analysis. 3 children in the analysis were found to be seropositive for measles, none for mumps, and 1 for rubella prior to immunisation. Seroconversion rates and geometric mean titres (GMT) in the initially seronegative children at 42 days post immunisation were as follows:

	Priorix MJR114A43	**Priorix MJR115A43**	**Priorix MJR116A43**	**M-M-RII**
Measles -n	25	27	22	26
Seroconversion	24 (96%)	27 (100%)	21 (96%)	25 (96%)
95% CI	80, 100	87, 100	77, 100	80, 100
GMT	3390	3777	2679	3431
95% CI	2782, 4129	3278, 4352	1899, 3782	2770, 4251
Mumps -n	25	27	20	23
Seroconversion	24 (96%)	27 (100%)	16 (80%)	22 (96%)
95% CI	80, 100	87, 100	56, 94	78, 100
GMT	1903	1575	1457	470
95% CI	1636, 2212	1349, 1838	1254, 1693	375, 589
Rubella - n	24	26	22	25
Seroconversion	24 (100%)	26 (100%)	22 (100%)	25 (100%)
95% CI	86, 100	87, 100	85, 100	86, 100
GMT	79	73	82	79
95% CI	60, 104	58, 93	61, 110	65, 96

No statistically significant differences were seen between the Priorix groups or between the pooled results for the Priorix children and the results for the Triviraten children for measles or rubella. For mumps no statistically significant differences were seen between the Priorix groups and the M-M-RII groups, but there was a statistically significant difference in seroconversion between the three Priorix groups ($p = 0.019$).

110 children were enrolled in the second part of the study. 93 age 12 to 22 months, 38 female and 55 male, were included in the immunogenicity analysis. Three children in the analysis were found to be seropositive for mumps, none for measles, and one for rubella prior to immunisation. Seroconversion rates and geometric mean titres (GMT) in the initially seronegative children at 60 days post immunisation were as follows:

	Priorix MJR124A43	**Priorix MJR125A43**	**Priorix MJR126A43**	**M-M-RII**
Measles -n	26	23	21	23
Seroconversion	26 (100%)	21 (91%)	20 (95%)	23 (100%)
95% CI	87, 100	72, 99	76, 100	85, 100
GMT	2765	3018	3431	3172
95% CI	2052, 3725	2273, 4008	2698, 4364	2525, 3985
Mumps -n	25	23	20	22
Seroconversion	25 (100%)	22 (96%)	19 (95%)	22 (100%)
95% CI	86, 100	78, 100	75, 100	85, 100
GMT	1446	1320	2104	1639
95% CI	1121, 1865	980, 1776	1465, 3021	1229, 2187
Rubella - n	25	23	21	23
Seroconversion	25 (100%)	22 (96%)	20 (95%)	23 (100%)
95% CI	86, 100	78, 100	76, 100	85, 100
GMT	65	82	89	128
95% CI	48, 89	63, 108	65, 121	94, 176

No statistically significant differences were seen between the Priorix groups or between the pooled results for the Priorix children and the results for the Triviraten children for measles or mumps or rubella.

4.3.8. Single blinded, randomized, multicentre study to assess the immunogenicity, safety, and reactogenicity of two lots of SmithKline Beecham Biologicals' live attenuated Measles (Schwarz strain) Mumps (RIT 4385 strain) Rubella (RA 27/3 strain) vaccine and of Merck, Sharp & Dohme's M-M-RII, given to healthy children at the age of 12 to 24 months. Study 120

255 children were enrolled in the study (which despite the title was a single centre study) and received vaccine. 252 age 12 to 23 months, 121 female and 122 male were included in the immunogenicity analysis. Three children included in the analysis was found to be seropositive for mumps, 24 for rubella, and none for measles prior to immunisation. Seroconversion rates and geometric mean titres (GMT) in the initially seronegative children at 60 days post immunisation were as follows:

	Priorix MJR115A43	**Priorix MJR124A42**	**M-M-RII**
Measles -n	85	84	83
Seroconversion	85 (100%)	84 (100%)	81 (98%)
95% CI	96, 100	96, 100	92, 100
GMT	3076	3641	3173
95% CI	2676, 3535	3218, 4118	2839, 3545
Mumps -n	84	82	83
Seroconversion	77 (92%)	78 (95%)	78 (94%)
95% CI	84, 97	88, 99	87, 98
GMT	934	900	1043
95% CI	796, 1097	767, 1057	893, 1218
Rubella - n	74	78	76
Seroconversion	74 (100%)	78 (100%)	76 (100%)
95% CI	95, 100	95, 100	95, 100
GMT	86	87	97
95% CI	77, 97	77, 99	86, 109

No statistically significant differences were seen between the groups.

4.4 Coadministration Study

Open, randomised, comparative assessment of the safety, reactogenicity and immunogenicity of SmithKline Beecham Biologicals' live attenuated Measles (Schwarz strain) Mumps (RIT 4385 strain) Rubella (RA 27/3 strain) vaccine when given alone and when coadministered with SmithKline Beecham Biologicals' live attenuated varicella vaccine (Oka-strain) in two separate injections in opposite arms, of Merck, Sharp & Dohme's M-M-RII and Berna's Triviraten, given to healthy children at the age of 12 to 24 months. Study 108

272 children were enrolled in the four arms of this study and received vaccine. 203 age 12 to 23 months, 91 female and 112 male were included in the immunogenicity analysis. One child included in the analysis was found to be seropositive for measles, none for mumps or rubella, and 3 for varicella prior to immunisation. Seroconversion rates and geometric mean titres (GMT) in the initially seronegative children at 60 days post immunisation were as follows:

	Priorix MJR124A42	**M-M-RII**	**Triviraten**	**Priorix MJR124A42 + varicella**
Measles -n	51	47	55	49
Seroconversion	49 (96%)	43 (92%)	53 (96%)	48 (98%)
95% CI	86, 100	80, 98	87, 100	89, 100
GMT	3295	3412	798	3053
95% CI	2812, 3860	2747, 4239	657, 968	2494, 3738
Mumps -n	51	47	56	49
Seroconversion	49 (96%)	44 (94%)	11 (20%)	48 (98%)
95% CI	86, 100	82, 99	10, 32	89, 100
GMT	1159	1002	534	1109
95% CI	947, 1419	815, 1230	346, 825	889, 1382
Rubella - n	51	47	56	49
Seroconversion	51 (100%)	46 (98%)	56 (100%)	48 (98%)
95% CI	93, 100	89, 100	94, 100	89, 100
GMT	89	69	91	69
95% CI	77, 103	58, 82	79, 104	59, 81

Apart from the significantly lower response to the mumps component of Triviraten, no differences are seen between the groups. In particular there is no evidence that coadministration of varicella vaccine adversely affects the response to Priorix.

4.5 Booster Study

Open, randomised, multicentre study to compare/assess the immunogenicity, safety and reactogenicity of SmithKline Beecham Biologicals' live attenuated Measles (Schwarz strain) Mumps (RIT 4385 strain) Rubella (RA 27/3 strain) vaccine and of Merck, Sharp & Dohme's M-M-RII, given as a booster to healthy children primed with a trivalent measles-mumps-rubella vaccine containing a Urabe strain mumps component or with M-M-RII. Study 121

An interim study report is presented for immunogenicity for 75 children entered in this study using Priorix as a booster immunisation.

Priming vaccine:	**M-M-RII**		**MMR (Urabe)**	
	Priorix MJR128A41	**M-M-RII**	**Priorix MJR128A41**	**M-M-RII**
Measles -n	23	25	13	12
GMT Pre-booster	706	1096	1787	2766
GMT Day 60	1217	1961	2667	4273
Response rate (%)	9	13	0	0
Mumps -n	21	23	9	12
GMT Pre-booster	1095	1211	1237	1756
GMT Day 60	4548	2954	4716	5510
Response rate	50	23	75	36
Rubella - n	23	23	13	12
GMT Pre-booster	95	82	61	62
GMT Day 60	136	119	109	120
Response rate	9	0	8	9

At the time of the booster immunisation two children in the first group were seronegative for measles, ten (four in the first group, two in the second group and four in the third group) were seronegative for mumps, and four (two in each of the first and second groups) were seronegative for rubella: all seroconverted after the booster immunisation. Booster responses were low for mumps and rubella, but higher for mumps. No difference was seen in relation to the vaccine used for priming.

4.6 Ongoing Trials

Worldwide eight trials continue to examine consistency of lots, including comparison of release lot versus mimic expiry lot, a real time stability study, and two further booster studies.

4.7. Statistical Assessment Of Efficacy

The results of twelve clinical trials were presented in support of this application and eight of these made randomised comparisons of the efficacy of Priorix in terms of seroconversion rates and geometric mean titres with another MMR vaccine in the absence of other simultaneous vaccinations. Seven of these trials investigated variation between three lots of Priorix (MJR114A43, MJR115A43 and MJR116A43).

Of 4813 children in the eight trials seroconversion data for the mumps vaccine are only given for 2092 (43%). However, results are consistent across all trials, including those where seroconversion data are given for high proportions of children thus there is no reason to think that the subsets with outcome data available were unrepresentative.

The seroconversion rates for the mumps component of the vaccine were high in all three lots of Priorix, lot MJR114A43 449/473 (94.9% [95%CI 93%-97%]), lot MJR115A43 458/464 (98.7% [95%CI 97%-100%]) and lot MJR116A43 435/459 (94.8% [95%CI 92%-97%]) and comparable with that for M-M-RII 354/370 (95.7% [95%CI 93%-98%]) or M-M-RVax 183/186 (98.4% [95%CI 95%-100%]) combined across trials.

Combined data from the trials shows heterogeneity between Priorix lots but the estimates of efficacy shows that this is not reflected in large differences in seroconversion rates.

Conclusion
There is convincing evidence for efficacy of the new mumps component of this vaccine.

5. SAFETY

5.1. Overview of Safety Data

Safety assessment for all trials consisted of direct ascertainment of reactogenicity, the expected adverse events related to immunisation, and monitoring of all adverse events for a variable period after immunisation.

Monitoring was performed by diary cards completed by parents, assisted in several of the trails by visits or telephone calls from study nurses. Symptoms and signs for which reports were specifically requested included:

- pain, swelling, redness at the injection site
- fever, measured by the parent according to standard instructions
- rash
- parotid or other salivary gland swelling
- suspected meningism, defined as fever and vomiting, neck stiffness, photophobia or febrile convulsion (not specifically solicited in study 106).

5.2. Reactogenicity

5.2.1. Assessment of the safety, reactogenicity and immunogenicity of two SmithKline Beecham Biologicals' live attenuated Measles (Schwarz strain) Mumps (RIT 4385 strain or RIT 4386 strain) Rubella (RA 27/3 strain) candidate vaccines. A single blind, randomised, controlled clinical study in healthy 15- 18-month old children. Study 102

180 children age 14 to 21 months, 88 female and 92 male were randomised to be immunised with one of the two candidate vaccines or with Merck, Sharp & Dohme's M-M-RII vaccine. For the reactogenicity assessment all 180 children were followed to 42 days post immunisation. Reported signs and symptoms were as follows were as follows:

	RIT 4385 strain	**RIT 4386 strain**	**M-M-RII**
n	60	60	60
Local			
Pain	0	0	0
Redness	36 (60%)	43 (72%)	40 (67%)
Swelling	16 (27%)	16 (27%)	26 (43%)
General			
Fever (up to 30 min post immunisation)	0	0	0
Allergic exanthemata	2 (3%)	2 (3%)	3 (5%)
Other exanthemata	0	1 (2%)	2 (3%)
Gland swelling	0	0	0
Meningism			
Convulsions	0	0	1

Assessor's Comment:

The convulsions reported in one patient in the M-M-RII group started two days after immunisation and continued for 10 days. As they were not considered by the investigator to have been related to the vaccine, they have not been included in the assessment of possible episodes of meningism by the Clinical Expert. This is surprising.

5.2.2. Comparative assessment of the immunogenicity and reactogenicity of three consecutive lots of SmithKline Beecham Biologicals' live attenuated Measles (Schwarz strain) Mumps (RIT 4385 strain) Rubella (RA 27/3 strain) vaccine and of Merck, Sharp & Dohme's M-M-RVax. A multicentre, single-blind randomised, controlled clinical study in healthy 12 to 18 month old children. Study 106

574 children age 11 to 16 months, 296 female and 278 male were randomised to be immunised with one of the two candidate vaccines or with Merck, Sharp & Dohme's M-M-RII vaccine. For the reactogenicity assessment 10 children were excluded from the analysis because of missing data. Reported reactions during the 42 day follow-up were as follows:

	Priorix MJR114A43	**Priorix MJR115A43**	**Priorix MJR116A43**	**M-M-RVax**
n	143	141	142	138
Local				
Pain	1 (1%)	2 (1%)	3 (2%)	3 (2%)
Redness	0	1 (1%)	0	1 (1%)
Swelling	0	0	0	1 (1%)
General				
Fever	23 (16%)	37 (26%)	26 (18%)	21 (15%)
Exanthema	1 (1%)	0	2 (1%)	0
Gland swelling	0	0	0	0
Meningism (not specifically solicited)				
Convulsions	0	0	0	1 (1%)

5.2.3. Comparative assessment of the immunogenicity and reactogenicity of three consecutive lots of SmithKline Beecham Biologicals' live attenuated Measles (Schwarz strain) Mumps (RIT 4385 strain) Rubella (RA 27/3 strain) vaccine and of Merck, Sharp & Dohme's M-M-RVax. A multicentre, single-blind randomised, controlled clinical study in healthy 15 to 18 month old children. Study 107

500 children were enrolled in the study; 488 received vaccine according to the protocol. 462 age 10 to 22 months, 197 female and 265 male were included in the reactogenicity assessment. 171 children in the analysis were found to be seropositive for measles, 4 for mumps, and 2 for rubella prior to immunisation. Symptoms and signs for 42 days post immunisation were as follows:

	Priorix MJR114A43	**Priorix MJR115A43**	**Priorix MJR116A43**	**M-M-RVax**
n	114	119	115	114
Local				
Pain	8 (7%)	7 (6%)	5 (4%)	18 (16%)
Redness	7 (6%)	6 (5%)	7 (6%)	9 (8%)
Swelling	4 (4%)	4 (3%)	4 (4%)	10 (9%)
General				
Fever	34 (30%)	34 (29%)	34 (30%)	33 (29%)
Rash	8 (7%)	9 (8%)0	10 (9%)	11 (10%)
Gland swelling	0	0	0	0
Parotid	2 (2%)	1 (1%)	1 (1%)	2 (2%)
Meningism				
Convulsions	0	0	0	0

5.2.4. Blinded, randomized, multicentre study to compare the safety, reactogenicity and immunogenicity of three lots of SmithKline Beecham Biologicals' live attenuated Measles (Schwarz strain) Mumps (RIT 4385 strain) Rubella (RA 27/3 strain) vaccine and of Merck, Sharp & Dohme's M-M-RII vaccine given to healthy children at the age of 12 to 24 months. Study 109

This study was divided into two parts with different lots of vaccine in the two parts. 332 children were enrolled in the first part of the study and vaccinated; 305 age 12 to 25 months, 142 female and 163 male, were included in the immunogenicity analysis. Signs and symptoms reported to 42 days post immunisation were as follows:

	Priorix MJR114A43	**Priorix MJR115A43**	**Priorix MJR116A43**	**M-M-RII**
n	76	77	75	77
Local				
Pain	4 (5%)	2 (3%)	4 (5%)	8 (10%)
Redness	4 (5%)	7 (9%)	11 (15%)	17 (22%)
Swelling	1 (1%)	0	3 (4%)	5 (7%)
General				
Fever	33 (43%)	25 (33%)	25 (33%)	35 (46%)
Rash	4 (5%)	10 (13%)0	3 (4%)	8 (10%)
Gland swelling				
Parotid	0	0	0	1 (1%)
Meningism				
Convulsions	0	1 (1%)	0	0

In the second part of the study the Priorix strains used were MJR124A42, MJR125A42 and MJR126A. 84 children were included in the reactogenicity analysis.

	Priorix MJR124A42	**Priorix MJR125A42**	**Priorix MJR126A43**	**M-M-RII**
n	22	22	22	18
Local				
Pain	1 (5%)	1 (5%)	0	0
Redness	2 (9%)	0	2 (9%)	3 (17%)
Swelling	0	0	0	1 (6%)
General				
Fever	7 (32%)	7 (32%)	8 (36%)	7 (39%)
Rash	0	1 (5%)0	1 (5%)0	0
Gland swelling				
Parotid	0	0	0	0
Meningism				
Convulsions	0	0	0	0

5.2.5. Blinded, randomized, multicentre study to compare the safety, reactogenicity and immunogenicity of three lots of SmithKline Beecham Biologicals' live attenuated Measles (Schwarz strain) Mumps (RIT 4385 strain) Rubella (RA 27/3 strain) vaccine and of Berna's Triviraten, given to healthy children 12 to 24 months old. Study 110

This study was divided into two parts with different lots of vaccine in the two parts. 1779 children were enrolled in the first part of the study. 1754 age 10 to 27 months, 871 female and 883 male, were included in the immunogenicity analysis with results as follows:

	Priorix MJR114A43	Priorix MJR115A43	Priorix MJR116A43	Triviraten
n	440	438	441	435
Local				
Pain	4 (1%)	6 (1%)	13 (3%)	11 (3%)
Redness	19 (4%)	25 (6%)	14 (3%)	24 (6%)
Swelling	5 (1%)	6 (1%)	8 (2%)0	8 (2%)0
General				
Fever	112 (25%)	95 (22%)	103 (23%)	73 (17%)
Rash	34 (8%)	32 (7%)	34 (8%)	28 (6%)
Gland swelling				
Parotid	4 (1%)	4 (1%)	7 (2%)	5 (1%)
Meningism				
Convulsions	0	1 (<0.5%)	0	0

1116 children were enrolled in the second part of the study. 1097 children age 11 to 23 months, 528 female and 569 male, were included in the immunogenicity analysis with results as follows:

	Priorix MJR124A42	Priorix MJR125A43	Priorix MJR126A42	Triviraten
n	272	270	278	276
Local				
Pain	4 (1%)	8 (3%)	2 (1%)	4 (1%)
Redness	4 (1%)	2 (1%)	6 (2%)	7 (2%)
Swelling	1 (<0.5%)	3 (1%)	1 (<0.5%)	3 (1%)0
General				
Fever	74 (27%)	80 (30%)	82 (30%)	63 (23%)
Rash	13 (5%)	11 (4%)	11 (4%)	13 (5%)
Gland swelling				
Parotid	3 (1%)	4 (1%)	4 (1%)	3 (1%)
Meningism				
Vomiting, mild neck stiffness	1 (<0.5%)	0	0	0

Assessor's Comment:

The single case of vomiting with mild neck stiffness is, apart from the children with convulsions, the only possible case of aseptic meningitis reported in the entire trial programme. As no lumbar puncture was performed, even this case cannot be considered confirmed.

5.2.6. Comparative assessment of the immunogenicity and reactogenicity of three consecutive lots of SmithKline Beecham Biologicals' live attenuated Measles (Schwarz strain) Mumps (RIT 4385 strain) Rubella (RA 27/3 strain) vaccine and of Merck, Sharp & Dohme's M-M-RVax. A single-blind randomised, controlled clinical study in healthy 15 to 18 month old children. Study 112

336 children were enrolled in the study and received vaccine. 326 age 14 to 21 months, 167 female and 159 male, were included in the reactogenicity analysis.

	Priorix MJR114A43	Priorix MJR115A43	Priorix MJR1116A43	M-M-RVax
n	82	80	82	82

Local				
Pain	6 (7%)	6 (7%)	7 (9%)	8 (10%)
Redness	21 (26%)	22 (27%)	22 (27%)	33 (40%)
Swelling	16 (20%)	15 (19%)	15 (18%)	19 (23%)0
General				
Fever	15 (18%)	11 (14%)	17 (21%)	23 (28%)
Rash				
Gland swelling				
Parotid	0	1 (1%)	1 (1%)	0
Meningism				
Convulsions	0	0	0	0

5.2.7. Blinded, multicentre, randomized, comparative study of the safety and reactogenicity of three lots of SmithKline Beecham Biologicals' live attenuated Measles (Schwarz strain) Mumps (RIT 4385 strain) Rubella (RA 27/3 strain) vaccine and of Merck, Sharp & Dohme's M-M-RII, given to healthy children at the age of 12 to 24 months. Study 114

This study, in which no immunogenicity assessments were made, was divided into two parts with different lots of vaccine in the two parts.

814 children were enrolled in the first part of the study. 692 age 9 to 25 months, 338 female and 354 male, were included in the immunogenicity analysis with results as follows:

	Priorix MJR114A43	**Priorix MJR115A43**	**Priorix MJR116A43**	**M-M-RII**
n	178	182	171	161
Local				
Pain	10 (6%)	10 (6%)	2 (1%)	16 (10%)
Redness	11 (6%)	18 (10%)	15 (9%)	15 (9%)
Swelling	3 (2%)	8 (4%)	1 (1%)0	6 (4%)
General				
Fever	77 (43%)	84 (46%)	73 (43%)	81 (50%)
Rash	10 (6%)	12 (7%)	11 (6%)	20 (12%)
Gland swelling				
Parotid	1 (1%)	0	2 (1%)	0
Meningism				
Convulsions	1 (1%)	0	0	0

935 children were enrolled in the second part of the study. 810 children age 11 to 35 months, 402 female and 408 male, were included in the immunogenicity analysis with results as follows:

	Priorix MJR124A42	**Priorix MJR125A43**	**Priorix MJR126A42**	**M-M-RII**
n	204	200	212	194
Local				
Pain	4 (2%)	5 (2%)	6 (3%)	7 (4%)
Redness	13 (6%)	15 (7%)	13 (6%)	20 (10%)
Swelling	4 (2%)	4 (2%)	3 (1.4%)	7 (3.6%)
General				
Fever	107 (52%)	81 (40%)	93 (44%)	88 (45%)
Rash	20 (10%)	10 (5%)	20 (10%)	13 (7%)
Gland swelling				
Parotid	1 (<0.5%)	0	0	2 (1%)
Meningism				
Convulsions	0	0	0	0

5.2.8. Blinded, randomized, multicentre study to compare/assess the safety and reactogenicity and to compare immunogenicity of three lots of SmithKline Beecham Biologicals' live attenuated Measles (Schwarz strain) Mumps (RIT 4385 strain) Rubella (RA 27/3 strain) vaccine and of Merck, Sharp & Dohme's M-M-RII, given to healthy children at the age of 12 to 24 months. Study 117

499 children age 12 to 23 months, 260 female and 239 male, were enrolled in the study and received vaccine; all were included in the immunogenicity analysis. Results were as follows:

	Priorix MJR114A43	**Priorix MJR115A43**	**Priorix MJR116A43**	**M-M-RII**
n	125	125	125	124
Local				
Pain	6 (5%)	5 (4%)	5 (4%)	20 (16%)
Redness	25 (20%)	23 (18%)	25 (20%)	47 (38%)
Swelling	4 (3%)	2 (2%)	3 (2%)	14 (11%)
General				
Fever	37 (30%)	43 (34%)	33 (26%)	47 (38%)
Rash	14 (11%)	13 (10%)	13 (10%)	17 (14%)
Gland swelling				
Parotid	1 (1%)	0	0	0
Meningism				
Convulsions	0	0	0	0

5.2.9. Blinded, randomized, multicentre study to assess the safety, reactogenicity and immunogenicity of three lots of SmithKline Beecham Biologicals' live attenuated Measles (Schwarz strain) Mumps (RIT 4385 strain) Rubella (RA 27/3 strain) vaccine and of Merck, Sharp & Dohme's M-M-RII, given to healthy children at the age of 12 to 24 months. Study 118

This study was divided into two parts with different lots of vaccine in the two parts. 248 children were enrolled in the first part of the study. 241 age 11 to 26 months, 113 female and 128 male, were included in the reactogenicity analysis.

	Priorix MJR114A43	**Priorix MJR115A43**	**Priorix MJR116A43**	**M-M-RII**
n	62	62	60	57
Local				
Pain	4 (6%)	3 (5%)	4 (7%)	5 (9%)
Redness	7 (11%)	9 (15%)	5 (8%)	7 (12%)
Swelling	6 (10%)	2 (3%)	3 (5%)	3 (5%)
General				
Fever	26 (42%)	27/62 (44%)	25 (42%)	18 (32%)
Rash	12 (19%)	3 (5%)	4 (7%)	6/57 (11%)
Gland swelling				
Parotid	0	0	0	0
Meningism				
Convulsions	0	0	1 (1%)	0

110 children were enrolled in the second part of the study. 100 children age 11 to 22 months, 41 female and 59 male, were included in the reactogenicity analysis with results as follows:

	Priorix MJR124A42	**Priorix MJR125A43**	**Priorix MJR126A42**	**M-M-RII**
n	26	25	25	24
Local				
Pain	4 (15%)	3 (12%)	0	1 (4%)
Redness	3 (12%)	2 (8%)	2 (8%)	0
Swelling	1 (4%)	2 (8%)	0	0
General				
Fever	8 (31%)	10 (40%)	11 (44%)	7 (29%)
Rash	0	0	1 (4%)	0
Gland swelling				
Parotid	0	0	0	0
Meningism				
Convulsions	0	0	0	0

5.2.10. Single blinded, randomized, multicentre study to assess the immunogenicity, safety, and reactogenicity of two lots of SmithKline Beecham Biologicals' live attenuated Measles (Schwarz strain) Mumps (RIT 4385 strain) Rubella (RA 27/3 strain) vaccine and of Merck, Sharp & Dohme's M-M-RII, given to healthy children at the age of 12 to 24 months. Study 120

255 children age 12 to 23 months, 122 female and 133 male were enrolled in the study (which despite the title was a single centre study) and received vaccine: all were included in the reactogenicity analysis.

	Priorix MJR115A43	**Priorix MJR124A42**	**M-M-RII**
n	85	85	85
Local			
Pain	0	2 (2%)	7 (8%)
Redness	14 (16%)	9 (11%)	23 (27%)
Swelling	2 (2%)	4 (5%)	14 (16%)
General			
Fever	24 (28%)	21 (25%)	23 (27%)
Rash	7 (8%)	6 (7%)	9 (11%)
Gland swelling			
Parotid	0	0	0
Meningism			
Convulsions	0	0	0

5.2.11. Open, randomised, comparative assessment of the safety, reactogenicity and immunogenicity of SmithKline Beecham Biologicals' live attenuated Measles (Schwarz strain) Mumps (RIT 4385 strain) Rubella (RA 27/3 strain) vaccine when given alone and when coadministered with SmithKline Beecham Biologicals' live attenuated varicella vaccine (Oka-strain) in two separate injections in opposite arms, of Merck, Sharp & Dohme's M-M-RII and Berna's Triviraten, given to healthy children at the age of 12 to 24 months. Study 108

272 children were enrolled in the four arms of this study and received vaccine. 261 age 11 to 23 months, 113 female and 148 male were included in the reactogenicity analysis.

	Priorix MJR124A42 Alone	**M-M-RII**	**Triviraten**	**Priorix MJR116A43 With varicella opposite arm**	**Varicella with Priorix MJR116A43 opposite arm**
n	68	62	70	61	61
Local					
Pain	5 (7%)	5 (8%)	2 (3%)	2 (3%)	2 (3%)
Redness	8 (12%)	9 (15%)	5 (7%)	2 (3%)	1 (2%)
Swelling	3 (4%)	1 (2%)	1 (1%)	2 (3%)	0
General					
Fever	33 (49%)	38 (61%)	26 (37%)	36 (59%)	
Rash	3 (4%)	3 (5%)	5 (7%)	3 (5%)	
Gland swelling					
Parotid	0	0	0	0	
Meningism					
Convulsions	0	0	0	0	

5.2.12. Open, randomised, multicentre study to compare/assess the immunogenicity, safety and reactogenicity of SmithKline Beecham Biologicals' live attenuated Measles (Schwarz strain) Mumps (RIT 4385 strain) Rubella (RA 27/3 strain) vaccine and of Merck, Sharp & Dohme's M-M-RII, given as a booster to healthy children primed with a trivalent measles-mumps-rubella vaccine containing a Urabe strain mumps component or with M-M-RII. Study 121

An interim study report is presented for reactogenicity for 75 children entered in this study using Priorix as a booster immunisation.

Booster:	Priorix MJR128A41	M-M-RII
n	38	37
Local		
Pain	4 (10%)	7 (19%)
Redness	4 (10%)	3 (8%)
Swelling	1 (3%)	0
General		
Fever	13 (34%)	8 (22%)
Rash- not reported		
Gland swelling		
Parotid	0	0
Meningism		
Convulsions	0	0

5.3. Adverse Events

The pattern of adverse events for which information was not specifically solicited and which were not classified as serious did not differ between sequences.

5.5. Serious Adverse Events

No serious adverse events were reported in Studies 102, 108, 109, or 121.

In Study 106 none of the seven serious adverse events reported (6 bronchopneumonia, 1 burns) were considered to be related to the vaccine.

In Study 107 one episode of Kawasaki's disease was not thought to be related to the vaccine.

In Study 110 one of the seven serious adverse events reported (all graded serious because of the need for admission to hospital, high fever and rash associated with Campylobacter and rotavirus infection, was thought related to the vaccine, the second lot of Priorix in the first part of the study. The other events reported included surgery for hypospadias [clearly unrelated to the vaccine], an episode of diarrhoea, vomiting and fever, an episode of febrile convulsion, an episode of acute laryngitis, an episode of arthritis and an episode of head injury.

In Study 112 none of the three serious adverse events reported, which all came from the group of children receiving M-M-RVax, were thought to be related to the vaccine. The diagnoses were high fever followed by acute glomerular nephritis, accidental poisoning, and allergic rash following beta-lactam antibiotic.

In Study 114 four of the eleven serious adverse events reported were thought to be possibly related to the study vaccine. In three of these the study vaccine was Priorix. In the first of these fever and massively enlargement of cervical lymph nodes together with rhinitis occurred two days after immunisation in association with neutropenia (stated as 20% differential white count, absolute count not provided) and the development of antibodies against neutrophils. Neutropenia was stated to be still present at the end of the study but fifteen months after immunisation the neutrophil count appears to have been normal. In the

second child fever from the day of immunisation and rash with enlarged lymph-nodes starting 10 days following immunisation were considered to be possibly related to the vaccine. In the third child fever lasted from three days to eight days following immunisation, in association with bronchopneumonia. The diagnoses for the other severe adverse events were febrile convulsion (included in table above), accidental poisoning (two cases), fever with vomiting and otitis media, gluteal abscess (injection was in the arm), fever with gastroenteritis and otitis media, and crying attacks with respiratory tract infection.
In Study 117 none of the four serious adverse events reported, which all came from the groups of children receiving Priorix, were thought to be related to the vaccine. The diagnoses were fever associated with either laryngitis or rhinitis or pneumonia.
In Study 118 one serious adverse event was reported, and was considered to be related to the vaccine, which was one of the Priorix strains. Epididymitis developed 21 days after vaccination, without salivary or parotid swelling. Spontaneous recovery occurred.
In Study 120 five serious adverse events were reported. None were considered to be related to the vaccine (which was Priorix in four cases and M-M-RII in one). The diagnoses were bronchopneumonia, salmonella gastroenteritis, frontal furunculosis, bronchopneumonia and febrile convulsion (on day 66 post immunisation, hence not included in reactogenicity analysis) and burns.
Examination of the serious adverse event reports from the ongoing studies reveals no cause for concern in terms of type or severity of events reported.

5.6. Deaths

No deaths appear to have been reported in any of the studies.

5.7 Medical Assessor's Conclusions on Reactogenicity and Safety

The incidences and types of adverse reaction seen with Priorix do not differ from those seen with the principal comparator vaccine M-M-RII. In particular the incidence of any possible signs of aseptic meningitis (convulsions, or, in one case only, mild neck stiffness) was similar in the two vaccines, very approximately 1 per 1,000. As febrile convulsions are common in this age-range, the incidence of aseptic meningitis is likely to be appreciably less. To demonstrate clinically important differences in incidence for events of this rarity would require trials of a size that exceeds the bounds of feasibility.
Incidences of other expected adverse events (parotid swelling , fever, rash and local reaction) were also similar between the vaccines.

6. CLINICAL EXPERT REPORT

It is a full, critical, review of the data, with the essential arguments clearly identified and summarised.

7. SUMMARY OF PRODUCT CHARACTERISTICS

The indications, dosing instructions and warnings are clear and appropriate.
The Summary of Product Characteristics makes the following claims:

Section 4.8 Undesirable effects

In the comparative studies, a statistically significant lower instance of local pain, redness and swelling was reported with 'Priorix' compared with the UK licensed comparator measles, mumps and rubella-combined vaccine. The instance of other adverse reactions listed above was similar in both vaccines.

Assessor's Comment:

The Clinical Expert provides a table of pooled data (table 3, page 13 of the Clinical Expert Report) which appears to support this claim. However a direct comparison in the Summary of Product Characteristics with 'the UK licensed comparator measles, mumps and rubella-combined vaccine' is potentially misleading as in the future other vaccines might be licensed. The claim might be rephrased as follows:

In comparative studies with other measles mumps and rubella vaccines, the instance of local pain, redness and swelling reported with 'Priorix' was low, while the instances of other adverse reactions were similar.

Section 5.2 Pharmacokinetic properties

In comparative studies, antibodies against measles, mumps and rubella were detected in 98.7%, 95.5% and 99.5% of previously seronegative vaccines who received 'Priorix' compared to 96.9% and 99.5% in the group receiving a comparator measles mumps and rubella-combined vaccine.

Assessor's Comment:

Percentage immunogenicity figures for the vaccine have already been quoted in the previous paragraph of the Summary of Product Characteristics. Without confidence intervals the percentage immunogenicity figures are unhelpful for comparing the two vaccines. It is unlikely that the small differences in immunogenicity seen in the comparative trials are of any clinical significance. This paragraph should be deleted.

8. PATIENT INFORMATION LEAFLET

The instructions and warnings are appropriate, except that the the leaflet states 'This vaccine is used for adults and children'. No reference to use in adults is made in the posology in the Summary of Product Characteristics and no data has been supplied on use in adults. All reference to use in adults should be removed from the Patient Information Leaflet.

9. LABEL

The labelling is appropriate.

10. MEDICAL ASSESSOR'S CONCLUSIONS

The immunogenicity data indicates that Priorix is likely to provide a high level of protection against measles, mumps and rubella.

The safety data are reassuring, in that the profile of adverse events seen after immunisation with Priorix does not differ from that of the principal comparator vaccine.

Adequate consistency in immunogenicity and adverse event profile has been shown between different lots.

On the basis of the Part IV data, the application should be approved, subject to minor changes in the comparative claims made in the Summary of Product Characteristics and removal of references to use in adults in the Patient Information Leaflet.

Medical Assessor
8th September 1997

The Committee is asked to consider the evidence in these papers, the applicant's expert reports, and the assessor's comments and conclusions and to advise the licensing authority.