Written Arguments in Response to Examiner's Written Opinion

The essence of the present invention is set forth on Page 2, lines 31-38 of the description. Briefly, it has been found that alginate gels containing relatively large amounts of polyhydric alcohols such as propylene glycol are stabilised against hydrolysis and consequent loss of viscosity during thermal sterilisation. The effective amount of polyhydric alcohol is 15-40% w/v, with the precise amount depending on the nature and concentration of the alginate being used, as set forth in the Examples.

Referring first to the references cited by the US Patent Examiner, these can distinguished from the present invention as follows:-

US-A-4393048 (Mason *et al.*) was considered in detail during the drafting of the present application, and is discussed on Page 1, lines 18-25 of the description. The Mason *et al.* reference discloses protective gel compositions for wounds comprising about 0.5 to 3% by weight of alkali metal alginate, and about 8 to 2% by weight of glycerol. These compositions would break down completely under autoclave sterilisation conditions to give a liquid product that is unsuitable for application to a wound. Mason *et al.* does not teach or suggest compositions according to the present invention having much higher contents of polyhydric alcohols, namely 15-40% w/v, which would be suitable for autoclave sterilisation. In fact, Mason *et al.* are completely silent on the subject of sterilisation of their wound covering gels, presumably because no satisfactory method of sterilising the gels described in Mason *et al.* exists.

US-A-5482932 (Thompson) describes aqueous alginate pastes useful as wound dressings. The pastes are not aqueous gels as recited in the claims of the present application, but dispersions of water-swellable calcium alginate fibres. If necessary, the claims of the present application could be distinguished further over Thompson by specifying that the alginate in the claimed aqueous gels is dissolved alginate. The reference to autoclave sterilisation in column 5, lines 10-13 of Thompson is irrelevant to the present invention, since the solid or semi-solid alginate fibres in the fibrous pastes of Thompson would be expected to resist hydrolysis better than an aqueous gel. Likewise, the statement in column 5, lines 17-19 of Thompson that "the alginate gel of the invention may contain a conventional preservative for medical alginates, for example propylene glycol" is not relevant to the present invention. The use as a preservative suggested in Thompson implies a relatively low level of propylene glycol in the alginate gels, in contrast to the high content of 15-40% w/v of propylene glycol in the aqueous gels according to the present invention.

US-A-5336501 (Czech *et al.*) likewise provides no signpost to the present claimed invention. The Czech reference describes solid cross-linked hydrogels based on a mixture of polymers, some of which are cross-linked. The polymers may comprise a small amount of alginate, but there is no suggestion that the alginate is the main gelling agent. The presence of cross-linked polymers means that the hydrogels can be sterilised by autoclave heating, but the skilled reader would in no way deduce from this that the presence of high

levels of polyhydric alcohol would result in an autoclave-sterilisable alginate gel. To put it in EPO terms, the technical effect on which the present application is based is not taught or suggested in the Czech reference. On the contrary, Czech teaches away from the present invention, because it teaches that the presence of a cross-linked polymer is essential.

Referring now to the other matters raised by the USPTO Examiner, I note first that the inventors Charlotte Maria Findlay and Craig Julian Hardy are joint inventors for all of the claims.

With regard to the claim rejection under 35 U.S.C. § 112, the precise conditions required to make an autoclave-sterilisable gel were researched at length by the inventors. I anticipated the objection that has been raised by the US Examiner, and every possible effort was made to pin down the precise conditions. However, it appears that the practice of this invention is somewhat empirical. The skilled person needs to experiment within the range of compositions recited in the claims to find particular compositions that are autoclave sterilisable. However, this merely requires the process of trial and error on the part of the skilled practitioner, using experimental procedures that are fully specified in the description. Whilst I am unfamiliar with US practice in this regard, I assume that the objection can be overcome by inserting suitable functional language into Claim 1.

The US Examiner has objected that the specification fails to describe the sterilising means. I assume that this objection can be overcome by incorporating the document named at Page 5, lines 9-10 into the specification by reference.

The terms "alginate", "polyhydric alcohol" and "sterilising" could be replaced by "water-soluble alginate salt", "C_3-C_6 dihydric or trihydric alcohol" and "heat sterilising", if necessary to overcome the Examiner's rejection. With regard to the term "gel", it seems that the meaning of this word would be clear to any person skilled in the art. The inventors would prefer not to include the viscosity range recited on Page 5, line 30, unless absolutely necessary.

Referring now to the objections raised in the Examination Report from Singapore, I have the following comments on the references cited therein:-

US-A-3640741 (Etes) is entirely irrelevant to the presently claimed invention, because it relates to non-aqueous plastic masses rather than aqueous gels. The specific problem addressed by the present invention is hydrolysis of alginate in alginate aqueous gels by autoclaving. This problem does not arise in the Etes reference, because there is no water in the plastic masses of Etes. On the contrary, Etes seeks to promote reaction between a polyhydric alcohol matrix and dissolved alginate in order to achieve cross-linking of the alginate into a solid plastic mass.

EP-A-0159168 describes a matrix for the transdermal administration of drugs. This reference is entirely irrelevant to the presently claimed invention because it does not relate to aqueous gels for wound treatment. On the contrary, the compositions of EP-A-0159168

are tacky compositions for application to intact skin. The compositions described in this reference are clearly unsuitable for application to a wound, because they are adherent. Furthermore, it is not apparent that the compositions described in EP-A-0159168 can be heat sterilised. Since the compositions are intended for application to intact skin, the issue of sterilisation is not addressed.

EP-A-0379147 describes an alginate gel for oral pharmaceutical administration. There is no teaching or suggestion of application of the gels to a wound. The gels are formed by mixing at 0-100°C, preferably 20-70°C, and there is no teaching of autoclave sterilisation. Moreover, the polyhydric alcohol is stated to function only as a solvent. The specific example in the description uses carrageenan as the gelling agent, and there is no suggestion that propylene glycol stabilises aqueous alginate gels against breakdown during autoclave sterilisation.

FR-A-2489145 describes aqueous gels for application to the surface of wounds. The gels may contain alginate as the gelling agent, and may contain glycerol and propylene glycol. However, there is no teaching or suggestion that the presence of high levels of polyhydric alcohols (15-40% w/v) can render aqueous alginate gels autoclave sterilisable. On the contrary, the specific example in the French reference describes heat sterilisation of a sodium carboxylmethyl cellulose gel. This is similar to the heat sterilisable hydroxyethyl cellulose described in WO84/00111 cited on Page 2 of the present application, and provides no indication of the novel technical effect on which the present invention is based.

US-A-4391799 and US-A-4393048 (Mason *et al.*) both relate to non-heat-sterilisable alginate gels containing relatively low levels of polyhydric alcohols, as discussed above.

US-A-5135755 is the Czech *et al.* reference discussed above.

To summarise, none of the cited documents addresses the problem of breakdown of aqueous alginate gels upon heat sterilisation. The assertions of lack of inventive step are based on hindsight analysis from the cited documents, and not on an objective analysis of the problem addressed by the present invention.