



## PATENTS ACT 1977

APPLICANT	Starna Scientific Limited
ISSUE	Inventive Step
HEARING OFFICER	Peter Mason

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## DECISION

### Introduction

1. This decision concerns patent application GB 1421819.2 “PCR validation tubes” in the name of Starna Scientific Limited, and whether the invention, as defined by the claims, comprises an inventive step as required by section 1(1)(b) of the Patents Act 1977 (herein after the “Act”). The application was filed on 8 December 2014 claiming priority to 6 December 2013 and was published on 11 November 2015.
2. In their initial examination report the examiner presented their view the independent claims did not involve the inventive step required by section 1(1) of the Act, in respect to cited prior art documents. After several rounds of correspondence and amendment to the claims the agent has been unable to convince the examiner that they are inventive. At this impasse, the agent has accepted the examiner’s suggestion to refer the application to a hearing officer.
3. The hearing took place on 4 August 2021 where the applicant was represented by Mr David Moore of Jensen and Son. Also present was my assistant senior patent examiner Sean O’Connor.
4. The only substantive matter before me is whether the invention involves an inventive step with respect to the cited prior art. Therefore, if I find that the claimed invention comprises an inventive step with respect to the prior art, I will return the application to the examiner to complete the substantive examination.

### The Invention

5. The application relates to a method of validating a polymerase chain reaction (PCR) thermal cycler. The method generally concerns suspending a fluorophore in a thermoplastic matrix, wherein the fluorophore has a predetermined property. The thermal cycler is validated by comparing measurements obtained by the thermal cycler, regarding the fluorophore/thermoplastic complex, with a predetermined range.

6. The claims have been amended since filing and are now presented, as filed on 27 January 2021. There is a single independent claim:

*1. A method of validating a thermal cycler, characterised by the steps of:*

*suspending a fluorophore in a thermoplastic polymer matrix, wherein the fluorophore has fluorescence characteristics within a predetermined uncertainty budget, and wherein the polymer matrix is selected from the group consisting of: methyl methacrylate (PMMA), polycarbonate (PC), polyoxymethylene (POM), chlorinated polyvinyl Chloride (CPVC) Or PVC/Acrylic copolymer, and the thermoplastic matrix is cut to the shape of a PCR tube; and*

*validating the thermal cycler using measurements obtained in the thermal cycler and the predetermined uncertainty of the fluorophore:*

*wherein validating the thermal cycler includes confirming that the measurements obtained the thermal cycler match the fluorescence characteristics of the fluorophore within the predetermined uncertainty budget.*

### **The law - Inventive step**

7. Section 1(1) of the Act sets out the requirements which need to be met for a patent to be granted:

8. A patent may be granted only for an invention in respect of which the following conditions are satisfied, that is to say –

*(a) the invention is new;*  
*(b) it involves an inventive step;*  
*(c) is capable of industrial application;*  
*(d) the grant of a patent for it is not excluded by subsections (2) and (3) or section 4A below;*  
*and references in this Act to a patentable invention shall be construed accordingly.*

9. Section 3 of the Act sets out how inventive step is determined:

*An invention shall be taken to involve an inventive step if it is not obvious to a person skilled in the art, having regard to any matter which forms part of the state of the art by virtue only of section 2(2) above (and disregarding section 2(3) above).*

10. Matter which “forms part of the state of the art by virtue only of section 2(2)” is all matter which was made available to the public before the priority date of the application in question. In this case all matter published before 6 December 2013.

11. It is well-established that the approach to adopt when assessing whether an invention involves an inventive step or not is to follow the steps originally set out by the Court of Appeal in *Windsurfing*<sup>1</sup> and reformulated by the Court in *Pozzoli*<sup>2</sup>:

- (1)(a) Identify the notional “person skilled in the art”*
- (1)(b) Identify the relevant common general knowledge of that person*
- (2) Identify the inventive concept of the claim in question or if that cannot readily be done, construe it*
- (3) Identify what, if any, differences exist between the matter cited as forming part of the “state of the art” and the inventive concept of the claim or the claim as construed*
- (4) Viewed without any knowledge of the alleged invention as claimed, do those differences constitute steps which would have been obvious to the person skilled in the art or do they require any degree of invention?*

### **Arguments and analysis**

12. The issue I must now consider is whether the invention as defined by the claims comprises an inventive step as required by section 1(1)(b) of the Act. As such, I will follow the reformulated *Windsurfing* steps set out above.

*Step 1 – Identify the notional person skilled in the art and their common general knowledge.*

13. The examiner considers the person skilled in the art to be someone involved in the design of real-time polymerase chain reaction (PCR) apparatuses, including their calibration and validation. The examiner maintains that the common general knowledge of such a person would extend to commonly used validation techniques, also including a background knowledge and understanding of materials commonly used in laboratory equipment generally, and PCR apparatus in particular. This would include knowledge of real-time PCR equipment, which would include a thermal cycler in combination with an optical system capable of detecting fluorescence radiation, along with means to control the apparatus and collect and analyse data.

14. Mr Moore, during the hearing, discusses three distinct people: the PCR apparatus user, the PCR apparatus manufacturer and the PCR validation service provider. Mr Moore further discusses the roles of these people with respect to validation and calibration. Here Mr Moore argued that the end user, for example a lab technician, would be responsible for calibration of the apparatus, and an external provider would be responsible for the validation of the apparatus. Mr Moore agreed that both the calibrator and validator would have a similar skill set and would be educated to a similar level. However, Mr Moore maintained that these services would be performed by distinct people where one would not have a detailed knowledge of the techniques employed by the other. In their skeleton arguments Mr Moore relies on a ThermoFisher ® brochure<sup>3</sup> [*which is 2(3) art but uncontested*] to demonstrate

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<sup>1</sup> *Windsurfing International Inc. v Tabur Marine (Great Britain) Ltd*, [1985] RPC 59

<sup>2</sup> *Pozzoli SPA v BDMO SA* [2007] EWCA Civ 588

<sup>3</sup> Thermo Fisher Scientific, 2018, Analytic Validation Consulting Services, Ref: COL06639 0518

that, in respect to ThermoFisher®, the business of validating is distinct from the business of production.

15. Mr Moore went on to explicitly state that the skilled addressee would be an apparatus calibrator, for example a lab technician, and therefore would not have a specialised knowledge or detailed understanding of fluorescents. Mr Moore acknowledged that the calibrator would know what validation is but would not have a detailed knowledge of specific validation procedures. Mr Moore's assertions, with respect to the skilled addressee during the hearing, seem at odds with the arguments presented beforehand where Mr Moore appears to identify the skilled person as a third party company involved in validation rather than a designer of a thermal cyler or a typical end user.

16. The process of calibration and validation of a thermal cyler are distinct from the process of design and manufacture of a thermal cyler. Any thermal cyler would inevitably require calibration and, depending on its service, may need validation. Therefore, the thermal cyler designer/manufacture would have some knowledge of calibration and validation and would have included some design feature in their thermal cyler to facilitate this. It is arguable that the designer/manufacture would be responsible for calibration of their thermocycler prior to sale however it is unlikely that they would additionally be responsible for validation. Therefore, I disagree with the examiner in respect to their identification of the skilled addressee.

17. I acknowledge that validation is typically provided by a third-party, however this procedure may additionally be carried out 'in-house'; this is alluded to by the ThermoFisher® document which reads "...on average we can help you complete the validation process 62-75% faster than on your own...". Furthermore, there is an abundance of third-party providers that deliver both calibration and validation services. The skilled person would be a technician working in the field of validation and would therefore have an in-depth knowledge of validation methods, techniques and equipment. The skilled person would, on occasion, work alongside a calibration technician. I agree with Mr Moore that the validation technician would have a similar academic grounding and skillset as the calibration technician, furthermore I would expect these technicians work alongside one another on occasion. Consequently, the skilled person, in addition to their expertise pertinent to validation, would have a good understanding of their colleagues role and practices. I have no doubt that the validation technician, when faced with a method of calibration that would have application in their own field would be able to identify it as such.

*Step 2 - Identify the inventive concept of the claim in question or if that cannot readily be done, construe it*

18. The examiner explicitly identifies that the inventive concept is a method of using a fluorophore suspended in a polymer matrix for validating a thermal cyler, where the polymer matrix is selected from one of polymethyl methacrylate (PMMA), polycarbonate (PC), polyoxymethylene (POM), chlorinated polyvinyl chloride (CPVC), or PVC/Acrylic copolymer. The examiner further observes that the inventive concept additionally incorporates the polymer matrix being formed into the shape of a PCR tube.

19. Mr Moore, throughout the correspondence, has refrained from explicitly setting out their interpretation of the inventive concept. Similarly, in their skeleton arguments they circumvent this step and instead choose to identify the problem addressed by the invention, which relates to validation of a device, and how validation differs from calibration. Mr Moore continued this line of reasoning throughout the hearing however when asked directly whether the inventive concept incorporated the thermoplastic polymer matrix being cut to the shape of a PCR tube, Mr Moore asserted that this particular feature *per se* is novel and agreed its inclusion into the inventive concept.

20. It seems to me, from the skeleton arguments and the hearing, that both the examiner and Mr Moore agree on the inventive concept. Furthermore, I agree with the examiner's identification of the inventive concept.

*Step 3 - Identify what, if any, differences exist between the matter cited as forming part of the "state of the art" and the inventive concept of the claim or the claim as construed*

21. In their final report of 11 February 2021, the examiner re-iterates their view with respect to the relevant prior art found, which are;

D1: US 2008/0178653 A1 20080731 (GUNSTREAM)

D2: WO 00/017627 A1 (TURNER)

D3: Journal of Fluorescence, Vol. 1, No. 3, 2005, Giebeler R., et al., "Performance Validation for Microplate Fluorimeters", pp. 363-375.

22. D1 concerns a method of calibrating emission data, and other information collected during a PCR over a single cycle, or a plurality of cycles. Paragraph [0003] identifies the disadvantages of calibrating a machine by using a well plate filled with a single dye, these disadvantages generally relate to lack of uniformity between instruments and the time it takes to cycle different dyes. D1 proposes a solution wherein a method of calibration uses a reference material comprising a plurality of different dyes in a single well plate, wherein these dyes may comprise a dry dye material. The well plate has a plurality of wells 204, 206, 208, 210 for receiving the dye material, however alternative support arrangements for the reference material are additionally disclosed.

23. D2 primarily concerns fluorometric standard comprising a housing 10, which receives a fluorescent fibre standard 14, used in the calibration of fluorometers. D2 additionally discloses several commercially available standards at page 7, and it is this disclosure that the examiner relies on to teach the invention. These standards are described as '...polymethylmethacrylate (PMMA) standards comprising fluorophores in various concentrations...".

24. D3 discloses the validation of fluorimeters using a solid-state standard used with a 96-well microplate, and discloses investigations based on three distinct polymers. The examiner argues that the microplate would, as a matter of course, comprise tubes that would be suitable for a PCR thermal cycler.

25. The examiner identifies two significant distinctions between the prior art and the invention relating to;

- (i) the validation of a thermal cycler (real-time PCR machine), and
- (ii) the specific polymers defined in claim 1.

26. The examiner argues that D1 and D3 are distinguishable from the invention with respect to both (i) and (ii), whereas D2 differs from the invention only with respect to (i). These distinctions are not contested.

27. I agree with the distinctions noted by the examiner. However, as confirmed by the examiner, the inventive concept of the invention additionally includes the polymer matrix being cut into the shape of a PCR tube. Despite this feature being seemingly asserted by the examiner there no explicit discussion of this feature in any of the arguments previously presented by either the examiner or Mr Moore.

28. In their letter dated 11<sup>th</sup> February 2021 the examiner refers to paragraph [0031], which reads; ‘...*suspending, inserting, wrapping, applying or some other method of capturing and/or encapsulating each dye, fluorescent marker or other reference material for spectral calibration in a medium than can **comprise for example a solid**, a polymer, or another medium*” [my emphasis]. I might presume that the examiner is relying on this disclosure to infer that the dye is formed of a solid in the shape of a PCR tube.

29. The applicant was given the opportunity to consider D1 paragraph [0031] and [0032], during the hearing. The applicant argued that these paragraphs merely amounted to generalised statements of the common general knowledge at the time of the disclosure relating to the ease of working with solid samples over liquid samples.

30. Paragraph [0031] simply recites a list of alternative methods of encapsulating a reference material in a list of alternative mediums in order to enable the advantages of utilising a solid sample. Paragraph [0032] merely recites how the reference materials may be arranged within/on a multi-well plate, or some other location. I am unable to identify anything in D1 that suggests that a thermoplastic polymer matrix, in which a fluorophore is suspended, is cut to the shape of a PCR tube. Therefore, this provides a further distinction between D1 and the present invention.

31. Turning to D2; the housing 10 receives a cylindrical shaped fluorescent fibre standard 14. D2 tells us that the housing is dimensioned to fit with a desired instrument however there is no additional disclosure relating to the shape of the standard *per se*. Turning to D3 there is no disclosure relating to the shape or form of the solid state standards. Therefore, this third distinction is applicable to D2 and D3 also.

*Step 4 – Viewed without any knowledge of the alleged invention as claimed, do those differences constitute steps which would have been obvious to the person skilled in the art or do they require any degree of invention*

32. I understand that D1 discloses the use of a dry dye as the reference material, and this reference material may be placed in a sample well, or an alternative region, of the well plate. However, there is insufficient detail relating to the dry dye material for me to conclude how the dry dye material is formed for placement in a respective well (i.e. in particulate, or capsule form), or in an alternative region such as an intestinal space, a sample support or alternative platform. Assuming the skilled person would understand that the dry dye is formed from a cut thermoplastic matrix, the skilled person would not be motivated to ensure thermoplastic matrix is cut in the shape of a PCR tube to replace the individual well. Furthermore, if the cut thermoplastic matrix is to be arranged in one of the alternative locations it seems unnecessary to cut the thermoplastic matrix into the shape of a PCR tube over any other shape.

33. Similar consideration is given with respect to the solid-state standards used with the 96-well microplate of D3. There is no disclosure in respect to the shape or form of the solid-state standard or how this standard is retained in the microplate. Without any additional disclosure I am unable to conclude that the skilled person would modify the arrangement such that the solid-state standard is provided in the form of a PCR tube. Therefore, the invention is not obvious with respect to D1 or D3.

34. Starting from D2 the standard is shaped to be received in a housing which is then placed in a fluorometer to be calibrated. The standard would therefore be shaped specifically to fit in the housing and not an existing feature of the machine such as a well plate or similar receptacle configured to receive a PCR tube. Consequently, the skilled person would have no motivation to provide the standard of D2 cut in the shape of a PCR tube. Therefore, the invention is not obvious with respect to D2.

35. I have determined that the invention provides an inventive step in regard to the cut shape of the thermoplastic matrix. Therefore, it is not necessary for me to consider the other distinctions.

## **Conclusion**

36. I find that the claims comprise an inventive step as required by section 1(1)(b) of the Act. I therefore refer the application back to the examiner to conclude the proceedings.

## **Appeal**

37. Any appeal must be lodged within 28 days after the date of this decision.

## **Peter Mason**

Deputy Director, acting for the Comptroller