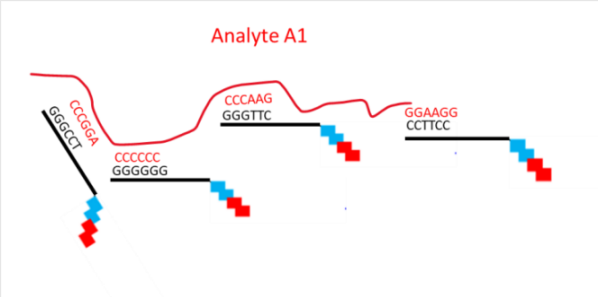
UPC Court of Appeal, 26 February 2024, Nanostring v 10x Genomics II



PATENT LAW – PROCEDURAL LAW

Munich Local Division had jurisdiction for provisional measures

- **because attacked embodiments had been offered in Germany** (**Article 33(1)(a) UPCA**)

1. The objection raised in the Appeal that the Munich Local Division of the Court of First Instance lacked jurisdiction to decide on the application for provisional measures is not well-founded. The Local Division affirmed its jurisdiction because the embodiments atacked as infringing the patent had been offered in Germany, **Art. 33(1)(a)**, **32(1)(c)**, **26(1) UPCA**. The Appeal has not shown that this assessment is incorrect.

Formal and substantive requirements regarding application for provisional measures (Rule 206(2) RoP)

- **a distinction must be made between the formal requirements of Rule 206(2)(a) RoP and the substantive requirements of Rule 206(2)(b) to (e) RoP.**
- Formal requirements shall be examined by the Registry as soon as possible **(Rule 208(1) RoP, Rule 16(2) RoP).** If deficiencies are not corrected within 14 days a decision by default may be issued **(Rule 16(5) RoP, Rule 355(1)(a) RoP)**
- The substantive requirements concern the merits of the application for provisional measures and must be considered by the judge when making orders (**Rules 209**, **211** and **212 RoP**). In the context of the orders to be made by the judge in the exercise of his discretion, non-compliance with the requirements set out in **R. 206.2(b) to (e) RoP** may be to the detriment of the Applicant.
- The alleged breach of **R. 206.2(c), (d) and (e) RoP** does not render the application inadmissible. In the present case, the Appeal has also not shown that the Court of First Instance - erroneously in law - did not consider the non-compliance with the requirements of **Rules 206.2(b) to (e) RoP** in its discretionary decision.

Applicants 2 are entitled to file the application for provisional measures.

- **Due to their corresponding entry in the Register for Unitary Patent Protection, Applicants 2 are to be treated as the proprietor of the patent at issue** (**Rule 8(4) RoP**, **Article 47(1) UPCA**.

According to the findings of the Court of First Instance, which are not contested in the Appeal, Applicant 1 is in any case entitled to file an application as the holder of a non-exclusive licence granted to it by Applicants 2 under **Art. 47(3) UPCA**.

Claim interpretation (**article 69 EPC**, **Interpretation Protocol)**

- **The UPC Court of Appeal proceeds from the following principles in accordance with Art. 69 of the Convention on the Grant of European Patents (EPC) and the Protocol on its Interpretation.**
- The patent claim is not only the starting point, but the decisive basis for determining the protective scope of a European patent.
- The interpretation of a patent claim does not depend solely on the strict, literal meaning of the wording used (see also the German and French language versions of the Protocol on Interpretation: “aus dem genauen Wortlaut der Patentansprüche”, “sens étroit et litéral du texte des revendications”).
- Rather, the description and the drawings must always be used as explanatory aids for the interpretation of the patent claim and not only to resolve any ambiguities in the patent claim.
- However, this does not mean that the patent claim merely serves as a guideline and that its subject-matter also extends to what, after examination of the description and drawings, appears to be the subject-matter for which the patent proprietor seeks protection.
- The patent claim is to be interpreted from the point of view of a person skilled in the art.
- In applying these principles, the aim is to combine adequate protection for the patent proprietor with sufficient legal certainty for third parties.
- These principles for the interpretation of a patent claim apply equally to the assessment of the infringement and the validity of a European patent. This follows from the function of the patent claims, which under the European Patent Convention serve to define the scope of protection of the patent under **Art. 69 EPC** and thus the rights of the patent proprietor in the designated Contracting States under **Art. 64 EPC**, taking into account the conditions for patentability under **Art. 52** to **57 EPC** (see **EPO EBA, 11 December 1989, G 2/88, OJ 1990, 93 para. 2.5**).

Court of First Instance’s interpretation

- **that a cell or issue sample within the meaning of claim 1 is to be understood as a sample which is still structurally recognisable as a cell or issue must be accepted.**
- Such an understanding is supported by the wording of the claim, which distinguishes between the plurality of analytes to be detected and the cell or issue sample, so that the two cannot be identical. Although the analytes are indeed part of the cell or issue sample, the cell or issue sample must be structurally recognisable as such

even beyond the analytes, which is expressed in the wording of the claim by the phrase "... analytes in a cell or issue sample".

- It is consistent with the wording of the claim understood in this way that at the beginning of the description it is stated that the need for multiplexing techniques in biology is often due to the fact that test samples are precious and researchers do not know precisely what to look for (patent at issue, para. 2).
- Such an interpretation is not precluded by the fact that the description in paragraphs 48 and 49 mentions various types of sample processing, including, in addition to those in which the cell or issue sample is preserved, such as fixation, permeabilisation, mounting on a solid support, blocking of non-specific binding sites (patent at issue, para. 49, first sentence), also those in which proteins or nucleic acids are isolated from a cell or issue sample, separated electrophoretically on a separation medium and then applied to a blo□ng membrane (patent at issue, para. 49, second sentence).
- **It does not follow from the mere mention in the description that the proteins or nucleic acids are to be regarded as analytes in a cell or issue sample within the meaning of patent claim 1 even after they have been processed as last mentioned.**

Contrary to the Court of First Instance's understanding,

- **it cannot be inferred from patent claim 1 that the detection reagents must remain bound to the respective analytes throughout the entire detection procedure according to feature group 4.**
- The Court of Appeal agrees with the Court of First Instance that the detection reagents must bind securely to the respective analytes and, in order to make this possible, a sufficient incubation time of the cell or issue sample together with the plurality of detection reagents must be provided, in accordance with feature 3.
- Contrary to the opinion of the Court of First Instance, however, the need for a sufficient incubation period does not preclude the decoder samples, once they have securely bound to the respective analytes, from being removed again at a later stage, for example together with the removal of the signal signatures provided for in feature 4.3, and from being replaced again with the same detection reagents.

This is consistent with the wording of claim 1, which provides for a detection method "comprising" the method steps "(c) incubating" and "(d) detecting" but does not specify that the former may not be carried out multiple times.

It is, on the balance of probability, more likely than not that the subject-matter of claim 1 will prove to be not patentable

- **the validity of the patent at issue is not established with a sufficient degree of certainty for the [preliminary] injunction requested to be issued.**

Standard of proof regarding order for provisional measures issued by way of summary proceedings

- **Since the order for provisional measures is issued by way of summary proceedings pursuant to R. 205 et seq. RoP, in which the opportunities for the parties to present facts and evidence are limited, the Court of Appeal agrees with the Court of First Instance that the standard of proof must not be set too high, in particular if delays associated with a reference to proceedings on the merits would cause irreparable harm to the proprietor of the patent**
- as provided for in **Art. 62(2) and (5)**, **60(5) UPCA** (see **CJEU, judgment of 28 April 2022, Phoenix Contact, C-44/21, EU:C:2022:309,** para. 32 with reference to **Art. 9(1)(a) Directive 2004/48/EC**).
- **On the other hand, it must not be set too low in order to prevent the defendant from being harmed by an order for a provisional measure that is revoked at a later date** pursuant to **Art. 62(5), Art. 60(8) and (9) UPCA**, **R. 213 RoP**, **Art. 62(2) UPCA**, cf. also **Art. 9(7) Directive 2004/48/EC**.

Burden of proof

- **facts giving rise to the entitlement to initiate proceedings and the infringement or imminent infringement of the patent, as well as other circumstances favourable to the infringement action, are to be presented and proven by the rightholder, whereas the burden of presentation and proof with regard to the facts from which the lack of validity of the patent is derived and other circumstances favourable to the invalidity or revocation lies with the opponent**
- **R. 211.2 RoP**, in conjunction with **Art. 62(4) UPCA** (see also **Art. 9(3) Directive 2004/48/EC**), provides that the court may invite the applicant for provisional measures to provide reasonable evidence to satisfy the court to a sufficient degree of certainty that the applicant is entitled to institute proceedings under **Art. 47 UPCA**, that the patent is valid and that his right is being infringed, or that such infringement is imminent.
- Such a sufficient degree of certainty requires that the court considers it at least more likely than not that the Applicant is entitled to initiate proceedings and that the patent is infringed. A sufficient degree of certainty is lacking if the court considers it on the balance of probabilities to be more likely than not that the patent is not valid.
- The burden of presentation and proof for facts allegedly establishing the entitlement to initiate proceedings and the infringement or imminent infringement of the patent, as well as for all other circumstances allegedly supporting the Applicant's request, lies with the Applicant, whereas, unless the subject-matter of the decision is the ordering of measures without hearing the defendant pursuant to **Art. 60(5)** in conjunction with **Art. 62(5) UPCA**, the burden of presentation and proof for facts concerning the lack of validity of the patent and other circumstances allegedly supporting the Defendant's position lies with the Defendant.
- **The aforementioned allocation of the burden of presentation and proof in summary proceedings is in**

line with the allocation of the burden of presentation and proof in proceedings on the merits, in which facts giving rise to the entitlement to initiate proceedings and the infringement or imminent infringement of the patent, as well as other circumstances favourable to the infringement action, are to be presented and proven by the rightholder (**Art. 54**, **63**, **64** and **68 UPCA**, **R. 13.1(f) and (l)-(n) RoP**), whereas the burden of presentation and proof with regard to the facts from which the lack of validity of the patent is derived and other circumstances favourable to the invalidity or revocation lies with the opponent (**Art. 54** and **65(1) UPCA**, **Rules 44(e)-(g)**, **25.1(b)-(d) RoP**).

More likely than not that the subject-matter of claim 1 in the version of the main request will prove to be obvious (article 56 EPC).

- **Likely that for a person skilled in the art at the priority date of the patent at issue, after successful application of an *in vitro* multiplex method for the detection of ASMs, the next step was to consider transferring the method to an *in situ* environment**

D6 would have been of interest to a person skilled in the art who, at the priority date of the patent at issue, was seeking to develop high-throughput optical multiplexing methods for detecting target molecules in a sample, as it discloses a method for detecting a plurality of amplified single molecules (ASMs) by encoding and decoding the single molecules, wherein the encoding is performed via probe-mediated generation of ring-shaped DNA and the decoding is performed by temporally sequential detection of the targeted ASMs (cf. D6, Abstract) (see also the Swedish Intellectual Property Office, PRV Consulting Report of 28 June 2023, B10, p. 5).

This is admittedly disclosed in D6 for ASMs ordered *in vitro* in an array format. However, given the demand for multiplex analysis techniques, especially for test samples, at the priority date (see patent at issue, para. 2), there was a need to consider whether the encoding and decoding method disclosed in D6 could be transferred to the detection of ASMs in cell or issue samples.

An incentive or confirmation for thinking in this direction also resulted from the indication in D6 that in the prior art rolling-circle ASMs had been used for the readout of various genotyping assays as well as for the detection of proteins and protein complexes *in situ* using proximity ligation. The fact that the "genotyping assays" were carried out in situ can be seen from footnote 20 of D6, which refers to Larsson et al, "In situ genotyping individual DNA molecules by target-primed rolling-circle amplification of Padlock probes", Nat. Methods 2004, 1, 227 ff, which describes an *in situ* procedure already according to the title. In addition, D6 refers to a publication on the *in situ* observation of protein complexes (Söderberg et al., *Direct observation of individual endogenous protein complexes* in situ *by proximity ligation*, Nat. Methods 2006, vol. 3 no. 12 [D19]).

That for a person skilled in the art at the priority date of the patent at issue, after successful application of an *in vitro* multiplex method for the detection of ASMs, the next step was to consider transferring the method to an *in situ* environment is further evidenced by B30 (Stougaard et al., In situ *detection of non-polyadenylated RNA molecules using Turtle Probes and target primed rolling circle PRINS*, BMC Biotechnology 2007, 7:69).

Reasonable expectation of success from a technical point of view

- **Problems such as "molecular crowding" or "autofluorescence" are problems that regularly arise in connection with the *in situ* detection of analytes in issue or cell samples – but which a person skilled in the art would have been able to deal with on the basis of their expertise at the priority date and which therefore would not have prevented them from carrying out tests in the aforementioned sense due to insufficient prospects of success**

The Applicants' objection that there was no reasonable expectation of success from a technical point of view because they would have been confronted with problems such as "molecular crowding" (the difficulty of distinguishing between multiple analytes occurring in close proximity) or "autofluorescence" (unpredictable interactions) in the cell or issue sample cannot be accepted either. In the opinion of the Court of Appeal, adjudicating with two technically qualified judges, these are problems that regularly arise in connection with the *in situ* detection of analytes in issue or cell samples – but which a person skilled in the art would have been able to deal with on the basis of their expertise at the priority date and which therefore would not have prevented them from carrying out tests in the aforementioned sense due to insufficient prospects of success (see also the Swedish Intellectual Property Office, PRV Consulting Report, B10, p. 5). This assessment is supported by the fact that the patent at issue does not provide any information on how to deal with the aforementioned problems with *in situ* detection, such as when using immunohistochemistry methods or RNA fluorescence in situ hybridisation (FISH) (patent at issue, cf. para. 48 et seq, para. 212 et seq, "Sample", para. 224 et seq "Applications of the detection reagents"; para. 234 "Immunohistochemistry"; para. 235 "In-situ-hybridisation", "Fluorescence in-situ hybridisation").

Obvious for a person in the art

- **who, proceeding from D6, was prompted to transfer the *in vitro* multiplex detection method disclosed therein to cell or issue samples, to also use the techniques of immunohistochemistry and/or fluorescence *in situ* hybridisation known to him or her on the basis of his or her expertise**

(see also, however, Bundespatentgericht, Qualifizierter Hinweis of 7 February 2023 [BP9], p. 10).

bb) Immunohistochemistry is a technique which, at the priority date, would have been known to a person skilled in the art, and by which analytes can be visualised for microscopic evaluation with the aid of labelled antibodies (cf. patent at issue, para. 234).

Fluorescence *in situ* hybridisation is a technique for detecting cellular DNA or RNA, also known to a person

skilled in the art at the priority date, in which the probe hybridising with the target analyte is detected by means of a fluorescent dye (see patent at issue, para. 235).
For a person skilled in the art who, proceeding from D6, was prompted to transfer the *in vitro* multiplex detection method disclosed therein to cell or issue samples, it was obvious to also use the techniques of immunohistochemistry and/or fluorescence *in situ* hybridisation known to him or her on the basis of his or her expertise (see also, however, Bundespatentgericht, Qualifizierter Hinweis of 7 February 2023 [BP9], p. 10).

Arguments regarding lack of inventive step auxiliary request, although only presented at oral hearing, are in the present case part of the subject-matter of the proceedings before the Court of Appeal (Rule 222 RoP). Applicants defence not unduly disadvantaged

- **Defendants expressly requested a "judicial reference", if a submission on the content of the request was required.**
- In view also of the fact that this is the first appeal case in which auxiliary requests and **R. 222.1** RoP are being used for the decision, the court instructed the parties at the oral hearing to also comment on the validity of the auxiliary request.
- Since the argumentation on the lack of inventiveness of the auxiliary request largely matches the argumentation on the inventiveness of the main request, the Applicants' defence was not unduly disadvantaged by this

Source: **Unified Patent Court** as **rectified at 11/03/2024**

UPC Court of Appeal,
26 February 2024
(Grabinski, Barutel, Blok, Friedrich, Schüler)
Reference number:
UPC_CoA_335/2023
APL_576355/2023
Order
of the Court of Appeal of the Unified Patent Court
issued on 26/02/2024
in the proceedings for provisional measures
concerning **EP 4 108 782**

HEADNOTES:

*1. Compliance with the requirements set out in **R. 206.2(b) to (e) RoP** concerns the merits of the application for provisional measures, the examination of which is the responsibility of the judge and must be considered by the judge when making orders under **Rules 209**, **211** and **212 RoP**.*

*2. The patent claim is not only the starting point, but the decisive basis for determining the protective scope of a European patent under **Art. 69 EPC** in conjunction with the **Protocol on the Interpretation of Art. 69 EPC**.*

The interpretation of a patent claim does not depend solely on the strict, literal meaning of the wording used. Rather, the description and the drawings must always be used as explanatory aids for the interpretation of the patent claim and not only to resolve any ambiguities in the patent claim.

~~This~~ However, this does not mean that the patent claim merely serves as a guideline ~~but~~ and that its subject-matter also extends to what, after examination of the description and drawings, appears to be the subject-matter for which the patent proprietor seeks protection.[1]

The patent claim is to be interpreted from the point of view of a person skilled in the art.

In applying these principles, the aim is to combine adequate protection for the patent proprietor with sufficient legal certainty for third parties.

These principles for the interpretation of a patent claim apply equally to the assessment of the infringement and the validity of a European patent.

*3. A sufficient degree of certainty pursuant to **R. 211.2 RoP**, in conjunction with **Art. 62(4) UPCA** (see also **Art. 9(3) Directive 2004/48/EC**) requires that the court considers it on the balance of probabilities at least more likely than not that the Applicant is entitled to initiate proceedings and that the patent is infringed. A sufficient degree of certainty is lacking if the court considers it on the balance of probabilities to be more likely than not that the patent is not valid. The burden of presentation and proof for facts allegedly establishing the entitlement to initiate proceedings and the infringement or imminent infringement of the patent, as well as for all other circumstances allegedly supporting the Applicant's request, lies with the Applicant, whereas, unless the subject-matter of the decision is the ordering of measures without hearing the defendant pursuant to Art. 60(5) in conjunction with **Art. 62(5) UPCA**, the burden of presentation and proof for facts concerning the lack of validity of the patent and other circumstances allegedly supporting the Defendant's position lies with the Defendant.*

KEYWORDS:
Appeal, application for provisional measures, burden of proof, claim construction, examination of formal requirements, extent of protection, infringement, inventive step, novelty, person skilled in the art, provisional injunction, sufficient degree of certainty, summary proceedings, validity of patent.

DEFENDANTS and APPELLANTS
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3. **NanoString Technologies Netherlands B.V.** Paasheuvelweg 25 - 1105BP - Amsterdam - NL
Represented by: Oliver Jan Jüngst, Attorney at Law (Bird & Bird LLP**)**

APPLICANTS and DEFENDANTS
1. **10x Genomics, Inc.** 6230 Stoneridge Mall Road - 94588-3260 - Pleasanton (CA) - US

[1] Editor IPPT: marked to show changes made with the **rectification of 11/03/2024**

2. **President and Fellows of Harvard College** Suite 727E, 1350 Massachusetts Avenue - 02138 - Cambridge (MA) - US
Represented by: Prof. Dr. Tilman Müller-Stoy, Attorney at Law (Bardehle Pagenberg Partnerschaft mbB)

PATENT AT ISSUE

EP 4108782

PANELS AND DECIDING JUDGES

First panel
Klaus Grabinski, presiding judge and judge-rapporteur
Françoise Barutel, legally qualified judge
Peter Blok, legally qualified judge
Rainer Friedrich, technically qualified judge
Cornelis Schüller, technically qualified judge

LANGUAGE OF THE PROCEEDINGS

German

IMPUGNED ORDER

Order ("Decision and orders") of the Court of First Instance (Munich Local Chamber) dated 19/09/2023 - UPC CFI 2/2023

ORAL HEARING OF:

18/12/2023

FACTS AND REQUESTS OF THE PARTIES

1. The Applicants and Respondents (hereinafter the "Applicants") seek a cease-and-desist order against the Defendants and Appellants (hereinafter the "Defendants") by way of provisional legal protection for direct and indirect infringement of the European patent with unitary effect (unitary patent) 4 108 782 (patent at issue).

The patent at issue was filed on 27 April 2022 as a divisional application of the application EP 18173059.9, which in turn had been filed as a divisional application for the application EP 12860433.7 (parent application). The parent application was filed on 21 December 2012 as an international application (PCT/US2012/071398) and led to the grant of European patent 2 794 928 (parent patent). The patent at issue claims US priority dated 22 December 2011. The mention of grant of the patent at issue was published on 7 June 2023.

The patent at issue relates to compositions and methods for analyte detection. Its claim 1 reads as follows in the language of proceedings under Art. 70(1) EPC:

> *A method for detecting a plurality of analytes in a cell or tissue sample, comprising:*
> *(a) mounting the cell or tissue sample on a solid support;*
> *(b) contacting the cell or tissue sample with a composition comprising a plurality of detection reagents, the plurality of detection reagents comprising a plurality of subpopulations of detection reagents;*
> *(c) incubating the cell or tissue sample together with the plurality of detection reagents for a sufficient amount of time to allow binding of the plurality of detection reagents to the analytes; wherein each subpopulation of the plurality of detection reagents targets a different analyte, wherein each of the plurality of detection reagents comprises: a probe reagent targeting an analyte of the plurality of analytes and one or a plurality of pre-determined subsequences, wherein the probe reagent and the one or the plurality of pre-determined subsequences are conjugated together;*
> *(d) detecting in a temporally-sequential manner the one or the plurality of pre-determined subsequences, wherein the detecting comprises:*
> *(i) hybridizing a set of decoder probes with a subsequence of the detection reagents, wherein the set of decoder probes comprises a plurality of subpopulations of decoder probes and wherein each subpopulation of the decoder probes comprises a detectable label, each detectable label producing a signal signature;*
> *(ii) detecting the signal signature produced by the hybridization of the set of decoder probes;*
> *(iii) removing the signal signature; and*
> *(iv) repeating (i) and (iii) using a different set of decoder probes to detect other subsequences of the detection reagents, thereby producing a temporal order of the signal signatures unique for each subpopulation of the plurality of detection reagents; and*
> *(e) using the temporal order of the signal signatures corresponding to the one or the plurality of the pre-determined subsequences of the detection reagent to identify a subpopulation of the detection reagents, thereby detecting the plurality of analytes in the cell or issue sample.*

The research on which the parent application is based was financially supported with public funds from the US National Institutes of Health (NIH). The funding is based on a contract between the Applicant and the NIH. The contract also gives rise to obligations for Applicant 2, the exact nature of which is disputed between the parties.

Applicants 2 are registered as the proprietor of the patent at issue. According to the contractual agreement, they have granted Applicant 1 an exclusive licence to the German part of the parent patent and "any divisional patent" thereof with effect from 14 February 2023, and an exclusive licence to all national parts of the parent patent except the German part and "any divisional patent" thereof with effect from 30 May 2023.

Defendant 1 is an American company. It is the parent company of a group of companies operating under the name "NanoString". Defendant 2 is the German sales and marketing company in this group of companies. Defendant 3 maintains the European headquarters of the group of companies in Amsterdam.

Contested embodiment 1 ("CosMx Spatial Molecular Imager", abbreviated as "CosMx SMI") enables highly sensitive, subcellular imaging of a variety of RNAs or proteins directly from individual cells in morphologically intact issue samples. Samples, in particular biological samples such as fixed cells and issue sections, can be automatically analysed for the presence of certain analytes, namely RNA and proteins. Contested embodiment 1 has been available on the

market since December 2022. It is also used in the Defendants' so-called CX-Lab in Amsterdam, whereby the data obtained is analysed in the cloud, on servers that are not operated on the territory of the UPC Contracting Member States.
Contested embodiment 2 is a detection reagent that can be used only for the detection of RNA. Contested embodiment 2 is sold in a kit as a so-called "CosMx RNA Panel" in a standard variant ("off-the-shelf RNA Add-On") and according to customer specifications ("Custom RNA Add-On Probes").
Contested embodiment 3 is a probe that binds as a secondary probe to the primary probe that has already bound to its analyte (RNA or protein); contested embodiment 3 is marketed in so-called "CosMx RNA Imaging Trays". These products are available for the detection of 100 RNAs (100-plex) or 1000 RNAs (1000-plex), each for 2 or 4 slides. Contested embodiment 3 can be used for the detection of RNA as well as for the detection of proteins.
The Defendants offer the contested embodiments individually or in combination.
The Defendant side repeatedly requested the Applicant 2 to put forward a licence offer on reasonable terms with regard to the patent at issue.
Defendant 1 has filed an Objection against the grant of the patent at issue with the European Patent Office.
On 1 June 2023, the Applicants applied to the Court of First Instance (Munich Local Division) for an order for a preliminary injunction for direct and indirect infringement of the patent at issue. In addition, the Applicants have requested the imposition of a penalty payment in the event of any breach of the court orders that they have requested.
The Applicants initially chose a wording for the application that matched claim 1 of the patent at issue word-for-word and referred geographically to "the participating Member States". In view of Defendant 1's objection, the Applicants later amended their application by naming the Contracting States of the UPC Agreement and deleting the words "one or" before "a plurality of pre-determined subsequences".
In response to the Court of First Instance's indication at the oral hearing that the question of the validity of the patent at issue was open after the preliminary deliberations and that the requests for orders in parallel proceedings concerning the parent patent had been lodged in a version restricting the patent claim of the parent patent, the Applicants added an auxiliary request to their main request.
The Defendants have requested that the Applicants' main and auxiliary requests be rejected and, in the alternative, that they be permitted to continue the allegedly infringing activity against the provision of security and, in the further alternative, that the granting of provisional measures be made dependent on the provision of security by the Applicants.
2. By its **Order ("Decision and Orders") dated 19 September 2023 (hereinafter the "Order"),** the Court of First Instance considered the Applicants' main request to be admissible and largely justified and essentially stated the following in its reasoning:
The Munich Local Division of the Unified Patent Court had jurisdiction to decide on the Application for provisional measures, since the contested embodiments had also been offered in Germany.
The request was admissible. The Request fulfilled the requirements of **R. 206.2(a), (c), (d) and (e)** of the Rules of Procedure of the Unified Patent Court (RoP). In this respect, it was not a question of content but of form. In that respect, the submissions in the Request were sufficient.
The Applicants were entitled to file an application. Applicant 2 was the registered proprietor of the patent at issue and Applicant 1 was entitled to file an application at least as the holder of a non-exclusive licence pursuant to **Art. 47(3)** of the Agreement on a Unified Patent Court (UPCA).
According to the wording of claim 1 of the patent at issue, a part of the genomic DNA that has been isolated from a cell and amplified cannot be termed a cell or issue sample according to the claim. For a subpopulation of the detection reagents, it is not necessary for the probe reagent to be identical. The only decisive factor is that it targets the same analyte. Claim 1 presupposes that the bond between the analyte and the detection reagent, established by incubating the cell or issue sample with the detection reagents, continues to exist during the second stage of the process. In addition to steps (i) and (iii), step (ii) is also the object of the repetition of the steps to be carried out for the detection of the subsequences in a temporally-sequential manner, since the intended use of the temporal order of the signal signatures would no longer be possible without repeating the detection of the signal signature provided for in step (ii).
Against the background of this interpretation, the fact that step (ii) was no longer provided for in the patent claim could not constitute an inadmissible extension of the content of the original application.
The Court of First Instance is also satisfied that the subject matter of patent claim 1 is novel. The object of the detection in D6 (Jenny Göransson et al., *A single molecule array for digital targeted molecular analyses*, Nucleic Acids Research, 2009, Vol. 37, No. 1, e7) is not analytes from cell or issue samples, but so-called amplified single molecules (ASMs), which are obtained from "padlock or selector probes". In addition, with D6 the bond between analyte and reagent is broken "after each imaging".
It was also not to be expected that the subject mater of patent claim 1 would be declared invalid due to a lack of inventive step. It was not shown what reason there was for a person skilled in the art to deviate from the solution, described in D8 (Dzifa Y. Duose et al., *Multiplexed and Reiterative Fluorescence Labeling via DNA Circuitry*, Bioconjugate Chem. 2010, 21, 2327-2331), for *in situ* analysis for cell or issue samples and instead apply a fundamentally different method from a fundamentally different context in order to be able to detect more analytes, as taught in D6. D6 itself does not give a person

skilled in the art any reason to transfer the encoding and decoding method disclosed for an array of ASMs to cell or issue samples that have been mounted on a solid support.
The Court of First Instance was also satisfied that a person skilled in the art would have been able to carry out the invention and, in particular, would have been able to choose an appropriate sequence length for the implementation of the patented method.
It was also sufficiently certain that patent claim 1 was directly and indirectly infringed. The fact that the detection is based on a cycle-based order of the signal signatures and thus not simply on a temporal order does not mean that the teaching according to the patent has not been realised. In addition, the fact that the data is analysed with a cloud-based solution outside the territory of the UPC Agreement does not mean that the patent at issue has not been infringed.
The order for provisional measures was necessary. The interest of the right holder in not having their rights infringed outweighs the interest of the potential infringer in securing now, through the continuation of the infringement, market share which it might be impossible for them to obtain at a later stage through a possible licence agreement. A licence claim of Defendant 2 under US law had not been established either on a contractual or antitrust basis. The same applies with regard to a licence claim under European law in accordance with the **"Huawei/ZTE" case law** of the European Court of Justice.
Considering and assessing all the circumstances of the case and weighing up all the interests of the parties, the measures requested should be ordered without the provision of security and a continuation of the infringement against the provision of security is not appropriate.
The Court of First Instance's Order instructed the Defendants

> *to cease and desist, in the territories of the Republic of Austria, the Kingdom of Belgium, the Republic of Bulgaria, the Kingdom of Denmark, the Republic of Estonia, the Republic of Finland, the French Republic, the Federal Republic of Germany, the Italian Republic, the Republic of Latvia, the Republic of Lithuania, the Grand Duchy of Luxembourg, the Republic of Malta, the Kingdom of the Netherlands, the Portuguese Republic, the Republic of Slovenia and/or the Kingdom of Sweden, from*
> *I. using or offering for use, in the territory of one or more of the States mentioned in A:*
> *a method for detecting a plurality of analytes in a cell or issue sample comprising*
> *(a) mounting the cell or issue sample on a solid support;*
> *(b) contacting the cell or issue sample with a composition comprising a plurality of detection reagents, the plurality of detection reagents comprising a plurality of subpopulations of detection reagents;*
> *(c) incubating the cell or issue sample together with the plurality of detection reagents for a sufficient amount of time to allow binding of the plurality of detection reagents to the analytes; wherein*
> *each subpopulation of the plurality of detection reagents targets a different analyte, wherein*
> *each of the plurality of detection reagents comprises: a probe reagent targeting an analyte of the plurality of analytes; and*
> *a plurality of pre-determined subsequences, wherein the probe reagent and the plurality of pre-determined subsequences are conjugated together;*
> *(d) detecting in a temporally-sequential manner the plurality of pre-determined subsequences, wherein the detecting comprises:*
> *(i) hybridizing a set of decoder probes with a subsequence of the detection reagents, wherein the set of decoder probes comprises a plurality of subpopulations of decoder probes and wherein each subpopulation of the decoder probes comprises a detectable label, each detectable label producing a signal signature;*
> *(ii) detecting the signal signature produced by the hybridization of the set of decoder probes;*
> *(iii) removing the signal signature; and*
> *(iv) repeating (i) and (iii) using a different set of decoder probes to detect other subsequences of the detection reagents, thereby producing a temporal order of the signal signatures unique for each subpopulation of the plurality of detection reagents; and*
> *(e) using the temporal order of the signal signatures corresponding to the plurality of the pre-determined subsequences of the detection reagent to identify a subpopulation of the detection reagents, thereby detecting the plurality of analytes in the cell or issue sample,*
> ***(direct infringement of claim 1 of EP 4 108 782)***
> *II. offering and/or supplying in the territory of one of the States referred to in A. for use of the method in the territory of one of the States referred to in A. or in the territories of several of these States for use in the territory of one or more of the States referred to under A:*
> *devices suitable for carrying out a method for detecting a plurality of RNAs in a cell or issue sample comprising*
> *(a) mounting the cell or issue sample on a solid support;*
> *(b) contacting the cell or issue sample with a composition comprising a plurality of detection reagents, the plurality of detection reagents comprising a plurality of subpopulations of detection reagents;*
> *(c) incubating the cell or issue sample together with the plurality of detection reagents for a sufficient amount of time to allow binding of the*

plurality of detection reagents to the RNAs; wherein
each subpopulation of the plurality of detection reagents targets a different analyte, wherein
each of the plurality of detection reagents comprises: a probe reagent targeting an RNA of the plurality of RNAs, and
a plurality of pre-determined subsequences, wherein the probe reagent and the plurality of pre-determined subsequences are conjugated together;
(d) detecting in a temporally-sequential manner the plurality of pre-determined subsequences, wherein the detecting comprises:
(i) hybridizing a set of decoder probes with a subsequence of the detection reagents, wherein the set of decoder probes comprises a plurality of subpopulations of decoder probes and wherein each subpopulation of the decoder probes comprises a detectable label, each detectable label producing a signal signature;
(ii) detecting the signal signature produced by the hybridization of the set of decoder probes;
(iii) removing the signal signature; and
(iv) repeating (i) and (iii) using a different set of decoder probes to detect other subsequences of the detection reagents, thereby producing a temporal order of the signal signatures unique for each subpopulation of the plurality of detection reagents; and
(e) using the temporal order of the signal signatures corresponding to the plurality of the pre-determined subsequences of the detection reagent to identify a subpopulation of the detection reagents, thereby detecting the plurality of RNAs in the cell or issue sample,
without
(1) stating explicitly, conspicuously and prominently on each offer, on the first page of the operating instructions, in the delivery documents and on the packaging that the devices may not be used for the detection of RNA in a method pursuant to section A.I. without the consent of Applicant 2) as proprietor of EP 4 108 782 and that they must not be used for the detection of RNA without the consent of Applicant 2),
(2) imposing on the purchasers a written obligation not to use the devices for the detection of RNA without the prior consent of Applicant 2), subject to the imposition of a reasonable contractual penalty to be paid to Applicant 2), to be determined by Applicant 2) and, if necessary, to be reviewed by the competent court, for each individual breach
(indirect infringement of claim 1 of EP 4 108 782)
III. offering and/or supplying in the territory of one of the States referred to in A. for use of the method in the territory of one of the States referred to in A. or in the territories of several of these States for use in the territory of one or more of the States referred to in A.
detection reagents suitable for carrying out a method for detecting a plurality of analytes in a cell or issue sample, comprising
(a) mounting the cell or issue sample on a solid support;
(b) contacting the cell or issue sample with a composition comprising a plurality of detection reagents, the plurality of detection reagents comprising a plurality of subpopulations of detection reagents;
(c) incubating the cell or issue sample together with the plurality of detection reagents for a sufficient amount of time to allow binding of the plurality of detection reagents to the analytes; wherein
each subpopulation of the plurality of detection reagents targets a different analyte, wherein
each of the plurality of detection reagents comprises: a probe reagent targeting an analyte of the plurality of analytes and
a plurality of pre-determined subsequences, wherein the probe reagent and the plurality of pre-determined subsequences are conjugated together;
(d) detecting in a temporally-sequential manner the plurality of pre-determined subsequences, wherein the detecting comprises:
(i) hybridizing a set of decoder probes with a subsequence of the detection reagents, wherein the set of decoder probes comprises a plurality of subpopulations of decoder probes and wherein each subpopulation of the decoder probes comprises a detectable label, each detectable label producing a signal signature;
(ii) detecting the signal signature produced by the hybridization of the set of decoder probes;
(iii) removing the signal signature; and
(iv) repeating (i) and (iii) using a different set of decoder probes to detect other subsequences of the detection reagents, thereby producing a temporal order of the signal signatures unique for each subpopulation of the plurality of detection reagents; and
(e) using the temporal order of the signal signatures corresponding to the plurality of the pre-determined subsequences of the detection reagent to
identify a subpopulation of the detection reagents, thereby detecting the plurality of analytes in the cell or issue sample,
(indirect infringement of claim 1 of EP 4 108 782)
IV. offering and/or supplying in the territory of one of the States referred to in A. for use of the method in the territory of one of the States referred to in A. or in the territories of several

of these States for use in the territory of one or more of the States referred to in A.
decoder probes suitable for carrying out a method for detecting a plurality of RNAs in a cell or issue sample, comprising
(a) mounting the cell or issue sample on a solid support;
(b) contacting the cell or issue sample with a composition comprising a plurality of detection reagents, the plurality of detection reagents comprising a plurality of subpopulations of detection reagents;
(c) incubating the cell or issue sample together with the plurality of detection reagents for a sufficient amount of time to allow binding of the plurality of detection reagents to the RNAs; wherein
each subpopulation of the plurality of detection reagents targets a different RNA, wherein
each of the plurality of detection reagents comprises: a probe reagent targeting an RNA of the plurality of RNAs and
a plurality of pre-determined subsequences, wherein the probe reagent and the plurality of pre-determined subsequences are conjugated together;
(d) detecting in a temporally-sequential manner the plurality of pre-determined subsequences, wherein the detecting comprises:
(i) hybridizing a set of decoder probes with a subsequence of the detection reagents, wherein the set of decoder probes comprises a plurality of subpopulations of decoder probes and wherein each subpopulation of the decoder probes comprises a detectable label, each detectable label producing a signal signature;
(ii) detecting the signal signature produced by the hybridization of the set of decoder probes;
(iii) removing the signal signature; and
(iv) repeating (i) and (iii) using a different set of decoder probes to detect other subsequences of the detection reagents, thereby producing a temporal order of the signal signatures unique for each subpopulation of the plurality of detection reagents; and
(e) using the temporal order of the signal signatures corresponding to the plurality of the pre-determined subsequences of the detection reagent to identify a subpopulation of the detection reagents, thereby detecting the plurality of RNAs in the cell or issue sample,
without
(1) stating explicitly, conspicuously and prominently on each offer, on the first page of the operating instructions, in the delivery documents and on the packaging that the decoder probes may not be used for the detection of RNA in a method pursuant to section A.I. without the consent of Applicant 2) as proprietor of EP 4 108 782 and that they must not be used for the detection of RNA without the consent of Applicant 2),
(2) imposing on the purchasers a writen obligation not to use the decoder probes for the detection of RNA without the prior consent of Applicant 2), subject to the imposition of a reasonable contractual penalty to be paid to Applicant 2), to be determined by Applicant 2) and, if necessary, to be reviewed by the competent court, for each individual breach
(indirect infringement of claim 1 of EP 4 108 782).

The Court of First Instance also ordered the respective Defendants to pay to the court a (possibly repeated) penalty payment of up to EUR 250,000 for each individual breach of these orders.
The Court of First Instance rejected the Applicants' other requests and the Defendants' requests.
3. The Defendants have brought an appeal against the Court of First Instance's Order and have substantiated it in a separate pleading essentially as follows:

The Local Division erred in law in assuming its jurisdiction.
The Court of First Instance's Order was erroneous in law because the Applicants had breached mandatory procedural rules.
The Court of First Instance erred in its narrow interpretation of the feature of a "cell or issue sample" in claim 1. It was also erroneous to infer that the detection reagents of a subpopulation did not have to be identical overall, but rather that a match of the pre-determined subsequences was sufficient. Furthermore, patent claim 1 does not require that the detection reagents remain bound to the corresponding analyte throughout the entire method.
According to the interpretation, there is already no infringement by the contested method because several subpopulations of detection reagents are used to identify each analyte. Furthermore, contrary to the wording of patent claim 1, a detection step (ii) is carried out in each hybridisation round and the identification of the detection reagents is carried out on a cycle basis instead of the mere temporal order provided for according to the claim. The data obtained in the laboratory at the headquarters in Amsterdam by applying the detection method is analysed on a server outside the territory of the UPC Contracting States.
The Court of First Instance erred in assuming that the patent at issue was most likely valid. Its subject-mater is not novel over D6. D6 discloses that genomic DNA is isolated from a blood sample and modified by RCA (rolling circle amplification) to yield ASMs (amplified single molecules). This does not cause the origin as a cell or issue sample within the meaning of patent claim 1 to be lost. Furthermore, claim 1 does not exclude the possibility that the signal signature is removed by washing after each staining. How this occurs at the molecular level, whether only the decoder probe or both the decoder probe and the detection reagent are

removed, remains undetermined (para. 181, Statement of grounds of appeal).
In any event, the subject-mater of claim 1 was not based on an inventive step. In this respect, D8 and D6 were suitable starting points. For a person skilled in the art starting from D6, it would be routine to want to apply *in vitro* results to an *in situ* or *in vivo* context. This also applies to ASMs, as can also be seen from B30 (Magnus Stougaard et al., In situ *detection of non-polyadenylated RNA molecules using Turtle Probes and target primed rolling circle PRINS*, BMC Biotechnology 2007, 7:69, htp://www.biomedcentral.com/1472-6750/7/69).
Contrary to the opinion of the Court of First Instance, the subject-mater of patent claim 1 goes beyond the content of the original application and the invention in the patent at issue is not disclosed so clearly and completely that a person skilled in the art could carry it out.
On the basis of the agreement with the NIH and US antitrust law as well as EU competition law from the point of view of abuse of a dominant market position pursuant to Art. 102 of the Treaty on the Functioning of the European Union (TFEU), and in accordance with the principles of the **Huawei case law** of the Court of Justice of the EU, Applicant 2 has an obligation to grant the Defendants a licence to the patent at issue.
The Court of First Instance did not take sufficient account of the fact that the issuing of a provisional injunction would cause irreparable harm to the Defendants, would be disproportionate and that the request lacked the necessary urgency.
In the alternative, the Defendants should at least be allowed to continue the allegedly infringing activity upon the provision of security and, in the further alternative, the effectiveness of the provisional injunction should be made dependent on the provision of appropriate security by the Applicants.

The Defendants request that the Court

revoke the Court of First Instance's Order and reject the Applicants' request for the granting of provisional measures,

in the alternative, allow them (the Defendants) to continue the allegedly infringing activity against the provision of security, the amount of which is set at the discretion of the Court, in the further alternative, make the effectiveness of the provisional measures dependent on the provision of security by the Applicants, the amount of which is to be determined by the court but should not be less than EUR 20,000,000,

order the Applicants to bear the costs of the proceedings,

declare the Decision (regarding the costs) immediately enforceable.

The Applicants request that the Court

reject the Appeal against the Order of the Court of First Instance,

in the alternative, rule in accordance with the Court of First Instance's prohibitory injunction, with the proviso that in each case after the words

"1. a method for detecting a plurality of analytes in a cell or issue sample,"
the words
"used in (i) immunohistochemistry and/or fluorescence *in situ* hybridisation,"
be inserted and
in each case after the words
"(e) using the temporal order of the signal signatures corresponding to the plurality of pre-determined subsequences of the detection reagent to identify a subpopulation of the detection reagents, thereby detecting the plurality of RNAs in the cell or issue sample,"
the words
"wherein the analytes are selected from the group consisting of proteins, peptides and nucleic acids, wherein the nucleic acids are selected from the group consisting of cellular RNA, messenger RNA, microRNA, ribosomal RNA and any combinations thereof"
be inserted,
order the Defendants to bear the costs of the appeal proceedings.

The Applicants defend the Order of the Court of First Instance.
The term cell or issue sample according to the claim is to be understood as a sample comprising one or more cells which may be organised in a issue, the location of the analytes relative to each other corresponding to the native location in the cell or issue. The assignment to a subpopulation according to the claim does not depend on whether the probe reagents of different detection reagents are chemically identical. Patent claim 1 is to be understood as meaning that the detection reagents bind once at their binding site and are then detected by repeated method steps. The detection according to steps (i) to (iii) provided for in patent claim 1 is repeated, according to (iv), until a unique code has been created for each subpopulation of the detection reagents.
Patent claim 1 is infringed by the Defendants' method. The repetition of the verification step (ii) and the creation of a so-called cycle-based order when using the infringing subject-matter do not change this, nor does the fact that, according to the Defendants' contested submission, the data matching of the cycle-based order of the signal signatures is to take place by means of a cloud-based solution on a server outside the territory of the UPC.
The subject-matter of claim 1 is novel. If claim 1 is interpreted correctly, D6 discloses neither the detection of analytes in a cell or issue sample nor that the sandwich probes remain on the respective analyte.
The subject-matter of claim 1 is also inventive. D8 does not teach the creation of a temporal order of signal signatures for different subpopulations and their use for the detection of different analytes and does not suggest this to a person skilled in the art. There is no reason to transfer D6 to the *in situ* context. The same applies to B30, which was only submited with the Statement of grounds of appeal and which uses "turtle probes" but no

"sandwich probes" or "selector probes" or comparable constructs. At most, B30 shows that at the priority date of the patent at issue, various probes and methods for the production of ASMs were known, these being of varying suitability for use *in situ*. It would be obvious to a person skilled in the art that a probe or method that could be successfully used *in vitro* would not necessarily work in the *in situ* context, and also that transferability from one type of analyte to another was not guaranteed.
The subject-matter of patent claim 1 was also disclosed in the original application and the invention could be carried out by a person skilled in the art on the basis of the information in the patent at issue.
The Defendants are not entitled to a licence claim, either on a contractual or antitrust basis under US law or due to abuse of a dominant market position under EU law.
The application for provisional measures was procedurally admissible and necessary in terms of both timing and substance.
There are no grounds for granting the Defendants the power to avert the enforceability of the injunction against the provision of security or to make the effectiveness of the provisional injunction dependent on the provision of security by the Applicants.
The auxiliary request is admissible. Claim 1, concretised by the addition of two features, is admissible. The methods used therein in immunohistochemistry ("IHC") or fluorescence *in situ* hybridisation ("FISH") are encompassed by claim 1, as is apparent from paragraphs 234 et seq. of the patent at issue. The analytes also further defined in claim 1 (cellular RNA, messenger RNA, microRNA, ribosomal RNA) are derived from dependent claims 7 and 8.
The Defendants request that the Applicants' application for a provisional injunction also be rejected in the version presented in the auxiliary request.

GROUNDS FOR THE ORDER
The Defendants' appeal against the order of the Court of First Instance (Munich Local Division) is admissible and well-founded.

1. The objection raised in the Appeal that the Munich Local Division of the Court of First Instance lacked jurisdiction to decide on the application for provisional measures is not well-founded. The Local Division affirmed its jurisdiction because the embodiments atacked as infringing the patent had been offered in Germany, **Art. 33(1)(a)**, **32(1)(c)**, **26(1) UPCA**. The Appeal has not shown that this assessment is incorrect.

2. The objection raised in the Appeal that the application for provisional measures was not admissible due to an infringement of **R. 206.2(c), (d) and (e) RoP** is not upheld.
In the case of **R. 206.2 RoP** concerning the application for provisional measures, a distinction must be made between the provision of letter (a) and the provisions of the other letters (b) to (e).
The requirements for the application for provisional measures set out in **R. 206.2(a) RoP** in conjunction with **Rules 13.1(a) to (i) RoP** are of a formal nature. They shall be examined by the Registry as soon as possible after the application has been filed (**R. 208.1 RoP** in conjunction with **R. 16.2 RoP**). If the examination reveals that the requirements have not been met, the Registry will give the Applicant the opportunity to correct the deficiencies within 14 days, in accordance with **R. 16.3(a) RoP**. If the deficiencies are not corrected within this period, a decision by default may be issued in accordance with **R. 16.5** in conjunction with **R. 355.1(a) RoP**.
By contrast, the requirements set out in **R. 206.2(b) to (e) RoP** relate to the content of the application for provisional measures. Accordingly, compliance with these requirements is not checked by the Registry and no time limit is set in the event of non-compliance, which can lead to a decision by default under **R. 355.1(a) RoP**. Rather, compliance with the requirements set out in **R. 206.2(b) to (e) RoP** concerns the merits of the application for provisional measures, the examination of which is the responsibility of the judge and must be considered by the judge when making orders under **Rules 209**, **211** and **212 RoP**. In the context of the orders to be made by the judge in the exercise of his discretion, non-compliance with the requirements set out in **R. 206.2(b) to (e) RoP** may be to the detriment of the Applicant.
Contrary to the Defendants' view the alleged breach of **R. 206.2(c), (d) and (e) RoP** does not render the application inadmissible. In the present case, the Appeal has also not shown that the Court of First Instance - erroneously in law - did not consider the non-compliance with the requirements of **Rules 206.2(b) to (e) RoP** in its discretionary decision.

3. The concerns raised in the Appeal against the entitlement of Applicants 2 to file the application are not justified. Due to their corresponding entry in the Register for Unitary Patent Protection, Applicants 2 are to be treated as the proprietor of the patent at issue, in accordance with **R. 8.4 RoP**. As such, they are entitled to apply for provisional measures in accordance with **Art. 47(1) UPCA**.
According to the findings of the Court of First Instance, which are not contested in the Appeal, Applicant 1 is in any case entitled to file an application as the holder of a non-exclusive licence granted to it by Applicants 2 under **Art. 47(3) UPCA**.

4. The patent at issue relates to a method for detecting a plurality of analytes in a cell or issue sample.
a) According to the description of the patent at issue, there is a need for multiplexing techniques in biology. Test samples are precious and researchers who want to analyse them do not know in advance what they have to look for or must first obtain this information from individual samples. It is therefore desirable for researchers to subject each sample to a large set of probes (patent at issue, para. 2).
According to the description, optical readout is widely used in biology and can be very effective. However, it is

typically limited to a relatively small number of available fluorophores or chromophores (patent at issue, para. 3).
Multiplexing in optical processes can be improved by increasing the number of available colours. Quantum dots, mixtures of fluorophores as new colours or nanostrings have been used for this purpose. However, there are also limitations and difficulties in this respect (patent at issue, para. 4).
The problem of the limited number of colours in optical displays could be addressed by subjecting the same sample to repeated detection using multiple small sets of different probes. However, the order of detection of different target analytes may need to be prioritised, because some target analytes in the sample can degrade in successive probings (patent at issue, para. 6).
b) Against this background, the problem underlying the invention is to develop high-throughput optical multiplexing methods for detecting target molecules in a sample (see patent at issue, para. 6).
c) According to claim 1 of the patent at issue in the version of the main request (the feature omited compared to the granted version is crossed out in each case), this problem is to be solved by the following method:
A method for detecting a plurality of analytes in a cell or issue sample, comprising:
1. (a) mounting the cell or issue sample on a solid support;
2. (b) contacting the cell or issue sample with a composition comprising a plurality of detection reagents,
2.1. the plurality of detection reagents comprising a plurality of subpopulations of detection reagents;
3. (c) incubating the cell or issue sample together with the plurality of detection reagents for a sufficient amount of time to allow binding of the plurality of detection reagents to the analytes;
3.1. wherein each subpopulation of the plurality of detection reagents targets a different analyte,
3.2. wherein each of the plurality of detection reagents comprises:
3.2.1. a probe reagent targeting an analyte of the plurality of analytes, and
3.2.2. ~~one or~~ a plurality of pre-determined subsequences,
3.2.3. wherein the probe reagent and ~~the one or~~ the plurality of pre-determined subsequences are conjugated together;
4. (d) detecting in a temporally-sequential manner ~~the one or~~ the plurality of pre-determined subsequences, wherein the detecting comprises:
4.1. (i) hybridising a set of decoder probes with a subsequence of the detection reagents,
4.1.1. wherein the set of decoder probes comprises a plurality of subpopulations of decoder probes and
4.1.2. wherein each subpopulation of the decoder probes comprises a detectable label,
4.1.3. each detectable label producing a signal signature;
4.2. (ii) detecting the signal signature produced by hybridisation of the set of decoder probes;
4.3. (iii) removing the signal signature; and
4.4. (iv) repeating (i) and (iii) using a different set of decoder probes to detect other subsequences of the detection reagents, thereby producing a temporal order of signal signatures unique for each subpopulation of the plurality of detection reagents; and
5. using the temporal order of the signal signatures corresponding to ~~the one or~~ the plurality of the pre-determined subsequences of the detection reagent to identify a subpopulation of the detection reagents, thereby detecting the plurality of analytes in the cell or issue sample.
d) Claim 1 of the patent at issue requires interpretation with regard to some of its features.

aa) The UPC Court of Appeal proceeds from the following principles in accordance with **Art. 69** of the Convention on the Grant of European Patents (EPC) and the **Protocol on its Interpretation.**
The patent claim is not only the starting point, but the decisive basis for determining the protective scope of a European patent.
The interpretation of a patent claim does not depend solely on the strict, literal meaning of the wording used (see also the German and French language versions of the Protocol on Interpretation: “aus dem genauen Wortlaut der Patentansprüche”, “sens étroit et litéral du texte des revendications”). Rather, the description and the drawings must always be used as explanatory aids for the interpretation of the patent claim and not only to resolve any ambiguities in the patent claim.
However, this does not mean that the patent claim merely serves as a guideline and that its subject-matter also extends to what, after examination of the description and drawings, appears to be the subject-matter for which the patent proprietor seeks protection.
The patent claim is to be interpreted from the point of view of a person skilled in the art.
In applying these principles, the aim is to combine adequate protection for the patent proprietor with sufficient legal certainty for third parties.
These principles for the interpretation of a patent claim apply equally to the assessment of the infringement and the validity of a European patent. This follows from the function of the patent claims, which under the European Patent Convention serve to define the scope of protection of the patent under **Art. 69 EPC** and thus the rights of the patent proprietor in the designated Contracting States under **Art. 64 EPC**, taking into account the conditions for patentability under **Art. 52** to **57 EPC** (see **EPO EBA, 11 December 1989, G 2/88, OJ 1990, 93 para. 2.5**).

bb) The Court of First Instance's interpretation that a cell or issue sample within the meaning of claim 1 is to be understood as a sample which is still structurally recognisable as a cell or issue must be accepted.
Such an understanding is supported by the wording of the claim, which distinguishes between the plurality of analytes to be detected and the cell or issue sample, so that the two cannot be identical. Although the analytes are indeed part of the cell or issue sample, the cell or

issue sample must be structurally recognisable as such even beyond the analytes, which is expressed in the wording of the claim by the phrase "... analytes in a cell or issue sample".
It is consistent with the wording of the claim understood in this way that at the beginning of the description it is stated that the need for multiplexing techniques in biology is often due to the fact that test samples are precious and researchers do not know precisely what to look for (patent at issue, para. 2).
Such an interpretation is not precluded by the fact that the description in paragraphs 48 and 49 mentions various types of sample processing, including, in addition to those in which the cell or issue sample is preserved, such as fixation, permeabilisation, mounting on a solid support, blocking of non-specific binding sites (patent at issue, para. 49, first sentence), also those in which proteins or nucleic acids are isolated from a cell or issue sample, separated electrophoretically on a separation medium and then applied to a blo□ng membrane (patent at issue, para. 49, second sentence). It does not follow from the mere mention in the description that the proteins or nucleic acids are to be regarded as analytes in a cell or issue sample within the meaning of patent claim 1 even after they have been processed as last mentioned.
The same applies to paragraphs 209 to 223 of the description, which contain, on the one hand, statements on analytes and target molecules and, on the other hand, statements on samples. Contrary to the view of the Defendants and their expert Dr Furneaux (B27, p. 3), the indication that a target molecule or an analyte can be a component of a whole cell, a issue or a body fluid, a cell or issue extract, a fractionated lysate thereof or a substantially purified molecule (patent at issue, para. 211, second sentence), does not lead to the conclusion that fractionated lysates or a substantially purified molecule are also to be regarded as analytes in a cell or issue sample according to claim 1.

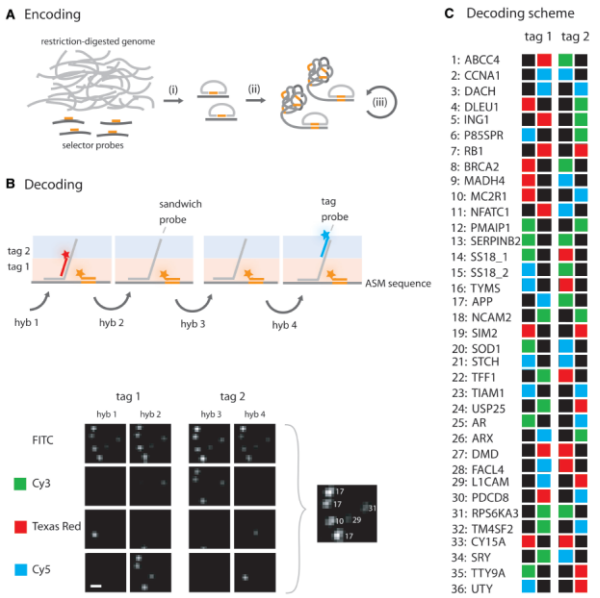
cc) Contrary to the Court of First Instance's understanding, it cannot be inferred from patent claim 1 that the detection reagents must remain bound to the respective analytes throughout the entire detection procedure according to feature group 4.
The Court of Appeal agrees with the Court of First Instance that the detection reagents must bind securely to the respective analytes and, in order to make this possible, a sufficient incubation time of the cell or issue sample together with the plurality of detection reagents must be provided, in accordance with feature 3. Contrary to the opinion of the Court of First Instance, however, the need for a sufficient incubation period does not preclude the decoder samples, once they have securely bound to the respective analytes, from being removed again at a later stage, for example together with the removal of the signal signatures provided for in feature 4.3, and from being replaced again with the same detection reagents.
This is consistent with the wording of claim 1, which provides for a detection method "comprising" the method steps "(c) incubating" and "(d) detecting" but does not specify that the former may not be carried out multiple times.
The argument put forward by the Applicants at the oral hearing with reference to paragraph 45 of the description of the patent at issue that repeated replacement of the detection reagents during the performance of the detection procedure is to be regarded as impracticable due to the long incubation time cannot be accepted. Paragraph 45 describes a wide range of possible incubation times. On the one hand, incubation periods of at least about 12, 24 or 48 hours or longer are mentioned. On the other hand, incubation times of at least about 30 seconds, 1, 5, 10, 15 or 30 minutes and further incubation times between these extremes are also described. If this wide range of incubation times is considered as a whole, it was also not impossible for practical reasons to consider as being in accordance with the claims a method in which the detection reagents, after binding with the analytes, are removed again with the signal signature and replaced by the same detection reagents.

5. The objection in the Appeal that, contrary to the judgement of the Court of First Instance, the validity of the patent at issue is not established with a sufficient degree of certainty for the injunction requested to be issued is rightly raised.
a) Since the order for provisional measures is issued by way of summary proceedings pursuant to **R. 205** et seq. RoP, in which the opportunities for the parties to present facts and evidence are limited, the Court of Appeal agrees with the Court of First Instance that the standard of proof must not be set too high, in particular if delays associated with a reference to proceedings on the merits would cause irreparable harm to the proprietor of the patent as provided for in **Art. 62(2) and (5)**, **60(5) UPCA** (see **CJEU, judgment of 28 April 2022, Phoenix Contact, C-44/21, EU:C:2022:309,** para. 32 with reference to **Art. 9(1)(a) Directive 2004/48/EC**).
On the other hand, it must not be set too low in order to prevent the defendant from being harmed by an order for a provisional measure that is revoked at a later date pursuant to **Art. 62(5), Art. 60(8) and (9) UPCA**, **R. 213 RoP**, **Art. 62(2) UPCA**, cf. also **Art. 9(7) Directive 2004/48/EC**.
R. 211.2 RoP, in conjunction with **Art. 62(4) UPCA** (see also **Art. 9(3) Directive 2004/48/EC**), provides that the court may invite the applicant for provisional measures to provide reasonable evidence to satisfy the court to a sufficient degree of certainty that the applicant is entitled to institute proceedings under **Art. 47 UPCA**, that the patent is valid and that his right is being infringed, or that such infringement is imminent.
Such a sufficient degree of certainty requires that the court considers it at least more likely than not that the Applicant is entitled to initiate proceedings and that the patent is infringed. A sufficient degree of certainty is lacking if the court considers it on the balance of probabilities to be more likely than not that the patent is not valid.

The burden of presentation and proof for facts allegedly establishing the entitlement to initiate proceedings and the infringement or imminent infringement of the patent, as well as for all other circumstances allegedly supporting the Applicant's request, lies with the Applicant, whereas, unless the subject-matter of the decision is the ordering of measures without hearing the defendant pursuant to **Art. 60(5)** in conjunction with **Art. 62(5) UPCA**, the burden of presentation and proof for facts concerning the lack of validity of the patent and other circumstances allegedly supporting the Defendant's position lies with the Defendant.
The aforementioned allocation of the burden of presentation and proof in summary proceedings is in line with the allocation of the burden of presentation and proof in proceedings on the merits, in which facts giving rise to the entitlement to initiate proceedings and the infringement or imminent infringement of the patent, as well as other circumstances favourable to the infringement action, are to be presented and proven by the rightholder (**Art. 54**, **63**, **64** and **68 UPCA**, **R. 13.1(f) and (l)-(n) RoP**), whereas the burden of presentation and proof with regard to the facts from which the lack of validity of the patent is derived and other circumstances favourable to the invalidity or revocation lies with the opponent (**Art. 54** and **65(1) UPCA**, **Rules 44(e)-(g)**, **25.1(b)-(d) RoP**).
b) Contrary to the opinion of the Court of First Instance, in the judgement of The Court of Appeal it is, on the balance of probability, more likely than not that the subject-matter of claim 1 in the version asserted in the main request will prove to be not patentable under **Art. 65(2) UPCA**, **Art. 52(1)**, **138(1)(a) EPC**.

aa) The Court of Appeal assumes the admissibility of the version of patent claim 1 asserted by the Applicants in the main request (deletion of the words “the one or” in features 3.2.2., 3.2.3, 4 and 5). The Appeal did not claim that the Court of First Instance was incorrect in finding that the claim version of the main request was admissible. Therefore, the admissibility of the version of the main request does not form part of the subject-matter of the proceedings before the Court of Appeal (R. 222.1 RoP in conjunction with R. 226(a)).

bb) The objection raised in the Appeal that the Court of First Instance incorrectly assumed that the subject-matter of patent claim 1 would prove to be novel over D6 is unfounded.
(1) D6 relates to an array format with a decoding scheme for targeted digital multiplex molecular analyses. As can also be seen from Figure 3 reproduced below, D6 discloses multiplex encoding and decoding of genomic loci.



As shown under “A”, genomic DNA circles are formed from specific genomic DNA sequences and selector probes (i) and the DNA circles are amplified by RCA (rolling-circle amplification) (ii) or otherwise enriched (iii) to generate amplified single molecules (ASMs). The ASMs are then immobilised and a random array is generated on a microscopy glass slide.
As shown under “B”, the ASMs immobilised in the array are decoded by sequential hybridisation of sandwich probes, tag probes (red or blue) and a general probe after they have been incubated for 1 hour on shake at 55°C (D6, p. 3, left-hand column under “Hybridisation of ASMs”). The sandwich probes are complementary to a specific ASM and contain two decoding tags (tag 1 and tag 2) that hybridise with corresponding tag probes. A small 20 x 20 pixel image section shows the tagged ASMs after the different hybridisation reactions together with an image showing the identified ASMs. The ASM arrays were decoded in four cycles of hybridisation and dehybridisation (D6, p. 4, left-hand column/p.5, right-hand column).
A decoding scheme used for multiplex decoding is shown under “C”, in which the names of the gene loci and the corresponding numbers are listed vertically and the markings of the two tags are shown horizontally. The coloured markers represent the fluorescent dyes Cy3 (green), Texas Red (red) and Cy5 (blue) and the black marker represents no detectable signal (D6, under Figure 3; Abstract; p. 4, right-hand column under “Multiplex targeted copy-number variation analysis”).
(2) D6 thus discloses all the features of claim 1 (see also Bundespatentgericht, Qualifizierter Hinweis of 7 February 2023 [BP9], p. 5 et seq, regarding the parent patent) with the exception of the feature that the method is intended to detect a plurality of analytes “in a cell or issue sample”, since the method described in D6 is intended to detect ASMs (amplified DNA molecules) and thus a plurality of analytes, but these are not present in a cell or issue sample. A person of average skill in the art would not consider a part of the genomic DNA that

has been isolated from a cell and amplified to yield the ASMs to be cell or issue matterial within the meaning of the patent. Contrary to the opinion of the Defendants, it is not sufficient for the sample to have a cellular origin. As established above, only a sample which is still structurally recognisable as a cell or issue is a cell or issue sample within the meaning of claim 1. It is undisputed that an ASM is not recognisable as a cell or issue.
According to D6, the ASMs are mounted on a glass slide and contacted and incubated with a plurality of sandwich probes in order to bind each to the other. The sandwich probes have the function of a plurality of detection reagents or a plurality of subpopulations thereof as defined in claim 1, as they target a specific ASM on the one hand and hybridise (tag 1 and tag 2) with a plurality of predetermined subsequences using a set of tag probes (the decoder probes as defined in claim 1) on the other hand. Each subpopulation of tag probes comprises a detectable tag that produces a signal signature (one of the fluorescent dyes Cy3, Texas Red or Cy5). The signal signatures generated by the hybridisation are captured (see the 20 x 20 pixel image sections in Figure 3) and thus detected. After detection, signal signatures are removed during dehybridisation, and a new hybridisation cycle begins with different sets of decoder probes.
The Court of First Instance and the Applicants correctly stated that in D6 the hybridisation and dehybridisation are carried out in four cycles, with the addition of new sandwich probes at each hybridisation. However, this circumstance does not conflict with the disclosure of the teaching of claim 1 since, as explained above, it does not require the binding between the detection reagents and the respective analytes to persist throughout the entire duration of the process.

cc) Contrary to the judgement of the Court of First Instance, it is more likely than not that the subject-matter of claim 1 in the version of the main request will prove to be obvious.
D6 would have been of interest to a person skilled in the art who, at the priority date of the patent at issue, was seeking to develop high-throughput optical multiplexing methods for detecting target molecules in a sample, as it discloses a method for detecting a plurality of amplified single molecules (ASMs) by encoding and decoding the single molecules, wherein the encoding is performed via probe-mediated generation of ring-shaped DNA and the decoding is performed by temporally sequential detection of the targeted ASMs (cf. D6, Abstract) (see also the Swedish Intellectual Property Office, PRV Consulting Report of 28 June 2023, B10, p. 5).
This is admittedly disclosed in D6 for ASMs ordered *in vitro* in an array format. However, given the demand for multiplex analysis techniques, especially for test samples, at the priority date (see patent at issue, para. 2), there was a need to consider whether the encoding and decoding method disclosed in D6 could be transferred to the detection of ASMs in cell or issue samples.
An incentive or confirmation for thinking in this direction also resulted from the indication in D6 that in the prior art rolling-circle ASMs had been used for the readout of various genotyping assays as well as for the detection of proteins and protein complexes *in situ* using proximity ligation. The fact that the "genotyping assays" were carried out in situ can be seen from footnote 20 of D6, which refers to Larsson et al, "In situ genotyping individual DNA molecules by target-primed rolling-circle amplification of Padlock probes", Nat. Methods 2004, 1, 227 ff, which describes an *in situ* procedure already according to the title. In addition, D6 refers to a publication on the *in situ* observation of protein complexes (Söderberg et al., *Direct observation of individual endogenous protein complexes* in situ *by proximity ligation*, Nat. Methods 2006, vol. 3 no. 12 [D19]).
That for a person skilled in the art at the priority date of the patent at issue, after successful application of an *in vitro* multiplex method for the detection of ASMs, the next step was to consider transferring the method to an *in situ* environment is further evidenced by B30 (Stougaard et al., In situ *detection of non-polyadenylated RNA molecules using Turtle Probes and target primed rolling circle PRINS*, BMC Biotechnology 2007, 7:69).
This publication describes a method for the detection of non-polyadenylated RNA molecules using “a new probe format” (“Turtle Probes”), which was initially carried out *in vitro* in “a controlled environment” (B30, p. 4, right-hand column, last para.) and, after successful implementation, was also tested *in situ* with positive results (B30, p. 4, left-hand column, - p.5; Abstract, Results).
Even if it is assumed with the Applicants that various probes and methods for the production of ASMs were known at the time, whose suitability for *in situ* application varied and that a person skilled in the art would not have readily concluded from the successful application of a probe or method *in vitro* that this probe or method would also work in an *in situ* context, it should be noted that this aspect did not prevent the authors of B30 from carrying out the detection procedure with “Turtle Probes” *in situ* after it had first been successfully performed *in vitro*. There are no apparent grounds why this would have been any different based on the detection method carried out *in vitro* with selector probes in D6.
The difference cited by the Applicants in this respect, namely that according to D6 the nucleic acids (analytes) were subjected to restriction digestion before the selector probes were used, whereas this was not necessary when using the “turtle probes” according to B30, is explained by the fact that in B30 the detection is aimed at RNA molecules, whereas the detection in D6 is aimed at genomic DNA material, which first had to be prepared for hybridisation with the selector probes by restriction digestion (cf. Figure 3 A and the explanation under Figure 3). Unlike in B30, there is no reason that would have prevented a person skilled in the art from applying the multiplex method for the detection of

nucleic acids disclosed *in vitro* in D6 to an *in situ* environment with cell or issue samples.
The Applicants' objection that there was no reasonable expectation of success from a technical point of view because they would have been confronted with problems such as "molecular crowding" (the difficulty of distinguishing between multiple analytes occurring in close proximity) or "autofluorescence" (unpredictable interactions) in the cell or issue sample cannot be accepted either. In the opinion of the Court of Appeal, adjudicating with two technically qualified judges, these are problems that regularly arise in connection with the *in situ* detection of analytes in issue or cell samples – but which a person skilled in the art would have been able to deal with on the basis of their expertise at the priority date and which therefore would not have prevented them from carrying out tests in the aforementioned sense due to insufficient prospects of success (see also the Swedish Intellectual Property Office, PRV Consulting Report, B10, p. 5). This assessment is supported by the fact that the patent at issue does not provide any information on how to deal with the aforementioned problems with *in situ* detection, such as when using immunohistochemistry methods or RNA fluorescence in situ hybridisation (FISH) (patent at issue, cf. para. 48 et seq, para. 212 et seq, "Sample", para. 224 et seq "Applications of the detection reagents"; para. 234 "Immunohistochemistry"; para. 235 "In-situ-hybridisation", "Fluorescence in-situ hybridisation").
Finally, the time component would not have given a person skilled in the art any grounds to refrain from attempting to transfer the method disclosed in D6 to the detection of analytes in cell or issue samples. On the contrary, it can be assumed that a person skilled in the art would have been able to adjust the time duration based on their expertise, taking into account other factors such as the binding affinities, the incubation conditions and the concentration of the selector probes, in such a way that the detection reagents would bind sufficiently firmly to the analytes. This assessment is confirmed by the fact that even the patent at issue, which in claim 1 provides for incubation for a period of time that is sufficient to enable the plurality of detection reagents to bind to the analytes, does not provide any more detailed information on the specific settng. Rather, the description in the patent at issue merely mentions times between 30 seconds and 48 hours or longer for contacting the samples with the detection reagents and factors that may be relevant to the length of the contact times, such as binding affinities, concentrations of the probe reagents or analytes, concentrations of the detection reagents and/or the incubation conditions (patent at issue, para. 45). This suggests that the patent at issue also assumes that a person skilled in the art would be capable of correctly measuring the time component based on his or her general qualifications.

c) Since, given all the above, it is more likely than not that the patent at issue will prove to be invalid in proceedings on the merits due to a lack of inventive step, there is no sufficient basis for the issuance of a preliminary injunction in accordance with the Applicants' main request.

6. The issuance of an injunction is also not justified on the basis of the Applicants' auxiliary request.
a) In this respect, it can remain undecided whether the auxiliary request is already inadmissible because the Defendants had no opportunity in the proceedings before the Court of First Instance to review the validity of the patent at issue in the form of the auxiliary request, since the Applicants only lodged this request at the oral hearing after the court had drawn the parties' attention to the fact that in the parallel proceedings concerning the parent patent, the requests for injunctive relief had been lodged in a version that restricted the patent claim of the parent patent.
b) The application for a preliminary injunction is in any case unfounded because on the balance of probability it is more likely than not that the patent at issue will not prove to be valid even in the version of the auxiliary request.
aa) With the auxiliary request, the Applicants assert an infringement of the patent at issue with the following two amendments to patent claim 1 compared to the version of the main application:
- The method of detecting a variety of analytes in a cell or issue sample is used in immunohistochemistry and/or florescence *in situ* hybridisation.
- The analytes are selected from the group consisting of proteins, peptides and nucleic acids, wherein the nucleic acids are selected from the group consisting of cellular RNA, messenger RNA, microRNA, ribosomal RNA and any combinations thereof.

bb) Immunohistochemistry is a technique which, at the priority date, would have been known to a person skilled in the art, and by which analytes can be visualised for microscopic evaluation with the aid of labelled antibodies (cf. patent at issue, para. 234).
Fluorescence *in situ* hybridisation is a technique for detecting cellular DNA or RNA, also known to a person skilled in the art at the priority date, in which the probe hybridising with the target analyte is detected by means of a fluorescent dye (see patent at issue, para. 235).
For a person skilled in the art who, proceeding from D6, was prompted to transfer the *in vitro* multiplex detection method disclosed therein to cell or issue samples, it was obvious to also use the techniques of immunohistochemistry and/or fluorescence *in situ* hybridisation known to him or her on the basis of his or her expertise (see also, however, Bundespatentgericht, Qualifizierter Hinweis of 7 February 2023 [BP9], p. 10).
From the point of view of a person skilled in the art, in addition to the DNA molecules explicitly mentioned in D6, RNA molecules and proteins and peptides could also be considered as analytes for an *in situ* multiplex detection method, as well as combinations thereof (see also D6, Abstract: "[t]he decoding strategy is generic in that the target can be any biomolecule which has been encoded into a DNA circle via a molecular probing reaction" and page 7 "[h]owever, any biomolecule that

can be represented as a DNA circle can be converted to an easily identifiable ASM. Padlock probes can be applied for gene-copy number analysis, as well as analysis of infectious pathogens and for mRNA expression. Also proteins or interacting pairs of proteins can be digitally monitored in this manner via the proximity ligation assay.").

(cc) The Court of Appeal holds that the fact that the Defendants did not present their arguments for the lack of inventive step until the oral hearing in the appeal proceedings did not violate **R. 222.1 RoP** in the present case. Although the Defendants focused their arguments regarding the auxiliary request exclusively on the admissibility of the request in the Statement of grounds of appeal, they expressly requested a "judicial reference" if a submission on the content of the request was required. In view also of the fact that this is the first appeal case in which auxiliary requests and **R. 222.1** RoP are being used for the decision, the court instructed the parties at the oral hearing to also comment on the validity of the auxiliary request. Since the argumentation on the lack of inventiveness of the auxiliary request largely matches the argumentation on the inventiveness of the main request, the Applicants' defence was not unduly disadvantaged by this.

7. As the unsuccessful party, the Applicants are required to bear the costs of the proceedings.

8. Since the Decision on costs has no directly enforceable character, its immediate enforceability cannot be ordered. The Defendants' request must be rejected in this respect.

ORDERS

1. On appeal by the Defendants, the orders of the Court of First Instance (Munich Local Division) are revoked and the Applicants' request for an injunction is rejected.
2. The Applicants are required to bear the costs of the proceedings.
3. The Defendants' request to declare order 2) immediately enforceable is rejected.
4. The amount in dispute is set at EUR 7 million.

Klaus Grabinski, President of the Court of Appeal and judge-rapporteur
Françoise Barutel, legally qualified judge
Peter Blok, legally qualified judge
Rainer Friedrich, technically qualified judge
Cornelis Schüler, technically qualified judge
Eurico Igreja, Employee of the Registry
