# Circulating Tumor Cells: isolation & detection

## Patent Landscape Analysis – February 2020

*What technology will make up the next FDA-approved CTC device? What kind of player will supply it: a newcomer, an established company or will a future acquisition change the game?*

**REPORT OUTLINE**


- CTC isolation & detection
- Patent landscape analysis
- February 2020
- Ref.: KM20002
- PDF >160 slides
- Excel file >5,500 patents
- €3,990 for a multi-user license

**REPORT'S KEY FEATURES:**

- **IP trends**, including time-evolution of published patents, and countries of patent filings
- Patents'**legal status**
- Ranking of **main patent assignees**
- **Key players' IP position** and **relative strength** of their patent portfolios
- **Summary of the IP related to the physical isolation**: size, deformability, electrical charges or density.
- **Summary of the IP related to the biological isolation**: positive or negative enrichment.
- **Summary of the IP related to the CTC detection**: nucleic acid, protein or functional assay.
- **Analysis of patent litigations and review of key patents**.
- **Excel database** containing all patents analyzed in the report, including biological and physical isolation and detection segmentations

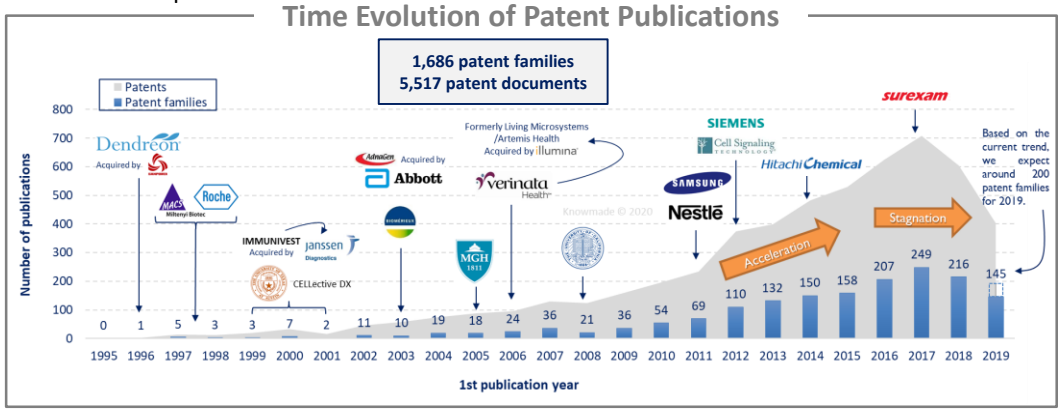
**LINKED REPORTS**

- Artificial Intelligence in Medical Diagnostics - Patent Landscape Analysis
- Nanopore Sequencing - Patent Landscape Analysis

## CTC isolation and detection, an essential step in cancer prognostic and personalized treatment

Cancer is the second leading cause of death worldwide and was responsible for an estimated 9.6 million deaths in 2018. Globally, about 1 in 6 deaths is due to cancer (source: WHO). One defining feature of cancer is the rapid creation of abnormal cells that grow beyond their usual boundaries, and which can then invade adjoining parts of the body and spread to other organs. The latter process is referred to as metastasizing. Metastasis is a major cause of death from cancer. Preventing or detecting metastasis outbreak has therefore become a main issue in cancer prognostic (to predict the development and the outcome of the cancer) and in personalized treatment. The discovery of circulating tumor cells (CTC) was a milestone in understanding tumoral progression, and their presence in the blood enables a less invasive biopsy (liquid biopsy) which is beneficial for the patient. Then, the development of devices to intercept and analyze these rare cells steeply increased in the last 10 years, as did the number of companies supplying them (e.g. Menarini Silicon Biosystems, GPB Scientific, Gilupi, Epic Sciences). However, this development seems to be slower than in other sectors, like the free circulating DNA area, and certain key facts could explain this lower progression. First, CTC are hard to transport and store, because cell integrity is difficult to maintain. To counteract this issue, most companies develop instruments which can be directly sold to end users, but they are expensive and complex to manufacture. Then, the transfer from laboratories to clinical practice is full of obstacles, like the complexity of clinical trials or the difficulty in getting authorization from administrative bodies (e.g. the FDA). However, understanding of CTC and technology to isolate them are advancing quickly. Monitoring these rare cells as a prognostic tool among patients is an increasingly confirmed practice, as is the significance of fully characterizing a cell to enable personalized treatment. CTC isolation & detection interests big companies and start-ups alike, and it is crucial to understand the intellectual property position and strategy of these different players. Such knowledge can help detect business risks and opportunities, anticipate emerging technologies, and enable strategic decisions to strengthen one's market position.

### Time Evolution of Patent Publications




The analysis of the time evolution of patent publications shows that CTC isolation and detection started to be investigated in the late 1990s with a first patent filed in 1995 by Dendreon (company acquired by San Power in 2017). Until 2009, there is a latent period, even if big pharmaceutical companies and some academics begin to take interest in CTC. From 2010 to 2016, an acceleration is observed with big newcomers (Nestlé, Samsung, Siemens or Hitachi Chemicals). In 2016-2017, publications stagnated despite the arrival of new players. The main patent assignees are US industrial players that develop an international intellectual property strategy. Europe and China are the main countries of protection, which appear to be strategic territories for these applicants.

## Analysis by segment

CTC could be isolated and detected using various methods. Therefore, a technological segmentation was made in this IP landscape, as follows:

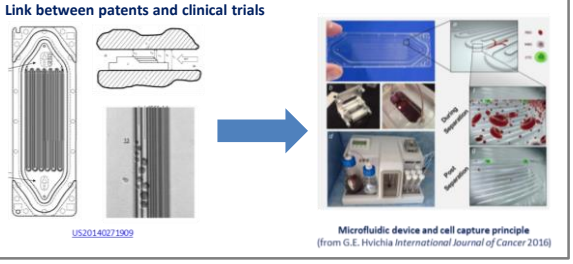
- **CTC isolation:** Efficient enrichment of CTC can be achieved by approaches that exploit differences between tumor cells and blood cells, including the differential expression of cell surface proteins or distinct physical properties of the cells.
  - **Physical isolation:** Assays are based on CTC physical characteristics including size, deformability, density and electrical charge.
  - **Biological isolation**: It is protein-based methods which rely mainly on specific markers that are detected by antibodies or by other particles like aptamers. The sample can be enriched in desired cells (positive isolation) or depleted in unwanted cells (negative isolation).
- **CTC detection:** Once CTC concentration is increased, for an unambiguous isolation of CTC, detection methods are necessary.
  - **Nucleic Acid**: DNA or RNA are identified by RT-PCR, FISH, etc.
  - **Protein**: Surface markers are detected by antibodies (anti-EpCam, Anti-Cytokeratin, etc.) and visualized by microscopy, FACS, etc.
  - **Functional assays**: EPISPOT or invasion assays.
- **Other technologies**: Raman spectroscopy, surface acoustic waves or the use of virus or phagocytic cells, etc.
- **Medical devices**: *In vivo* apparatus like an implantable device or apheresis.

### Segment Analysis

**Main IP players**

| Assignee (Top 25 ranked by strenght score) | Player country | No of patent families | % of player's CTC Portfolio | No of patent publications | Number of granted patents: All countries | USA | Europe | Japan | China | Korea | WO | Taiwan | India | Number of pending patents: All countries | USA | Europe | Japan | China | Korea | WO | Taiwan | India |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| [redacted] | US | 13 | 87% | 122 | 42 | 10 | 13 | 3 | 2 | 2 | | | | 11 | 1 | 1 | 2 | 2 | | | 2 | 2 |
| [redacted] | US | 13 | 28% | 80 | 21 | 8 | 6 | 2 | 2 | | | | | 34 | 5 | 8 | 2 | 6 | 2 | 1 | | 2 |
| [redacted] | US/BE | 9 | 16% | 68 | 22 | 3 | 5 | 2 | 2 | 1 | | | | 14 | 2 | 3 | | 1 | 1 | 1 | | |
| [redacted] | JP | 5 | 83% | 109 | 84 | 3 | 13 | 6 | 1 | 1 | | | 1 | 19 | 1 | 2 | 1 | 2 | 2 | | | 2 |
| [redacted] | DE | 5 | 83% | 109 | 64 | 3 | 13 | 6 | 1 | 1 | | | 1 | 19 | 1 | 2 | 1 | 2 | 2 | | | 2 |
| [redacted] | US | 2 | 12% | 16 | 9 | 5 | 1 | | 1 | | | | | 2 | | 1 | | 1 | | | | |
| [redacted] | US | 2 | 12% | 16 | 9 | 5 | 1 | | 1 | | | | | 2 | | 1 | | 1 | | | | |
| [redacted] | US | 1 | 4% | 15 | 8 | 5 | 1 | | 1 | | | | | 2 | | 1 | | 1 | | | | |
| [redacted] | US | 3 | 100% | 28 | 17 | 3 | 5 | | 2 | | | | | 4 | 4 | | | | | | | |
| [redacted] | US | 2 | 100% | 11 | 2 | 1 | 1 | | | | | | | | | | | | | | | |
| [redacted] | CH | 4 | 29% | 22 | 4 | 1 | 1 | | | | | | | 10 | 0 | 2 | 1 | 1 | 1 | 1 | 1 | |
| [redacted] | US | 3 | 100% | 15 | 5 | 3 | 1 | | | | | | | | | | | | | | | |
| [redacted] | GB | 2 | 100% | 17 | 1 | | 1 | | | | | | | | | | | | | | | |
| [redacted] | US | 3 | 75% | 37 | 7 | 2 | | 1 | | 1 | | | | 3 | | | 1 | | | | 1 | 1 |
| [redacted] | US | 2 | 100% | 13 | 4 | 2 | 1 | | | | | | | | | | | | | | | |
| [redacted] | FR | 2 | 100% | 6 | | | | | | | | | | | | | | | | | | |
| [redacted] | US | 1 | 100% | 23 | 15 | 3 | 4 | | 2 | | | | | 2 | 2 | | | | | | | |
| [redacted] | FR | 1 | 17% | 4 | | | | | | | | | | | | | | | | | | |
| [redacted] | FR | 1 | 100% | 4 | | | | | | | | | | | | | | | | | | |
| [redacted] | FR | 1 | 100% | 4 | | | | | | | | | | | | | | | | | | |
| [redacted] | DE | 1 | 50% | 60 | 44 | 1 | 10 | 4 | 1 | 1 | | | 1 | 3 | | | 1 | | | | | |
| [redacted] | CH | 6 | 55% | 24 | 2 | 1 | | | 1 | | | | | 39 | 3 | 5 | 4 | 2 | 3 | 1 | 1 | |
| [redacted] | US | 10 | 53% | 54 | 1 | | 1 | | | | | | | 32 | 10 | 12 | 3 | 4 | | | | |
| [redacted] | US | 2 | 100% | 46 | 13 | 1 | 2 | 2 | | | | | | 23 | 1 | 1 | 1 | 2 | 1 | | | 2 |
| [redacted] | IT | 1 | 6% | 27 | 17 | 3 | 3 | 2 | 1 | 1 | | | | 2 | 1 | 1 | | | | | | |

**Link between patents and clinical trials**



US20140271909

Microfluidic device and cell capture principle (from G.E. Hvichia *International Journal of Cancer* 2016)

*For each segment, the patent publication timeline and the patent portfolios of main players were analyzed. If the technology results in a clinical trial, the corresponding patent, the clinical trial and the scientific publication are described.*

## Identifying the companies that have recently emerged in the IP landscape

Among the players that have filed patents related to CTC isolation and detection, **over 60 newcomers were identified**. These companies are established companies and startup firms developing their first products in the CTC area. These technologies are mainly related to CTC positive enrichment, size-based isolation or nucleic acid detection. Numerous IP newcomers are based in Asia and in the US while some are based in Europe. It is possible that one of these innovative companies could become one of the next healthcare unicorns that the big corporations will be tempted to acquire.

## Key patent analysis

**This IP study includes selection and description of key patents.** The key patent analysis includes the legal state of the family for each of the main territories, the number of received citations, the review of the main claim(s), the description of interesting features about the innovation disclosures and relevant figures illustrating how the innovation works. The description also contains information about the fact that the patent family was involved in a patent litigation in the USA.

### Key Patent Analysis

| | |
|---|---|
| Title | Microfluidic devices and methods for cell sorting, cell culture and cells based diagnostics and therapeutics |
| Assignee(s) | BIOPICO SYSTEMS |
| 1st priority date: | 2012-01-10 |
| 1st publication date: | 2014-09-04 |
| Publication number of a representative member of the family : | US9149806 |

| | | |
|---|---|---|
| Legal status | Granted | US |
| | Pending | No pending applications left |
| Family involved in a US Patent Infringement case? | NO | |
| Received citation count | 48 | |
| Number of citing assignees | 44 | |

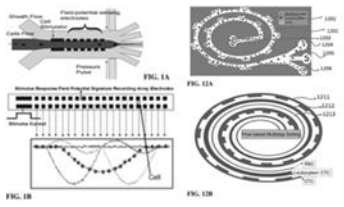
**Abstract:**

Microfluidic devices and methods that use cells such as cancer cells, stem cells, blood cells for preprocessing, sorting for various biodiagnostics or therapeutical applications are described. Microfluidics electrical sensing such as measurement of field potential or current and phenomena such as immiscible fluidics, inertial fluidics are used as the basis for cell and molecular processing (e.g., characterizing, sorting, isolation, processing, amplification) of different particles, chemical compositions or biospecies (e.g., different cells, cells containing different substances, different particles, different biochemical compositions, proteins, enzymes etc.). Specifically this invention discloses a few sorting schemes for stem cells, whole blood and circulating tumor cells and also extracting serum from whole blood. Further medical diagnostics technology utilizing high throughput single cell PCR is described using immiscible fluidics couple with single or multi cells trapping technology.

**Key figures:**

Fig. 1 A) Schematic configuration of the stem cell sorting fluidic and electrodes array system; B) Representation of electrode array for impedance sensing, stimulus current and discrete recording of time domain stimulus response using 20 electrodes in the path of flow cells.

Fig 12. A) CTC enrichment using decreasing width gradient periodic pinching regions in spiral channel inertial fluidics; B) Modified f-biopsy chip to isolate CTC of overlapping sizes using multistep sorting of blood.



**Claims:**

1. A method for high throughput cell sorting based on on-the-fly flow based field potential sensing, the method comprising:
stimulating a cell; sensing field potential signals of the cell as the cell flows through an array of spatially located electrodes after the cell being stimulated; identifying a cellular phenotype of the cell based on the field potential signals sensed from the array of spatially located electrodes; sorting the cell based on the cellular phenotype.

5. A method of size or density based sorting blood cells for the separation of different components of blood cells such as RBC, leukocytes, lymphocytes, T cells, monocytes, dendritic cells, other rare cells and cancer cells including circulating tumor cells using yoked multispiral channel with plurality of loops working at inertial microfluidics which consists of:
a. A inlet channel where the unsorted whole blood or pre-processed multiple cellular components blood or other cells in reagent is introduced; b. Two or more outlets where different components of the cells are collected from different spiral channels connected to each other by side channels called "yoked" channels; c. Expansion channels or regions in the spiral channels where smaller size or lesser density cells are sidelined for transferring to adjacent spiral channels; d. One or more spiral channels with parameterized expansion regions where cells of multiple sizes or densities undergo inertial fluidic sorting in to the adjacent channel if any; e. Width gradient of the spiral channel from the inlet to outlets for efficient sorting of cells with balanced fluidic pressure; f. Aspect ratio of the channel width and depth ranging from 0.5 to 5 or more at varying flow rates under inertial fluid dynamics regime so that the sorting from the main spiral channel to adjacent spiral channel is enabled by lift force and Dean drag force.

Moreover, the report also includes an **Excel database** with the **>1,680 patents** analyzed in this study. This useful patent database allows for **multi-criteria searches** and includes patent publication numbers, hyperlinks to the original documents, priority dates, titles, abstracts, patent assignees, each patent's current legal status and segmentation to which it belongs.

**Companies mentioned in this report** (non-exhaustive list)
ABBOTT, ABBVIE, ARKRAY, ASTELLAS, AVIVA BIOSCIENCES, BECTON DICKINSON, BIOCEPT, CELSEE, CREATV MICROTECH, CYTOGEN, CYTTEL BIOSCIENCES, DECIPHER BIOSCIENCE, EPIC SCIENCES, EUTROPICS PHARMACEUTICALS, GENCURIX, GENOBIO, GILUPI, GPB SCIENTIFIC, HITACHI CHEMICAL, ILLUMINA, JANSSEN DIAGNOSTICS, JUSBIO SCIENCES, KONICA MINOLTA, LUNG LIFE AI, MENARINI SILICON BIOSYSTEMS, NESTLE, RARECYTE, ROCHE, GENENTECH, SUMITOMO, SUREXAM, TOSOH

## TABLE OF CONTENTS



## AUTHORS


**Dr. Fabienne MASSA**
Fabienne works at Knowmade in the field of Biotechnology and Life Sciences. She holds a PhD in Molecular and Cellular Biology from the IPMC (Nice, France). She also holds a Master of Business Management from IAE (Nice, France) and she previously worked in the pharmaceutical industry.
Contact: fabienne.massa@knowmade.fr

**Dr. Brice SAGOT**
CTO and co-founder of Knowmade, Brice leads the Biotechnology and Life Sciences department. He holds a PhD in Molecular Biology from the University of Nice Sophia-Antipolis (France).
Contact: brice.sagot@knowmade.fr


## ABOUT KNOWMADE

Specialized in the analysis of patents and scientific information, Knowmade provides technology intelligence and IP strategy consulting services. The company supports the business development of R&D organizations, industrial companies, and investors by offering them a deep understanding of their IP environment and technology trends. Knowmade operates in the following industrial sectors: compound semiconductors, power electronics, RF devices and technologies, solid-state lighting and display, photonics, memory, MEMS and sensors, semiconductor manufacturing and advanced packaging, battery and energy management, biotechnology, pharmaceuticals, medical devices, medical imaging, and agri-food. Knowmade's experts provide prior art search, patent landscape analysis, scientific literature analysis, patent valuation, IP due diligence, and freedom-to-operate analysis. The company also delivers litigation/licensing support, technology scouting, and IP/technology observation. Knowmade's analysts combine their technical and patent expertise with powerful analytics tools and proprietary methodologies, delivering invaluable patent analyses and scientific reviews.

# ORDER FORM

# Circulating Tumor Cells: isolation & detection

## Patent Landscape Analysis – February 2020

*Ref.: KM20002*

**SHIP TO**

Name (Mr/Ms/Dr/Pr):

Job Title:

Company:

Address:

City:

State:

Postcode/Zip:

Country:

VAT ID Number for EU members:

Tel:

Email:

Date:

**PAYMENT METHODS**

**Order online**: Click here

**Check**

To pay your invoice using a check, please mail your check to the following address**:**

KnowMade S.A.R.L.
2405 route des Dolines, BP 65
06902 Valbonne Sophia Antipolis
FRANCE

**Money Transfer**

To pay your invoice using a bank money wire transfer, please contact your bank to complete the process. Here is the information you will need to submit the payment:

Payee: KnowMade S.A.R.L.
Bank: Banque Populaire Méditerranée, CAP 3000 Quartier du lac, 06700 St Laurent du Var
IBAN: FR76 1460 7003 6360 6214 5695 139
BIC/SWIFT: CCBPFRPPMAR

**Paypal**

To pay your invoice via PayPal, you must first register at www.paypal.com. You can then send money to KnowMade S.A.R.L. by entering our email address (contact@knowmade.fr) as the recipient, and entering the invoice amount.

**RETURN ORDER BY:**

**Email:** contact@knowmade.fr
**Mail**: KnowMade S.A.R.L. 2405 route des Dolines, 06902 Valbonne Sophia Antipolis, FRANCE

**PRODUCT ORDER**
**€3,990 – Multi user license***

For the price in dollars, please use the current day's exchange rate. French customers, please add 20% for VAT.
Upon payment reception, all reports are delivered electronically in pdf format

**The report can be shared with the employees of the Company purchasing the report. Subsidiaries and joint-ventures are excluded. Please be aware that the report is watermarked on each page, with the name of the recipient and the organization (the name mentioned on the PO). This watermark also reaffirms that report sharing is not allowed.*

*I hereby accept Knowmade's Terms and Conditions of Sale*
**Signature**:

# TERMS AND CONDITIONS OF SALES

**Definitions**

"Acceptance": Action by which the Buyer accepts the terms and conditions of sale in their entirety. It is done by signing the purchase order which mentions "I hereby accept Knowmade's Terms and Conditions of Sale".

"Buyer": Any business user (i.e. any person acting in the course of its business activities, for its business needs) entering into the following general conditions to the exclusion of consumers acting in their personal interests.

"Contracting Parties" or "Parties": The Seller on the one hand and the Buyer on the other hand.

"Intellectual Property Rights" ("IPR") means any rights held by the Seller in its Products, including any patents, trademarks, registered models, designs, copyrights, inventions, commercial secrets and know-how, technical information, company or trading names and any other intellectual property rights or similar in any part of the world, notwithstanding the fact that they have been registered or not and including any pending registration of one of the above mentioned rights.

"License": For the reports and databases, 2 different licenses are proposed. The buyer has to choose one license:

1. Single user license: a single individual at the company can use the report.
2. Multi user license : The report can be shared with the employees of the company purchasing the report. Subsidiaries & joint-ventures are excluded.

"Products": Reports are established in PowerPoint and delivered on a PDF format and the database may include Excel files.

"Seller": Based in Sophia Antipolis (France headquarters), Knowmade is a technology intelligence company specialized in the research and analysis of scientific and technical information. We provide patent landscapes and scientific state of the art with high added value to businesses and research laboratories. Our intelligence digests play a key role to define your innovation and development strategy.

**1. Scope**

1.1 The Contracting Parties undertake to observe the following general conditions when agreed by the Buyer and the Seller. ANY ADDITIONAL, DIFFERENT, OR CONFLICTING TERMS AND CONDITIONS IN ANY OTHER DOCUMENTS ISSUED BY THE BUYER AT ANY TIME ARE HEREBY OBJECTED TO BY THE SELLER, SHALL BE WHOLLY INAPPLICABLE TO ANY SALE MADE HEREUNDER AND SHALL NOT BE BINDING IN ANY WAY ON THE SELLER.

1.2 This agreement becomes valid and enforceable between the Contracting Parties after clear and non-equivocal consent by any duly authorized person representing the Buyer. For these purposes, the Buyer accepts these conditions of sales when signing the purchase order which mentions "I hereby accept Knowmade's Terms and Conditions of Sale". This results in acceptance by the Buyer.

1.3 Orders are deemed to be accepted only upon written acceptance and confirmation by the Seller, within [7 days] from the date of order, to be sent either by email or to the Buyer's address. In the absence of any confirmation in writing, orders shall be deemed to have been accepted.

**2. Mailing of Products**

2.1 Products are sent by email to the Buyer:

- within [1] month from the order for Products already released; or
- within a reasonable time for Products ordered prior to their effective release. In this case, the Seller shall use its best endeavours to inform the Buyer of an indicative release date and the evolution of the work in progress.

2.2 Some weeks prior to the release date the Seller can propose a pre-release discount to the Buyer.

The Seller shall by no means be responsible for any delay in respect of article 2.2 above, and including in cases where a new event or access to new contradictory information would require for the analyst extra time to compute or compare the data in order to enable the Seller to deliver a high quality Products.

2.3 The mailing of the Product will occur only upon payment by the Buyer, in accordance with the conditions contained in article 3.

2.4 The mailing is operated through electronic means either by email via the sales department. If the Product's electronic delivery format is defective, the Seller undertakes to replace it at no charge to the Buyer provided that it is informed of the defective formatting within 90 days from the date of the original download or receipt of the Product.

2.5 The person receiving the Products on behalf of the Buyer shall immediately verify the quality of the Products and their conformity to the order. Any claim for apparent defects or for non-conformity shall be sent in writing to the Seller within 8 days of receipt of the Products. For this purpose, the Buyer agrees to produce sufficient evidence of such defects.

2.6 No return of Products shall be accepted without prior information to the Seller, even in case of delayed delivery. Any Product returned to the Seller without providing prior information to the Seller as required under article 2.5 shall remain at the Buyer's risk.

**3. Price, invoicing, and payment**

3.1 Prices are given in the orders corresponding to each Product sold on a unit basis or corresponding to annual subscriptions. They are expressed to be inclusive of all taxes. The prices may be reevaluated from time to time. The effective price is deemed to be the one applicable at the time of the order.

3.2 Payments due by the Buyer shall be sent by cheque payable to Knowmade, PayPal, or by electronic transfer to the following account:

Banque Populaire Méditerranée, CAP 3000 Quartier du lac, 06700 St Laurent du Var

BIC or SWIFT code: CCBPFRPPMAR

IBAN: : FR76 1460 7003 6360 6214 5695 139

To ensure payment, the Seller reserves the right to request down payments from the Buyer. In this case, the need of down payments will be mentioned on the order.

3.3 Payment is due by the Buyer to the Seller within 30 days from invoice date, except in the case of a particular written agreement. If the Buyer fails to pay within this time and fails to contact the Seller, the latter shall be entitled to invoice interest in arrears based on the annual rate Refi of the «BCE» + 7 points, in accordance with article L. 441-6 of the French Commercial Code. Our publications (report, database, tool...) are delivered only after reception of the payment.

3.4 In the event of termination of the contract, or of misconduct, during the contract, the Seller will have the right to invoice at the stage in progress, and to take legal action for damages.

**4. Liabilities**

4.1 The Buyer or any other individual or legal person acting on its behalf, being a business user buying the Products for its business activities, shall be solely responsible for choosing the Products and for the use and interpretations he makes of the documents it purchases, of the results he obtains, and of the advice and acts it deduces thereof.

4.2 The Seller shall only be liable for (i) direct and (ii) foreseeable pecuniary loss, caused by the Products or arising from a material breach of this agreement
4.3 In no event shall the Seller be liable for:
a) damages of any kind, including without limitation, incidental or consequential damages (including, but not limited to, damages for loss of profits, business interruption and loss of programs or information) arising out of the use of or inability to use the Seller's website or the Products, or any information provided on the website, or in the Products;
b) any claim attributable to errors, omissions or other inaccuracies in the Product or interpretations thereof.
4.4 All the information contained in the Products has been obtained from sources believed to be reliable. The Seller does not warrant the accuracy, completeness adequacy or reliability of such information, which cannot be guaranteed to be free from errors.
4.5 All the Products that the Seller sells may, upon prior notice to the Buyer from time to time be modified by or substituted with similar Products meeting the needs of the Buyer. This modification shall not lead to the liability of the Seller, provided that the Seller ensures the substituted Product is similar to the Product initially ordered.
4.6 In the case where, after inspection, it is acknowledged that the Products contain defects, the Seller undertakes to replace the defective products as far as the supplies allow and without indemnities or compensation of any kind for labor costs, delays, loss caused or any other reason. The replacement is guaranteed for a maximum of two months starting from the delivery date. Any replacement is excluded for any event as set out in article 5 below.
4.7 The deadlines that the Seller is asked to state for the mailing of the Products are given for information only and are not guaranteed. If such deadlines are not met, it shall not lead to any damages or cancellation of the orders, except for non-acceptable delays exceeding [4] months from the stated deadline, without information from the Seller. In such case only, the Buyer shall be entitled to ask for a reimbursement of its first down payment to the exclusion of any further damages.
4.8 The Seller does not make any warranties, express or implied, including, without limitation, those of saleability and fitness for a particular purpose, with respect to the Products. Although the Seller shall take reasonable steps to screen Products for infection of viruses, worms, Trojan horses or other codes containing contaminating or destructive properties before making the Products available, the Seller cannot guarantee that any Product will be free from infection.

**5. Force majeure**
The Seller shall not be liable for any delay in performance directly or indirectly caused by or resulting from acts of nature, fire, flood, accident, riot, war, government intervention, embargoes, strikes, labor difficulties, equipment failure, late deliveries by suppliers or other difficulties which are beyond the control, and not the fault of the Seller.

**6. Protection of the Seller's intellectual property**
6.1 All intellectual property rights attached to the Products are and remain the property of the Seller and are protected under French and international copyright law and conventions.
6.2 The Buyer agreed not to disclose, copy, reproduce, redistribute, resell or publish the Product, or any part of it to any other party other than employees of its company. The Buyer shall have the right to use the Products solely for its own internal information purposes. In particular, the Buyer shall therefore not use the Product for purposes such as:
- Information storage and retrieval systems;
- Recordings and re-transmittals over any network (including any local area network);
- use in any timesharing, service bureau, bulletin board or similar arrangement or public display;
- Posting any Product to any other online service (including bulletin boards or the Internet);
- Licensing, leasing, selling, offering for sale or assigning the Product.
6.3 The Buyer shall be solely responsible towards the Seller of all infringements of this obligation, whether this infringement comes from its employees or any person to whom the Buyer has sent the Products and shall personally take care of any related proceedings, and the Buyer shall bear related financial consequences in their entirety.
6.4 The Buyer shall define within its company point of contact for the needs of the contract. This person will be the recipient of each new report in PDF format. This person shall also be responsible for respect of the copyrights and will guaranty that the Products are not disseminated out of the company.

**7. Termination**
7.1 If the Buyer cancels the order in whole or in part or postpones the date of mailing, the Buyer shall indemnify the Seller for the entire costs that have been incurred as at the date of notification by the Buyer of such delay or cancellation. This may also apply for any other direct or indirect consequential loss that may be borne by the Seller, following this decision.
7.2 In the event of breach by one Party under these conditions or the order, the non-breaching Party may send a notification to the other by recorded delivery letter upon which, after a period of thirty (30) days without solving the problem, the non-breaching Party shall be entitled to terminate all the pending orders, without being liable for any compensation.

**8. Miscellaneous**
All the provisions of these Terms and Conditions are for the benefit of the Seller itself, but also for its licensors, employees and agents. Each of them is entitled to assert and enforce those provisions against the Buyer.
Any notices under these Terms and Conditions shall be given in writing. They shall be effective upon receipt by the other Party.
The Seller may, from time to time, update these Terms and Conditions and the Buyer, is deemed to have accepted the latest version of these terms and conditions, provided they have been communicated to him in due time.

**9. Governing law and jurisdiction**
9.1 Any dispute arising out or linked to these Terms and Conditions or to any contract (orders) entered into in application of these Terms and Conditions shall be settled by the French Commercial Courts of Grasse, which shall have exclusive jurisdiction upon such issues.
9.2 French law shall govern the relation between the Buyer and the Seller, in accordance with these Terms and Conditions.