Analysis of the consequences of a cliff edge scenario in Brexit on the availability and regulatory oversight of pharmaceuticals and medical devices

Ministry of Health, Welfare and Sports

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Building a better working world

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Impact on Medicinal Products

Building a better working world

Cliff edge Brexit impact on Medicinal Products Executive summary

In case of a no deal scenario, on the 29th of March 2019, the **UK will become a "third country" to the EU27**

The UK becoming a "third country" will **impact the pharma value chain** in Europe in an unprecedented way

In order to bring a medicinal product to the European market, the company selling product needs to be the Marketing Authorization Holder (MAH). In order to ensure this authorization remains valid after Brexit, the **MAH needs to continue to comply to several requirements**:

- **GMP inspection** is considered to be performed by an EU27 inspectorate;
- **Quality control & batch release activities** must take place on EU27 ground;
- **Marketing Authorization Holder** (legal entity) must be located in EU27;
- **Marketing Authorization Reference Member State** must be part an EU27 Member State;
- **QPPV** must be located on EU27 ground; and
- **PSMF** must be located on EU27 ground.

In case the MAH does not comply, he will not be allowed to sell products on the European market - potentially leading to **product unavailability** for the patient.

Based on the available quantitative data and stakeholder interviews, we identified:

- A **range of ATCs which are prone to shortages** (and of which the criticality can be further analyzed, and for which alternatives can then possibly be identified)
- A considerable number of patients in the Netherlands use medicinal products where UK plays a role (e.g. import, RMS, etc.). Potential shortages of certain medicinal products may occur and affect patients if no alternatives are available.
- A clear need for increasing **stakeholders** (hospitals, pharmacies & authorization holders) **awareness** and supporting action to tackle in an anticipated manner possible Brexit consequences.

The pharma value chain in Europe and main requirements impacted by a cliff edge Brexit

In order to ensure product safety, the EU requires that the **production of Medicinal Products** is done according to predefined EU requirements.

It is key that all transportation and packaging of pharmaceutical products ensures safe use of these products. In addition, activities for **quality control testing and batch release** need to be performed as per EU requirements.

In order to make a product available on the EU market, the company needs to have a **Marketing Authorization** (centralized or decentralized).

Once the product has reached the market, it is crucial that the safety of all medicines is monitored throughout their use. Therefore, specific **pharmacovigilance regulation** needs to be complied to by the Marketing Authorization Holder.

MAJOR BREXIT RISKS

- Raw material uncertainty (out of scope)
- GMP inspection to be performed by an EU Inspectorate
- Quality control and batch release to take place on EU ground
- Product flow physically transiting through UK to go through customs
- Marketing Authorization Holder (legal entity) to be located in EU
- Reference Member State to be part of EU
- Qualified Person for Pharmacovigilance (QPPV) to be located inside EU
- Pharmacovigilance System Master File (PSMF) to be located in EU

How to bring a medicinal product to the market in the EU?

When bringing a medicinal product in one, several or all EU Member States, the company who is bringing the product in the market required a **Marketing Authorization (MA)** and is then called the **Marketing Authorization Holder** (Directive 2001/83/EC and Regulation (EC) No. 726/2004). Marketing authorizations can be obtained via a centralized as well as a national approach.

National procedure			Centralized procedure
Local procedure	**Decentralized procedure**	**Mutual Recognition Procedure**	
■ Procedure for authorizing products within one EU Member State ■ Application to be submitted on a local level	■ Procedure for simultaneously authorizing products across several EU Member States if no single authorization has been granted yet ■ Identical applications are simultaneously submitted to authorities of the Reference Member State (RMS) and to all other concerned member states ■ The RMS takes the lead and continues the process ■ In case of disagreement, CMDh/CMDv and if necessary CHMP/ CVMP takes up the case	■ If Marketing Authorization is granted in one Member State (RMS), it can be recognized in other concerned EU Member States (i.e. Concerned Member States, CMS) ■ The CMS are asked to recognize the authorization of the RMS ■ In case of disagreement, CMDh/CMDv and if necessary CHMP/ CVMP takes up the case	■ The MA is valid for all EEA – one product name for all Member States ■ A single MA application should be submitted to the EMA ■ Assessment carried out by CHMP for human medicine/ CVMP for veterinary medicine ■ Final decision made by EC, based on reports from EMA ■ Compulsory for biotech products, Oncology, Diabetes, AIDS, Neurodegenerative diseases Orphan Drugs and NCEs

For obtaining a Marketing Authorization, a range of requirements need to be complied to, among which GxP testing. The **key components** that are being tested are the **testing/ lab facilities, manufacturing & wholesale/distribution practices and the product specifications**.

Once obtained, the Marketing Authorization remains **valid for five years**. Perpetual validity for the product can be obtained after a first renewal.

Main GxP requirements directly impacted by a cliff edge Brexit

For obtaining Marketing Authorization in the EEA, the applicant needs to prove compliance to several requirements among which **GxP (Good x Practices)**. These guidelines have as objective to ensure that products within regulated industries are produced in a safe environment and are fit for purpose, while being produced against the highest quality standards.

Good Manufacturing Practices (GMP)

- Set of measures related to the manufacturing of Pharmaceutical products
- Renewal often triggered by the manufacturer himself, as the GMP certificate is also required for commercial trades within the Pharma ecosystem
- Testing to be performed according to EU GMP requirements, by an EU Inspectorate (usually the local Inspectorate)
- Manufacturing outside EU should also be tested by an EU Inspectorate
- Quality control & batch release
  - To take place before releasing product on market
  - Occurs against approved product specifications defined in the MA
  - Testing to be done on EEA ground, or in countries with Mutual Recognition Agreement (MRA) where release is recognized as valid within EU
  - Qualified person to be located in the EU

Good Distribution Practices (GDP)

- Set of measures related to the wholesale distribution of Pharmaceutical products
- Also applies to the sourcing, storage and transportation of the API
- Anyone engaged in the distribution of medicinal products in the EEA must hold a wholesale distribution authorization issued by the Member State – to be requested in each state separately
- Testing to be performed according to EU GDP requirements, by EU inspectorate or the local inspectorate (for NL: IGJ)

Good Pharmacovigilance Practices (GVP)

- Set of measures drawn up to facilitate performance of Pharmacovigilance
- Testing to be performed according to EU GVP standards, by EU inspectorate (PRAC) or the local inspectorate (for NL: IGJ)
- Qualified person for Pharmacovigilance (QPPV) should be located in the EU
- Pharmacovigilance System Master File (PSMF) should be located in the EU
- PRAC can always initiate additional re-evaluations – often the result of previous indications

Key regulatory bodies involved in selected activities in the pharma value chain

Good Manufacturing Practices (GMP)

- Assessed by local inspectorate
- For NL: IGJ
- For UK: MHRA

SOURCING & PRODUCTION

Marketing Authorization Application

- To be submitted to European Medicines Agency (EMA) for centralized procedures
- To national authority for non-centralized procedures (e.g. MHRA & CBG)

LOGISTICS

Good Distribution Practices (GDP)

- Assessed by local inspectorate
- For NL: IGJ
- For UK: MHRA

Marketing Authorization Assessment

- Centralized procedure or Mutual Recognition procedure
- Decentralized procedure: local regulatory authority

MARKET

Marketing Authorization Approval

Assessment by European Commission, based on reports from EMA

CONTINUOUS MONITORING

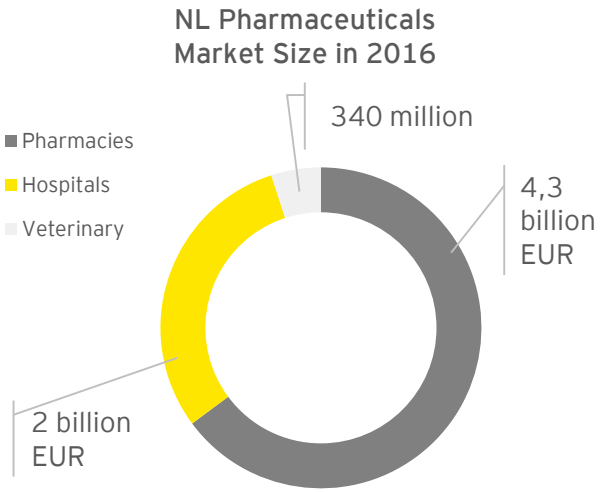
Good Pharmacovigilance Practices (GVP)

Assessment performed by IGJ for NL

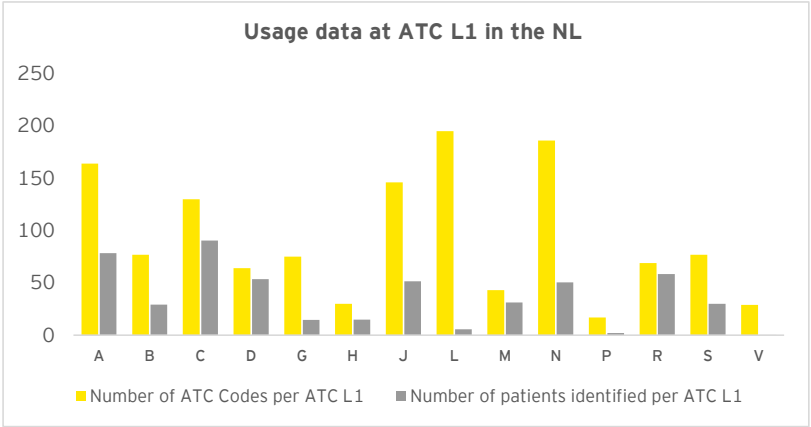
Quantitative overview of the pharma market in the Netherlands

- Total **Pharma market value** in the Netherlands is estimated at a total of **6,64 billion EUR** (2016 data).

- The overall pharma consumption can be spread into **medication routed through pharmacies** (extramural), **hospitals** (intramural) and specific to **veterinary purposes**. Pharmacies represent the biggest share (65%), while veterinary medicines only represent a minor value share (5%).



Source: GIP/ Zorginstituut



Source data: GIPdatabank – See List of ATC Codes L1 at the end of the document

- Within the scope of this study, available usage data identified a total of **1302 different Anatomical Therapeutic Chemicals** (ATC*, by default at level 5) in the Netherlands. The number of ATCs, for each ATC category (i.e. ATC L1), is represented on the above figure; with the corresponding impacted patient population (in 100.000's).

* ATC codes allow for classifying the active substances of medicines in a hierarchy with five levels, with the first level indicating the anatomical / pharmacological group. Through this report, ATC level 5 is the lowest level of granularity used for differentiating drugs.

ATC Codes Level 1

- A Alimentary tract and metabolism
- B Blood and blood forming organs
- C Cardiovascular system
- D Dermatologicals
- G Genito-urinary system and sex hormones
- H Systemic hormonal preparations, excluding sex hormones and insulins
- J Antiinfectives for systemic use
- L Antineoplastic and immunomodulating agents
- M Musculo-skeletal system
- N Nervous system
- P Antiparasitic products, insecticides and repellents
- R Respiratory system
- S Sensory organs
- V Various

Methodology for quantitative assessment

Multiple different data sources have been used for supporting the quantitative assessment of identified risks.
Most risks are evaluated on the basis of a joint dataset, combining Usage, MA, MAH and Sites data; while GMP and PV risks are assessed separately.

Usage
- Description: ATC Codes and Corresponding patient volume data; for all prescribed extramural medicines and for all expensive intramural human medications.
- Usage: Used in the analysis to give a sense of volumes on gaps identified at ATC levels.
- Source: GIPdatabank (via Zorginstituut Nederland)
- Cleaning operations: Reconnect extramural and intramural datasets.
- Limitations: Unavailability of non-prescription or inexpensive medical ATCs.

MA
- Description: Listing of all marketing authorization allowing commercialization of products in NL (i.e. all centralized MA, and all decentralized MAs valid for NL)
- Usage: Identify what marketing authorizations have a RMS which is relying on UK, and serves as joint between ATCs, MAH data and sites data.
- Source: CBG Data and EMA Data
- Cleaning operations: Multiple MA rows connected to multiple ATCs – to be broken down.
- Limitations: -

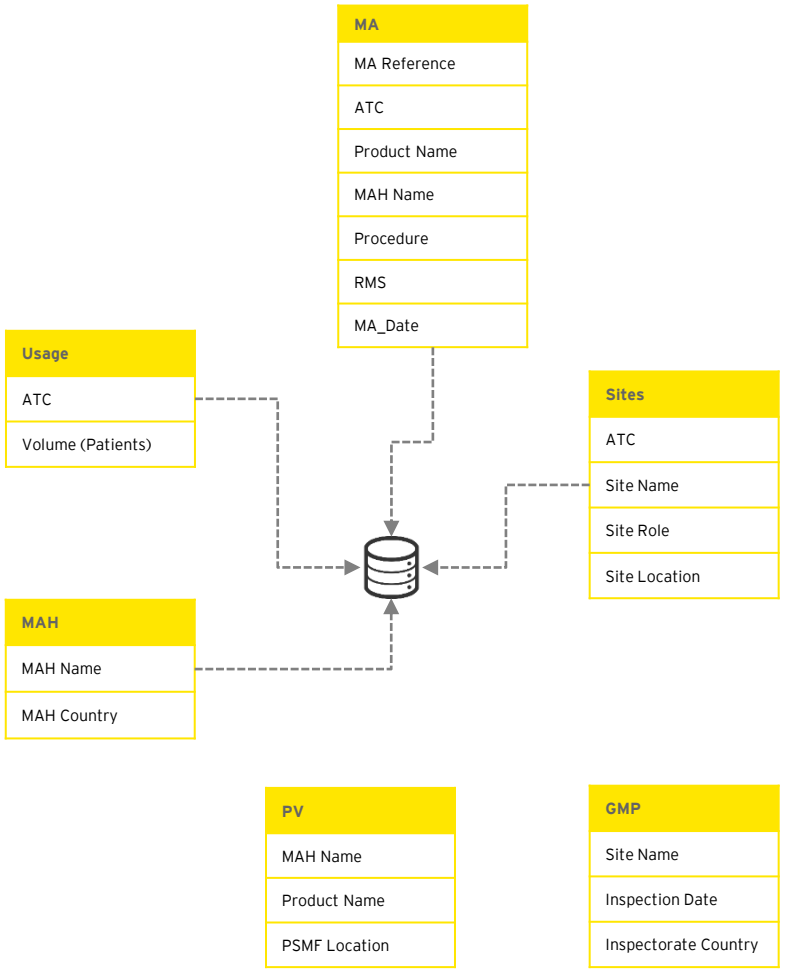
MAH
- Description: Listing of MAH details.
- Usage: Identify what marketing authorization holders have their legal entity based in the UK.
- Source: CBG Data and EMA Data
- Cleaning operations: CBG Data to include information about country leveraged in priority; missing MAH from EMA list to be completed manually based on web search.
- Limitations: -

Sites
- Description: Listing of all sites connected to a marketing authorization in scope.
- Usage: Identify sites which are located in the UK.
- Source: CBG Data
- Cleaning operations: -
- Limitations: No information available for sites that are connected to a centralized MA. Also, no information on QC sites.

PV
- Description: Identification of all PSMF data.
- Usage: Identify PSMF that are located in the UK.
- Source: Article 57 Database
- Cleaning operations: -
- Limitations: No data available about the location of the QPPV, and all PV data to be provided for EU – no NL specific information.

GMP
- Description: Listing of GMP certificates.
- Usage: Identify GMP certificates that are connected with the UK inspectorate.
- Source: EudraGMDP
- Cleaning operations: -
- Limitations: All GMP data to be provided for EU – no NL specific information.

Other comments & limitations
- Multiple assessments are done based on the share of MA, MAH or sites being directly impacted by Brexit; i.e. there is no weighting based on individual volumes / patients.
- Some products might actually correspond to multiple ATCs, which might induce that an ATC appearing as being at risk (i.e. highly depending on UK) could actually correspond to a product labelled on multiple ATCs, with alternative roles taken-up by the UK.



Risk #1 – Physical entry in EU via the UK

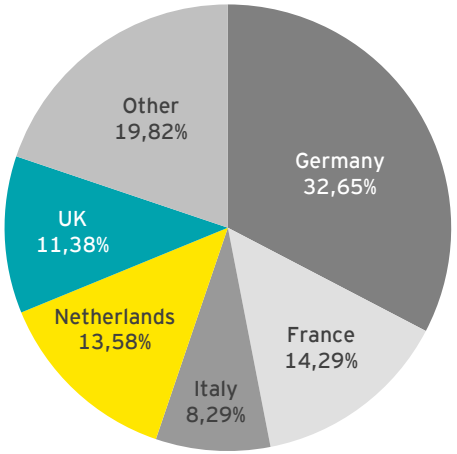
	Physical entry in EU via the UK
Issue rationale	Independently from regulatory requirements, **any product coming from the UK or transiting through the UK will be considered as coming from a third country** and will have to go through customs before entering the EU market. This is mainly expected to induce additional delays in UK-enabled supply chains.
Safety & availability (patient impact)	Due to customs activity and corresponding time impact (i.e. likely longer border times), the **timely availability of certain products might be uncertain** / jeopardized.
Surveillance	Additional workload expected for customs, for all products transiting through the UK.
Possible solutions	■ Actions need to be made for **complying with customs requirements** as per third country (e.g. importer required for finished goods produced in the UK). ■ **Stockpiling** may bring additional reassurance that product availability on the European market remains guaranteed. Some key pharmaceutical actors have already publicly reported their stockpiling activities. ■ Products transiting through the UK need to be considered as transiting through a third party country, implying that **industrial and distribution planning** activities need to be amended accordingly. ■ **Restructuring the physical supply chain** to avoid UK would solve the issue. However, depending on the supply chain changes which would be required, significant costs could be occurred by impacted actors.
Recommendations	Larger actors (e.g. pharma manufacturers and large wholesalers) are expected to anticipate these issues and to apply an approach for the UK as for flows transiting through third party countries. More attention should be brought to **smaller players which might not have experience** in dealing with these flows nor enough firepower to actively monitor potential Brexit consequences.

Risk #1 – Physical entry in EU via the UK

- The UK is a key player in the Pharma landscape in Europe. The **UK exports a significant percentage of medicinal products to other European countries** (see figure) and these medicinal products need to comply to with the EU regulation before being allowed to be marketed.

- In 2017, the UK dispatched pharmaceutical products for a total value of 13,93 billion EUR to EU countries.
  - **1,977 billion EUR or 14,20% of the total dispatched value was delivered in the Netherlands** (to be put in perspective with a local NL Pharma market value of 6,64 billion EUR).
  - After Germany (31,91%), the Netherlands is the second biggest buyer in the EU of pharmaceutical products dispatched from the UK.

Share of total intra EU export (in €) of pharmaceutical products & preparations (in 2016)



Source: Eurostat

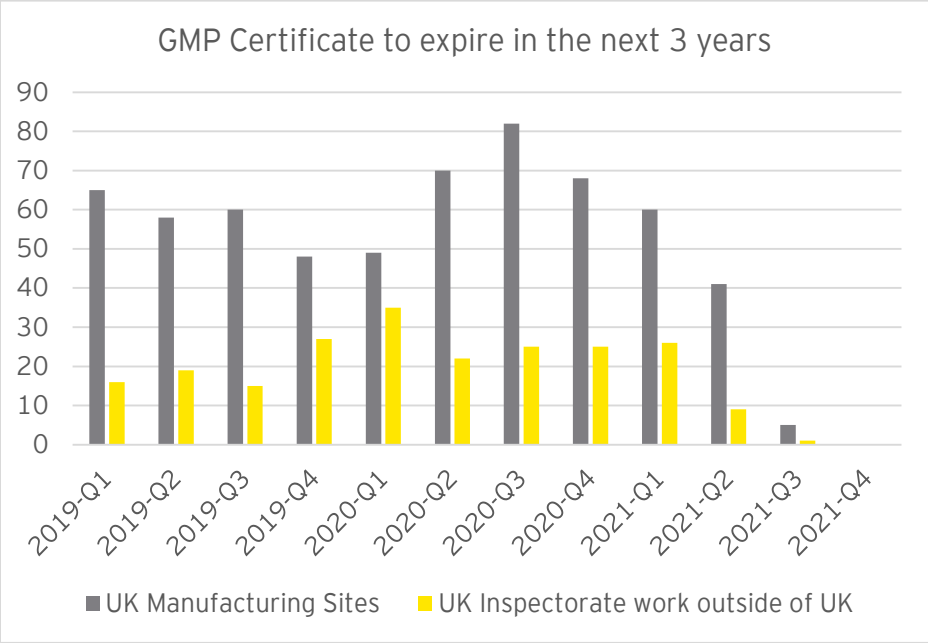
Risk #2 – GMP Inspection by UK Inspector

	GMP Inspection by UK Inspector
Issue rationale	All manufacturing (and QP/QC) activities need to have GMP compliance which is considered to be assessed by an inspectorate based in EU – what regards finished goods. Although certificates issued by the UK inspectorate could still be valid for their normal duration in case of a no-deal scenario, any future GMP inspection (including in the case of a new Marketing Application) can not be handled by the UK inspectorate. In addition, **it may occur that inspections being performed by the UK inspectorate become invalid** at the time of the Brexit (independently from the actual expiry date).
Safety & availability (patient impact)	If GMP inspections being performed by UK inspectorates become invalid, **product availability may be endangered** as the process needs to be restarted by an EU inspectorate. Without GMP compliance, a product cannot be brought to the market in the EU.
Surveillance	As GMP inspections cannot be performed by the UK inspectorate anymore, a significantly **increased workload for European inspectorates** can be expected (for compliance of UK plants, and for compliance of non-EU plants which were inspected by the UK inspectorate). In the case all existing certificates become invalid at the time of the Brexit, the workload for other inspectorate could be extremely high (cf. quantitative data).
Possible solutions	■ **Future GMP inspections** to be handled by non-UK inspectorates. ■ **Shift pending inspections** by UK inspectorate to European inspectorates before a no-deal Brexit becomes reality. ■ Possible **re-inspection for UK certificates** at the time of the Brexit (pending confirmation on this topic).
Recommendations	-

Risk #2 – GMP Inspection by UK Inspector

- A **significant share of GMP certificates have been delivered by the UK Inspectorate**:
  - A total of 697 UK sites currently have a valid GMP certificate, and would require an EU-based inspection in the case these sites deliver to the other Member States; and
  - A total of 340 Non-EU sites have been inspected by UK Inspectorate and currently have a valid GMP certificate, and would require an EU-based inspection the case these sites deliver to the other Member States.

- In case all these sites would require an **inspection from an EU inspectorate at the expiry of the GMP certificate**, the expected additional workload corresponds to a **12-14% increase** (in number of inspections, based on total number of valid certificates = 8.493).
- In the case all these sites would require an inspection from an EU inspectorate before the Brexit, the expected additional workload will be incredibly high (12-14% additional workload to be absorbed would require to be executed in less than 6 months instead of 3 years).



Source data: EudraGMDP Database

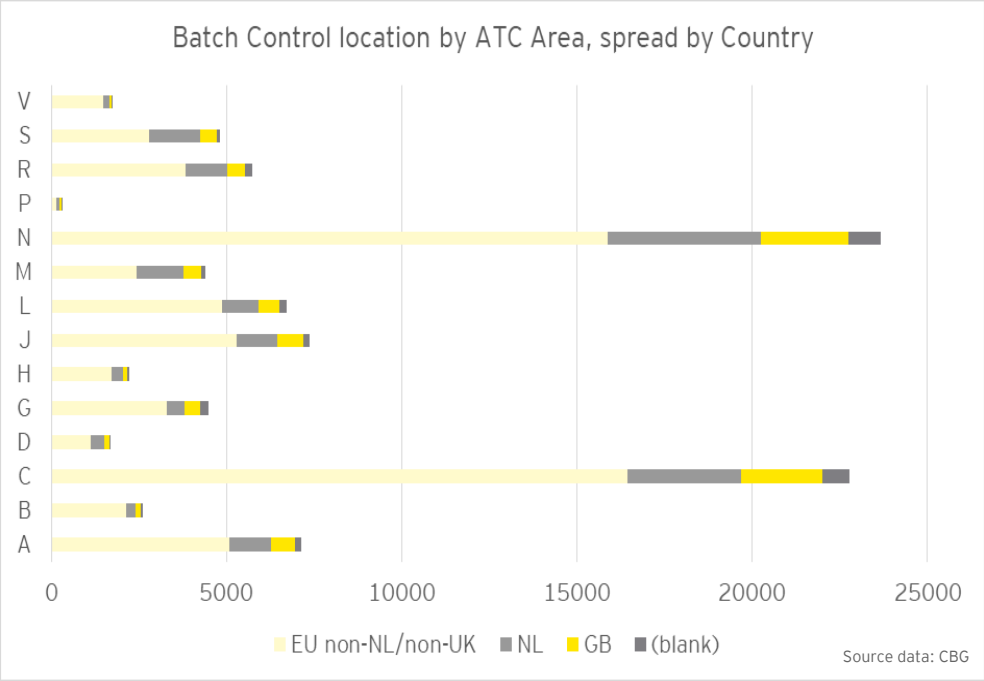
Key assumptions

- Inspections for Manufacturing Sites located in EU are done by the Local MS Inspectorate
- All UK Inspectorate certificates can be identified by the certificate number starting by "UK" or by "VMDGMP"

Risk #3 – Quality control testing and batch release taking place in the UK

	Quality control testing and batch release taking place in the UK
Issue rationale	Directive 2001/83/EC requires that **each batch of medicinal products is to be tested against its products specifications** (i.e. Quality Control – QC) on an EU approved site, and is **certified as having been manufactured in accordance with GMP**, on a site and by a Qualified Person based in EU (i.e. Batch Release – BR). In case of a cliff-edge Brexit, batch releases and quality controls currently being performed in the UK will become invalid.
Safety & availability (patient impact)	If QC activities currently undertaken in the UK are not transferred – or replicated – in an EU location, MAH are **not allowed to bring their products to the European market**. This can lead to a product shortage in EU and NL if not tackled adequately. Similarly, BR must occur on EU ground and failure of compliance is expected to have similar implications.
Surveillance	The work performed in UK labs for execution of QC for products to reach Europe will no longer be recognized in EU, and **EU based labs / sites will have to cover for the workload**. Similarly, **QR work must be performed from within the EU** and a **QP must be identified on EU ground**.
Possible solutions	**Change the supply chain to have QC activities and BR activities taken care within Europe** (can either be transferring the activity or replicating it in EU). For QC , it is expected that MAH will transfer their work to an EU location as QC performed in EU is expected to be recognised by the UK. For BR, it is expected that MAH with production outside of UK will move, as EU BR is expected to be recognised by the UK; while local UK production aimed at being provided to the local market will require a BR performed in the UK (then requiring to duplicate activities). QC and BR can be done by using or deploying dedicated facilities, or outsourced to a third party provider. *Note that change of QP is subject to availability of qualified profiles in other EU Member States.*
Recommendations	-

Risk #3 – Quality control testing and batch release taking place in the UK



- When looking at all available quality control / batch release sites data, it appears that **10% of these sites are located in the UK**.
- When looking at ATC level, it appears that **3% of studied ATCs have only a QC/BR** site in the UK; while 6% have more than 50% of their QC/BR sites located in the UK.

Key assumptions

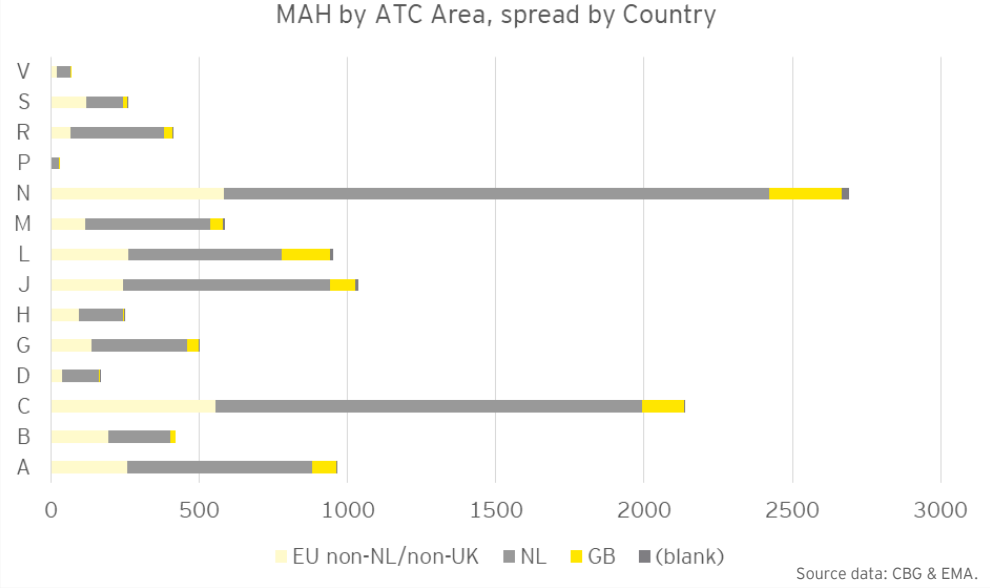
- Analysis performed for MA that are not going through central procedure (CBG data). No data available for MA delivered through EMA – however assumed to be covered considering intensive work and push from EMA at that level.
- No separate data available for quality control sites – assumption that QC and BR are performed at the same location.

Risk #4 – MAH entity being UK entity

	MAH entity being UK entity
Issue rationale	Directive 2001/83/EC requires that **Marketing Authorization Holders are located in Europe**. This implies that current UK-based Marketing Authorization Holders will not be valid in case of a no-deal scenario.
Safety & availability (patient impact)	If Marketing Authorization Holders are not recognized in EU, the businesses are **not allowed to bring their products to the European market** (fines up to 5% of European turnover). This can lead to a product shortage in EU and NL if not tackled adequately.
Surveillance	A transfer of the Marketing Authorizations or obtaining a new Marketing Authorization will be required, leading to **additional workload** for the EMA for centralized procedures or national entities (e.g. CBG) for all other procedures types.
Possible solutions	■ **Transfer Marketing Authorization to another legal entity** (for existing MA as well as for ongoing applications).
Recommendations	Review medicinal products with known MAH being UK based. In case of a **small company with no EU-based entity**, and in the case no other MAH is known for those products, specific follow-up should be organized with the MAH.

Risk #4 – MAH entity being UK entity

- A **significant share of ATCs (28%) is connected to a MAH being a UK legal** entity.



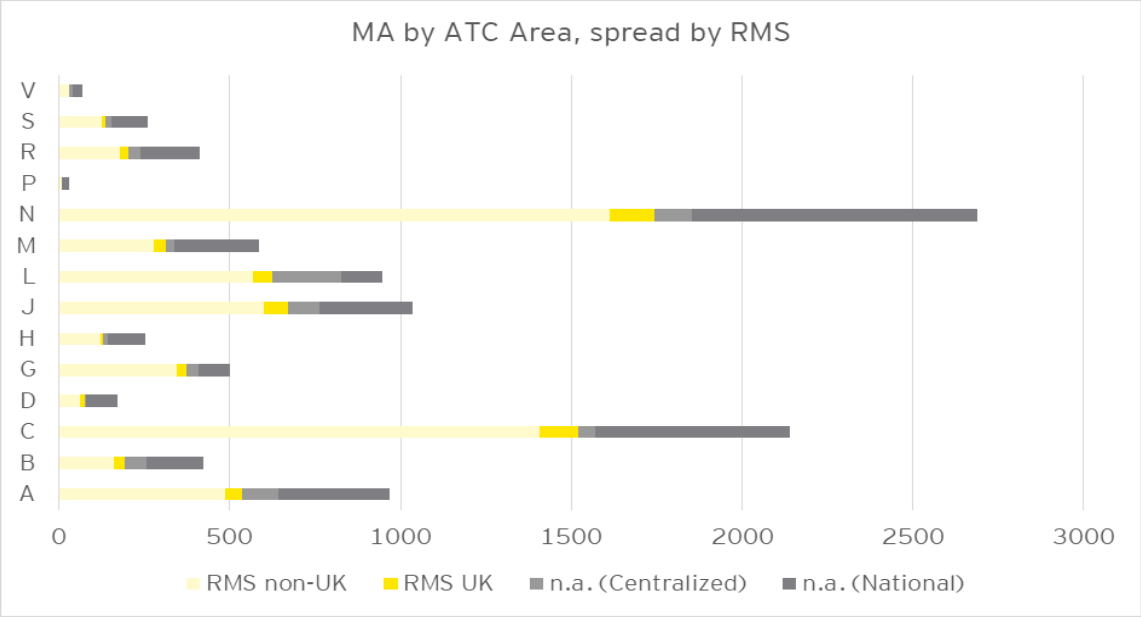
Key assumptions

- Data contains both out-patient as well as expensive in-patient medication (source: Zorginstituut Nederland)

Risk #5 – MA Reference Member State being UK

	MA Reference Member State being UK
Issue rationale	All National Marketing Authorizations recognized in the EU (decentralized and mutual recognition procedure) **rely on a Reference Member State – i.e. EU Member State -** as per Directive 2004/27/EC. In case the RMS is UK, it is possible that Marketing Authorization becomes invalid, although there is no legal certainty on this matter; and variations might be made impossible.
Safety & availability (patient impact)	When Marketing Authorizations are not recognized in EU anymore, the businesses are **not allowed to bring their products to the European market**. This can lead to a product shortage in EU and NL if not tackled adequately.
Surveillance	The above requiring a transfer of RMS, it is expected that additional workload must be covered by EU actors (non-UK), leading to **additional workload to be absorbed** by the remaining EU Member States.
Possible solutions	■ MAH to organize **change of RMS for their MA** (this is not applicable in the case of pending procedures). ■ MAH to apply for **new Marketing Authorization via a RMS located in the EU** (in the case of pending procedure). To do so, a new RMS is to be selected by the MAH out of the available CMS. To date however, there is uncertainly on the time required for completing this process.
Recommendations	Review medicinal products with known RMS being UK. In case of small companies, and in the case no other alternative MAH is known for those products, specific **follow-up should be organized with the MAH**.

Risk #5 – MA Reference Member State being UK



- MA by ATC delivered where UK is RMS is representing a small share of total MA by ATC (5,4%).
- A range of ATC appear to be connected with UK being the only (or majoritarian, i.e. >50% MA where UK is RMS) RMS (and national procedure).

Key assumptions

- Data contains both out-patient as well as expensive in-patient medication (source: Zorginstituut Nederland)

Risk #6 – Qualified Person for Pharmacovigilance in UK

	Qualified Person for Pharmacovigilance in UK
Issue rationale	Regulation (EU) No 1235/2010 and Directive 2001/83 require that the **Qualified Person for Pharmacovigilance (QPPV) resides and operates in the EU**.
Safety & availability (patient impact)	If Marketing Authorizations would become invalid due to a QPPV in the UK, businesses will **not be able to bring their products to the market** in Europe. This may lead to a lack of product availability in the EU.
Surveillance	-
Possible solutions	■ MAH to select a **new QPPV that resides and operates on European grounds**, and perform an update in the EC Art. 57 Database (no variation required) ■ MAH to **outsource the QPPV to a third party provider residing in EU**, and perform an update in the EC Art. 57 Database (no variation required) *Note that change of QPPV is subject to availability of qualified profiles in other EU Member States.*
Recommendations	Review Marketing Authorization Holders with a QPPV in the UK and **increase awareness** on the potential consequences this may have.

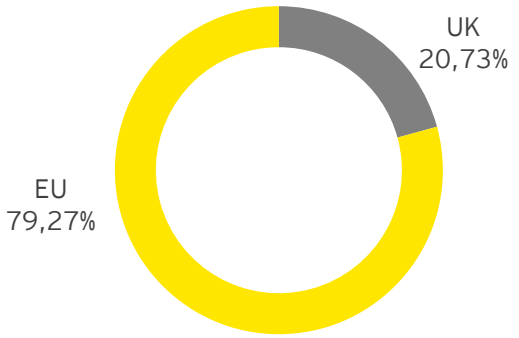
Risk #7 – PSMF in UK

	PSMF in UK
Issue rationale	EU Directive 2010/84/EU requires that each MAH has a **Pharmacovigilance System Master File (PSMF) that is located in the EU**. The Commission Implementing Regulation (EU) No 520/2012 also states that the PSMF must be located either at the site where the main pharmacovigilance activities of the MAH are performed or at the site in the Union where the QPPV operates.
Safety & availability (patient impact)	If the Marketing Authorization is not valid anymore due to a PSMF in the UK, businesses **should not bring their products to the market in Europe**. This may lead to a lack of product availability in the EU.
Surveillance	-
Possible solutions	**PSMF location to be changed** to a European location – and to be updated in the Article 57 Database.
Recommendations	Review companies with PSMF location being UK. In case of small companies, and in the case no other alternative entity is known for these companies, specific **follow-up should be organized with the MAH**.

Risk #6/#7 – Qualified person for Pharmacovigilance and PSMF in UK

- When looking at PSMF entries recorded in the Article 57 Database, it appears that a **significant share** (20,7%) **of entries are indicating a PSMF file located in the UK** (for all PSMF entries connected to a European authorization or an authorization valid in the Netherlands, i.e. items which are or could be marketed in the Netherlands).
- About 14% of all Marketing Authorizations granted in NL have their PSMF UK.
- About 1/2 of Marketing Authorizations that are granted using the centralized approach have their PSMF in the UK.
- This spread shows that 20% of the biggest MAH covering 80% of entries. Key **focus would then be on smaller companies**, which only have 1-2 entries and are not necessarily expected to have enough capacity to monitor Brexit careful and take appropriate action.

EU/UK PSMF spread



Source: Article 57 Database

Key assumptions

- PSMF and QPPV are located at the same location, as only the PSMF location is made available in Article 57 database
- Volumes are calculated at "entry" level in the PSMF file; each entry being unique what regards its product, route of administration, product authorization country and marketing authorization holder.

Additional considerations

- Significant **efforts are being undertaken by key bodies** (e.g. EMA and CMDh) to ensure that all pharmaceutical products can still be supplied in the EU27 in the case of a cliff-edge Brexit;
- **Major pharmaceutical players** have been communicating about ongoing efforts to reduce the impact of a potential cliff-edge Brexit, e.g. ongoing stockpiling activities;
- There is overall high **uncertainty about the legal set-up** for upcoming month, as this scenario is unprecedented;
- As major pharmaceutical players have to reconsider their value chain with Brexit, it is expected that they use this exercise to rethink their way of working and e.g. rationalize their product portfolio. There might therefore be an **indirect impact on availability or pricing** based on independent business decisions being taken;
- **Parallel trade implications** are considered as out of scope for this study;
- **Specific requirements** connected to a short range of products are not detailed (e.g. customs specificities regarding drug precursors, or medicinal products requiring specific handling).

Risk consolidation, assessment & quantification

	Assessment Summary	Impact estimate	Level of risk / Priority
Risk #1 – Physical entry in EU via the UK	Customs inspections may lead to additional supply delays, especially in case actors do not foresee this impact in their supply chain planning activities; and highest risk stands for products where supply chain is tightly managed (e.g. refrigerated products).	A significant share of products being imported from the UK market. Expectation that impact of these will be mitigated by major players (e.g. through stockpiling) while the biggest risk stands with smaller players.	■■■
Risk #2 – GxP Inspection by UK Inspector	No immediate impact expected on the market (from the time GMP certificates emitted by UK inspectorates would remain valid until their normal expiry date), main impact for bodies which will have to cover workload of UK inspectorate. Strong impact in the case UK inspectorates GMP certificates become invalid at the time of the Brexit.	Limited impact expected on patients from the time renewal of GMP is not required before actual certificate expiry date. An issue could occur in the case all certificates delivered by the UK Inspectorate would become invalid at the time of the UK, as workload to be absorbed by inspectorate would be very high (13% workload increase of 3 years to be absorbed in less than 6 months).	■■
Risk #3 – Quality control testing and batch release taking place in the UK	Need for relocating quality control and batch release to an EU location for a range of ATCs to ensure product availability. Impact reinforced by an expected limited availability of QPs profiles.	41 ATC codes affected when looking at ATCs with BR/QR sites in UK only 52 additional ATC codes affected when looking at ATCs with majority of BR/QR sites in UK	■■■
Risk #4 – MAH entity being UK entity	Series of entities where the MA needs to be transferred to a new MAH being not UK-based. Expected limited impact for big companies (able to flex group structure if required) and higher impact for smaller companies.	128 ATC codes affected when looking at ATCs with MAH being based in UK only 30 additional ATC codes affected when looking at ATCs with majority of MAH being based in UK	■■■
Risk #5 – MA Reference Member State being UK	MA will not be considered valid in the case of national procedure leveraging UK as RMS. For those, the MA needs to be transferred to another RMS – which is expected to require a limited effort.	7 ATC codes affected when looking at ATCs with RMS being UK only 19 additional AC codes affected when looking at ATCs with majority of RMS being UK	■
Risk #6 – Qualified Person for Pharmacovigilance in UK	In the case of QPPV being UK based, a new QPPV must be identified in EU. Although complexity for the change is expected to be limited from a regulatory standpoint, complexity comes with the limited availability of QPPV profiles.	N/A (cf. next point on PSMF)	■■
Risk #7 – PSMF in UK	PSMF in UK will not be tolerated, and there is a need for moving PSMF location to the EU.	21% of all medicinal products that can be marketed in the Netherlands have their PSMF located in the UK.	■

Recommendations to VWS

	Conclusions/Recommendations
#1	**Review the list of identified ATC items** to confirm: the lack of substitute, the level of criticality, possible substitutions
#2	**Encourage companies efforts** in taking into account possible Brexit consequences; with a focus on educating and ensuring awareness of **smaller players**
#3	Increase **awareness at the end of the chain**, for actors being mainly focused on medical components and not necessarily aware of Brexit implications: need for 1) awareness; 2) limiting distribution of false information
#4	Further investigate how stated risks would be impacted in the case **other Brexit scenarios** are being pursued
#5	Support the need for further **clarification from relevant bodies** on expected future requirements, e.g. what regards the validity of GMP certificates emitted by the UK inspectorate
#6	Further investigate options for **deploying a monitoring system at VWS level**, granting continuous availability to updated data sources similar to the ones using throughout this exercise

Impact on Medical Devices and In Vitro Diagnostics

Building a better working world

Executive summary
Medical Devices and In Vitro Diagnostics

In case of a no deal scenario on the 29th of March 2019, the UK will become a "third country" to the EU

The UK becoming a "third country" will impact the value chain of medical devices and in vitro diagnostics in Europe in an unprecedented way

In order to obtain market authorization and establish product launches in the EU for medical devices (MDs) and in vitro diagnostic devices (IVDs), the authorized representative for the products must be based in the EU and the products are required to conform to essential requirements and processes ultimately demonstrated by means of a valid CE marking. Notified bodies are companies authorized by the EU to carry out EU Directive compliance checks and are performing the necessary quality assurance and product certification processes. Currently, UK notified bodies play a significant role in certifying, i.e. CE marking, of MDs and IVDs for the EU market. In order to realize valid CE markings, notified bodies need to be in or recognized by the EU.

After a no deal Brexit, the EU no longer acknowledges UK notified bodies. Therefore, post-Brexit certificate validity is uncertain and audit schedules may be at risk. This could lead to potential shortages of products whose CE certificates are currently obtained in the UK. Additionally, driven by uncertainties around CE marking validity, notified bodies that want to continue to play a role in EU MD and IVD certifications need to relocate from the UK to EU countries (already observed for part of the UK NBs). The Brexit related CE marking invalidity risk also triggers medical device companies that are currently acquiring CE certificates via UK notified bodies to switch to EU27 notified bodies. The abovementioned aspects are both likely to increase the (merely administrative) burden on EU27 notified bodies and other competent bodies in addition to the already grown workload related to the upcoming EU Medical Device and In Vitro Diagnostics Regulations (EU MDR and IVDR). Divergent information from UK and EU27 sides around recognition of regulatory processes as well as observed data scarcity around which individual products are assessed by the UK notified bodies further increases complexity and uncertainty, and makes it challenging to take appropriate contingency measures. Abovementioned hard Brexit-related CE invalidity risk and other aspects described in this report, could both directly and indirectly lead to (temporary) medical device product unavailability for the patient.

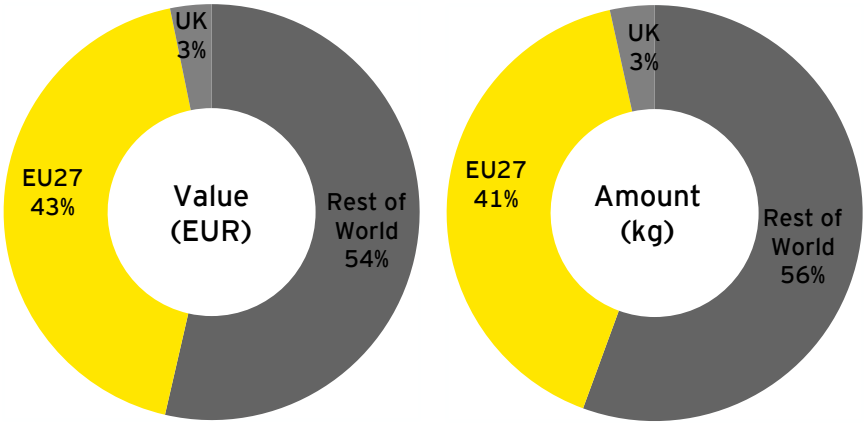
Based on the available quantitative data and stakeholder interviews, we identified that:

- the most eminent risk is related to CE certificates issued by notified bodies in the UK and related uncertainty of CE validity after a hard Brexit. A substantial part of all MDs and IVDs for the Dutch and EU market is currently authorized via UK notified bodies.
- Possible capacity issues at EU27 notified bodies and to a lower extent at EU27 country competent authorities; filling the regulatory gap left by the UK cannot be solved on the short term by recruiting new people. The global pool of expert talent in this area is limited and UK based talent will not all be willing to move out of the UK.
- Six product subcategories (combined nomenclature CN8) where the Netherlands imports 10% – 28% of these product categories from the UK with respect to the total global import.
- A clear need to increase awareness and to prepare stakeholders (especially care providers) of possible hard Brexit implications with respect to potentially discontinued product availability and safety (CE marks).

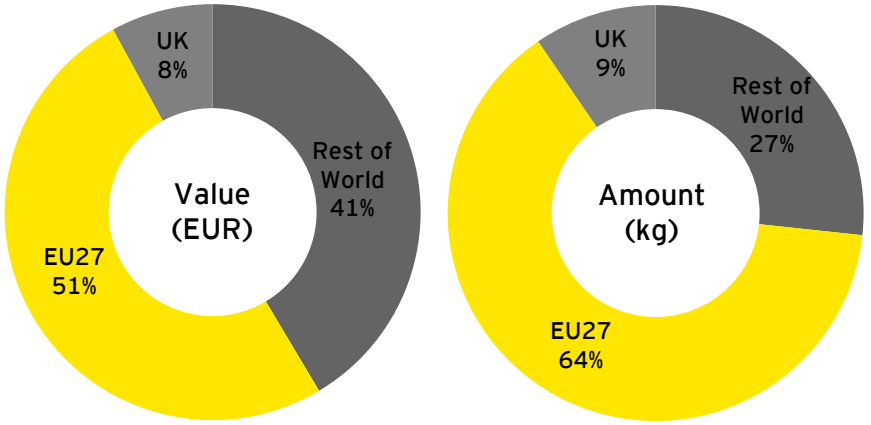
Medical devices market
A selection of highlighted Dutch, UK and EU market facts

- The Dutch Medical devices market has an estimated size of € 4.7 bn (€ 2.4 bn intramural, € 2.3 bn extramural).[1]
- The Netherlands is the 2nd **largest importer and exporter** of medical devices in the EU **in terms of value (EUR)** [2] and the 4th **in terms of volume (kg)**[3]**.** This might suggest that in most of the cases of Brexit-related product shortages , the Netherlands is relatively well positioned to come up with supply chain and product sourcing alternatives.
- There are ~500,000 medical devices and ~27,000 Medical Device companies (95% SMEs) in the EU.[2]
- 9 out of 10,000 working people in the Netherlands work in the Medical Device / Medtech sector. In the EU >675,000 employees.[2]
- In the EU we spend €203 per capita on MedTech (on average 10% of GDP).[3]
- In 2015, approximately **3000 medical manufacturers were counted in the United Kingdom**. Their primary focus was in the field of **orthopaedics**, but they also lead in the production of **imaging**, **diagnostics**, and **cardiovascular devices.**[4]
  - Illustrative examples:[5]
    - A manufacturer of orthopaedic implants, produces certain of its products for the rest of the world in South Wales.
    - Blood collection needles and tubes are manufactured in very high volumes in South West England.
- Figures below show the Dutch import and export of medical devices and in vitro diagnostic products to and from the UK, EU27 and rest of world countries. In relation to the total Dutch MD and IVD import and export values, the UK appears to play a relatively minor role.

Distribution of medical device and in vitro diagnostics import into the Netherlands:



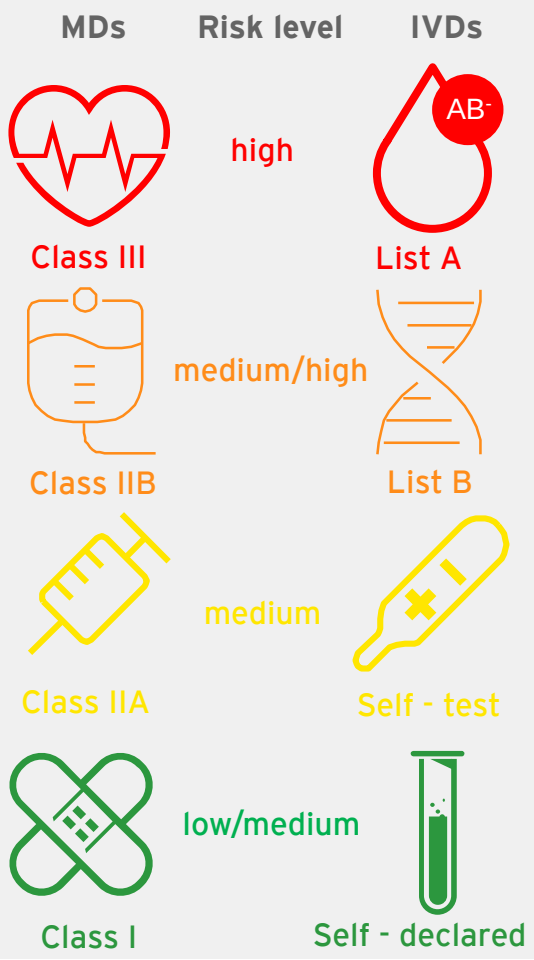
Distribution of medical device and in vitro diagnostics export out of the Netherlands:



1) The medtech market in the Netherlands, KPMG
2) MedTech Europe, position papers on website
3) Eurostat data 2017
4) UK – Overview of medical device industry and healthcare statistics, website EMERGO
5) Brexit and the impact on patient access to medicines and medical technologies, Brexit Health Alliance, January 2018
6) EY Analysis based on Eurostat data 2017

Medical devices (MDs) and In Vitro Diagnostics (IVDs)
Definitions and classifications

Classification



Medical Device Definition

- Article 1.2a:

'medical device' means any instrument, apparatus, appliance, material or other article, whether used alone or in combination, including the software necessary for its proper application intended by the manufacturer to be used for human beings for the purpose of:

- diagnosis, prevention, monitoring, treatment or alleviation of disease,
- diagnosis, monitoring, treatment, alleviation of or compensation for an injury or handicap,
- investigation, replacement or modification of the anatomy or of a physiological process,
- control of conception,

and which does not achieve its principal intended action in or on the human body by pharmacological, immunological or metabolic means, but which may be assisted in its function by such means;

See MDD 93/42/EEC for additional info on:

- 1.2b: 'accessory'
- 1.2c: 'device used for in vitro diagnosis'
- 1.2d: 'custom made device'
- 1.2e: 'device intended for clinical investigation'

In Vitro Diagnostic medical device Definition

- Article 1.2b:

'in vitro diagnostic medical device` means any medical device which is a reagent, reagent product, calibrator, control material, kit, instrument, apparatus, equipment, or system, whether used alone or in combination, intended by the manufacturer to be used in vitro for the examination of specimens, including blood and tissue donations, derived from the human body, solely or principally for the purpose of providing information:

- concerning a physiological or pathological state, or
- concerning a congenital abnormality, or
- to determine the safety and compatibility with potential recipients, or
- to monitor therapeutic measures.

Specimen receptacles are considered to be in vitro diagnostic medical devices. 'Specimen receptacles` are those devices, whether vacuum-type or not, specifically intended by their manufacturers for the primary containment and preservation of specimens derived from the human body for the purpose of in vitro diagnostic examination.

Products for general laboratory use are not in vitro diagnostic medical devices unless such products, in view of their characteristics, are specifically intended by their manufacturer to be used for in vitro diagnostic examination.

Sources: Directive 93/42/EEC and Directive 98/79/EC

Descriptions of stakeholders involved in regulatory and market authorization procedures for the EU market

In order to get marketing approval for a medical device in one, several, or all EU member states, the following key stakeholders are involved and particularly relevant mentioning in the context of a cliff edge Brexit: the **competent authority**, **a notified body,** and **an authorized representative**.

Competent Authority (CA)

- The national authority responsible for setting up and carrying out the necessary procedures for the assessment and notification of conformity assessment bodies and the designation and monitoring of notified bodies
- **MHRA** is CA of UK
- **VWS/directie GMT (and IGJ)** is CA of NL

Notified Body (NB)

- A conformity assessment body officially designated by the national authority to carry out the procedures for conformity assessment within the meaning of applicable Union harmonisation legislation
- NBs in NL concerning MDs
  - Dekra Certifications B.V.
  - Dare!! Certifications
- NBs in UK concerning MDs
  - BSI
  - LQRA
  - SGS
  - UL International
- After a hard Brexit, the UK is considered a third country, while for EU market access of MDs and IVDs the NB must be in the EU27.

Authorized Representative (EC-REP)

- An authorized representative is any natural or legal person established in the EU who, explicitly designated by the manufacturer from a third country, acts and may be addressed by authorities and bodies in the EU instead of the manufacturer with regard to the latter's obligations under these Directives.
- After a hard Brexit, the UK is considered a third country, while for EU market access of MDs and IVDs the EC-REP must be in the EU27.

UK notified bodies are currently taking steps to open office locations and get new NB designations in EU27 countries, some in the Netherlands. See also page 38.

Sources: NANDO database, European Commission website: http://ec.europa.eu/growth/tools-databases/nando/ and Directive 90/385/EEC

Medical Devices CE conformity route

High level, schematic representation of the medical device market authorization process

R&D

Determine applicable directive

Determine device classification

For MDs: Class I, IIa, IIb or III/AIMD

For IVDs: list A, B, self-test or self-declare

Implement quality management system

Prepare technical file/dossier/ if needed, perform clinical trials

Audit by Notified Body

(except for class I (non-sterile, non-measuring device)

CE marking and ISO 13485

(for Class I and IVD self-certification possible)

Declaration of Conformity

Registration at CIBG for Class I and IVD

Other classes via NBs

If required, appoint an authorized representative

EC REP

Start

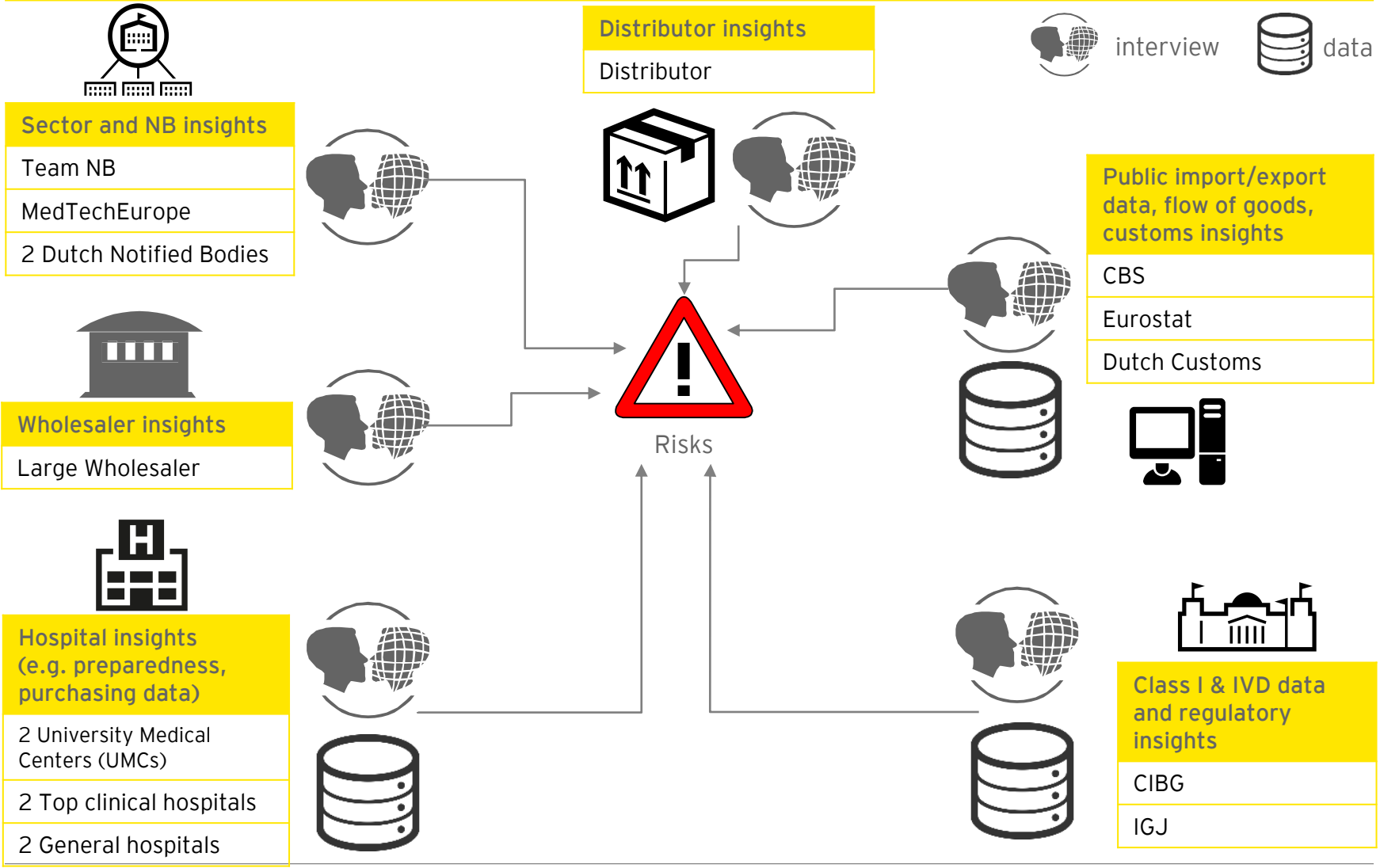
Renewal

Sources:
Overview created based on content at the websites of EMERGO: Europe CE Marking Regulatory Process for medical devices, and BSI: CE Marking and EU Directives.

Methodology

Connecting data from different sources with insights from interviews

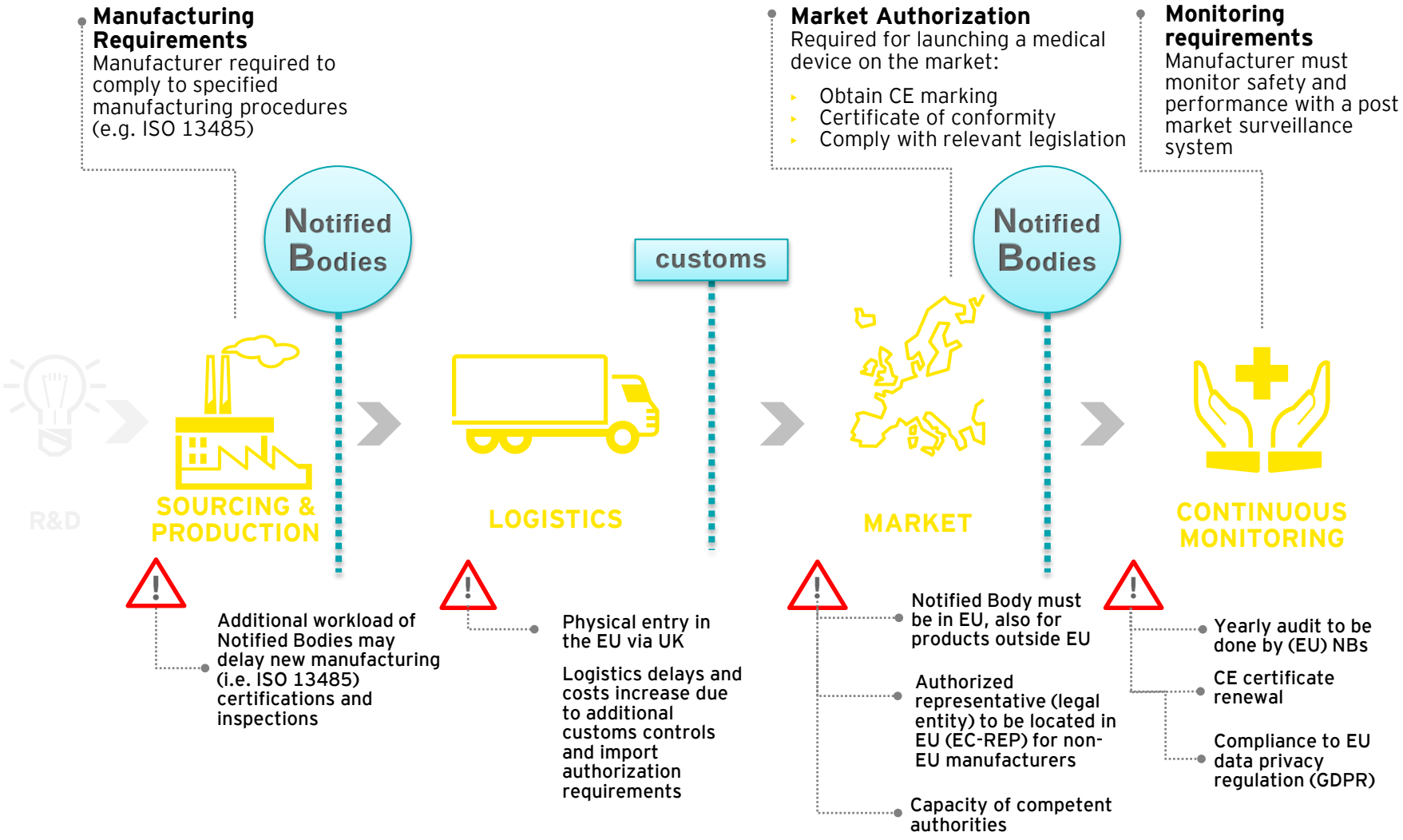
Relatively more interviews* were performed compared to the pharmaceutical product part of this study, due to the observed data scarcity on individual product level



* Certain company and institution names have been anonymized for confidentiality reasons.

The Medical Devices and In Vitro Diagnostics value chain in the EU

and their identified risk areas in the context of Brexit



Overview of identified risks ⚠ - Medical devices and In Vitro Diagnostics

	Risks
#1	UK Notified Body – loss of recognition
#2	EU27 Notified Bodies - capacity constraints
#3	Increased workload competent authorities EU27
#4	Physical entry to EU27 via the UK (products manufactured in the UK and elsewhere)
#5	Authorized representative in the UK – loss of recognition
#6	Data centers or service providers in the UK and inhibited data transfer

Risk #1 – UK Notified Body – loss of EU recognition

Uncertainties around validity of UK CE markings

UK Notified Body – loss of EU recognition	
Issue rationale	Approx. 30-50% of all medical devices and IVDs is currently authorized via UK notified bodies.[1] After a hard Brexit, UK Notified Bodies (NBs) are not recognized by the EU. It is therefore highly uncertain whether product certifications by UK NBs are still valid after 29 March 2019. New products with a CE mark issued by a UK notified body after the no deal date will not be allowed to be sold or bought within the EU27 because of invalid CE certificates.[1] Moreover, although it is generally assumed that CE marks issued by UK NBs prior to the no deal date will still remain valid,[1] to our knowledge, there is neither an existing legal framework in place confirming this assumption, nor this is formally agreed upon during the ongoing UK/EU negotiations. The uncertainties around UK CE mark validity has forced several UK NBs to transfer their offices to an EU27 country and apply for new NB designations.[2] Also medical device companies are expected to switch from UK to EU27 NBs. However, related to the involved costs, long transfer times and longstanding relationships with current UK NBs, most of the medtech companies will initially rely on the NBs to mitigate their CE validity risks.[1]
Safety & Availability (patient impact)	Shortages and product unavailability may occur, because of potential abrupt invalidity of CE marks. New products with UK NB CE may probably not be sold or bought within EU27 after a hard Brexit. Products in stock and authorized prior to 29 March 2019 may probably still be sold, though this assumption cannot be confirmed based on existing legislation. At the same time, competent authorities should be cautious to continue recognizing the UK NB certified products for authorization on the EU27 market after the no-deal date (e.g. via discretionary exemptions), since this may support easier market entrance of fake products on the EU27 market and thus could impair patient safety.[3] Since specific IT products also fall under the definition of medical devices, the availability of such software may be at risk as well, particularly taking into account the fact that each software update usually requires a new certification.
Surveillance	Yearly audit performed by UK NB are at risk because UK NBs are not recognized anymore by the EU. All products affiliated with UK NBs must be audited by EU27 NBs after no deal Brexit, and consequently the surveillance tasks and responsibilities will be dependent on the EU27. This increases the workload for EU27 (incl. NL) NBs, who have already felt an increase in workload because of implementing the upcoming EU MDR/IVDR regulations.[1]
Possible actions	► Medical device companies may transfer from UK NB to EU27 NB (takes typically 6 – 9 months[3], which is not possible anymore given the current time frame prior to Brexit) ► UK NB moving to EU27 (takes ~1.5 years for designation,[1] which are not available anymore given the current time frame prior to Brexit). UK NBs that are now relocating initiated this process a long time ago. ► Longer term option (not an option for a no deal scenario): EU27 formally accepts UK NBs via a mutual recognition agreement (takes years and a transition period is required for this) ► In case of urgent critical shortages (mainly as emergency tool), the Minister may issue a discretionary exemption for individual products on the basis of an advice from IGJ ((Wmh art 8).[3] This is only possible as a short term measure and under certain terms & conditions.
Recommendation	► Facilitate the UK NBs in their relocation and MD and IVD NB redesignation journeys in the EU27, and approve accompanying files. Based on a recent statement by the large UK NB, BSI, in which is referred to ongoing discussions with the designating authority and regulatory bodies in the EU and the Netherlands, it appears that manufacturers do not require relabeling of their products if already placed on the market prior to the no deal date.[4] ► The Netherlands should steer to acknowledging UK NBs on a EU level. However, they are dependent on other EU27 countries.

1) Estimation range (30-50%) based on registrations of class I and IVD at Dutch CIBG, interviews with Team NB, MedTech Europe and a Dutch UMC, Brexit Health Alliance Briefing January 2018 – Brexit and the impact on patient access to medicines and medical technologies, and statements on BSI website: BSI Medical Devices and Brexit. CE validity, medtech company and NB relocation and EU MDR statements based on interviews with MedTech Europe and TeamNB.

2) See news on websites BSI, LRQA, and Intertek

3) Based on Interview IGJ and Wet op de medische hulpmiddelen (Wmh)

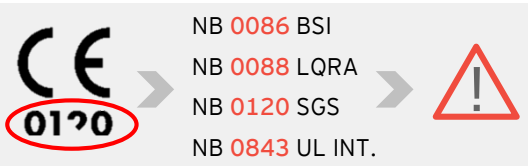
4) article Medtech Views: What does Brexit mean for Notified Bodies, Gary Slack, BSI, 14 Sept 2018

Risk #1 – UK Notified Bodies

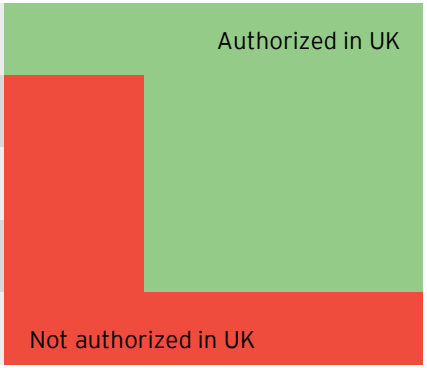
UK NBs take action by applying for designation of MDs, AIMDs, and IVDs in EU27

UK notified bodies are under competitive strain, and after Brexit, products certified using their UK CE codes (as shown on the right) will not be acknowledged by the EU. Through different approaches, most of them are actively seeking routes to expand and retain their services within the EU27 after a possible hard Brexit (further described on this page).[1] ~30-50%[2] of all medical devices are certified in the UK, mostly by BSI. 24 of the world's top 25 global medical device manufacturers choose BSI as their notified body for CE marking certification against the applicable EU Directives.[3] For devices of higher risk classes the share of UK certifications (~55-60%) appears even slightly higher.[4, 5] A limited number of stakeholder conversations and specific UK sources suggest that therapeutic areas exposed to the highest risks related to Brexit related MD certificate invalidation are respiratory[6], cardiovascular[4,7], orthopaedics,[4,7,8] neonatology,[6] radiology,[6] and radiotherapy.[6]

Cheat sheet UK NBs



Directive NBs	90/385/ EEC	93/42/ EEC	98/79/ EC
BSI			
LRQA			
SGS			
UL int.			
Intertek			



BSI

- BSI has achieved accreditation for issue ISO 13485 certificate by RvA in the Netherlands
- BSI achieved designation as a medical device NB in the Netherlands on November 13th, 2018.
- MDR application submitted end of 2017

LRQA

- LRQA is actively expanding approvals. Mostly in the Netherlands: 93/42/EEC and 98/79/EC already submitted.
- The applications are in various stages of assessment, with an expectation of obtaining approvals around the end of 2018

SGS

- SGS retains capability and capacity in the UK. Will work closely with SGS notified bodies in Europe to ensure all customer certification requirements can be met

UL International

- *"Until we know more about the details of the exit agreement, we will continue to move forward business as usual"*

Intertek

- Moved to Sweden and has withdrawn all its activities from the UK.

Sources:
1) Press releases and websites of notified bodies mentioned on this page
2) Estimation range (30-50%) based on registrations of class I and IVD at Dutch CIBG, interviews with Team NB, MedTech Europe and a Dutch UMC, Brexit Health Alliance Briefing January 2018 – Brexit and the impact on patient access to medicines and medical technologies, and statements on BSI website: BSI Medical Devices and Brexit.
3) BSI Website, Fact & Figures , https://www.bsigroup.com/
4) Interview Medtech Europe
5) Interview Team NB
6) Interviews 2 Dutch UMCs
7) UK – Overview of medical device industry and healthcare statistics, website EMERGO
8) Brexit and the impact on patient access to medicines and medical technologies, Brexit Health Alliance, January 2018

Risk #1 – Overview of registered Medical Devices Class I and IVDs in NL

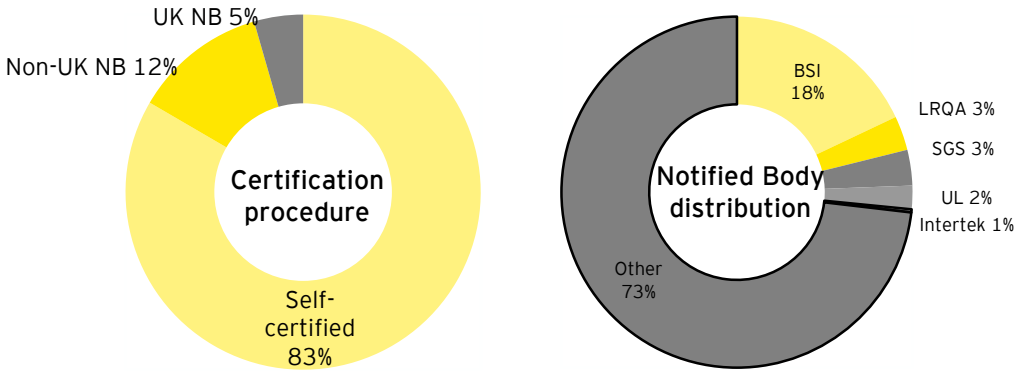
These classes are mostly self-certified, but 4% of the registered devices involve UK NBs

Table 1 below depicts the total number and different types of class I medical devices and IVDs registered at the CIBG in the Netherlands. Classes Is, Im, and Ism refer to a subtype of class I products being sterile (Is), comprising a measuring function (Im), or both (Ism). The table shows that a total of 14495 products are registered, of which approx. 60% are class I MD products and approx. 40 % are IVD. For 2405 products (17 %) NBs play a role, whereas the majority of products (~83%) are self-certified (further visualized in the diagrams below). Of the 2405 products where NBs are used for certification a total of 646 products use UK based NBs, which equals ~4% of the total registered devices. BSI is the most involved UK NB being involved in 432 product certifications. Based on the individual product list, approx. 30 % of the products with UK NBs involved were found to be related to orthopaedic devices and linked to one company, Howmedica Osteonics Corporation, part of the multinational Stryker. Other specific patterns, e.g. around potential UK NB dependencies of specific class I and IVD product types and/or therapeutic areas have not been identified .

Table 1: medical device and IVD products registered at CIBG

Category	Number of products	%	NB involved	UK NB	BSI	LRQA	SGS	UL	Intertek
Class I	7733	53	1152*	286	214	55	8	4	5
Class Is	608	4	571	160	120	6	31	2	1
Class Im	230	2	227	73	69	0	4	0	0
Class Ism	7	0	7	4	1	3	0	0	0
IVD selftest	50	0	32	12	0	5	0	7	0
IVD list A	80	1	49	38	4	2	0	32	0
IVD list B	222	2	188	43	6	0	30	7	0
IVD other	5422	37	49	19	14	4	0	0	1
System/procedure pack	143	1	30	11	4	1	6	0	0
total	14495	100	2405	646	432	76	79	52	7

Diagrams 1 and 2: certification details of CIBG registered products (distribution based on number of products)



Source: EY analysis using CIBG registration data for IVDs and class I MD

*Class I products do not require NB involvement, indicating a potential subcategory registration error

Risk #2 – EU27 Notified Body – capacity constraints

Both Brexit and EU MDR/IVDR put strain on NBs

EU27 Notified Body capacity

Issue rationale	The EU MDR/IVDR implementation increases NB workload significantly[1,2]. In addition to market authorization processes for new products, a large portion of products that are currently self-certified will now require some form of NB involvement. Some NBs will decrease their scope or cease to exist because they cannot meet the challenging MDR/IVDR requirements[1]. The MDR/IVDR has resulted in a decrease of the number and / or scope of existing NBs.[3] Besides EU MDR/IVDR implementation, a hard Brexit will exert additional pressure on total NB capacity by: 1) resulting in transfers of UK NBs to EU27, or 2) existing EU27 NBs taking over product CE marking trajectories of UK NBs. Also these actions and related tasks will lead to time pressure and likely longer product authorization throughput times, and lack of capacity and available knowledgeable experts. Despite efforts of NBs increasing their staff the past years this may not be sufficient to deal with the expected hard Brexit related workload increase.[4] Recent communications with two Dutch NBs confirm this.[5] Even without taking Brexit into account, the Dutch NBs do not appear to have the capacity available to assist to new clients, where at the same time they observe many additional client requests related to Brexit. Many medical device companies indicate they find it challenging to find an alternative EU27 NB that has the capacity to fulfill their demand.[5]
Safety & Availability (patient impact)	Possibility of rush jobs because of the capacity problems, thus decreasing quality of procedures which may impact safety. Shortages because of expiring certificates and invalid UK NB issued CEs that cannot be immediately addressed due to extended product file throughput times, necessary time-consuming transfer procedures to other NBs, and NB capacity issues. In the situation that competent bodies decide to continue recognizing specific UK NB certified products for authorization on the EU27 market (e.g. via discretionary exemptions), this may increase the risk for confusion around certification status and consequently inadequate customs control, which may enhance the chance of fake products entering the EU market.
Surveillance	If UK NBs are not recognized by the EU27 or are not designated in the EU27 in time, the yearly audit may be at risk. This may increase the workload for Dutch or EU27 NBs. All CE certificates now issued by UK NBs may probably not be issued by UK NBs from April 1st 2019 and onwards. The same holds for inspections now done by UK NBs, these tasks must be taken over by the EU27 NBs. Though CE certificates (e.g. for products certified prior to the Brexit date) may be valid, UK NBs will not be authorized by the EU to perform inspections and quality control tasks related to these products.
Possible actions	▸ UK NBs should transfer to EU27 including qualified personnel and files/data/reports before no deal Brexit date. ▸ Accept individual products via discretionary exemption in case of a critical shortage ((Wmh art 8).[6] Due to the additional patient safety risks involved and high impact on work load competent bodies, this should be considered as an emergency measure only and always takes place for a short period and under certain terms & conditions.
Recommendation	▸ Assist a smooth transition of NBs from UK to NL/EU27, and facilitate the timely transfer of all product files in order to ensure continued EU market access of medical devices with valid CE markings after the no deal date. NB number cannot be transferred and therefore new number should be there as of 1 April 2019 (see Risk #1) ▸ Keep hiring and retaining qualified staff ▸ Find a way to monitor workload shifts, e.g. related to the distribution UK NBs' tasks over all EU27 NBs

1) Interviews Team NB and MedTech Europe
2) Medical Device Regulation: A necessary step towards more patient and user safety, Medical Writing (vol. 26, nr. 2), Claudia Frumento, June 2017.
3) NANDO, number of notified bodies before MDR/IVDR publication: 83, to date: 55 in NANDO
4) Team NB press release - NBs comparison of capacities, August 2018
5) Interviews with two Dutch Notified Bodies
6) Wet op de medische hulpmiddelen (Wmh) and Interview IGJ

Risk #2 – EU27 Notified Body capacity constraints

Key observations

- **As ~30-50%[1] of devices are currently certified and audited by UK NBs.** In the case of a hard Brexit, where UK NBs and their CE marked products are not acknowledged, these tasks will need to be transferred to EU27 NBs (or UK NBs will need to move to EU27 countries first and get redesignated).

- A no deal Brexit will likely **cause a sudden increase in product file transfer applications to EU27 NBs** leading to significant higher workloads. Dutch notified bodies have already received several of such transfer requests, but are not able to fulfill the demand. It is unlikely that all product files for devices currently certified by UK NBs can be transferred to alternative EU27 NBs prior to the no deal date, also given the fact that NBs already demonstrate significant challenges right now to cope with the existing workload.[2]

- **Without taking into account Brexit, NBs already experienced a significant workload increase as a result of the upcoming EU MDR/IVDR requirements.** NBs are taking efforts to expand and have recently shown an approximate 27% increase in their FTEs, which aligns with Team NB members' willingness to increase capacity[3]

- **Relocation and redesignation of UK notified bodies to EU27 could assist in (partially) resolving uncertainties around Brexit related CE mark invalidation,** and opens up the possibility to transfer product files from the UK to EU27 at a higher rate. However, it is not a guarantee that this will entirely mitigate NB capacity issues. As observed during the EMA transfer to the NL,[4] also for UK NBs not all experienced and qualified personnel will be open to move to EU27 countries.

1) Estimation range (30-50%) based on registrations of class I and IVD at Dutch CIBG, interviews with Team NB, MedTech Europe and a Dutch UMC, Brexit Health Alliance Briefing January 2018 – Brexit and the impact on patient access to medicines and medical technologies, and statements on BSI website: BSI Medical Devices and Brexit. CE validity, medtech company and NB relocation and EU MDR statements based on interviews with MedTech Europe and TeamNB.

2) Interviews with two Dutch Notified Bodies

3) Team NB press release - NBs comparison of capacities, August 2018

4) Brexit preparedness: EMA to further temporarily scale back and suspend activities, EMA press release, August 2018

Risk #3 – Increased workload competent authorities EU27

Capacity vs. uncertain hard Brexit provoked workload

Increased workload EU27 Competent Authorities	
Issue rationale	After a hard Brexit, any tasks performed by the MHRA with respect to designation and oversight of NBs, as well as vigilance, safety alerts and guidance, will only be done on national (UK) level, and not on EU level anymore[1]. The UK is currently a large European contributor in this area and a hard Brexit will require a shift of the abovementioned tasks to EU27 countries, incl. The Netherlands. For the Netherlands, the increased work shift is largely linked to the foreseen transfer of one or multiple UK Notified Bodies to the Netherlands, which may increase future capacity requirements for the Dutch Inspectorate (IGJ).[2] Preparations appear to be in progress to respond to the expected changes. However, the relative large uncertainty regarding absolute workload increases, e.g. linked to poor insights in the number of product files to be transferred to the relocated NBs and existing NBs, should still be marked as a medium risk and monitored carefully over time.
Safety & Availability (patient impact)	As for medicinal products inspections, the IGJ will see an increase of tasks around overseeing NBs, which might lead to a strain on capacity when no actions are taken. Currently a couple of UK NBs have applied for designation in NL and according to internal sources current capacity of the IGJ is sufficient to match the additional workload[3]. Nevertheless, workload is at this stage relatively difficult to estimate, e.g. by the possibility of more NBs transferring to NL and the poor insights in total file numbers to be processed in the Netherlands. When over time capacity becomes insufficient, this will have a negative impact on product safety and surveillance.
Surveillance	Surveillance tasks will increase for all EU27 inspectorates because MHRA responsibilities will shift to EU27. Inspections of EU joint commissions will be required for UK manufacturers, potentially increasing the workload for IGJ.
Possible actions	▸ Intensify and leverage the EU27 inspectorate network (e.g. such as seen for medicinal evaluation boards in the EU) and discuss potential distribution of MHRA tasks across EU27 level to share the burden and minimize potential capacity issues ▸ Acknowledge MHRA via mutual recognition agreements (likely to take too much time, so a transition period is required) ▸ Keep investing in the number of qualified personnel at IGJ to match workload increase. The challenge lies in the fact that everyone is recruiting from the same pool of experts and average up-to-speed training takes more than a year
Recommendation	▸ A more centralized approach, where EU27 inspectorates distribute tasks throughout the EU27, could reduce the potential risk of local country capacity issues, because workload is shared. The drawback here is that the Netherlands will become more dependent on other EU27 countries, when it comes to its own market surveillance. ▸ Continued focus on increasing the number of qualified personnel at IGJ, despite multiple organizations recruiting capable experts from the same talent pool ▸ Continue workload estimations based on latest Brexit and market developments.

1) Guidance UK Government, How medicines, medical devices and clinical trials would be regulated if there's no Brexit deal, September 2018
2) Press releases BSI and LRQA
3) Interviews IGJ

Risk #4 – Physical entry to EU27 via the UK

Products manufactured in the UK and elsewhere

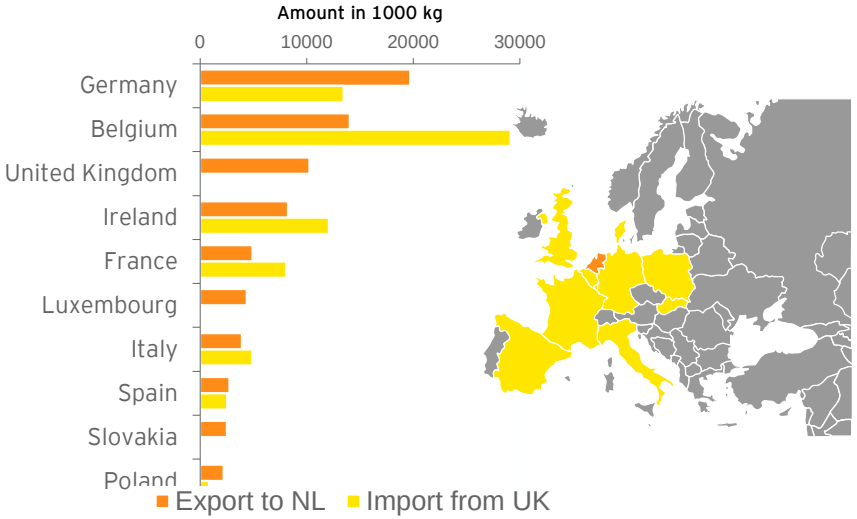
Entry to EU27 via the UK	
Issue rationale	Independently from regulatory requirements, any product coming from the UK to the EU will now require import authorizations and have to go through additional customs checks, before entering the European market. This could result in delays in the overall supply chain potentially affecting timely product availability to patients. In addition, a number of items may incur irrecoverable import duties and, potentially recoverable, import VAT, leading to increasing costs of goods and thus overall healthcare costs. Although in relation to the total Dutch MD and IVD import and export values, the UK appears to play a relatively minor role, there is a possibility that the supply chain of specific individual products are negatively affected. Given the lack of medical device and IVD import and export data on the individual product level, it was not possible to indicate concrete examples of such products during this study.
Safety & Availability (patient impact)	Products are expected to incur delays and additional (compliance) costs, impacting availability. Furthermore, it is possible that required (EU) customs authorities, physical checks and/or documentary reviews may deviate in practice from what is prescribed in EU law – potentially impacting the safety of products available on the Dutch market.
Surveillance	While additional border control would in theory lead to additional surveillance by way of (double) customs checks, in practice the expected lack of appropriate capacity may deteriorate the quality of customs controls.
Possible actions	▸ Medical device companies to reorganize supply chain without UK dependencies, identifying alternative EU27 entries ▸ Medical device companies to reallocate stock from UK to a location within EU27 before March 29th, 2019. ▸ Rigorous planning of customs activities and resources to and mitigate delay risks ▸ Readjust supply chain plannings and safety stocks considering UK as 'Third country' instead of a EU country'. This however, does not take into account the unique event Brexit is and practical issues that are likely to happen as of the no deal date. It may also be easier implemented by global players than by SMEs. Unfortunately, in the MedTech sector 95% is SME.[1] ▸ For important perishable or emergency products, fast lanes may be made available.
Recommendation	▸ Additional effort on the planning of customs activities (and corresponding) delays in the supply chain may allow continuous availability of products, albeit it cannot be excluded that due to capacity issues, customs control quality may decline and throughput times increase. Increased investments in customs activities and resources are likely to result in higher prices. ▸ Relevant companies should be encouraged to reallocate their stock independent of other Brexit related problems. UK warehouses may transfer to EU27 countries.

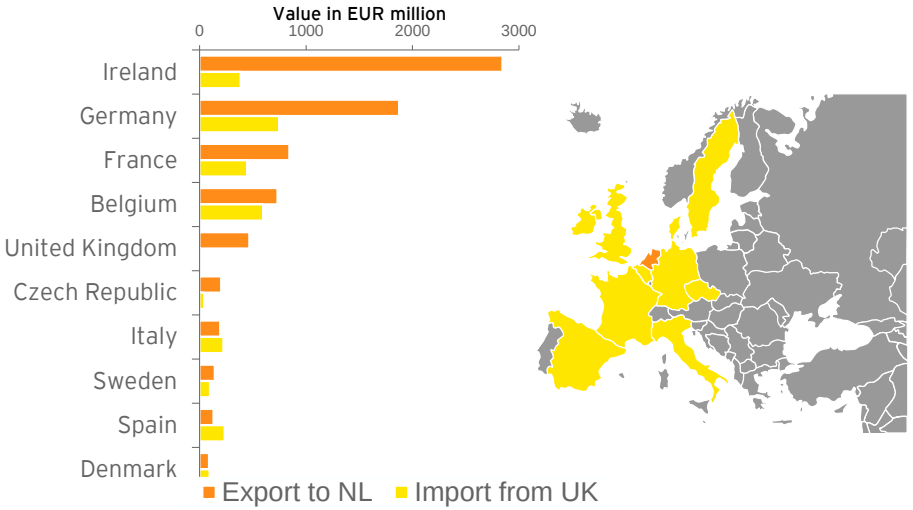
1) MedTech Europe, Fact & Figures, website

Risk #4 – Most important EU medical devices suppliers to NL

UK ranks 3rd and 5th on the list of EU MD suppliers to the Netherland in terms of volume/kg and value, respectively.

The figures below show medical device export levels to the Netherlands (both in terms of kilograms of product (kg; left picture) and in value (€ millions; right picture) for the (in Dutch perspective) most important medical device supplying EU countries. It also shows for each medical device supplying country the respective medical device import levels from the UK. On page 30, it was shown that more than half of the medical devices imports into the Netherlands come from rest of world countries. Besides rest of world countries, it is clear from the figures below that the Netherlands is more dependent on other EU countries for its medical device supplies than on the UK, such as Germany, Belgium, Ireland and France. Import data from UK shown in the figures below are purely indicative and it should be stated that a high import from the UK in this plot does not indicate a potential risk, since the rest of world product streams are not included here and the imported products from the UK do not directly link to the products exported to the Netherlands.





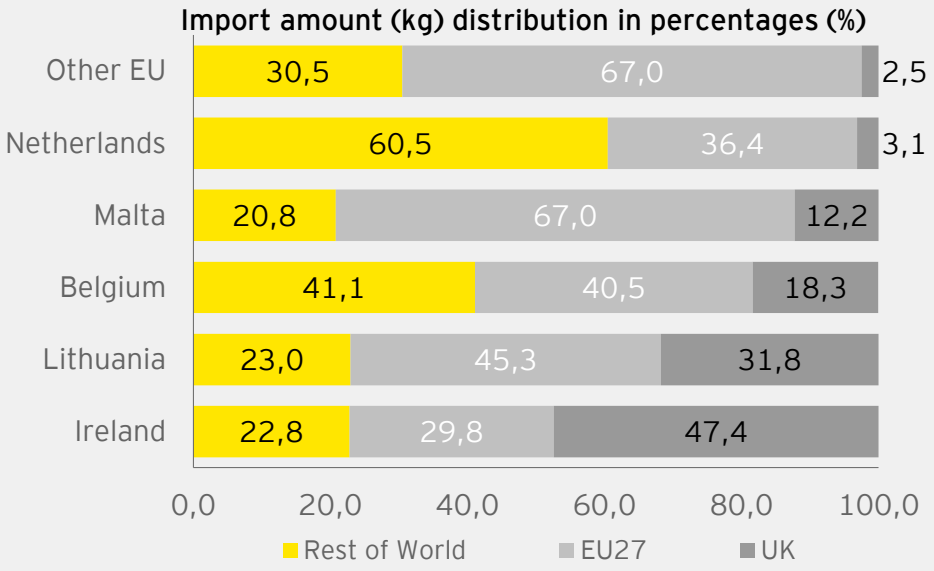
Source: EY analysis based on Eurostat 2017 data

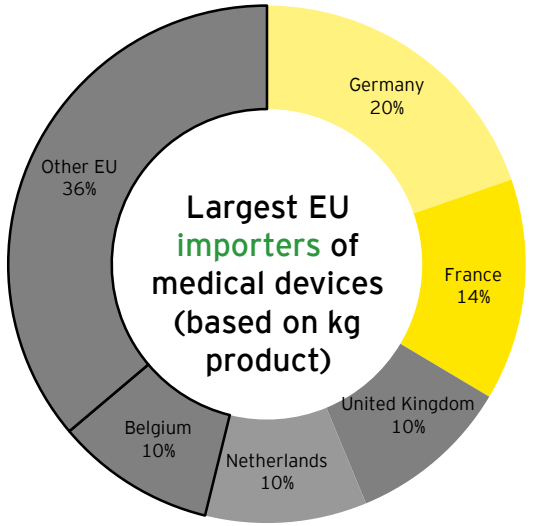
Risk #4 – EU's dependence on UK as medical devices distributor

Although UK is a top 5 importer of medical devices in the EU, most EU countries are relatively independent of the UK based on overall import/export percentages

- The UK imports approx. 160 million kg of medical device products worldwide, which puts the UK in the top 5 medical device importing countries in the EU (see upper diagram on the right).
- The UK exports approx. 80 million kg to EU27 countries, representing approx. 6% of total EU27 medical devices import. The UK exports approx. 32 million kg to rest of the world countries. (see lower diagram on the right).
- Ireland, Lithuania, Belgium and Malta imported the highest amount of medical devices from the UK (as depicted in the plot below).

On average UK accounts for ~6% of medical devices and IVDs supply in EU27 countries. Ireland, Lithuania, Belgium, Malta show relatively the largest UK import:





Source: EY analysis based on Eurostat 2017 data

Risk #4 – Medical devices imported from UK to NL

Medical devices imported from the UK represent only 3% of the total medical device import into the Netherlands.
6 MD product subcategories identified with highest import levels from the UK ranging from 10-30% of the total MD import into NL

CBS data analysis revealed that the import of medical devices from the UK represents 3 % of the total global medical devices import in the Netherlands, although specific product subcategories were found with higher dependence on import from the UK.

For instance, 6 subcategories of medical devices were found, where more than 10% till approx. 30 % of the import is derived from the UK. These subcategories are displayed in the table below. The table shows that the subcategory with highest UK import shares (approx. 28 %) is related to parts and accessories of hearing aids.

Because during this study, import data was not available on the individual MD and IVD product level, in this analysis we were limited to the use of subcategories. Although subcategory import/export data suggests a limited, almost negligible dependence of NL on import from the UK, this does not directly imply there are no supply risks for individual products. It is still likely that specific products exist currently solely manufactured in the UK and/or imported via UK.

Total of 6 identified subcategories with highest import from the UK to NL (ranging from approx. 10-30%)

Subcategory code (CN8)	Subcategory description	NL import from UK	NL import from EU27	NL import from World
90219010	Parts and accessories of hearing aids, n.e.s.	27,98%	60,27%	11,75%
90229080	X-ray generators other than X-ray tubes, high tension generators, control panels and desks, screens, examination or treatment tables, chairs and the like, and general parts and accessories for apparatus of heading 9022, n.e.s.	21,88%	26,83%	51,29%
90013000	Contact lenses	18,80%	59,95%	21,24%
90200000	Breathing appliances and gas masks (excl. protective masks having neither mechanical parts nor replaceable filters, and artificial respiration or other therapeutic respiration apparatus)	15,98%	65,56%	18,46%
90221400	Apparatus based on the use of X-rays, for medical, surgical or veterinary uses (excl. for dental purposes and computer tomography apparatus)	15,86%	45,27%	38,87%
90213100	Artificial joints for orthopaedic purposes	12,30%	36,20%	51,50%

Source: EY analysis based on CBS 2017 data

Risk #4 - Analysis of import alternatives for 6 identified MD subcategories with highest import from the UK

Sufficient alternative import streams exist for the 6 subcategories from other EU27 countries

The table below shows the 6 identified MD subcategories with the relatively highest import percentages from the UK described on page 46 together with the top 3 EU countries supplying the corresponding subcategory to the Netherlands. For these supplying countries. their import and export details in relation to NL and UK are shown. Most supplying countries are net exporters (indicated in green), suggesting they are manufacturing countries. Percentages in last two columns show the import percentages from UK and export percentages to NL for the respective countries. Based on the import/export data in the table below, it can be concluded that alternative EU countries exist for import of these 6 subcategories without being affected themselves by Brexit related UK import and export delays. As mentioned previously, it is still possible that supply issues can still occur with individual and/or niche products. These insights cannot be distilled from the available subcategory data.

Table: Top 3 suppliers of the 6 identified medical device subcategories and their relative UK dependencies

Subcategory code (CN8)	Subcategory description	Top EU27 (Eurostat) net exporters in green	Export to NL (x 1000kg)	Total Export (x 1000 kg)	Import from UK (x 1000kg)	Total import (x 1000kg)	% Import from UK	% Export to NL
90219010	Parts and accessories of hearing aids, n.e.s.	1.Spain	23,9	32,2	1,4	102,5	1,37%	74,22%
		2.Germany	3,6	184,0	15,3	62,7	24,40%	1,96%
		3. Denmark	1,7	416,9	1,2	61,0	1,97%	0,41%
90229080	X-ray generators other than X-ray tubes, high tension generators, control panels and desks, screens, examination or treatment tables, chairs and the like, and general parts and accessories for apparatus of heading 9022, n.e.s.	1.Germany	108,1	988,3	105,9	1071,8	9,88%	10,94%
		2. France	59,6	823,6	143,9	520,2	27,66%	7,24%
		3. Czech Republic	41,0	188,0	9,0	36,7	24,52%	21,81%
90013000	Contact lenses	1. Ireland	629,8	11055,9	127,4	150,0	84,93%	5,70%
		2. Germany	97,7	39564	104,4	3059,7	3,41%	0,25%
		3. Belgium	20,9	473,3	77,4	2779,9	2,78%	4,42%
90200000	Breathing appliances and gas masks (excl. protective masks having neither mechanical parts nor replaceable filters, and artificial respiration or other therapeutic respiration apparatus)	1. Germany	163,7	2873,9	1096,0	2299,4	47,66%	5,70%
		2. Belgium	57,0	149,3	32,2	328,8	9,79%	38,18%
		3. France	14,5	524,6	448,0	1282,0	34,95%	2,76%
90221400	Apparatus based on the use of X-rays, for medical, surgical or veterinary uses (excl. for dental purposes and computer tomography apparatus)	1. Italy	174,9	2560,8	1604,3	6482,4	24,75%	6,83%
		2. Germany	149,2	8898,9	118,1	1637,2	7,21%	1,68%
		3. France	123,6	4903,2	0,2	1244,4	0,02%	2,52%
90213100	Artificial joints for orthopaedic purposes	1. France	435,1	1288,7	27,9	658,4	4,24%	33,76%
		2. Ireland	254,1	2843,4	545,4	1070,4	50,95%	8,94%
		3. Germany	92,3	1040,6	5,6	929,9	0,60%	8,87%

Source: EY analysis based on CBS 2017 and Eurostat 2017 data

Risk #5 – Authorized Representative (EC-REP) in the UK
Loss of EU recognition

Legal entity: the EC-REP in the UK	
Issue rationale	Authorized representatives need to be located in Europe (Directive 90/385/EEC); which means current UK-based EC-REP will not be recognized in the EU after a hard Brexit. This will result in hampered market access on the EU27 market for (often rest of world) companies using an UK-based EC-REP.
Safety & Availability (patient impact)	Capacity issues could arise when it comes to identifying suitable and experienced alternative legal representative candidates in EU27. Ultimately, this could affect (at least temporarily) the availability of medical devices products on the EU market. Additionally, renewal of authorized representatives results in additional workload and financial implications to manufacturers,[1,2] which in turn could be translated in higher product prices contributing to increased healthcare costs.
Possible actions	▸ Companies/manufacturers can transfer EC-REPs normally within a few weeks to EU27,[1] although cost and potential capacity issues at alternative EU27 authorized representatives is a possible risk. ▸ Inform relevant stakeholders about possible consequences of having a UK EC-REP with respect to Brexit. ▸ On EU level steer on recognizing UK authorized representatives via mutual recognition agreements.
Recommendation	▸ Manufacturers currently using UK based EC-REPs should appoint an alternative EC-REP in an EU27 country before the no deal Brexit date. ▸ Manufacturers and the EU27 authorized representatives may require information about possible consequences of passivity in this area and recommended actions to take.

1) Interview Team NB
2) Website EMERGO, European Authorized Representative for Medical Device Companies

Risk #5 – UK based Authorized Representatives

- The procedure for changing EC-REP is costly, but can be done in a period of multiple weeks.[1] This procedure is mainly administrative of nature and involves changing/moving documents/files/etc.
- The European Association of Authorized Representatives has 3 members that are in the UK (highlighted in red).[2] Abnovo Ltd and its clients may potentially be affected the most.

Overview of Authorized Representatives in the UK and EU:

This is not an exhaustive list of authorized representatives

EAAR Member	Location	EAAR Member	Location
Abnovo Ltd	United Kingdom	Medical Risk Management	The Netherlands
Advena Ltd	United Kingdom & Malta	Medical Technology Promedt Consulting GmbH	Germany & USA
CEpartner4U BV	The Netherlands	MedPass International Ltd	France
CMC Medical Devices & Drugs S.L.	Spain	Obelis s.a. European Authorized Representative Center	Belgium
Donawa Lifescience Consulting s.r.l.	Italy	QAdvis AB	Sweden
EMDAR BV (part of Emergo)	The Netherlands	Qarad European Regulatory Services	Belgium & Italy & the Netherlands
Emergo Europe	The Netherlands	Qmed Consulting ApS	Denmark
Medical Device & QA Services Ltd	United Kingdom (part of Advena Ltd)	Tecno-Med Ingenieros S.L.	Spain
Medical Device Safety Service GmbH	Germany		

1) Interview Team NB
2) European Association of Authorized Representatives (EAAR) website

Risk #6 – Data centers or service providers in the UK and inhibited data transfer

UK data centers and other third parties that store EU27 data

Issue rationale	Health technology is increasingly being used in healthcare, and related to this also the quantity of data generated grows exponentially. This technology often incorporates cloud data storage, which could be located in the UK, also given the fact that the UK is the 2nd biggest player in data centers, service providers and network infrastructure in Europe.[1] Typical data might include electronic patient data records, personal device data, clinical research data, and other type of personal data. After a hard Brexit, the new General Data Protection Regulation 2016/679 (GDPR) does not apply anymore to the United Kingdom. In the context of transfer of personal health data, the UK will then be regarded as a third country. In this case, data transfer will only be allowed if the controller or processor has provided "appropriate safeguards". These safeguards include: a) use of standard EU data protection clauses, b) binding corporate rules: legally binding data protection rules approved by the competent data protection authority which apply within a corporate group, c) approved codes of conduct together with binding and enforceable commitments of the controller or processor in the third country, and d) approved certification mechanisms together with binding and enforceable commitments of the controller or processor in the third country.[2] When no safeguards are arranged before the no deal date, either inhibition of MD related data transfer between the EU and UK could potentially lead to product surveillance compromises, or personal data may be exposed to a protection risk.
Safety & Availability (patient impact)	Most electronic health record (EHR) data is stored on site, backups may be stored encrypted in the cloud.[3] There is general unawareness where possible data may be stored.[3] Like the product supply chains in medical technology, also the data supply chains (data flows) are complex and fragmented.
Surveillance	If UK NB and MHRA data is not shared with the EU27, surveillance may be at risk.
Possible actions	▸ Before the no deal Brexit date, EU based medical companies and institutions need to have the abovementioned data exchange safeguards in place between them and their UK based partners, such as data centers, clinical research organizations, and other service providers. Third countries may control or process data given the safeguards set up by the European Commission. Standard contractual clauses exist for data transfers from data controllers or processers in the EU to data controllers or processers outside the EU (decision 2001/497/EC, 2004/915/EC, and 2010/87/EU). ▸ Transfer all data to EU27 based data centers ▸ Longer term: Agree on how to transfer data between EU and UK and on EU GDPR compliance procedures, e.g. adequacy decisions based on article 45 of regulation (EU) 2016/679. Dependent on EU/UK negotiations.
Recommendation	▸ Create awareness at medical companies and institutions as well as healthcare providers that they should assess where they keep personal data linked to MD and IVD products and what type of data is located where. ▸ Start mapping the data supply chain (data flow mapping). For instance, the IT department could typically create an overview on what applications are used from which companies, while the finance department could check which companies or service providers are contracted. ▸ Based on the international data flow insights, potential Brexit risk mitigating actions, all representing a significant administrative burden and additional costs, could include: ▪ the set-up of standard EU data transfer contracts and clauses for UK/EU data transfers from data controllers or processers in the EU to the relevant data controllers or processers in the UK (important part of the data protection safeguards). ▪ (Often larger) corporations may decide to migrate their data from UK servers to EU servers.

1) Cloudscene, World's Top Data Centers, Rack Solutions
2) Notice to stakeholders, Withdrawal of the United Kingdom from the Union and EU rules in the field of data protection, 9 January 2018, European Commission
3) Interviews hospitals

Risk consolidation, assessment & quantification

Risk	Assessment Summary	Impact estimate	Level of risk / priority
#1 UK Notified Body loss of recognition	After 29 March 2019, the EU no longer acknowledges UK notified bodies in the case of a cliff edge Brexit, and certificates by UK NBs are not recognized. All MDs and IVDs certified by a UK NB would now need to undergo a certification procedure with an EU27 NB, resulting in the risk of not being authorized for marketing on the Dutch and EU market in case of non-compliance or incomplete certification procedures at the alternative EU NBs. In any case, all MD and IVD products requiring a certificate should not rely on an UK NB in case of an expected issuance after 29 March 2019. The risk should also be considered for IT products which fall in the category of MD, specifically because each new software version requires a new certification.	Possible shortages of a certain number of products due to suddenly invalidated CE marks and simultaneously delays in alternative CE renewals by EU27 NBs, related to the large product file volumes to be transferred from UK to EU27 NBs. It is assumed that products already on the market will be eligible for sell-off.	
#2 EU27 Notified Body capacity constraints	All certification workload, which is currently covered by UK NBs will have to be covered by EU27 NBs (except for MDs and IVDs, which were certified in the UK and dedicated to the UK market only). UK NBs that want to continue to play a role in EU certifications of MDs and IVDs need to relocate to the EU and obtain an EU27 NB designation (already observed for various UK NBs, such as BSI). The additional Brexit related workload will be added to existing capacity pressures experienced by EU NBs related to the implementation of the new EU regulations on medical devices and in vitro diagnostics (EU 2017/745 and EU 2017/746).	The Brexit related workload increase might result in additional delays and/or longer processing times in the certification process and consequently increased time-to-market for certain MD and IVD products. Risk for products (at least temporary) not getting CE certificates or CE expiries before renewal.	
#3 Increased workload competent authorities EU27	Many activities currently conducted by the MHRA will need to be reallocated to EU27, likely to increase the workload for all competent authorities (inspectorates).	Extra workload may increase procedure times and increase risks in safety and surveillance	
#4 Physical entry to EU27 via the UK (products manufactured in the UK and elsewhere)	Products transiting through UK will have to undergo customs inspections. This may lead to additional supply delays, especially in case actors do not foresee this impact in their supply chain planning activities. Smaller organizations that do not necessarily have the capacity to anticipate on these changes (e.g. through adequate planning or stockpiling) could be constrained. On average only 3% of total medical devices import in the Netherlands comes from UK.	Potential risk of unavailability for a specific number of products being imported from the UK market.	
#5 Authorized representative in the UK loss of recognition	According to directive 2007/47/EC, the EC-REP is required to be in the EU27. Changing the EC-REP can be done in a period of multiple weeks, but can be complex and results in an increased administrative burden and additional costs due to the need to update technical documentation, etc.	Potential risk for temporary product unavailability in case mitigation actions by the non-EU manufacturers, i.e. change of EC-REP, is initiated too late. Potential for CE mark to expire before renewal and workload increase and potentially longer processing times at EC-REPs	
#6 Data centers or service providers in the UK and inhibited data transfer	EU General Data Protection Regulation does not apply anymore to the UK; UK will be regarded as a third country. Although data is increasingly being digitized and stored on the cloud, EHR are generally stored on site. GDPR would require data to be stored within the EU27 countries or third party safeguards / agreements should be in place	Potential data exchange challenges, when no safeguards are arranged before the no deal date. May lead to minor product surveillance compromises, or personal data may be exposed to a protection risk.	

Additional considerations

A series of additional items should be considered, as they impact the overall risk levels and probability:

- For medical devices, the observed data scarcity around individual products and their corresponding supply chain and regulatory routes, creates an intrinsic risk: without these individual product data and related insights, it will be very challenging to predict the highest risk products, and to develop directed mitigation actions.
- The medical device supply chain is complex and just-in-time stocks are favored by most parties. If delays or shortages of specific medical devices occur, the market runs dry in 2 – 6 weeks.[1]
- Major medical device players have to reconsider their value chain as a result of Brexit. This could induce further product portfolio rationalization, leading to indirect impact on availability or pricing based on independent business decisions being taken. In this study, (parallel) trade and market implications have been considered as out of scope, but this does not mean we do not foresee such eventualities.
- Major medtech industries and other stakeholders have been communicating about ongoing efforts to reduce the impact of a potential cliff edge Brexit, e.g. by stock splitting across EU and UK, as well as supply chain optimization efforts. Furthermore, various UK NBs have been relocated to EU27 countries, including the Netherlands, in order to continue their business in EU certification of MD and IVD products. For instance, BSI (a UK based NB) recently achieved designation as a medical device NB in the Netherlands.
- For medical device companies, potential risk mitigating actions are costly and many of these actions will not be an option anymore before the no deal date, e.g. changing a notified body is a costly and time-consuming process with long lead times that typically takes up 6 months to a year, whereas changing an EC-REP is done in multiple weeks against significant costs.
- While it is assumed that products in stock with a CE mark issued by a UK NB before the hard Brexit date may be permitted for sale in the EU market, there is still a degree of uncertainty here, as this scenario is unprecedented.
- Larger MD and IVD wholesalers generally use multiple sourcing strategies, also as part of their regular business contingency strategy. This means that when a UK source is temporarily unavailable, alternative sources may potentially compensate the UK origin products in a relatively short time span.[1]
- Specific requirements and potential risks regarding raw materials, intermediate products, and MD product parts were considered out of scope and were not further detailed.
- The current implementation of EU MDR/IVDR processes significantly impacts the medical device and health ecosystem. Although we touched upon this regulation, further detailing of potential synergies with Brexit was out of scope.
- We analyzed MD and IVD import/export streams from various EU27 countries on a higher level and for product subcategories (due to unavailable data on individual products). Extensive analysis of import/export and transit streams as well as a deep dive into intra-EU country dependencies was out of scope.

1) Based on different hospital and wholesaler interviews

Conclusions/Recommendations

	Recommendations
#1	After a hard Brexit, the loss of recognition of UK NBs by the EU, appears by far the highest risk that could negatively affect the availability of certain medical devices and in vitro diagnostics products on the Dutch market. **Facilitating the UK NBs in their relocation and MD and IVD NB redesignations in the EU27** as well as having a **constructive dialogue with EU27 NBs** about other risk mitigating solutions is therefore highly recommended.
#2	Need to further **identify risks on the specific product level,** both in terms of CE certification risks and related to supply chain and customs related risks. Given the public unavailability of the required data for this, it is necessary to involve the specific NBs and medical device companies more tightly.
#3	**Review the list of registered class I medical devices and in vitro diagnostics in the Netherlands with potential regulatory (CE mark) risks** to confirm: the lack of substitute, the level of criticality, possible substitutions
#4	**Encourage companies efforts** in taking into account possible Brexit consequences, mainly regarding **NBs**, **EC-REPs** and **customs**; with the emphasis on educating and ensuring awareness of **smaller players, which represent the majority (~95%) of the medical device companies**
#5	Increase **awareness among end-users of medical devices. Hospitals** seem to be **mildly aware of,** but **not prepared** for possible cliff edge Brexit implications. They would need to think about their preparation strategies, as they tend to rely on their suppliers (e.g. for stockpiling) and the government.
#6	Continuously monitor additional legislation, regulatory changes or guidance, and keep tracing the development and nuance of existing information.

Impact on Medical Research

Building a better working world

Executive summary
Medical research

In case of a no-deal scenario on the 29th of March 2019, the **UK will become a "third country" to the EU**

The UK becoming a "third country" will **impact medical research, particularly clinical studies** in Europe

Prior to market authorization of a new medicinal product or medical device to the European market, a thorough product research & development trajectory takes place. Though very much dependent on the type of product, these R&D phases are often time-consuming and costly. Typically, an R&D process starts with preclinical research and proof-of-concept studies in laboratory environment, after which the investigational medicinal products or medical device prototypes enter a clinical phase where safety and efficacy of the specific new therapeutic products are thoroughly evaluated in humans, both healthy volunteers and patients. These R&D processes, particularly those linked to clinical studies, are subjected to strict regulatory and compliance requirements, described in a variety of EU directives. While progressing through the R&D value chain, also the corresponding costs rise significantly. E.g. for pharma companies, total average development costs of a new drug product are currently estimated in the range of $2bn - 2.6bn[1,2]. After a Brexit no-deal date, Dutch companies and institutions performing clinical trial studies together with UK partners and/or sponsors would still need to comply to various key requirements, including:

- **GxP inspections, around Good Manufacturing (GMP), Good Laboratory (GLP) and Good Clinical Practices (GCP)** should be performed by an EU inspectorate
- **Import authorization** required for investigational product batches
- **For investigational medicinal products, batch release** to take place on EU ground by an EU based Qualified Person (QP)
- **The clinical study sponsor or legal representative** to be based in the EU

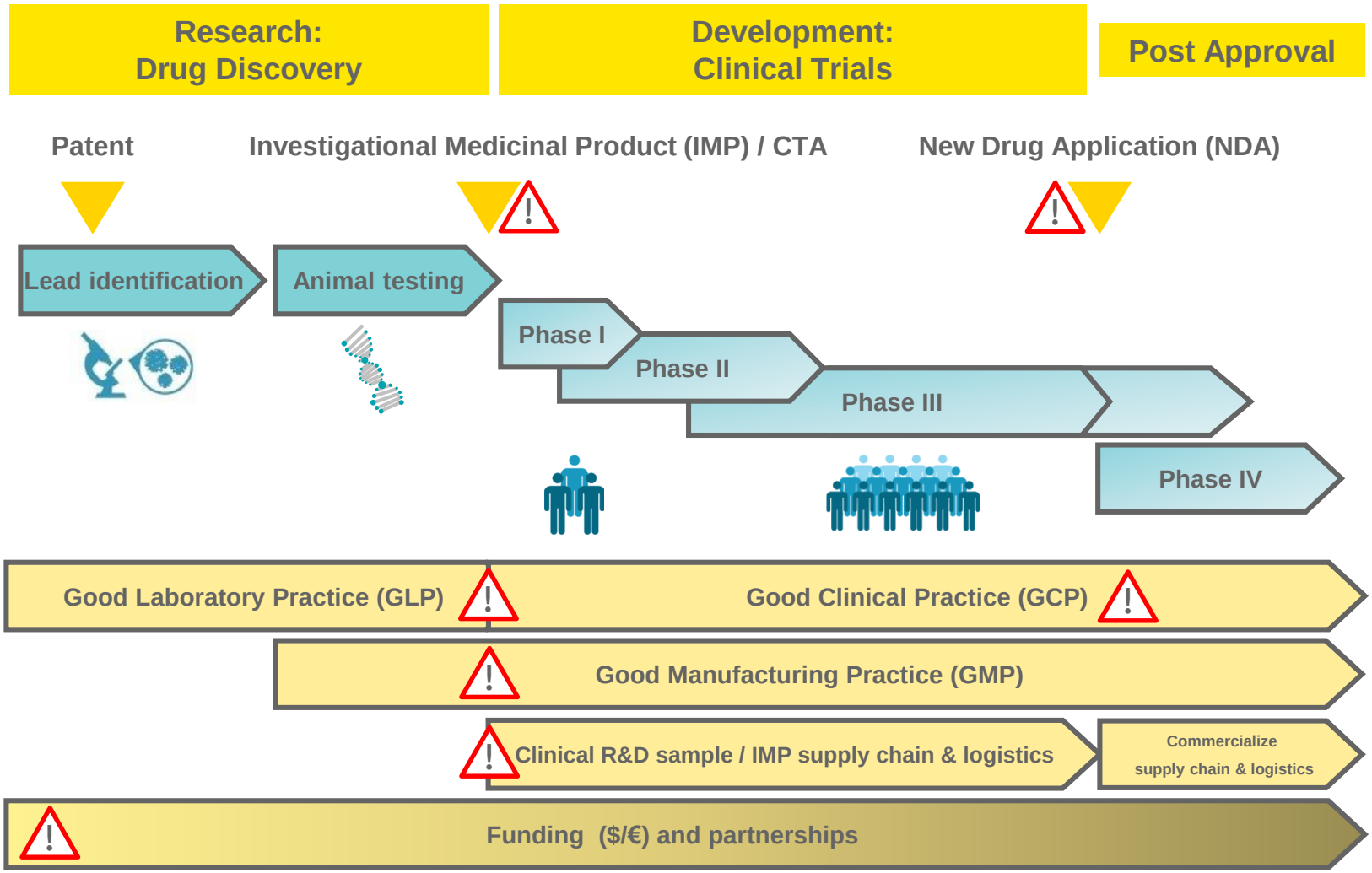
In case organizations performing clinical R&D studies do not comply to the abovementioned key requirements, their clinical trials could be significantly disturbed, delayed or terminated. After a no deal Brexit, the availability of investigational product batches is expected to be impacted on the short term, while other negative effects are more likely to be observed on the longer term. Related to the importance of international collaborations in medical research, Brexit will also impact in other ways.

In this part of the study, we found that:

- for UK/NL collaborative clinical studies and corresponding investigational pharmaceutical and medical device product batches, **supply chain & logistics processes, regulatory processes and/or batch quality release processes** could be hampered and potentially affect ongoing and near future clinical trials. Though the countries of origin for the investigational products are not available in public databases for each individual study, it is estimated that for at least 100-150 of the **registered studies in NL with UK sponsors or applicants** and **studies in the UK with NL sponsors or collaborators** may be disturbed when no actions are undertaken prior to the no-deal date.
- when no actions are taken, **delays could occur during clinical trial authorization and clinical trial regulatory processes**, due to uncertainties in the post-Brexit regulatory framework re GxP certifications and uncertain Brexit related workload shifts from UK to EU.
- **Brexit could significantly deteriorate R&D collaboration opportunities** between NL and UK, could make **data exchange more challenging**, and is likely to **result in a decrease in funding**, e.g. in terms of granted subsidies and venture capital for NL institutions and companies.
- although ongoing negotiations and/or last-minute agreements around 29 March 2019 could severely reduce the described Brexit impact on medical research studies, **raising stakeholder awareness,** e.g. towards clinical study sponsors and applicants, incl. pharma and medtech industries, (academic) hospitals, and CROs, to ensure they take the appropriate risk mitigation steps, is recommended.

1) A new future for R&D? Measuring the return from pharmaceutical innovation 2017, Deloitte
2) The Pharmaceutical Industry and Global Health, Facts and Figures 2017, IFPMA.

Overview of the pharma R&D process



Key stakeholders – pharma R&D process

Research: Drug Discovery		Development: Clinical Trials		Post Approval	
Patent applications	European patent office (EPO), patent attorneys, universities, pharma or medtech companies (often start-ups/scale-ups)	**Submission of clinical research file for clinical trial registration**	CCMO (Netherlands), MHRA (UK), FDA (USA), Universities, pharma or medtech companies	**Phase IV clinical trials**	CROs and other third parties (e.g. sample logistics, analytical companies) Local inspector (IGJ; Netherlands) / MHRA (UK)
Preclinical R&D, incl. lead/target identification, animal testing, etc	Universities, pharma or medtech companies (often start-ups/scale-ups), Centrale Commissie Dierproeven (CCD) for approval to do animal studies.	**Good Manufacturing Practice (GMP)**	Local inspector (IGJ; Netherlands) / MHRA (UK)	**Post Market Surveillance**	EMA, companies, IGJ (e.g. drug side effects), MHRA
Good Laboratory Practice (GLP)	Local inspector (IGJ; Netherlands) / MHRA (UK)	**Clinical trial execution** ► **Phase I – III**	CROs and other third parties (e.g. sample logistics, analytical companies) Local inspector (IGJ; Netherlands) / MHRA (UK)		
		Good clinical practice (GCP)	Local inspector (IGJ; Netherlands) / MHRA (UK)		
		NDA (New Drug Application) file	EMA, local EU country MEBs, dependent on registration procedure		
Funding	Subsidies: EU, local Investors: PE/VC, large industry funds, EIB, EIF	**Funding**	Subsidies: EU, local Investors: PE/VC, EIB, EIF, large industry funds becoming more important	**Funding**	Government, large industry

Clinical trials & Investigational Medicinal Products supply Value chain

In order to ensure product quality, the EU requires that the production of Investigational Medicinal Products is done according to European legislative requirements.

It is key that all transportation, packaging, and storage of IMPs ensures safe use of products. Therefore, the distributor needs to comply to the highest standards in this field in order to take ownership on the logistics in the EU.

To put clinical trial patient safety first, a clinical trial in the EU, is performed according to European legislative requirements.

Once the clinical trials are running, it is crucial that clinical trial data and results (also on e.g. adverse effects) can be exchanged freely among the clinical trial's direct stakeholders and competent bodies, though respecting EU privacy rules and regulations.

SOURCING & PRODUCTION

- Raw material uncertainty (out of scope)
- GMP inspection to be performed by EU inspectorate

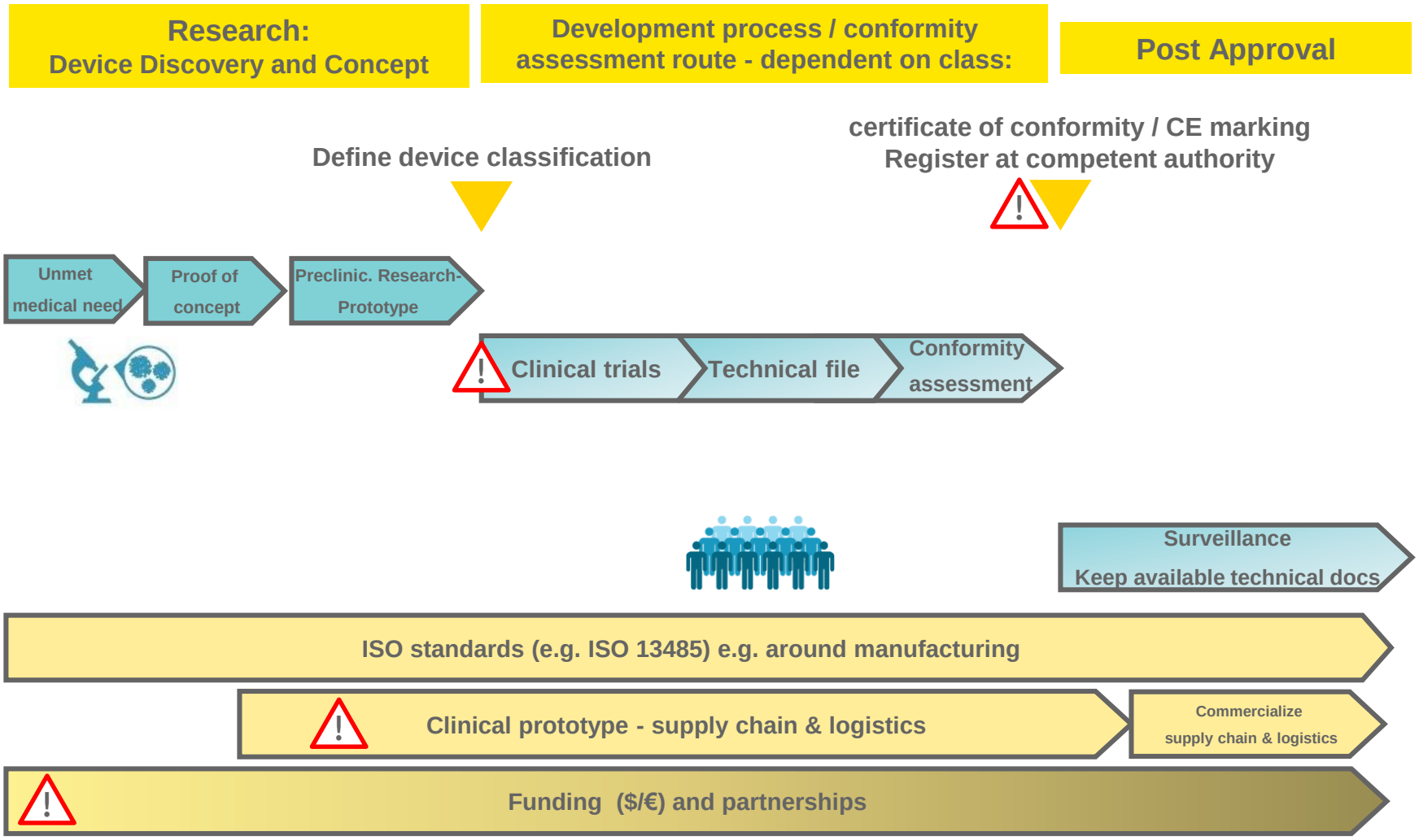
LOGISTICS

- IMP batch release to take place on EU grounds with an EU Qualified Person (testing still possible in third countries)
- Possible distribution delays due to customs controls & requirement import authorization

Clinical trial site

- A clinical study performed in the EU needs an EU based sponsor or legal representative
- GLP and GCP inspections to be performed by EU inspectorate
- EU data privacy regulations (GDPR) do not apply anymore to the UK

Overview of the medical device R&D process



Key stakeholders – Medtech R&D process

Research: Device Discovery and Concept		Development: Clinical evaluation / conformity assessment route		Post Approval	
Patent applications	European patent office (EPO), patent attorneys, universities, pharma or medtech companies (often start-ups/scale-ups)	**Submission of clinical research file for clinical trial registration**	CCMO (Netherlands), MHRA (UK), FDA (USA), Universities, pharma or medtech companies	**Post Market Surveillance**	Notified bodies, MHRA/IGJ, Market authorization holders
Preclinical R&D and product design	Universities, medtech companies (often start-ups/scale-ups), Centrale Commissie Dierproeven (CCD) for approval to do animal studies. Optional: independent assessment bodies - ISO 14971 – risk assessment/safety design	**Manufacturing: Quality Management System (ISO 13485)**	Notified Bodies, subcontractors/third parties, MHRA/IGJ: monitor Notified Bodies in their respective countries		
		Clinical trial execution	CROs, other third parties Local inspector (IGJ; Netherlands) / MHRA (UK) to be notified in case of no CE or other indication		
		Good clinical practice ISO 14155:2011	Independent assessment bodies		
		Compile technical dossier / CE marking	Notified bodies, competent authorities for registration (CIBG; class I / IVDs), MHRA		
Funding	Subsidies: EU, local Investors: PE/VC, large industry funds, EIB, EIF	**Funding**	Subsidies: EU, local Investors: PE/VC, EIB, EIF, large industry funds becoming more important	**Funding**	Government, large industry

Identified risks ⚠ – medical research

Risk #1 – Availability of clinical R&D samples / investigational products

Risk #2 – Regulatory processes before, during, after clinical trials

Risk #3 – Lack of efficient collaboration and access to expertise

Risk #4 – Research funding challenge

Risk #5 – Data exchange / poor accessibility

Affecting particularly clinical studies, but also pre-clinical studies

Risk #1 – Availability of clinical R&D samples / investigational products

	Physical transport of R&D samples between EU and the UK and batch release
Issue rationale	Any product coming from the UK has to go through **customs** before entering the EU mainland / European market, and vice versa. Despite representing no commercial value yet, this also includes samples for R&D purposes (both for preclinical and clinical research), including investigational medicinal products (IMPs), medical device prototypes, analyses samples, etc. The need for a Brexit-provoked import authorization and switch of R&D samples running through third country-EU customs procedures instead of the faster pre-Brexit intra-EU procedures will increase the expected **workload for customs**. Additionally, for clinical trials, each batch of an investigational medicinal product is to be released from an EU site, and by a Qualified Person (QP) based in the EU (Directive 2001/83/EC, Annex 16). While a large part of IMPs for EU studies is currently tested and released in the UK, **batch releases of Investigational Medicinal Products** and related quality checks being performed in the UK will become invalid in the event of a no-deal. Though additional analytical tests shall not be mandatory (Directive 2003/94/EC), in this case (partially) duplicate quality checks on EU mainland by an EU based QP is formally required to allow for batch release. Also medical device prototypes need to fulfil stringent specifications criteria when first used in humans, which are described in the technical dossier, and need to be guaranteed by the applied manufacturing process design and quality management system (e.g. ISO13485). For clinical medical device prototypes however, batch release locations and QP locations are not concretely specified by EU legislation.
Patient impact	It is expected that additional controls and/or prolonged throughput times at the border occur. This might jeopardize the availability of certain investigational products used for clinical trials. Particularly for medicinal products, the need for duplicate quality checks and batch release tasks could result in an additional delay of investigational product supply. Delay in product supply may delay or in worst case lead to termination of a clinical trial. In the hypothetical case that a clinical trial involves patients with a life threatening or debilitating disease with no remaining viable treatment options, this results in significant health impact of these patients.
Impact on key stakeholders (NL))	Increased customs workload related to required import authorizations and additional checks Increased workload for QPs and medicinal product regulatory bodies in the EU Change of QP location required for IMPs Increased complexity clinical trial planning
Possible actions	Stockpiling specific investigational products where appropriate Initiate workload estimation and planning initiatives at customs departments Moving QP location, EU QP workload estimations – investigate QP hiring needs Moving the clinical trial sample supply chain to the EU will remove the full risk, though may be a costly exercise Create awareness on how to manage and prevent potential clinical trial supply chain issues re UK/NL linked trials Prepare for setting-up an EU coordinated mutual recognition agreement (MRA (or ACAA)) for IMP batch release

Risk #2 – Regulatory aspects before, during, after clinical trials

	Potential capacity challenges Medical ethical committees / GxP inspections / Market authorization bodies
Issue rationale	Prior to the start of a research trial with human subjects (clinical trial), a **request for authorization of a clinical trial** first needs to be assessed by a competent authority in the concerning EU member state. I.e. by submitting a complete research file to the accredited medical research ethics committee (MREC) and/or CCMO, and MHRA in the Netherlands and UK, respectively. For a clinical trial authorization, it is required that the sponsor or legal representative of the study is based in the EU. Brexit might impact here in mainly two ways. Firstly, companies might chose to move their clinical supply chain routes as well as formal sponsor and QP locations inside the EU after Brexit (for both economical reasons and e.g. reasons in risk #1). Secondly, to perform clinical multi-country trials in more than one EU country the European Voluntary Harmonisation Procedure (VHP) currently exists in the EU. This procedure significantly reduces the multinational clinical trial authorization period to 60 days and is used by around 20% of all applications for clinical trials to be conducted in more than one European country (source: HMA). In fact, the VHP is the predecessor of the upcoming EU clinical trial regulation (EU CTR; probably effective in 2020). Given the current dominant role of the MHRA in the clinical trial authorization network incl. VHP and upcoming EU CTR, we might see a post-Brexit workload shift in this area from the MHRA to competent authorities in other EU27 countries. Together with the potential Brexit induced increase of future number of clinical trials in the Netherlands, this could result in delays of NL and multinational clinical trial approvals, and subsequently a decrease of patient access to new experimental therapies. In the EU, **GxP licenses**, are required for bringing an investigational medicinal product toward the clinical development phase (tests in humans). GxP licenses include GMP, GLP, and GCP, representing good manufacturing, good laboratory and good clinical practices. Although certificates issued by the UK inspectorate are expected to remain valid for their normal duration in case of a no-deal scenario, any future required GxP inspections, for instance when a license expires or when aiming for a new clinical study of a new investigational medicinal product, cannot be handled anymore by the UK inspectorate, but should be performed by an EU27 based inspectorate. In addition, there is also a probability that a small number of inspections by the UK inspectorate that are ongoing around the time of the no-deal Brexit will become formally invalid. After successful completion of a clinical trial, the medicinal product or medical devices' technical file requires assessment by a regulatory body to ultimately receive **market authorization**. Processes here are similar as described in other parts of the study. For pharma, Directive 2004/27/EC requires that the Reference Member State for the centralized and mutual recognition procedures is part of the European Union. For medical devices, the concerned notified body needs to be within EU27. Ongoing marketing authorization procedures in the UK that will be finalized after 29 March 2019, will therefore be invalid after a hard Brexit. Consequently, in order to ensure the launch of their new products in the EU, companies with pending applications in the UK will now require to apply for a new marketing authorization at a EU27 regulatory body. This will cause an additional workload for all EU27 regulatory bodies incl. MEBs in EU27 (incl. CBG), and medical devices notified bodies, Moreover, the relocation of the EMA and (temporary) reduced work force also remains an uncertainty[1].
Patient impact	Delayed start of new clinical trials Delay of ongoing clinical trials related to GxP license invalidity Decrease or delay of patient access to new experimental therapies
Impact on key stakeholders (NL)	Increased workload clinical trial authorization bodies As GxP inspections (i.e. GCP, GLP and GMP) cannot be performed by UK teams anymore, an increased workload for EU inspectorates can be expected (see also data page: Risks #1 and #2 potential capacity issues). Increased workload at EU27 medicinal evaluation boards (CBG in NL), EMA, and EU27 Notified Bodies UK based companies could end up with duplicate (and therefore higher cost) EU marketing authorization procedures, and vice versa. UK companies or companies entering the EU market through the UK need to re-assign or move to sponsor/legal representative and QP locations inside EU
Possible actions	Increase awareness of companies to check necessary requirements in terms of re-assignment sponsor and QP locations Carefully plan GxP inspections around Brexit date (March 29): e.g. shift pending inspections by UK inspectorate to European inspectorates in advance. Further intensify the collaboration with and leverage the EU27 inspectorate network and medicinal evaluation board network. Enhance collaboration clinical trial authorization network and already start with / accelerate tasks around upcoming CTR (EU no. 536/2015) Companies to apply for new Marketing Authorization via a Reference Member State / Notified Body located in the EU instead of UK

1) EMA press release 1 August 2018 - Brexit preparedness: EMA to further temporarily scale back and suspend activities.

Risks #1 and #2
'UK linked' studies in the Netherlands according to CCMO database[1]

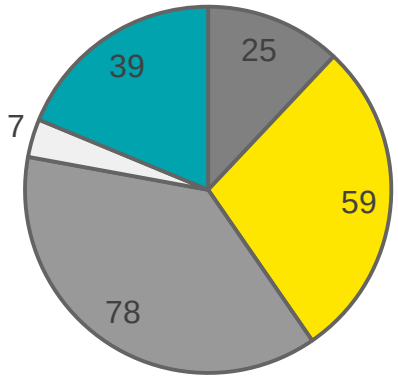
- 750 EU trials with UK as sponsor scheduled to be ongoing in March 2019[2]
- total clinical trial authorization (CTA) assessments in NL in 2017: 1657 (of which 548 pharma and 224 medical devices)[3]
- 'UK linked' indicates the involvement of either a UK sponsor, or UK applicant

208 'UK linked' ongoing studies registered in the Netherlands on 17-sept-2018:

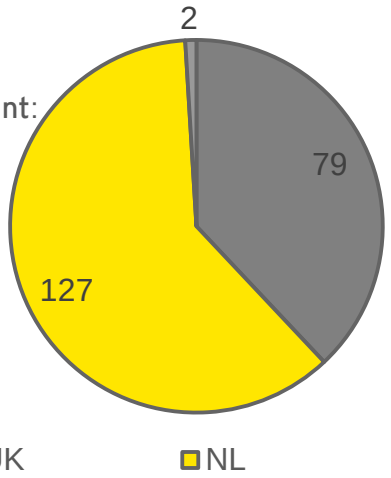
123 studies with intended end date > 31 March 2019

135 studies with UK based sponsor

Study phase:



Country of applicant:



Of 79 UK applicants: 55 are CRO, 21 Pharma industry, 3 medtech + other industry → sponsors from different countries

Of 127 NL applicants: 68 are CRO, 43 university medical centers, 16 hospitals → all studies UK sponsored

Type of UK sponsor for 127 studies with NL applicants: pharma companies: 83 (majority: GSK (6), BMS (13), Japanese pharma: Takeda, Eisai, Astellas (13)), and biotechs: 7 (incl. 4 x Biogen)

1) The CCMO data apply to clinical trials that are subject to Medical Research Involving the Human Subjects Act (abbreviated as WMO in Dutch language). The scope of the CCMO database is therefore smaller compared to clinicaltrials.gov.
2) EFPIA Brexit survey; November 2017
3) CCMO annual report 2017

Risks #1 and #2
'UK linked' studies in the Netherlands according to clinicaltrials.gov[1]

145 studies on NL sites by UK HQ sponsors/collaborators:

Top list – UK HQ based sponsors/collaborators in (> 4) NL clinical trials	
Company	**Nr. of trials**
AstraZeneca	62
GSK (GlaxoSmithKline)	26
Amphia Hospital	9
LivaNova	8
MedImmune LLC	8
University College, London	8
Viiv Healthcare	7
Foundation for Liver Research	5
King's College London	5
University of Oxford	5
Cancer Research UK	4
Queen Mary University of London	4

Total number of running clinical trials in the Netherlands			
Intervention type	**Total clinical trials in NL**	**Trials with UK HQ sponsor/ collaborator**	**% of trials with UK HQ sponsor/ collaborator**
Drug/ Biological	1301	96	7%
Device	339	11	3%
Other	209	12	6%
Unknown	199	7	4%
Procedure	154	9	6%
Behavioral	55	4	7%
Dietary supplement	55	3	5%
Diagnostic	39	0	0%
Radiation	36	1	3%
Genetic	12	2	17%
Total	**2399**	**145**	**6%**

Source: clinicaltrials.gov

- Data available as on 30th July 2018
- Only active trials were screened by selecting categories:

  1) Not yet recruiting, 2) recruiting, 3) Enrolling by invitation, 4) Active, not recruiting

Remark: this list is composed of companies with HQ in UK. UK entities of non-NL HQ multinational companies also run trials in the UK. However, no exact data on what trials are exactly sponsored by what UK entities is available. Examples: US HQ BMS with many registered NL trials in CCMO database as UK sponsor

1) The CCMO data apply to clinical trials that are subject to Medical Research Involving the Human Subjects Act (abbreviated as WMO in Dutch language). The scope of the CCMO database is therefore smaller compared to clinicaltrials.gov.

Risks #1 and #2
'NL linked' studies in the UK according to clinicaltrials.gov:

59 studies on UK sites by Dutch HQ sponsors/collaborators:

Top list – Netherlands HQ based sponsors/collaborators in (> 5) UK clinical trials	
Company	**Nr. of trials**
Galapagos NV	13
Leiden University Medical Center	10
Radboud University	10
Academisch Medisch Centrum - Universiteit van Amsterdam (AMC-UvA)	9
Erasmus Medical Center	8
The Netherlands Cancer Institute	6
University Medical Center Groningen	6

Remark: this list is composed of companies with HQ in NL. NL entities of non-NL HQ multinational companies also run trials in the UK. However, no exact data on what trials are exactly sponsored by what NL entities is available. Examples based on manual screen: Genmab (Danish HQ):4 trials, Acerta Pharma BV (now part of AstraZeneca): 9 trials, several other Dutch academic hospitals < 5 trials each, Medtronic Bakken Research Center: 3 trials, Janssen (multiple trials), etc.

Total number of running clinical trials in the UK			
Intervention type	**Total clinical trials in UK**	**Trials with Dutch HQ sponsor/ collaborator**	**% of trials with Dutch HQ sponsor/ collaborator**
Drug/ Biological	2324	21	1%
Device	527	7	1%
Other	489	7	1%
Unknown	400	7	2%
Procedure	261	6	2%
Behavioral	177	3	2%
Dietary supplement	127	1	1%
Diagnostic	77	3	4%
Radiation	46	3	7%
Genetic	42	1	2%
Total:	**4470**	**59**	**1%**

Source: clinicaltrials.gov

- Data available as on 30th July 2018
- Only active trials were screened by selecting categories:

  1) Not yet recruiting, 2) recruiting, 3) Enrolling by invitation, 4) Active, not recruiting

1) The CCMO data apply to clinical trials that are subject to Medical Research Involving the Human Subjects Act (abbreviated as WMO in Dutch language). The scope of the CCMO database is therefore smaller compared to clinicaltrials.gov.

Risks #1 and #2
Potential capacity issues

- Average annual number of clinical trial applications – 2007 to 2015

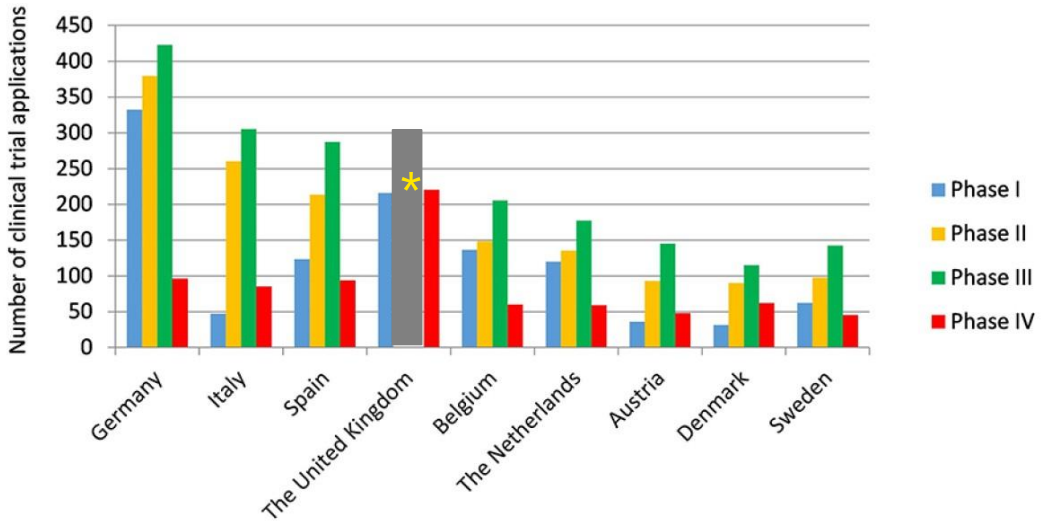


Figure . The average annually number of clinical trial applications by trial phase in nine Western European countries. The average annually number of clinical trial applications is based on data from 2007 to 2015. Phases can overlap. Thus, the summarised number of clinical trial applications for all trial phases is not necessarily equal to the total number of clinical trial applications registered. In the UK, phase II and III clinical trials are registered together and could therefore not be separated. The average number of clinical trial applications for phase II and III in the UK is 590. *Data from Denmark regarding the number of clinical trial applications by trial phase are only from 2010 to 2015. Data from Italy and Spain refer to the numbers of *authorised* clinical trials and not clinical trial *applications*.

Source of figure: Dombernowsky T, et al., Development in the number of clinical trial applications in Western Europe from 2007 to 2015: retrospective study of data from national competent authorities BMJ Open 2017; **7**:e015579. doi: 10.1136/bmjopen-2016-015579

- **In 2017, number of new clinical trials in UK has decreased 25 %** from an yearly average of 806 studies in previous 8 years to 597 initiated studies (source: Reuters, 9 October 2018). This may suggest companies already shifting their geographic clinical trial coverage, although further investigation around the total number of clinical trial applications in 2017 at all EU27/EEA countries would be required to confirm this.
- **GMP certificates** – see medicinal products chapter
- **Batch release of Investigational Medicinal Products (IMPs) for EU trials** (source: EFPIA survey, Nov 2017)**:**
  - 40 QPs for clinical batches present in UK
  - 70 % of EU investigational medicinal product released in UK
- **Market authorization procedures new products:**
  - est. 30-50 %* of **medical devices** assessment work needed for the authorisation of products to be placed on the EU market takes place in the UK.
  - **Innovative new medicines**:
    - MHRA makes significant contribution to the work of EMA and in 2016 led up to 20 % of the centralized procedures. (source: EFPIA briefing Dec. 2017)
    - MHRA contributes to 20-40 % of EU decentralized procedures. (range based on: EFPIA briefing Dec. 2017, interview CBG)

*Estimation range based on registrations of class I medical devices and in vitro diagnotics at Dutch CIBG, interviews with Team NB and MedTech Europe, Brexit Health Alliance Briefing January 2018 – Brexit and the impact on patient access to medicines and medical technologies, and statements on BSI website: BSI Medical Devices and Brexit.

Risk #3
Lack of efficient collaboration and access to expertise

	Possible lack of expertise and efficient NL/UK collaborations
Issue rationale	**The UK Life Sciences & Health ecosystem** and pharmaceutical industry plays a **key role in the EU**. Particularly, the 'golden triangle' of London-Oxford-Cambridge including four global top 10 universities (based on the QS World Universities Ranking) for pre-clinical, clinical and health research serves as a critical contributor to the EU Life Sciences & Health industry. The UK life sciences ecosystem clearly differentiates in terms of sector expertise (not only scientifically, but also in terms of investor/analysts and entrepreneurial know-how), talent attraction, and investment opportunities. Besides a strong product pipeline, the UK's position as European center of life sciences & health expertise is clearly demonstrated by its **dominant involvement in EU funded collaborative research programs**, such as Horizon 2020, Innovative Medicines Inititiative (IMI), and others.[1] Between 2007 and 2016, UK contributed to almost 20 % of the total research work carried out within EU health programs.[2] In Horizon 2020, e.g. UK disproportionally takes a coordinating role, and UK institutions are highly present in almost 50 % of the granted proposals. In the first 3 years of this EU framework's existence, 695 clinical trials have been part of Horizon 2020 studies.[3] Also the Netherlands comprises a strong Life Sciences & Health ecosystem with a high concentration of health and life sciences companies, world-class universities and a long history of strategic partnerships linking science, industry and government. In comparison to institutions in other EU countries, **Dutch Life Sciences & Health institutions work together to a much higher extent** with UK institutions in EU subsidized collaborative programs, such as Horizon 2020. NL and UK are very likeminded in research terms, where both countries focus on research excellence. Besides serving as a funding tool, current EU collaborative research programs, incl. Horizon 2020, are just as important to stimulate and set-up European research collaborations, and to realize the required expert firepower for breakthrough innovations. After a potential no-deal Brexit, UK medical institutions and companies would **no longer have access to the EU Research & Innovation programs**, since current regulations imply that (without specific agreements in place) **non-EU countries are not allowed to participate and/or take a coordinating role anymore** in a typical Horizon 2020 project or other EU R&D framework program. Given the disproportional number of NL/UK collaborations, on the short term, this will most likely lead to less new NL/UK consortia applying to Horizon 2020 EU research grants and will demand our institutions to more often take the lead. In addition to currently ongoing EU R&D programs, it is uncertain whether the UK will join future EU R&D framework programs, such as the upcoming FP9 Horizon Europe. It is clear however, that UK leaving the EU greatly diminishes its influence on the future EU R&D agenda, which on the longer term gives other EU countries relatively more strength in driving forward their research priorities. These are expected to be less in line with the Dutch and UK research excellence ambitions. Although the exact net consequences are yet unknown and will be greatly dependent on current and future UK/EU negotiations, Brexit will impact the way how UK and NL involved medical research consortiums will look like and operate in the future, and will also lead to a potential shift in research priorities. A lower number and/or less efficient UK/NL partnerships **could inhibit the development and market introduction of new innovative therapies**, whereas at the same time the UK not participating in EU collaborative R&D program also offers additional opportunities for the Dutch Health & Life Sciences R&D ecosystem to fill the Brexit-created gap and strengthen its research excellence footprint in the EU.
Patient impact	Potential slow down or termination of specific UK involved pre-Brexit research programs could hamper pre-clinical and clinical knowledge building, which may ultimately be translated in delayed therapy pipeline development, consequently increasing time-to-market for specific innovative products. Decrease or delay of patient access to certain new experimental therapies
Impact on key stakeholders (NL)	More efforts needed from medical companies and research institutions to successfully assemble a best-in-class EU partnership/consortium More efforts needed from Dutch companies and research institutions to apply for EU subsidized R&D grants → need to take up more coordinating roles Dutch companies and research institutions to find alternative research partners in other EU countries Potential expertise gaps in very specific research disciplines
Possible solutions	Evaluate current critical UK/NL R&D partnerships, incl. clinical trials Stimulate and intensify R&D collaborations with other EU partners Discuss alternative collaborative R&D options with the UK / aim for accelerated negotiations re involvement UK in EU R&D frameworks + conditions

1) Websites of European Commission and Horizon 2020: https://ec.europa.eu/programmes/horizon2020/en/ and Innovative Medicines Inititiative (IMI): https://www.imi.europa.eu/. Data further elaborated and presented on page 70-74.
2) EFPIA Brexit Briefing, December 2017
3) Report: Horizon 2020 in full swing – Three years on – Key fact and figures 2014-2016

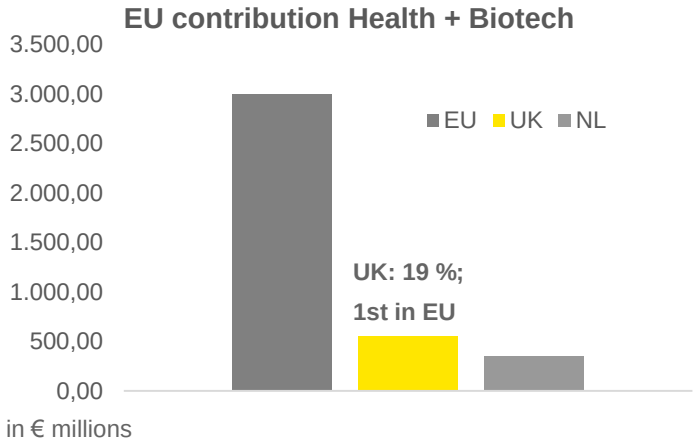
Risk #4
Research funding challenge

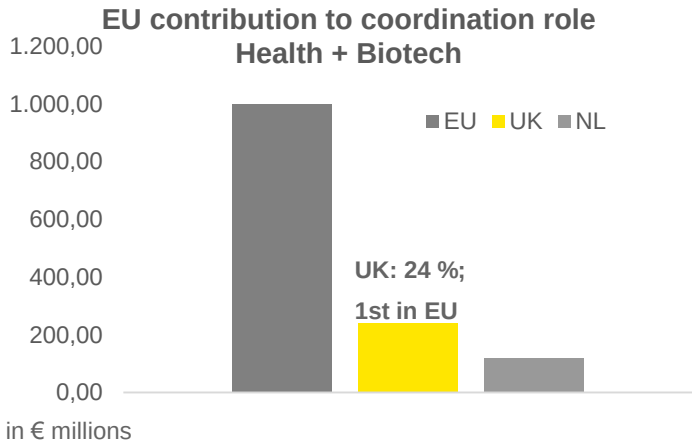
	Potential funding challenges that will delay the development of new products for the NL market
Issue rationale	Brexit could significantly impact funding and consequently the continuity of Dutch and EU medical research (both clinical and pre-clinical) in two ways: First of all, as discussed in risk #3 around expertise and efficient collaboration, Horizon 2020 and other European Research & Innovation programs play a key role in the collaboration between Dutch and UK medical research institutions and life sciences companies. When it comes to funding from such EU R&D framework programs, the UK benefits most from the EU's research programs compared to all other EU countries. During the EU FP7 program (formally run from 2007-2013), the UK for instance received 16 % of the total funding (€8.8 billion), while the UK's contribution to the EU was only 11,5 % (€5.4 billion).[1] Also in the current Horizon 2020 framework program and Innovative Medicines Initiative (IMI, largest R&D public-private partnership) that both include significant funding of clinical studies, similar observations are done, where the UK disproportionally benefits in terms of EU funding. After Brexit, the UK institutions and industry will not have access anymore to these EU R&D framework programs. Also for future EU research and development programs, incl. the upcoming Horizon Europe (FP9) framework the degree of UK participation (if any) is still unclear and will likely dependent on the negotiations around the nature of UK's involvement, as well as terms & conditions around third / associated country participation. **Purely based on financial figures (described above)**, it is fair to state that the "fading away" of the 'best in class' would mean that the net financial position (i.e. relative share in EU Framework Programs) of the remaining 27 Member States (EU27) would improve. In practice however, this is by far not automatically true for the Netherlands and other EU countries that relatively frequently collaborate in UK involved and/or led research consortia. In such consortia, UK institutions and companies play a dominant role, where they frequently take the lead/coordination role in projects and grant application writing, and likely contribute to significantly higher grant application success rates. In summary, Brexit will provoke a dual impact on Dutch Health and Life Sciences R&D institutions and R&D intensive companies: 1) a positive effect and large opportunity related to UK organizations being unable to compete with NL and other EU27 based organizations for acquiring EU R&D subsidies, and 2) a negative effect and potential risk related to UK organizations being unavailable as consortium partner and leader for NL involved consortia. This means that if Dutch organizations do not fill the gap left by UK institutions and companies, and NL does not sufficiently exploit the abovementioned positive opportunity after Brexit, e.g. by more frequently taking the lead and coordinator roles in grant applications and EU R&D programs, there is a risk (at least on the short term) that the negative effect will dominate and finally **leads to a potential decrease in granted subsidies for NL institutions and companies.** Ultimately, this could result in slower progress of specific new drug or medical device products to the market place. Secondly, the **UK Venture Capital (VC) and Private Equity (PE) ecosystem might be affected by Brexit**. The UK venture capital market makes up more than a third of the total venture capital raised in Europe. The UK comprises different best-in-class life sciences & health VC firms, e.g. Medicxi, Abingworth, etc. Such firms invest in life sciences SMEs and scale-ups (including Dutch companies), which allows them to perform the (often clinical) research in order to bring new biotech and medtech products one step ahead toward the market place. The UK VC and PE firms are currently reliant on EU funds, particularly via the European Investment Bank and European Investment Fund (EIF). After Brexit there is a possibility that EIF will invest less in UK VCs than remaining EU27 VCs. Although not attributable to a certain EIF strategy, but rather a result of Brexit uncertainties in the UK, EIB and EIF investments in UK based VCs have already decreased significantly during the last year. Although the decrease of EU investments in UK VC and PE firms is also considered as a positive opportunity in the way that more capital would be left available to invest in Dutch based VC and PE firms, there is a risk that lower EU investments in UK PE and VC firms lead to a decrease in successful funding possibilities for life sciences SMEs and scale-ups in the Netherlands after Brexit. Ultimately, in the most pessimistic scenario, this would lead to a reduction of new clinical trials and subsequently a slow down of specific product developments.
Patient impact	Slow down of development of part of the NL therapy pipeline, both pre-clinical and clinical studies, and delay of specific experimental therapies in the clinic Potential delay in certain parts of medical research could ultimately result in a decrease or delay of specific innovative products on the market
Impact on key stakeholders (NL)	More challenging to acquire funding / potential decrease in funding for pre-clinical and clinical trials Need to take more coordinating roles / NL to take the lead in more programs Need to find funding alternatives, additional investors and research partners in other EU countries
Possible solutions	Evaluate current critical UK/NL R&D partnerships Create awareness at Dutch research institutions and R&D intensive health and life sciences companies around the impact of Brexit on potential R&D budgets Stimulate R&D collaborations/funding with other EU partners or evaluate alternative R&D funding options for UK involved consortia Stimulate and facilitate building of alternative investor relationships Aim for accelerated negotiations re involvement UK in EU R&D frameworks + conditions

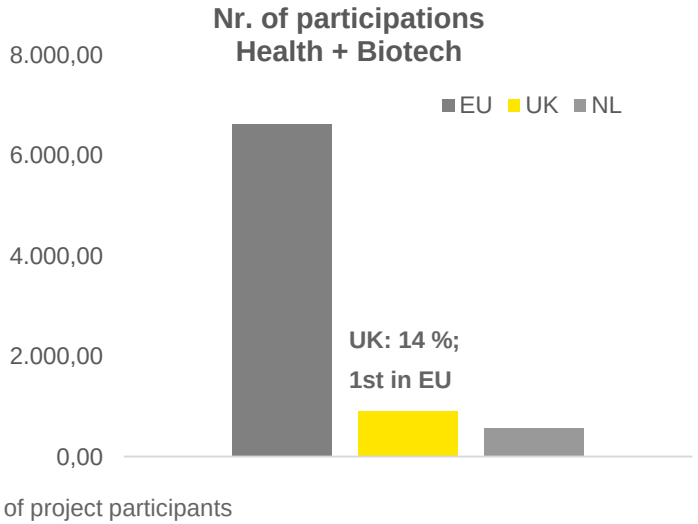
1) UK research and the European Union: The role of the EU in funding UK research, The Royal Society 2018

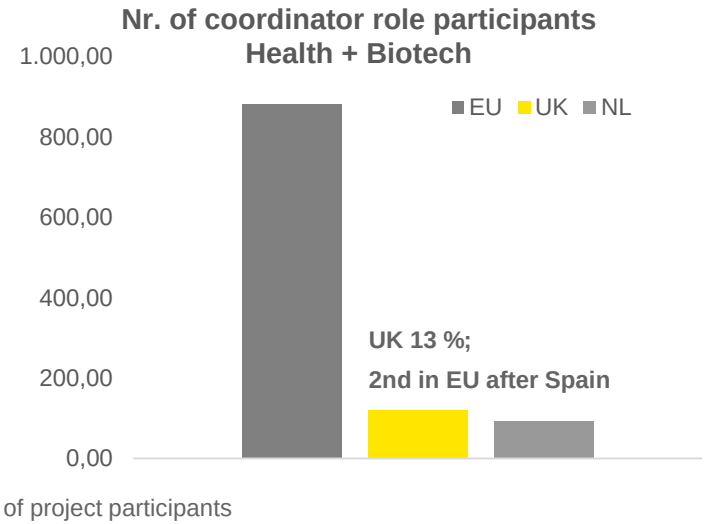
Risks #3 and #4

UK's dominant share in collaborative EU subsidy projects: Horizon 2020 contributions, and the relatively strong role of the Netherlands as reference.





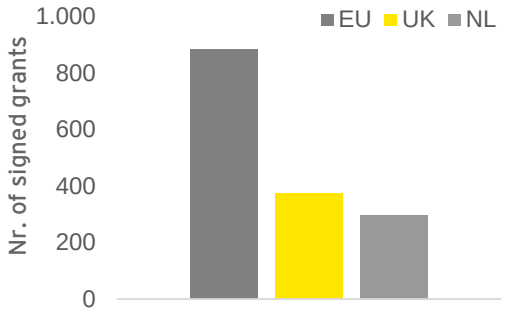




source: created from Horizon 2020 dashboard accessible via Horizon 2020 Participant Portal; European Commission website; data updated on 19 October 2018; filtered for thematic priorities: Biotechnology and Health, demographic change and wellbeing

Risks #3 and #4
UK's dominant role in collaborative EU subsidy projects Horizon 2020 contributions

UK and NL involvement in Horizon 2020 Health & Biotech grants (in nr. of signed grants)



- UK involved in approx. 42 % (nr. 1 in EU) of the signed Horizon 2020 grants against 33 % (nr. 3 in EU) for the Netherlands (left figure).
- A total of 5 UK institutions present in the top list of EU Horizon 2020 grant acquirers, against 2 NL institutions (table below).

Top 10 institutions in the EU based on Health Horizon 2020 subsidies

Legal Name	Country	City	H2020 Participations	H2020 Net EU Contribution
LONDON SCHOOL OF HYGIENE AND TROPICAL MEDICINE	United Kingdom	LONDON	15	€ 68 million
INSTITUT NATIONAL DE LA SANTE ET DE LA RECHERCHE MEDICALE	France	PARIS	70	€ 57 million
THE CHANCELLOR, MASTERS AND SCHOLARS OF THE UNIVERSITY OF OXFORD	United Kingdom	OXFORD	48	€ 51 million
STICHTING KATHOLIEKE UNIVERSITEIT	Netherlands	NIJMEGEN	32	€ 39 million
KING'S COLLEGE LONDON	United Kingdom	LONDON	30	€ 37 million
IMPERIAL COLLEGE OF SCIENCE TECHNOLOGY AND MEDICINE	United Kingdom	LONDON	28	€ 37 million
UNIVERSITY COLLEGE LONDON	United Kingdom	LONDON	44	€ 36 million
FONDAZIONE PENTA-FOR THE TREATMENT AND CARE OF CHILDREN WITH HIV-ONLUS	Italy	PADOVA	3	€ 35 million
KAROLINSKA INSTITUTET	Sweden	STOCKHOLM	48	€ 27 million
ERASMUS UNIVERSITAIR MEDISCH CENTRUM ROTTERDAM	Netherlands	ROTTERDAM	37	€ 29 million

source: created from Horizon 2020 dashboard accessible via Horizon 2020 Participant Portal; European Commission website; data updated on 11 September 2018; filtered for thematic priorities: Biotechnology and Health, demographic change and wellbeing

Risks #3 and #4
Strong UK and NL partnerships and collaborations in Horizon 2020

- From 2014-2016: 695 clinical trials in the EU run by and funded by Horizon 2020 projects[1]
- Dutch medical research institutions highly abundant in top UK institutions' collaborators list:[2]

Legal Name	Total nr. of collaborators	Main Dutch collaboration partners in top 50 collaborators
LONDON SCHOOL OF HYGIENE AND TROPICAL MEDICINE	612	*ACADEMISCH ZIEKENHUIS LEIDEN (10), ERASMUS UNIVERSITAIR MEDISCH CENTRUM ROTTERDAM (7), STICHTING VU (6), STICHTING BIOMEDICAL PRIMATE RESEARCH CENTER (6), Academisch Medisch Centrum bij de Universiteit van Amsterdam (5), UNIVERSITEIT MAASTRICHT (5), STICHTING WAGENINGEN RESEARCH (5), WAGENINGEN UNIVERSITY (4)*
THE CHANCELLOR, MASTERS AND SCHOLARS OF THE UNIVERSITY OF OXFORD	2979	*STICHTING KATHOLIEKE UNIVERSITEIT (33), ACADEMISCH ZIEKENHUIS LEIDEN (30), STICHTING VU (24), UNIVERSITEIT VAN AMSTERDAM (23), ERASMUS UNIVERSITAIR MEDISCH CENTRUM ROTTERDAM (23), UNIVERSITEIT UTRECHT (22), TECHNISCHE UNIVERSITEIT DELFT (21)*
KING'S COLLEGE LONDON	1848	*STICHTING KATHOLIEKE UNIVERSITEIT (29), ACADEMISCH ZIEKENHUIS LEIDEN (24), ERASMUS UNIVERSITAIR MEDISCH CENTRUM ROTTERDAM (22), UNIVERSITEIT MAASTRICHT (21), STICHTING VU (16), KONINKLIJKE NEDERLANDSE AKADEMIE VAN WETENSCHAPPEN - KNAW (14), NEDERLANDSE ORGANISATIE VOOR TOEGEPAST NATUURWETENSCHAPPELIJK ONDERZOEK TNO (14), ACADEMISCH ZIEKENHUIS GRONINGEN (13)*
IMPERIAL COLLEGE OF SCIENCE TECHNOLOGY AND MEDICINE	3241	*TECHNISCHE UNIVERSITEIT DELFT (31), NEDERLANDSE ORGANISATIE VOOR TOEGEPAST NATUURWETENSCHAPPELIJK ONDERZOEK TNO (26), ERASMUS UNIVERSITAIR MEDISCH CENTRUM ROTTERDAM (25), UNIVERSITEIT TWENTE (23), UNIVERSITEIT MAASTRICHT (22), STICHTING VU (21), STICHTING KATHOLIEKE UNIVERSITEIT (21)*
UNIVERSITY COLLEGE LONDON	3143	*STICHTING KATHOLIEKE UNIVERSITEIT (51), ERASMUS UNIVERSITAIR MEDISCH CENTRUM ROTTERDAM (32), ACADEMISCH ZIEKENHUIS LEIDEN (26), STICHTING VU (26), UNIVERSITEIT UTRECHT (22), UNIVERSITAIR MEDISCH CENTRUM UTRECHT (22), UNIVERSITEIT LEIDEN (20), Academisch Medisch Centrum bij de Universiteit van Amsterdam (20), TECHNISCHE UNIVERSITEIT EINDHOVEN (20), UNIVERSITEIT MAASTRICHT (19)*

1) report Horizon 2020 in full swing – Three years on – Key fact and figures 2014-2016
2) created from Horizon 2020 dashboard accessible via Horizon 2020 Participant Portal; European Commission website; data updated on 11 sept 2018; filtered for thematic priorities: Biotechnology and Health, demographic change and wellbeing

Risks #3 and #4 – Expertise areas of 5 highlighted UK top institutions on the previous page and links to Dutch Healthcare and Life Sciences expertise

Word Cloud based on search keywords linked to the top UK institutions: London School of Hygiene and Tropical Medicine, University of Oxford, King's college London, Imperial College of Science Technology and Medicine, and University College London. A larger word size represents a higher number of identical key words.[1]

- The above Word Cloud highlights the key expertise of UK institutions in mainly the following areas: molecular and biological disease mechanisms, cellular interactions, neuroscience and related diseases, genomics, diagnostics, imaging, and engineering. The UK is considered a leader on global public health issues, such as dementia and anti-microbial resistance, and new technologies such as genomics.[2]
- UK expertise appears to be generally in line with expertise in the Netherlands. The Netherlands maintains strong positions in biopharmaceuticals, human and veterinary vaccines, and regenerative medicine. Many biotech products available on the market and in development are for the treatment of cancer, infectious and parasitic diseases, and diseases of the nervous system. Dutch Public-Private Partnerships (PPPs) receive worldwide acclaim, especially in the areas of oncology, medical technology and regenerative medicines, bio-banks and vaccines.[3]

1) created from Horizon 2020 dashboard accessible via Horizon 2020 Participant Portal; European Commission website; data updated on 11 sept 2018; filtered for thematic priorities: Biotechnology and Health, demographic change and wellbeing
2) Brexit: Implications for Pharma and Life Sciences companies, Feb 2018, PwC
3) Bidbook The Netherlands, Europe's most attractive and innovative biopharmaceutical environment, October 2018, PharmInvestHolland

Risks #3 and #4 - UK's high share in collaborative EU subsidy projects: Innovative Medicines Initiative (IMI) contributions, and the role of the Netherlands as reference

IMI1 programme from 2008-2013 and IMI2 from 2014-2020 representing total budgets of €2 billion and €3,276 billion, respectively

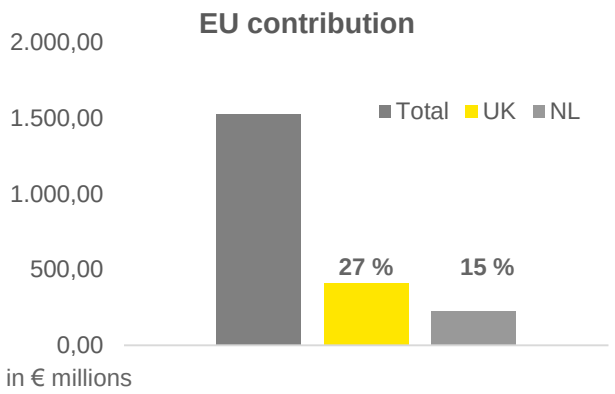
Key figures for UK and NL in IMI (Innovative Medicines Initiative):[1]

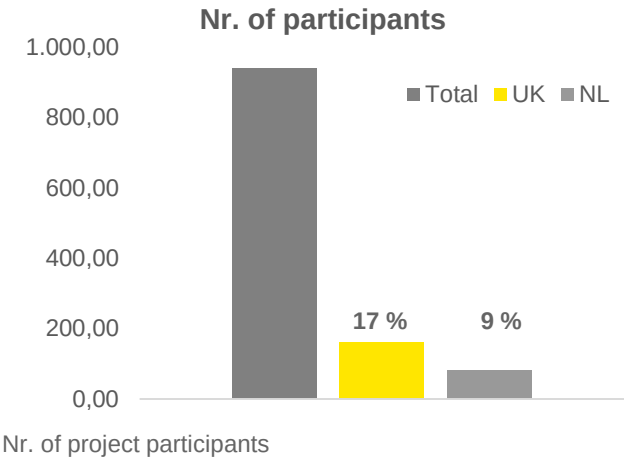
- UK has received 27 % of total IMI funding from EU commission (largest amount of any country – 412.6m EUR) versus 15 % for the Netherlands. Of all IMI participants, 17 % and 9 % are UK and Dutch participants, respectively (see figures on the right).

Statistics related to type and role of UK participants in IMI:

- The UK provides the 2nd highest number academic participants (14 %) and the highest number of participating small medium enterprises (SMEs; 22%), which receive highest levels of IMI funding of any country. As a comparison, The Netherlands provides 7 % and 14 % of the participating academic institutions organizations and SMEs, respectively.[1]
- The UK has the highest number of managing entities of any country, demonstrating a key leadership role in these European research projects.[2]
- Universities in the top European academic life science clusters attracted 38% of all IMI academic funding. Of these, the so-called 'Golden Triangle' in the UK received the highest levels of funding.[2]
- The UK has leveraged particularly high proportions of funding in respiratory diseases, vaccine development, infectious diseases, and diabetes.[2]

Today's UK and NL share of granted IMI 1 and 2 funding





1) Extracted from Innovative Medicines Initiative website: Maps and Statistics section: Oct 2018
2) ABPI report September - UK Participation in the Innovative Medicines Initiative 2016

Risks #3 and #4 – The UK and Dutch life sciences ecosystems
some facts and figures

Number of companies in the Life Sciences industry

Country	Biotechnology	Biotech – therapeutics	Medtech	Pharmaceutical
Austria	119	44	23	18
Belgium	260	47	60	40
Denmark	171	68	93	12
Finland	83	21	41	6
France	802	180	182	85
Germany	1,073	178	531	102
Ireland	119	28	59	49
Italy	437	58	97	83
Netherlands	459	112	114	41
Norway	151	32	43	7
Spain	525	89	113	94
Sweden	500	170	282	46
Switzerland	463	159	264	76
UK	1,180	328	319	121
Australia	219	106	65	31
Canada	940	248	370	111
Israel	275	134	449	28
Singapore	75	19	27	25
Taiwan	194	55	85	41
US - CA	1,718	794	506	56

Source: www.biotechgate.com 2018

Biotech product pipeline:

Both the Netherlands and the UK have strong healthcare & life sciences sectors that offer an attractive climate for new innovative biotech, medtech and healthcare companies to settle and grow. Two key differences between the Dutch and UK life sciences hubs lie within the number of enterprises and size of product pipelines. The above figure on the left[1] shows that the UK houses 2-3 fold more life sciences companies than the Netherlands, which is also reflected in product pipelines and raised capital. The above figure on the right[1] displays the biotech pipelines for several European countries and others. It shows that the UK has the strongest biotech product pipeline in Europe, consisting of approx. 5 times more investigational therapeutic products than the Dutch biotech pipeline. Furthermore, in 2017 approx. € 530 million of VC capital was raised by UK biotech companies vs. less than € 100 million by Dutch biotech companies.[2,3] In this context, it is fair to state that compared to the Netherlands, the UK life sciences ecosystem is more mature and although still not comparable, it gets closest to the globally leading US hubs in the Boston area and Bay area.

1) Adapted from Site selection for Life Sciences Companies in Europe, 2018 edition, KPMG
2) 2018 M&A Firepower report – Life Sciences Deals and Data, EY
3) Bidbook The Netherlands, Europe's most attractive and innovative biopharmaceutical environment, October 2018, PharmInvestHolland

Risks #3 and #4 – Impact on UK Venture Capital funding

- In 2017, European VC firms have done approx. €1.5 billion of VC investments in Healthcare and Biotech throughout Europe.[1] The UK venture capital (VC) market makes up more than a third of the total venture capital raised in Europe. **UK and Switzerland contribute now to 55 % of the European total biotech venture capital.**[2,3] UK venture capital investment provides significant financial returns for the European Investment Fund (EIF). After Brexit however, the UK VC firms may lose access to EU funds including the EIF and loans of the European Investment Bank (EIB). First signs of this scenario have recently been described in the press (see left figure below for such an example).
- According to the EIF, total investment activity (all industry sectors together) backed by EIF represented 41 % of total investments in Europe in 2014.[4] The below figure on the right shows the overall flow of European VC investments by UK and Ireland VC firms that are backed by EIF. It shows that although VCs often show a 'home'-bias for their investments (as also observed for VCs in other European countries; data not shown), UK&I also significantly invests in the Netherlands. After Brexit the UK VC investment flow to the Netherlands could be reduced, affecting funding of Dutch companies, incl. biotechs and healthtechs , when this is not compensated by VC investments from other countries.

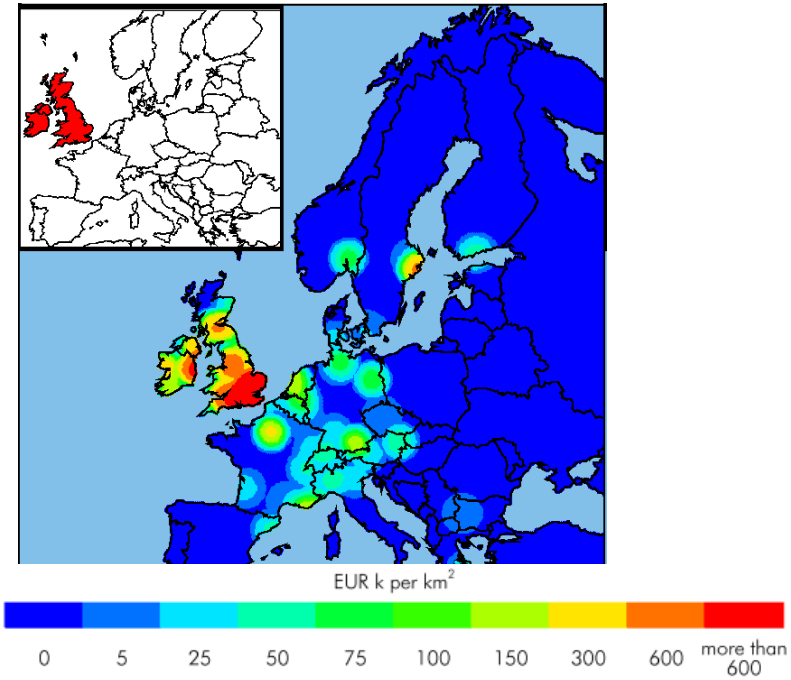
European Investment Bank pulls back on UK funding after Brexit

France, Germany main recipients of venture capital as tech start-ups hit by move to quit EU

EIB's Luxembourg headquarters. Last year the UK accounted for 8% of its equity investments compared with 27% the year before

The UK accounted for 8 per cent of the EIB's equity investments compared with 27 per cent the year before

Source: Financial Times, Aliya Ram, April 20, 2018



EIF backed VC investments from UK&I

Cumulated initial and follow-on investments as of end 2014. Regions of origination marked in red in superimposed maps. All amounts expressed in EUR 2005 prices.

Adjusted from The European venture capital landscape: an EIF perspective, European Investment Fund, working paper 2016/34

1) 2017 European Private Equity activity report, Invest Europe
2) Report: Building something great: UK's Global Bioscience Cluster 2016, UK BioIndustry Association (BIA), May 2017
3) EFPIA Brexit Briefing, December 2017
4) The European venture capital landscape: an EIF perspective, European Investment Fund, working paper 2016/34

Risk #5 – Data exchange / poor accessibility

	No/limited data access and sharing, and lack of research information
Issue rationale	When a hard Brexit takes place, the new **General Data Protection Regulation 2016/679 (GDPR) does not apply anymore to the United Kingdom**. In the context of transfer of personal data, the UK will be regarded as a third country. For a third country, the EU has the two following options when it comes to exchange of data (source: Notice to stakeholders 9 January 2018, European Commission): 1) an "adequacy decision" could be taken before or at 29 March 2019, which allows the free flow of personal data from the EU without the EU data exporter having to implement any additional safeguards or being subject to further conditions, and 2) as also for other third countries, data transfer is allowed if the controller or processor has provided "appropriate safeguards". These safeguards include: a) use of standard EU data protection clauses, b) binding corporate rules: legally binding data protection rules approved by the competent data protection authority which apply within a corporate group, c) approved codes of conduct together with binding and enforceable commitments of the controller or processor in the third country, and d) approved certification mechanisms together with binding and enforceable commitments of the controller or processor in the third country. In the absence of an "adequacy decision" or of "appropriate safeguards" a transfer or a set of transfers may take place on the basis of so-called "derogations": they allow transfers in specific cases, such as based on consent, for the performance of a contract, for the exercise of legal claims or for important reasons of public interest. When no adequacy decision has been taken at a no-deal scenario, UK partners / companies that participate in Dutch and EU clinical trial studies will be **required to have implemented appropriate data protection safeguards that protect the interests of clinical trial patients as good as GDPR standards**. Furthermore, **no legal framework is in place describing the UK's use of the EU databases for clinical trial data, e.g. the current EudraCT database and the future EU portal** linked to the upcoming clinical trial regulation (CTR). After no deal Brexit, except for specifically described paediatric Investigations, UK-specific trial information will therefore no longer have to be submitted to EudraCT. Despite the fact that most of the large clinical trial sponsors (i.e. in the Netherlands mainly big pharma) are used to exchange data with third countries, and thus are expected to fulfill the additionally required safeguards, a no-deal Brexit could still create inhibited or inefficient EU/UK transfer of personal and clinical data (e.g. in the EudraCT database), and subsequently potential risks of study delays, suboptimal set-up of new clinical trials, or misinterpreted study results.
Patient impact	Potential disturbance of clinical trial planning or delays of ongoing studies due to data exchange and sharing issues. Suboptimal clinical trial set-ups or result misinterpretations.
Impact on key stakeholders (NL)	Decreased insights and data availability around clinical trials at UK sites EU clinical trial database inaccessible by the UK Increase time efforts for companies to realize additional safeguards for data transfer
Possible solutions	Transfer of data centers to EU countries / move clinical trial sites from UK to EU. Raise awareness at trial sponsors and/or applicants in order to realize timely establishment of data transfer safeguards

Risk #5

Discontinuation of UK access to EU clinical trials database (EudraCT). Summary of recent EC statements around submission of clinical trial information:

Provisions of EU law relating to clinical trials* provide for the submission of certain clinical trial information to the EU clinical trials database EudraCT.[1]

Regarding protocol-related information, as of the withdrawal date, **UK-specific trial information will no longer have to be submitted to EudraCT**, except when the trial is part of an agreed Paediatric Investigation Plan and the United Kingdom is the only country in which the protocol has been submitted.

Regarding result-related information, results of clinical trials conducted in the United Kingdom and completed before the withdrawal date must be submitted to EudraCT if the reporting of these results is due before the withdrawal date. Results of clinical trials conducted only in the United Kingdom and results of multi-country trials where the United Kingdom was the only EU/EEA Member state where the clinical trial was conducted have to be submitted to EudraCT, also after the withdrawal date, if this is required for non-EU/EEA studies (i.e. if the trial is part of an agreed Paediatric Investigation Plan or falls in the scope of Article 46 of Regulation (EC) No 1901/2006).

*Cf. Articles 41 and 46 of Regulation (EC) No 1901/2006 of the European Parliament and of the Council of 12 December 2006 on medicinal products for paediatric use (OJ L 378, 27.12.2006, p. 1), Article 57 of Regulation (EC) No 726/2004 of the European Parliament and of the Council of 31 March 2004 laying down Community procedures for the authorisation and supervision of medicinal products for human and veterinary use and establishing a European Medicines Agency (OJ L 136, 30.4.2004, p. 1), and the implementation guidelines published in EudraLex, Volume 10 (https://ec.europa.eu/health/documents/eudralex/vol-10_en).

1) Notice to stakeholders, Withdrawal of the United Kingdom and EU rules in the field of clinical trials, 6 September 2018, European Commission

Risk consolidation, assessment & quantification

Risk	Assessment Summary	Patient impact estimate	Level of risk / priority
#1 **Availability of clinical R&D samples / investigational products**	Brexit-provoked **import authorization requirements** will increase the expected workload and average throughput times for customs. Additionally, investigational medicinal product (IMP) batches are to be **released from an EU site**, and by a Qualified Person (QP) based in the EU. Currently, 70 % of EU investigational medicinal products are released in UK. Both additional customs workload and need for duplicate quality and batch release checks could result in a delay of investigational product supply and potentially disturbed clinical trials.	Delay in investigational product supply may disturb clinical trial planning, delay or in worst case lead to termination of a clinical trial. May affect certain patients in likely a limited number of clinical trials, but in the case a clinical trial involves patients with no remaining viable treatment options, health impact of these patients could be severe. Risk: short term	■ ■ ■
#2 **Regulatory processes before, during, after clinical trials**	**Delays could occur during the regulatory and authorization processes prior to, during, or after a clinical study.** A workload shift from UK to EU27 and thus NL could occur, due to the UK regulatory bodies (i.e. MHRA) not contributing anymore to the EU regulatory ecosystem. Also a larger number of future clinical trials in EU27. incl. the Netherlands, is to be expected. Attention needs to be paid to potential workload increase estimates and capacity of NL clinical trial authorization bodies, inspection, and market authorization bodies.	Potential delays or disturbances in: - New clinical trial authorizations - GxP licenses - New product market authorizations - Patient access to new experimental therapies (ultimate consequence of abovementioned points) Risk: short/medium term	■ ■ ■
#3 **Lack of efficient collaboration and access to expertise**	The UK plays a dominant and leading role in the EU Life Sciences & Health ecosystem. Compared to other EU27 countries, **Dutch Life Sciences & Health institutions and companies work together to a relatively higher extent with UK institutions**, and share a similar R&D agenda. Brexit could deteriorate R&D collaboration opportunities between NL and UK.	Slow down of NL clinical pipeline development, and (mainly on the longer term) a decrease or delay of patient access to certain experimental therapies Risk: medium/long term	■
#4 **Research funding challenge**	**UK institutions play a dominant and leading role in acquiring funds for EU collaborative research programs.** Here, NL institutions and companies are frequent collaboration partners. A sudden rule out of UK institutions could lead to exclusion of UK partners, or more challenging future consortium set-ups and a decrease in granted subsidies for NL institutions and companies. Additionally, the UK venture capital market making up more than a third of the total **venture capital raised in Europe might be affected by Brexit**, leading to potentially less funding opportunities for NL scale-ups.	Slow down of NL clinical pipeline development, and mainly on the longer term) a decrease or delay of patient access to certain experimental therapies Risk: medium/long term	■ ■
#5 **Data exchange / poor accessibility**	EU General Data Protection Regulation does not apply anymore to the UK; UK will be regarded as a third country. Until agreements have been made on EU/UK transfer of personal and clinical data, **uncertainty about sharing clinical results and data will exist**, leading to ineffective set-up of new clinical trials or delays of ongoing studies.	Affects all UK involved clinical research studies. Potential disturbance of clinical trial planning or delays. Risk: short/medium term	■ ■

Selection of recommendations

Risk #1 – Availability of clinical R&D samples / investigational products

- Review and tightly monitor expected workload shifts at customs departments and EU QPs.
- Raise awareness and push towards clinical trial sponsors and applicants to anticipate on their end, e.g. by stockpiling where appropriate, changing supply chain routes, and taking other appropriate measures, such as changing QP location, etc.

Risk #2 – Regulatory processes before, during, after clinical trials

- Review and tightly monitor expected workload shifts from UK to NL clinical trial authorization bodies, inspectorates, and market authorization bodies, and where possible push towards appropriate mitigating actions, e.g. in advance shifting of pending files and inspections from UK to EU27 bodies, and stimulate collaboration and workload sharing in the EU regulatory networks.

Risk #3 – Lack of efficient collaboration and access to expertise

- Evaluate and define critical UK/NL R&D partnerships in more detail, incl. clinical trials.
- Stimulate R&D collaborations with other (non-UK) EU partners and simultaneously discuss alternative collaborative R&D options with UK.

Risk #4 – Research funding challenge

- Create awareness around the potential impact of Brexit on potential (mainly indirect) R&D budget disruption for Dutch companies and R&D institutions.
- Push towards R&D institutions and companies to anticipate on their end, e.g. by starting enhanced R&D funding trajectories with other EU partners or evaluate alternative R&D funding options for UK involved consortia.
- Stimulate and facilitate building of alternative global investor relationships.

Risk #5 – Data exchange / accessibility

- Raise awareness at trial sponsors and/or applicants in order to realize timely establishment of data transfer safeguards.
- Keep track on ongoing discussions / news around access UK to EU databases, also looking forward to EU portal of upcoming EU CTR.

Final remark

Building a better working world

Final remark

The exact circumstances and outcomes of Brexit are currently unknown, the regulatory uncertainty is still high and a range of parameters are changing at an incredibly high pace. Major regulatory actors and bodies neither have a complete nor a final view on the regulatory frame that will be ultimately applicable. Despite this uncertainty, major players within the ecosystem are undertaking a range of actions to mitigate and tackle risks, with statistics on Brexit readiness that are expected to change from one day to another. As a result, it is imperative to continue to scan for additional legislation, regulatory changes or guidance, keep tracing the development and nuance of existing information, evaluate the impact on the market segment and conduct risk-based preparations for the worst likely scenarios to ensure continuity of product supply and quality of patient care.

Appendix

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Acronyms

AIMD	Active Implantable Medical Device
ATC	Anatomical Therapeutic Chemical
API	Active Pharmaceutical Ingredient
BR	Batch Release
CA/NA	Competent Authority / Notifying Authority
CBG	College ter Beoordeling van Geneesmiddelen
CCMO	Centrale Commissie Mensgebonden Onderzoek
CE	Conformité Européenne
CER	Clinical Evaluation Report
CT	Clinical Trial
CTR	Clinical Trial Regulation
CHMP	Committee for Medicinal Products for Human Use
CVMP	Committee for Medicinal Products for Veterinary Use
EC-REP	Authorized Representative
EEA	European Economic Area
EMA	European Medicines Agency
EU	European Union
EU27	European Union post cliff-edge Brexit
EU28	European Union pre Brexit
FTA	Free Trade Agreement
GxP	Good Practices
GDP	Good Distribution Practices
GDPR	General Data Protection Regulation
GMP	Good Manufacturing Practices
GMT	Directie Geneesmiddelen en Medische Technologie
GVP	Good Pharmacovigilance Practices
IGJ	Inspectie Gezondheidszorg en Jeugd
IMP	Investigational Medicinal Product
IVD	In Vitro Diagnostic medical device
IVDR	In Vitro Diagnostic Regulation
MA	Marketing Authorization
MAH	Marketing Authorization Holder
MD	Medical Device
MDD	Medical Device Directive
MDR	Medical Device Regulation
Medtech	Medical Technology
MHRA	Medicines and Healthcare products Regulatory Agency
MRA	Mutual Recognition Agreement
MREC	Medical Research Ethics Committee
MRP	Mutual Recognition Procedure
MS	Member State
NB	Notified Body
NL	The Netherlands
PMS	Post Market Surveillance
PRAC	Pharmacovigilance Risk Assessment Committee
PV	Pharmacovigilance
PSMF	Pharmacovigilance System Master File
QC	Quality Control
QMS	Quality Management System
QP	Qualified Person
QPPV	Qualified Person for Pharmacovigilance
RMS	Reference Member State
UK	United Kingdom
VWS	Ministerie van Volksgezondheid, Welzijn en Sport

Supplementary materials provided to VWS:

1. Lists of pharmaceutical products (ATC codes) per defined risk area (excel file)
2. List of class I and IVD products using UK NBs registered by CIBG (excel file)
3. Overview of performed interviews (PDF file)