STATE OF ART

Introduction :

The WHO defines the *access to healthcare* as the availability of affordable and permanent health facilities in less than an hour's walk.

The example of Africa is a representative of this global problem:

In 2015, about 1.6 million of Africans died from diseases that could be treated through rapid access to proper medicines, vaccines and other health needed services. There is one crucial need for an appropriate and affordable local medicine. Indeed only 2% of the drugs used in Africa are produced on site. This results in a compelling need for imported medicines which are too expensive to be sustainable solution.

According to 2013 statistics from the World Bank, about 80 percent of Africans, mostly those with low or middle incomes, depend on public institutions for medical needs.
However, these institutions suffer from chronic shortages of drugs. Patients then die of easily curable diseases.

According to WHO, there are many origins of the lack of access to care. The main ones are the lack of financial and material resources as well as qualified personnel.

In addition, many African countries do not have the technical, financial or human resources to comply with current *Best Practices* (installed by the USAfor the large-scale production of some drugs. However, it has been proven that local production improves access to medicines while decreasing the cost of production[ref?].

Thus only 37 out of 54 Africanstates produce drugs, like South Africa, Morocco and Tunisia for instance. The quantity and the price of the available medicines does not allow their access to the whole population.

Many humanitarian organizations such as MSF or UNICEF [trop aggressif]are viewed as a current solution. They work to fill this lack of access to care by being the logistical and financial link between suppliers and regions in need. The expanded programs they implement prove their worth more and more. However, they also have to deal with obstacles like developing countries have to face.

To sum up, the main issues come from low financial means, the transport of medicines, the lack of qualified personnel and from the lack of institutes developed for the stock and the manufacturing of drugs. They all lead to a crippling dependence of certain contries of Africa toward industrialized countries regarding their own access to healthcare.

http://www.un.org/africarenewal/fr/magazine/décembre-2016-mars-2017/mourir-faute-de-médicaments

Health status :

Maladies infectieuses :

Total and vaccine preventable diseases cause specific deaths, children under age 5, by WHO region, 2008

	All cause	Pneumococcal diseases	Rotavirus diarrhea	Hib	Pertussis	Measles	Tetanus
AFR	4,202,000	247,000	217,000	94,000	84,000	25,000	27,000
AMR	284,000	13,000	8,000	1,000	2,000	-	1,000
EMR	1,237,000	68,000	90,000	32,000	19,000	7,000	14,000
EUR	148,000	7,000	3,000	3,000	-	-	-
SEAR	2,390,000	107,000	127,000	52,000	90,000	84,000	17,000
WPR	534,000	33,000	8,000	17,000	1,000	2,000	4,000
Total	8,795,000	476,000	453,000	199,000	195,000	118,000	63,000

Number rounded to thousand

WHO provides protocols and guidelines for assessing the *disease burden* using a variety of methods such as disease surveillance, rapid assessments, or population-based studies

http://www.who.int/immunization/monitoring_surveillance/burden/estimates/en/

Hepatitis B levels vary widely by WHO Regions. The heaviest burden lies in the African Region and the Western Pacific Region.

Western Pacific Region: 6.2% of the population (115 million)

African Region: 6.1% of the population (60 million)

Eastern Mediterranean Region: 3.3% of the population (21 million)

South-East Asia Region: 2% of the population (39 million)

European Region: 1.6% of the population (15 million)

Region of the Americas: 0.7% of the population (7 million)

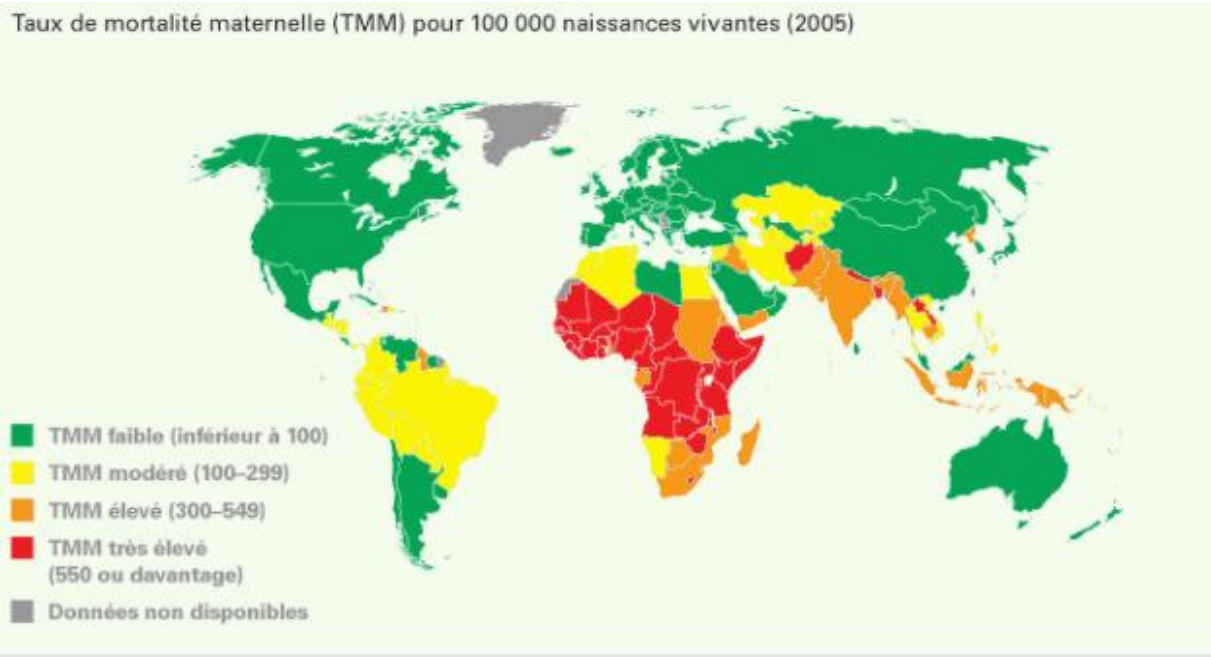
http://www.who.int/mediacentre/news/releases/2017/global-hepatitis-report/fr/

Maternal death : The two main causes are hemorrhage and eclampsia

Amongst developing countries with a mortality rate of 450*, sub-Saharan Africa and South Asia have the highest maternal mortality rates which run to 920* and 500* respectively. 400 *is the reference is the world average rate. Western countries, for example, are clearly below average with a rate of 8*.

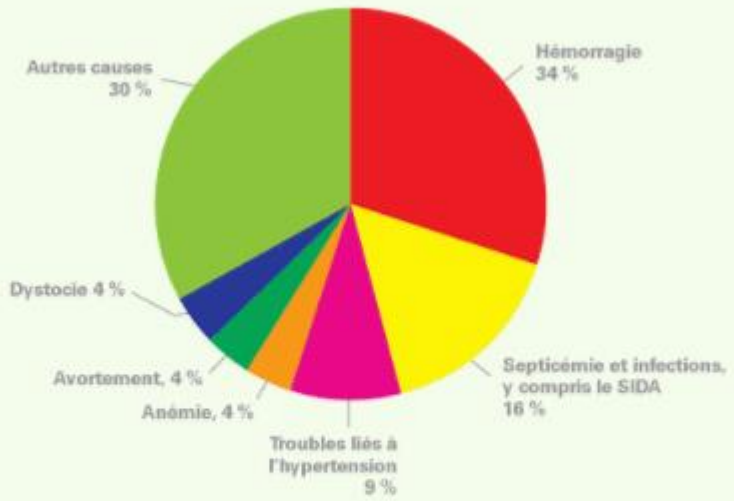
NB(*): The mortality rate was calculated per 100,000 live births, by region (2005)

The risk of maternal death is 1 out of 22 birth in sub-Saharan Africa compared to 1 out of8000 in industrialized countries (2005)



The main causes of maternal death are related to anesthesia and caesarean section in major occidental countries.
In developing countries, it is mainly caused by hemorrhage (sub-Saharan Africa and South Asia) and hypertension-related disorders during pregnancy (Latin America / Caribbean).

Classement par cause des décès maternels en Afrique, en pourcentage (1997-2002)



Note : les autres causes comprennent les grossesses extra-utérines, embolies, autres causes directes et indirectes et décès non classés. Le total figurant dans le camembert ne correspond pas à 100 % parce que l'on a arrondi les chiffres.

Source des chiffres cités aux pages 26–27 : Organisation mondiale de la Santé, UNICEF, Fonds des Nations Unies pour la population et Banque mondiale. *Mortalité maternelle en 2005-2007. Causes des décès maternels* : Khan, Khalid S., et al., 2006 « WHO Analysis of Causes of Maternal Deaths: A Systematic Review », *The Lancet*, vol. 367, no. 9516, 1er avril 2006, pp. 1066-1074.

https://books.google.fr/books?id=FIpEwwGZbkkC&pg=PA26&lpg=PA26&dq=hémorragie+décès+asie&source=bl&ots=5uwnSN8M-c&sig=j9BdpzKKutT1Mh0Xs7RFQXs0uJg&hl=fr&sa=X&ved=0ahUKEwjA78_X7uvWAhUQEVAKHT68Br4Q6AEIKzAI#v=onepage&q&f=false

http://www.who.int/mediacentre/factsheets/fs348/fr/

The lack of access to healthcare : The example of vaccines in Africa

In the same logic as for all medicines, vaccine sales in low- and middle-income countries were estimated at 1.6 billion in 2008. This represents only 10% of the global market. Of this 10%, 40% is sold to[by?] UNICEF, which represents about 5% 4 ;) of the global vaccine market

On the one hand, the multinationals producing them such as Merck or Sanofi, sustain high development cost, required for the production of these drugs.. Along with profit these companies make, this explains the high price of vaccines and the fact they have been developed by and for the richer countries, their main main consumer.

On the other hand, emerging public or private [NGO?] providers do not have the financial means and knowledge of regulatory mechanisms to invest in research and development. This results in a high-volume commercial model of less complex and older vaccines. These vaccines are sold to neighboring countries and to NGOs such as UNICEF.

In the end, the local population only has access to the old and locally produced vaccines, without constant strict regulatory oversight,or the one often provide during humanitarian campaigns.

Vaccines are therefore good representatives of the problems that revolve around access to medicines. Indeed, the population lacks vaccines adapted to current needs for financial reasons and local production logistics.

vaccins_etat_des_lieux_dec_2010_3.pdf

DPT Vaccination coverage :

[1] Selon les estimations de la couverture vaccinale par l'OMS et l'UNICEF
[2] Le DTC est presque universellement administré sous la forme d'un vaccin conjugué qui cible également l'*Haemophilus influenzae* de type b (Hib) et le virus de l'hépatite B.

DTC3 = DPT : diphtheria-tetanus-pertussis vaccine

Immunization+for+All+-+FR.pdf

The vaccine against HBV (Hepatitis B virus)

[We could think that the cause of the issues regarding the absence of widespread use of this vaccine is the result of an absence of implication of the governments. In fact, the major problem is financial. It's no use for the concerned states to authorize the use of treatments they don't have the ressouces to fund.

This is one explanation of the huge gap between the awarness of the HIV epidemia and the dramatic lack of ressources dedicated to the HBV epidemia in Africa. The HBV epidemia began centuries before the HIV epidemia and will continue for a long time without proper effort from the states. Its number of victims in Africa is comparable to the one of HIV, tuberculosis or malaria. Moreover, the mortality due to hepatitis tends to rise in the last years.

https://humanitaire.revues.org/3142

« There are vaccines and drugs to fight HBV and WHO is committed to ensure

these medicines cover anyone who needs them » said Dr Margaret Chan, Director-General of WHO

Although overall hepatitis mortality increases the number of new HBV infections is declining thanks to a better coverage of HBV vaccination on children.

Indeed, in 2015 the mortality was mostlyconcerning the 257 millions adults born before the introduction of the hepatits B vaccine, who lived with chronic infection of the virus.

Therefore, in order to reduce the mortality of the next generations, it is necessary to find ways to sustain the future vaccination campaigns and ensure the sustainability of the treatments.

http://www.who.int/mediacentre/news/releases/2017/global-hepatitis-report/fr/

Conclusion :

[Following the example of Hepatitis B, the lack of serotherapy as a treatment for these infectious diseases takes part in the significant mortality caused by overall infections. In addition, maternal mortality also mainly affects middle-income countries, whose inhabitants cannot afford the necessary treatments. The isolation from health establishments also plays an important role in the lack of medical care for pregnancy in these regions of the world.]

Report regarding Bioproduction of Thepatical use proteins.

Legal Issues

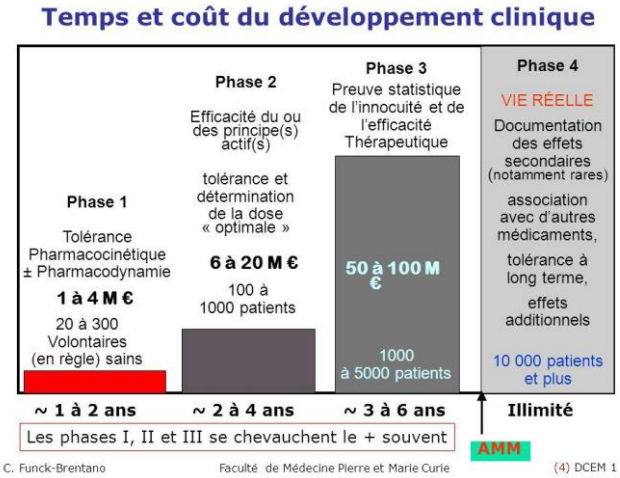
As a part of our Human Practises collaboration, we asked the Jurist of the Evry/Paris-Saclay team, Maxime de la Fouchardière, to help us about the legal issues that could come with the production if recombinant proteins in France and in general in the EU.

Studying and producing proteins for the research.

Our first question was about the production of recombinant proteins for the research purposes, would it create any issues.
Maxime told us that research in France and moreover in Europe knows actually very few regulations regarding the act in itself or its subject. This freedom is guaranteed by the French Code of Research. Besides this legal freedom, there are strong regulations regarding biomedicals studies, if they are conduct on animals or on human beings. Nevertheless, if GMO in research are authorized, their use and their deliberate release is strictly set by the French Environment Code.
It means for us, that we can use and produce recombinant proteins as long as the GMO we use to produce them are safely keeped.

But let’s not forget that our project is to produce recombinant proteins for human therapeutic use. Maxime then explained us that in France the drug market is tightly controlled by the French Agency for Drugs Safety, the ANSM. According to the Fench Public Health Code, is considered as a drug every substance that is said to have any curative or preventive properties. To be authorized, a drug

candidate must go through the Drug Marketing Authorization process or AMM in France. This a difficult procedure where the drug need to fulfil precise criteria: it must have a favorable risk-benefits balance, have a therapeutic effect and have the same composition as the one registered in the application form. It must go to through several phase of test on animals and humans where lot of data will be gathered to provide the right information on the well-use of the drug.



This whole process can take up to 10 years and costs billions of euros.

However, it exist few case where a drug can be selled with no AMM:

The Temporary Authorization of Use (ATU): if a drug doesn't have any AMM and has significant positive result in the clinical trials, doctors can be authorized to prescribe the drug. But this is only possible if the disease concerned is sufficiently rare or severe.

The Temporary Recommendation of Use (RTU): grant the possibility for a doctor to prescribe a drug if there is no other possibility of treatments, with conditions ruled by the ANSM

Doing further analyse on how our box and the protein It produce could be used in the market, we thought that the we could produce protein or hormone used in the livestock industry.

Maxime has then given us insight on how such molecules could be authorized:
In France, and on the Eurpean scale, the companies that want to sell a new molecule on the European market, must get their products assess buy the European Food Safety Agency (ENSA). They will go through a process where they must produce a study the risk of their molecule, and the result will be analyzed by the ENSA, which will allow the molecule if it doesn't present any harmful effect for the human and animal health and doesn't show any unacceptable risk for the environment. If allowed the molecule will be registered in the list of authorized molecules.
To be then authorized in France the molecule will be analyzed by the French regulating agency for food and sanitary security (ANSES). The ANSES will verify if the molecule registered has the right compositon, and basically do a similar work as the ENSA.

This whole process is much shorter than the AMM and can take up to 3 to 5 years.

ENTREPRENEURSHIP

Days after days, the recombinant proteins production is growing as a vital industrial science, in major fields of work such as healthcare or agronomy. Optimization of this production, in fact reducing the cost and time of production of these molecules is the main priorty of companies of this sector. Another major challenge remain to further automatize these process.
When we started the project our main goal was to find a solution that could help to resolve the issues of the lack of access to proper healthcare. In developing contries.To do so, we investigated the causes of the healthcare failures in different regions of the world that leads to a lower life span compared to developed countries. Beyond a lack of basal hygienic prevention in an environment often favourable to the growth of various pathologenes, the lack of *access* to healthcare appeared as the an obvious source of this lower quality of health.

Through our box, we focused more specifically on the lack of access to preventive and curative protein drugs. We want to innovate in the way we produce already existing therapeutic molecules.

We have then focused 3 main causes of the lack of access to drugs in the world :
1) The lack of financial means for the purchase and setting up of drug production
2) Geographical isolation of the countries concerned3) Storage and transport of drugs issues

Strategic Business Unit (SBU) :

In order to have a more general view of the drug market, we have set up a SBUtable around the question of the lack of access to healthcare.

The BioMaker Factory	**Lack of access to healthcare**
Alternative Solutions Companies from developed or in developing countries (LOGOS)	**Client expectations profile**

	Companies	**TBMF**
Geographical accessibility	**+ /-**	**++**
Affordability	**+ /-**	**++**
Significant amount /storage	**+ /-**	**-**
Emergency / Quick obtaining	**+**	**-**
Multiple drugs through a same tool	**+**	**++**
Safe	**++**	**++**
Userfriendly	**+**	**++ (automation)**
Efficiency **Risk-Benefit balance**	**++**	**++**

Users

Geographically isolated countries and / or having financial problems

Hospitals / clinics
Local dispensaries
NGO
Any access to care system

Large companies do not provide sufficient answers to the 3 main lack of access to care in the developing countries. This explains the specific lack of drugs in these countries even though there are existing treatments.

In addition, this table allows us to highlight the customers expectations and place the contribution of our box according to them.

Our major difference from large companies lies in the ability to get instantaneously a significant amount of therapeutic molecules to treat the medical emergency developing countries lives.

Moreover, for a simplified heterologous synthesis we limited our box to the production of protein drugs for now, which is already a sufficient challenge.

Although, criterias tend vary, depending on of the client expectations profile, there is a notable market around drugs needed in a quantity and in a short time lapse which correspond to one cycle production of our box. This specifity ou our project will be a key asset for our future business development
Moreover, the local production through our box bypasses the storage and transport of drugs issues that can often occur, and allow a controlled and reliable production of these drug which a main issue, in sub-Saharan Africa for example.

We can therefore place our box on the market of protein drugs wtih a punctual need that can wait for a 5 hours production and that are needed in **micrograms to milligrams per dose.** This drugs dosage would enable the treatment of multiple people with one cycle of production of our box.

In this market, we can answer the 3 main causes of the lack of access to healthcare mentioned before. We are therefore innovating on the production process of already existing protein drugs. Thus, our strategic segment is the developing countries.

Drug candidates:

We then researched therapeutic proteins which are nowadays needed, and matching with the specific reasons regarding the lack of access to healthcare we explain before and that our box can xonstitue a solution for.

The pathology treated by these drug candidates has to:

- Allow a minimum action time of about 5 hours
- Be curable by a quantity of active substances from micrograms to milligrams

We then selected the 3 types of diseases, we presented in the state of art of the current medical needs worldwide.

Some examples of treatments The BioMaker Factory could make available :

Vaccines

	Per dose (1 person) – in IV ou in IM	
DPT	Diphtheria toxin	2 UI
	Pertussis toxin	8 µg
	Tetanus toxin	20 UI
	Pertactine	2,5 µg
HBV	Surface antigen	20 µg
HPV	HPV proteins	20-40 µg

Serotherapies **Action time : 1h ≤ x ≤ 10 days**

	Per dose (1 person) - in IV ou in IM	
Diphteria	Diphteria Ig	10 000-100 000 UI
Tetanus	Tetanus Ig	3000-6000 UI

Maternity **Action time : Few hours to few days**

	Per dose (1 person) - in IV ou in IM	
Hemorrhage	Antihemophilic Factor	250-2000 UI
	Desmopressine	1-4 µg

IM : Intramuscular

IV : Intravenous

We have presented here the pathologies illustaring the most the mortality due to the lack of access to healthcare.

However, we can imagine that our box can also respond to certain chronic conditions.

Besides, we should not forget that our box is not frozen project. Around its role of automated production and purification, it leaves a large room for its optimization and allows us to work on a decreased production time and an increased quantity of production.

The possible optimization of the box could also revolve in the creation of a more or less storage, an ephemeral method to compensate for the time variable of production.

It should be noted that this box is also a solution to the ethical problems related to obtaining of some serum proteins from animal immunization or for the production of hormones, in fact animal use for the production of drugs in general. But also to the problem of immunogenicity of these serotherapies in humans.

Potential partners:

As described in the human practices part we talked to MSF and the start up MedTrucks to know more about the qualitative and quantitative data from the field. Then, our discussions went forward to thinking on a possible partnership with each of them in the futur. More precisely, our discussion with MedTrucks first focused on the abilities of their trucks to insert our box. The size of some of their trucks allows our partnership.

In fact, we all think that working in partnership could change the face of the actual access to healthcare through the assembly of our box and their travels in places and knowledge of the work in the ground.

We are also currently working on a potential partnership with a woman working on the creation of a clinic in a isolated region of Cameroon.

Limit on a short term of our box to palliate the lack of access to the care: the various Regulations

Going forward with this new mode of production:

We can easily imagine many other uses for our box.

The necessary production of these proteins must therefore be consistent with the capacity of the box in terms of time and quantity of production. Thus, we can offer a specific production between manual work at the benchtop and companies large-scale bioproduction. This would be a major gain of time and money relative to the optimization of a specific strain research and to the production of the protein by a research laboratory engineer.

In addition, this box is an invitation to the development of synthetic biology in the countries it will be used in. We can hope for an independent development of these countries through diverse and varied opportunities in this field.
Ultimately, this would be the source of potential local partners and threfore enable the specific development of our own strain libraryaccording to the local needs and regulations for instance ?

SWOT

The BioMaker Factory

Strength	**Weakness**
- Geographical accessibility - Affordability - Userfriendly - Multidisciplinary - Promotion of local independance - Time and money saving for protein production in laboratory	- Need the optimization of the intrinsic processes of the box : toward an unique process for the production fo various proteins
Opportunities	**Treats**
- Partnerships with health and research organizations - Partnerships with different suppliers and industries - Gain of money via maintenance of the box and the specific production of proteins sotfware	In a short time : - Regulation about processes and products including medicines - Regulation about GMOs -Industries. Eventhough there is no well established developed market around the automated average scale production of specific proteins