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Producing, Controlling and Stabilizing Pasteur's Anthrax Vaccine: Creating a New Industry and a Health Market

Maurice Cassier

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**Argument**

When Pasteur and Chamberland hastily set up their small biological industry to meet the agricultural demand for the anthrax vaccine, their methods for preparation and production had not yet been stabilized. The process of learning how to standardize biological products was accelerated in 1882 when vaccination accidents required the revision of production norms as the first hypotheses on fixity, inalterability, and transportability of vaccines were invalidated and replaced by procedures for continuous monitoring of the calibration of vaccines and the renewal of vaccine strains. Initially, the incompleteness and ongoing development of production standards justified Pasteur's monopoly on the production of the anthrax vaccine under his immediate supervision. Later on, the Pasteur Institute maintained control of these standards in the framework of a commercial monopoly that it established on the veterinary vaccines first sent and then cultivated abroad by the Société de Vulgarisation du Vaccin Charbonneux Pasteur, founded in 1886.

In the controversy in the 1880s between Koch and Pasteur over the anthrax vaccine, Koch accused Pasteur of incompletely divulging his method for attenuating anthrax bacilli – which made their reproduction long and uncertain – and of delivering vaccines that were so unstable and impure that their large-scale distribution in agriculture was risky both for humans and for animals (Koch 1882). Koch analyzed in detail the failures of the anthrax vaccine at the beginning of 1882 in Germany and France, and directly questioned the quality of the vaccines produced by the Paris laboratory: “Is there a general artificial immunity or was the virus vaccine worthless? .... These examples ought to be enough to show that the vaccine delivered by Mr Pasteur since the 1<sup>st</sup> April of this year was either too weak or too strong, and consequently had even weaker effects than the vaccine supplied last winter” (ibid.). Koch claimed that Pasteur's method had no practical utility because its standardization was incomplete. Koch contrasted the lack of stability of Pasteur's products with a finer graduation of the vaccines that he himself had developed with his colleagues. The question of standards was at the heart of the vaccination controversy.

Pasteur had stated in his report on the June 1881 Pouilly le Fort demonstration that his vaccines were fixed, which meant reproducible at will without having to renew the origin or to worry about their variations. He claimed furthermore that they were unalterable and transportable,

irrespective of distance and the location of production laboratories. However, a year later he had to admit his disillusionment: “Practice has shown that the vaccines were weakened, so that various kinds of accident occurred . . . rather than being something set and immutable, as previously assumed, viruses are variable, they change with time, climatic conditions, etc.” (Pasteur 1933, vol. 6, 387).

Mass producing and distributing the anthrax vaccine before production methods and products had been stabilized posed a great challenge. It involved setting up a new biological industry and simultaneously solving, step by step, problems of calibration, reproducibility, conservation, and transport of vaccines – all problems that had been underestimated during the early months of diffusion of the vaccine (Chamberland 1883). The existence of a vaccine industry implies the ability to produce homogeneous, stable, and reproducible entities at will, from a material that one has purposely modified and whose variability one systematically seeks to exploit. In an article published in 1996, entitled “La métaphore vaccine,” Anne Marie Moulin summed up the problem of vaccine production: “How to promulgate a bacterian order that is both stable and transformable?” It was precisely in practice, through multiple public demonstrations and the industrialization and early commercial diffusion of the anthrax vaccine, that the Pastoriens managed to create the first standards via a process of “learning by doing,” to use the term coined in 1962 by Nobel prize-winner for economics, Kenneth Arrow.

Recent historiography (Worboys 1991; Geison 1995) has shown that the success of Louis Pasteur’s anthrax vaccine was based precisely on the fact that it was mass produced whereas the production of his rivals, if not his precursors, remained on a laboratory scale, with limited experimentation. The Pastoriens were already in the industrial field when their rivals and critics were still at the laboratory stage. This was true both in France (the vaccine of Toussaint, a veterinarian, was tested in 1880) and in the United Kingdom (Greenfield’s vaccine was also tested in 1880). It was the introduction of Pasteur’s vaccine into agricultural practice that explained its success, even though Koch considered this to be premature in view of the vaccine’s imperfections. Pasteur was able to tell his critics that the innocuousness of his vaccines was based on statistics concerning the inoculation of several hundred thousand animals and that the rapid adoption of his vaccine by veterinarians and breeders, in France and throughout the world, was a guarantee of its efficacy and its practical utility – contrary to the “scientific fetishism” of his opponents (Pasteur 1933, vol. 6, 416).

We will see that this new biotechnological industry was still very small and its standards rudimentary. Yet it was already based on a division of work between the research laboratory and the laboratory that produced and dispatched vaccines. It had a separate accounting system and separate marketing tools (at the time this was referred to as the *vulgarization* of the Pasteur anthrax vaccine, that is, its diffusion in agricultural practice and the up-scaling of production). A private commercial company was founded, which had a monopoly on the exploitation and sale of the anthrax vaccine abroad. These were the components of early industrialization which was recognized as such by

Pasteur's contemporaries, above all by parliament which granted Pasteur a national award in 1883 for having created a new industry.

The recent historiography of the anthrax vaccine has focused on the Pouilly le Fort secret by referring to Louis Pasteur's laboratory notebooks which only became public in 1971 (Théodoridès 1977; Cadeddu 1987; Geison 1995; Grmek 1996). These authors show the gap between public science, i.e. the method of preparing the vaccine divulged by Pasteur at the Academy of Science, and private science, i.e. the method actually used to produce the Pouilly le Fort vaccines, as it was recorded in the laboratory notebooks. Yet these studies stop at the point where Pasteur and his co-inventors, especially Chamberland, set up this new industry and health-product market. Although Geison's conclusion does consider the link between the Pouilly le Fort secret and the commercial implications of the anthrax vaccine, this article will focus on the granting of scientific property rights to the discovery between Toussaint and Pasteur, far more than on the construction of the industrial and commercial monopoly on the vaccine. Very few studies have examined the industrialization of anthrax vaccine production. The subject is merely touched on in the book by Salomon Bayet on the Pastorian revolution (Salomon-Bayet 1986). Anne-Marie Moulin and Annick Guenel (1993) and Ilana Löwy (1994) have analyzed the birth of the health industry at the Pasteur Institute, but their articles focus primarily on the diphtheria vaccine as regards standardization and monopoly. In their study on the Pasteur Institute and the pharmaceutical industry, published in 1986, Liebenau and Robson mentioned the launching of the commercial distribution of the anthrax vaccine and the problems involved, but on this subject their sources and investigation remain limited. Mendelsohn's work, published in 2005, is the most recent study of the standardization and industrialization of the anthrax vaccine. He shows how the mass production of anthrax vaccines and their commercialization helped to establish a new conception of heredity. Here industry was the vehicle of the diffusion of scientific ideas, and it proved to be highly effective. Yet Mendelsohn's subject was the production and circulation of scientific ideas, rather than the birth of a new health industry.

In our research on the anthrax vaccine we have used archives related to Pasteur's vaccine in order to explore the construction of a new biological industry and a new health-product market. The idea is to combine the history of science and that of industry, and to explore two elements that we consider crucial in the creation of an industry and a health market: the establishment of technical standards and the use of legal means of appropriation (Cassier 2005). The present paper explores two aspects if not two phases of relations between standards and monopoly. Initially Pasteur deemed it imperative to monopolize production of the vaccine in order to solve technical problems and directly control the quality of products. He thus wanted to ensure that the reputation of his vaccine and the adoption of the very principle of artificial immunity were not compromised. He justified the monopoly on the grounds that the standards were not yet completely stabilized and were, in fact, in the making. To use the terminology of M. Callon (1994), we could talk of an "emergent network" over which Pasteur wanted exclusive control in order to guarantee its success and deployment. Exclusive control

was thus the guarantee of extension of the network. Once the standards were relatively stabilized, Pasteur wanted to control the distribution of products by establishing license contracts guaranteeing his laboratory's technical monopoly and the commercial monopoly of the private company set up in 1886 to expand the veterinary vaccine market. In the terminology of M. Callon (1994) we refer here to a network in the process of stabilization, owing to the possession of technical standards, the definition of license contracts, and the use of industrial property rights, especially Pasteur's commercial name, and trademark law.

Part 1 of this article describes the phase of establishing the production laboratory and dispatching anthrax vaccines, even while the standards were still being defined. In this case the standards stemmed from industrialization and not vice versa. The Pastorianians endeavored to stabilize their vaccines adopting solutions to the problems they encountered as they were developing their mass distribution. Part 2 analyzes the forces that motivated the construction of the commercial monopoly. The analysis is based on the rich information found in the archives of the Société de Vulgarisation du Vaccin Charbonneux which tells how the vaccine was marketed and licensed. Part 3 examines the tensions weighing on the commercial monopoly and the technical standards of Pasteur's vaccine.

## **1. Production and Stabilization**

The creation of a new vaccine industry was both celebrated or disputed by Pasteur's contemporaries. In 1883, two years after the Pouilly le Fort public demonstration, Paul Bert, a scientist and MP, justified the national award granted to Pasteur in the following terms:

It is therefore not surprising that orders for the anthrax vaccine have arrived from all over. To satisfy them, it was necessary to install a small industry outside the ENS laboratory which has become too small. From there, vials containing vaccines of both degrees are sent every day to farmers in all countries, carriage paid. The laboratory supplies them at a price of 10 centimes per dose for sheep and 20 centimes for large animals.<sup>1</sup>

One of Pasteur's staunchest opponents, Dr. Lutaud, also mentioned the establishment of an industrial activity: "He immediately organized a sort of factory, a depot for the sale of his vaccines, at 22 rue Vauquelin in Paris. In order to avoid the criticism that was more than likely to be levelled at the commercial side to this business, he chose as a figurehead a certain Mr Boutroux" (Lutaud 1887, 411). Dr. Lutaud perfectly summed up the simultaneous creation of a new industry and a new veterinary vaccine market, as well as the separation between the factory and the research laboratory. The reasons were both to increase the scale of the production and to separate the academic institutions from the commercial side.

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<sup>1</sup> Report of 2 July 1883, National Assembly. Report proposing to double the allowance and its payment to the widow and orphans of Pasteur. The ENS laboratory was to be maintained.

The production of several thousand doses of vaccines annually to satisfy breeders' demands involved a spin-off of a small industrial laboratory from the original academic laboratory: "As from today [the Pouilly-le-Fort trial in May 1881] farmers in the areas in which anthrax is prevalent will order this vaccine. I precipitately have to organize, in addition to my laboratory, a dispensary and a dispatch office" (Pasteur 1951 vol. 4, 173-174). This spin-off established the division of work between research (at the Rue d'Ulm laboratory run by Pasteur), production (at the laboratory at 14 rue Vauquelin, entrusted to his associate Chamberland), and commerce, taking and dispatching orders (at 28 rue Vauquelin supervised by Boutroux, an assistant chemist at the Ecole Normale). In 1888 the Russian biologist Gamaléia, who had learned the method for attenuating the anthrax bacillus so that it could be transported to Russia, clearly distinguished the Rue Vauquelin laboratory, dedicated to production, from the one at the Rue d'Ulm where Pasteur did his research. It was in the latter and not the former that Gamaleia learned the technology: "My studies have not included the technique for manufacturing vaccines for practical use, as it is used at the Rue Vauquelin by Mr Chamberland ... Owing to Mr Pasteur and Mr Roux's kindness, I was able, during my stay in Paris, to study the basic principles of the attenuation of the anthrax bacillus at the Rue d'Ulm laboratory" (Gamaléia 1888).

The spin-off of the production laboratory was based on the technology transfer of human resources from the original laboratory, primarily by the secondment of one of the co-inventors of the vaccine, Charles Chamberland. Chamberland was particularly well qualified to perform this transfer and to continue his cooperation with Pasteur. He had participated in all the steps of research on anthrax since 1877 and was fully involved in technical development, including the reproduction of vaccine preparation techniques developed by Pasteur's rival, Toussaint. Chamberland was even the co-author of the vaccine attenuated by potassium dichromate, used at Pouilly le Fort, though neither Chamberland nor Pasteur ever divulged this fact. Thus, he mastered the different attenuation methods with which Pasteur's laboratory had experimented, and was capable of managing its industrial development. Chamberland could also rely on interaction with Pasteur's laboratory to improve or perfect the production method. A book on the diffusion of Pasteur's vaccines in agricultural practice and the upscaling of production, published in 1886, mentioned "Pasteur's laboratories" in the Rue d'Ulm and the Rue Vauquelin, between which Pasteur circulated (Tignol 1886). The testimony of Adrien Loir, who kept an eye on the vaccines at the Rue Vauquelin when Chamberland was absent, confirms Pasteur's occasional visits to the production site. Yet, according to Loir, and this was important, Pasteur had not been informed of certain preparation details altered by Chamberland:

Pasteur said to me: "what are you doing here?" I carried on with a manipulation, inserted the rubber bung and, putting down the vial, answered him that Chamberland had told me to put about one cubic centimetre of bacillus subtilis culture into each anthrax vaccine vial. ... It was a precaution that Pasteur had never thought of and that Chamberland had never spoken about to him. (Loir 1938)

This production secret of Chamberland attests to the effective separation between the two laboratories, one devoted to industry and the other to discovery. It is important here to emphasize that we have no detailed descriptions of the production methods used in the Rue Vauquelin laboratory, apart from the above quotation incidentally through Loir, whereas we are informed on the culture methods at the Rue d'Ulm laboratory, which are recorded in Pasteur's laboratory notebooks. We know that even if the exchange of technical information between the Rue Vauquelin and the Rue d'Ulm laboratories was incomplete, Pasteur's laboratory gave its full scientific support during the crisis of the anthrax vaccine stability in 1882. The laboratory notebooks inform us of the numerous experiments conducted by Pasteur to establish the causes of the variability of anthrax vaccines during their successive cultures, to test different vaccine families attenuated by oxygen or potassium dichromate, or to select vaccine origins for mass production.<sup>2</sup>

Just as today's biotechnology start-ups maintain ongoing scientific interaction with the university from which they originated for technology transfer and launching new research, so the Rue Vauquelin production laboratory relied on the Rue d'Ulm academic laboratory for new technical solutions or new products such as a swine fever vaccine, also developed during that period. Production itself had to become a specialized and routine task: "a person taken in my laboratory, who is intelligent, will have no occupation other than the preparation of the vaccine for the whole year and will have an assistant."<sup>3</sup> Pasteur expected his production manager to closely monitor the quality of the vaccines. When unexplained vaccination accidents occurred, Pasteur suspected Chamberland of not monitoring vaccine preparation closely enough:

In November and December the vaccines were too weak. It was necessary to reinforce them. This was not done enough since they produced a shorter period of immunity. Reports on the virulence of the first and the second were not satisfactory to me. In a sense one would need to do only that. That is what I expect from Chamberland, but sometimes the zeal dies out.  
(Pasteur 1951, vol. 3, 316)

The Rue Vauquelin laboratory remained small in the early 1880s, with only four assistant chemists:

Mr Pasteur is putting into practice the results already achieved and we can foresee the time when vaccine production will become a major service. In the Rue Vauquelin laboratory they are preparing vaccines for anthrax, erysipelas and chicken cholera. The records kept at the laboratory show that in a single month, 200,000 doses of anthrax vaccine were dispatched in

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<sup>2</sup> "Cahiers de laboratoire de L. Pasteur," BNF 18016 10<sup>ème</sup> cahier (10 Nov. 1880 – 10 April 1882) and BNF NAF 18017 (10 April 1882 – 9 November 1883).

<sup>3</sup> Letter by the Prefect of the Seine et Marne *département*, published in the *Supplément de la Revue Médicale*, 1 October 1881, document 17945.

France; this represented prophylaxis against anthrax for 100,000 head of livestock (sheep, cattle, horses).<sup>4</sup>

The number of doses sent within France and abroad grew considerably in the weeks following Pouilly le Fort: 164,000 inoculations in 1881; up to 700,000 in 1882; and more than 900,000 in 1885; it then declined slightly: 800,000 inoculations in 1886.

From 1882 the anthrax vaccine laboratory had a system of analytical accounting that detailed expenditures for production, packaging, and dispatching of the vaccine. The accounting sheets were headed “Vaccin Charbonneux F. Boutroux, 28 rue Vauquelin, Paris.” The “statement of expenditures in 1882 for manufacturing and dispatching the anthrax vaccine”<sup>5</sup> showed the cost price of a vaccine vial to be 2.13 Francs. On this basis the selling price of 2.50 Francs was calculated. This accounting shows the very modest cost of vaccine cultures (150 Francs for culture mediums and 500 Francs for gas and electricity out of a total budget of 19,216 francs that year, that is 3 per cent of all expenditures), whereas expenses pertaining to vialing and dispatching amounted to over 6,000 Francs (30 per cent of all expenditures), administrative costs to over 4,000 Francs (close to 25 per cent), and commercial management to 6,000 Francs (30 per cent of the budget). A further cost was technicians’ salaries, paid with a grant from the Ministry of Agriculture.<sup>6</sup> With this accounting it was possible to calculate the profits derived from vaccine sales, which were distributed to the inventors. Pasteur received two-fifths; he gave one-fifth to each of his co-inventors Chamberland and Roux; and one-fifth was placed in a reserve fund. In 1887, when the Pasteur Institute was created, the three inventors left their share of the profits to the new institute.<sup>7</sup> In that year the Board of Directors of the Pasteur Institute assessed annual income from vaccines at around 25,000 Francs, while operating expenses were estimated at between 130,000 and 150,000 Francs. The Rue Vauquelin’s autonomy was also attested by the license contracts for commercial exploitation of the anthrax vaccine, which were in Chamberland’s name and signed directly by him and not by Pasteur. Finally, from 1882 the commercial entity had marketing material under the name *Vaccin Charbonneux Boutroux* (Boutroux Anthrax Vaccine), consisting of brochures, posters, and practical guides which associated the trade name with technical recommendations for the conservation and use of the vaccines.<sup>8</sup> We will see that later, in 1886, the name *Vaccins Charbonneux Pasteur* became the trade name used for the sale of vaccines abroad.

The product itself, the vaccine, was put into vials of varying capacity, to inoculate 50, 100, or 200 sheep, or 25, 50, or 100 cows or horses. The vials were marked in different colors to distinguish

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<sup>4</sup> Report by M. E. Millaud, Senator, “for the appropriation of a part of the Villeneuve l’Etang domain for Mr Pasteur’s experiments on the prophylaxis of contagious animal diseases,” 13 November 1884 session. Document 18630.

<sup>5</sup> Musée Pasteur, Doc. 17640.

<sup>6</sup> Musée Pasteur, Doc. 18476.

<sup>7</sup> Board meeting of 25 March 1887: “This considerable income which is legitimately the property of Mr Pasteur and his collaborators, Mr Pasteur is prepared to forego ... This great example of disinterestedness.”

<sup>8</sup> “Vaccinations charbonneuses.” Musée Pasteur, LPG1 46, Document 17993.



between the two vaccines of increasing virulence used for the vaccination: blue for the first degree and red for the second degree. The tubes were hermetically closed with rubber bungs or in some cases soldered closed as an extra guarantee (Chamberland 1883). The vialing of the anthrax vaccine protected it from impurities and allowed it to be transported to distant lands. This transportability of Pasteur's vaccine was compared to that of Toussaint which did not have the same advantage (Micé 1883). But to what extent were these mass-produced vials of vaccines (Klein 1882) standardized and calibrated by the laboratory chemists, and of reliable quality so that their efficacy could be guaranteed? Were they really stable enough to be stored and transported over long distances?

Several justifications can be given for standardization. First, Pasteur's laboratory, which was both the inventor and producer of the anthrax vaccine, had to produce its own standards in the absence of any public standard set by the government or of comparable products developed by rivals. Comparative trials were carried out in France between Pasteur's vaccine and that of Chauveau de Lyon, but in 1888 only, and Chauveau's vaccine was not mass produced.<sup>9</sup> In terms used by the economist Kindelberger, the anthrax vaccine standards were neither public standards, set and imposed by the state, nor collective standards elaborated and adopted by a profession, but private standards, developed by a single laboratory (Kindelberger 1983).

Second, still according to Kindelberger, there is a particular interest in establishing quality standards for drugs: protecting the consumer. Pasteur's laboratory had to standardize the virulence of its vaccines accurately so that breeders and veterinarians would be guaranteed of their efficacy and reliability, and persuaded to adopt the practice of artificially immunizing their herds and flocks. Standardizing vaccines, which meant measuring their virulence, was crucial to sanitary security. Unstable or non-standard vaccines were likely to carry a risk for both animals and humans, warned Koch, who claimed that Pasteur's vaccines were sometimes too weak and sometimes too strong (Koch 1882). The gap in the virulence between the two vaccines used to produce artificial immunity had to be carefully regulated and stable. If the first-degree vaccine was too strong, it could produce vaccination accidents; if it was too weak, there were likely to be accidents with the second-degree vaccination.

Third, the careful calibration of vaccines had economic implications. Unreliable vaccines would destroy the confidence of veterinarians and breeders. The expected benefits from vaccination would not be enough to justify their use. In 1887 Charles Chamberland considered that "vaccination has no real economic advantage if mortality among large animals does not decline by 1 per cent and among sheep by at least 2 per cent" (Chamberland 1887).

Finally, apart from the advantages of quality standards for guaranteeing the harmlessness and practical usefulness of vaccines, compliance with standards is a classical element in establishing commercial transactions (Kindelberger 1983). The license contracts of the Pasteur Anthrax Vaccine

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<sup>9</sup> Letter by M. Rossignol, 15 June 1888. BNF, NAF 18102 MF 22319.

monopoly stipulated obligations concerning quality, incumbent on the supplier of the vaccines: “Mr Chamberland undertakes to carefully ensure the source and quality of the vaccine which will be sold under the name Pasteur Anthrax Vaccine, with a seal guaranteeing its origin.”<sup>10</sup> The commercial reputation of Pasteur’s anthrax vaccine was closely related to standardization. The quality standard was advantageous for both commercial transactions and for animal health policy.

The standardization of anthrax vaccines was a particularly complex task insofar as the Pasteur vaccine principle was based on the use of two successive vaccines of increasing virulence. These two vaccines were the signature of Pasteur’s anthrax vaccine. The handbook distributed in 1883 by the Boutroux laboratory provided the justification:

In order not to transmit to animals a disease that could be serious, we do two preventive inoculations: the first with a highly attenuated bacillus (1<sup>st</sup> vaccination), which gives the animals a slight temperature, and a second, twelve to fifteen days later, with a more virulent bacillus (2<sup>nd</sup> vaccine). This would kill some of the animals had they not been partially protected by the preceding inoculation but after the partial prevention the animals have only a slight temperature. They are then fully vaccinated, which means they are unaffected by anthrax.<sup>11</sup>

The graduation of vaccines implied the development of a scale of virulence. For this purpose the Pastorianians established the first elements of a biological standardization of vaccinal products. In the absence of a classification connecting the morphology of bacilli to their relative virulence, despite research on the subject during the same period (Gamaléia 1888), and without molecular knowledge to identify bacteria with a low level of virulence, the graduation of the virulence of vaccines was based on their biological effects on the inoculated animals.<sup>12</sup> The Pastorianians developed a series of tests and physiological observations to graduate vaccines of increasing virulence in order to be able to have as complete a series as possible, from relatively weak vaccines to relatively strong ones.

They then chose the first-degree vaccine and the second-degree vaccine according to the appropriate ratio of virulence to produce immunity without too much risk. This biological standardization was based on analysis of the inoculated animals’ temperature curves, on the percentage of surviving animals, and on the duration of their survival, as well as on clinical observations, especially of oedema due to vaccination. Pasteur had formulated the principle in 1880 in his work on the chicken cholera vaccine: “When, by operating in the same conditions on the same number of animals of the same species, the proportion of mortality is the same over the same period of time, we note that for our successive cultures the virulence is the same” (Pasteur 1933, vol. 6, 325). These measurements were nevertheless subject to uncertainties relative to the weight of the tested

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<sup>10</sup> Contract with the Compagnie de Vulgarisation du Vaccin Charbonneux Pasteur in April 1886. Archives IP, DR. DOS 1, Document 10587.

<sup>11</sup> “Vaccinations charbonneuses,” Musée Pasteur, LPG1 46, document 17993.

<sup>12</sup> The principles of biological standardization have been studied by C. Sinding (2002) in respect of insulin in the period between the two World Wars.

animals, which had not been measured, or to the species of experimental animals, which are not all susceptible to anthrax to the same degree.

The accuracy of these measurements of virulence was improved as the production laboratory's experience increased. The accumulation of observations and measurements made it possible to infer a number of elementary rules for the chemist: "If there is oedema after the 1<sup>st</sup> vaccination at the point of inoculation, it is because this vaccine is too strong. If there is oedema at the point of inoculation after the second vaccination, it is because the first vaccine is too weak. If the virus that is virulent or fatal for non-vaccinated animals kills vaccinated animals, it is because the vaccines are too weak ... If after inoculation with the 2<sup>nd</sup> vaccine the animals' temperature exceeds 41°, this vaccine is too strong and should not be used."<sup>13</sup> These rules contributed towards progressive standardization. The rulebooks drafted by Roux in 1885 and completed in 1889 were a recording of this work of building anthrax vaccine production standards.

Another major obstacle existed for standardization of anthrax vaccines, at least during the first two years of its mass diffusion, in 1881 and 1882: the lack of stabilization of the method for attenuating microbes. We know that the instability of the attenuation method developed by Pasteur, based on heat and exposure to air, led to the decision to use Bichromate vaccines prepared chemically by Chamberland during the public demonstration at Pouilly-le-Fort in May 1881.<sup>14</sup> Competition between these two methods was still on-going in early 1882 during Thuillier's trials in Germany. In a letter dated 24 April 1882, Thuillier announced to Pasteur the "Bad news: three sheep dead, one almost lost, and three others with high temperatures" (Franck and Wrotnowska 1969, 132). In this letter we learn that in April 1882, almost a year after Pouilly-le-Fort, Pasteur still used vaccines from several origins, some prepared with bichromate and others by heat: "The contradiction of your results at Vincennes and mine at Pakisch lead me to believe that the double vaccination is preferable to the single vaccination only when two vaccines of the same origin are used, that is, two heat vaccines without passage through guinea pigs or mice, two bichromate vaccines without passage either, a first if mice and the second that has passed finally through some mice, or a second one guinea pig with a first that has passed through a young guinea pig" (ibid). Thus, for the same vaccination trial, the Pastorians used two vaccines of different origins. The correspondence between Pasteur and Thuillier shows us that Pasteur ran an experiment on the experimental farm in Vincennes in parallel with that of Thuillier at Packish, where the efficacy of vaccines had been tested a few days earlier. For this purpose Pasteur bought a batch of sheep from Germany at La Villette market: "The 2<sup>nd</sup> vaccine that you inoculated yesterday was given immediately on 7 April at the De la Faisanderie farm, to ten German sheep purchased at La Villette, without a first vaccine like yours ... Keep this to yourself for the moment since it is subject to the result of the farm trial on our ten German sheep" (ibid). The use of two

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<sup>13</sup> Emile Roux, "Notes sur le charbon et la vaccination charbonneuse." ROU 4, document 10612, 1885.

<sup>14</sup> 10<sup>ème</sup> cahier de laboratoire 1881 (10th laboratory notebooks), note by Pasteur dated 5 May 1881, BNF, NAF 18106.

vaccines prepared according to different methods and this experiment conducted in parallel in Paris and Germany attests to the uncertain nature of the products and processes used at the time.<sup>15</sup>

At the time, Pasteur also tested the composition of the vaccine, in the form of spores or filaments. During the Budapest and Kapuvar experiments in September and October 1881 in Hungary, Pasteur's representative, Thuillier, used two very different types of vaccine: recent vaccines composed of filaments, cultivated on site, and old vaccines composed of spores, from Paris. The Hungarian Commission's report mentioned "recent cultures with only filaments and no spores" and "old cultures, brought from Paris with only spores" (ibid., 84). The composition of the vaccines, with either filaments or spores or a combination of both, was still not set. Thuillier drew an important conclusion on the transportability of anthrax vaccines: "the experiment on the batch of four sheep, vaccinated with old cultures, brought from Paris in sealed vials, has shown that in these conditions the vaccine can travel long distances without losing any of its admirable virtues" (ibid., 108).

During the same period, in the early autumn of 1881, Pasteur was still very unsure about the duration of conservation and storage of his vaccines: "All the vaccines that have left my laboratory over the past month are from recent cultures. Manufacturing implies the storage and use of prepared vials over long periods. Problems, which are probably easy to solve, can arise in the conservation of vaccines, the shape of jars, etc."<sup>16</sup>

While Pasteur and Chamberland were working on increasing the scale of vaccine production during the summer and autumn of 1881, the first vaccination accidents occurred both in France and abroad. The number of these accidents multiplied in early 1882, to the extent that the Société Centrale Vétérinaire held a meeting in June of that year, attended by Pasteur, to attempt to explain these failures and to reassure veterinarians who were doubting the quality and efficacy of the anthrax vaccine. The problem of the stability and quality of vaccines moved beyond Pasteur's laboratory, and was discussed by the vaccination "popularizers." During this meeting, Pasteur had to agree that the anthrax vaccines that he thought were "fixed and inalterable" had proved to be variable and unstable. He even proposed an insurance fund to cover vaccination risks: "By taking a sum of 10 centimes from each vaccination, we could create a sufficiently large fund to guarantee coverage of all losses" (Pasteur 1933, vol. 6, 389).

These problems of quality and efficacy of vaccines prompted a return to the research laboratory. Laboratory notebooks from the year 1882 show intense activity in the laboratory and many trials on neighboring farms to study the change of virulence of vaccine strains in successive cultures, the ageing of vaccines in ovens or vials, and the search for new strains to serve as new vaccine origins. In March 1882 Pasteur noted the weakening of the virulence of vaccines with successive cultures: "Five deaths by the second culture and not a single death by the eightieth; hence there is

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<sup>15</sup> Note that in 1888, Gamaleia learned the attenuation method using potassium dichromate. He transferred it to Russia where it was used routinely in production.

<sup>16</sup> Letter to the Prefect of Seine et Marne *département*, summer 1881, published in *La Semaine Médicale*, 1 October 1881. Musée Pasteur, LP G1 46, document 17945.

unquestionably a weakening of repetitive cultures, despite the germs.”<sup>17</sup> He also noticed that vaccines weakened as they aged in the vials. It was therefore necessary to prevent their weakening in two ways: first, by periodically renewing their origins and, second, by ensuring that they were fresh and carefully preserved.

This phase of acute crisis in the production of anthrax vaccines lasted for several months in 1882: “These experiments were lengthy and tricky” (Chamberland 1883, 284). Chamberland’s account published in 1883 corroborated this work, step by step. Chamberland tells us that the reproduction of new effective vaccines took place in two stages. From March to October 1882 Pasteur’s laboratory provided a new vaccine which finally proved to be slightly too strong: “According to the data supplied to us by several veterinarians, we concluded that the first vaccine was a little too strong and that in a few flocks some sheep had died after being inoculated with this first vaccine” (ibid., 294). This vaccine strain was nevertheless preserved to serve as a “Special vaccine” or for “revaccination” as it had the advantage, said Chamberland, “of directly and completely vaccinating the animals that were protected from spontaneous anthrax. The origin of this vaccine is carefully preserved and will be sent to those veterinarians who request it” (ibid.). To obtain a balanced vaccine, the Pasteurians undertook a painstaking reproduction of vaccines that had been used a year earlier, during the summer of 1881: “We believed, following the accidents which occurred, that we should revert to vaccines identical to those that were used in 1881 ... we were able to reproduce, so to speak mathematically, the vaccines used during the summer of 1881” (ibid.). This work of reconstitution of vaccines from the summer of 1881 reveals a great deal about the creation of product standards. First, Pasteur’s laboratory had not kept these seeds, which were weakened during the successive cultures in the autumn and winter of 1881. It was necessary to recreate them. Second, Pasteur and Chamberland had sufficient archives concerning the culture and calibration of vaccines to carry out this work of “identical” or quasi-identical reproduction. But this archaeological work required time and many biological tests. Third, Chamberland draws our attention to the value of the preservation of the origins of vaccines: the origin of the vaccine used for revaccination in the summer of 1882 was “carefully” preserved. Yet, considering the aging of spores in vials, even sealed, this origin also needed to be reproduced periodically.

The discovery of the variability of vaccine strains and the ageing of vaccines changed the economy of vaccines and of their standards. First, insofar as vaccines were not fixed, there would be a cost involved in testing and continuously recreating their origins: “Above all, it is necessary constantly to verify the value of the vaccines and to prepare new ones. This is not as simple as it seems, but we will manage” (Franck and Wrotnowska 1969, 198). Second, while vaccine culture in itself cost little, it was the work of selection and calibration of the origins that represented the most expensive part of the

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<sup>17</sup> BNF NAF 18106, 10<sup>ème</sup> cahier, 14 mars 1882. On 23 May 1882, Pasteur wrote: “Note that the lessening of virulence exists and is proved by the fact that mortality appeared only after five days and not after 36 or 48 hours, and that the two control animals died only after seven days and five days.”

enterprise – as well as being its strategic part. Third, the variability of vaccines required both an internal monitoring device (regular biological tests on seeds and vaccines) and the mobilization of an external monitoring system consisting of veterinarians and breeders. In this sense users participated in the work of stabilizing vaccines.<sup>18</sup> The fourth point concerns the conservation and transport of anthrax vaccines. Not only were the vaccines weakened by successive cultures, they also aged in vials and bottles. Instructions on the use of freshly-prepared vaccines were also sent to users. Vaccination manuals distributed by the Laboratoires Boutroux from 1882 recommended immediate use on reception: “Except in circumstances beyond one’s control, vaccines should be inoculated upon reception, when they are fresh.”<sup>19</sup>

New principles for the organization of production were thus established. These were specified by Chamberland in 1883: “I therefore think that for distant countries, for all those where it takes the vaccine over 15 or 20 days to reach its destination, it would be highly advantageous, if not indispensable, to set up small laboratories for producing fresh vaccine that would be dispatched throughout the neighbouring area.” This drastic revision of the production, circulation, and use of the vaccines occurred during the course of their industrialization and commercialization, through a process of “learning by doing” (Arrow 1962) and “learning by using” (Rosenberg 1982). The users, especially veterinarians, were mobilized to monitor the quality of vaccines.

## **2. Standards and Monopoly**

While Thuillier was in Hungary where Pasteur had sent him in September and October 1881 to perform public demonstrations of the anthrax vaccine in Budapest and Kapuvar, he revealed the importance of industrial property rights to control the vaccine preparation technology: “The Hungarians are even greater admirers of your discovery than I thought at first . . . . The demonstration experiments that I am performing are actually of only moderate interest to them – they are so convinced in advance of success. What interests them more is to know (1) how to prepare pure cultures, (2) how to make the vaccine” (Franck and Wrotnowska 1969, 90-91). The Hungarian Agriculture Minister’s real interest in the demonstrations was to appropriate Pasteur’s technology: “His Excellency, the Minister of Agriculture, Baron de Kémeny, has appointed a commission of 9 members . . . . not to observe the experiment itself, but rather to learn from me every step in the preparation of the vaccine” (ibid.). The Hungarians asked Thuillier to teach them “all the manipulations for preparing the vaccine. That is, they wanted to learn how to take a pure blood sample from an animal and to cultivate it in a pure state in a pure culture medium (of which they were also to learn the preparation), to maintain this culture at 42–43°, constantly pure throughout the attenuation period, to take pure samples from this culture at 42°, from time to time, to cultivate them, and to

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<sup>18</sup> Christiane Sinding (2002) clearly shows the role of clinicians and patients in the definition of insulin standards.

<sup>19</sup> “Principes de vaccination ,” Laboratoire Boutroux, 1883. LP. G1 46, document 17993.

determine the virulence in order to obtain vaccine N°2 and then N°1” (ibid.). This operation of technology transfer would even be accompanied by a guarantee of results: “Not only would I have to show them all that, they would also have to do it in front of me, with the obligation for me to guarantee them against any mistake.” This was where this request for technology transfer overlapped with the stakes of appropriating the invention and the resulting industrial rent: “In this way, they would be in a position to produce, without any fear of failure, all the vaccine they might need. Once they had mastered the process their national pride would be boosted by making the Germans, Russians, and all those who so wished, dependent on their industry.” The Hungarians would thus become the direct rivals of Pasteur’s laboratory: “They want to save Jean and Eugène<sup>20</sup> a lot of work” (ibid.).

Pasteur refused this technology transfer request. In a letter to Baron Kemeny, dated 4 October 1881,<sup>21</sup> he justified this refusal by two main arguments which illuminate the issue of standardization. First, Pasteur explained – beyond published knowledge – the importance of the laboratory know-how required for the preparation of the vaccine, as well as the duration and cost of this process: “This preparation is simple in theory. I published it in the reports of the Académie des Sciences de Paris. Its application is time-consuming and expensive for obtaining absolute certainty. But to guarantee its full value one needs a great deal of time and even expenditures. Every day one has to test, so to speak, the state of the virulent anthrax parasite as it is gradually altered, and this testing can be achieved only by means of inoculations practiced on animals, and finally on a large enough number of sheep” (ibid.). Apart from mastering the microbe attenuation technique, Pasteur insisted on the cost of calibrating vaccines to graduate their virulence, and thus on the importance of operations of biological standardization on animals. The necessary interval for microbe attenuation and vaccine calibration tests was too long: “It would take too much time for Mr Thuillier to do this study” (ibid.).

Second, Pasteur felt that his preparation method was not sufficiently stable to be transferred: “Moreover, allow me to point out that, by precaution and in order not to compromise the success of a tricky method, I very much wish that for at least one year, all vaccines used by livestock breeders be prepared by me or under my immediate supervision” (ibid.). The invention was still in progress; it had to remain under the inventors’ control: “there are still a few details to examine and for the moment only I can do so.”<sup>22</sup> The vaccine’s reputation and future adoption could be compromised by bad preparations. Before thinking of spreading its production to local laboratories, the network of adoption had to be consolidated and expanded: “For the moment, it is necessary to convince farmers and large landowners of the advantages of the method.”

Pasteur outlined the industrial and commercial organization that he had in mind. He described the launching of his small industrial laboratory: “Moreover, I am presently setting up a sort of factory.

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<sup>20</sup> Jean Arconi and Eugène Viala, technicians in Pasteur’s laboratory.

<sup>21</sup> Musée Pasteur, carton Charbon.

<sup>22</sup> This sentence was ruled out in the manuscript.

I already have no less than two hectolitres of liquid ready to be transformed into vaccine. Next spring I will be able to send vials of vaccine liquid to distant places, at low prices, at cost or close to it.” His Paris laboratory was to mass produce vaccines which would be sent abroad. He proposed a trade agreement: “After France, Hungary would be the preferred nation” (ibid.). Then, to meet a growing demand, he conceived of setting up a production laboratory in Hungary: “If the practice of vaccination spreads more and more, as I hope, I will be able only gradually to deliver all the vaccine requested. A factory could be set up in Hungary and I would be the first to guarantee its success by providing precise instructions” (ibid.). The latter phase confirmed both the importance of the know-how to transfer and Pasteur’s refusal to share it with the Hungarians in the immediate future.<sup>23</sup>

Questions relating to the stabilization and standardization of the anthrax vaccine overlapped with questions concerning its appropriation and commercialization. First, the refusal to transfer the technology to Hungary was justified by the difficulty of transferring a method that was still largely unstable. Concentration of production in Pasteur’s laboratory under “his immediate supervision” would allow for the method to be perfected and the quality of products to be controlled. In return, this situation represented a *de facto* monopoly of this laboratory on vaccine production and commercialization. The Hungarians were unable to establish a competing industry. Second, these negotiations showed the importance of the tasks involved in biological standardization of vaccines, which were “lengthy and costly,” as Pasteur put it. They were not easy to reproduce and whoever possessed them had an advantage over their rivals or imitators. Owning standards, when they are undisclosed, also creates a monopoly.<sup>24</sup> Note that these standards had a dual existence: in the form of rules for measuring virulence, and in that of vaccine strains which, once calibrated and selected for the first or second vaccine, served as origins for further production. Finally, this industrial and commercial configuration related to the fact that vaccines were supposed to be stable and transportable. Remember that in Hungary Thuillier had tested vaccines composed of spores brought from Paris, to assess their transportability. If the vaccines produced by Paris were inalterable and transportable, there was no need to spread production to local laboratories. But subsequent events in 1881 and 1882 changed this.

Once it became clear that the vaccines aged, the extension of the market abroad implied the delocalization of production and a policy in favor of spin-off laboratories. At the same time, Pasteur wanted to maintain control over the core knowledge of vaccine preparation, that is, the selection and calibration of spores. He set out his argument in 1884 in a letter addressed to the British Ambassador

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<sup>23</sup> A letter by Thuillier dated 29 October 1881 announced the imminent creation of a local laboratory in Hungary: “the Hungarians now consider as sure the establishment of a factory in their country next autumn and until then they will order large quantities of vaccine” (Franck and Wrotnowska 1969, 102). In fact a Pasteur-Chamberland laboratory was set up in Budapest soon afterwards, “under the patronage of the Royal Hungarian Ministry of Agriculture.”

<sup>24</sup> Initially, the emergence of standards justified Pasteur’s monopoly as he had to control the quality and perfection of the method; afterwards it was their ownership, in the form of rules, measurements and calibrated strains, that was the basis for appropriation.



who wished to establish local production of the anthrax vaccine in India.<sup>25</sup> In this letter Pasteur discussed two options for the creation of a local laboratory. The first, which he preferred, consisted in setting up a local vaccine production laboratory in India, for cultivating the seeds sent from Paris: “from France we could thus send to India the seeds required by the small laboratory mentioned above.” The Paris laboratory would also transfer the know-how by sending “An intelligent young man, familiar with chemical studies” for a short stay in India. Note that a visit of a few weeks would not be sufficient to learn the elementary rules of vaccine culture. The second option, which he refused, would consist in completely duplicating the Paris laboratory in India. He justified his refusal in terms of the cost of reproducing production standards: “I consider that this manner of proceeding would lead to very serious problems, as the control tests on herds and flocks take a very long time and are extremely costly, yet essential for establishing the virulence of the two vaccines” (ibid.). Reproducing biological standardization in India would be equivalent to wasting resources: “All this has already been done by my laboratory, and no longer has to be done in France ... I undertake to start at the same point for India, that is, with these same French vaccines” (ibid.). In this way the Paris laboratory retained its technical monopoly on attenuation methods, biological standards, and the origins and references of vaccines. Several laboratories were created abroad on this model (Chamberland 1887). For instance, the Budapest laboratory, created under the patronage of the Hungarian Ministry of Agriculture, received the vaccine spores from Paris and cultivated them. It relied on the Paris laboratory for any alterations to culture techniques.

The commercial policy for veterinarian vaccines was boosted in 1886 when new sources of funding were required to set up and finance the Pasteur Institute. Foreign accounts<sup>26</sup> for the years 1889 to 1892 inform us of the income of the Pasteur Institute in Austria-Hungary, Italy, and India. A private company was set up, the Société de Vulgarisation du Vaccin Charbonneux, to intensify the marketing of the anthrax vaccine and expand the market abroad via spin-off of local laboratories.<sup>27</sup> The preamble of the agreement noted that “Pasteur’s anthrax vaccine has until now received only one restricted application abroad due to the absence of any publicity and the problems involved in sending it to certain countries. In these conditions, it has been recognized that its popularization is not possible without setting up laboratories abroad.”

The contract signed in April 1886 between Chamberland’s laboratory and the Société de Vulgarisation du Vaccin Charbonneux, as well as the subsequent contracts signed from 1887 to 1896 between this company and local laboratories in Russia, Siam, and Australia, renewed the Paris laboratory’s monopoly on vaccine standards, while the local laboratories received the know-how for

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<sup>25</sup> This letter was reproduced in the Tignol 1886.

<sup>26</sup> Doc 10610, Pasteur Institute Archives.

<sup>27</sup> “Traité entre M. Chamberland et M de Sainte Marie en vue de la création de laboratoires du Vaccin Charbonneux Pasteur à l’étranger” (“Agreement between Mr Chamberland and Mr de Sainte Marie with a view to setting up a Pasteur anthrax vaccine laboratories abroad”). IP Direction DR DOS 1, Document 10 587.

cultivating the seeds that were sent to them.<sup>28</sup> The preamble of the 1886 agreement was clear on this point: “Mr de Ste Marie [*the agent of the monopoly*] proposed to Mr Chamberland to take charge of this creation provided that the chemists of the said laboratories were trained by him and remained under his technical supervision, and that the seeds and medium for preparing each vaccine were provided by Mr Pasteur’s laboratory in Paris.” The Paris laboratory demanded very strict technical management of the local laboratory, via the training of local technicians and the monitoring of their practices. “The chemist running each laboratory will be chosen by Mr de Ste Marie, but will be trained and taught by Mr Chamberland. He will be under Mr de Ste Marie’s supervision, but for all technical questions he will have to comply with the instructions of Mr Chamberland who will retain the right to demand his replacement should he fail to do so. Moreover, he will have to answer all Mr Chamberland’s technical questions.”<sup>29</sup> The strict technical control imposed on local laboratories was designed to align their culture practices with Pastorian standards. These contracts imposed Pasteur’s anthrax vaccine standards in several ways: via chemists’ training and Chamberland’s technical supervision, but also via the supply of seeds and culture medium from Paris. In this way, the standards were already embedded in the vaccines. The supply of calibrated vaccines in pure mediums ready for use reduced the risks of bad preparations. At the same time, this strong technical hierarchy between the central laboratory and local laboratories limited the possibilities of local inventions, especially vaccines better adapted to local breeds or to breeding conditions in other countries.

Significantly, Pasteur’s monopoly on the anthrax vaccine was in no way based on patents, which at the time were not allowed on remedies in France, including for veterinarian use (Cassier 2005). Although Pasteur patented many of his biotechnological processes applied to agriculture and the agri-food industry, he filed no patent claim on the methods for preparing his vaccines, contrary to the allegations of some of his contemporaries (Lutaud 1887). The Pastorians’ monopoly on the anthrax vaccine was based on the possession of vaccine strains, on their technical know-how protected by secrecy – “the details of production” referred to by Pasteur – and on contract law which protected Pasteur’s commercial name. The contract between Chamberland’s production laboratory and the Société de Vulgarisation du Vaccin Charbonneux Pasteur gave legal existence to the monopoly on the exploitation of the invention: “Mr. Chamberland grants Mr. De Sainte Marie the exclusive monopoly to create laboratories abroad (with the exception of France and its colonies) for the diffusion and exploitation of the anthrax vaccine under the name of ‘Laboratoire du vaccin charbonneux Pasteur’.” The various contracts signed between the Société de Vulgarisation du Vaccin Charbonneux and local laboratories in Russia, Australia, Cambodia, and India delimited exclusive territorial concessions in all these countries for the sale of the vaccine: “as from this day, Mr. Chamberland will no longer be able to sell the anthrax vaccine for his own profit in the countries in which the monopoly has been granted

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<sup>28</sup> Contracts were also signed with local laboratories in Austria-Hungary, Italy, and South America. For a detailed study of these contracts, see Cassier 2005.

<sup>29</sup> Article 3 of the agreement.

to Mr. De Sainte Marie”(Article 8). Use of the inventors’ names was clearly defined by the contract. Monopoly on the exploitation of the vaccine was based on the exclusive use of Pasteur’s name. The contract stipulated guarantees on the origin of the vaccines: “Mr. Chamberland undertakes to guarantee the origin and high quality of the vaccine sold under the name of Pasteur anthrax vaccine with the stamp indicating its origin”(article 5). The new company would be able to use the inventors’ names to mobilize capital, subject to the inventors’ prior approval: “There is to be no financial advertising for selling stocks bearing the names of Messrs. Pasteur, Chamberland and Roux without prior submittal to and approval by Mr. Chamberland” (Article 14).

### **3. Tensions over the Anthrax Vaccine Monopoly and Standards**

On two occasions tension arose between the private commercial company and Chamberland who was in charge of the vaccine production service in the new Pasteur Institute. Differences concerned the delimitation of the monopoly granted to the commercial company, which the company wanted to expand but which the Pasteur Institute wanted to restrict in order to control its business and profits from vaccines more directly.

In 1888 the Director of the Société de Vulgarisation du Vaccin Charbonneux proposed broadening the scope of its commercial monopoly. He wanted to capture the markets served directly by the Pasteur Laboratory, especially in France and its colonies. His justification was that it was necessary to clearly distinguish between philanthropy and business: “Do you not fear that the day the Institute trades its doses itself, the members think of demanding a substantial price cut on the grounds that the Institute can only have a philanthropic aim? And do you not think that the diffusion of the vaccine in agricultural practice will be slowed down by the powerless position in which the Institute will find itself to do its own advertising?” Total externalization of the commercial function made it possible to lift all ambiguity as to the not-for-profit nature of the Pasteur Institute which, in this new scheme, was entirely devoted to production and technology management: “The first result of this combination – the transfer of the French market to the Société de Vulgarisation – would be to ensure profits for the Institute without it being suspected of commercial speculation.” This type of functional restructuring between industry and trade favored the rationalization of the new Institute: “The vaccine service that was to be transferred to this new institution for the production of doses will have two different roles: producing the vaccine for export without directly exploiting it, and producing for France by directly exploiting it. It seems that the situation would be clearer and more favourable to the diffusion of the vaccine if the Institute were relieved of all commercial responsibilities and if the commercial side remained independent.”<sup>30</sup> During that period the new Pasteur Institute relied heavily on profits from vaccines to survive financially. As it turned out, the transfer of the French market was not accepted.

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<sup>30</sup> Letter from M. de Sainte Marie to M. C. Chamberland, 27 May 1888. Doc 10599.

Pasteur was also suspicious of the Société de Vulgarisation du Vaccin Charbonneux which delayed informing him of its income from the vaccine sold abroad. In June 1891 he asked his nephew Adrien Loir, then in Australia to promote the use of the anthrax vaccine, to inform him of the funds that he transferred to the company: “In a letter by you to your mother, dated 2 November 1890 and received on 28 December of the same year, you informed your parents that Mr de Sainte Marie received approximately 25,000 Francs for vaccinations that had already been performed. Today again, 15 June 1891, Mr de Sainte Marie mentions a sum of 5,000 Francs. He is clearly not up to date. Mr Chamberland must write to you about this and I would like you please, every time you send an account or money to Mr de Sainte Marie, to inform me of it by copying the letter.”<sup>31</sup>

In 1892 the Société de Vulgarisation was replaced by the Société du Vaccin Charbonneux Pasteur. New investors injected capital and requested a renegotiation of the contract concluded in 1886 by Mr de Sainte Marie. The commercial company wanted gradually to integrate vaccine production. Initially it envisaged the creation of a laboratory in Paris, responsible for cultivating spores provided by Pasteur (this would concern only the vaccine sent abroad, to countries without laboratories): “Mssrs Pasteur, Chamberland and Roux will be relieved of the production costs that they have carried until now, and will simply have to provide Paris with the spores.” In a second stage, it envisaged a total transfer of vaccine production know-how: “Mssrs Pasteur, Chamberland and Roux will, in a period of five years, starting in 1898, be able to relieve themselves of having to supply spores and instructing the assistant chemists, once they have transferred the know-how to the agent so that he can produce the spores himself and instruct the assistant chemists.”<sup>32</sup> The commercial company wanted to extend its monopoly and integrate production and sales into its organization, whereas the Pasteur Institute threatened to take back the sale of its vaccines if the company did not attain a minimum turnover. The new company was eventually set up but with half as much capital as planned, as the shareholders were wary of a “restrictive monopoly.”<sup>33</sup> Open conflict erupted in 1895 over the commercialization of anti-diphtheria serum by the Société du Vaccin Charbonneux. Chamberland had a lawyer issue a formal notice to the company, instructing it to change its letterhead which read: “Société du Vaccin Charbonneux Pasteur. Directeur Technique du laboratoire M. Chamberland. Vaccins Pasteur, marque depose. Sérum antidiphthérique” (literally: “Pasteur Anthrax Vaccin Company. Technical Director of the laboratory M. Chamberland. Pasteur vaccines, trade name. Anti-diphtheria serum”). Chamberland refused to accept the confusion between his name and the diphtheria serum.

This highly integrated and hierarchical system for the production and commercialization of the anthrax vaccine, which allowed for capturing the vaccine innovation rent and for strict control over production standards, generated a number of points of tension, especially in the 1890s and 1900s.

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<sup>31</sup> Letter from Pasteur to Adrien Loir dated 15 June 1891. Musée Pasteur, Museum collection.

<sup>32</sup> Amendment to the agreement between Mr de Sainte Marie and Mssrs Pasteur, Chamberland and Roux, 19 April 1886, 21 January 1892. Doc 10590.

<sup>33</sup> Letter by the Compagnie de Vulgarisation du Vaccin Charbonneux to Chamberland, 2 August 1892. Doc 10589.

The first point of tension stemmed from the persistent dilemma between the two options of either sending vaccines abroad or creating local laboratories. In 1902 this controversy arose again, relative to the ineffectiveness of Pasteur's vaccines used in Colombia, which a local veterinarian ascribed to "the crossing through the Tropics."<sup>34</sup> The veterinarian in question recommended the creation of a local laboratory: "There is no solution other than setting up a bacteriological laboratory for the production of fresh vaccines. It would be under the responsibility of a competent man, so that the vaccines were prepared as the owners needed them." The director of the Laboratoire des Vaccins Pasteur pour l'Etranger was hostile to this alternative: "The author strongly recommends preventive vaccination and repeats his idea of setting up a laboratory in his country. We have already heard this refrain."<sup>35</sup> He recommended the more flexible management of vaccine orders while recognizing the risks of alteration due to heat.<sup>36</sup> The fear of seeing the commercial monopoly eroded was evident while the problems of conservation of vaccines transported over long distances remained unsolved.

A second disagreement arose between the central laboratory and local laboratories on the subject of compliance with production standards and the quality of vaccines produced abroad. In 1896 the director of the Pasteur-Chamberland laboratory in Budapest again spoke about the culture processes that he applied and certain difficulties that he encountered. Remember that the Pasteur-Chamberland laboratory received vaccine seeds from Paris in accordance with the usual division of work: "The service functions in this way in Vienna, Austria-Hungary. Material is regularly sent and the cultures are done in the Vienna laboratory which every month receives seeds from the Pasteur Institute."<sup>37</sup> First point: the head of the Budapest laboratory refuted the explanation given by his Parisian correspondent on the subject of the quality of his culture mediums: "In the past few days I have corresponded with Mr Rebour on the subject of anthrax vaccine seeds and I am in possession of his letter of 3 June signed by you. Initially this answer surprised me greatly since I could not believe that there was any mistake regarding the mediums, for I produce them myself with great care, not wanting to entrust this to anyone as by experience I know that there is always an attempt to breach the instructions no matter how precise and formal they are." While exonerating the quality of his mediums, the laboratory director pointed out a local particularity: although Budapest received seeds from Paris, the laboratory produced its own mediums. This production attested to the know-how of the local chemist. The explanation also reveals a great deal regarding the application of the production

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<sup>34</sup> "How can the vaccine's preventive impotence be explained? We can assume that the vaccine is altered when going through tropical climates, due either to heat or to the interval between its production and its use." IP Direction, DR.DOS 1, document 10 606.

<sup>35</sup> Letter from G. Dayez, director of the Laboratoire des Vaccins Pasteur pour l'Etranger, to C. Chamberland, 5 November 1902. IP Direction, DR DOS 1, document 10603-10606.

<sup>36</sup> Throughout the first part of the century, the Pasteur Institute's anthrax vaccine service ran tests on the conservation of vaccines sent to distant countries. In 1922 the head of the tests noted: "it seems to me that the vaccines are losing their virulence, or even their stability, when they are sent far (South Africa, the colonies)." In 1923 the vaccine services tested vaccines which had been sent to Colombia and back. Institut Pasteur, Service du Vaccin charbonneux, Documents SVC, 1,2,3.

<sup>37</sup> Letter from Pasteur to a Mexican correspondent, 8 May 1889. Pasteur Institute, IP Direction, DR COR 1, document 27919.

guidelines distributed by Paris: local chemists were always susceptible to introducing variations in their implementation of the process. To overcome these difficulties, since the quality of the seeds and mediums did not seem to be the cause, the laboratory head examined the culture equipment, that is, the oven. Note here that the Parisian laboratory also normalized the use of culture equipment. Roux's notebook drafted in 1889 on anthrax vaccine seeds includes a description of Pasteur's oven "used abroad for the anthrax vaccine culture," as well as detailed instructions for use (assembling the apparatus, getting it going and running it).<sup>38</sup> The Budapest laboratory head made an improvement to this equipment: "I therefore looked elsewhere and think I have found the cause of the insufficient aeration and evacuation of gas from the oven. I am making some improvements which I hope will have a good result, and which I will immediately communicate." Hence, local production of the anthrax vaccine did not seem to pose major problems: "until now we have had no complaints about the anthrax vaccinations." There were nevertheless problems regarding the efficacy of the vaccine for swine erysipelas: "unfortunately the same cannot be said for erysipelas even though our cultures are superb, for there are no complaints about a lack of efficacy. We have had failures in many places, but few or no accidents." The local director proposed reverting to a former mode of culture but was waiting for the order from Paris to modify his practice: "faced with these failures which unfortunately occur among our best customers, we wonder whether the flask to flask cultures are not the cause of these successive failures and whether it would not be a good idea to revert to the former manner of proceeding. ... Either way, I will wait for your instructions before making the slightest change." Thus, Paris exercised strict technical control.

A third point of tension arose with the diffusion of Pasteur's anthrax vaccine in Australia. This vaccine was challenged there far more strongly until the ousting of the dual vaccination and Pasteur's commercial monopoly, consequent to the development of a local vaccine by two Australians, a breeder, John Alexander Gunn, and a biologist, John Mac Garvie Smith, who interacted directly with the Pastors (Todd 1990). In 1890, A. Loir set up a local laboratory financed by the government, where he cultivated seeds from Paris.<sup>39</sup> Local production and sale of the vaccine in Australia was under license from the Société de Vulgarisation du Vaccin Charbonneux pour l'Étranger, which had the monopoly on the Pasteur vaccine.<sup>40</sup> Pasteur's anthrax vaccine nevertheless proved to be ill-suited to local breeding conditions. In a well-documented report addressed to Chamberland in 1893,<sup>41</sup> Dr Momont, the Pasteur Institute representative, listed the specific characteristics of Australian extensive livestock farming, including the large size of farms and flocks, the long distances for sending vaccines,

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<sup>38</sup> "Vaccin Charbonneux. Semence et manipulation," Emile Roux, 1889, ROU 4, document 10611.

<sup>39</sup> "The 'foundation' for the vaccine is sent from France and will arrive once every three months or perhaps monthly. It comes in minute glass tubes hermetically sealed, which are placed in large tubes of glass .... The appliances are simple, but there are secrets in the cultivation of the vaccine which are not easily mastered. M. Loir informs us that it will be at all times necessary to obtain the supplies of vaccine, which we may term 'the foundation,' direct from France," Sydney Mail, 9 August 1890. Musée Pasteur, dossiers de collecte du Musée.

<sup>40</sup> Parliament of New South Wales, 25 June 1890. Musée Pasteur, dossiers de collecte du Musée.

<sup>41</sup> IP Direction DR DOS 1, document 10598.

and the fact that Pasteur vaccines were too expensive compared to the value of the animals. He concluded by requesting an adjustment of Pasteur's vaccine: "The practice of vaccinating livestock will spread very little, if at all, if particular measures are not taken in Australia. It is all the more indispensable since attempts have been made to try to obtain a colonial vaccine. The main argument for this attempt is the considerable reduction of the vaccine price." Most crucial was the wish to obtain a vaccine in a single dose rather than two successive vaccines applied at a 15-day interval by Pasteur's method. The cost of gathering and monitoring batches of sheep to vaccinate was far too high with two doses of vaccine, not to mention problems of transport: "Another cause for expenditures is the necessity of gathering the sheep twice for the second vaccination, since we are unable to keep them together in the interval between the two vaccinations." The creation of a single vaccination dose would require giving up the standard of two vaccines and undertaking in-depth research. Even though they were competent to implement such changes, Pasteur's local representatives lacked sufficient autonomy to innovate. They were limited both by the standard of two successive vaccines and by the monopoly of the *Compagnie de Vulgarisation du Vaccin Charbonneux Pasteur à l'Étranger*. Finally, it was two locals, a breeder and a biologist who had benefited from the knowledge transfer by the Pastorian with whom they had worked, who made this innovation. Their single vaccine soon took over and replaced that of Pasteur<sup>42</sup>.

## **Conclusion**

Standards and appropriation are fairly closely related. We have seen that initially Pasteur justified the refusal to transfer his production on the grounds that his method and products still lacked stability. The concern to control the quality of vaccines in a phase of emergence of standards justified the monopoly. Appropriation was then supported by the ownership of standards. The commercial monopoly that applied to the anthrax vaccine, via a system of contracts and licenses, was reinforced by the technical monopoly based on the exclusive competence of the central laboratory for preparation of vaccine seed. The concession contracts signed with local laboratories abroad established exclusive control of the Paris laboratory over technical standards. This system of ownership left little leeway for local laboratories, and was likely to be challenged by imitators or inventors able to create and impose a new product and production standard, as in the case of two Australians in the 1890s. Surprisingly, it was a breeder with no formal training in biology who initiated this process of moving away from the Pastorian standard. Hence, in this case it was the user who shifted the standard, aided by a renegade biologist from the Pasteur Institute of Australia. The monopoly, justified by commercial contracts concluded with private laboratories, was nevertheless not absolute. Pasteur and Roux authorized Gamaléia at the Odessa Institute to copy and transfer the technology for manufacturing the anthrax

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<sup>42</sup> This invention was recounted by Jan Todd, who noted that the preparation of a vaccine in a single dose necessitated very strict quality control procedures (Todd 1990).

vaccine and for routine vaccination (Gamaléia 1888). This transfer took place via the academic laboratory in the Rue d'Ulm, without passing through Chamberland's production laboratory.

This strict control over product characteristics via the distribution of seed offered a guarantee of quality and reduced the risks of faulty preparations. From this point of view, tight control of local laboratories producing anthrax vaccine contrasted with the very free distribution of the raw material and preparation methods of rabies vaccine to the rabies institutes created throughout the world. While the private status of the anthrax vaccine facilitated control over local production, the free status of the rabies vaccine made the task more difficult. Pasteur did send representatives to advise the local chemists who prepared the rabies vaccine, but these chemists noted differing practices and unequal quality of the vaccines produced. In September 1886 Perdrix, an assistant chemist at the Ecole Normale, was sent to Russia to advise several rabies laboratories being set up in Moscow and Saint Petersburg. His letters to Pasteur attested to the assistant chemists' lack of know-how and failure to apply the method for preparing spinal marrow from a rabid rabbit that they had been taught in Paris.<sup>43</sup> At the same time, the power of control of Pasteur's envoy was limited. He was sometimes refused access to the rabies vaccine preparation rooms and was unable to assert a right of control.<sup>44</sup> Although the rapid dissemination of the method for preparing the rabies vaccine was accompanied by lesser control over standardization, it favored local adjustments and innovative improvements. Innovations in the rabies vaccine preparation method were introduced in Poland by Bujwid, who changed the temperature for preparing spinal marrow (Bujwid 1889); in Russia by Gamaléia, who adapted spinal marrow preparation to the small size of Russian rabbits (Gamaléia 1887); and in Indochina by Calmette, who invented a new method for conserving the vaccine (Calmette 1891). Several rabies laboratories, spawned by the Pasteur laboratory's spin-off, developed their own research and frequently published in the *Annales de l'Institut Pasteur*. This dynamic was possible owing to the public good status of the Pasteur Institute's preparation method for rabies and the rabies virus, which were freely circulated in a potentially very open network of laboratories<sup>45</sup> – unlike the tightly controlled circulation of anthrax vaccine spores in the commercial network created in the early 1880s.

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<sup>43</sup> Letters written by Perdrix during his visit to Russia in 1886, Fonds Perdrix, Archives of the Pasteur Institute.

<sup>44</sup> Fond Léon Perdrix, PDR 1. Letter dated 6 September 1886.

<sup>45</sup> The expansion of the network of rabies institutes is highlighted in Barton 2006.



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