CONVERGENCIA
Revista de Ciencias Sociales

Construction processes of "worhormoning" of genetically modified animal organisms: the case of the cloned transgenic cow (Argentina 1996-2006)

Hernán Thomas
Universidad Nacional de Quilmes, Argentina / thomas@unq.edu.ar
Mariano Fressoli
Universidad Nacional de Quilmes, Argentina / mfressoli@unq.edu.ar
Diego Aguiar
Universidad Nacional de Quilmes, Argentina / daguiar@unq.edu.ar

Abstract: This work analyses the socio-technical trajectory of the construction of a genetically modified animal in Argentina. We aim to reconstruct the diverse working ways of a singular GMO animal: high vertebrates used as human protein factories for pharmaceutical purposes. The particularities of this case lead to the research of two entwined problems. In the first place, the study in-the-making of the construction's process of a technological artifact helps to show how "working" is built. In the second place, the analysis of the construction of the "working" of a GMO animal may get us some clues to understand how at the same time that "working" is constructed the relation nature-culture is re-constructed and re-defined.
Keywords: Working, socio-technical artifacts, constructivism, transgenic organism, nature/culture.

Resumen: Este trabajo realiza un análisis de la trayectoria sociotécnica de la construcción de un organismo animal genéticamente modificado en la Argentina. Para ello intentamos reconstruir las diversas formas de funcionamiento de un OAGM singular: animales superiores utilizados cómo productores de proteínas humanas de uso farmacéutico. Las particularidades de este caso llevan a la indagación de dos problemas entrelazados. En primer lugar, el estudio in the making del proceso de construcción de un artefacto tecnológico permite visualizar cómo se construye "funcionamiento". En segundo lugar, el análisis de la construcción del "funcionamiento" de un organismo genéticamente modificado nos da pistas para comprender de qué modo al mismo tiempo que se construye "funcionamiento", se reconstruye y redefine la relación entre naturaleza y cultura.
Palabras clave: Funcionamiento, artefactos sociotécnicos, constructivismo, organismos transgénicos, naturaleza/cultura.

ISSN 1405-1435, UAEM, Mexico, num. 42, September-December 2006, pp 140-168

1. Introduction[1]

In 1996, a group of researchers from an Argentinean enterprise, associated with research and development public centers, decided to begin the construction of a singular technological artifact: a genetically modified animal organism (GMAO) producer of human proteins, and the main means of production of the project "pharmaceutical cask".

At the beginning this artifact was visualized as a potential solution to the increment of the scale of recombinant drug production, to satisfy its increasing demand. During this development other problems were constructed, there were some contingencies and solutions were given, solutions that implied changes in the species of the organism to be created, of the protein to be produced and the kind of organization that will be requiring this artifact.

Although in 2002 the birth of a GMAO producer of a recombinant drug was announced, this fact did not constitute itself a definite solution to the problem proposed at the beginning. As a consequence of this development new problems have risen (regulatory, technical, cultural), that gradually modified the original form of the project. Due to these reasons this process is not stabilized. Notwithstanding these problems, for the members of the enterprise, it can be argued that the project "pharmaceutical cask" presents different forms of "working".

Differently form the studies that describe lineally the history of the technological artifacts (such as the process that goes from the conception, design selection, development and application); the in-the-making study allows observing simultaneous and divergent construction processes of its "working". Through this concept two problems can be avoided: on one hand, the notion of the working challenges the static character given to the technological artifacts. On the other hand, when admitting the possibility of several working ways, this notion allows decentralizing the object giving

[1] This work is part of a research done with the support from the National Agency of Scientific and Technologic Support (ANPCYT) and the National Council of Scientific and Technical Research (CONICET).

account for the different meanings that coexist ingrown in a technological Bijker, 1995) —in the field of the sociology of technology. It is worth mentioning, finally, the appearance of a research line based on the "technisation des connaissances" (Mignot and Poncet, 1998).

It is possible to detect a relatively reduced development of the topic by the Latin American authors. Already in the seventies, the matter was proposed in anti-ethical terms, in a context of a polemic that opposed "scientifists" with whom it was pleaded for a "science committed to the social needs (Varsavsky, 1969). Since then, there have been few researches —in the field of the sociology of the science in Latin America— that provide elements for the understanding of this tension. Only until recent times it is possible to register some of the studies directed to the construction of an interpretative agenda on the appropriateness and usefulness of the production of knowledge in the local context. Among these works some of the researches worth mentioning are: Vessuri (1993) in Venezuela; Cueto (1989) in Peru; Velho (1985), Velho and Dagnino (1998), and Dagnino and Thomas (1997, 1999) in Brazil; Charum and Prado (1995) in Colombia; Thomas (1995), Kreimer (1999), Kreimer and Thomas (2003, 2004), Vaccarezza (1990, 1994), Vaccarezza and Zabala (2002) in Argentina, and partially the articles published in the collective volume published by Gómez and Jaramillo (1997).

However, it is important to mention that in both the notions of *usefulness* and *appropriateness* have received more attention (in particular related to the production of scientific knowledge), few have been the sociological studies on the construction processes of the woeking of technology. It is possible to register only two lines on this sense.[2]

[2] Probably due to the scarce development reached by the social studies of technology in Latin America, there are practically no analyses on the working construction processes in the region. Only obliquely, some critics to the transference of technology —generated in the independentist matrix— address problems related to the no-working of technologies —developed in central countries— in peripheral contexts.

The first approximation, of a tentative character, is developed by Michael Mulkay (1979), who tries to analyze which is the relation between the validity of knowledge and the practical application. This requires the consideration of the way in which the scientific knowledge is re-elaborated according to the conditions of technical application in different social contexts and uses. Mulkay rejects the linear model that states that "the science develops knowledge, technology applies it". He acknowledges that it is possible and necessary to sociologically analyze the construction of the "working" of an artifact (as a meaning attributed by different actors), and he calls the attention of the scarce amount of studies that take this problem as an axis.

This is one of the starting points that integrate the second approximation to the notion of "working" made from the studies of Social Construction of the Technology (SCOT), developed by Trevor Pinch and Wiebe Bijker.

This theoretical approximation emerged as an extension of the social studies of the science (particularly, of the relativist program by Collins at Bath University) to the problems the analysis of technological artifacts presented, in this way inheriting their initial conceptual tools —relevant social groups, interpretative flexibility— (Pinch and Bijker, 1987). So, the study of the emergence of a technological artifact is achieved by means of the analysis of the social controversies from which this is established.

For the SCOT framework it is fundamental to provide an answer to the following questions: why a technological artifact is as it is and not differently? Why certain artifact becomes more successful than others? And what are the social and technical articulations that favor the success of an artifact over other artifact? (Bruun and Hukkinen, 2003).

The answers to these questions are looked for taking into account two basic relativist positionings. The first affirms that the technological artifacts are constructed as heterogeneous ensembles between social actors and artifacts. Therefore, it is not possible to consider the artifacts as merely technological (or the other way around, the social forms as purely social), but as the result of the dynamics of constitution processes of "socio-technical ensembles" (Bijker, 1995).

The second positioning parts from considering the form of an artifact or technology as contingent. This is; the design of the artifacts is built as the result of the disputes, pressures, negotiations and convergences that are forming the heterogeneous ensemble between actors and objects.

The contingence indicates at the same time the open character of the technological construction processes as the need of a relativist approach, because the socio-technical artifacts that are seen as successful by certain social groups can, at the same time, being considered as failures by other groups. Throughout their existence and, fundamentally, during their generation process, the different actors involved in the process give the artifact divergent meanings.

The concept "interpretative flexibility" allows deconstructing the oneness of the artifact, giving account of this diversity of sense assignations. So, the interpretative flexibility allows visualizing how the different social actors who participate in the construction propose problems and solutions that intervene on the very design of the artifact. As the actors agree on the meanings of the artifact, "stabilization degrees" of the artifact are generated. If, eventually, the consensus is generalized, a "closure" time takes place: of closing of the interpretative flexibilization process of the artifact's sense. When the closure and stabilization phenomenon is produced, there is a darkening of the facts that led to the final construction of the artifact and with it, of its contingence: the artifact becomes a "black box". Even if Bijker thinks that the interpretative flexibility of the artifacts is never definitively closed, he mentions that the process tends toward the irreversibility of the artifacts' form. The problematic effect of irreversibility is that it makes it difficult to "conceive the world as it was before the closure" (Bijker, 1995: 271).

For these authors the social construction of the "working machines" of an artifact appears, in this approach, as an extension of the Bloor's principle of symmetry:

> This is analogous to argue that "Nature" cannot play the role of *explanas*, in the sense stated by Bloor (1973, 1976) in his "strong program". "Nature"

> cannot be invoked to explain the truth of the scientific beliefs, nor the specific sociologic circumstances can be invoked exclusively to explain the falseness of the scientific beliefs. This "symmetry principle" strives for the impartiality regarding the truth or falseness of the scientific beliefs from the scientist who analyzes the scientific developments (Bijker, 1995: 75-76).

Through the concept of interpretative flexibility, Pinch and Bijker (1987) extend this principle to argument that the "working" or "non-working" of the machines should be analyzed symmetrically. The "working" of a machine should not be considered as the *explanas*, but as the *explnanadum*. "The working of a machine should not be considered as the cause of its success, but as the result of having been accepted by relevant social groups" (Bijker, 1995: 119).

Bijker (1995) explains that the "working" of the artifacts is not something given, "intrinsic to the artifact's characteristics", but it is a contingence that is socially and culturally constructed: "the success of an artifact is precisely that thing that needs to be explained. For a sociological theory it should not be the explanans, but the *explanandum*" (Pinch and Bijker, 1987: 24). The construction process of a "working" is the theoretical interest point of this work. The empirical base analysis of a construction process of a technological artifact in the making (in this case of a GMAO) allows observing the generation (conception, proposal, establishment of the problem-solution, negotiation) not of one, but of several simultaneous and divergent social meanings or forms of "working".

With this objective, the article analyzes the socio-technical trajectory of the "working" construction process of the "pharmaceutical cask" project and of its main means of production —a cloned transgenic cow—, developed by an Argentinean firm between 1996 and 2006.

A socio-technical trajectory (Thomas *et al.*, 2004) is a process of co-evolution of products, productive processes and organizations and institutions, user-producer and user-purveyor relations, learning processes, rationalities. Policies and strategies of an actor (signature, institution of I+D, universities, etc.), or similarly, of a determined technological framework (nuclear technology, siderurgy, etc.) (Bijker, 1995).

Taking as a starting point a socio-technical element in particular, for example a technology (artifact, process, a determined organization), a signature, an I+D group, this concept —of an absolutely diachronic nature— allows ordering causal relations among heterogeneous elements in temporal sequences. So, the concept results particularly adequate to analyze construction sequences of problem-solution relations and "working" construction process of an artifact or of a technology.

3) The selected case: the "pharmaceutical cask" project

The selected case for the analysis constitutes a relevant experience of technological development: the area of pharmaceutical biotechnology. The construction company of the analyzed artifact is a family business of Argentinean capitals. It began operating in 1980 as the Biotechnological Area of a pharmaceutical group, then in 1983 it became independent within the group.

In 1990 the company launched to the market it first biotechnological generic product: recombinant erythropoietin, which was soon followed by other six recombinant generic molecules commercialized in national and international markets. From the late 1990's, the company started its consolidation and diversification phase when facing new projects (research in genic therapies, development of products and new ways of producing recombinant drugs).

Currently, the company employs about 360 people, from which 30% are professional researchers. The annual invoicing is of about 24 million dollars and the investment in I+D reached, in 2005, something close to two million dollars.

Company's invoicing and I+D expenses			
	Year 2003	Year 2004	Year 2005
Annual invoicing in USD	19.778.031	22.046.927	23.918.092
Expense in I+D in USD	1.625.355	1.993.292	2.093.173
Percentage	8.22	9.04	8.75

Source: Company's Administration Management.

The enterprise occupies a significant position in the local biotechnological sector. According to recent data, in Argentina the total sales of the biotechnological companies of the Health Sector for year 2002/2003 added approximately 36 million dollars, and the expenses in I+D in the sector reached 5.5 million dollars. In this way, the expense in I+D of the enterprise during 2003 constituted 30% of the total invested by the sector (Bisang *et al.*, 2005).[3]

Along with enterprises as GTC Biotherapeuthics, this company is one of the few pharmaceutical in the world that has begun the processes of increment of the recombinant molecules production scale by means of cloning and transgenesis of superior animal organisms.

4) Construction process of "working" of a GMAO.

First phase: the construction of a problem

In the middle nineties, the company started to align three different facts to establish the coordinates of a new development strategy. These were: the foreseen fall of the main recombinant drugs patents, the difficulty to increase the capacity of production of such proteins with the traditional systems, and the intention of learning and acquiring abilities on new technologies.

Perception of the market of biogenerics

From 2006 the patent of eleven recombinant drugs would expire, whose annual sale volume worldwide is about thirteen billion dollars (Nieminen and Nordström, 2004). Some of these drugs, such as the Interferon alpha 2b, the Filgrastim, the erythropoietin of the Human Growth Hormone were already produced by the company. There are still several quarrels on the way the biogeneric's market will take, and its characteristics are still uncertain (Chamberlain, 2004). Despite that, given the sales volume of these drugs, the opportunity of competing in this market is tempting if the products were obtained at competitive prices. However, the new production strategy had to be made.

[3] Although according to complementary calculations, the investment of the company is lower than the average expense in I+D of the sector, which would reach 15.5%.

Increment of the production scale

In this context, one of the most difficult problems is the construction of mechanisms to increase the production scale of the recombinant molecules. The cellular or bacterial culture plants face several problems, for example: intensive automation requirements and high production costs and very specific consumables. In the central countries it is calculated that the cost of the construction of a new cellular culture production plant of 10 thousand litters was between 250 and 500 million dollars, not taking into account the construction and approval times that could take up to five years (Dyck *et al*., 2003). Minding this fact, the chairs of the company decided to face a risky and relatively unusual project, the construction of genetically modified animals as producers of human proteins.

Acquisition of new technologies

Lastly, other strategic matters taken into account by the heads and researchers of the company was the desire of acquiring knowledge and abilities in the handling of transgenic technologies in animals, as one of the company's managers states:

> Honestly at the beginning [the project] was about curiosity, […] when there is good technology and one knows people who are working on that, you want to get that technology although there is not a very clear initial objective.

Here the challenge and the opportunity were fit together in the new technology with the desire of solving problems. For the company's researchers, the existence of technical-cognitive challenge was imposed, at the beginning, regarding the effective usefulness of the project.

The construction of a problem

At this phase the heads and researchers from the company start to build a problem: to compete in the biogeneric market increasing their production scale available and at the same time reducing the costs of the bacterial or cellular culture systems. Seeing this problem, an unusual solution strategy

is created: the construction of a GMAO as producer bioreactors of recombinant human proteins. This strategy is the first notion of the working that, in general, is maintained throughout the artifact's trajectory, further the changes in the problem's forms, its reach, the form of the artifact and of the very actors that constructed it. Due to the difficulties this solution presented, such strategy of increment of the scale was considered only by a handful of companies around the world. The analyzed company was the only case known in Latin America.

Second phase: toward a bioreactor producer of human proteins. Socio-technical limitations of the first form of the project. Creation of new problems.

In 1996, the company signed a series of agreements with public institutions of research (mainly with the University of Buenos Aires [UBA], specially with the Institute of Research on Genetics and Molecular Biology [INGEBI] and the National Council of Scientific and Technical Research [CONICET]), in order to begin the development of a new bioreactor. The strategy of association with other companies or public institutions for I+D is much extended in the biotechnological sector (Rabinow, 1996; Fransman, 2001).

In such case, the researchers of the company did not have many of the knowledge and equipment necessary to face this kind of development. So, at this phase it was necessary to form an I+D group where a total of twelve groups, between public, external private and from the company took part. The coordination of the project was shared by the company and one of the public institutions, whereas the technological liaison of the UBA (UBATEC) was in charge of the administration; the project's financing was done by means of a credit of approximately one million dollars from the Ministry of Science and Technology (SECYT) and from the CONICET. At the beginning, the intention of the project was to obtain transgenic cows and goats for the production of human proteins: the (human plasminogen tissue activator: htPA). This protein was not among the molecules previously produced by the company.

Given the diversity of disciplines involved (veterinary, embryology, biotechnology) and the different institutional adscription of the researchers,

the project needed precise attention and coordination among the different work groups. One part of the public research teams were located in what Shinn (2000) calls knowledge production disciplinary regimen, with which they paid more attention to the publishing and prestige requirements of their field than to the work's characteristics directed toward a project, characteristic of a transversal regimen. The clash of two differential production regimens was an obstacle in the required coordination for the "working" of the development.

Micro-injection technique

In order to generate the transgenic embryo the recombinant DNA micro-injection technique was used. This technique consists in the injection of a solution containing coding DNA for the selected protein in the pronucleolus of a fertilized ovocyte. The same technique was successfully used in mice in 1980, and from this it was possible to create transgenic goats, pigs, sheep and cows (Brink *et al*., 2000). However, such technique presents some drawbacks, among which we can mention the low transgenic birth rate: less than 5% for goats, sheep and cows (Brink *et al*., 2000: 141).

Negative conjunction of technical and social facts. Construction of the project's "no-working"

During this period the company came across several difficulties. The limitations of the micro-injection were negatively combined with organizational problems, as well as differences in the research criteria among the company's and some of the public institutions' work teams. As a consequence, the results during this phase were discouraging: transgenic mice were produced but they were not successful in the case of the goats and cows. Due to these drawbacks and to the lack of results, in 1998, the company's t manager and the chairman decided to cancel the project early, even when almost 80% of the funds for its development were already given. The company's executive criterion was that under this socio-technical articulation (low efficiency of the recombinant micro-injection and the lack of coordination among the research teams) the strategy to solve the problem produced the "no-working" of the "pharmaceutical cask".

At this point, a new problem was created by the company's researchers: the need of proposing a new solution strategy that linked different biotechnological techniques with a new organizational form.

Third phase: new solution strategies. Redefinition of the artifact and of the socio-technical strategy, new problems

By March 2000, after a year and a half the project "pharmaceutical cask" was suspended, the company's executives decided to re-start the generation of GMAOs, but this time doing some modifications that can be qualified as socio-technically significant. Partly, this change is related to radical changes in the biotechnology scenario due to the first adult superior animal cloning from somatic cells (Kolata, 1998).

Although at the beginning there were some doubts about the possibility of repeating this experience, for the members of the company, this fact revitalized the intentions of constructining an animal bioreactor and the negotiations to restart the project began, using now the recent technique of nuclear transference. It was necessary, once more, to obtain capacities and materials the company did not have at hand, for that, an Argentinean living abroad was contacted, this person has vast experience in cloning and it was decided to invest in equipment for its development.

Cloning and transgenesis

In the cloning of superior animals the technique of nuclear transference is used as methodology. This technique consists in the introduction of a nucleus of non-differentiated fetal cells in the non-fertilized enucleated ovule of a donor animal. After this is activated by an electric pulse and maintained cultured by a short period of time, the produced embryo is later transferred to a receptor animal until it is delivered.

In contradistinction of the micro-injection technique, the nuclear transference technique allows "selecting and expanding the characterized cells as transgenic, previous to the generation of transferable embryos", reducing the birth rate of non-transgenic animals (Brink *et al.*, 2000: 143-144). One of the decisive points of the cloning process is the preparation of the donor cells so that these enter in a *G0* state, which modifies its

growth and allows the synchronization between the donor nucleus and the receptor cell.

To this new technique were added the technical-cognitive capabilities available in the company such as the ones referred to identification, isolation and transfection of genes, that were already being used in the making of the company's drugs. Besides that, a new cloning laboratory was created for which new equipment for the micro-manipulation of embryos, as well as culture stoves and others were acquired. At the same time an information gathering on the cares for cloned animals began; mainly from specialized journals.

Lastly, a complete field operating theatre was built adapting elements (sterility of the theatre and the floor, illumination of the place, pulleys for animal handling, breathing intubations instruments, etc.) destined to the special care needed at the birth of cloned animals.

New organizational form: cooptation of *in-house* resources and production

At the same time it was decided to concentrate the direction of the research team in one member of the company: the development manager, who was in charge of the coordination of the whole program. This executive decided to hire part of the personnel from the public research centers that had participated in the previous phase of the development. In this way the company ensured the control of most of the project's phases; areas such as cloning and veterinary tasks rendered account directly to the company's executives.

At the beginning of this phase of the project, the research teams began to develop simultaneously the cloning of goats and cows. The first cloning attempt was done on cows and resulted in the birth of a dead animal on January 28th, 2002. Although this fact cannot be totally considered as successful it demonstrated the "working" of a significant part of the project: the technical capabilities acquired in cloning and the feasibility of doing it on bovines. Added to this it was considered the higher availability and cognitive capacities on this species (veterinary, embryology, artificial insemination) over caprines. As a consequence it was decided to discard the cloning of the latter and continue with the construction of transgenic

cows.

At this point, the company decided to change the protein they intended to produce through the animal bioreactor. Whereas in the first phase it was tried to produce htPA (human plasminogen tissue activator), during this phase it was decided to produce the human growth hormone (hGH).

Among the reasons for this change we can mention the need of the researchers to reduce the project's risk level. Whereas choosing the htPA implied the incorporation of a new product for the company, at the same time it was necessary to develop identification, isolation and genes transfixion, as well as the purification method. Conversely, the hGH was a molecule that had already being produced by the company, and the processes for its recombinant expression in bacteria and its latter purification.

By October 2002, two months after the birth of the first cloned calf, there were four cloned calves. Three of them are transgenic, carriers of the gene that expressed the hGH. A year later, the company announced that one of the transgenic calves had started to produce milk containing the hGH.

Positive conjunction of the social and technical facts. First form of "working" of the GMAO at a pilot scale

During this phase there were some changes in the construction of the "pharmaceutical cask" project regarding the previous socio-technical configuration.

There were simultaneous organizational and technical modifications. It was decided to concentrate the coordination of the resources on the company's chairs. At the same time, the human resources from the research institutes that participated in the first phase were co-opted and strong investment on instrumental and infrastructure was done in order to be able to house the research within the company's premises.

The company reused the genetic engineering capabilities and, at the same time, it incorporated technicians capable of handling new cloning, neonatology and veterinary techniques.

The new cloning technique improved considerable the efficiency of the

transgenesis process in comparison to the micro-injection technique. However, its availability does not explain by itself the birth of the cloned calves. In its articulation with a new organization of a socio-technical network under the direct coordination of the company, which shape the conditions of the projects "working".

In this way, the transgenic clones constitute a singular artifact, the transgenic cows that are presented as the first "solution" to the problem proposed in the first stage: the need of competing in the biogeneric market with "production platforms" of more efficient and less expensive proteins than the traditional ones. In this process some decisions that importantly modified the first drafts of the problem were made: from transgenic goats it was moved to the construction of transgenic bovines, at the same time the kind of drug was also changed, from htPA to hGH. Simultaneously it was changed from an organizational model that privileged the "hybrid institutions" (Fransman, 2001) to the strong projects management that co-opted resources, imposed development times and promoted the *in-house* production.

All these modifications implied a reassigning of the problem-solution relation, of the proposed strategies and of the ways of constructing the "working", but also of the actors that participated in the project, of the techniques and equipments used, and also of the way these were shipped.

Differently from the second phase, these re-significations resulted in a decrement of the "interpretative flexibility" as well as of the construction of the "working" of the "pharmaceutical cask". Once the "pharmaceutical cask" started "working" at pilot scale, the company started changing the scale. With this, new problems arose, but also what the company called "working" started to extend and become more complex.

Yet, far from being shut down, the project's "working" still faced other technical and social challenges that created new problems, other solution strategies and, eventually, new "working" forms.

Fourth phase: from the pilot scale to the productive. Constructing the "working" further the laboratory

The birth of the first cloned and transgenic animal, and the testing in October 2003 of the expression of the protein in the milk of one of the calves made possible the extension and diversification of the projects reaches. During this phase the project's problems changed, from the pilot to the productive scale, but also the actors were added and its complexity increased.

Increasing the project's scale

During these phases the production of transgenic clones continued until having approximately twelve of animals capable of producing the hGH in their milk; one part of the animals was obtained through the cloning of clones. Acquiring a transgenic bull was also proposed in order to continue increasing the transgenic herd by means of sexual reproduction. In this way, the project's researchers intend to sustain their production line of transgenic calves avoiding the expensive technical cloning and transgenesis process. The birth of the first male transgenic calf was announced in December 2004.

As the project was consolidated, some measures were taken to construct their "working" at a productive scale. It was invested on equipment and safety personnel for the premises. An animal circulation control mechanism was set up in order to separate the clones and the receptor cows from the transgenic animals, of which complete clinic records were made and were established controls and a specific diet in charge of a group of veterinaries who, in shifts, are 24 hours a day there. Lastly, the arrangements to obtain four patents on the processes for the production of transgenic animals, and the production and purification of the proteins obtained from the milk of transgenic cows process.

Once the herd of cows producers of hGH was obtained, it was decided to use the idle capacity of the work team to start working on the construction of GMAO producers of other recombinant proteins.

The emerging of new actors and problems. The regulatory problem

Other of the problems the company had to face is related to the absence of established regulations, for both the creation of GMAO as well as on the possibility of producing recombinant medicines in animal bioreactors. This legal gap facilitated a smooth interaction between the company's members and the personnel from the regulatory organisms. In Argentina, for the case of the "pharmaceutical cask", the regulations are divided between the approval of drugs phase and pharmaceutical processes, from the National Administration of Medicines, Food and Medical Technology (ANMAT) and the phase of approval of genetically modified organisms and their liberation in the wild, that corresponds to the Argentinean Advisory Commission of Agricultural Biotechnology (CONABIA).

The world legislation on pharmaceutical products did not have until recently any witness case of production of medicines from animal bioreactors (Larrick and Thomas, 2001; Dyck *et al.*, 2003). One of the main drawbacks for its approval had been the possibility of infections by unknown viruses or diseases such as the "mad cow" disease. Recently the European Medicines Agency (EMEA) approved the commercialization of the drug "Atryn" produced in transgenic goats by the company GTC Biotherapeutics.

In the case of the norms on liberation of the animals in the field, the company collaborates with the Argentinean Advisory Commission of Agricultural Biotechnology (CONABIA) in the elaboration of the regulations. In the case of the "pharmaceutical cask", the approval of the ruling that regulates the requirements for GMAO projects was done in July 2003, after the birth of the first GMAO. The approval of the liberation of the animals was obtained in December 2005. The lack of experience in the country regarding the care of transgenic animals and the little experiences known on the field have led to the continuous negotiations of the sanitary measurements between the CONABIA staff and the company's personnel.

Nonetheless, there are still open issues in Argentina that prevent the artifact's closing. These are related to the lack of legal definitive approval of the GMAO generated.

The "working" complexization

At this phase there can be seen several processes that diversify the productive reach of the "pharmaceutical cask" of the GMAO. The change to a productive scale presents new interpretation problems and operative differences. This represents a complexization of the production process of the "working" that modified the socio-technical ensemble. The change of the project's scale increased the interdisciplinary dialogue inside and outside the company, as new actors and disciplines were integrated. This passage cannot be considered simply as a diffusion of the artifact, but it implies a real re-signification process (of the artifact and the actors involved) from the laboratory to the productive scale.

The co-construction of control processes with the regulatory organisms, the attainment of patents, the security and the health of the bioreactor, etc., are elements that reinforce and extend the "working" of the "pharmaceutical cask", even when the GMAO is not legally approved.

In this sense, it is necessary to ask if the absence of legal closure means that the artifact is not working appropriately, or it does not do it for other actors (ANMAT). But answering in an affirmative way to this question implies considering only one way of "working", among the numerous the company is constructing. The "pharmaceutical cask" changed from being an hGH production system to be thought of as a bioreactor capable of producing several proteins. At the same time, it is considered as a way of acquiring knowledge and abilities on new technological processes (and their property under the shape of patents), which can be negotiated with other companies. In this sense, the analyzed artifact supports several forms of "working".

In the following section we will consider in which way the company constructs, from the same artifact, other forms of "working".

5) Other forms of "working". Construction of prestige, biotechnology resignification

There are two other construction forms of the "working" of the "pharmaceutical cask" that are closely related to the company's strategy.

This strategy is based on the scientific divulgation of the construction of cloned calves. The stake is double: on one hand, when exhibiting the development of the "pharmaceutical cask", the company's executives simultaneously build capital based on their technological capacities in the sense used by Callon (2006); this is, not only as the generation of a stock of prestige and capacities, but rather as a mobilization and incorporation of interests strategy to include new actors.

It is essential to mention the importance of this point. Although the "pharmaceutical cask" literally is not in conditions to produce commercial products due to the lack of legal approval of the production system, the members of the company consider that it does work in other senses. In such a case, the generation of prestige is a keystone, as it is the accumulation of scientific-technical capacities, capable of becoming re-used in other contexts.

On the other hand, this divulgation strategy also constructs information on the definition of biotechnology and transgenics, contributing to the social acceptance of the total product.

The divulgation of the "pharmaceutical cask" was posted in different spaces. On the one hand, the company did, through some of their researchers, informative talks on the "pharmaceutical cask" directed to the scientific as well as to the education institutions or general public. In some cases, these talks were organized along with the commercial representatives of the company, mainly to the interior of the country.

At the same time, the case of the transgenic cow and its different phases have been referred to constantly in the main written media of the country: Clarín, La Nación. In this way, the "Pharmaceutical cask" project researchers and executives have been able to place the company as an outstanding example of the national biotechnological (scientific-technological) capacity (Vitagliano and Villapando, 2003).

Lastly, the company has edited three divulgation videos, among which is; "*A brief introduction to biotechnology*" and an informative video on the project. In these works two differentiated works coexist. On the one hand, the information on the development of a transgenic cow focuses on the

generation of a more efficient mechanism for the production of recombinant proteins. On the other hand, in the *Brief introduction to biotechnology*, the company presents a complex metaphor of the science and the relation between nature and culture. This reads:

- All living organisms share a genetic code,
- Men have intervened uninterruptedly in the nature's evolution process, even not knowing the notion or "working" of the genes.
- Through the creation of the molecular biology nature can be rationally intervened.
- The genetically modified organisms are programmed, their information is faithfully transmitted and with no errors.

In this way, the construction of the "functioning" of the "pharmaceutical cask" also becomes a resignification of the biotechnology for the researchers. With this, the "evolution" continuity of the genetic engineering techniques is "naturalized" (Franklin, 2003) with the traditional processes of variation's selection. In these practices —in the discursive as well as in the bio-technological— what is understood as "nature" and "living organisms" is reconfigured (Landecker, 2005). For the integrants of the project the construction of the "working" of the "pharmaceutical cask" project also implies "naturalize" the constructed GMAO and the new ways of intervening in the nature-culture relation.

6) Conclusions

About the GMAO construction processes

The construction of the "working" of a GMAO is a complex and open process where can intervene different actors and disciplines. The analysis of the different phases of this proves has been focused on understanding how the construction of the "working" of the "pharmaceutical cask" project varies according to the artifact's design, to the techniques used in its construction, to the actors involved in the construction of the problem and to the solution strategies. The different configurations of this "socio-technical ensemble" can lead to the constitution of the "no-working" of

the artifact (as in the second phase), or to the "successful" development of the "working" produced in the third phase.

The construction of GMAOs is a co-evolutional socio-technical process that requires the alignment and coordination —handling— of a heterogeneous multiplicity of elements, from cognitive, economic and organizational resources to living beings and, even the very construction of "the natural" to work.

Even if this process of construction of the "working" is clearly perceptible in the macro-social context: in the regulatory debates or in the bio-ethical controversies, the analyzed case allows observing the materiality of the resignifications and manipulations of the sense at the level of a GMOs producing company. On the other hand, it allows overcoming the binary opposition to reveal multiple sequences of the construction of significants, "working" and viability of the developed bio-technologies.

The construction of the "working" of a GMAO is a continuous process that, even if it seems that it centered on the artifact, it also needs resignifications and translations and "naturalization" processes. So, the divulgation tasks of the project's researchers also constituted other form of constructing "working".

Most of the problem-solving strategies if constructing "working" can be re-read from this resignification process. That is why the daily testing of the animals' health and the change of the reproduction of the transgenic cows —from cloning to sexual reproduction— are also a "naturalization" of the GMAO.

The construction process of the "working" of a GMAO implies "deconstructing and reconstructing" the discourses and practices related to nature / culture. It would be naïve to affirm that the modification of the relation between nature and culture is produced directly and exclusively through the introduction of a technique or the modification of an organism. The construction of artifacts that manipulate and transform the biologic not only modifies nature, but it needs resignification and social translation processes that "naturalize" the technological intervention at the same time that construct and normalize new forms of "working".

About the concept of "working"

The analysis of artifacts that are still under construction, where the artifacts and technologies have not being closed down semiotically yet, still allows perceiving effects and practices of designs and materials the actors construct as different forms of "working".

From the exercise performed, there is a new perception of the analytical-explicative potential of the concept. The notion of "working", dynamics, continuous and plural, implies descriptive explicative advantages over the more static and discontinuous of "closure". Even the idea of "re-aperture of the closing process" of the interpretative flexibility considered by Bijker implies the existence of a "stop and go" dynamic that, even if it is possible to detect in some socio-technical trajectories, is not generalizable to the series of technologies or as consensual as appears in the "closed down and stabilized" black boxes. In fact, it could even be proposed that the notion of closure implies an "automatization" of the artifact, incoherent with the orientation of the constructivist approach, or, in other words studied in matters of "working", even the processes of apparent "closure" seem as active dynamics, in constant change, negotiation and problematization. It only depends on the level and reach the analysis (macro, meso, micro) is deployed.

From this perspective, it is appropriate to differentiate the concepts of closure and stabilization. Whereas "closure" is a static moment, a stop of the interpretative flexibility process time generated by an "observation effect" from the analyst, "stabilization" is one of the dynamic names of the socio-technically constructed "working".

The notion of "working" does not imply, as that of "closure", the necessary convergence of the meanings adjudged by different relevant social groups. Obviously, it is possible to detect negotiations of sense in the "working" construction process, but this does not imply the homogeneous uniqueness of the process' result, as the concept of "closure" tends to imply. In fact, the plurality of senses adjudged can be maintained even after the "working" has been stabilized.

In a methodological sense, it is still possible to deconstruct the uniqueness of the meaning in one relevant social group, both in the time as in the plurality of the senses assigned to the artifact by the same actor. Or, in other words, as in Bijker one meaning/"working" —monolithically— corresponds to every relevant social group, it is possible to reconstruct analytically the different sense assignments that the same actor can perform, considered from the perspective of the subjects that constitute it. So, it is possible to give account of the diversity of forms of "working" (for example: economic, productive, cognitive, ethical, cultural) the same actor is capable of constructing.

The concept of "working" holds the theoretical advantages of the artifacts' interpretative flexibility phase, at the same time that avoids being trapped by the look that privileges the artifacts' semiotic "closure". When talking about "working" it is possible to analyze the modification and redefinitions introduced in the artifact and in the co-evolutionary process of actors and objects that constitute it. Besides, it is possible to detect other forms of "working" that are superposed and coexist with the "working" projected in the first place.

Finally, in this work we have tried to show that the "functioning" of a socio-technical artifact is a process of continuous construction, deployed from the very beginning of its conception and design. And that even after a certain degree of "stabilization", there are adjustments and modifications happening that construct new and different forms of "working".

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Hernán Eduardo Thomas. Professional researcher —CONICET. Titular professor of the National University Quilmes (Research and Studies Centre - Institute of Social Studies of Science and Technology). His research lines are: sociology of technology, economy of the technological change, scientific and technological politics. His most recent publications are: along with some other authors, *Producción y uso social de conocimientos. Estudios sociales de la ciencia y la tecnología en América Latina*, UNQ, Bernal, 2004; with Gianella, C., *Insumos para una planificación estratégica de políticas públicas de ciencia, tecnología, innovación y educación superior*, Buenos Aires: UNSAM, 2005; with some other authors "Por uma política de ciência e tecnología de esquerda", in *Alternativas* (series Espacio Pedagógico), año 8, num 32, 2004.

Juan Mariano Fressoli. MA in Cultural Studies, University of London. Institute of Studies on Science and Technology, University of Quilmes. His research lines are: sociology of technology, economy of the technological change, vitalism. His most recent publications are: "Vitalismo y No-linealidad. Scott Lash y el regreso de la Lebenssoziologie", in *Revista Espacios*, num 29, Universidad Nacional de la Patagonia Austral, Río Gallegos, Argentina, 2005; "La ciudad y el recorrido del secreto", in Vernik, Esteban [comp.], *Escritos contra la cosificación. Acerca de Georg Simmel*, Buenos Aires: Altamira, 2000.

Diego Aguiar. B. Sc in Sociology, National University of la Plata, Institute of Studies on Science and Technology. His research lines are: sociology of technology and economy of the technological change. His most recent publications are: along with other authors "Estudio sobre los ingresantes a la carrera de sociología 2004. Caracterización del perfil socio-cultural de los ingresantes y su evolución en los últimos años", in *Revista*

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Sent to dictum: August 17th, 2006.

Approval: September 17th, 2006.