How Can a Biotech Tool Reveal what's Going on under the Surface of Three Hyped Biotech Regions? The Embedding of ÄKTApilot in the US, China and Taiwan

Enrico Baraldi, Åse Linné, Tommy Shih, Alexandra Waluszewski

Enrico Baraldi
Department of Business Studies and Uppsala STS, Uppsala University, Sweden
E-mail: Enrico.Baraldi@fek.uu.se

Åse Linné
Department of Business Studies, Uppsala University, Sweden
E-mail: Ase.Linne@fek.uu.se

Tommy Shih
Department of Business Studies, Uppsala University, Sweden
E-mail: Tommy.Shih@fek.uu.se

Alexandra Waluszewski
Uppsala STS, Centre for Science and Technology Studies, Uppsala University, Sweden
E-mail: Alexandra.Waluszewski@sts.uu.se

Abstract

What can a biotech tool, ÄKTApilot™, supplied by GE Healthcare Uppsala, tell us about its users and use context? And what can the embedding of this biotech device in three substantially different use contexts, the US, China and Taiwan, tell us about how a science-related resource gets an economic value? Whereas many studies of biotech are concerned with the *provision* of science, this paper focuses on the *utilization* of science-related resources. We investigate how the focal biotech tool is embedded in three use contexts in order to shed light on what goes on under the surface of these hyped biotech regions. The utilization of ÄKTApilot is in fact an indicator of the state of advancement in pharmaceutical R&D. We start from the resource interfaces that embed this biotech tool within a *micro-context* of use, but we also investigate systematically the traces and the effects in such micro-interactions of the broader *macro-context*. Because of different interplays between micro-interactions and macro factors, ÄKTApilot has been embedded very differently in the three countries: it is most strongly embedded in the US context, but much less so in the Chinese and especially the Taiwanese context. We finally discuss the possibility to apply policy recipes in order to create an "instant industrialisation", i.e. to speed up not only the supply, but also the *utilization* of science-related resources. However, the importance of micro-interactions in creating value from science suggests the inherent limits of much managerial and policy wisdom.

Keywords: biotech, resource utilization, embedding, micro-interactions, macro-context.

Can a biotech tool indicate what's going on in different use contexts?

What can a biotech tool, ÄKTApilot™, tell us about its users and use context? What can the embedding of this biotech device in three different user contexts, the US, China/Shanghai and Taiwan, tell us about how a science-related resource gets an economic value? What interfaces in the micro- and macro-context are involved in this process? These challenging questions are the focus of this paper and these issues are consequently investigated from a user perspective on *resource utilisation*.

Why choosing ÄKTApilot, a *protein separation* tool utilized in the development of biotech drugs, as focal resource for this investigation? ÄKTApilot is quite special, because it is capable of working at a scale between the typical *research lab* and the *production plant*. Therefore ÄKTApilot enters into use only when a protein development project has passed through the early phase of drug discovery and has entered preclinical stages. ÄKTApilot is used then in the downstream steps leading to large-scale manufacturing. After the chemical composition of a protein and the genetic profile of the engineered cells that will produce it have been defined, *protein separation labs* take over a drug project to identify the adequate process[1] for isolating the target substance from a soup including contaminants such as dead cell walls (see for an overview Fox Keller, 2000: 46-66, and Grace, 1997: 31-49). The role of ÄKTApilot is to marginally modify and tune the separation methods for being applied on larger machines. Thus, ÄKTApilot is employed for making the lab-scale technique transferable to a full industrial setting. The embedding of ÄKTApilot in a user context can thus work as an indicator of the users' engagement in *downstream* drug development and commercialization.

The firm producing and selling ÄKTApilot is GE Healthcare Uppsala (formerly Amersham Biosciences, formerly Pharmacia Biotech[2]), a worldwide leader in protein separation technology, with deep historical roots in the *chromatography* technique, dating back to the 1950s and the first ever separation gels developed by the Institute of Biochemistry at Uppsala University and by the pharmaceutical firm Pharmacia (Janson, 1987, Andersson, 1996, and Waluszewski, 2004). Stand-alone parts were increasingly integrated into more complex separation equipment, culminating in the 1980s with the launch of the first fully integrated and computerized separation systems (Andersson, 1996: 247-293).

GE's separation tools cover both manufacturing and lab-scale separation needs. For lab scale applications, GE Healthcare Uppsala developed in the last 20 years the ÄKTA™ platform, composed of a dozen tools of varying size and flow-rate capacity. But until the early 2000s, GE had no chromatography system that could link the gap between laboratory work and the manufacturing process: to fill this gap it was necessary a tool that could easily shift between a wide range of flow-rates (from 4 to 400 ml/min) and respect the stringent *sanitary requirements* for actual pharmaceutical production. The step from lab-scale to process-scale is a big one in a drug R&D project, and it is essential to test the production process at an intermediate scale. Therefore, the customers' need to link lab- and process scale closer together, induced GE to start developing ÄKTApilot, a tool capable to scale up or down (hence the name "pilot") a protein separation process. Started in 1999, the development received inspiration from US customers and involved the long-term customer Biovitrum, Stockholm, in specifying and testing the tool: ÄKTApilot was officially launched in December 2002.

In two years as many as 300 ÄKTApilot have been sold worldwide. Since ÄKTApilot respects the FDA sanitary requirements for production, some customers are also using it for small-scale production of clinical trial material, thereby extending even more downstream from process development the scope of ÄKTApilot. Therefore, a customer who purchases and *actively utilizes* ÄKTApilot is usually closer to the downstream phases in drug R&D. In other words, using ÄKTApilot implies being closer to the completion of the painful R&D process culminating with the actual manufacturing and launch of a drug. From the most research intensive phases of drug discovery, often dealing with over 5,000 compounds (Robbins-Roth, 2000: 117), these users have considerably narrowed their R&D funnel, to about 5 compounds, when ÄKTApilot enters on the scene.

The R&D activities carried out by these customers were thoroughly investigated by GE Healthcare Uppsala so that ÄKTApilot could fit into these activities in terms of technical functions such as flow-rate and sanitization. GE also interacts worldwide with its customers in order to allow them actually

[1] The process is first tested at a small scale, with separation tools that produce small amounts due to their minute flow-rate, and then at an increasingly larger scale, starting from ÄKTApilot, through pilot plants and all the way to full-scale production plants.
[2] Amersham Biosciences was acquired in April 2004 by General Electric and became a division of GE Healthcare. The firm had then more than 2000 products, 5000 employees and a turnover of £670 million (270 of which from separation products).

perform the expected functions with ÄKTApilot. Even if users are offered training on this machine, many quickly learn its technical functions because they have already installed instruments from GE's ÄKTA platform, all sharing the same functioning logic and steering software Unicorn. GE also provides all customers with ongoing repair and maintenance to avoid costly delays in their R&D projects.

The above picture of the utilization of ÄKTApilot is common to all its users around the world, from Sweden to Taiwan, and from US to China. However, there are also important differences in the concrete ways in which ÄKTApilot is utilized and actually *provides value* to its users. These differences are firstly user-specific and depend on how this biotech tool is *embedded within the other resources that are activated around it* (Penrose, 1959: 25, 74-75). For instance, how often ÄKTApilot is utilized depends on how often the unit performing actual tests requires test materials; or the validation requirements on how ÄKTApilot is utilized increase dramatically if a company uses ÄKTApilot to produce clinical materials to be injected into humans. But the differences in how ÄKTApilot is utilized and the value it provides depend not only on this *micro-context* represented by the specific *network of resources* (Håkansson & Waluszewski, 2002) that surround ÄKTApilot: there are also broader forces that become manifest within this specific network, but that have their origin on a *macro-context* level[3].

In fact, if one expands the perspective to *national contexts*, one can notice that ÄKTApilot is embedded in rather similar ways within all the use networks in the same country, whereas similar use networks utilize and extract value from ÄKTApilot in very different ways just because they belong to different macro-contexts. For instance, users in China have bigger problems in learning how to use ÄKTApilot than US-based users, because of the different types of training these individuals received at school and on their job: American users are trained in practical process work and in using computers (both a must to fully exploit ÄKTApilot), whereas Chinese users are more theoretically skilled and perform several tasks manually. And also the type of organization using ÄKTApilot can be affected by macro-contextual factors: in Taiwan, for instance, the national government has strong ambitions in building-up the country's biotech industry, starting from R&D performed at state-owned labs capable to sell to private firms both their discoveries and the services of their instrumentation. Therefore, in this macro-context the users of ÄKTApilot are state-owned labs trying to figure out how to sell the capacity of ÄKTApilot to external users. By converse, in the US, where the state does not steer as strongly biotech R&D, users of ÄKTApilot are private firms dealing with own downstream drug development.

To summarize: how, when, by whom and why ÄKTApilot is utilized depends both on *micro-embedding* processes (the single user and its surrounding resource network) and on *macro-embedding* processes (those related to a national context). The purpose of this paper is thus to discuss how these micro and macro embedding processes intervene in the utilization pattern of ÄKTApilot, our focal biotech tool. More precisely (and restrictively), we aim to understand how the macro-contextual processes affect and become visible *through* the micro interaction texture around the focal tool. To tackle this issue we need to answer these two questions: (1) which specific micro and macro factors are visible in the various *interfaces* (Håkansson & Waluszewski, 2002: 190-200, and Baraldi, 2003: 17-19) between ÄKTApilot and the other resources affecting its utilization?; (2) how do the specific micro and macro factors affect each of these interfaces and hence ÄKTApilot's utilization patterns?

In order to provide variety to the macro processes we chose three substantially different national contexts: the *US*, *China/Shanghai* and *Taiwan*. In this way, we can empirically illustrate how the macro forces become visible in different national contexts and the effects they produce on specific interfaces around ÄKTApilot. Next to the ambition to provide such illustration, this paper also aims at a more general contribution: to suggest an empirically viable approach to analyse a complex theoretical issue, that is, the linkages between macro-contexts, filled with institutionally generalized forces, and micro-contexts, filled with specified interactions among clearly identified actors and resources.

This paper is organized as follows: the next section deals with our theoretical frame and the concepts that we use in our analysis of the micro-macro interplay. Then, we present our methodology, followed by the empirical material showing the utilization of ÄKTApilot in the three macro-contexts. Next, we analyse in detail the macro processes that affect a series of interfaces around ÄKTApilot in these three contexts. Finally, we conclude the paper with a discussion about the possibility to affect the micro-interaction and the utilization of this tool by affecting macro processes. Or, to put it simply, is it

[3] These micro- and macro processes are depicted as "internal" and "external" interaction processes in the IMP network perspective (see e.g. Håkansson & Waluszewski, 2002).

possible to create an "instant industrialisation" (Sturgeon, 2000), i.e. to speed up (e.g., through national policies) the value creation process in the biotech industry? Since ÄKTApilot is utilized in downstream phases, *artificially* stimulating use requires pushing the biotech firms in a national context to make such progress in their R&D activities as to reach such phases as pre-clinical, clinical and manufacturing[4]. Can policy measures concretely promote this progress? Can policy create macro-micro linkages that affect the concrete utilization of this tool through all relevant interfaces? These and other questions are tackled in our final comments, but we now turn to our theoretical section.

Seeing science-related innovations from a user perspective

The development and use of new scientific knowledge in disciplines such as molecular biology, biochemistry and genetics has during the last decades produced science-related resources of significant economic value. These science-related innovations include, for instance, recombinant DNA-based drugs, gene therapy and genetic screening (for an overview of these technologies see Enriquez & Goldberg, 2000, Fox Keller, 2000, Grace, 1997, and Robbins-Roth, 2000). When investigating the progress made within biotechnology, the management and the policy literature put a great emphasis on the sources of such innovations, that is, on academic research and science. The suggested recipes to help biotech companies to innovate or whole regions to grow a local biotech industry regularly stress the importance of bringing together the two key ingredients of *science* and *business*: simply put, have a scientist with a brilliant idea come close to an entrepreneur capable to commercialize it.

However, these recipes miss the importance of intermediate and final *users*, that is, those who really are willing to use and are ready to pay for any new technology. The problem is not "simply" that innovations and technical development are challenging tasks that take long time[5]: in fact, transforming cutting-edge science into *useful economic resources* requires more than just scientists, entrepreneurs and venture capitalists. The "little" extra that innovations require is the *actual use* for the new science-related technology. In fact, whereas new scientific theories and methods are rather easy to envisage, it is much more difficult to find actual industrial and commercial users for most of the scientific ideas or techniques created almost everyday. Any policy recipe limited to simply bringing science and business together, so that the latter can more easily commercialize the former, miss the key issue of how valuable an innovation actually is, and its users are the only tribunal that can assess it. Our theoretical review stresses therefore the importance of the using-side perspective of resource utilisation, which is essential to attribute the actual value to an innovation: in short, no use ergo no value for any resource.

How do new resources get a use?

The issue of how new techno-scientific resources become embedded into a user context is neglected in contemporary policy and managerial recipes and it is played down by most of the technology policy literature. The user side is usually taken for granted. One explanation for this neglect of the user side is given by Malmberg & Maskell (2002), who claim that, although cluster approaches (see e.g., Porter, 2000) represent a wide variety of theoretical assumptions, they all focus on "permanent advantages" that are assumed to accrue *only* to the firms *located within* geographical clusters. The cluster and the innovation system (Lundvall, 1992, Nelson, 1993) perspectives share the common assumption that what happens *inside* these systems is much more important for innovations that the interactions stretching outside them. However, as it often happens, most users are located *outside* the originating clusters and innovation systems. Another shared assumption in these approaches is the importance of competition and rivalry between autonomous economic actors that carry out their development endeavours in lonely solitude, a clear remnant from the traditional neo-classic market model.

However, within the innovation literature there are remarkable exceptions to these traditional paradigms and the neglect of the user side of innovations: for instance, the work of von Hippel (1986, 1988, and 1998) stands as an important reminder of the importance of users for the success of innovations, not only because innovating firms need to interact with users to commercialize new products but also because users themselves can often be a key source of innovative ideas (von Hippel, 1986 and 1988: 11-26). But it is within the marketing literature and in particular within *industrial*

[4] An alternative would be to push these biotech firms enter applications that are independent from the drug R&D funnel but that would benefit from using ÄKTApilot, such as the supply of purified antibodies to diagnostics and molecular medicine needs.
[5] Uppsala's "Life-Science/Biotech Valley" is at least seven decades old (Waluszewski, 2004), and even the role model for policy and management, Silicon Valley, is a hundred years old (Kenney, 2000).

marketing and the *IMP* tradition (Håkansson, 1982, 1987, and 1989, Ford et al., 1998) that the user is most explicitly considered as an essential element of the innovation process. The *industrial network* approach stretches even further and assigns full priority to the *supply-use interface* (Håkansson & Snehota, 1995, Håkansson & Waluszewski, 2002).

The industrial network approach helps to see the interaction patterns neglected by the "widely held model for economic development" (Sturgeon, 2000: 16) that colours most of the technology policy and innovation management literature. Instead of observing interactions only within a cluster or innovation system, this approach expands our focus to how resources (products) get an economic value by becoming embedded into user contexts that can be located very far away from the originating regions. By taking this different vantage point, the ambition of this paper is to study the micro-interactions behind the utilization of a science-related innovation both *within* and *across* several macro contexts.

Economic value: created through use

This study analyses how a specific resource, the protein separation tool ÄKTApilot, becomes embedded within user contexts while being utilized together with several other resources. We have mapped the interactions of this biotech tool with other resources, including the firm that produces it, the organizations that use it and several other resources such as products and other equipment. In doing this, we have focused upon how the technical, economic and social features of these related resources get activated in several using contexts. In this way we were brought to abandon one of the tenets of classical economic theory, that is, that the economic value of a resource is independent of how this resource is combined with other resources. Moreover we were also brought to recognize how resource combinations stretching across distant places can be much more important for the value of a resource than those combinations happening within a given spatial agglomerations.

Therefore, our theoretical approach stresses that what creates value is the very manner in which resources are combined – over organizational and spatial borders (Waluszewski, 2004). If, as Edith Penrose (1959) suggests, it is the way a resource is activated that creates its "services", then its value depends on how it is combined with other resources – within one organisation, within the relationships between organisations or even through indirect relationships. Thus, in order to grasp how the features and the value of resources emerge, we need a research tool that allows capturing the *interaction between heterogeneous resources*, regardless of which actors represent them and of where they are located. This analytical toolbox, developed in Håkansson & Waluszewski (2002), emerged from the industrial network approach and the IMP tradition, and their underlying assumption that a company's technological, social and economic features are the result of its interaction with other companies (see e.g., Axelsson & Easton, 1992, Håkansson & Snehota 1995, Håkansson & Waluszewski, 2002, and, for more recent work, the website www.impgroup.org).

This approach treats the interplay between organisations ranging from more distant interactions to close relationships, whereby both social and technological resources are confronted and adapted. It is an approach stressing that developments occur when organizations encounter one another (Ibid). These assumptions are included into our research toolbox, which focuses on direct and indirect interactions, viewed as the drivers behind the development of any resource. This investigation toolbox categorizes resources into four types, each one developed through a specific form of interaction process (Ibid: 34-38). Two types of resources are mainly social and organizational: *organizational units*, developed through co-operation process, and *relationships*, developed through networking processes. Two other types of resources are mainly physical and technical: *products*, developed through buying-selling processes, and *facilities*, developed through producing-using processes.

This research toolbox analyses how an organization's technical and commercial solutions are developed and utilized in interaction with its direct and indirect counterparts. Thus, we can map how resources are confronted and remodelled in relation to each other over time and place (see Wedin, 2001, and Baraldi, 2003, for applications). In mapping interaction processes, this "resource interaction" toolbox applies the key concept of *interface* between resources (Håkansson & Waluszewski, 2002: 190-2000): a resource interface is the contact surface across which two resources affect each other technically, economically and socially. An example of an interface between our focal biotech tool and a product is the rate of utilization of ÄKTApilot for a specific drug candidate; while an example of an interface between ÄKTApilot and an organizational unit is the time it took a specific lab to learn how to use it. One can identify several interfaces that either involve directly this focal resource and another

resource item (a product, a facility, a unit or a relationship) or that involve distant resources, which are important for how the focal resource is used and for how it generates value. Resource interfaces help systematically go through the resource interactions around a focal resource, such as ÄKTApilot. In doing so, we describe this resource's *micro-context of utilization*: by looking at a few relevant resource interfaces one can understand how a resource is *embedded* in a specific network of resources that contribute together (through specific interfaces) to let emerge the actual value of this resource.

Micro-interactions and macro-contexts of use

However, the ambition of this paper is to take a further step from the level of micro-interaction tackled by our "resource interaction" toolbox: the ambition is to understand the interplay between these *micro-interactions* (resource interfaces) and the broader *macro-context processes* that stretch at the level of a whole national arena[6]. How do these macro-processes intervene in a micro-context of use? We can now state with more precision how we concretely investigate this interplay: *we analyse how the macro-context factors affect and become manifest in the specific interfaces around the focal biotech tool*. This approach led also us from a methodological point of view. Moreover, we highlight the traces of macro-context in each resource interface shown in our empirical material and in the subsequent analysis.

What are then the macro-context processes that we shall search in the micro-level? Since our purpose is not discussing how these factors emerge or develop, a simple list is enough, with references to the literature that is mostly concerned with them. A comprehensive review of the macro-context factors that affect innovations is presented by Tidd, Pavitt & Bessant (2001) under the heading "the national and competitive environment[7]" (Ibid: 85-104). Inspired by Porter (1990), Nelson (1993) and Teece (1986), these authors identify a series of technical, economic, and institutional factors that characterize specific countries, or to use the expression of Nelson (1993), "national innovation systems", that is, the macro-contexts within which micro-interactions take place[8]. Tidd et al. (Ibid) also identify more sector-specific issues that define the "regime of appropriability", that is, a series of environmental factors[9] to which all firms belonging to a given industry need to "obey" and which they have very limited possibilities to affect (Teece, 1986: 287). Even if appropriability factors are tightly linked to a sector and its technology, these scholars stress that we can expect variations across different national contexts, especially in the strength of intellectual property rights (IPRs).

It turns out that the literature streams that are mostly concerned with macro-factors are precisely those streams that we criticised above, namely the innovation system (Lundvall, 1992, Nelson, 1993) and cluster (Porter, 2000) perspectives. But the concern with macro-factors of these perspectives differs profoundly from that of this paper. Innovation system and cluster approaches discuss theoretically and normatively these macro-factors, relying on the assumptions of traditional economics (see Waluszewski, 2004, for a critique). For example, these perspective are concerned with (1) how a single firm can take advantage of the *given* macro-context factors in order to exploit its own innovations[10] and/or (2) how a policy maker can try to *influence* these factors and thereby *stimulate the innovativeness of the firms* located in a certain macro-context[11]. The ambition with our study is rather different: to map empirically the actual macro-processes in their interplay with micro-interactions. Put simply, instead of focusing upon *theoretical assumption and normative ambition* we investigate how macro and micro interactions empirically present themselves. How do macro-processes intervene in the micro-embedding of a biotech tool? How are the macro-processes related to the value that is created by embedding the focal biotech tool in a certain context? How are macro-factors acted upon by the actors that handle the resources activated in the micro-processes?

This way of conceiving the macro-micro interplay reflects that suggested by other authors within the IMP tradition. For instance, Andersson, Håkansson & Johanson (1994: 5) posit that the effect of the

[6] We recognize that a micro-context of use (the resource network around ÄKTApilot) can very well be exposed to more than one macro-context (e.g., a lab using ÄKTApilot and having interactions with foreign partners). However, introducing this complication in our reasoning would not change its basic nature and our analysis of how the micro and the macro contexts interplay.
[7] "The national and competitive *environment*" is indeed a term that covers exactly the factors that belong to what we termed instead "macro-context". For our choice of the term "context" instead of "environment" see note 12.
[8] Among the most important macro-factors presented by Tidd et al. (2001) are national patterns of *demand and prices*, local inter-firm *rivalry*, *country-specific competencie*s in production and scientific research (due to national education systems, vocational skills and national industrial history), and *corporate governance institutions* (e.g., the US versus the Taiwanese style).
[9] The factors that define a sector's regime of appropriability include *secrecy and tacitness* of a technology, importance of *time-to-market* in R&D, *industry standard*s, and the legal protection on *intellectual property rights* (Tidd et al., 2001: 100-104).
[10] See Porter (1990) and the Dynamic Capabilities View of Teece & Pisano (1994).
[11] See the national innovation system approach.

macro environment is mediated through the firm's *specific network context*. We can expect this micro-context to be not only a network, but also to be populated by several resources that both *mediate* the effect of the macro environment (i.e., our "macro-context") and *are affected* by it. Moreover, Håkansson & Snehota (1989: 192) separate clearly, from the broader environment, a so called context, which includes only the entities related to a firm, composing the enacted business network around it. Therefore, we can implicitly assign to the environment all the elements that are outside this network context. Thus, using the terminology of these authors, this paper aims to investigate the interplay between "context" and "environment"[12]. Finally, within other inter-organizational approaches than the IMP tradition, Van de Ven at al. (1999), for instance, also distinguish between a *specific interaction network* and a macroscopic context (Ibid: 15-16). Such a macro-view is applied to analyse how infrastructural and institutional processes affect an innovation (Ibid: 52-53 and chap 6).

Method: investigating the use of a biotech tool in several contexts

How is a science-related innovation – i.e., an innovation related to science on both its supplier and user side – embedded in order to *produce economic value*? How is the embedding at micro-level related to a macro-context populated by institutions, technical trajectories, and policy ambitions? We use *two units of analysis* in order to tackle these questions: (1) specific networks of resources that embed focal biotech tool so that it creates value to its users 2) the broader national contexts that embed in turn these micro-interactions.

As for the first unit of analysis, we identified the *networks of relevant resources* that affect the utilization of the focal biotech tool in a variety (19 in all) of micro-contexts of use. A particular emphasis has been put in tracing the interactions between the identified resources, according to the analytical toolbox presented above (Håkansson & Waluszewski, 2002). In this way, we can shed light on how specific interaction patterns embed the utilization of ÄKTApilot at several users. In practice, we were addressed by the sales organization of GE Healthcare Uppsala to a few *organizational units* that utilize this biotech tool. Then we investigated these units, their activities and their other resources, namely other *facilities* (production and lab instruments) and *products*. We also included the other key units to which the users are connected and their *relationships*, spread in this embedding network.

As for the second unit of analysis, we chose three macro-contexts represented by three countries: the US, China and Taiwan. These contexts share the label of challenging biotech regions, but present wide differences in their scientific, industrial and institutional settings. An interesting initial question was thus how these differences affect the process of micro-embedding of the focal biotech tool and the possibilities of extracting value from it. These differences and the dimensions along which they can be mapped will appear clearer from our empirical accounts and analysis. But we can already stress the importance of the following macro-processes: the local *company governance structures* (VCs, stock exchange, public funding), the nature of *national pharmaceutical industry* and its *international relations*, the *regulatory setting* (e.g., FDA), *IPRs*, and the *national science and development policies*.

Our choice of studying micro-interactions and macro-contexts "through the eyes" of ÄKTApilot is particularly important: the utilization of this specific biotech tool signals that users (and their national biotech fields) are in the downstream stages of drug development, as mentioned in the introduction. Therefore, we employ the presence and use of this biotech tools as an indirect marker that the development stage achieved by the users in a macro-context is beyond the stages of academic research and drug discovery. More precisely, the widespread presence of ÄKTApilot is a *positive* indicator that the users in a country must have reached downstream phases in drug development[13].

But why are we so concerned with the "measurement" of the development stage in the drug R&D pipeline generally reached by the users in a country? And why don't we use a more direct measure of this advancement state? Let us start from the second question: the available official sources (e.g.,

[12] In this paper we chose however to use the term *macro*-context for what Anderson et al. (1994) and Håkansson & Snehota (1989) call environment. We introduce instead the distinction between a *macro* and a *micro* context. We use the term context for both the micro and the macro level in order to stress that traces of environmental factors become manifest and part themselves of the micro-interactions in the network, as visible by looking at concrete resource interfaces (Håkansson & Waluszewski, 2002).
[13] What about instead the absence of this tool in a country? Because ÄKTApilot is the most advanced tool currently available for process scale-up, its absence indicates that the users in a country, if they have reached downstream phases, do not utilize state-of-the-art technology, either because of cost reasons or because of their preference for less automated technologies.

FDA) on drug R&D pipeline status only cover products in the clinical stage, while largely neglecting those in preclinical stages. Indeed, pharmaceutical firms are keen on keeping confidential the actual number and type of projects in the grey zone drug discovery-preclinical trials, because this reveals their R&D efficiency and time-to-market too clearly. Therefore, we need other indirect markers than official statistics in order to capture the overall development stage of the users in a certain macro-context. Coming to our first question, the performance of preclinical R&D is an important indicator of how far from propagandistic proclaims and basic academic research a national use context has come. Since ÄKTApilot provides value only if users are at least in preclinical stages, the "measurement" of the advancement of a macro-context is pivotal to tackle a key question that we address in our closing comments: what possibilities exist to artificially create and speed up the use of this techno-scientific resource given its embeddness in micro-interactions and in a macro-context?

Even if the macro and the micro units of analysis must be kept separate, taking together all the micro-contexts of use analysed for each country – namely 15 for the US, 2 for China and 2 for Taiwan – provides an illustration of each respective country. Moreover, these very numbers are strongly representative of the global spread of ÄKTApilot, and arguably of the advancement state in drug R&D of these three countries. But our use of at least a couple of micro-contexts of use for each country aims to provide some form of variation in the interplay between macro-context and micro-interactions also within a very same macro-context. In fact, even if the macro-context may be common to all user-centred networks in a same country, the specific factors within this macro-context that get activated and affect the micro-interactions around ÄKTApilot may vary from an individual user to another[14].

Moreover, the individual users and their industrial networks characterize and put a face to the national contexts. Thus we avoid presenting and analysing user contexts in all too abstract, interaction-free ways. Coming to the level of specific actors and of the individual relevant resources also enables penetrating the micro-interaction patterns that embed the use of the focal biotech tool, while singling out the particular macro-processes that matter for this embedding process. This is especially useful for our purposes, because we will capture macro-processes not simply as generalized features "hanging in the air" (e.g., broad institutional frameworks) but only in so far as they are *filtered* in the behaviour of the investigated actors and in the specific resource interfaces emerging in the actual use of ÄKTApilot.

The data sources for this study reflect our multi-level case design: for the macro-context factors we relied on country-specific published sources (some of which are presented in the reference list) and on longer stays (2 to 12 months) in the three countries. Being living in these macro-contexts for longer periods was important for personally experiencing several softer macro-factors, such as cultural cues and local mentalities. Moreover, meetings with local public officials and participation to local biotech events further shaped our picture of the macro-factors. For the micro-contexts, we employed several personal semi-structured interviews to map the resource networks around each of our 19 ÄKTApilot users[15]. In each using organization we interviewed up to four people involved in purchasing or using the machine. The total of 36 user interviews are so distributed across the three countries: 25 in the US, 6 in China and 5 in Taiwan. We spoke with process development scientists working at protein purification labs, process engineering departments and pilot plants. Out interview covered such issues as the reasons for buying ÄKTApilot, the purchase process, the actual pattern of utilization, and the interplay between the using unit and upstream/downstream units. Finally, circa 40 meetings and talks with GE's R&D and sales personnel, either at Uppsala headquarters or in each of the three countries, shaped a better understanding of the technology behind ÄKTApilot, its general utilization patterns and country-specific macro-factors. We also used brochures and using manuals about ÄKTApilot.

Using ÄKTApilot in the US, China and Taiwan: interfaces and macro-contexts

Our empirical accounts present how ÄKTApilot is utilized and creates economic value in micro-contexts belonging to three national macro-contexts. The Chinese and Taiwanese contexts present strong ambitions to build biotech clusters, whereas the US macro-context has had in place a very strong pharmaceutical and biotech industry for several years. We start therefore with the US, where ÄKTApilot has been favourably embedded in several using networks and micro-interactions, and move

[14] For instance, a small biotech firm using ÄKTApilot to produce vaccines for the US Biodifence faces much less regulatory pressures from FDA than a larger pharma aiming to start clinical trials on an expected block-buster.
[15] The details concerning the using units in our sample are presented in the empirical sections. For confidentiality reasons, we cannot however reveal the identity of most of the using organizations that we contacted.

then to the other two macro-contexts, where embedding on the using side has not gone as far. For each country, we start with a description of the macro-context and move then to the micro-contexts of use around ÄKTApilot. We penetrate 7 key resource interfaces around ÄKTApilot: (1) with the using units, (2) with financing units, (3) with upstream units (e.g., research units), (4) with downstream units (e.g., production plants and clinical trials), (5) with GE Healthcare, (6) with the products/projects under development, (7) with other facilities and equipment. These 7 interfaces are presented in figure 1.

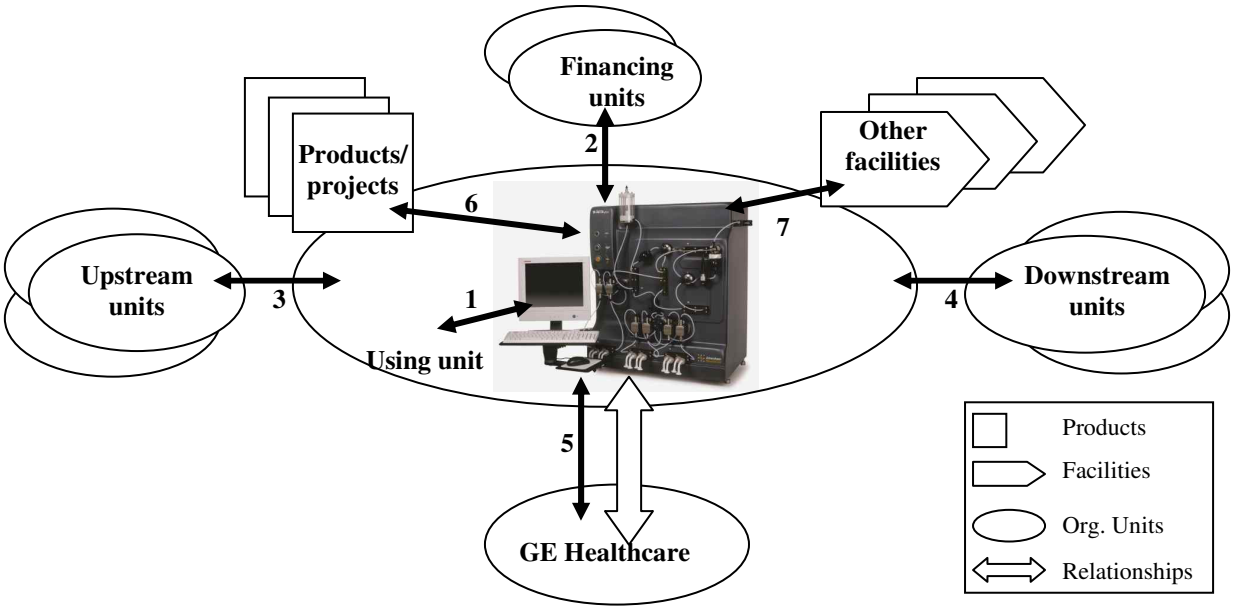

Figure 1: Seven key interfaces around ÄKTApilot

ÄKTApilot in the US: macro-context, user side and resource interfaces

The US is the world's leading country in biotech, where the first official biotech firm, Genentech, was created in the mid 1970s to exploit commercially the discovery of recombinant DNA made at UCSF and Stanford University. In 1980 Genentech became the first biotech company to reach an IPO (initial public offering) and in 1982 it launched the first biotech therapeutics, human insulin, licensed to the big pharmaceutical firm Ely Lilly (Robbins-Roth, 2000: 25). In 20 years over two hundred biotech-based drugs have been approved for the American market by the FDA (the US Food & Drug Administration) and more than half of them have been developed by American companies (www.bio.org).

In two decades the US biotech industry has grown to include in 2004 1,473 *strictly* biotech companies, that is, companies dealing exclusively with recombinant DNA-based therapeutics and diagnostics (www.bio.org). 314 of these firms have reached an IPO and their shares are traded on the stock exchange with a market capitalization of $311 billion in March 2004. In 2003 the US biotech industry employed 200,000 employees and sold for about $40 billion (www.bio.org). These figures double if one also includes the biotech divisions of big pharmaceutical firms, also known as "big pharmas", such as Wyeth, Schering-Plough, Merck, and Pfizer. American biotech firms are active in all segments of biotech (diagnostics, therapeutics and tool making) and worldwide leaders, with champions such as Amgen, Chiron and Genentech. Most US biotech firms are located in a few regions: the San Francisco Bay Area, San Diego, Boston, New Jersey (especially the big pharmas) and North Carolina.

Behind a strong private sector, there is an important *public* system funding research at universities: the National Institutes of Health (NIH) dedicated much of its total funds ($27 billion in 2003) to research projects that led to important biotech discoveries at such universities as UCSF, Berkeley, Stanford and Harvard (www.nih.gov). American universities lie at the forefront in scientific research and teaching. NIH also funds explorative research at companies provided that a university partner is involved. Another important public actor is the FDA, the global *role model* for regulation and monitoring of drug R&D. FDA's requirements were translated into the funnel-like template that is taken today to represent the R&D pipeline: all drugs are taken through the stages of "drug discovery", "pre-clinical testing" and

three-phased “clinical testing” prior to “market launch approval”. FDA constantly monitors the drugs on the market and takes action if adverse reactions emerge (like in the recent case of Merck’s Vioxx).

US biotech firms are mostly financed by private sources: *venture capital*, with $3.5 billion in 2003, and the *stock exchange*, with over $4 billion in 2003 (www.bio.org). Very active VCs have financed thousands of small biotech start-ups with the clear goal of taking them either to an IPO or to being purchased by a larger company. The FDA pipeline explicitly enters the valuation models utilized by VC firms and big pharmas to set the price of a smaller biotech firm. But big pharmas are not themselves tightly evaluated against the FDA pipeline: being listed on the stock exchange, they are exposed to the profit expectations of shareholders and to the constant monitoring by stock analysts. To keep shareholders and analysts happy these firms, with sales already over the $10 billion mark, need to grow by 10-20% yearly (Scientific American, 2000: 66): this requires introducing to pre-clinical trials 3-5 new drugs each year. But since the internal drug discovery strength of most big pharmas is capable to come up with only 1-1,5 new entities per year (Ibid), the stock market expectations push them to find external sources of drug candidates. Thus big pharmas seek small innovative biotech firms to buy, create joint-ventures or research agreements with. When big pharmas sign cooperation agreements with biotech firms, the latter are paid upon reaching specific *milestones* in FDA’s approval framework.

In the American context IPRs are of paramount importance, because they are a ground for evaluating firms (especially small ones with low sales) and because they are weapons to protect one’s innovation. The strong IPR regime creates almost a frantic search for discoveries to be patented and launched. But you have to do this as *quickly as possible*: the stock exchange and VC firms evaluate a firm not only based on the static metric of its patent portfolio, but also on how they score on the drug R&D pipeline, as we saw above. Their market capitalization or their chance to obtain further financing from VCs and partners totally depends on how many projects a biotech firm has in the various phases.

Such macro pressures create a climate of racing for quickly bringing drug projects through the phases of the R&D pipeline and to market launch. *Time* seems to be even more important than *costs* in the American context, even if, at the bottom line, project times and project costs are closely related. In fact, the longer a project stays in the pipeline and the more it costs. Small delays in the downstream phases of clinical trials can have tremendous consequences: for a blockbuster drug, a single day of delayed clinical trials costs as much as $1 million in lost revenues (The Scientist, 2004). The cost of one day’s delay in drug discovery is instead under $1,000. Within this context, both the stock market and specific investors have strong expectations on *how fast* biotech firms perform R&D activities, because speed is viewed as the main factor affecting the economic viability and growth of bio-pharmaceutical firms.

The US subsidiary selling ÄKTApilot was established by Pharmacia in the 1950s and moved in 1964 to Piscataway (NJ), near Rutgers University and several big pharmas such as Johnson & Johnson and Schering Plough. The growth of the US market for GE Healthcare Uppsala has been impressive: today this is its largest, covering well over one third of total sales. About 1,000 people are employed here, mostly as service personnel and salesmen, geographically spread to be near the major customers, located in the areas mentioned above. The size of the US market is mirrored by the sales of ÄKTApilot: of the 300-something machines sold until the end of 2004, about 100 have been shipped to the US.

1. Interface with using units: We interviewed 15 units that use ÄKTApilot, all of which are process development and pilot plant subunits of biotech firms. This reflects the fact that all but three ÄKTApilot are placed at private companies involved in specific product development projects. The number and type of using units is summarized in the following table according to the type of firm they belong to.

N. of using units	Type of firm	N. of firms	N. employees	N. of ÄKTApilot
2 (1+1)	Small biotech not listed on stock exchange	2	120-160	3
3 (2+1)	Medium biotech listed on stock exchange	2	360-600	5
4 (2+2)	Large biotech listed on stock exchange	2	>3,000	10
2	Medium biotech belonging big pharma	1	400	4
4 (2+1+1)	Big pharma’s biotech division	3	>30,000	4

Table 1: The 15 American units using ÄKTApilot and the firms they belong to

American firms started buying ÄKTApilot right after its launch, because they viewed it as a *missing tool* in their attempt to scale-up protein separation processes and to *automate* laboratory work. These firms

were also very quick in starting using the tool: high levels of skills and long-term experience in protein separation allowed most users to perform actual runs only a few days after installation. Many units bought and use more than one ÄKTApilot (up to 5) and do so quite intensively compared to other lab tools, typically on a weekly basis. Individual users (up to 10 for each machine) are very skilled both in routine runs and in programming ÄKTApilot, writing own strings of control software. The *application* for which ÄKTApilot is utilized depends on the type of unit: *protein chemistry labs* tend to use it in a more "discovery" oriented fashion, to test several substances and combinations of complementary materials (columns and media), because both the substance and the specification of the separation process are at an early stage; *process development units* focus instead on a given substance and simply search for methods to produce it in larger quantities; finally, *pilot plants* or *technology transfer units* have already a given separation process that they either implement to manufacture the actual substance or that they formalize to be transferred to other locations, maybe abroad.

2. Interface with financing units: All the 26 ÄKTApilot utilized by the 15 units above were financed by the internal means of the 10 firms interviewed, without any public funding. For a purchase of this size, around $100,000, the single units have a relative freedom in their decision making. Most firms have procedures that require for amounts around this level the approval of a senior manager, typically the head of the lab (the exception in our sample is a mid-sized biotech firms belonging to a big pharma, which requires a division's head to approve the purchase). Even if the cost of the machine per se is not an issue, the purchase is viewed as an investment and needs to be included in a *yearly purchase budget*. Moreover, one must show the concrete need for an ÄKTApilot, based on the existence of concrete projects where to use it. If this is secured, the decision is approved in a matter of weeks to avoid delays in a project. A special case in our sample is a small biotech firm that did not own one of its two ÄKTApilot, but borrowed it from a US Biodefence subcontractor to manufacture a vaccine.

3. Interface with upstream units: The units upstream the actual using unit include both those that *originate* a protein project and those that *physically manufacture* the inputs that ÄKTApilot purifies. The former units have identified an interesting therapeutic molecule and by now, similarly to a relay race, they have left the baton to process development units that have the task to (1) figure out how to produce this molecule and (2) supply the doses for pre-clinical and clinical trials. For smaller biotech firms the very idea for a new drug tend to have its origin inside internal drug discovery labs, whereas for big pharmas and larger biotech firms the original source of a protein project lies often outside their boundaries, in a smaller biotech firm. But as soon as an R&D project is purchased and set into motion at larger firms, their own *chemistry composition labs* take control over it. Internal labs are also involved in genetically engineering the cell lines that will physically "produce" the un-purified protein: this stage physically performed by internal units called *bioreactors*, typically located door-to-door with the actual ÄKTApilot users. The bioreactor units deliver a mixture of proteins, dead cells and other contaminants that needs to be separated to obtain a purified protein. Among the above units and the typical ÄKTApilot users (process dev. labs), interaction is scant and information flows in a single direction: drug discovery units → chemistry labs → genetic engineering labs → bioreactors → process dev. labs.

However, among the ÄKTApilot users there are units that operate even more downstream in the R&D pipeline than process dev. labs: these are *process engineering units*, *pilot plants* and *technology transfer units*. These more downstream ÄKTApilot users receive from process dev. labs a set of "purification protocols", that is, instructions on which method to apply in order to purify a protein. Among these downstream units, all involved in different ways (and at different sizes) with developing manufacturing processes, there is a bit more interaction: purification protocols can be the object of joint discussions and even been modified by an upstream unit based on suggestions coming from a downstream one. This interaction is also partly facilitated if both units use ÄKTApilot.

4. Interface with downstream units: The units downstream the actual using unit include both units involved in *pre-clinical/clinical trials* and *manufacturing* units. As for the former, big pharmas and large biotech firms have own large trial units that have two major roles: (1) interacting with the hospitals that concretely perform trials, even tough these contacts are rigidly regulated by the FDA rules in order to ensure independent and reliable test results; (2) ordering test doses of a drug from pilot plants or from the unit using ÄKTApilot, if small doses are needed. The interplay between the unit using ÄKTApilot and internal trial units is very scant, except when the small doses that ÄKTApilot can produce are enough for a trial. However, interaction is in these cases unilateral and ÄKTA users simply produce the amount ordered by trial units. Moreover, within big pharmas and large biotech firms, the unit using ÄKTApilot has no interaction with (and often no knowledge about) whoever performs the trials. But the

situation is different in smaller biotech firms, where the ÄKTA-using unit has direct contacts with the hospitals performing the trials: one respondent at a process development lab knew that ÄKTApilot allowed producing a more purified protein that reduced casualties among test animals at the hospital performing their pre-clinical trials, making tests more reliable, fast and less costly. All interaction with external units, both downstream and upstream, is strongly regulated by *formal contracts* that put a strong emphasis on the assignment of IPRs and set high penalties in case of infringement.

5. Interface with GE Healthcare: GE Healthcare has long-term relationships with most ÄKTApilot users, who yearly purchase several of their other products (such as columns and separation media). The daily content of this relationship focuses on *service contracts* aiming at securing rapid repairs, because users experience often a strong time pressure and delaying a project can have very negative consequences. Training the users is instead less important, because most are very proficient and true chromatography experts. These relationships are also governed by formal issues such as non-disclosure agreements motivated by confidentiality concerns. GE does not interact with a central unit, but with single users who have limited contacts with each other even if they belong to the same firm.

6. Interface with projects/products: The number and type of projects/products for which ÄKTApilot is utilized vary greatly at each using unit. Protein chemistry labs apply Äkta to as many as 100 different products per year, each one being a potential drug. Process development labs, being involved with drug projects already in pre-clinical or clinical stage, are instead more focussed: from a dozen per year in medium/large biotech firms to a single substance, which is typical of small biotech firms relying on one single project or of fully project-specific units created by big pharmas to further develop just one single pivotal drug already on the market, but maybe to be extended to new treatments. For users involved in several projects, ÄKTApilot has proved especially useful because its sanitary design allows quick cleaning, so that the machine can be easily shifted from a project to another: this made it easier for the using unit to plan in detail and schedule several projects.

As for the type of proteins, the great majority of projects where ÄKTApilot is used concern *monoclonal antibodies*. These products may have been in the R&D pipeline for anything between a year (for chemistry labs) to a full decade (for late clinical trials or upgraded drugs). Despite its sanitary design (and the ease to have ÄKTApilot approved by FDA as a GMP, Good Manufacturing Practice, facility) only a couple of the interviewed firms utilize ÄKTApilot to manufacture substances to be injected into humans. All users have very clear ideas of where exactly in the FDA-inspired R&D template ÄKTApilot comes into the picture in these projects, because that template affects what they concretely can and cannot do with the machine (e.g., GMP requirements or sanitization).

7. Interface with other facilities: The unit using ÄKTApilot (e.g., a process dev. lab) also uses other research tools, many if which are provided by GE. For instance, ÄKTAexplorer, a machine with a smaller flow-rate but greater measuring precision, is utilized to define the final chemical details of a protein, as far as they are left open by chemistry labs. At many users ÄKTApilot was introduced to substitute older separation tools by competing firms, such as Millipore's K-Prime. ÄKTApilot provided important advantages to all users in terms of increase reliability, precision and possibility to automate the process, especially thanks to its Unicorn software. ÄKTApilot has also an important interface with all larger scale manufacturing equipment, because it provides the *separation protocols* that pilot plants adapt to these larger facilities. The only two ÄKTApilot employed to produce human trials materials use are included in GMP facilities, requiring a cold room and protective measures.

ÄKTApilot in China: macro-context, user side and resource interfaces

Compared to the US, China has less experience of modern biotech research and manufacturing. However, on behalf of the Chinese government, the Chinese Academy of Science is encouraged to create a *"modern science civilization and innovation culture"* through the *"dissemination of scientific knowledge, spirit and methodology throughout society by adopting open and networked means"* (http://english.cas.cn/Eng2003/page/home.asp). This reflects the ambition of the Chinese government to create a *national innovation system* to develop high-tech industries, among which biotechnology is officially pledged. In an attempt to catch up and compete with the West China initiated the first policy for biotech, the 863-plan, in 1986. Since then several central and regional level policies, programs and reforms promoted biotech as a means to create "future economic growth" and "global competitiveness".

An increased focus on the development of biotech can be seen since the mid 1990s. For instance, in 1998 the Chinese Academy of Science launched the Knowledge Innovation Program: 80 research institutes will be consolidated and re-organised to act as a science base for high-tech innovation. Moreover, 30 special National Key Laboratories related to biotech have been established (Huang & Wang, 2003). The Chinese government also actively promotes international cooperation to achieve results in the biotech industry. The Chinese state is also the main financer of biotech ventures: approximately 80% of all capital invested in China has a governmental origin (Kenney et al., 2002).

Governmental action has created a visible imprint in the amount of biotech firms in China: there are about 500 biotech firms, even though the definition is wide and includes even brewery/food. Around 140 drugs are claimed to be in the pipeline, but only 13 are in the later phase, i.e. clinical phase 3 (Louët, 2004). In 2002, the Chinese State and Food and Drug Administration (SFDA) had approved 20 biotech drugs for sales on the Chinese market (Economist, 2002). Thus, despite the substantial amount of biotech firms, it has turned out to be difficult for these to commercialise their research. The majority of the firms that produce biotech drugs still focus on copying already existing products. To counteract this situation and develop regulations, the SFDA was established in 1998. The SFDA approves drugs and divides products in 5 different classes. Class 1 is a totally new product worldwide, while class 5 is an already existing product with only a different formulation. Traditionally Chinese biotech firms have focused on developing class 3-5 drugs. This has resulted in a fierce *price competition* between several firms producing the same or similar products. To further strengthen the quality of Chinese products the government decided that all companies that produce pharmaceuticals should have GMP-approved facilities by June 2004. International pressures, especially from WTO, have pushed China to develop stricter regulations regarding IPR and bio-safety issues.

China's fastest growing region, Shanghai, shares the central government expectations on biotech as a future "cash cow". The Shanghai municipality too aims to create an "innovation system" around biotech and has accordingly implemented several policies and programs supporting original innovation, research commercialisation, internal R&D, international cooperation, cooperation academia-industry and technology transfer. Another direct action to promote this industry is the creation of government-owned investor firms, for example of Shanghai Science and Technology Invest Corporation in 1992. Moreover, the regional government introduced regulations to boost commercialisation and encouraged patent application through financial support. These governmental activities resulted in around 280 biotech companies in Shanghai. However, only a small part of them are really involved in biotech and most of them have not reached clinical phases (Li, 2003).

1. Interface with using units: Abut 10 ÄKTApilot have been sold in China to five different customers most of which are based in Shanghai. We focus here on how ÄKTApilot is embedded in two of these using units. One using unit is part of a big state-owned pharmaceutical firm and the other unit is a private biotech company. The former has a 50-year-long history of producing chemical drugs, while the latter was recently established, in 1995, but is part of a larger private pharmaceutical group. As a reaction to government's emphasis on biotech both firms started biotech activities in the mid 1990s.

Both units develop anti-cancer drugs, but only one has a biotech product on the market. The two units got their ÄKTApilot installed in spring 2004, but use it for different purposes and in different stages of the R&D pipeline. The state-owned unit uses ÄKTApilot for producing samples for pre-clinical trials, while the private unit bought ÄKTApilot to be used in actual manufacturing, further downstream in the R&D pipeline. None of the units have yet received market approvals from SFDA for any of the projects where ÄKTApilot is used. Therefore, the private unit has used ÄKTApilot just a few times to validate the production process. The state owned unit used instead ÄKTApilot daily during a four-month period, but then their compounds lost chemical activity and had to return upstream, to basic research. One person in each unit is responsible for running ÄKTApilot, although 2-3 others use it. Chinese users simply perform routines runs on the machine, while more complex problems need to be solved together with GE. Their lack practical experience, reflecting an education system that emphasises theoretical issues, also implies that they need extensive *training and support services* from GE.

2. Interface with financing units: The main financiers of biotechnology ventures in China are central and regional governments. Both for the private and the state-owned users of ÄKTApilot some financing were public. Among the sources of financing for the projects where ÄKTApilot are the "863-program", the "Key Science & Technology Development Projects" of Shanghai, the 10th National five-year-plan "Key Science and Technology Projects", and the "New Technology Development Fund". The

units using ÄKTApilot also have *governmental approval* status for their projects, which provides advantages such as tax deductions in the initial R&D stages and even reimbursement of some R&D costs if the project reaches manufacturing. This shows the government's concern with moving projects to manufacturing new products that contribute economic growth, and not only with generating research. Receiving governmental funds signals the importance of a using unit and, especially in the early stages, attracts other financiers to invest. The private user unit received funds from both private investors (Chinese and American) and from an investment firm owned by the city of Shanghai (an investment of RMB 100 million over 6-7 years).

Even if the technical choice of the system to buy is taken by actual users, the top management has to accept the purchase. A purchasing department is in charge of the contractual agreement and the negotiation with GE. The purchasing process of ÄKTApilot is long, partly because of a long negotiation process: in average it takes six months from the decision to purchase a new system to signing the purchase contract. On top of that there is another three months before the delivery of ÄKTApilot. Cleary in a Chinese context time is not regarded as something that creates costs.

3. Interface with upstream units: The original idea and the technique used in the development of the anti-cancer drugs for the both using units can be traced to *foreign units*. Chinese policy emphasises and promotes international cooperation, as source of both new technology and investments. Hence, the interaction between the using units and their foreign counterparts falls within this policy ambition of both the central and regional (Shanghai) governments. By finding partners outside of China, the units have learnt new techniques and developed new bio-drugs, enhancing the Chinese biotech base.

However, the relationship between the two using units and their foreign partners are quite different. The state-owned unit interacts intensively and daily with a Korean partner. The role of the Korean partner is improving basic research, while the Chinese unit focuses on the commercialization and production process of the anti-cancer drug. A formal agreement was signed in 2003 and the Chinese firm will pay US$ 500,000 for the patent licensed and the technology transferred: the Koreans own the patent but the Chinese will own the final product. The relationship between the private unit and their American partner is not instead as intense. The American unit came the whole way to completing pre-clinical trials before the project was transferred to the Chinese unit. All clinical trials have been performed in China, but no intense technical interactions have occurred. However, along with the transfer of the technology, the American unit and the Chinese unit formed a joint venture in 1999. This falls within the Chinese policy's encouragement of joint ventures as a way to gain technical knowledge for Chinese firms, while offering access to the Chinese market to the foreign partner. The difference in these relationships may be explained by the fact that the two user units are in different R&D stages. Other upstream units are much nearer the ÄKTApilot users: bioreactors that produce the un-purified protein are located just next door.

4. Interface with downstream units: As the state-owned unit just entered the pre-clinical phase, they have just started to build up the production of samples for the coming trials. Therefore it is not clear which downstream units they will interact, except that it will be some hospital performing the actual trials. Contacts with research departments, universities and hospitals are crucial in the coming clinical phase. The private unit is instead waiting for the final drug approval from SFDA and has contacts with the university hospitals employed during the clinical trials. These hospitals are located in several Chinese cities and may act as early distributors of the drug. This is an example of the cooperation industry-academia promoted by the Chinese policy to stimulate biotech and economic growth.

5. Interface with GE Healthcare: GE has supplied both using units for 4-5 years with chromatography systems, media and columns. Both units were familiar with the ÄKTA platform, having used for 5 years ÄKTAexplorer. The experience and embeddeness of this system facilitated choosing ÄKTApilot for the next stage: ÄKTApilot had the right scale for producing pre-clinical samples for the state-owned unit and enough of final product for the private unit. The choice of an expensive tool such as ÄKTApilot can have been induced by the fact that the two drug projects have "government status", which means that the units will get tax reduction on imported material. Imported and high-quality systems reflect the public ambition to produce new products with state-of-the-art technology and according to current requirements, not only copying existing products, which has been the case before in China. The individual users are those with the closest relationship to GE, especially with the technical supervisor, the sales rep., and support and service personnel. GE provided 2-3 days training for each ÄKTApilot

installed, but Chinese users need constant support on practical issues since they are not as expert in chromatography. Hence, GE Health Uppsala puts a lot of emphasise on training and support in China.

6. Interface with projects/products: The using units have been involved in biotech since the mid 1990s, but the transfer of technology enabled them to jump some R&D stages, thereby shortening project times. A biotech industry with a short history makes however available just a few projects. Thus each ÄKTApilot is used for just one specific project, that is, one drug and one specific protein. The private unit produces a virus-based anti-cancer drug, while the other state owned unit develops an anti-cancer pill. Both using units aim for class 1 new product approval for their anti-cancer drugs: what does this indicate? The expectation is to sell the future products worldwide; but this requires developing the drug according to stringent requirements: not only those of SFDA for the Chinese market, but also those of the US FDA for foreign markets. Both units searched patent protection (some of which are granted and some are still pending) in developing a new drug. This reflects the government initiatives to strengthen IPR to stimulate high-quality biotech products in China. Clearly, the local government has great expectations, especially on the private unit approaching manufacturing.

7. Interface with other facilities: The units using ÄKTApilot also use ÄKTAexplorer in earlier phases. The private unit has a new GMP-approved production facility in Shanghai that manufactures also a previous drug. In order to receive the approval to start production of the virus-based drug, SFDA has to validate the production process. The state-owned unit has instead just entered the pre-clinical phase and has not planed the manufacturing process. Their existing production facility produces 200 relatively low-level drugs. When the new Class 1 cancer drug will reach the manufacturing phase they will need to build a new high-quality and GMP-approved production facility.

ÄKTApilot in Taiwan: macro-context, user side and resource interfaces

Similarly to China, biotech is regarded as a key future technology by the Taiwanese government. Biotech is part of the so called “Twin star two trillion project” and an imperative part of the “Challenge 2008 six year national development plan”. The government aims to transform Taiwan into a “Green Silicon Island” where “sustained economic growth” and “global competitiveness” will be driven by high-tech industries (www.biotecheast.com). Through the *Biotechnology industry promotion program*, which provides policy-induced mechanisms to integrate resources and knowledge, the government hopes to speed up industrialization. The Ministry of Economic Affairs (MOEA) highlights this ambition as follows:

“In the coming decade, the biotechnology industry may very well be the major driving force behind Taiwan’s economic development. We believe that with government policies driving the development of the industry, as well as the all-out promotion efforts under the direction of the Ministry of Economic Affairs, the biotechnology industry will retrace the steps of its illustrious predecessors – the semiconductor industry and the information products industry. We look forward to the day when Taiwan will be able to boast a booming biotechnology industry. This will not only fire up the engines of national progress, but also Taiwan’s entry into the global biotech business network, ensuring continued economic prosperity.”

Since 1995 there has been massive government support to the biotech industry, through the creation of a friendly environment for biotech investment and the provision of financing. The government has targeted three big national research programs: “Biotechnology and Pharmaceuticals”, “Genomic Medicine” and “Agricultural Biotechnology”. The statistics of 2004 shows that Taiwan had 223 biotech-related companies, but the goal of MOEA is to boost a biotech industry with around 500 private firms within the next few years, including 18 large-scale internationally competitive companies with a capitalization of NTD 500 million. The target is certainly impressive at a first glance, but a part of the explanation to the growth in the number of biotech firms is the government’s broad definition of biotech, which includes everything from fermentation to proteomics, health foods to genomics medicine and biopharmaceuticals. The Taiwanese biotech industry has so far focused on health foods, medical devices and cosmetics. The broad definition has led to many non-biotech firms starting to use biotech methods to modify their products in order to fit into the definition of a biotech company. Behind these endeavours is the search of the generous incentives and financial aid provided by the government.

However, the targeted areas of biopharmaceuticals and genomic medicine have not yet produced significant results in terms of breakthrough products. And the growth prospects, including start-ups, are not so optimistic for the near future. The industry has also had difficulty in attracting private

investments. Both local and global pharmaceutical, VC and biotech-related firms have been cautious in investing in the Taiwanese biotech industry, so that a major part of the financing derives from public channels. 40-50% of the financing to the private industry comes from the government and in the case of (semi)governmental research centres and institutes this rate reaches 80-90%.

In order to develop the Taiwanese biotech industry in the targeted areas government-sponsored research centres have been assigned the task to lead the way. The proposed development model for the biotech industry is similar to the one successfully applied to the semiconductor industry. This industry was developed in Taiwan in the 1970s, under the pressure of the government's effort to upgrade the national technological capabilities. In order to achieve a quick move into these high-tech areas the government instituted an "open lab" policy, whereby semi-governmental research centres opened up their labs to the private industry to share and provide technology and information. The main idea was to have these centres develop technologies for an industry with limited R&D capabilities. Hence the task was to lead the way into new technologies through a strict central guidance.

This development plan seems to have been relatively easy to apply to the semiconductor industry. However it has been difficult to replicate in the biotech industry. Transferring knowledge and technologies from these centres to the private industry has so far shown to be more difficult than expected, with very few successful cases. Some of the leading research centres within biotech are the Industrial Technology Research Institute, the Centre for Disease Control Development, the Centre for Biotechnology, the National Health Research Institute, and Academia Sinica. These institutions focus on different areas of biotech, but the common feature is that they all concentrate on *applied* research.

1. Interface with using units: There are currently five ÄKTApilot systems in Taiwan. Two have been purchased by two private firms and two by a governmental research centre and a semi-governmental research centre. Furthermore one ÄKTApilot is located at a private university. Here we focus on the embedding of the ÄKTApilot at the using units of the two public research centres. The purpose of the governmental research centre is mainly to engage in disease control. The organization responds directly to the Department of Health, and is an important vaccine centre. The unit using ÄKTApilot works on several vaccines, against Japanese Encephalitis, Tetanus etc. Because of the contamination risks associated with working on different viruses, the ÄKTApilot is used just for one project at a time.

The semi-governmental research centre is mainly financed by the government on a contract basis but it is supposed to function as an autonomous, non-profit R&D organization. The organization carries out its function in two complementary ways. Firstly, it vertically links the domestic academic sector and the industrial sector through the promotion of applied scientific technology: its labs and pilot plants develop technologies derived from academic research and work to transfer them to private firms. Secondly, it introduces and adapts suitable technologies from around the world to transfer them to the Taiwanese biotech industry. The applied research at this centre is divided into several programs including biopharmaceutical products, genomic medicine, Chinese herbal medicine, preclinical studies, medical devices and industrial technology. The specific unit using ÄKTApilot currently does applied research on a wide base of protein-based applications in drug development, antibodies and insulin.

2. Interface with financing units: The main financial contributions to the biotech are allocated through public funding channels. The financiers include the National Science Council, MOEA and the Ministry of Financial Affairs. The (semi)governmental research centres receive about 80-90% of their project funding through public sources. A few projects are initiated in cooperation with private firms which usually contribute with partial financing. The process for obtaining public funds starts when the responsible team for a new project applies for funds to a state agency. An assigned committee at the agency reviews the project and its *commercial feasibility*. The variables taken into consideration include commercial value, development time, and fit with government goals. If funds are allocated to the project, the project manager decides on how to use the grant for the best purpose. However, the purchase of ÄKTApilot at the two centres was not related to a specific project, but the purpose was to use it in any projects that needed to do scale-up protein purification. The project managers viewed the system as a very important tool to bridge the gap between lab and production scale purification.

3. Interface with upstream units: The development of the biotech industry in Taiwan has led to the emergence of several organizations specialized in different R&D stages. Under this specialization agenda the function of the (semi)governmental research centres is to bridge upstream academic research and private industry. The research centres only undertake R&D at a *midstream level*, such as

pre-clinical stage, and do not have any basic research ambitions. An important task is therefore to find discoveries upstream and take over those with potential commercial application. The research centres actively seek new projects through constant contacts with universities and laboratories all over Taiwan and abroad. In addition, these centres have an open lab policy inviting both academia and private industry to do joint research collaboration.

The units using ÄKTApilot at the two centres currently work on two projects, one using proteins from cell cultures and the other plasmid DNA for gene therapy. The first project was acquired from a university. Projects overtaken from a university entail sometimes research collaboration, but the research centre takes control of any further development. Transfers like these are facilitated by the fact that the research grants are usually publicly funded. Researchers at public institutes are not allowed by the current regulations to use their research results to set up a company, because the results formally belong to the school and by extension the financier, hence often the government. The project at the other research centre derives from cooperation with a private company, which needed technical help: the centre contributes technical knowledge, facilities (including ÄKTApilot) and some financing for the continued R&D. The research centre has two options after developing the technology: to set up a spin-off company with the private partner or to licence the technology to the partner.

4. Interface with downstream units: One of the major roles of the research centres is to pro-actively sustain the development of the Taiwanese biotech industry. Since these research centres are to function as non-profit organizations an important task to transfer their products to the private industry or to spin off the research unit into a private company. The results in these areas so far have been mixed. Several technology transfers have occurred or are on their way, but no transfer has yet led to a competitive product. Earlier on the semi-governmental centres focused on transferring technologies *directly* from academia to the industry. However it was difficult to find projects suitable for transfer to private firms. The Taiwanese biotech firms had not the same R&D and financial resources, nor the experience of their American and European counterparts. Projects from abroad could not easily be transferred because of genetic incompatibility among patients, etc. Such problems led to the research centres focussing on developing the university projects before transferring them to private firms.

One recent example is a vaccine against Japanese encephalitis. The governmental research centre first developed the separation protocols and toxicity tests for the vaccine and then transferred it to a private company in 2002. The assignment to a private partner is preceded by a public announcement that a technology is available and then the interested firms who applied are screened by the research center and the responsible state agency. But in the case of the Japanese encephalitis vaccine there was only one company that showed interest in the product. The patent and commercial rights were then sold to the private firm for a royalty and technology transfer fee paid to the research centre. The vaccine is however not yet commercialized, also because the transfer is still far from complete. The delay partly depends on the fact that the vaccine still needs clinical trials. Despite the government aid, the private company also has serious budget problems and very small research capabilities. Hence this company is still dependent on the research centre to bring the vaccine through the R&D pipeline.

5. Interface with GE Healthcare: GE has a close relationship with the units using ÄKTApilot. The users have experience of other systems in the ÄKTA platform and are rather proficient. The relationship consists mainly of regular maintenance and service contacts including supplies of media and columns. GE Healthcare also arranges several training seminars every year, but since the individual users work with the ÄKTApilot on a daily basis their need for technical help is only occasional. These instances include for example problems in system operation or trouble shooting (i.e., when the results after running a test are not optimal).

6. Interface with projects/products: ÄKTApilot is used in projects related to gene-therapy, vaccines and antibody production. Only the vaccine project has reached the clinical phase: here ÄKTApilot is important because it is used to scale up purification samples for clinical testing. For users involved in several projects, ÄKTApilot has also proved useful because it is easy to clean and there is a smaller risk of contamination. However, the vaccine project requires ÄKTApilot to be used only for one project, especially because this project is undergoing bio-safety test for exclude contamination problems.

7. Interface with other facilities: The research facilities at the two research centres are used for a variety of biotech applications at different R&D stages. Therefore, these centres have several systems used in combination with ÄKTApilot: for instance, smaller scale systems such as ÄKTApurifier and

ÄKTAexplorer, but also bigger purification systems such as bio-processors. As mentioned before, the purchases of ÄKTApilot at the two centres were not related to a specific project but were an effort to upgrade the research facilities in case of possible future use. Lately the semi-governmental research centre has put an increased emphasis on attracting *contract research*. For this purpose this centre is on the way of setting up Taiwan's first approved GMP pilot plant for biopharmaceutical products. The hardware for the plant includes several systems from the ÄKTA platform.

Analysis and discussion: the macro-contexts as reflected in micro-interfaces

We perform now our analysis by looking more precisely at how a few key macro factors are *reflected* in and *affect* how ÄKTApilot is utilized and embedded within the network around the using units. In order to see the effects and traces of the macro-context we focus on the 7 interfaces that we reviewed in the empirical part and that were graphically presented in figure 1 The results of our analysis are summarized on table 2, for each of the 7 interfaces and for each of the three national use contexts. In each cell we highlight the relevant macro factors that play a major role for the corresponding interface. Then we review in more detail these interfaces and how ÄKTApilot is embedded in the three macro-context, starting from the country where ÄKTApilot is less strongly embedded, Taiwan, then moving to China and finally to the country where the tools is most strongly embedded, that is, the US.

Countries / Interfaces	**Taiwanese use context**	**Chinese use context**	**American use context**
1- Using unit	Strong *governmental* links to using units. But to increase flexibility some research centres are *semi-private*	*Govt*. strongly affects definition of using units' biotech activities. *Education system* negatively affects skills of individual users.	*Time-to-market issues* motivate using ÄKTApilot. Embedding facilitated by *general user skills* and chromatography experience
2- Financing units	*Government* as biggest financier. It influences biotech devel. by sponsoring projects that adheres to the *national biotech plan*. Adherence and long-term goals more important than *speed*	*Strong govt. involvement* in financing biotech. *"Govt approval status"* facilitates embedding and R&D project start. Negotiating prices part of the Chinese culture: *time* has limited value/cost.	*Time-to-market pressure* speed up purchase process. Economic *investment logic* for existing projects motivates purchase. *No public financing* intervenes
3- Upstream units	*IPR regulation* blocks university start-ups. *Semiconductor model:* upstream research at universities transferred to (semi)governmental research centre	Government encourages *international cooperation* and joint ventures as a source of projects	*VC and stock market* require formal IPRs for small biotech firms. *FDA funnel*, *stock market's time pressure* and *intense rivalry* create high specialization, silos mentality and scant interactions
4- Downstream units	*Semiconductor model*: technology transfer from "open labs" is the way to build up the Taiwanese biotech industry	Government encourages *cooperation industry-academia*. But *immature biotech sector* limits current downstream linkages	*FDA rules*, *stock market's time pressure* and *intense rivalry* create high specialization, silos mentality and formal IPR contracting
5- GE Healthcare	*Semiconductor model:* projects to the govt. centres made them key customers. Tech transfers make slowly private firms also become key customers. Relationship based on maintenance. Technical support less important because of *skilled and experienced user*s	*"Government approval status"* for a project facilitates buying ÄKTApilot. ÄKTApilot reflects intention to produce according to *SFDA requirements*. GE provides extensive training and support because users *generally lack chromatography experience*	*Advanced industry* explains strong links to US customers, also for ÄKTApilot inspiration. *Rivalry among customers* and *secrecy issues* induce formalism. *General skills* minimize training needs, but *time-to-market issues* require quick repairs
6- Products/ projects	Few projects and products for ÄKTApilot because the *industry is still nascent*: Few products are at a stage where ÄKTApilot is most useful (preclin. and clinical stage)	*Immature biotech industry*: no parallel projects (one drug one machine). SFDA requirements, patent regulations and IPR affects project choice: *Class 1 products*	*Advanced industry* provides several projects in right stage for ÄKTApilot. *FDA rules* define how ÄKTApilot should be used in a project
7- Other facilities	*New policy* brought attention to GMP approval of facilities and contract research activities	*Govt. pressure* for having GMP-approved facilities	*FDA rules* affect GMP validation. *Time-to-market* and *reliability* favour ÄKTApilot Vs other tools

Table 2: The macro-context factors visible in the seven resource interfaces

The embedding of ÄKTApilot and the macro-factors in the Taiwanese context

Biotech is a nascent industry in Taiwan. The government-targeted areas of biopharmaceuticals and genomics have not yet given significant results. This situation is reflected by the number of ÄKTApilot systems sold in Taiwan, so far only a handful. The biotech industry is on the other hand aggressively

supported by the state. In an effort to speed up the progress in the more advanced biotech areas of genomics and biopharmaceuticals, the government has mandated (semi)governmental research centres to lead the way for the industry functioning as a bridge between academia and industry.

The interface with the *using units* (1) well reflects the tight links to the state of the Taiwanese biotech industry. The purchase of ÄKTApilot by the government-related research centres reveals the ambition of the state to move the local industry into biopharmaceuticals. But to increase flexibility and links to industry, some centres are semi-private. The interface with *financing units* (2) directly involves state agencies and exemplifies the massive government support. Time is not as important issue in the (semi)governmental research institutes as in the private industry. The research centres have been able to conduct their R&D at a slower pace and their own discretion, without venture capitalists breathing on their neck pushing for fast results. The government however decides the direction of R&D through financing certain projects adhering to the government biotech promotion plan.

The interfaces with *upstream units* (3) show that all projects are acquired from external labs and universities because the (semi)governmental research centres do not undertake basic research. The Taiwanese IPR regulations on commercial rights over university discoveries refrain individual scientists from commercialize their discoveries by starting up own firms. The government applies instead the "semiconductor model" that assigns the research centres the role of bridges between upstream research and downstream development. However this has been a much more difficult agenda than expected: the midstream R&D of research centres has been difficult to transfer directly to *downstream units* (4), according to the "open lab" policy. Therefore the research centres have tried to develop the technologies, before passing it on to the private industry. The interfaces with downstream units are however still quite limited, with few private companies with commercial products.

The interface with *GE Healthcare* (5) entails long-term relationships and increasing needs of more advanced separation systems. The constant upgrading of facilities and incoming projects at the using units has also increased the skills of users, so that less training is needed. As technology transfer proceeds, private firms acquiring projects from research centres are becoming targeted customers. The interface with *products/projects* (6) suggests that the Taiwanese biotech industry is still in a nascent phase: ÄKTApilot is used only in a few projects because there are not enough projects that have reached the required maturity. The government development plan also influences the interface with *other facilities* (7), as shown by the increased efforts to set up GMP facilities for contract research and manufacturing. ÄKTApilot has mostly been purchased in an effort to upgrade research facilities.

The embedding of ÄKTApilot and the macro-factors in the Chinese context

The embedding of ÄKTApilot in China has just started, with about ten systems sold to five customers. Like in the case of Taiwan, ÄKTApilot is mainly embedded on an *organisational level*, with units and relationships connected to it. However, there is still more to be done on the *technical level*: a positive sign is the private unit that has finished the development journey and is waiting for the final drug approval. An important finding is that the embedding of ÄKTApilot will take time, much because biotech is a relatively new phenomenon in China, negotiations and sales are very time-consuming and users still need extensive training and support. Like in Taiwan, the micro-interactions around ÄKTApilot in Shanghai show that the national and regional government has been a central actor.

The interface with the *using units* (1) is strongly influenced by the government involvement: the increased public emphasis to develop the biotech industry in the middle of 1990s resulted in that the state-owned using units diversified their business to also include biotech activities. The private unit established their business during the same period. The Chinese education system pervades the skills of the individual user and as a result Chinese users need more support and training: the lack of this experience has complicated the embedding of ÄKTApilot in China. The interfaces with *financing units* (2) reflect a strong government involvement, both for state-owned and private units. Both the studied units had received public funds. Along with public investments there are high expectations on these units to contribute to the growth of the whole biotech industry. Moreover, "government approval status" on projects have facilitated the embedding of ÄKTApilot and acted as a mean to develop new projects according to SFDA requirements. The purchases of ÄKTApilot also reflect the Chinese negotiation process, where time has limited value or cost. In average the purchasing process takes more then six months plus three months for the delivery.

The Chinese government encouragement to gain new technical knowledge through international cooperation is clearly reflected in the micro interfaces with *upstream units* (3). The project origin for both units can be traced to foreign units. One of the units also formed a joint venture with the project source. Technology transfer is expected to generate new knowledge and speed up the growth of the Chinese biotech industry. Interfaces with *downstream units* (4) are somewhat limited: the embedding process has not come that far yet, maybe because of the immaturity of the Chinese biotech industry. Still, reflecting state policies to stimulate industry-academia relations, the private unit has established contacts with university hospitals potentially useful for distributing the approved drug.

The interface with *GE Healthcare* (5) also reflects that ”government approval status” facilitates the embedding of ÄKTApilot. By purchasing ÄKTApilot, a system complying with sanitary requirements, the units show an effort to develop a drug according to SFDA regulations. Long-term relationships between the using units and GE Healthcare have also facilitated the embedding of ÄKTApilot. But the lack of practical chromatography experience has forced GE to intense interactions in order to provide extensive support and training for the individual users. The interface with *products/projects* (6) reveals that the Chinese biotech industry is still immature: each ÄKTApilot is used just for one project/product because there are no other projects and products in the right phase. The units studied only have one or two biotech projects so far. The SFDA and IPR regulations also influence the use of ÄKTApilot: in order to receive a Class 1 drug approval the using units have to comply with SFDA requirements and negotiate IPRs for new drugs. The government also influence the interface with *other facilities* (7): for instance, the decision that all drug manufacturers should have GMP-approved facilities by June 2004 forced the using units to do so.

In summary, the embedding of ÄKTApilot in the Chinese and Taiwanese contexts strongly depends on the government involvement. Policy-related issues can be traced in several interfaces, but whether these public measures will result in a technically advanced user structure is still an open question.

The embedding of ÄKTApilot and the macro-factors in the American context

The US context is the one where the embedding of ÄKTApilot has gone the longest way, not only in terms of installed machines (over 100), but also because ÄKTApilot has become an indispensable tool in the process development activities of its users. Organizationally, ÄKTApilot is strongly embedded through a very frequent utilization at its direct using units, but its effects can be felt also in upstream and downstream units. Technically, ÄKTApilot is now an important part of the technical structure that handles hundreds of R&D proteins and projects.

Embedding in the interface with the *using unit* (1) is facilitated by a generally high process development experience and computer skills, and by the need to automate separation that derives from strong pressures to shorten drugs time-to-market. The interface with *financing* units (2) also reflects time-to-market issues in the fact that purchase decisions are approved quickly (a matter of weeks more than months). Time issues are much more important than cost issues for this strictly *private investment*, provided that it is motivated by ongoing projects.

The interfaces with *upstream and downstream units* (3 and 4) are strongly affected by the FDA-inspired R&D funnel. This normative frame affects how large firms *organize* their R&D: units such as validation & technology transfer units exist because FDA requires exact reproduction of a manufacturing process wherever it is transferred. And generally each individual unit is *extremely specialized* and the coordination among units is strictly *sequential* (i.e., as linear as FDA’s pipeline), with minimal interaction, generating a sort of “silos mentality” even between units located door-to-door. This interface pattern is a result of (1) the strong time-to-market pressure that the stock market exerts on US biotech to have them grow rapidly (10-20% yearly), and (2) of the intense rivalry between competing firms, which result in true innovation races that cause a strong concern with secrecy to defend any form of proprietary knowledge. This also explains why formal IPRs contracts play a dominating role on the interaction with whatever *external* upstream or downstream units may be needed. For smaller firms, IPRs and contracts with large pharmas are moreover a hot currency that affects how venture capitalist and the stock market evaluate them.

The interface with *GE Healthcare* (5) reflects the importance of the local pharmaceutical industry, which induced this supplier to establish a strong basis in the US. American users are so important that they were even contacted to get inspirations to develop ÄKTApilot in the first place. Moreover, their

skills are in general so high that GE needs to provide them minimal training. Fear of leakages of secrets to competitors increases the formalism in GE's customer relationships, where confidentiality is the object of explicit contracts. Also the silos mentality mentioned above surfaces in GE's customer interfaces, kept with several users of the same machine who are seldom aware of other users in the same firm. Finally, time-to-market pressures are evident in the customer need of reliable and fast maintenance service to avoid project delays.

Also the interface with *products/projects* (6) reflects the strong development of the US biotech industry, which makes very many products available for ÄKTApilot to work on. Moreover, this very successful national industry has many projects that have gone a long way from drug discovery into the phases where ÄKTApilot is utilized. Another macro-factor visible in this interface are the FDA template and requirements: they affect how ÄKTApilot is utilized on the products, depending the stage they reached in R&D, with sanitization requirements that are clearly steered by FDA. The interface with *other facilities* (7) is also affected by official norms, such as the FDA protocols that require placing ÄKTApilot into GMP-approved facilities for the production of substances to be injected into humans. The strong concern typical of American users with time-to-market, high quality and reliability issues also gave an advantage to ÄKTApilot compared to other competing tools.

ÄKTApilot's embedding within the US context is favoured especially by the strong market expectations for US biotech firms to launch new products at increasing pace. Contrary to the Chinese and Taiwanese contexts, Instead, the macro-factors related to the American public policy on science and development are almost absent in the micro-interactions around ÄKTApilot[16].

Final comments: embedding and instant industrialization

The investigation of the resource interfaces around ÄKTApilot in the US, Chinese and Taiwanese use contexts has opened the door to what goes on after the supply and installation of a biotech tool. In other words, we provided a picture of the micro- and macro processes that embed a new economic resource into use contexts, including how this focal resource is combined with other resources in several interfaces. We can point out three main conclusions concerning, respectively, (1) the role of resource suppliers, (2) the interplay between micro- and macro-processes, and (3) the possibility to affect embedding by manipulating the macro-factors.

First, the embedding process is largely outside the reach of the supplying company[17]. As among others von Hippel (1988, 1998) has made us aware about, this is a process that to a large extent lies in the hand of those representing the resource combinations on the user side. The embedding of a new resource such as ÄKTApilot and the value that it produces depend on *each single activated interface* with resources on the user side, such as the seven interfaces that was discussed above. Thus, the role of the supplying company is mostly identifying what happens in these resource interfaces, and translating these micro-processes into a device that is still possible to produce, maintain and support by utilising the resources available at the supplying side.

Second, our material clearly shows how such micro-processes are affected by macro-processes in the use context. Table 2 summarizes a few macro-factors that affect the embedding of a resource: for instance, financing forms (public or private), VC and stock exchange pressures, industrial policies (the "Semiconductor model"), education systems, IPRs and other rules and norms (FDA). As for the *nature* of the interplay between macro-processes and micro-interactions, our material suggests that there is no direct and linear causality between *one* macro-factor (public financing or stock market pressures) and *one* micro-interaction (the interface with financing units or with products). Macro-processes and micro-interactions hang together in much more complex ways: several macro-factors can differently affect the very same resource interface and do so in diverging directions. For instance, the Chinese policies favouring industry-academia cooperation may well facilitate interfaces with downstream units, but an immature biotech sector actually limits such interfaces. Moreover, micro-interactions are *per se* complex because resource interfaces affect each other: for instance, GE's interface with one user depends on this user's interface with specific products, on interfaces with other users, etc. etc. These complex micro-interaction patterns make even more indeterminate the effects of macro-factors on a

[16] There are in fact only remote and indirect connections with the drug projects started at US Universities with NIH's public funds or with the government pressure to cut healthcare costs by inducing the development of new, more cost-efficient treatments.
[17] See Harrison & Waluszewski (2004) for a study of the development of user networks around a biotech tool.

single interface: for instance, if a using unit lacks interfaces with products, public financing of equipment purchases cannot favour a strong interface between ÄKTApilot and the using unit.

Third, the above discussion on the complexity of the macro-micro linkages implies that micro-interactions cannot be directly and linearly managed through changes in the macro-processes. Even though manipulating the macro-processes can influence micro-processes, policy measures (public funds or IPR rules) can more easily stimulate some, but not all, micro-interactions on *the supply side*, such as investing in a new biotech tool or acquiring a new drug project. Micro-interactions on *the use side* are instead much more impermeable to policy measures because they entail the creation of actual (not only planned) economic value for users. And value emerges idiosyncratically in resource combinations that take time and are unique to every *micro*-context. What is, for instance, the effect of a generalized policy favouring international cooperation, if the actual micro-interaction between two organizational units has no useful application in terms of a drug project that is in turn really useful to some other actor? The difficulties to steer the embedding of a new technology on the use side are likely to be independent from the political and economic system, as the Chinese and Taiwanese cases indicate. What instead can be determinant in facilitating this embedding is the historically-determined presence in a macro-context of a structure *already filled* with several micro-interactions that can rapidly extract value from the new technology: this is clearly the case of the US context, as opposed to the other two. A biotech industry with a 40-years-old history and even older customer relationships with GE Healthcare Uppsala provide a much more favourable context for embedding ÄKTApilot than a nascent biotech industry that has not yet reached downstream drug development.

However, it is precisely the policy ambition to turn nascent biotech industries overnight into strong ones that we question here. Our findings are in line with those of scholars engaged in long-term empirical studies of industrialisation processes. Sturgeon (2000) poses the intriguing question of whether "instant industrialisation" ever occurred: "The idea that so much could grow in so short time within such a small geographical area sent planning bodies from Albuquerque to Zimbabwe scrambling to grow the next Silicon Valley on their own backyard." But this *myth* overshadows the more typical, unglamorous and multi-faceted micro-interaction patterns reflected in empirical studies of how new firms, products and utilization emerged. The industrialisation of the Silicon Valley did not occur overnight; it has a development history stretching over more than hundred years – and over several different places (Ibid: 16). Thus, what is lost in all success stories focusing on *some* aspect of a much more complicated interaction pattern is first that industrialization processes are complex and hence partly random, so that *"anyplace can be Silicon Valley"* (Ibid: 47). Second, and more severely, the policy recipes inspired by this role model are built on vague understandings of how new economic resources actually get a use and become valuable. Third, the effects of these policy measures are easier to attain on certain processes on the supply side – however, to influence the important processes on the user side seems to be much harder.

We certainly cannot conclude that the policies aiming at instant industrialization in biotech are generally doomed to fail, but without an understanding of the above micro-interactions, which the policy-steered macro-factors somehow needs to affect, these policies would produce the effects of a caterpillar on a patient that needs instead surgical precision.

Reference list

Anderson, J. C., Håkansson, H. & Johanson, J., 1994, Dyadic Business Relationships Within a Business Network Context, *Journal of Marketing*, Vol. 58, Issue 4, October 1994, pp. 1-15.

Andersson, P., 1996, *The emergence and change of Pharmacia Biotech 1959-1995: the power of the slow flow and the drama of great events*, Doctoral Thesis, Stockholm School of Economics.

Axelsson, B., & Easton, G. (eds.), 1992, *Industrial Networks – A New View of Reality,* Routledge: London.

Baraldi, E., 2003, *When Information Technology Faces Resource Interaction. Using IT Tools to Handle Products at IKEA and Edsbyn*, PhD Thesis, Department of Business Studies, Uppsala Univ.

Economist, 2002, *Biotech's yin and yang*, Vol. 365.

Enriquez, J., & Goldberg, R. A., 2000, Transforming Life, Transforming Business: The Life-Science Revolution, *Harvard Business Review*, Mar/Apr2000, Vol. 78, Issue 2, pp. 94-104.

Ford, D., et al. (eds.), 1998, *Managing Business Relationships*, Wiley: Chichester.

Fox Keller, E., 2000, *The Century of the Gene*, Harvard University Press: Cambridge, MA, London.

Grace, E. S., 1997. *Biotechnology Unzipped. Promises and Realities*, Joseph Henry Press: Washington.

Harrison, D., & Waluszewski, A., 2004, *How to Create Lead-Users and New Economic Resources.* Paper presented at the 20th IMP Conference, Copenhagen, 2004.

Huang, J., & Wang, Q., 2003, *Biotechnology policy and regulation in China*, Institute of Development Studies, Brighton.

Håkansson, H. (ed.), 1982, *International Marketing and Purchasing of Industrial Goods: an Interactive Approach*, Wiley: Chichester.

Håkansson, H. (ed.), 1987, *Industrial Technological Development – A Network Approach*, Croom Helm: London, Sidney, Dover, New Hampshire.

Håkansson, H., 1989, *Corporate Technological Behaviour. Cooperation and Networks*, Routledge: London.

Håkansson, H., & Snehota, I., 1989, No Business is an Island: the Network Concept of Business Strategy, *Scandinavian Journal of Management*, Vol. 5, No. 3, 1989, pp. 187-200.

Håkansson, H., & Snehota, I. (eds.), 1995, *Developing Relationships in Business Networks*, Routledge: London.

Håkansson, H., & Waluszewski, A., 2002, *Managing Technological Development. IKEA, the environment and technology*, Routledge: London.

Janson, J-C., 1987, On the History of the Development of Sephadex®, *Chromatographia*, Vol. 23, No. 5, May 1987, pp. 361-369.

Kenney, M. (ed.), 2000, *Understanding Silicon Valley. The Anatomy of an Entrepreneurial Region*, Stanford University Press: Stanford, CA.

Kenney, M., Han, K., & Tanaka, S. 2002, *Scattering Geese: The Venture Capital Industries of East Asia: A Report to the World Bank*, Berkeley Roundtable on the International Economy. Paper BRIEWP146. http://repositories.cdlib.org/brie/BRIEWP146.

Li, Y.P., (ed.), 2003, Shanghai 2003, *Asia Pacific Biotech*, Vol. 7, No. 5.

Louët, S., 2004, Can China bring its own pipeline to the market?, *Nature Biotechnology*, Vol. 22, Dec, 2004, pp. 1497-1499.

Lundvall, B-Å (ed.), 1992, *National Systems of Innovation: Towards a Theory of Innovation and Interactive Learning*, Pinter: London.

Malmberg, A., Maskell, P., The elusive concept of localization economies: towards a knowledge-based theory of spatial clustering. *Environment Planning* 2002, vol. 34, pp. 429-449

Nelson, R. (ed.), 1993, *National Innovation Systems: A Comparative Analysis*, Oxford University Press: New York.

Penrose, E., 1959, *The Theory of the Growth of the Firm*, Reprint 1995, Oxford University Press: New York.

Porter, M. E., 1990, *The Competitive Advantage of Nations*, Macmillan: London.

Porter, M. E., 2000, Locations, Clusters and Company Strategy, In: Clark, G. L. et al. (eds.), 2000, *Handbook of Economic Geography*, Oxford University Press: Oxford.

Robbins-Roth, C., 2000, *From Alchemy to IPO. The Business of Biotechnology*, Perseus Publishing, Cambridge, MA.

Scientific American, 2000, *Beyond The Human Genome*, July 2000, pp. 64-69, by Carol Ezzell.

The Scientist, 2004, *BRANY: Trying Trials Together*, Vol. 18, Nov. 22, 2004, by Vicki Browner.

Sturgeon, T. J., 2000, *How Silicon Valley Came to Be*, In: Kenney, M. (ed.), *Understanding Silicon Valley. The Anatomy of an Entrepreneurial Region*, Stanford University Press: Stanford, CA.

Teece, D. J,, 1986, Profiting from technological innovation: Implications for integration, collaboration, licensing and public policy, *Research Policy*, Vol. 15, Issue 6, pp. 285-305.

Teece, D. J., & Pisano, G. P., 1994, The Dynamic Capabilities of Firms: an Introduction, *Industrial & Corporate Change*, Vol. 3, Issue 3, pp. 537-556.

Tidd, J., Bessant, J., & Pavitt K., 2001, *Managing Innovation, Integrating Technological, Market and Organizational Change*, Second edition, Wiley: Chichester.

Van de Ven, A., Polley, D., Garud, R., & Venkataraman, S., 1999, *The Innovation Journey*, Oxford University Press: New York, Oxford.

von Hippel, E., 1986, Lead Users: A Source of Novel Product Concepts, *Management Scienc*e, Vol. 32, No. 7, pp. 791-805.

von Hippel, E., 1988, *The Sources of Innovation*, Oxford University Press: New York.

von Hippel, E., 1998, Economics of Product Development by Users: The Impact of “Sticky” Local Information, *Management Science*, Vol. 44, No. 5, 1998, pp. 629-644.

Waluszewski, A., 2004, A competing or co-operating cluster or seven decades of combinatory resources? What’s behind a prospering biotech valley?, *Scandinavian Journal of Management*, Vol. 20, pp. 125-150.

Wedin, T., 2001, *Networks and Demand. The Use of Electricity in an Industrial Process,* Doctoral Thesis, Department of Business Studies, Uppsala University.

Online sources

www.bio.org

www.biotecheast.com

www.nih.gov

http://english.cas.cn/Eng2003/page/home.asp