Drivers and barriers of cross-border sectoral ecosystems: The Pharmaceutical sector in an all-island context

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Abstract

This paper explores drivers and barriers to cross-border economic integration in the Ireland-Northern Ireland context. Via a case-study of the Irish pharmaceutical sector, we show that potential economic benefits of an all-island sectoral ecosystem have been recognised by businesses and policymakers in both jurisdictions. However, those economic benefits within the pharmaceutical sector have not materialised. We explore this situation by employing the concept of *proximity*. Proximity refers not only to geographic or spatial proximity, but also encompasses cognitive, organizational, institutional, and social proximities. Our findings indicate that a mix of proximities are necessary in order to overcome impediments to cross-border economic integration. While industry actors may enjoy geographical proximity due to their business locations and cognitive proximity in terms of overlapping industry and scientific knowledge, without the requisite institutional and social proximities cross-border economic integration may struggle to achieve its potential.

Introduction

Recent research into cross-border economic integration processes has brought to the fore some inconvenient truths. Even in instances of enhanced cross-border mobility, common language, similar levels of human capital, and ongoing policy initiatives aimed at fostering greater cross-border co-operation, studies across a range of cross-border settings in the EU and further afield reveal that negative border effects can prove very difficult to overcome.[1] Perhaps one of the more striking examples of this in an economic context can be seen in a recent study of cross-border cooperation amongst automotive enterprises in the EU region of Saar-Lor-Lux, which consists of five sub-regions belonging to four nation states and is one of the largest and most institutionalized cross-border regions in Europe.[2] Despite automotive clusters in each of the five sub-regions, the study found that while many enterprises expressed an interest in cross-

[1] In addition to the EU cross-border studies discussed in this paper, see Cappellano (2020) for a study of the Cascadia (US-Can) border region which spans from Vancouver to Seattle. Cappellano notes: "A very fragmented innovation ecosystem exists in Cascadia. Despite the great potential for collaboration, there is not much interaction among actors across the border." Francesco Cappellano, *Cross Border Innovation Economies: The Cascadia Innovation Corridor Case*, (Bellingham, WA: Border Policy Research Institute Mendoza et al. (2020) provide study of the contrasting economic and social goals of actors in the San Diego–Tijuana cross-border region. The authors note: "both challenger and incumbent actors consider that the further development of cross-border cooperation and governance is fragile, and depends on institutions beyond local power dynamics. [..] Both types of actors considered that the border is a region with specific features that is negatively affected by the policies of national governments that prioritize security." Jorge Eduardo Mendoza and Bruno Dupeyron, Economic Integration, Emerging Fields and Cross-border Governance: The Case of San Diego–Tijuana, *Journal of Borderlands Studies* 35:1 (2020), 55-74: 72.

[1] Christoph K. Hahn, The transboundary automotive region of Saar-Lor-Lux: Political fantasy or economic reality? *Geoforum* 48 (2013),102–113

[1] Hahn, "The transboundary automotive region", 111

[1] Claire Nauwelaers, Karen Maguire, and Giulia Ajmone Marsan, The case of Oresund (Denmark-Sweden) - Regions and Innovation: Collaborating Across Borders (OECD Regional Development Working Papers No. 21, 2013), 11.

[1] See Gilles Duranton, Philippe Martin, Thierry Mayer, and Florian Mayneris, *The Economics of Clusters*. (Oxford: Oxford University Press, 2010), or Gregory M. Spencer, Tara Vinodrai, Meric S. Gertler, and David A. Wolfe (2010) Do clusters make a difference? Defining and assessing their economic performance, *Regional Studies* 44(6) (2010), 697–715.Publications, 2019), 25. Mendoza et al. (2020) provide study of the contrasting economic and social goals of actors in the San Diego–Tijuana cross-border region. The authors note: "both challenger and incumbent actors consider that the further development of cross-border cooperation and governance is fragile, and depends on institutions beyond local power dynamics. [..] Both types of actors considered that the border is a region with specific features that is negatively affected by the policies of national governments that prioritize security." Jorge Eduardo Mendoza and Bruno Dupeyron, Economic Integration, Emerging Fields and Cross-border Governance: The Case of San Diego–Tijuana, *Journal of Borderlands Studies* 35:1 (2020), 55-74: 72.

[2] Christoph K. Hahn, The transboundary automotive region of Saar-Lor-Lux: Political fantasy or economic reality? *Geoforum* 48 (2013),102–113

border relationships, actual cross-border collaboration was rare. The author concluded that "the image of such a situation characterized by extensive cross-border cooperation, which is promoted by regional politicians, is more imagination than economic reality."[3] Indeed, even regions such as Öresund that have achieved a relatively high degree of cross-border integration have encountered challenges arising from, for example, a lack of national level cross-border policies and a need to develop a stronger internal regional identity.[4] Of course, case studies are by their nature context-specific and their findings might not extend to all cross-border settings. However, if enhancing cross-border economic integration has proved to be challenging in what would appear to be fertile environments for such integration, then such cautionary tales should be given due regard.

This paper explores drivers and barriers pertaining to cross-border economic integration in the Ireland-Northern Ireland context. In particular, we focus on economic relationships across industry actors in an all-island setting. We illustrate this via the concept of *ecosystem*, which in analogy to the biological term has been used in recent research to characterise the web of symbiotic relationships in which industry actors operate. Within a given sector or industry, an ecosystem depicts a community comprised of individuals, firms and organisations that interact with each other to their mutual benefit. The ecosystem concept is particularly well suited for exploring issues related to cross-border economic integration, as the spatial extent of such an ecosystem is unlikely to be well defined by administrative boundaries. While the ecosystem in which an enterprise operates is not necessarily spatially bounded, the influence of adjacent actors including other enterprises in the same sector is likely to considerably greater than that

[3] Hahn, "The transboundary automotive region", 111

[4] Claire Nauwelaers, Karen Maguire, and Giulia Ajmone Marsan, The case of Oresund (Denmark-Sweden) - Regions and Innovation: Collaborating Across Borders (OECD Regional Development Working Papers No. 21, 2013), 11.

of actors that are further away.[5] This implies that clusters or sectoral concentrations may play an important role in the development and functioning of an sectoral ecosystem. However, as noted above, the national border may give rise to border effects which hinder the development of optimal ecosystems across adjacent border regions. It is this tension between ecosystem and border effect that this paper seeks to explore.

In what follows, we present a case-study of the Irish and Northern Irish pharmaceutical sectors. Through this case-study we ascertain, via 32 interviews with corporate and institutional stakeholders on both sides of the border, the potential economic benefits of an all-island ecosystem in the pharmaceutical sector. However, we show that the potential economic benefits of an all-island the pharmaceutical sector have not been realised. This paper seeks to understand what impediments prevent the development of this all-island ecosystem and why these impediments have proven to be persistent.

This paper explores the functioning of the all-island Pharmaceutical sector ecosystem via the concept of *proximity*. Proximity refers not only to geographic or spatial proximity, but encompasses a range of relational proximities, but extend to cognitive, organizational, institutional, and social proximities (discussed in the next section).[6] The pharmaceutical case-study presented in this paper provides a basis for discussing the role of proximity or lack thereof between actors - in terms of their cognitive knowledge bases, organizational memberships, institutional structures, and social relations – in facilitating or impeding cross-border economic integration. Our findings indicate that a mix of proximities are necessary in order to overcome

[5] See Gilles Duranton, Philippe Martin, Thierry Mayer, and Florian Mayneris, *The Economics of Clusters*. (Oxford: Oxford University Press, 2010), or Gregory M. Spencer, Tara Vinodrai, Meric S. Gertler, and David A. Wolfe (2010) Do clusters make a difference? Defining and assessing their economic performance, *Regional Studies* 44(6) (2010), 697–715.

[6] See, for example: Ron Boschma, Proximity and innovation. A critical assessment, Regional Studies 39 (2005), 61–74.

impediments to cross-border integration. While industry actors may enjoy geographical proximity due to their business locations and cognitive proximity in terms of overlapping industry and scientific knowledge, without the requisite institutional and social proximities cross-border economic integration may struggle to achieve its potential.

Ecosystems, Proximity and Borders

The concept of *ecosystem* brings together related streams of literature from a diverse set of research fields, including business management, economic geography, innovation studies, and regional development. Two particularly prominent uses of the ecosystem concept to emanate from this breadth of research areas are *knowledge ecosystems* and *business ecosystems*.

A business ecosystem refers to an interrelated system of companies, who create value by combining their skills and assets.[7] The ecosystem is a networked entity within which firms engage in both collaborative and competitive relationships with one another. A firm's presence within such an ecosystem can enable it to source competences beyond its own skillset as it seeks to commercialise a product or service. With the ecosystem, firms can also access resources and information pertinent to their competitive environment.[8] A knowledge ecosystem, on the other hand, is a network of knowledge flows comprising of firms and a wider set of public and private sector actors.[9] Universities and public research organizations are seen as being central in generating technological innovation within the system, and firms derive

[7] James F. Moore, Predators and prey: a new ecology of competition, *Harvard Business Review* 71 (3) (1993) 75–86; James F. Moore, Business Ecosystems and the view from the firm, *The Antitrust Bulletin* 51 (1) (2006), 31-75.

[8] Marco Iansiti and Roy Levien, *The keystone advantage: What the new dynamics of business ecosystems mean for strategy, innovation, and sustainability* (Boston: Harvard Business School Press, 2004); Shaker A. Zahra and Satish Nambisan, Entrepreneurship and strategic thinking in business ecosystems, *Business Horizons* 55 (2012), 219–229.

[9] Paul Almeida and Bruce Kogut, Localization of knowledge and the mobility of engineers in regional networks. *Management Science* 45 (1999) 905–917; Bart Clarysse, Mike Wright, Johan Bruneel, and Aarti Mahajan, Creating value in ecosystems: crossing the chasm between knowledge and business ecosystems, *Research Policy*, 43(7) (2014), 1164-76.; Leonardo Augusto de Vasconcelos Gomes, Ana Lucia Figueiredo Facin, Mario Sergio Salerno, Rodrigo Kazuo Ikenami, Unpacking the innovation ecosystem construct: evolution, gaps and trends, *Technological Forecasting & Social Change*, 136 (2018), 30-48.

benefits within this ecosystem in the form of knowledge spillovers and availability of specialised labour.[10] Knowledge ecosystems tend to be characterised by features such as: a diversity of organizational forms, in order to enhance the adaptive capacity of the knowledge ecosystem; the presence of one or more anchor organizations, whose basic and applied research triggers technological innovation via R&D collaborations with local industry; and the presence of a mechanism for cross-network alignment between the various industry and academic actors.[11]

Given that many industry actors may be common to both types of ecosystem, business ecosystems and knowledge ecosystems may be viewed as overlapping ecosystems. Indeed, Clarysse et al. contend that policy support for publicly funded regional innovation initiatives is implicitly predicated on the assumption that the technological innovations generated by knowledge ecosystems will automatically lead to the formation of business ecosystems.[12] However, Clarysse et al. set out significant points of difference between knowledge ecosystems and business ecosystems: (i) the function of knowledge ecosystems is the generation of new knowledge whereas business ecosystems are formed in order to establish competitive advantage and create value; (ii) knowledge ecosystems and business ecosystems can have distinct geographies – depending on the extent to which businesses operate within global value networks, or the extent to which universities collaborate with local or global research partners; and (iii) knowledge ecosystems and business ecosystems have different key players - a university or public research office in the knowledge ecosystem and one or more large companies in a business ecosystem.[13]

[10] Mike Wright, Bart Clarysse, Andy Lockett, and Mirjam Knockaert, Mid-range universities' linkages with industry: knowledge types and the role of intermediaries, *Research Policy* 37 (8) (2008), 1205–1223.
[11] Ajay Agrawal and Iain M. Cockburn, University research, industrial R&D and the anchor tenant hypothesis. NBER Working Paper 9212 (2002).
[12] Clarysse et al. "Creating value in ecosystems", 1164.
[13] Clarysse et al. "Creating value in ecosystems", 1166.

Ecosystems and networked knowledge flow have become prominent concepts in understandings of cross-border economic integration processes. As Hahn notes, traditional economic approaches to regional economic development emphasise quantitative variables, such as costs or physical distance, and underplay the role of networked actors tend to characterize the workings of the economy in an "under-socialized" manner.[14] A relational perspective, such as that characterised by ecosystems, augments traditional economic concerns by focussing attention on the role of private and public sectors actors, interactions and knowledge flow, the overarching set of institutions, and the wider social context of regional development.[15] Furthermore, and of particularly relevance for this paper given the territorial dimension inherent in the cross-border context, an ecosystems approach provides an opportunity to explore the role of proximity in the cross-border integration process. The tensions between business and knowledge ecosystems noted above potentially add to the complexity of cross-border economic integration and, as discussed below, the concept of proximity offers a useful means of exploring this complexity.

While there are many possible forms of cross-border economic integration, recent research into cross-border innovation activities has proven to be insightful in exploring factors that help and hinder cross-border co-operation. As Lundquist and Trippl note, integration and enlargement of local consumer and factor markets, enhancing labour mobility, extending the division of labour and specialization are probably all easier initial approaches to cross-border integration than seeking to cultivate a cross-border innovation-oriented growth path.[16] Indeed, as van den Broek et al. succinctly state: "Border regions are not often associated with innovation and

[14] Christoph K. Hahn, The transboundary automotive region of Saar-Lor-Lux: Political fantasy or economic reality? *Geoforum* 48 (2013),102–113: 103.
[15] Harald Bathelt, Geographies of production: growth regimes in spatial perspective 3 – toward a relational view of economic action and policy. *Progress in Human Geography* 30 (2) (2006), 223–236.
[16] Karl- Johan Lundquist and Michaela Trippl, Distance, proximity and types of cross-border innovation system: a conceptual analysis, *Regional Studies*, 47(3) (2013), 450–460.

economic prosperity."[17] However, studies of cross-border integration need not be confined merely to economic development of adjacent local areas on either side of a given border. Cross-border integration can also be viewed as bringing together a range of multilevel institutional architectures from both sides of the border – some of which may be local or regional but others which are national in scope.[18] The literature on cross-border innovation activities helps to provide insights into the ease or difficulty of mapping these multilevel institutional architectures onto one another at a cross-border level.

Extant literature on cross-border innovation has emphasised the role of proximity as a determinant of cross-border innovation activities. Proximity in this context extends beyond mere spatial proximity and encompasses a range of relational proximities.[19] A typology of the various proximities that feature in this line of literature is provided in Table 1 (below).

[17] Jos van den Broek, Paul Benneworth, and Roel Rutten, Border blocking effects in collaborative firm innovation, *European Planning Studies*, 26:7 (2018), 1330-1346: 1330.
[18] Jos van den Broek and Huub Smulders, Institutional hindrances in cross-border regional innovation systems. Regional Studies, *Regional Science* 2(1) (2015), 116–122.
[19] Francesco Cappellano and Teemu Makkonen, The Proximity Puzzle in Cross-Border Regions, *Planning Practice & Research* 35:3 (2020), 283-301.; Lundquist and Trippl, "Distance, proximity and types of cross-border innovation system", 452-454.

Table 1: Typology of proximities in cross-border research

Types of proximity	**Description**
Geographical	Territorial, physical cross-border proximity; the ease of mobility for people and goods in terms of time and cost.[20]
Cognitive	The degree of overlap between two actors concerning their knowledge bases.[21]
Organizational	Membership of the same organizational entity.[22]
Institutional	Proximity in terms of formal institutions (e.g. laws and regulations) and informal institutional structures (e.g. values, norms, beliefs).[23]
Social	Proximity in terms of embedded relations between agents at the micro-level.[24]

Source: adapted from Cappellano and Makkonen (2020a) and Lunquist and Trippl (2013)

However, recent research into cross-border innovation has begun to speak of a *proximity puzzle*.[25] Cappellano and Makkonen, in their study of cross-border cooperation in the US-Canadian Cascadia region find that even though high levels of cognitive proximity (as measured by co-publications, co-patents, and networking) are evident at a cross-border level, economic integration in the cross-border region has remained relatively low.[26] As well as indicating that cognitive proximity may be a necessary but not sufficient condition for cross-border economic growth, Cappellano and Makkonen highlight the need for a greater

[20] Jerker Moodysson and Ola Jonsson, Knowledge collaboration and proximity: the spatial organization of biotech innovation projects, *European Urban and Regional Studies* 14 (2007), 116–131; André Torre, Temporary geographical proximity in knowledge transmission, *Regional Studies* 42 (2008), 869–889.

[21] Bart Nooteboom, Wim van Haverbeke, Geert Duysters, Victor Gilsing, and Ad van den Oord, Optimal cognitive distance and absorptive capacity, *Research Policy* 36 (2007), 1016–1034; Tom Broekel and Ron Boschma, Knowledge networks in the Dutch aviation industry: The proximity paradox, *Journal of Economic Geography* 12(2) (2011), 409–433.

[22] Pierre-Alexandre Balland, Proximity and the evolution of collaboration networks: Evidence from research and development projects within the global navigation satellite system (GNSS) industry, *Regional Studies*, 46(6) (2012), 741–756.

[23] Ron Boschma, Proximity and innovation. A critical assessment, Regional Studies 39 (2005), 61–74.

[24] Boschma, Proximity and innovation, 61-74.

[25] Broekel and Boschma, "Knowledge networks in the Dutch aviation industry", 409-433.

[26] Cappellano and Makkonen "The Proximity Puzzle in Cross-Border Regions", 283-301.

understanding of how differing proximity types and extents may facilitate or hinder cross-border cooperation.[27]

In an EU context, a similar finding emerges from Hahn's study of transboundary cooperation amongst automotive firms in the Saar-Lor-Lux region – a region which consists of five sub-regions belonging to four EU member states.[28] Despite the presence of automotive clusters in each of the five sub-regions and continued policy support for greater cross-border co-operation, Hahn finds little evidence of transboundary interaction between the automotive firms. Hahn attributes this firstly to the "multitude of diverging attitudes toward cross-border relations" at a firm-level among the automotive enterprises in the region, and secondly due to a range of border effects such as "cultural and linguistic barriers as well as the existence of prejudices and local patriotism" – all of which, Hahn notes, serve to reduce cross-border proximity. Echoing Jukarainen, Hahn calls for greater recognition in cross-border studies of the role of "everyday" economic interactions and behaviours in impeding or enhancing cross-border co-operation.[29] In the proximity typology outlined in Table X, Hahn's finding point of insufficient cross-border social and (informal) institutional proximity rather than a dearth of cognitive proximity.

Embeddedness of individual actors in existing formal and informal institutions on either side of a given border is further explored in a series of studies by van den Broek and co-authors. For example, van den Broek and Smulders, in a study of the horticultural industry in the Dutch region of Venlo and the German Lower Rhine region, characterise cross-border cooperation as an aggregate of micro-level behaviours: "At a micro-level, the border expresses itself through the behavioural pattern of individuals who cooperate across borders. The accumulation of all individual cross-border cooperation strategies results in a macro-effect, which reflects the

[27] Cappellano and Makkonen "The Proximity Puzzle in Cross-Border Regions", 294
[28] Hahn, "The transboundary automotive region", 102:113.
[29] Pirjo Jukarainen, Border research in practice and theory, *Cooperation and Conflict: Journal of the Nordic International Studies Association* 41 (4) (2006), 470– 473.; Hahn, "The transboundary automotive region", 103.

systematicness of cross-border cooperation".[30] van den Broek et al., in a study of firm-level collaboration in the Dutch-Flemish border region, argue that firms – particularly SMEs - may lack the capacity to build new networks across borders.[31] Characterising firm-level cross border innovation collaboration as a four stage process (initiation - partner selection – set-up – realization), van den Broek et al. argue that the first two stages are particularly onerous for firms, as they may lack both a meaningful rationale for seeking a cross-border partner and knowledge of potential collaboration partners on the other side of the border, particularly in activities outside of their own core competence.[32] In addition to this, Klatt and Herrmann note that borders can manifest themselves in a range of administrative obstacles to cross-border interaction, ranging from differing tax systems, social security systems, legislation and vocational training systems – all of which have to be navigated by firms engaging in cross-border collaboration.[33] Indeed, given the prevalence of such cross-border information barriers, Cappellano and Makkenon highlight the pivotal role that non-governmental intermediary organisations can play in supporting cross-border entrepreneurship, innovation and competitiveness through their capacity to share knowledge and provide access to funding streams, co-working spaces and cross-border networks.[34]

Taken as a whole, it appears that firms and other industry actors must balance a complex set of proximities that influence their capacity to engage in cross-border co-operation. Firms, in their everyday activities at a micro level, are embedded in an existing institutional and social context that conditions their behaviours, and this context can hinder relational proximities developing

[30] van den Broek and Smulders, "Institutional hindrances", 117.
[31] van den Broek et al., "Border blocking effects in collaborative firm innovation", 1330.
[32] van den Broek et al., "Border blocking effects in collaborative firm innovation", 1333-1334.
[33] Martin Klatt and Hayo Herrmann, Half empty or half full? Over 30 years of regional cross-border cooperation within the EU: Experiences at the Dutch–German and Danish–German border, *Journal of Borderlands Studies* 26(1) (2011), 65–87.
[34] Francesco Cappellano and Teemu Makkonen, Cross-border regional innovation ecosystems: the role of non-profit organizations in cross-border cooperation at the US-Mexico border, *GeoJournal* 85 (2020), 1515–1528.

between firms at a cross-border level. In what follows, we explore the role of these proximities in the context of a particular cross-border ecosystem: the Ireland-Northern Ireland pharmaceutical sector.

Data and Methodology

The case study presented in the next section analysing development of the Irish and Northern Irish pharmaceutical sectors, sets out the key ecosystem components, and demonstrates the benefits and potential for a more integrated all-island sectoral ecosystem. The sectoral context in terms of output, employment, exports, and innovative activity is also outlined, informed by secondary source quantitative datasets, as well as policy documents and academic literature. Subsequent analysis and discussion then identifies impediments to the further development an all-island ecosystem.

The case-study is based on qualitative data, collected via an extensive set of interviews. Interviews were undertaken with institutions and companies on both sides of the border - 10 government departments or associated agencies, 3 industry associations, 5 research and/or education institutes, and 4 pharmaceutical companies. In all, 32 interviews were undertaken in 2015 while additional interviews were conducted in 2021, mainly to collect data on recent developments. The set of institutions interviewed was selected with a view to representing the full range of cross-border institutions that could potentially contribute an all-island pharmaceutical sector ecosystem. Companies for interview were selected on the basis of their involvement in the research and innovation ecosystems.

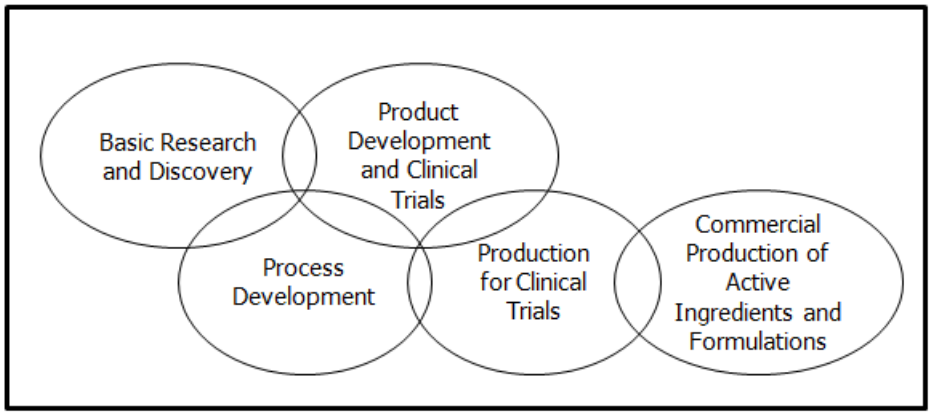
Interviews were conducted in a semi-structured format and the duration of each interview was circa one hour. Interviews sought to ascertain the level of cross-border integration and the

benefits of further integration in the areas of research and innovation, education and training, and markets for products and services. Interviews also explored barriers to further cross-border integration of the two national ecosystems. Customised interview guides were tailored to the type of institution and its involvement in the different elements of the ecosystem.

The Pharmaceutical Sectors in Ireland and Northern Ireland

Figure 1 presents a simplified depiction of the value chain of the pharmaceutical industry. A basic model includes the following segments: discovery, product development and clinical trials, process research and development, active ingredient manufacturing, drug product manufacturing (formulation). Discovery covers the initial product R&D activities, i.e. research into the causes of diseases and the identification of small or large molecules that have a pharmacological effect. Product development includes the further development of these compounds, and notably their testing in pre-clinical and clinical trials. Process R&D is concerned with the development of safe and efficient manufacturing processes at commercial scale. Manufacturing encompasses the production of active ingredients and drug products (formulations). The pharmaceutical sectors in Northern Ireland and Ireland are focussed on selected elements of this value chain.

Fig. 1. Value chain pharmaceutical industry



Source: based on Van Egeraat (2010)[35]

The pharmaceutical ecosystem involves a diverse range of actors. The business segment includes both 'big pharma' companies and smaller dedicated biotech companies. These depend strongly on the technology developed by pharma equipment vendors, engineering companies and services providers. All these are supported by enterprise agencies and focused business and employers associations. Academic Institutions develop the requisite human resources, knowledge and technology. The clinical segment is represented by hospitals, clinical trials units, medical and para-medical staff. In addition to actors on the island of Ireland, a range of organisations outside these jurisdictions play an important role in the sectoral ecosystems, for example the UK Research Councils, Cancer Research UK, and EU institutions.

In 2015, the pharmaceutical sector (SIC 21) in Northern Ireland employed about 1900 employees in 16 companies (Northern Ireland Census of Employment). Most of the employees are concentrated in a handful of large indigenous, research active multinational pharmaceutical companies. Very few foreign pharmaceutical companies operate in Northern Ireland. The

[35] Chris Van Egeraat, The Scale and Scope of Process R&D in the Irish Pharmaceutical Industry, *Irish Geography* 43(1), 2010, pp. 35-58.

number of small dedicated biotechnology companies active in pharmaceutical drug discovery is also small.

Policy documents (Matrix, 2008[36]; DETI, 2014[37]) and institutional interviews reveal a two-pronged vision and related strategy for developing the pharmaceutical sector in Northern Ireland. The first strategy is to nurture the development of existing indigenous players and stimulate new indigenous company formation. A second strategy is to stimulate public sector R&D activity. Both the private and public segments of the ecosystem are oriented towards translational research activity, which makes the findings from basic science useful for practical healthcare and pharmaceutical applications. For the pharmaceutical sector this entails a strong integration of basic research, applied research and clinical trials activity.

The policy documents state that Northern Ireland has some of the building blocks in place but is lacking critical mass. The solution is partly sought in effective networking to foster collaboration. The interviews underpinning the study suggest that existing formal networks and collaborative programs have a predominantly local focus. It is argued that the realm of collaboration should extend beyond Northern Ireland, particularly to the Republic of Ireland and the rest of the UK.

The pharmaceutical sector of Ireland is substantially larger than that of Northern Ireland. In 2015, the commercial segment of the pharmaceutical sector employed about 17,600 workers in 88 companies (Forfás Employment Survey). The majority of the workforce is employed in foreign companies, mainly involved in production activities. Their role in the high-value

[36] MATRIX. *Life and Health Sciences Horizon Panel Report*. Vol. 2. Belfast*:* Matrix, The Northern Ireland Science Industry Panel, 2008.
[37] DETI, *Framework for Smart Specialisation* (Draft), Belfast: Department of Enterprise Trade and Investment, 2014.

generating functions of drug discovery and product development has remained very limited. Since the mid-1990s subsidiaries of foreign companies have begun to play an increasing role in process R&D functions, adding pilot plant capability (Van Egeraat and Curran, 2013).[38]This has facilitated the up-grading of production facilities into global strategic launch sites.

The indigenous pharmaceutical industry segment is relatively small, particularly since Elan, long the biggest indigenous success story, was partly acquired by foreign interests. The number of new indigenous small dedicated biotechnology companies active in pharmaceutical drug discovery is also relatively small.

In the early 2000s, the Irish government developed a vision of a less truncated pharmaceutical industry. One of the strategies was to stimulate multinational pharma companies to upgrade the production activities of the subsidiaries by adding upstream activities, notably process R&D. This positioned plants as multi-product global strategic launch plants that could also produce clinical trials material. Part of the vision was to position Ireland as a global centre for process development and new product launch. In parallel, the Irish government established a major science and technology funding program in the form of Science Foundation Ireland (SFI). It was envisaged that this would be the source of university spin-outs that could add to an indigenous research-based element to the pharma cluster. However, the number of university spin-outs involved in pharmaceuticals has remained limited. The enterprise strategy is now being rebalanced, with more attention being paid to the production / process development cluster.

[38] Chris van Egeraat and Declan Curran, Spatial Concentration in the Irish Pharmaceutical Industry: The Role of Government Intervention and Agglomeration Economies, *Journal for Economics and Social Geography*,104:3 (2013), 338-358.

Both Ireland and Northern Ireland have built, and are developing, strengths in the area of translational research in pharmaceuticals. In Ireland this strength is concentrated in process research and development. In Northern Ireland, on the other hand, the focus is on product research and development.

Current and Potential Level of Cross-Border Integration of the Pharmaceutical Ecosystem

This section discusses the current and potential level of cross-border integration of the pharmaceutical ecosystem. The labour market for the pharmaceutical industry is highly integrated. We will therefore focus on the levels of integration in the areas of Research, Technology & Innovation; Education & Training; and Market for Products and Services.

Research, Technology & Innovation

The research and innovation element of the pharmaceutical ecosystem involves a large number of actors, lines of coordination and funding. In Ireland, Science Foundation Ireland (SFI) is the government's largest research funding body. Through its various programmes SFI funds a range of research centres and principle investigators active in pharmaceuticals. The other two enterprise agencies, IDA Ireland and Enterprise Ireland (EI) have co-funded pharma technology centres. Finally, the Health Research Board funds a variety of clinical research groups and facilities. Northern Ireland does not have an equivalent of SFI. Comparable types of funding are here provided by the centralised Research Councils UK, notably Biotechnology and Biological Sciences Research Council (BBSRC) and the Medical Research Council (MRC). Invest Northern Ireland (INI) has co-funded the Northern Ireland Centre for Stratified Medicine. The HSC R&D has funded clinical research networks and units.

The literature and interviews suggest that most of the current research centres, institutions and many of the networks have primarily a national orientation. The initial partners of research centres, technology centres and institutions are typically from within the country. Similarly, although most researchers would nurture their own *informal* international networks, the *formally* created networks tend to have a strong national focus.

The main exception takes the form of pharma-related projects funded under the US-Ireland R&D Partnership Program. The overall goal is to increase the level of collaborative R&D across the three jurisdictions. Other exceptions include a small number of SFI funded projects which include a Northern Ireland company or Principal Investigator. Examples of purposefully developed cross-border networks include the North West Health Innovation Corridor and the Diabetes Network, but these are relatively small networks in the overall ecosystem.

Clinical trials are an important component of the pharmaceutical innovation process. They support the drug discovery and development functions of public sector research institutes and private sector pharmaceutical companies. They are generally conducted in clinical trials units linked to hospitals. Clinical trial units typically offer access to patients and clinical trial services to public sector research groups and/or pharmaceutical companies wishing to trial their drugs at various stages of development. Ireland and Northern Ireland operated separate clinical trials ecosystems and, individually, the countries have a limited recruitment base.

As regards potential, interviewees generally espoused the idea of further integrating the level of all-island coordination of research centres and networks. The centres, institutions and researchers in each jurisdiction have different strengths and there are clear synergies that could produce significant economies of scope. Centres, groups and researchers would benefit

strongly from shared efforts and experience in applications for funding. There are very few institutional governance-related restrictions to strengthening all-island coordination. But the interviews paint a picture of a very low level of cross-border familiarity across the research landscape.

A strengthened all-island research ecosystem would require genuine all-island research centres, institutes and formal networks. The development of such centres and networks and institutes requires visibility, familiarity and trust. The SFI's Industry Fellowship program offers a good vehicle to build informal networks with which to enhance the level of familiarity and trust. However, the cross-border uptake of this and other programmes is very low and the problem is one of a lack of interest or awareness.

In addition, there is a need to increase the visibility of North-South collaboration opportunities in general. This could take the form of all-island show-casing events dedicated to the pharma industry, where centres, institutions, companies, researchers, and funding bodies can connect. This would serve to enhance the visibility of opportunities and could again support the nurturing of informal networks which can serve as the basis for more formal levels of coordination.

Another element of the strategy could be the fostering of formal all-island centres, institutions and networks. Again, existing programmes can assist in the delivery of this, such as the agreement that SFI reached with the then Department of Employment and Learning (DEL) in Northern Ireland to encourage applications, co-funded by the two organisations, between groups in Ireland and Northern Ireland. Likewise, the SFI Research Centre Spokes program offers opportunities for companies and researchers from anywhere in the world to become

involved in the SFI Research Centres. There are other opportunities here with no obvious governance barriers. But, here too, there appears to be a lack of interest or awareness. The deepest form of coordination would involve all-island research centres or technology centres that are developed as single-entity virtual centres. Such centres would be designed for North-South joint funding from establishment under single management.

In relation to the clinical trials component, Interviewees suggest that, currently, Ireland and particularly Northern Ireland are not reaching the full potential in terms of clinical trials activity. The main barrier for further development is the limited scale of recruitment. International pharmaceutical companies and other users are attracted by organisations that can provide efficient access to a sizeable patient recruitment base. Research has established that the optimal scale of population for co-ordinating recruitment is about 6 million (HSC R&D, 2014).

An all-island interoperable clinical trials co-ordination network would operate at a more efficient scale. Establishing such a network is not without challenges. First, the clinical trials ecosystems are complex, involving a substantial number of institutions, governance structures and funding streams. Second, the two health systems are organised differently, with a different balance between public and private provision. And finally, there is the fact of the two legal jurisdictions leading to issues related to contracts with pharmaceutical companies. But all these issues are not necessarily insurmountable. In fact, as discussed in the next section, this may become the first significant example of cross-border integration of the two pharma ecosystems.

Education and Training

Interviewees noted the experience across the island of significant skills shortages in certain areas of the pharmaceutical labour force. This is particularly the case for high calibre (MSc and PhD level) staff in areas such as chemistry, chemical engineering and bio-informatics, while industry is also calling for 'industry ready' graduates. The two countries operate essentially separate systems for education and training. The interviews pointed to limited levels of planning and co-ordination across the two education and training systems. The level of cross-border promotion of education and training programs has also been quite limited. Some of the specialised post-graduate training programs relevant to the pharmaceutical industry are not marketed across the border at all. Finally, although private sector companies are involved in higher education course provision, and offer industry placements to students from higher education institutions in the same jurisdiction, this research has found very little evidence of all-island industry-academic partnering.

As regards potential for cross-border integration, the provision of education and training to create high calibre and specialised labour is subject to economies of scale and, individually, the two countries do not have sufficient student numbers to operate at the optimal efficient scale. Greater co-ordination of education and training across the two jurisdictions could work towards this end.

An obvious and easy step towards greater cross-border co-ordination of education and training would be to intensify the cross-border promotion of existing specialised post-graduate training programs. Examples of specialised programs that could benefit include those offered by the National Institute for Bioprocessing Research and Training (NIBRT) in UCD and the Clinical Translational Research and Innovation Centre (C-TRIC) in Derry/Londonderry. NIBRT is the

only specialist bioprocess training facility on the island while C-TRIC provides the only specialist translational medicine programme on the island.

Interviewees also suggested the development of all-island Masters/PhD programmes, targeting advanced skills shortages. This could take the form of a flexible Masters program in, for example, bio-process engineering, delivered by an all-island virtual centre, where academics from individual institutions offer a set of core modules and/or optional modules within their area of specialism in a centrally located institution with academics travelling to that location. Further potential lies in all-island industry-academia partnering with companies in the South offering industry placements to students from the North and vice versa. Another aspect could involve staff from private sector pharmaceutical companies being involved in teaching provision in both jurisdictions. Private sector pharmaceutical companies are expressing an interest, but the research suggests a lack of cross-border visibility of opportunities.

Markets for Products and Services

The big pharmaceutical companies operating in the North and the South typically already supply global markets. For these companies, the two markets are virtually fully integrated. However, the same is not true for the pharma vendor sector. The pharmaceutical production companies spend billions of dollars on sophisticated works, goods and services. On both sides of the border, a number of companies have tapped into this market and some developed into significant export-oriented companies. However, most of the advanced engineering and process control technology and services continue to be imported, creating substantial opportunities for existing or new indigenous companies.

Interviewees point to very limited cross-border supply linkages and perceive substantial opportunities for cross-border selling of services and products. Further integration of the vendor markets would provide important economies of scope and synergies. The strong indigenous engineering tradition in Northern Ireland could play an important role in cultivating related variety.

Apart from the schemes run by InterTradeIreland, there are very few initiatives to further integrate the vendor markets. At the time of the research there was no communication between INI and EI to explore possibilities. Part of the reason is related to the feeling that such initiatives may simply generate additional competition among a wider set of companies, which would bring additional pressures to bear on these companies.

The further integration of an all-island vendor market requires enhanced cross-border visibility of opportunities. This could be achieved through the organisation of all-island show-casing events involving potential vendors, MNEs, and research centres. A more ambitious step could be to expand the IDA Global Sourcing Initiative to cover Northern Ireland.

Explaining the Relatively Low Level of Cross-Border Integration

The previous section suggests that a more integrated all-island pharmaceutical sectoral ecosystem would bring benefits. A greater all-Island co-ordination of advanced education and training will provide additional pooling benefits operating at an all-Island scale. An integrated all-Island sectoral ecosystem will provide benefits of scale and scope to the vendor sector which, in turn, will translate into benefits to the pharmaceutical companies, irrespective of their

location on the Island. Similarly, the enhanced technology spillovers, derived from integrated research centres and networks and clinical trials systems will operate at an all-Island scale and benefit companies irrespective of their location on the Island.

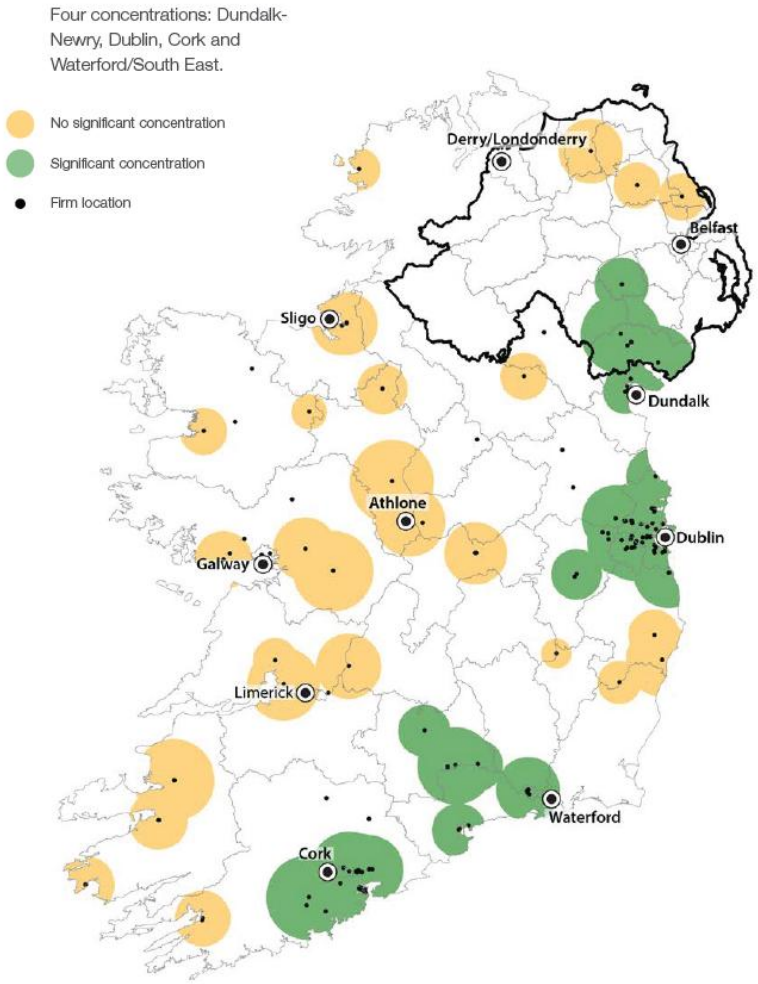
This section will explore the reasons for the low level of cross-border integration, employing the typology of proximity introduced in the literature review. We start with an investigation of the influence of geographical proximity/distance followed by a discussion of the role of different types of relational proximity (cognitive, organisational, institutional and social).

Geographical Proximity

Figure 2 depicts the geography and spatial concentrations of pharmaceutical industry on the Island of Ireland based on employment and firm numbers.[39] The spatial configuration of the pharmaceutical industry is characterised by four distinct groupings: a Cork grouping; a south-east grouping linking Waterford and Kilkenny; a Dublin grouping and a cross-border grouping stretching from Dundalk to Lough Neagh.

[39] For details regarding the concentration index see: Chris Van Egeraat, Edgar Morgenroth, Rutger Kroes, Declan Curran, and Justin Gleeson, A measure for identifying substantial geographic concentrations, *Papers in Regional Science*, 97 (2) (2016), 258-300.

Figure 2: Spatial concentrations of pharmaceutical industry on the Island of Ireland



Note: Shaded areas signify the (merged) labour fields of pharmaceutical plants. Significant concentrations (in green) denote areas that reach the cut-off concentration index for the pharmaceutical industry. For details, see van Egeraat et al. "A measure for identifying substantial geographic concentrations", 258-300.

The groupings have, to an extent, distinct foci. The Cork grouping is involved in manufacturing of both active pharmaceutical ingredients and drug products. The south-east grouping focuses on drug product manufacturing. The Dublin grouping is involved in both active ingredients and drug products with a strong focus on biopharmaceuticals. Finally, the cross-border grouping has a strong services and research element.

The mapping exercise and the interviews do suggest that the spatial configuration of the industry is partly driven by labour market issues and that the advantages related to a pooled market of workers are, to an extent, regionally bounded, benefiting regional groupings of firms. Beyond the regional level, firms also derive benefits from a pooled market of workers in Ireland/Northern Ireland, a market that is fully integrated (see also Van Egeraat and Curran, 2013). The interviews suggest that firms do enjoy technology spill-over effects. However, these are not regionally bounded and currently operate at the national levels. The spill-over effects benefit all firms more or less equally, irrespective of their location in the individual countries. However, currently very little technology 'spills over the border'. The research found more limited evidence of agglomeration economies related to specialised vendors, again operating at the national scale.

The spatial distribution suggests a relatively high level of geographical proximity between the pharmaceutical ecosystems North and South. The distance between the Dublin and cross-border grouping is far smaller than the distance between the Dublin and Cork grouping, two groupings that are strongly integrated in single national ecosystem. This would suggest that the reason for the limited level of cross-border integration does not lie in the lack of geographical proximity. The section below explores the role of other forms of proximity.

Relational Proximity

This section explores the role of the different types of relational proximity. We will show how the pharmaceutical ecosystems on both sides of the border are characterised by a high level of cognitive proximity. However, lower levels of organisational, institutional and social proximity are impeding cross-border integration.

Since we are dealing with the same industrial sector, the pharmaceutical ecosystems on both sides of the border are clearly characterised by a high level of cognitive proximity. In addition, the two pharmaceutical ecosystems complement each other. The ecosystem in the South is focused on production/ process development while the ecosystem in the North has a stronger research focus. Both Ireland and Northern Ireland have built, and are developing, strengths in the area of translational research in pharmaceuticals. However, in Ireland this strength is concentrated in process research and development. In Northern Ireland, the focus is on product research and development. This adds an element of related variety (Frenken et al., 2007)[40] which would support innovation and long-term sustainability of an integrated cross-border pharmaceutical ecosystem. Similarly, the strong indigenous engineering tradition in Northern Ireland could play an important role in cultivating related variety. The high level of cognitive proximity and related variety can potentially provide high levels of economies of scale and scope and should be conducive to the development of an integrated cross-border pharmaceutical ecosystem.

Organisational proximity is defined as the extent to which relations are shared in an organisational arrangement, either within or between organisations. While too much organisational proximity can lead to a lack of flexibility, too little organisational proximity can lead to a lack of control. Loosely coupled systems can satisfy both requirements (Boschma, 2005).[41] This research found little evidence of organisational proximity between companies or research organisations on both sides of the border, either hierarchical or loosely coupled. There are few pharmaceutical companies with operations on both sides of the border and the business

[40] Koen Frenken, Frank van Oort, and Thijs Nicolaas Verburg, Related Variety, Unrelated Variety and Regional Economic Growth, *Regional Studies* 41(5) (2007), 685-697.
[41] Boschma, "Proximity and innovation", 61-74.

networks operate largely at a national scale. Most of the current research centres, institutions and many of the formally created research networks have primarily a national orientation.

Institutional proximity is associated with the institutional framework at the macro-level. The notion of intuitional proximity includes both the idea of economic actors sharing the same institutional rules as well as cultural habits and values. These institutions can enable knowledge transfer and innovation. Institutional proximity deals with macro-level trust based on common institutions. A culture of *shared* trust is often regarded as a capability that supports learning and innovation: information is transmitted more easily with cultural proximity and a common language. Too little institutional proximity is detrimental to collective action and innovation due to weak formal institutions and a lack of social cohesion (Boschma, 2005).

To an extent we observe a level of institutional proximity between the two jurisdictions. The two countries share a common language. The formal institutions (such as the legal system), although not shared, are relatively similar. But the two jurisdictions have their own enterprise policy frameworks and support infrastructures. These institutional infrastructures are running very much in parallel, with little by way of all-island co-ordination between equivalent bodies. The state support agencies (IDA and EI in Ireland and INI in Northern Ireland) cater largely for their national client base. Similarly, the industry associations (IBEC and its PharmaChemical division in Ireland and CBI and the Northern Ireland section of the Association of the British Pharmaceutical Industry in Northern Ireland) draw their membership from within their own jurisdiction.

The last 10 years has seen a small number of examples of cross-border support and networking initiatives undertaken by these organisations but these remain the exception and are not

organised on a structural basis. Some of these cross-border initiatives are organised by individual agencies, as opposed to genuine all-island events, leading to duplication of efforts. The IBEC-CBI Joint Business Council was abolished and had operated mainly as a lobbying organisation dealing with high level issues (as opposed to providing more direct enterprise support). The main exception in the landscape is InterTradeIreland which was set up as an all-island body to stimulate economic co-operation through, amongst others, business programmes and the support of networks and partnerships.

A number of smaller industry associations had been establishing themselves as All-island Organisations. For example, BioBusiness, a business association for the Life and Health Technology sector in Northern Ireland and Ireland, provides an advocacy role for the industry in the North, as well as enterprise support and networking services in both North and South. It remains, however, a relatively small association with limited resources and limited visibility in the South.

So far, we have established the presence of high levels of geographical and cognitive proximity between the two ecosystems, which should be conducive to cross-border integration. In addition, we observe some level of institutional proximity, including a number of structures linking the two institutional settings. This has led to a number of initiatives to further integrate the two pharmaceutical ecosystems. For example, in 2015 Intertrade Ireland started two projects, one to development of an all-island biotech ecosystem and one to develop all-Island pharmaceutical vendor network. Several meetings and discussions involving partners North and South led to nothing. The most successful initiative has been the attempt to develop an all-island interoperable clinical trials co-ordination network. Here too, for a long time the discussions between partners from both jurisdictions made little progress. The project only

gained momentum with the introduction of a US partner. In 2021, after six years of discussion, the initiative culminated in the signing of a Memorandum of Understanding to reinvigorate the Ireland - Northern Ireland – NCI Cancer Consortium.

This opens the question of the role of social proximity. Whereas institutional proximity is defined in terms of the institutional framework at the macro-level, and trust based on common institutions, social proximity is associated with the socially embedded (individual) relations between agents at the micro-level. Relations between actors are socially embedded when they involve trust based on friendship, kinship and experience.

Clearly, a level of social proximity exists in the areas and towns directly straddling the border (Creamer et al., 2008).[42] But at the level of the Island of Ireland, 100 years with the presence of a border has significantly reduced the level of social ties and micro-level relations can even exhibit distrust and social distance.

We found little evidence of social proximity playing a positive role in interactive learning and innovation processes in the cross-border pharmaceutical ecosystem. The lack of social proximity may also effect the level of institutional proximity. Boschma (2005)[43] points out that social and institutional forms of proximity may be strongly interconnected, because the ways in which intra- and inter-organisational relations are governed are deeply embedded in institutional settings. In the context of the island of Ireland the causation may be reversed. A lack of social proximity and individual-level trust can seriously hamper the functioning and

[42] Caroline Creamer, Neale Blair, Brendan O'Keefe, and Chris van Egeraat, Tough Love: Local Cross-Border Co-operation Faces the Challenge of Sustainability, *Journal of Cross Border Studies* 9 (1) (2008), 80-95.
[43] Boschma, "Proximity and innovation", 61-74.

effectiveness of the cross-border institutional arrangements created to support and promote, amongst other things, cross-border ecosystems.

Conclusion

As illustrated by the case-study of the Irish pharmaceutical sector presented in this paper, potential economic benefits of an all-island ecosystem – arising from greater economies of scale and scope – have been recognised by businesses, institutions and policymakers in both jurisdictions. However, there still appears to be impediments to the realisation of those economic benefits within the pharmaceutical sector. This paper seeks to understand what exactly these impediments are, and why they persist. The concept of ecosystem is utilised as it allows us to consider an optimal economic arrangement in the context of border effects. We then discuss the extent to which an all-island business ecosystem has emerged in the pharmaceutical sector, utilising a typology of geographic and relational proximities as a means to analyse drivers and barriers to the development of such an ecosystem. Analysis based on our case-study indicates that while geographic and cognitive proximity across pharma sector actors may be necessary for cross-border economic collaboration, they are not in themselves sufficient to ensure that such collaboration occurs. Rather it appears that a mix of institutional and social proximities are also required in order to support meaningful cross-border economic collaboration.

As discussed in the previous section, we find a relatively limited degree of institutional proximity among pharmaceutical industry actors in an all-island context, with institutional infrastructures tending to run in parallel in both jurisdictions. Research in other cross-border settings has recognised that cross-border integration can be impeded not just by the absence or thinness of institutions, a potential impediment to cross-border integration, but also by rigidities

inherent in existing institutions. As van den Broek and Smulders note, "the embeddedness of actors in their respective institutional architectures can help to explain how cooperation problems occur."[44] Indeed, Cappellano and Makkonen posit that some cross-border settings may be over-institutionalised, with the integration process being an unduly top-down one. They characterise the European regional cross-border institution building as being typically dominated by public sector actors. Instead, based on their empirical study of cross-border cooperation at the US-Mexico border, Cappellano and Makkonen advocate a greater role for non-governmental organisations emerging from the business sector. These actors, they contend, are best positioned to place a greater emphasis on "supporting entrepreneurship, innovation and competitiveness by sharing knowledge and by providing access to funding streams, co-working spaces and cross-border networks" in dynamic, agile and mainly self-governed network structures that can generate a high frequency of face-to-face cross-border contacts through business meetings and events.[45]

Notwithstanding the relatively limited degree of institutional proximity observed, our case-study suggests that it is a lack of social proximity that has proven to be a persistent barrier to the development of a cross-border pharmaceutical ecosystem. This is also evident in Hahn's study of the Saar-Lor-Lux cross-border region. Hahn finds that border effects can hamper cross-border integration in both disruptive and protective ways, via "cultural and linguistic barriers as well as the existence of prejudices and local patriotism which all reduce proximity".[46] Similarly, van den Broek et al. – in their study of firm-level collaboration in the Dutch-Flemish border region – note that the actual undertaking of cross-border business collaboration may encounter negative border effects, whereby "the absence of regular project

[44] van den Broek and Smulders, "Institutional hindrances", 121.
[45] Cappellano and Makkonen, "Cross-border regional innovation ecosystems", 1525.
[46] Hahn, "The transboundary automotive region", 111.

meetings, in which partners develop detailed mutual understandings of mutual capacities and needs, makes it hard for them to introduce third parties into these relationships across these borders." [47] Van den Broek et al. conclude that, without regular interactions, information exchange, and build-up of mutual interdependence, the border will continue to negatively impact upon firm-level cross-border collaboration.

As illustrated in our study, the limited interaction of the Irish and Northern Irish pharmaceutical sectors may be best understood at the level of individual and firm-level cross-border routines and relationships. While macro-level institution building – both within and across economic sectors - may be a necessary ingredient in cultivating greater cross-border economic integration, greater social proximity at a micro-level will be needed in order to develop all-island business ecosystems. However, given the historical context and legacy of the border, social proximity at the micro-level will not be easy to achieve. While it may be more easily achieved in the context of a united Ireland, that is not to say that a united Ireland is a requirement for – or a guarantee of – social proximity at the micro-level.

[47] van den Broek et al., "Border blocking effects in collaborative firm innovation", 1342.