TESIS DOCTORAL

2022

EL SECTOR FARMACÉUTICO: EFICIENCIA, RENTABILIDAD Y COVID-19

RICARDO FRANCISCO DÍAZ RAMOS

DIRECTORA:

BLANCA SÁNCHEZ-ROBLES RUTE

PROGRAMA DE DOCTORADO EN ECONOMÍA Y EMPRESA

Departamento de Análisis Económico
Facultad de Ciencias Económicas y Empresariales

UNED

Departamento de Análisis Económico
Facultad de Ciencias Económicas y Empresariales
Universidad Nacional de Educación a Distancia (UNED)

EL SECTOR FARMACÉUTICO: EFICIENCIA, RENTABILIDAD Y COVID-19

Ricardo Francisco Díaz Ramos
Licenciado en Farmacia

Directora:
Dra. Blanca Sánchez-Robles Rute

RECONOCIMIENTOS

Todo mi agradecimiento y mi más profunda admiración para mi directora de tesis, Blanca Sánchez-Robles. Su capacidad para **ENSEÑAR** (con mayúsculas y en negrita), sugerir ideas, visualizar la solución a problemas complicados y explorar nuevos caminos han sido decisivos en el presente trabajo. Sin sus charlas motivadoras, su paciencia y su visión de adonde debíamos llegar no habría sido posible concluir esta tesis.

A mis padres por transmitirme la cultura del esfuerzo por la que ellos siempre se guiaron. Ellos han sido siempre mi más directa inspiración y el modelo que he imitado desde que tengo memoria. A pesar de no estar presentes desde hace años, siguen siendo mi referente a la hora de emprender cualquier nueva aventura. A mis hermanas por estar siempre ahí y mantenerme anclado a mis orígenes.

A mi mujer y mis hijos por su apoyo incondicional en todas mis aventuras y en cada nueva etapa de nuestras vidas. Son la mejor motivación posible para avanzar y seguir explorando. Todo mi agradecimiento por su cariño, amor y paciencia.

RESUMEN

La importancia de la industria farmacéutica y biotecnológica en la mejora de la esperanza de vida de la población a través del progreso de la medicina, que se sustenta en buena parte en el desarrollo de nuevos tratamientos, es incuestionable. Dicha industria contribuye además a crear puestos de trabajo de alto valor y a la creación de riqueza.

La pandemia de Covid-19 ha agitado los cimientos de la industria farmacéutica, que debió adaptarse en muy poco tiempo para seguir produciendo y desarrollando medicamentos en una situación incierta en la que el aporte de suministros, la distribución de su producción y la disponibilidad de la mano de obra estuvieron, en mayor o menor medida, comprometidos. Por otro lado, la industria farmacéutica aceptó el desafío que supuso desarrollar vacunas para poner freno al enorme problema de salud creado por la pandemia y a su impacto en la economía global.

En dicho contexto, la presente tesis pretende evaluar qué empresas farmacéuticas resultan más eficientes en el uso de sus recursos. Se diferencia para ello entre compañías principalmente productoras que no invierten en el desarrollo de nuevos tratamientos y compañías que, además de producir, invierten parte de sus beneficios y recursos en I+D para continuar desarrollando nuevos fármacos y remedios.

Asimismo, la creciente importancia de las empresas que ofrecen servicios de investigación clínica (CROs), que permiten a las empresas farmacéuticas y biotecnológicas externalizar el desarrollo de nuevos tratamientos, hace que resulte relevante analizar qué compañías de este sector resultan más eficientes y cómo dichos datos de eficiencia se comparan con los de la industria farmacéutica y biotecnológica.

Por último, se pretende discernir si aquellas empresas farmacéuticas y biotecnológicas que han invertido en el desarrollo de una vacuna contra el virus Covid-19 han tenido un comportamiento en los mercados de valores diferente al de aquellas que no han invertido en dicho desarrollo.

TABLA DE CONTENIDOS

LISTA DE FIGURAS

LISTA DE TABLAS

CHAPTER 1.

El Sector Farmacéutico: Eficiencia, Rentabilidad y Covid-19

CHAPTER 1.
El Sector Farmacéutico: Eficiencia, Rentabilidad y Covid-19

1.1 Introducción

La industria farmacéutica contribuye de manera decisiva al bienestar y a la mejora de las condiciones de vida de la población en general. No es posible explicar el aumento tan notable de la esperanza de vida en el último siglo en los países desarrollados, en los que el acceso a un sistema de salud y a tratamientos médicos de calidad están en mayor o menor medida garantizados, sin la contribución de la industria farmacéutica.

El desarrollo de nuevos tratamientos en forma de fármacos, dispositivos médicos o productos biotecnológicos es un factor decisivo que permite avanzar a la medicina y que ha hecho posible una aproximación mucho más exitosa en las últimas décadas al tratamiento de enfermedades incapacitantes o potencialmente mortales. Si bien el desarrollo clínico de nuevos tratamientos o la ampliación de las indicaciones de tratamientos existentes puede ser llevada a cabo por organismos públicos, tales como fundaciones o los propios centros de tratamiento, la mayor parte de los ensayos clínicos se promueve por empresas farmacéuticas o biotecnológicas.

Con el fin de competir en una posición favorable, las empresas del sector farmacéutico necesitan invertir en el desarrollo de nuevos tratamientos cada vez más eficaces y seguros cuyas ventas, una vez concluido su desarrollo clínico, retroalimentarán a su vez la futura inversión en otros tratamientos. Existen en cualquier caso empresas farmacéuticas que no invierten en desarrollar nuevos tratamientos o que lo hacen de manera limitada y que se benefician de la producción de fármacos o remedios cuya patente ya ha prescrito.

En este contexto, eficiencia es un término frecuente en la industria farmacéutica a la hora de implementar nuevas políticas o procedimientos de trabajo, adquirir nuevos equipos o sistemas y en general cuando se toma cualquier decisión estratégica de inversión. La búsqueda de la eficiencia es clave en una industria altamente especializada y regulada para garantizar la competitividad, el retorno de la inversión y, en último término, la supervivencia. Existen diferentes estrategias a la hora de llevar a cabo el desarrollo clínico, entre ellas la externalización a empresas especializadas o CROs.

Nuevos desafíos como la crisis causada por la pandemia de Covid-19 unidos a la necesidad de tratamientos cada vez más eficaces y seguros requieren de inversiones altamente costosas. En paralelo la presión de los reguladores y de los sistemas públicos de salud para ajustar el gasto farmacéutico hacen que la mejora de la productividad y la búsqueda de la eficiencia se tornen clave.

1.2 La Industria Farmacéutica y las CROs, contexto

La permanente necesidad de desarrollar tratamientos innovadores hace que la industria farmacéutica y biotecnológica se posicionen entre las que dedican mayor porcentaje de ingresos a I+D, tan sólo por detrás de la industria de semiconductores y comunicaciones (Lakdawalla, 2018).

Dicha búsqueda de nuevos tratamientos se lleva a cabo mediante el proceso de desarrollo clínico. Las etapas del desarrollo clínico incluyen el modelado molecular de nuevas entidades químicas, los tests pre-clinicos en animales y los ensayos clínicos en humanos (voluntarios sanos o pacientes en función de la patología a tratar y de la fase del ensayo clínico). Esta última etapa es la más costosa en cuanto a inversión requerida por la necesidad de testar el nuevo tratamiento en investigación en multitud de pacientes -en ocasiones decenas de miles- durante varias fases de estudio y en diversos centros de investigación que pueden estar localizados en varios países. El coste medio del desarrollo de un nuevo fármaco en 2020 fue de US$ 1.335,9 millones (Wouters et al., 2020) con una tasa de éxito muy baja: sólo una de cada 5.000 — 10.000 nuevas moléculas completarán todas las fases tras mostrarse al menos tan seguras y eficaces como los tratamientos ya autorizados y disponibles en el mercado. Estas cifras dan una idea clara de la complejidad y la inversión necesaria para desarrollar nuevos medicamentos.

Los ensayos clínicos pueden ser llevados a cabo por las compañías farmacéuticas y de biotecnología mediante la utilización de recursos internos o pueden ser externalizados, total o parcialmente, a compañías especializadas llamadas Organizaciones de Investigación por Contrato u Organizaciones de Investigación Clínica (ambas acepciones son válidas), conocidas como CROs por sus siglas en inglés. Se prevé que el mercado mundial de servicios de las CROs crezca de US$ 73.380 millones en 2022 a 163.480 millones en 2029 (Fortune Business Insight, 2022). Las CROs permiten ajustar los plazos del desarrollo clínico y una distribución más eficiente de los recursos de las compañías farmacéuticas (Piachaud, 2002) por lo que son cada vez más utilizadas por las mismas en busca de mejoras en la productividad y la eficiencia de los recursos de que disponen.

1.3 Aportaciones de la Tesis Doctoral

En la presente tesis doctoral se enfocan tres estudios relacionados cuyas características se exponen a continuación.

1.3.1 Análisis No Paramétrico de Eficiencia: Aplicación a la Industria Farmacéutica

El aumento de los costes de la investigación (I+D), la búsqueda de la especialización, la finalización del periodo de patente de los tratamientos existentes y el control del gasto sanitario por parte de las autoridades públicas correspondientes, entre otros factores, imponen estrategias para mejorar la eficiencia y la productividad de las empresas farmacéuticas.

En el presente paper analizamos empíricamente qué empresas farmacéuticas resultan más eficientes en el periodo comprendido entre 2010 y 2018. La eficiencia en dicho análisis es definida como las unidades de producción resultantes por cada unidad de entrada (*output* resultante por unidad de *input*).

Para ello se tienen en consideración datos procedentes de la base de datos *Amadeus* de empresas farmacéuticas y biotecnológicas europeas de diferentes tamaños y perfiles, a diferencia de otros estudios anteriores en los que la aproximación ha sido una comparación de firmas locales o no se han tenido en cuenta empresas del sector biotecnológico. Dentro del conjunto de empresas analizado hemos diferenciado entre aquellas que son principalmente productoras de productos farmacéuticos y aquellas que, además de producir, se dedican a la investigación y desarrollo de nuevos productos. En esta segunda categoría se incluyen las empresas biotecnológicas.

Con dichos datos se ha realizado una exploración de la eficiencia en dos etapas. En la primera de ellas se ha utilizado la técnica DEA (*data envelopment analysis*). Esta técnica computa a su vez la eficiencia mediante programación linear en dos pasos: en el primero se define una frontera y en el segundo se evalúa la distancia de cada unidad en evaluación o DMU (*decission-making unit*) a dicha frontera. Las DMUs más eficientes son aquellas que determinan la frontera y tienen una eficiencia igual a 1.

En el segundo análisis se tienen en cuenta una serie de variables potencialmente relacionadas con la eficiencia y se comparan los resultados utilizando tres modelos diferentes: Tobit, *pure random-effects* y Simar–Wilson.

Los resultados obtenidos sugieren que el nivel de eficiencia de la industria farmacéutica Europea es moderado y que la tendencia es decreciente durante el periodo 2010-2018.

Se observa además una relación entre el tamaño de las empresas -definido por el volumen de negocio durante el periodo en consideración- y la eficiencia, resultando las empresas muy grandes

y muy pequeñas más eficientes que aquellas que tienen un tamaño mediano o pequeño. Estos resultados sugieren que las empresas del sector se benefician de economías de escala -empresas muy grandes- o de altos niveles de especialización -empresas muy pequeñas-, factores ambos que acontecen en menor medida en empresas de tamaño medio.

En cuanto a la actividad, las compañías principalmente fabricantes de productos farmacéuticos resultan más eficientes que aquellas que realizan además I+D. Este resultado puede ser explicado por el hecho de que numerosas compañías enfocadas en el I+D, entre ellas las empresas de biotecnología, son relativamente recientes y no han conseguido sacar aún el máximo provecho de la curva de aprendizaje. El hecho asimismo de que dichas compañías estén especializadas en algunos proyectos que, a la larga, tienen bajas probabilidades de éxito puede explicar su menor productividad.

Los resultados muestran asimismo que una estructura financiera sólida, un coste de empleados ajustado y unos márgenes de beneficio elevados se relacionan con mayores niveles de eficiencia. El país de origen de la firma también parece influir en la eficiencia.

1.3.2 Eficiencia en la Industria de las CROs, 2012-2020. Un Análisis No-Paramétrico DEA

La externalización de servicios de investigación clínica por parte de laboratorios farmacéuticos, fabricantes de dispositivos médicos y empresas biotecnológicas se ha extendido notablemente en los últimos años a la búsqueda de menores costes en el desarrollo de nuevos tratamientos y de un mayor control de los riesgos.

Las CROs emergieron a finales de la década de 1970 como compañías especializadas en servicios de desarrollo clínico. Hasta entonces eran las propias compañías farmacéuticas quienes debían llevar a cabo internamente el desarrollo de sus nuevos productos o los ensayos clínicos para la extensión de las indicaciones terapéuticas de los productos ya existentes y comercializados.

La externalización permite a los desarrolladores de nuevos tratamientos un mayor control del riesgo asociado al lanzamiento de nuevos remedios. Continúa existiendo para ellos el riesgo de que el producto en evaluación sea o no exitoso a la hora de cumplir los objetivos de seguridad y eficacia que se planteen pero el riesgo operacional asociado a la gestión de los ensayos clínicos y de la asignación de recursos -mano de obra principalmente- a los mismos son traspasados en buena parte a las CROs. Existen además otras ventajas operacionales de la externalización como son una eventual reducción de los tiempos de aprobación -por parte de comités éticos y autoridades reguladoras- y menores plazos de reclutamiento de pacientes por la especialización y cobertura, en muchas ocasiones global, que ofrecen las CROs. Esto se traduce en unos tiempos de desarrollo de los nuevos tratamientos más ajustados que podrán ser aprobados y estar disponibles en el mercado en un plazo más reducido.

Así pues, las CROs se han convertido en un actor clave a la hora de apoyar el desarrollo de nuevos fármacos, productos biotecnológicos y dispositivos médicos. El número de productos en desarrollo en los que han colaborado las CROs se ha triplicado en los últimos 20 años, acelerándose especialmente durante la última década.

El presente estudio analiza empíricamente la eficiencia de la industria de las CROs basándose en una muestra de empresas de todo el mundo entre los años 2012-2020 mediante la técnica no paramétrica DEA (*data envelopment analysis*). Se ha trabajado para ello con micro-datos de la base de datos de empresas Orbis. Las variables analizadas incluyen el volumen de ventas, el número de empleados, los activos y los ingresos.

No se ha encontrado en la literatura ningún estudio de eficiencia de una muestra de CROs, por lo que la aportación realizada en este capítulo es innovadora.

Los niveles medios de eficiencia del sector son, en general, altos y aumentan año a año durante el periodo analizado. Además, los resultados son robustos: son muy similares incluso si se emplean diferentes variables y modelos de estimación alternativos.

Profundizando en el análisis y diferenciando los resultados por tamaño de la empresa -hemos clasificado la muestra en CROs grandes, medianas y pequeñas en función del número de empleados-, se observa que las CROs grandes son claramente más eficientes, seguidas por las pequeñas y con las medianas en último lugar. Esto puede sugerir que las empresas mayores se benefician de una imagen de marca, de una distribución geográfica más amplia, del acceso a las últimas tecnologías y de la posibilidad de establecer alianzas comerciales estables. Las empresas pequeñas podrían beneficiarse de su mayor especialización por área terapéutica o por servicio lo que convierte a muchas de ellas en empresas de nicho. Las empresas medianas no se beneficiarían o lo harían en menor medida de estos factores.

Dado que el grupo de las CROs mayores es el más eficiente, se concluye que la tendencia actual de consolidación de empresas mediante fusiones y adquisiciones continuará en el futuro.

1.3.3 El Impacto de la Pandemia de Covid-19 en las Cotizaciones en Bolsa de las Empresas Biofarmacéuticas

La industria farmacéutica ha hecho un esfuerzo de adaptación durante la pandemia de Covid-19 para continuar operando, produciendo y distribuyendo medicamentos en un contexto en que los problemas logísticos, la falta de suministros y la incertidumbre causada por la caída abrupta de la actividad marcaban el paso en cada sector de la economía. La industria farmacéutica ha sido desde el principio parte fundamental en la recuperación de la pandemia por su esfuerzo para buscar tratamientos eficaces y desarrollar tests diagnósticos y vacunas contra el nuevo virus que desembocaron en la puesta a disposición de manera global de diversas vacunas.

Dichas vacunas han sido clave para reducir la transmisión, la incidencia y la mortalidad asociadas al virus Covid-19. El desarrollo de las mismas ha sido inusualmente rápido dada la urgencia por salvar vidas y el impacto global en la economía de la pandemia.

Las vacunas, como cualquier otro remedio antes de ser autorizado por las autoridades reguladoras, deben ser testadas en humanos y deben para ello someterse a ensayos clínicos en diversas fases. El esfuerzo conjunto de la industria farmacéutica y biotecnológica, los gobiernos, el capital privado, las autoridades y el personal sanitario sirvió para acelerar su desarrollo como nunca antes había acontecido. Así pues, sólo nueve meses después de la declaración de la pandemia de Covid-19 por parte de la ONU, el laboratorio farmacéutico Pfizer obtuvo la primera autorización de emergencia por parte de la FDA -autoridad reguladora Norteamericana- para su vacuna.

En el presente artículo analizamos el comportamiento en bolsa de aquellas empresas farmacéuticas y biotecnológicas que han comercializado vacunas contra el virus Covid-19 y lo comparamos con el del top 10 de las compañías farmacéuticas por volumen de facturación. Los objetivos son por un lado evaluar si a corto plazo aquellas empresas que han desarrollado y comercializado una vacuna han tenido un mejor comportamiento en bolsa y por otro analizar el impacto en las cotizaciones de los principales hitos en el desarrollo de la pandemia desde la declaración de los primeros casos en China.

Hasta abril de 2022, diez vacunas han recibido la autorización de uso de emergencia de la ONU. Seis de ellas son producidas por empresas que cotizan en bolsa: *Nuvaxovid* de Novavax, *Spikevax* de Moderna, *Comirnaty* de Pfizer, *Ad26.COV2.S* de Johnson & Johnson/Janssen, *Vaxzevria* de Oxford/AstraZeneca y *Covilo* de Sinopharm. Dos de estas compañías pertenecen al mencionado top 10 de la industria farmacéutica: Pfizer y Johnson&Johnson.

El análisis de las cotizaciones se ha dividido en dos periodos: i) de julio de 2011 a diciembre de 2019 (periodo prepandemia) que nos da una visión más amplia de la evolución de estas compañías en bolsa, y ii) de diciembre de 2019 a diciembre de 2021 (periodo de pandemia).

En el primer periodo (julio de 2011 a diciembre de 2019), la mayor parte de las compañías evolucionó positivamente aunque de manera heterogénea: sólo algunas empresas consiguieron mejorar la cotización del índice Dow Jones (DJ). De las cuatro compañías no pertenecientes al top 10, tres de ellas tuvieron una evolución peor que el índice DJ.

En el segundo periodo (diciembre de 2019 a diciembre de 2021), los resultados también son heterogéneos. Si bien la mayoría de las empresas mostraron una evolución positiva de su cotización, el precio de la acción de Novartis, Merck y Takeda decreció en este periodo. Algunas de las grandes farmas tuvieron un mejor comportamiento que el DJ (que creció un 27%), entre ellas Pfizer, Roche y AbbVie. De las dos compañías dentro del top 10 que han desarrollado una vacuna, J&J creció por debajo del DJ y Pfizer lo hizo por encima. Entre los restantes desarrolladores de una vacuna, AZ y Sinopharm crecieron de manera parecida al DJ mientras que Moderna y Novavax

dispararon su cotización un 1.198% y un 3.495% respectivamente. Estos resultados sugieren que el comportamiento de las grandes farmacéuticas tradicionales que invirtieron en el desarrollo de una vacuna fue positivo mientras que el de aquellas empresas más pequeñas -no tradicionales- fue extraordinariamente favorable.

A continuación, se revisaron los resultados del impacto de los principales hitos en el desarrollo de la pandemia utilizando la técnica del análisis de eventos. Diferenciamos en este análisis dos subperiodos, el primero de ellos más influido por noticias sobre la expansión del virus durante los 5 primeros meses de pandemia y el segundo relacionado con noticias sobre el desarrollo de las vacunas y su aprobación entre noviembre de 2020 y abril de 2021.

En general podemos concluir que el impacto de las noticias de la primera etapa en los valores de cotización fue limitado. Sólo dos compañías del grupo analizado mostraron un CAAR (rentabilidad anormal media acumulada) alto y significativo, Novamax y Moderna. En el segundo periodo los anuncios acerca del resultado de los estudios de fase III de las vacunas de Pfizer, Moderna and Novavax mostraron un impacto positivo pero no los de Johnson&Johnson y AstraZeneca. Las aprobaciones de las vacunas por parte de las autoridades reguladoras parecen haber sido descontadas por el mercado con anterioridad. El anuncio de la compra de un gran stock de vacunas a Moderna tuvo un impacto muy positivo en la cotización de esta empresa.

El análisis del precio de las acciones muestra que las compañías biofarmacéuticas tuvieron un comportamiento variado tras su inversión en el desarrollo de vacunas para tratar el virus Covid-19. Podemos distinguir tres situaciones diferenciadas: i) dos empresas han visto su inversión claramente recompensada por el mercado y han reaccionado positivamente a los anuncios sobre los distintos hitos de la pandemia, Pfizer y Moderna, aunque en el primer caso no es descartable que otros factores hayan influido en dicho éxito puesto que es una farmacéutica tradicional con muchos otros productos en el mercado; ii) otras dos compañías tradicionales, Johnson&Johnson y AstraZeneca han sido menos exitosas con resultados modestos. Una posible explicación es que el impacto de los ingresos por las vacunas haya quedado dilluido puesto que el portfolio de productos comercializados por ambas es muy amplio; iii) una empresa biotecnológica, Novavax, mostró una evolución positiva en bolsa al principio de la pandemia pero su valoración empeoró significativamente después. Es posible que los inversores no hayan visto reflejadas las expectativas en unos mejores resultados financieros tras la comercialización de la vacuna y hayan reaccionado de manera negativa, vendiendo sus acciones de la empresa.

1.4 Conclusiones y resumen del capítulo

La presente tesis analiza la eficiencia de empresas farmacéuticas principalmente "manufactureras" frente a aquellas que, además de producir medicamentos, invierten en I+D para desarrollar nuevos tratamientos. Las primeras resultan más eficientes que las segundas durante el periodo analizado.

Con respecto al mercado de las CROs, los resultados de eficiencia de la muestra analizada indican que las empresas mayores dentro de este sector se beneficiarían de una serie de ventajas que les aporta su mayor tamaño. Asimismo, existe un pool de empresas pequeñas dentro del sector que se benefician de su especialización como empresas de nicho.

El análisis de la cotización de las acciones de las empresas farmacéuticas y biotecnológicas durante la pandemia de Covid-19 muestra que, excepto en el caso de Pfizer y Moderna, no es posible concluir que las empresas que han invertido en el desarrollo de una vacuna contra el virus se han beneficiado directamente de ello y que, por tanto, han visto recompensada dicha inversión y posterior comercialización de la respectiva vacuna en su cotización en bolsa.

CHAPTER 2.

Non-Parametric Analysis of Efficiency: An Application to the Pharmaceutical Industry

CHAPTER 2.

Non-Parametric Analysis of Efficiency: An Application to the Pharmaceutical Industry

Abstract

Increases in the cost of research, specialization and reductions in public expenditure in health are changing the economic environment for the pharmaceutical industry. Gains in productivity and efficiency are increasingly important in order for firms to succeed in this environment. We analyze empirically the performance of efficiency in the pharmaceutical industry over the period 2010–2018. We work with microdata from a large sample of European firms of different characteristics regarding size, main activity, country of origin and other idiosyncratic features. We compute efficiency scores for the firms in the sample on a yearly basis by means of non-parametric data envelopment analysis (DEA) techniques. Basic results show a moderate average level of efficiency for the firms which encompass the sample. Efficiency is higher for companies which engage in manufacturing and distribution than for firms focusing on research and development (R&D) activities. Large firms display higher levels of efficiency than medium-size and small firms. Our estimates point to a decreasing pattern of average efficiency over the years 2010–2018. Furthermore, we explore the potential correlation of efficiency with particular aspects of the firms' performance. Profit margins and financial solvency are positively correlated with efficiency, whereas employee costs display a negative correlation. Institutional aspects of the countries of origin also influence efficiency levels.

2.1 Introduction

Pharmaceutical companies contribute crucially to the health and welfare of individuals. This issue is particularly relevant nowadays: as the Covid-19 pandemic has shown, no country is immune to the emergence of new diseases. Furthermore, the population in many countries is experiencing deep demographic transformations which increase life expectancy and raise new challenges for policymakers. Not surprisingly, the performance of the industry directly affects some of the Sustainable Development Goals of the 2030 Agenda for Sustainable Development.

The economic importance of the industry is also paramount. The pharmaceutical sector employs highly skilled labor and exhibits one of the largest figures of research and development (R&D) intensity (defined as expenditure in R&D as a share of sales). As recent contributions in the field of macroeconomics have shown, human capital and R&D are key drivers of economic growth, productivity and prosperity (Lucas, 1998; Romer, 1986; Romer, 1990).

The pharmaceutical industry is facing new challenges because of several factors. New diseases as the Covid-19 demand quick, pathbreaking solutions. R&D costs grow because conditions become chronic and more complicated. Paradoxically, the progress in molecular biology which increases the range of potential innovations also raises the complexity of decisions related to the R&D strategy. New investments seek increasingly *high risk/high premium* drugs (Pammoli et al., 2011). Official agencies accumulate requirements for drug approvals. Firms must cope with the expiration of patents and with reductions in public expenditure in healthcare due to stability measures and fiscal adjustments.

Meanwhile the business model in the industry has experienced deep transformations over the last decades. Some firms have specialized in particular steps of the value chain, as R&D in the biotechnological sphere or clinical research, this last in the case of contract research organizations (CROs). Reductions in R&D productivity have brought about mergers and acquisitions, partly to profit from the expertise in research and the pipeline of other companies. Shimura et al. (2014) argue that Japanese firms engaged in mergers and acquisitions over 1980–1997 to handle the declining productivity of R&D. Other firms outsource activities or engage in technological alliances (Shin et al., 2018; Rafols et al., 2012). In this context, firms must strive to increase their levels of productivity and efficiency, which may become a strategic asset (Gascón et al., 2012).

In parallel, empirical research on productivity and efficiency (defined as output per unit of inputs) has grown over the last decades. Mathematical techniques such as data envelopment analysis (DEA) have facilitated the empirical assessment of efficiency at the country, entity or firm level. The literature has explored the levels and trends of efficiency in many activities and areas such as banking (Jiang, & He, 2018), farming (Kumbhakar et al., 2012), food (Wang et al., 2020), universities (Chen, & Soo, 2010), airlines (Lozano, & Gutierrez, 2014), shipping (Lin et al., 2020), oil (Zhou et al., 2019), electricity distribution (Kuosmanen et al., 2013; Cherchye et al., 2015) and energy consumption (Orea et al., 2015; Alarenan et al., 2019), to quote just a few examples.

Recent meta-analyses and compilations of DEA exercises can be found in Ahn et al., 2018, for the public sector, Sueyoshi et al, 2017, for energy and the environment, Odeck, & Bråthen, 2012, for seaports, Fall et al., 2018, for microfinance institutions and Marchetti, & Wanke, 2019, for rail transport. Emrouznejad, & Yang, 2018, provide a thorough list of the main journal articles on DEA methodology and applications published between 1978 and 2016.

Researchers have also dealt with more theoretical aspects of the DEA model. Examples are Emrouznejad, & Thanassoulis, 2005, which describes a dynamic version of DEA that allows intertemporal links between inputs and outputs to be considered, and Hu et al., 2020, which provides an alternative to the inverse DEA model. Furthermore, Wei, & Wang, 2017, explore the features of the model when the data are imprecise and Khezrimotlagh et al., 2019 devise a DEA algorithm suitable to deal with Big Data.

The analysis of efficiency in the pharmaceutical industry has also been addressed in the recent past (Gascon et al., 2016; You et al., 2010) although the number of contributions in this regard is comparatively sparse. Most of the studies in this area perform their analyses at the country level and/or focus on a (usually small) sample of companies. Examples are Mao et al., 2014, for China; Sueyoshi, & Goto, 2014; Hashimoto et al., 2008, for Japan; Shin et al., 2018, for US; Al-Refaie et al., 2018, for Jordan and Mazumdar et al., 2009, for India.

We intend to complement this literature with a two-stages analysis of efficiency within a relatively large sample of European firms. In the first stage we compute efficiency levels for the firms in our sample. In the second stage we explore by statistical modelling the connection between the efficiency scores obtained in the first stage and a set of variables potentially correlated with efficiency.

We are especially interested in the assessment of efficiency by type of activity and firm size. More specifically, we want to explore whether large firms exhibit higher levels of efficiency, which would be consistent with the potential presence of scale economies in the industry. Furthermore, it is feasible that firms which primarily operate in the R&D niche enjoy a different level of efficiency, on average, than companies with activities along the entire value chain. Finally, we want to explore the data to find common patterns and detect possible features of the economic and institutional framework and firm management strategy which can be correlated with efficiency.

In parallel, our empirical exercise may prove useful to illustrate how to apply modern mathematical, non-parametric techniques in order to get insights about the performance of firms in a particular industry, and how these tools are related to more traditional, parametric approaches.

Our paper is closely related to three DEA explorations of the pharmaceutical industry: Shin et al., 2018; Gascón et al., 2016; Mazumdar et al., 2009. Gascón et al., 2016, analyze efficiency in a sample of 37 large firms from different countries over 2008–2013. They report an average level of efficiency in their sample of 0.9345 and find that firms with higher level of efficiency carry out more financial transactions with other companies.

We complement this exploration in several dimensions. First, our sample is different, broader and more heterogeneous, since it encompasses a large group of European firms, of different sizes and profiles. Second, we report an average efficiency score of 0.34. We think that this figure is a more accurate reflection of the mean efficiency for the whole industry, at least for the European case.

Third, we carry out a two-stage exploration of efficiency whereby in the second stage we look at variables potentially correlated with the efficiency levels obtained in the first stage. Gascón et al, 2016, omit the second stage because it is somehow controversial. It is true that the literature has not reached a consensus yet on the right specification for the second stage; nonetheless, we think that this analysis can still provide some valid insights about efficiency.

Fourth, we work with a more recent time horizon, 2010–2018, and examine the dynamic performance of efficiency over time; they look at data from 2008–2013 but perform their analysis on average terms, so they do not uncover the pattern of efficiency over time.

Another related investigation is Shin et al, 2018. They employ proprietary data from a sample encompassed by 700 US pharmaceutical firms over the period 2001–2016. They assess the connection between open innovation methods and efficiency.

Mazumdar et al., 2009, utilize data from a financial database to examine the performance of a group of Indian firms over the years 1991–2005. They perform a two-stage analysis. In the second stage they examine the determinants of efficiency in their sample by regression tools.

In contrast to Shin et al., 2018; Mazumdar et al., 2009, we work with a sample made up of European firms and explore the potential impact of alternative aspects of firm management and country characteristics. While Mazumdar et al., 2009, employ only a Tobit specification in the second stage of their analysis, we utilize also a pure random-effects and a Simar–Wilson procedure, and perform a comparison of the three methods.

We contribute to the literature in several ways. To the best of our knowledge, we are the first to perform a DEA analysis for a relatively large sample of European pharmaceutical firms, of different sizes and main activities, fully exploiting the time dimension of the data.

The inclusion of biotechnological companies in our sample and the exploration of their specific performance are also novel features of our investigation.

We introduce in the second stage of our empirical work a set of variables potentially correlated with efficiency, capturing different aspects of firm management and the macroeconomic environment where companies operate. Employing these variables is original as well in these kinds of analysis.

Finally, we compare the results for the second stage of three different estimation procedures (Tobit, pure random-effects, Simar–Wilson, 2007). While the estimates yielded by the Tobit and the pure random-effects specifications are rather close, the Simar–Wilson tool provides larger point estimates. Nonetheless, the quantification of the marginal effects of the main covariates are more similar, and therefore the Simar–Wilson method may also be useful in applied research.

Our investigation suggests that the level of efficiency in the European pharmaceutical industry is moderate and has displayed a decreasing trend over the period 2010–2018. We find a connection between size and efficiency for the firms in our sample, where larger and very small firms tend to perform better as far as efficiency is concerned. Instead, efficiency is smaller for medium and small firms.

In terms of activity, companies operating over the complete value chain register higher levels of efficiency than firms that specialize in the R&D area. Moreover, the geographical market where firms operate seems to matter for their efficiency. Higher margins, sound financial management and lower levels of employee cost are also positively correlated with efficiency according to our results.

The structure of this paper is the following: Section 2.2 describes the theoretical background of our investigation. Section 2.3 describes the data and empirical strategy pursued. Sections 2.4 and 2.5 discuss the main results of our analysis and Section 2.6 concludes.

2.2 Theoretical Background

Conventional microeconomic theory assumes that firms optimize by producing the maximum possible quantity of output for a given input endowment or, equivalently, by producing a given amount of output with the minimum feasible inputs; this is tantamount to presupposing that they are efficient.

Empirical evidence and casual observation suggest that this is not necessarily the case. Inefficiencies exist and may arise due to managerial practices (Bloom et al., 2016) or cultural beliefs (Bénabou, & Tirole, 2016). Moreover, some features of the macroeconomic environment where companies operate, as information asymmetries or market rigidities, may also be detrimental for firms' productivity, as some important breakthroughs in macroeconomics in the last decades have pointed out.

Modern applied research pursues productivity analyses through two main avenues: stochastic frontier analysis (SFA) and DEA. While the intuition of both approaches is similar, the procedures are different.

In both cases the starting point is the idea of an efficient combination of inputs and outputs which encompasses a production function or *frontier*. The units of analysis are the so-called *decision-making units* or DMUs, i.e., the firms, organizations, institutions etc. whose efficiency is explored. The main difference between SFA and DEA lies in their methodology. SFA estimates the (continuous) production function by statistical techniques; DEA fits a piecewise hull enveloping the data which is assumed to approximate the true frontier, without making any statistical assumption about the data-generating process.

SFA originated with the pathbreaking contributions of Aigner et al., 1977; Meeusen, & Broeck, 1977. In this setting, deviations from the estimated production function can be decomposed in statistical noise and inefficiency. Therefore, the error term in these models is usually composite (Kumbhakar et al., 2017).

An SFA model may be described by Equation (1)

$$\begin{aligned} y_i &= m(x_i; \beta) + \varepsilon_i \\ \varepsilon_i &= v_i - u_i \\ v_i &\sim N(0, \sigma_v^2) \\ u_i &\sim F \end{aligned} \qquad (1)$$

where y_i is (log) output for the *ith* decision-making unit or DMU, x_i is a vector of inputs for the *ith* DMU, ε_i the vector of parameters to be estimated, u_i captures the (one sided) inefficiency of the *ith* DMU and v_i represents stochastic shocks. m(.) is the production function, usually assumed to be

Cobb Douglas or Translog. The estimation is ordinarily implemented by maximum likelihood or other appropriate methodologies.

The stochastic shock is usually considered normal with zero mean and known variance, whereas different distributions have been advocated and estimated in the literature for the term capturing inefficiency (for a thorough review, see Kumbhakar et al., 2017).

The assumption about the error term may be too restrictive. Sometimes it may be preferable to work with a more flexible specification which involves fewer hypotheses. This is why non-parametric techniques, and in particular DEA, have been developed and used increasingly in recent years.

In the applied work, nonetheless, parametric and non-parametric tools sometimes intertwine: the non-parametric approach may be complemented by some statistical analyses, usually by regression procedures, which explore the output of DEA and employ inference to generalize its results to a non-deterministic setting.

2.2.1 Data Envelopment Analysis

The seminal paper for DEA is Charnes et al., 1978. This technique computes efficiency by linear programming. The technique operates in two steps: first, it constructs the frontier from the data; second, it computes the distance of each unit to the frontier. It is assumed that the DMUs with the greatest efficiency determine the frontier and have efficiency of 1.

Not all efficient DMUs, however, need to be real: they can be fictitious, i.e., linear combinations of other units. This assumes, in turn, that inputs can be used continuously, i.e., they are divisible. Moreover, it presupposes that the efficiency frontier is a convex set, and hence the linear combination of two points belonging to the feasible set are also feasible. The efficient DMUs which generate a fictitious unit are called referees.

The ideas of frontier and distance encompass an intuitively appealing way to address the study of efficiency. Consider a simple example, firms from an industry which produce a single output y by means of an input x (Figure 2.1) (this example can be immediately generalized to the case of a vector of outputs and a vector of inputs). There are several firms or DMUs dubbed A, B, C, D, and E. The coordinates for each point in the x, y, space symbolize the input employed and the output produced by each firm. The frontier (solid line) represents *optimal* combinations of inputs and outputs. It is immediate to notice that B provides more output than A, $y_B > y_A$, while using the same amount of input since $x_A = x_B$. Alternatively, D and E produce the same output, $y_D = y_E$, but firm D consumes a smaller amount of input than E, $x_D < x_E$.

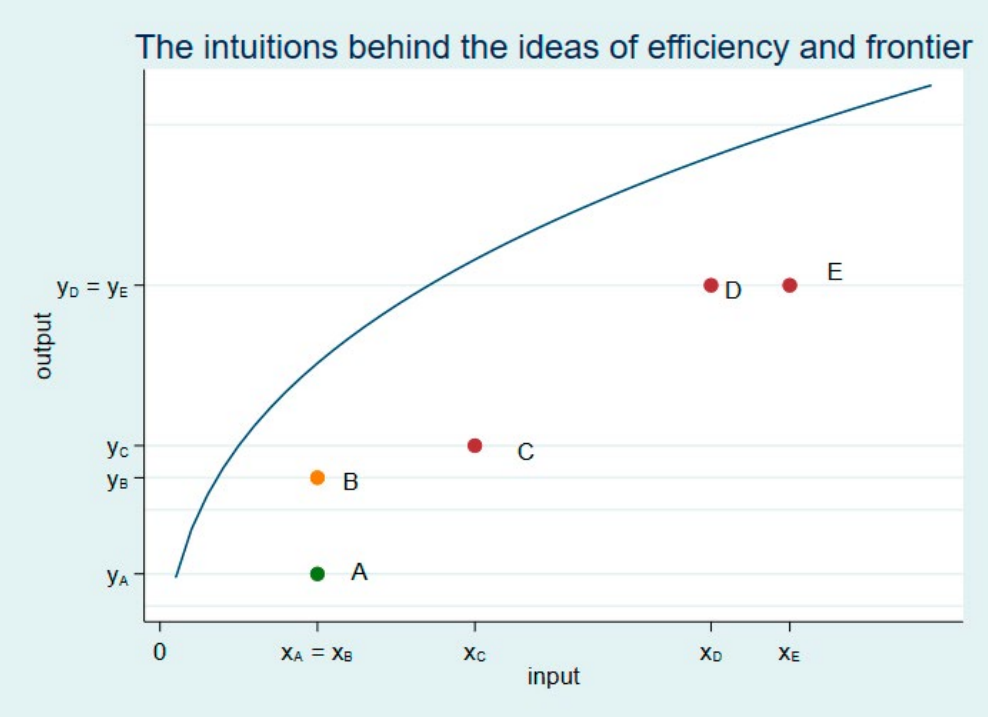

Figure 2.1. The intuitions behind the ideas of efficiency and frontier.
Note: The figure portrays the ideas of efficiency and frontier. x is input and y is output. The concave solid line represents the technology or frontier of possibilities of production, the maximum attainable amount of output for each value of the input endowment. The dots A, B, C, D and E represent decision-making units or DMUs, i.e., firms, organizations, institutions, etc., whose efficiency is considered. Intuitively, B is more efficient than A because it produces more output than A (yB > YA) with the same amount of input (xB = xA). Similarly, D is more efficient than E since D uses a smaller amount of input (xD < XE) to produce the same amount of output (YD = YE). The closer a DMU is to the frontier, the larger its level of efficiency.
Source: own elaboration.

We say than B is more efficient than A and that D is more efficient than E. The closer a firm to the frontier, the larger its efficiency. Conversely, the deviations from the frontier can be understood as inefficiencies.

It is clear from Figure 2.1 that optimality can be defined in two alternative ways, maximum output per unit of input or minimal consumption of resources to attain a certain level of output. The first approach is named *output oriented* while the second is called *input oriented*.

Suppose there are N DMUs with a technology characterized by constant returns to scale. For the *i*th firm we can define the following ratio of outputs to inputs:

$$\text{ratio i} = \frac{a' y_i}{\beta' x_i}$$

$$i = 1, \ldots, N$$

where y_i is a vector of M outputs and x_i a vector of K inputs.

The maximization of efficiency implies the following problem:

$$\max_{\alpha,\beta} \quad \frac{a' y_i}{\beta' x_i}$$

subject to the following constraints:

$$\frac{a' y_s}{\beta' x_s} \leq 1, s = 1, ..., N \tag{2}$$

$$\alpha_m \geq 0, m = 1, ..., M \tag{3}$$

$$\beta_k \geq 0, k = 1, ..., K \tag{4}$$

The restriction given by Equation (2) implies that the efficiencies of all firms have to be less or equal that 1. Restrictions given by (3) and (4) rule out negative weights of outputs and inputs.

Intuitively, the problem seeks the optimal weights such that the efficiency of the firm *i* is maximized, while operating within the feasible set implied by the constraints.

Imposing the restriction $\beta' x_i = 1$ this fractional programming problem can be linearized (Banker et al., 1984) and transformed into the following:

$$\max_{\alpha,\beta} \quad a' y_i$$

subject to:

$$\beta' x_i = 1$$

$$\alpha' y_s - \beta' x_s \leq 0, \quad s = 1, ... N$$

$$\alpha \geq 0$$

$$\beta \geq 0$$

which can be written in the envelopment form as:

$$\min_{\theta,\lambda} \theta_i$$

subject to:

$$\sum_{s=1}^{N} \lambda_s y_s - y_i \geq 0$$

$$\theta_i x_i - \sum_{s=1}^{N} \lambda_s x_s \geq 0$$

$$\lambda_s \geq 0$$

where θ_i is the input oriented *efficiency score* for the *ith* firm.

λ stands for the set of multipliers in the linear combinations of the DMUs' inputs and outputs, i.e., the weight of each DMU within the peer group of DMUs.

This set up can also be applied to a technology exhibiting variable returns to scale by adding the convexity condition:

$$\sum_{s=1}^{N} \lambda_s = 1$$

This is an optimization problem, with linear objective function and constraints, solvable by linear programming.

The value of θ_i, the input-oriented technical efficiency score for the *i*th firm, indicates to what extent the inputs can be reduced in percent while keeping the output constant. For example, if DMU i has an efficiency score of 90%, it can reduce all inputs by 10% while offering the same amount of output. Notice the difference between this set up and the statistical approach of SFA as presented in Equation (1) above.

The empirical exercise described in this paper employs the non-parametric, DEA formulation of the optimization problem as the baseline for analysis.

2.3 Material and Method: Data and Empirical Strategy

Data have been gathered primarily from Amadeus (Van Dijk, 2020) a rich database comprising disaggregated economic and financial information from a large number of European companies. Gascón et al., 2016; Mazumdar et al., 2009, employ also financial information from similar databases for their analyses.

Within the pharmaceutical industry, we have selected two main categories of firms in Amadeus according to their main activity:

(i) Manufacture of basic pharmaceutical products and pharmaceutical preparations;

(ii) Research and experimental development on biotechnology.

They will be labelled henceforth *manufacturers* and *R&D firms*, respectively. The two subgroups correspond to NACE (Nomenclature statistique des Activités Économiques dans la Communauté Européenne) codes 2110, 2120 (for manufacturers) and 7211 (for R&D firms). This is equivalent to NAICS (North American Industry Classification System) codes 541714 and 541715.

We work with yearly observations over the time horizon 2010–2018.

Following part of the literature on DEA, our research design has two stages (see Appendix A for an explanatory diagram of the design of our empirical exercise). The stages are detailed in Sections 4 and 5, respectively. In the first stage we compute the efficiency scores of the firms in our sample by DEA. In the second stage we design and estimate several statistical models to explore potential variables correlated with the efficiency scores; these models provide information regarding the sign of the correlation between the efficiency score and each variable, its statistical significance and its size.

Ordinarily, non-parametric techniques cannot be applied to data structured in panels because of tractability considerations, as is common, instead, with other methodologies which allow for an explicit time dimension and have been successfully employed with panels. We circumvent this problem computing measures of efficiency year by year. This feature may be regarded as a drawback on a priori grounds; nonetheless, the estimation of efficiency measures performed on a yearly basis has been useful to uncover interesting patterns in their evolution over time.

We have started to work with a sample encompassed by more than 4000 observations from 482 firms over the nine years in the period 2010–2018, evenly split among manufacturers and R&D firms.

For the computation of efficiency for a particular year, however, we have dismissed those observations corresponding to firms which do not report data of turnover, employees and/or assets for that same year. After discarding the firms with missing values, we end up with samples comprising around 200 companies for each year, of different sizes, geographical origins and performances over time. The samples, therefore, are quite representative of the industry.

In the case of multinationals, firms correspond to headquarters. In our selection of companies we have discarded local affiliates because internal accounting procedures of multinationals may reduce their degree of comparability.

Nominal variables have been deflated using the Harmonized European Index from Eurostat (Eurostat, 2020).

Our measure of output is turnover in real terms (in constant euros of 2015). The inputs labor and capital are proxied by the number of employees and total assets in real terms, respectively. Total assets in real terms are also measured in constant euros of 2015. The choice of these variables has been made in accordance with other contributions performing similar analyses, as Shin et al., 2018; Gascón et al., 2016; Sueyoshi, & Goto, 2014.

Economic and financial conditions have been captured by cash flow over turnover, profit margin and average cost of employees, among others (see Appendix B).

We have constructed dummies for size, country of origin, main activity and years. The specific details will be provided in Sections 4 and 5 below.

Figure 2.2 conveys some information for selected variables, disaggregated in manufacturers and R&D firms. Real turnover is expressed in constant euros of 2015. It is apparent from the Figure that the firms encompassing the first category are considerably larger than those in the second, as shown by the average real turnover and average number of employees.

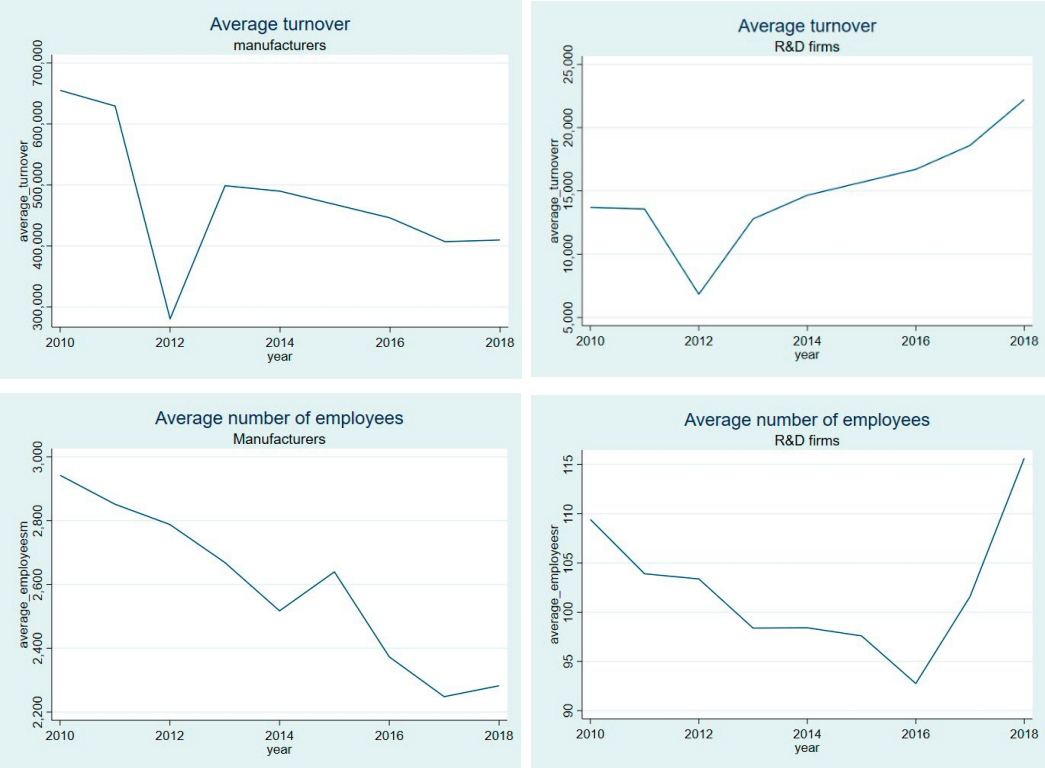

Figure 2.2. Average real turnover (in constant euros of 2015) and average number of employees over time by main activity.

Notes: The figure displays the time pattern for average real turnover and average number of employees over 2010–2018, disaggregated by main activity of firms. Averages have been computed from the data year by year. Two main categories are considered: firms whose main activity is the manufacture of basic pharmaceutical products (manufacturers), and companies focused on research and experimental development on biotechnology (research and development (R&D) firms). Average turnover exhibits a decreasing trend over the period, with a big drop in 2012 for manufacturers, and an increasing trend for R&D firms since 2013. Average number of employees decreases over the period for the first category of firms and increases since 2016 for the second. Source: own elaboration with data from the Amadeus data base).

It is also clear that both variables have experienced a decreasing pattern over time for manufacturers, with a very pronounced drop in 2012 in the case of real turnover. This is consistent with the increasingly difficult environment in which they operate. For R&D firms, the pattern is less straightforward.

Average real turnover has also plummeted in 2012 but has increased thereafter. Average number of employees falls until 2016 and rises in the last years of the period.

These trends may be associated to the progressive outsourcing of some stages of the value chain, which were traditionally performed by manufacturers and now are increasingly implemented by CROs and other biotechnological firms.

Two more considerations about our empirical strategy are in order. First, and as stated above, the DEA analysis can be implemented in an output oriented or input oriented setting. We have followed this second approach since it seems intuitively more appealing and conforming with firms' experience: their plans to increase efficiency are usually linked to reduction in costs, rather than to expansions in output.

Secondly, the relevant role played by R&D in this industry suggests that scale economies might be prevalent, but this is a controversial issue which the literature has not been able to settle yet. Henderson et al., 1993, found evidence in favor of this hypothesis; Cockburn, & Henderson, 2001, however, did not, although they did suggest that economies of scope and accumulated knowhow were important for the firms in the sector. Danzon et al., 2005, encountered knowledge spillovers among firms in Phase I of clinical research and diseconomies of scope in later phases. Sueyoshi, & Goto, 2014, find that 60% of the firms in their sample of Japanese chemical and pharmaceutical companies operate with either increasing or decreasing returns to scale.

There is no consensus yet, therefore, on the degree of homogeneity of the production function in the industry. Anyhow, since the existence of increasing returns to scale cannot be ruled out, we have chosen to employ a variable returns to scale model as our theoretical framework, rather than a constant returns to scale. Gascón et al., 2016, follow a similar approach.

2.4 Stage 1: Computation of Efficiency Scores

Pharmaceutical and biotechnological firms share some activities and hence compete with each other in certain stages of the value chain. We are interested in assessing whether the companies specialized in R&D activities are more or less efficient, being thus better or more poorly positioned to succeed and survive, than companies which are mainly producers and sellers. Hence, we analyze the firms in the industry jointly, i.e., with respect to an efficient frontier common for all of them (nonetheless, we have performed the analysis separately in each of the subgroups and basic results carry over).

Tables 2.1–2.5 and Figures 2.3 and 2.4 summarize some summary statistics about the efficiency of the firms that encompass our sample, as obtained employing DEA in our sample on a yearly basis.

Table 2.1. Efficiency in the pharma and biotechnological European industry by activity, 2010–2018.

	Efficiency Mean	Standard Deviation	Coefficient of Variation
Whole sample	0.341	0.265	0.777
Manufacturers	0.381	0.266	0.698
R&D firms	0.281	0.251	0.893

Note: the table summarizes selected statistics for efficiency levels, computed as described in the main text. We classify firms in two groups, manufacturers and R&D firms, according to their main activity. Source: Own elaboration.

The mean efficiency for the entire sample and over the period 2010–2018 is 0.341. Thus, firms in our sample could increase their efficiency on average in 0.659 points or 65.9%. It seems a reasonable figure. Shin et al., 2018, report values of efficiency between 0.42 and 0.58. Their sample is made up by US firms; it seems sensible to think that US firms are, by and large, more efficient than their European counterparts because the general level of efficiency of the US economy is larger and its regulatory burden is smaller. Furthermore, US pharmaceutical firms are larger, on average, than European firms and, as we shall argue below, our results suggest that larger firms are more efficient. The standard deviation is 0.265, which suggests a noticeable degree of dispersion in the sample.

The results are not very different from those obtained by Hashimoto, & Haneda, 2008; they find that the average efficiency for a sample of Japanese firms is 0.68 for 1983–1987 and 0.47 for 1988–1993.

If we classify the firms according to their main activity, we find that the mean efficiency for the manufacturers is 0.381 whereas for the R&D firms the figure is smaller, 0.281. This is a somewhat surprising result: the common practice in the industry whereby manufacturers outsource

some activities to R&D and biotechnological specialized companies like CROs would suggest on a priori grounds that the former be more efficient that the latter. Otherwise, the outsourcing could be questioned on economic grounds. This is not what we find, however.

One possible explanation for our results is that many manufacturers have been in the market longer, and their historical performance have endowed them with expertise, knowhow and managerial practices which have increased their productivity. This is related to the phenomenon called learning curve in engineering or learning by doing in economics. A classical example is provided by Arrow, 1962, who noticed that the number of hours necessary to produce an airframe was a decreasing function of the number of airframes already produced. Instead, many R&D firms are still relatively young; it is feasible, therefore, that there is still room for them to optimize their processes and value chains and improve their productivity and efficiency.

In addition, the R&D activity in order to develop new drugs is very risky. Success rates are low. Only a modest percentage of molecules are able to complete clinical phases successfully and enter the final market. Hay et al., 2014, report that only 10.4% of the drugs entering the clinical stage gain approval by the US Food and Drug Administration (FDA). Biotechnological firms displaying small sizes and relatively reduced pipelines may thus be very affected by failures in the R&D stage. These episodes, in turn, will entail lower levels of productivity.

Notice also that the standard deviation for R&D firms is comparatively high, 0.251. In fact the coefficient of variation, as measured by the ratio standard deviation to mean, is higher for this category. This implies that heterogeneity is more pronounced for this kind of firm.

In order to assess the connection between relative efficiency and size, we have created six categories of firms. Five of these categories (from very big to very small) are linked to the intervals delimited by the 95, 75, 50 and 25 percentiles of real turnover over the period. In particular, the classification is as follows:

- Huge: if the average real turnover over the period exceeds 2000 million euros.
- Very big: if the average real turnover is less or equal than 2000 million euros and higher than 426.92 million euros.
- Quite big: if the average real turnover is less or equal than 426.92 million euros and higher than 38.86 million euros.
- Medium: if the average real turnover is less or equal than 38.86 million euros and higher than 8.10 million euros.
- Small: if the average real turnover is less or equal than 8.10 million euros and higher than 2.10 million euros.
- Very small: if the average real turnover is less or equal than 2.10 million euros.

Table 2.2 displays summary statistics for relative efficiency classified according to these categories. The largest companies in the sample, those with turnover larger than 2000 million euros, have the highest level of efficiency in the sample, 0.98. In other words, most of them encompass the efficient frontier or are very close to it. There is very little dispersion within this category and the coefficient of variation is almost negligible.

For very big companies, with turnover roughly between 500 and 2000 million euros, efficiency is also remarkably high, 0.765 in average terms. The potential gains in efficiency for this category are only around 25% on average. Firms in the next turnover interval have a smaller record, 0.425. Medium-size firms register lower levels of efficiency on average, 0.312; this is slightly below the figure for the whole sample and period, 0.341.

Small firms, with turnover between 2.10 and 8.10 million euros, register the smallest value of average efficiency, only 0.267. Interestingly, their record is worse than that of the very small firms, with turnover below 2.10 million euros: this last category attains an indicator of 0.318, slightly above medium size firms. This result is consistent with Mazumdar et al., 2009, which find that small pharmaceutical firms display smaller levels of efficiency for the case of India.

Higher degrees of flexibility and capacity to adapt to the environment, more agile management and lower levels of conflicts among partners which characterize very small firms may be behind this result. The comparatives advantages provided by specialization may also play a role.

The performance within those categories, as reported by the coefficient of variation, is not uniform. Dispersion is maximum for the very small firms (0.9), whereas more limited for very big firms (0.267). Dispersion in the other categories is similar and quite high: between 0.6 and 0.71.

The implications of these results are interesting. There is not a monotonic, clear cut relationship between size, as captured by turnover, and relative efficiency. Our findings suggest that larger firms are more efficient but only beyond a certain threshold of income, located around 500 million euros. Companies above this figure are considerably more efficient, suggesting the possibility of scale economies for high levels of turnover. Firms with turnover between 38 and 500 thousand million euros also perform better than the whole sample, although their particular advantage amounts just to less than 10 points.

Intermediate and small firms do not profit from scale economies neither from the flexibility and specialization associated to very small firms, and therefore register the poorest results as far as efficiency is concerned.

Table 2.2. Relative efficiency in the pharma and biotechnological European industry by size, 2010–2018.

	Mean	Standard Deviation	Coefficient of Variation
Huge	0.98	0.039	0.039
Very big	0.765	0.205	0.267
Quite big	0.425	0.266	0.625
Medium	0.312	0.218	0.698
Small	0.267	0.19	0.71
Very Small	0.318	0.288	0.9

Note: the table summarizes selected statistics for efficiency levels, disaggregated by size of the firms (proxied by real turnover). The thresholds are described in the main text. Source: Own elaboration.

Table 2.3 and Figure 2.3 provide the dynamic context to these results by detailing the performance over the years 2010–2018. Average efficiency plummets from the beginning of the period until 2015, to recover thereafter. In year 2017, efficiency falls again, to increase in 2018, but it does not recover to the levels attained before 2010. Between 2010 and 2018 efficiency diminishes by almost 10 points. The decrease is especially acute for manufacturers, whereas R&D firms only lose 4 points on average.

These results are consistent with Shin et al., 2018, who also document a decrease in efficiency for most of the firms in their sample for 2010–2015.

Table 2.3. Efficiency in the pharma and biotechnological European industry by activity, yearly results, 2010–2018.

	2010	2011	2012	2013	2014	2015	2016	2017	2018
Whole sample	0.428	0.392	0.348	0.308	0.304	0.292	0.383	0.311	0.334
Manufacturers	0.481	0.449	0.391	0.351	0.334	0.335	0.409	0.34	0.367
R&D firms	0.338	0.277	0.263	0.243	0.267	0.231	0.345	0.272	0.294

Note: the table details average levels of efficiency by year and main activity of firms. Efficiency is computed as described in the main text. Source: Own elaboration.

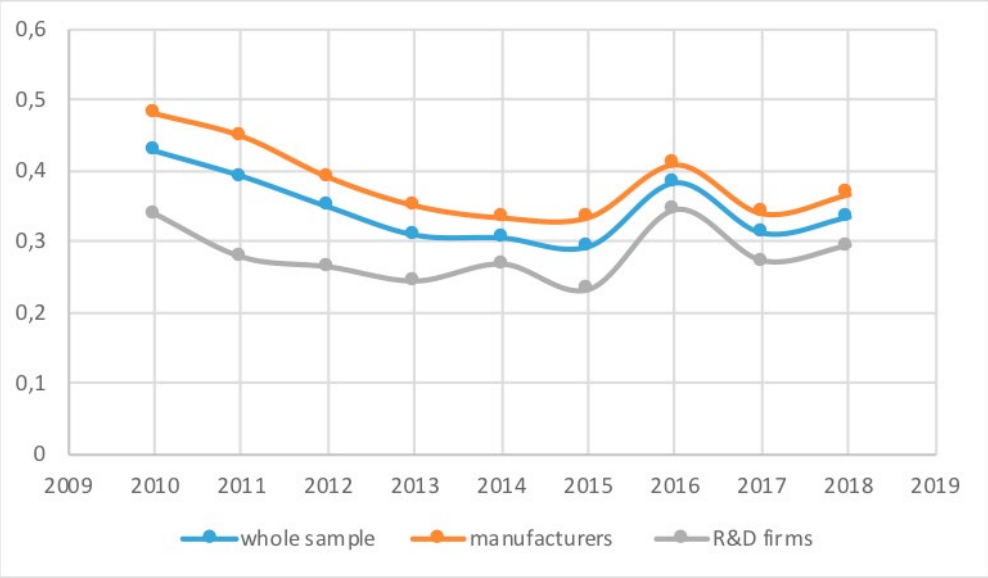

Figure 2.3. Efficiency in the pharma and biotechnological European industry by main activity, 2010–2018.

Note: the figure summarizes the yearly trend of average efficiency, for the whole sample and disaggregated by categories corresponding to the main activity of firms. Efficiency decreases over the period, with a partial recovery in 2015–2016. Source: own elaboration.

Table 2.4. Variables correlated with efficiency, Tobit estimations. Dependent variable is efficiency.

	Model 1	Model 2	Model 3	Model 4
profit_margin	0.1539 ***			
	(7.00)			
Germany	0.0799	0.1178 **	0.0818	0.1045 *
	(1.38)	(2.02)	(1.49)	(1.89)
Spain	−0.0232	−0.0614	0.0305	0.0435
	(0.44)	(1.10)	(0.54)	(0.87)
France	0.0100	0.0544	−0.0117	0.0167
	(0.17)	(0.94)	(0.21)	(0.31)
Sweden	0.2977 ***	0.2615 ***	0.2389 ***	0.3008 ***
	(3.93)	(3.44)	(3.45)	(4.13)
Italy	0.1421 ***	0.1549 ***	0.1587 ***	0.1374 ***
	(2.62)	(2.85)	(2.85)	(2.79)
UK	0.1389 ***	0.1637 ***	0.1128 ***	0.1356 ***
	(3.62)	(4.16)	(2.88)	(3.64)
Manufacturers	0.0660 **		0.1599 ***	
	(2.00)		(4.96)	
Huge	0.2054 **			0.2393 ***
	(2.49)			(3.02)
Verybig	0.1276 ***			0.1163 ***
	(3.61)			(3.24)
Quitebig	0.0215			0.0179
	(1.39)			(1.09)
year2014	−0.0795 ***	−0.0744 ***	−0.0633 ***	−0.0738 ***
	(6.90)	(6.37)	(5.88)	(6.16)
year2015	−0.1733 ***	−0.0758 ***	−0.0556 ***	−0.1537 ***
	(4.97)	(4.69)	(5.31)	(4.35)
year2016	0.0373 ***	0.0465 ***	0.0439 ***	0.0441 ***
	(3.32)	(4.12)	(4.34)	(3.79)
cash_flow		0.1650 ***		
		(6.86)		
Biotech		−0.1384 ***		−0.0494
		(4.21)		(1.59)
Medium		−0.0300 *		
		(1.81)		
Small		−0.0614 ***		
		(3.22)		

Table 2.4. (**Cont**)

	Model 1	Model 2	Model 3	Model 4
Verysmall		−0.0069		
		(0.29)		
collection_period			−0.0226 ***	
			(4.44)	
employee_cost				−0.3739 ***
				(10.22)
_cons	0.2808 ***	0.3788 ***	0.2245 ***	0.4390 ***
	(7.95)	(12.50)	(6.37)	(15.49)
Likelihood Ratio test of σ2u = 0: X2(1)	928.17 ***	980.9 ***	1505.81 ***	771.79 ***
Likelihood Ratio test of σ^2u = 0: *p* value	0	0	0	0
Number observations	1547	1344	1850	1353

Notes: The table summarizes the results from the Tobit estimation of Equation (6). Dependent variable is efficiency computed in Stage 1. Cons stands for the intercept. For the rest of variables, see main text. Data are organized in a panel varying across firms and time over 2010–2018. In order to circumvent heteroskedasticity, estimations have been performed with corrected standard errors; the variance-covariance matrix of the estimators is the matrix of second derivatives of the likelihood function. LR test of $\sigma^2_u = 0$ distributed as X2(1). * $p < 0.1$; ** $p < 0.05$; *** $p < 0.01$.

Table 2.5. Variables correlated with efficiency, random effects estimations. Dependent variable is efficiency.

	Model 5	Model 6	Model 7	Model 8
profit_margin	0.1531 ***			
	(5.33)			
Germany	0.0702	0.1064 *	0.0740	0.0908 *
	(1.23)	(1.85)	(1.41)	(1.70)
Spain	−0.0210	−0.0598 **	0.0304	0.0427
	(0.55)	(2.04)	(0.66)	(0.87)
France	0.0093	0.0504	−0.0150	0.0128
	(0.19)	(1.08)	(0.32)	(0.28)
Sweden	0.2779 ***	0.2420 ***	0.2280 ***	0.2922 ***
	(3.07)	(3.23)	(3.32)	(3.78)
Italy	0.1375 **	0.1488 ***	0.1529 ***	0.1336 ***
	(2.52)	(2.74)	(2.86)	(2.78)
UK	0.1340 ***	0.1538 ***	0.1041 **	0.1295 ***
	(3.44)	(3.91)	(2.51)	(3.70)
Manufacturers	0.0619 *		0.1534 ***	
	(1.93)		(4.81)	
Huge	0.1189 ***			0.1649 ***
	(2.63)			(3.72)
Verybig	0.1277 ***			0.1247 ***
	(4.28)			(4.06)
Quitebig	0.0233 *			0.0218
	(1.71)			(1.56)
year2014	−0.0778 ***	−0.0736 ***	−0.0625 ***	−0.0728 ***
	(8.64)	(7.67)	(7.14)	(7.90)
year2015	−0.1712 ***	−0.0792 ***	−0.0558 ***	−0.1596 ***
	(6.11)	(6.84)	(7.03)	(5.51)
year2016	0.0366 ***	0.0450 ***	0.0430 ***	0.0430 ***
	(4.09)	(4.52)	(4.78)	(4.46)
cash_flow		0.1661 ***		
		(5.83)		
Biotech		−0.1298 ***		−0.0421
		(4.42)		(1.44)
Medium		−0.0349 **		
		(2.48)		
Small		−0.0648 ***		
		(3.62)		

Table 2.5. (Cont)

	Model 5	Model 6	Model 7	Model 8
Verysmall		−0.0092		
		(0.33)		
collection_period			−0.0226 ***	
			(3.97)	
employee_cost				−0.3701 ***
				(7.83)
_cons	0.2786 ***	0.3767 ***	0.2257 ***	0.4312 ***
	(7.92)	(15.55)	(6.51)	(19.16)
LR test of $\sigma^2u = 0$: X2(1)	1306.01 ***	1656.88 ***	2561.80 ***	1156.37 ***
LR test of σ2u = 0: p value	0	0	0	0
Number of observations	1547	1344	1850	1353

Notes: The table summarizes the results from a pure Random-effects estimation of Equation (5). Dependent variable is efficiency computed in Stage 1. Cons stands for the intercept. For the rest of variables, see main text. Data are organized in a panel varying across firms and time over 2010–2018. Robust standard errors clustered at the firm level. LR test of $\sigma^2_u = 0$ distributed as X2(1). * $p < 0.1$; ** $p < 0.05$; *** $p < 0.01$.

Figure 2.4 portrays the behavior of firms over time classified according to their size. The largest companies exhibit a fairly consistent performance over time. Instead, for quite big companies the fall of efficiency between the beginning and end of the period is almost 20 points.

At the beginning of the period, in 2010, the efficiency of quite large firms was well above that of the entire sample, while this is not the case anymore in 2018. This category has been affected the most by the drop of efficiency over time.

Medium-sized and small firms exhibit a reduction of 10 points over time, whereas very small firms register a rather stable performance.

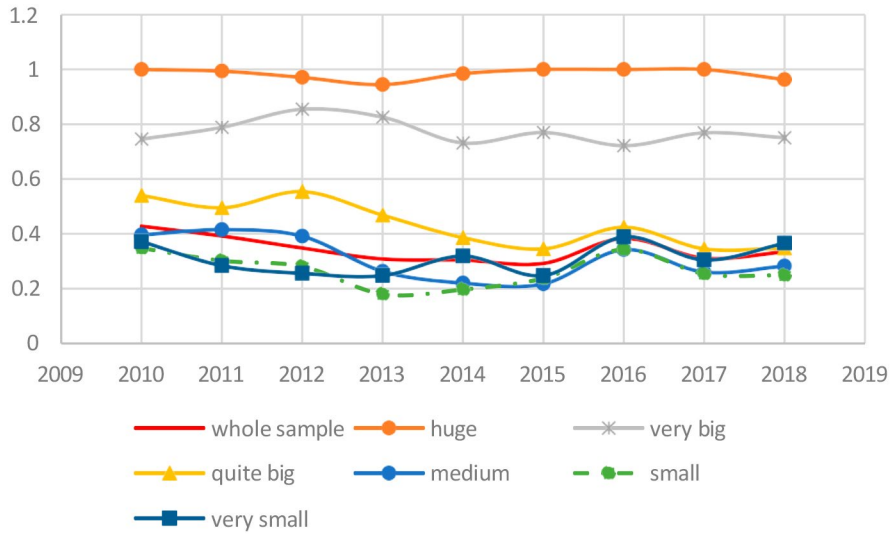

Figure 2.4. Average efficiency, pharma and biotechnological industry by size, 2010–2018.
Note: the figure summarizes the yearly trend of average efficiency of the firms in our sample, disaggregated by size of firms. Size is proxied by real turnover. Efficiency decreases over the period for all categories except for the huge and very big firms. The thresholds are detailed in the main text. Source: own elaboration.

2.5 Stage 2: Variables Correlated with Efficiency

2.5.1 Overview

In the second stage of this research we have performed a regression analysis in order to explore several aspects of the firms' economic setting and management which may be correlated with efficiency. Efficiency is proxied by the efficiency scores obtained in the first stage, as detailed in Section 4.

The basic framework is a statistical model described in very general terms by Equation (5):

$$\theta = f(x; \upsilon) \tag{5}$$

where θ is a vector containing the efficiency scores, x is a matrix of covariates and υ is the error term.

There are several statistical issues to be considered here.

First, the literature has not reached a consensus about the data generation process underlying Equation (5). Researchers have widely used the Tobit model and ordinary least squares (OLS) (see, for example, Mazumdar et al., 2009; Bravo-Ureta et al., 2006).

Since the efficiency scores are censored at a maximum of 1 by construction, the Tobit specification seems especially appropriate for this analysis. In addition, Hoff, 2007; McDonald, 2009, argue that OLS provide consistent estimates which are quite similar to those obtained with Tobit and are, therefore, a convenient procedure. Banker, & Natajaran, 2008, show, by means of Monte Carlo simulations, that OLS and Tobit outperform other procedures when employed in the second stage of DEA analyses.

Sinar, & Wilson, 2007, however, have argued that the true data generation process for the efficiency scores is not a censored but a truncated distribution; they discard the analysis of the efficiency scores performed according to Tobit or ordinary least squares because this assessment would not rely on the *true* distribution of the data. With censored data, the *true* value of the variable is not known because of the measurement scale; in this particular case, since efficiency has an upper bound of 1. With truncated data, instead, the true value of the variable is unknown because of the sample limitations. The difference in practice between a censored and a truncation distribution may be unclear. Furthermore, they claim that the efficiency scores are affected by serial correlation. Since the Tobit procedure does not correct for this problem, the estimates obtained from the Tobit model are, in their view, biased. This issue is also controversial, since Banker, & Natarajan, 2008, have argued that OLS and Tobit procedures are valid even if the X variables are correlated.

Simar, & Wilson, 2007, propose an alternative estimation technique which employs a truncated model, computes new standard errors by bootstrapping the data and corrects the biases in the estimates. There are downsides for this procedure. McDonald, 2009, argues that the Simar–Wilson estimates lack robustness. Furthermore, the Simar–Wilson technique is convoluted and intensive in computing time. Furthermore, as we shall show below, the point estimates computed by the Simar–Wilson method are bigger than those obtained by Tobit or ordinary least squares, although the difference may not be very relevant in applied research.

The debate is still open. According to McDonald, 2009, the controversy about the correct statistical model underlying the data is ultimately methodological and exceeds the scope of our research. By and large, we agree with McDonald, 2009, and think that Tobit and ordinary least squares have helped obtain valid insights about the efficiency in numerous industries or activities, and thus can be employed in applied research.

Meanwhile, since the controversy has not been settled yet, we have decided to adopt a conservative strategy, employ the three methods and compare their results.

Second, the data we are going to use to estimate Equation (5) encompass a panel and hence comprises observations from firms at different points in time.

As is well known, panel data can be assessed by fixed effects or random effects models. Greene, 2004, shows that Tobit models with fixed effects produce coefficients which are overestimated and asymptotic variances which are biased downwards. Moreover, our specification includes as regressors time-invariant characteristics of firms (such as country of origin, for example); these characteristics would be perfectly collinear with the terms capturing the idiosyncratic features of firms in a fixed effects model. In this case we cannot employ a Hausman test to compare the fixed effects and random effects models because our model cannot be specified within a fixed effects setting.

These considerations advise the utilization of random-effects models. This is the approach followed, for example, by Mazumdar et al., 2009.

Finally, at this point we are searching for correlations among efficiency and different aspects of firm idiosyncrasies and management. Looking for causality relationships exceeds the scope of this paper and is left for future research.

We shall start by discussing the main qualitative implications of this exercise, for reasons which will be apparent below.

2.5.2 Qualitative Implications

2.5.2.1 *Tobit Estimation*

Typically, a Tobit model distinguishes between the latent or unobservable dependent variable and the observable dependent variable, where the observed variable is a censored version of the unobserved. Equation (6) represents a random-effects Tobit specification for the second stage of our analysis:

$$\begin{gathered}\theta^*_{\text{it}} = x_{\text{it}}\beta + u_{\text{i}} + \varepsilon_{\text{it}} \\ \theta_{\text{it}} = 1 \; if \; \theta^*_{\text{it}} \geq 1 \\ \theta_{\text{it}} = \theta^*_{\text{it}} \quad if \; 0 \leq \theta^*_{\text{it}} \leq 1 \\ \theta_{\text{it}} = 0 \; if \; \theta^*_{\text{it}} \leq 0 \\ i = 1, 2, \ldots, n. \\ t = 2010, 2011, \ldots, 2018\end{gathered} \tag{6}$$

where θ^*_{it} is the latent or unobservable efficiency, θ_{it} is the observable efficiency, x_{it} is a matrix of covariates, β is a vector of coefficients, u_i is the time invariant component of the error term, ε_{it} is the time-varying component of the error term, i indexes firms and t time.

In the estimation of Equation (6) we have included several indicators as covariates in order to capture different dimensions of firms, such as main activity, size, margins, financial management and personnel costs. We have also included time dummies to capture the impact of the business cycle and country dummies to allow for idiosyncratic aspects related to the markets where firms operate. The data are structured in a panel over the period 2010–2018 in order to exploit both the cross section and time variations.

Table 2.4 shows a first set of results obtained from the estimation by maximum likelihood of the model described by Equation (6). In order to avoid multicollinearity among the regressors, we have not included all covariates simultaneously; instead, we have added them sequentially, conforming different specifications of the baseline Equation (6). In other words, Equation (6) describes Models 1–4, the differences among them being the variables considered in x_{it} in each case.

To correct for heteroskedasticity, estimations have been performed with the observed information matrix (OIM) corrected standard errors. In this particular case, the variance-covariance matrix of the estimators is the matrix of second derivatives of the likelihood function. This correction for heteroskedasticity is robust to the violation of normality if distribution is symmetrical.

The last lines of Table 2.4 include the results from a Lagrange multiplier Breusch–Pagan likelihood ratio test of whether the variance of the time invariant component of the error term is equal to zero. This test is can be regarded as an indirect text of the appropriateness of the random effect model. The null hypothesis of equality to 0 of the variance of the u_i component of the error term is rejected at the 99% significance level for the four models, hence supporting the utilization of the random-effects model.

Dummies for countries capture different aspects: on the one hand, cultural and institutional aspects and managerial practices (Bénabou, & Tirole, 2016). On the other, regulatory and microeconomic and macroeconomics conditions of the particular markets where the firms operate. Regulatory aspects and institutional and macroeconomic conditions in the host country have been shown to impact the performance of multinational firms (Bengoa, & Sánchez-Robles, 2005; Bengoa-Calvo et al., 2017).

Dummies for the United Kingdom (UK), Italy and Sweden are positive and highly significant in all specifications, implying that the institutional framework in these countries, the size of their markets and/or their macroeconomic and institutional conditions affect the efficiency of firms positively. The dummy for Germany is also positive and significant in two specifications (models 2 and 4), although in one of them at a smaller significance level (90% in model 4).

Instead, the dummies for Spain and France display positive and negative signs and are not significant.

UK pharmaceutical firms feature a swift decision-making process which facilitates a successful and fast adjustment to changing market conditions (Casper, & Matraves, 2003). Moreover, the level of distortions in the UK economy is low and factor markets are relatively flexible. In addition, the dynamic biotechnological landscape of the country has allowed the surge of alliances and collaborations. These facts may explain the positive sign of the UK dummy.

German firms typically work in less-flexible environments than their British counterparts; their access to bank funding, though, is comparatively easy. Since sound finance is one important determinant of firms' success, as will be detailed below, the availability of funding seems quite relevant for the performance of companies in the sector and help explain the positive sign of the dummy.

The Italian industry is populated by highly skilled, agile firms, with a large component of exports and close ties to US companies. These companies encompass an important hub for foreign investment in the industry, which in turn enhances the productivity of local firms through technology diffusion and *learning by watching*.

Swedish pharmaceutical and biotechnological firms benefit from a market with limited regulation where bureaucracy is kept at a minimum, government support and a highly skilled workforce. These aspects would explain the successful performance of the Swedish pharmaceutical industry.

The positive signs of the country dummies, therefore, are in accordance with particular features of their institutional frameworks and/or industries.

These features, however, are not present in the French and Spanish cases. The French pharmaceutical market has historically been very protected by an outdated industrial policy. Spanish companies have been damaged by a rigid labor market and a low level of interaction between universities, research centers and firms.

We have also captured the main activity of the firms by means of dummies variables. The dummy *manufacturers* is equal to 1 for those firms whose main activity corresponds to NACE codes 2110 and 2120, and 0 otherwise. Conversely, the dummy *biotech* is 1 for firms included under the 7211 NACE code and 0 otherwise.

The dummy manufacturers are positively and significantly correlated with efficiency (columns 1 and 3), while biotech displays a negative and significant correlation in one model (column 2) and is not significant in the other (column 4). Overall, these findings are in accordance with those reported in Section 2.4 above, which suggest consistently higher levels of efficiency for firms engaged in the production and commercialization of pharmaceutical articles.

Dummies for size have been assigned according to the thresholds detailed in Section 2.4 above. Again, the results for the estimations agree with the trends reported in the previous Section. Firms characterized by large sizes, as conveyed by their levels of turnover, are more efficient than their counterparts, since the dummies huge and very big are positively and significantly correlated with efficiency (Models 1 and 4). The dummy that is quite big is positive but not significant.

The positive correlation between size and efficiency, however, holds only for the first two categories we defined, i.e., for sales larger than 426.92 million euros or the 95 percentile in the distribution. For companies with real turnover between 38.86 and 426.92 million euros results are inconclusive.

Those companies whose level of sales is less or equal than 38.86 million and more than 2.10 million euros register smaller efficiency figures *ceteris paribus*, since the dummies medium and small are negative and significant (column 2). Finally, we do not find a significant correlation between the dummy capturing the *very small* level of sales and efficiency (column 2). This is not surprising since firms with sales lower than the 25% percentile register poor levels of efficiency in some years but are capable of surpassing the figure attained by medium and small others.

The results for the dummy variables reflecting size and activity are thus consistent with those reported in the previous section. They are also in accord with Mazumdar et al., 2009, who disclose a negative correlation between size and efficiency for a sample of Indian pharmaceutical firms.

Let us turn to the discussion of the variables capturing other aspects of firms in the industry.

As portrayed by column 1 of Table 2.4, the profit margin is positively and significantly correlated, at the 99% significance level, with efficiency. This means that more efficient firms operate with higher margins. This result makes sense because the industry we are scrutinizing provides goods and services characterized by high added value which can be reflected in large margins. In fact, Scherer, & Kleinke, 2001, argues that deviations from trend in profit margins are highly correlated with expenditure in R&D for pharmaceutical companies, thus confirming the links between efficiency, margins and R&D.

Interestingly, this finding suggests that successful firm strategies in this sector are featured by both high margins and high intensity of resource utilizations, at the same time. It is common to see that companies tend to choose to focus either on the achievement of high profits per unit or in the optimization of the installed capacity. This dichotomy, however, is not present in the companies in the pharmaceutical industry, according to our results.

The literature has documented that cash flow influences R&D expenditure in the case of the industry we are considering (Lakdawalla, 2018). Mondrego, & Barge-Gil, 2019, provide some additional evidence since they find that, for the Spanish firms, the proportion of expenditure in R&D financed with internal resources is 75% for pharmaceuticals and 40% for the rest of the industries. Again, we are confronted with another differential feature of this industry. Whereas it is commonly accepted that firms should heavily rely on external funding and increase their profitability through financial leverage, the empirical evidence for this industry suggests that successful companies enjoy comparatively low ratios of indebtedness. This prudent financial structure is consistent with the high risk and long maturing period associated with the R&D activity.

To test this idea in our sample, we have included in the analysis some variables which capture particular elements of financial management. Column 2 shows that cashflow (as a percentage of sales) is indeed positively and significantly correlated with efficiency. The level of significance is very high, 99%.

Column 3, in turn, displays the estimation results when the variable collection period is included as a regressor in the baseline specification. The point estimate is negative and significant at the 99% level. Higher collection periods increase the amount of working capital necessary to run the daily activity of the firm, while shorter spans imply a sounder financial management. Our findings, therefore, are consistent with the literature, and stress the importance of exhibiting solid, well-financed balance sheets in order to register high levels of productivity. In more detail, Mazumdar et al., 2009, argue that the low efficiency scores achieved by some firms in their sample is associated to their inability to access financial resources.

Column 4 includes a variable capturing the cost of labor, average cost per employee, as a percentage of sales. It is highly significant and negatively correlated with efficiency.

In terms of the validations of Models 1–4, and as stated above, the literature has shown that the Tobit model provides consistent estimates (Hoff, 2007; McDonald, 2009; Banker, & Natarajan, 2008; Greene, 2003).

Moreover, it has been argued that the severity of the problem implied by the presence of heteroskedasticity in Tobit models is a function of the degree of censoring. In our case, censoring is limited, and affects only to 6–7% of the data.

Since the estimations have been performed with OIM corrected standard errors, they are robust to the presence of heteroskedasticity. These standard errors are also robust to the violation of normality if the distribution is symmetric.

Finally, and as detailed below, results from Tobit are quite similar to those obtained by random-effects models. All these considerations lend countenance to the models described in this subsection.

2.5.2.2 *Classical Estimation*

In order to assess the robustness of these findings we have performed two complementary analyses. First, we have considered a pure random-effects model, as described by Equation (7).

$$\theta_{it} = x_{it}\beta + u_i + \varepsilon_{it} \quad (7)$$

where θ_{it} is efficiency, x_{it} is a matrix of covariates, β is a vector of coefficients, u_i is the time invariant component of the error term, ε_{it} is the time-varying component of the error term, i indexes firms and t time.

The estimation has been carried out with robust standard errors, in the spirit of Eicker, 1965; Huber, 1965; White, 1980, clustered at the firm level. This procedure is widely recommended in the literature in these types of estimations (Stock, & Watson, 2006). Table 2.5 summarizes the specification and results for Models 5–8, estimated according to (7).

We see that the main conclusions obtained from the Tobit specification regarding the correlation of efficiency with selected variables carry over to the classical, pure random effects specification. The only remarkable differences are related to the dummy for Spain, which is now negative and significant at the 95% level (Model 6), and the dummy quite big, now significant at the 90% level.

Furthermore, the point estimates of the coefficients are very similar in the censored and the non-censored model. These results are reassuring and consistent with Hoff, 2007; McDonald, 2009, who document this kind of similarity when Tobit and ordinary least squares are employed in the second stage analysis.

The last two lines of Table 2.5 display the results from the Lagrange multiplier Breusch–Pagan test for the presence of random effects. The null hypothesis of no random effects is rejected at conventional levels.

In terms of the validation of Models 5–8, we can invoke the result according to which OLS produces unbiased and consistent estimates because of the central limit theorem for large enough samples. In addition, the literature has also shown the consistency of OLS second-stage estimators for the particular case of DEA analyses. Moreover, cluster robust standard errors yield estimates that are robust to the presence of heteroskedasticity and correlation in the error term.

2.5.2.3 *Simar–Wilson Estimation*

We have employed the Simar, & Wilson, 2007, methodology as a further robustness test. Accordingly, we have replicated the estimations described above, this time employing their technique. These are Models 9–12, whose detailed specifications and results are displayed in Table 2.6.

Once again, we see that the basic findings obtained by the Tobit and classical random effects estimations regarding the sign and significance of covariates carry over when the Simar, & Wilson, 2007, procedure, based upon a truncated distribution for the data and bootstrapping, is employed.

As reported above, this tool aims to remove the alleged bias in the estimation due to correlation among residuals. It computes new standard errors and corrected parameters. In contrast to the Tobit and classical frameworks, the literature has not provided enough evidence yet to illustrate the properties of this estimator.

Table 2.6. Variables correlated with efficiency, Simar–Wilson estimations. Dependent variable is efficiency.

	Model 9	Model 10	Model 11	Model 12
profit_margin	0.3089 ***			
	(9.31)			
Germany	0.1287 ***	0.1562 ***	0.1405 ***	0.1204 ***
	(4.43)	(4.93)	(3.64)	(4.09)
Spain	−0.0356	−0.0971 ***	−0.0098	0.0053
	(1.36)	(3.25)	(0.24)	(0.20)
France	0.0342	0.0684 *	−0.1606 ***	−0.0364
	(0.92)	(1.72)	(3.06)	(0.97)
Sweden	0.2958 ***	0.2602 ***	0.3352 ***	0.3539 ***
	(8.04)	(6.04)	(7.06)	(8.41)
Italy	0.1548 ***	0.1539 ***	0.2307 ***	0.1506 ***
	(6.13)	(5.67)	(6.41)	(5.99)

Table 2.5. (Cont)	Model 9	Model 10	Model 11	Model 12
UK	0.1439 ***	0.1596 ***	0.1370 ***	0.1396 ***
	(6.89)	(7.33)	(4.97)	(6.81)
Manufacturers	0.0859 ***		0.3157 ***	
	(4.54)		(10.51)	
Huge	0.7812 **			0.8741 **
	(2.06)			(2.45)
Verybig	0.4284 ***			0.3849 ***
	(9.48)			(8.47)
Quitebig	0.0552 ***			0.0678 ***
	(2.98)			(3.63)
year2014	−0.0994 ***	−0.1072 ***	−0.0982 ***	−0.0977 ***
	(4.20)	(4.16)	(2.80)	(3.77)
year2015	−0.4586 ***	−0.1540 ***	−0.1161 ***	−0.4179 ***
	(9.43)	(5.15)	(3.40)	(8.48)
year2016	0.0652 ***	0.0651 ***	0.0902 ***	0.0785 ***
	(3.04)	(2.76)	(3.07)	(3.66)
cash_flow		0.3351 ***		
		(8.31)		
Biotech		−0.1790 ***		−0.0229
		(8.07)		(1.15)
Medium		−0.1294 ***		
		(6.36)		
Small		−0.1091 ***		
		(4.63)		
Verysmall		0.0192		
		(0.60)		
collection_period			−0.0568 ***	
			(4.11)	
employee_cost				−0.6340 ***
				(10.95)
_cons	0.1328 ***	0.3237 ***	−0.0524	0.3822 ***
	(6.01)	(15.50)	(1.24)	(20.23)
Number of observations	1446	1257	1741	1264

Notes: The table summarizes the results from the Simar–Wilson estimation of Equation (5). Dependent variable in the estimations is efficiency. Data are set in a panel varying across firms and time. * $p < 0.1$; ** $p < 0.05$; *** $p < 0.01$.

2.5.3 **Quantitative Implications**

From the comparisons of Tables 2.4 – 2.6 we observe that Tobit and pure random-effects models yield point estimates which are rather similar. Instead, estimates obtained by the Simar–Wilson methodology are larger.

In contrast to what happens in the classical regression model, the marginal effect or impact of the individual regressor x_j on the dependent variable, defined as:

$$\frac{\partial \theta}{\partial x_j}$$

is not directly measured by the point estimates of regressions estimated by Tobit or Simar–Wilson methodologies, since they are non-linear models.

In order to extract more quantitative implications of the different estimations described in Section 2.5.2 above, we have computed the marginal effects of selected variables on efficiency implied by these two methods.

Basic results are displayed in Table 2.7. In order to facilitate comparisons, we have added the point estimates obtained by the pure random-effects estimation.

The variable exerting the highest impact on efficiency is employee cost. According to our results, an increase of one unit in the employee cost reduces efficiency in an amount which is comprised in the interval (0.368, 0.42).

If the profit margin rises in one unit, the correspondent increase in efficiency is around 0.15–0.2. The improvement of the financial position (as captured by cash flow/income) in one unit brings about a positive change in efficiency of 0.162–0.218. Finally, the increase of the collection period in one unit reduces efficiency around 0.02.

In our view, these findings have some interesting economic implications and may be useful for managers, owners and other stakeholders of firms in the industry. The efforts to contain personnel costs and increase margins translate directly into higher levels of productivity. Firms in the industry should also strive to achieve an adequate combination of external and internal finance, aligned with the risky and slow-paced nature of R&D activities.

There are implications for policymakers and policy analysts as well. Efficiency in the pharmaceutical sector, according to the empirical evidence presented here, hinges on the sound functioning of labor markets and financial markets. Measures to improve their behavior may have a noticeable impact on the performance of the firms in the industry.

It is apparent from Table 2.7 that the marginal effects obtained by the Tobit and the classical specifications are remarkably close, whereas those yielded by the Simar–Wilson procedure are slightly larger. It is important to notice that the difference among the Tobit/pure random effects results, on the one hand, and the Simar–Wilson, on the other, is smaller regarding the marginal effects (Table 2.7) that if we compare the point estimates (Tables 2.4–2.6).

This fact has several interesting implications:

- As far the particular goal of this subsection is concerned, the Simar–Wilson tool implies marginal effects slightly larger (about 15–35%) but of the same order of magnitude than those obtained from Tobit/pure random-effects model.
- In general terms, more research at the theoretical level and probably Monte Carlo simulations are necessary to know in more detail the properties of the Simar–Wilson estimator. This exceeds the scope of this paper.
- The Simar–Wilson procedure may be useful for applied research, especially in conjunction with other methodologies, although it has a higher cost in computing time if compared with Tobit or classical models.

Table 2.7. Comparison of marginal effects, Tobit, Simar–Wilson and random effects estimations.

Variable	Tobit	Simar–Wilson	Random Effects
Profit margin	0.1511	0.2053	0.1531
Cash flow/income	0.1628	0.2189	0.1661
Collection period	−0.0223	−0.026	−0.0226
Employee cost	−0.3683	−0.4215	−0.3701

Notes: The table details the marginal effects on efficiency levels of each one of the variables displayed in the first column. These marginal effects have been recovered from the Tobit (Models 1–4) and the Simar–Wilson (Models 9–12) estimations. The last column displays the marginal effects obtained in the pure random-effects models (Models 5–8) to facilitate the comparison; since this framework is linear, the marginal effects coincide with the point estimates of the variables as reported in Table 5.

2.6 Concluding Remarks

The pharmaceutical industry has experienced deep changes in the last few decades. The cost of R&D has soared while market conditions have become tougher. Companies have confronted these challenges by different strategies such as mergers, acquisitions, outsourcing and alliances. It remains an open question whether these transformations have brought about an increase in the efficiency of the firms that make up the industry.

We examine this issue employing disaggregated microdata from a large sample of European medium and large firms belonging to the pharmaceutical and biotechnological industry. In the first stage of our research, we perform a non-parametric DEA analysis of efficiency over the period 2010–2018. In the second stage we analyze which potential features of the environmental framework and management are correlated with efficiency by regression techniques.

The consideration of a large sample of European firms, disaggregating by main activity and isolating the performance of biotechnological firms is a novel feature of this paper. The comparison of the results provided by the Tobit, classical and Simar–Wilson frameworks for the second stage is also a contribution of the investigation presented here.

The main insights from our analysis are the following:

- The average level of efficiency in the industry is moderate, 0.341. This figure is not far from results obtained by other studies for alternative samples. Efficiency exhibits a decreasing trend over the years 2010–2018.
- Efficiency levels display a large level of heterogeneity when particular dimensions of companies are considered. Efficiency is higher for those companies whose main activity is manufacturing of pharmaceutical products than for firms focused on R&D activities. This result may be traced to the relative youth of R&D firms, which cannot fully exploit the learning curve yet. The specialization of this kind of firms in a few projects, characterized by low rates of success, may also be a relevant factor in this respect.
- We find a complex relationship between size and efficiency. By and large, bigger firms are more efficient, but only beyond the threshold of 426.92 million euros of turnover per year. Medium-size and small firms register the poorest levels of efficiency, whereas very small firms perform slightly better. This suggests that firms may benefit from either scale economies or high levels of specialization, while the middle ground does not yield good results.
- Our findings suggest that sound financial structures, lower employee costs and higher margins are correlated with higher levels of efficiency. Moreover, the idiosyncratic aspects of the country of origin of the firms may foster or jeopardize productivity.

Our results convey some messages for policymakers. The survival and buoyancy of companies in the pharmaceutical industry seems closely linked to the sound functioning of the labor and capital markets. The experience of selected countries, in particular the UK, suggests as well that the existence of agile, dynamic biotechnological firms is beneficial for the whole sector.

Finally, the higher levels of efficiency obtained for larger firms suggest that mergers and acquisitions may enhance the performance of pharmaceutical companies due to the influence of scale economies. These financial transactions should not be discouraged or jeopardized by policymakers on the basis of an allegedly anti-competitive strategy. It is important to keep in mind that the pharmaceutical and biotechnological industry relies heavily on R&D, and that R&D is only feasible for firms if their size is big enough.

We have also found that very small firms display a sounder behavior than medium size companies. The link between size and performance for the sector is thus nuanced. This suggests that industrial policies intending to enhance the sector should be horizontal rather than vertical: instead of featuring active interventions in favor of a particular firm size, it is better to adopt a less activist stance since it is hard to determine on an a priori basis which is the efficient scale of operations.

Our investigation has several limits. The time horizon is relatively short; it would be convenient to increase it whenever new data are available. We have computed efficiency scores in Stage 1 only by a non-parametric technique, DEA; another computation by means of parametric SFA would be useful to check whether efficiency scores are very sensible to the tool employed.

In stage 2 we have investigated the correlations among efficiency scores and other variables, but we have not explored the direction of causality among them. This last issue could be addressed by introducing lags and leads of the variables and/or employing other econometric techniques, such as general methods of moment or instrumental variables.

One of the techniques we have employed in Stage 2 is the Simar–Wilson estimation. It seems to be useful in applied work, especially in combination with other techniques. More evidence about its performance would be convenient, nonetheless.

Finally, and although country dummies have provided useful information about the potential impact of institutional and economic aspects on efficiency, they are ultimately dummies or *the measure of our ignorance*; it would be interesting to go one step further and characterize the specific features of the various countries which enhance or jeopardize efficiency. This could be done by introducing macroeconomic and institutional variables in the Stage 2 models.

These limitations suggest promising directions for new research.

Appendix A

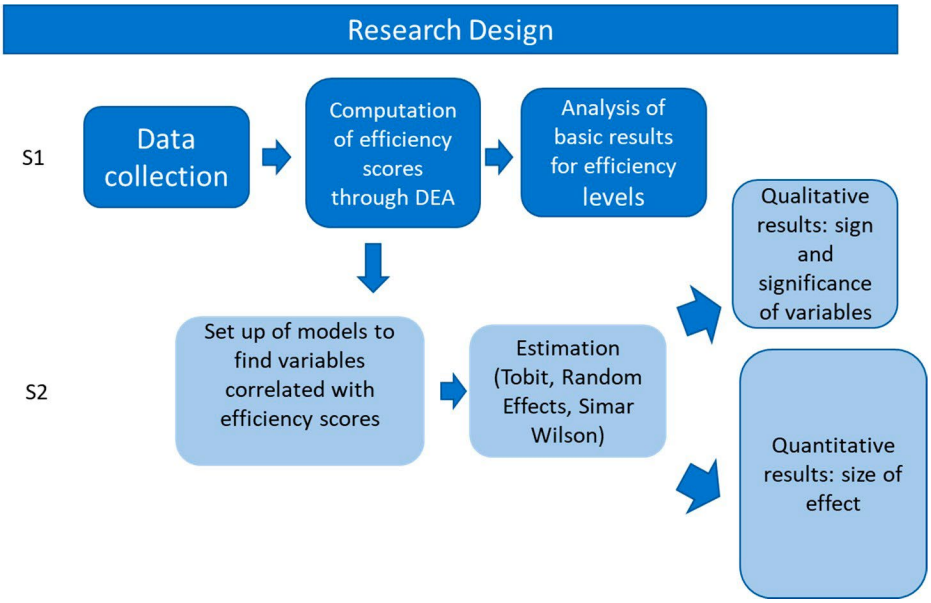

Figure A1. Explanatory diagram of our research design (S1 and S2 are Stage 1 and Stage 2).

Appendix B

Table B1. Variables definition and sources.

Variable	Description	Source
OPRE—Operating Revenue (Turnover)	Total Operating Revenues (Net Sales + Other Operating Revenues + Stock Variations)	Amadeus
TOAS—Total Assets	Total Assets (Fixed Assets + Current Assets)	Amadeus Amadeus
PRMA—Profit Margin (%)	(Profit Before Tax/Operating Revenue)	
EMPL—Number of Employees	Total Number of Employees included in the Company's payroll	Amadeus
CFOP—Cash Flow/Operating Revenue (%)	(Cash Flow/Operating Revenue) * 100	Amadeus
SCT—Cost of Employees/ Operating Revenue (%)	(Cost of Employees/Operating Revenue) * 100	Amadeus
COLL—Collection Period (days)	(Debtors/Operating Revenue) * 360	Amadeus
Yearly deflator	Computed from the Harmonized European Index	Eurostat

References

Ahn, H.; Afsharian, M.; Emrouznejad, A.; Banker, R.D. Recent developments on the use of DEA in the public sector. *Socio-Econ. Plan. Sci.* **2018**, *61*, 1–3.

Aigner, D.; Lovell, C.; Schmidt, P. Formulation and estimation of stochastic frontier production function models. *J. Econ.* **1977**, *6*, 21–37.

Al-Refaie, A.; Wu, C.-W.; Sawalheh, M. DEA window analysis for assessing efficiency of blistering process in a pharmaceutical industry. *Neural Comput. Appl.* **2018**, *31*, 3703–3717.

Alarenan, S.; Gasim, A.A.; Hunt, L.C.; Muhsen, A.R. Measuring underlying energy efficiency in the GCC countries using a newly constructed dataset. *Energy Transit.* **2019**, *3*, 31–44.

Arrow, K.J. The Economic Implications of Learning by Doing. *Rev. Econ. Stud.* **1962**, *29*, 155.

Banker, R.D.; Charnes, A.; Cooper, W.W. Some Models for Estimating Technical and Scale Inefficiencies in Data Envelopment Analysis. *Manag. Sci.* **1984**, *30*, 1078–1092.

Banker, R.D.; Natarajan, R. Evaluating Contextual Variables Affecting Productivity Using Data Envelopment Analysis. *Oper. Res.* **2008**, *56*, 48–58.

Bénabou, R.; Tirole, J. Mindful Economics: The Production, Consumption, and Value of Beliefs. *J. Econ. Perspect.* **2016**, *30*, 141–164.

Bengoa-Calvo, M.; Sanchez-Robles, B.; Shachmurove, Y. Back to BITs and Bites: Do Trade and Investment Agreements Promote Foreign Direct Investment within Latin America? *SSRN Electron. J.* **2017**, 3083980.

Bengoa, M.; Sanchez-Robles, B. Policy shocks as a source of endogenous growth. *J. Policy Model.* **2005**, *27*, 249–261.

Bloom, N.; Lemos, R.; Sadun, R.; Scur, D.; Van Reenen, J. International Data on Measuring Management Practices. *Am. Econ. Rev.* **2016**, *106*, 152–156.

Bravo-Ureta, B.E.; Solís, D.; López, V.H.M.; Maripani, J.F.; Thiam, A.; Rivas, T. Technical efficiency in farming: A meta-regression analysis. *J. Prod. Anal.* **2006**, *27*, 57–72.

Casper, S.; Matraves, C. Institutional frameworks and innovation in the German and UK pharmaceutical industry. *Res. Policy* **2003**, *32*, 1865–1879.

Charnes, A.; Cooper, W.; Rhodes, E. Measuring the efficiency of decision making units. *Eur. J. Oper. Res.* **1978**, *2*, 429–444.

Chen, C.F.; Soo, K.T. Some university students are more equal than others: Efficiency evidence from England. *Econ. Bull.* **2010**, *30*, 2697–2708.

Cherchye, L.; De Rock, B.; Walheer, B. Multi-output efficiency with good and bad outputs. *Eur. J. Oper. Res.* **2015**, *240*, 872–881.

Cockburn, I.; Henderson, R.M. Scale and scope in drug development: Unpacking the advantages of size in pharmaceutical research. *J. Health Econ.* **2001**, *20*, 1033–1057.

Danzon, P.M.; Nicholson, S.; Pereira, N.S. Productivity in pharmaceutical-biotechnology R&D: The role of experience and alliances. *J. Health Econ.* **2005**, *24*, 317–339.

Eicker, F. Limit theorems for regressions with unequal and dependent errors. In Proceedings of the Fifth Berkeley Symposium on Mathematical Statistics and Probability, Davis, CA, USA, 21 June–18 July **1965**.

Emrouznejad, A.; Yang, G.-L. A survey and analysis of the first 40 years of scholarly literature in DEA: 1978–2016. *Socio-Econ. Plan. Sci.* **2018**, *61*, 4–8.

Emrouznejad, A.; Thanassoulis, E. A mathematical model for dynamic efficiency using data envelopment analysis. *Appl. Math. Comput.* **2005**, *160*, 363–378.

Eurostat. Available online: https://appsso.eurostat.ec.europa.eu/nui/show.do?dataset=prc_hicp_aind&lang=en (accessed on 5 May 2020).

Fall, F.; Akim, A.-M.; Wassongma, H. DEA and SFA research on the efficiency of microfinance institutions: A meta-analysis. *World Dev.* **2018**, *107*, 176–188.

Gascón, F.; Lozano, J.; Ponte, B.; De La Fuente, D. Measuring the efficiency of large pharmaceutical companies: An industry analysis. *Eur. J. Health Econ.* **2016**, *18*, 587–608.

Greene, W. The behaviour of the maximum likelihood estimator of limited dependent variable models in the presence of fixed effects. *Econ. J.* **2004**, *7*, 98–119.

Greene, W.H. *Econometric Analysis Fifth Edition*; Prentice Hall: New York, NY, USA, **2003**.

Hashimoto, A.; Haneda, S. Measuring the change in R&D efficiency of the Japanese pharmaceutical industry. *Res. Policy* **2008**, *37*, 1829–1836.

Hay, M.; Thomas, D.W.; Craighead, J.L.; Economides, C.; Rosenthal, J. Clinical development success rates for investigational drugs. *Nat. Biotechnol.* **2014**, *32*, 40–51.

Henderson, R.; Cockburn, I. Scale, Scope and Spillovers: The Determinants of Research Productivity in the Pharmaceutical Industry. *RAND J. Econ.* **1993**, *27*, 32–59.

Hoff, A. Second stage DEA: Comparison of approaches for modelling the DEA score. *Eur. J. Oper. Res.* **2007**, *181*, 425–435.

Hu, X.-Y.; Li, J.; Li, X.; Cui, J. A Revised Inverse Data Envelopment Analysis Model Based on Radial Models. *Mathematics* **2020**, *8*, 803.

Huber, P.J. The behavior of maximum likelihood estimates under nonstandard conditions. In Proceedings of the Fifth Berkeley Symposium on Mathematical Statistics and Probability, Davis, CA, USA, 21 June–18 July **1965**; pp. 221–233.

Jiang, H.; He, Y. Applying Data Envelopment Analysis in Measuring the Efficiency of Chinese Listed Banks in the Context of Macroprudential Framework. *Mathematics* **2018**, *6*, 184.

Khezrimotlagh, D.; Zhu, J.; Cook, W.D.; Toloo, M. Data envelopment analysis and big data. *Eur. J. Oper. Res.* **2019**, *274*, 1047–1054.

Kumbhakar, S.C.; Lien, G.; Hardaker, J.B. Technical efficiency in competing panel data models: A study of Norwegian grain farming. *J. Prod. Anal.* **2012**, *41*, 321–337.

Kumbhakar, S.C.; Parmeter, C.F.; Zelenyuk, V. Stochastic frontier analysis: Foundations and advances I. *Handbook of Production Economics*; Springer: New York, NY, USA, **2017**.

Kuosmanen, T.; Saastamoinen, A.; Sipiläinen, T. What is the best practice for benchmark regulation of electricity distribution? Comparison of DEA, SFA and StoNED methods. *Energy Policy* **2013**, *61*, 740–750.

Lakdawalla, D.N. Economics of the Pharmaceutical Industry. *J. Econ. Lit.* **2018**, *56*, 397–449.

Lin, B.-H.; Lee, H.-S.; Chung, C.-C. The Construction and Implication of Group Scale Efficiency Evaluation Model for Bulk Shipping Corporations. *Mathematics* **2020**, *8*, 702.

Lozano, S.; Gutiérrez, E. A slacks-based network DEA efficiency analysis of European airlines. *Transp. Plan. Technol.* **2014**, *37*, 623–637.

Lucas, R.E. On the mechanics of economic growth. *J. Monet. Econ.* **1988**, *22*, 3–42.

Mao, Y.; Li, J.; Liu, Y. Evaluating business performance of China's pharmaceutical companies based on data envelopment analysis. *Stud. Ethno-Med.* **2014**, *8*, 51–60.

Marchetti, D.; Wanke, P.F. Efficiency in rail transport: Evaluation of the main drivers through meta-analysis with resampling. *Transp. Res. Part A Policy Pract.* **2019**, *120*, 83–100.

Mazumdar, M.; Rajeev, M.; Ray, S.C. *Output and Input Efficiency of Manufacturing Firms in India: A Case of the Indian Pharmaceutical Sector*; Institute for Social and Economic Change: Bangalore, India, **2009**.

McDonald, J. Using least squares and tobit in second stage DEA efficiency analyses. *Eur. J. Oper. Res.* **2009**, *197*, 792–798.

Meeusen, W.; Broeck, J.V.D. Efficiency Estimation from Cobb-Douglas Production Functions with Composed Error. *Int. Econ. Rev.* **1977**, *18*, 435.

Mondrego, A.; Barge-Gil, A. La I+D en el sector farmacéutico español en el periodo 2003–2015. *Pap. Econ. Esp.* **2019**, *160*, 76–93.

Odeck, J.; Bråthen, S. A meta-analysis of DEA and SFA studies of the technical efficiency of seaports: A comparison of fixed and random-effects regression models. *Transp. Res. Part A Policy Pract.* **2012**, *46*, 1574–1585.

Orea, L.; Llorca, M.; Filippini, M. A new approach to measuring the rebound effect associated to energy efficiency improvements: An application to the US residential energy demand. *Energy Econ.* **2015**, *49*, 599–609.

Pammolli, F.; Magazzini, L.; Riccaboni, M. The productivity crisis in pharmaceutical R&D. *Nat. Rev. Drug Discov.* **2011**, *10*, 428–438.

Rafols, I.; Hoekman, J.; Siepel, J.; Nightingale, P.; Hopkins, M.M.; O'Hare, A.; Perianes-Rodriguez, A. Big Pharma, Little Science? A Bibliometric Perspective on Big Pharma's R&D Decline. *SSRN Electron. J.* **2012**, *81*, 22–38.

Romer, P.M. Endogenous Technological Change. *J. Political Econ.* **1990**, *98*, S71–S102.

Romer, P.M. Increasing Returns and Long-Run Growth. *J. Political Econ.* **1986**, *94*, 1002–1037.

Scherer, F.; Kleinke, J. The Link Between Gross Profitability and Pharmaceutical R&D Spending. *Health Aff.* **2001**, *20*, 216–220.

Shimura, H.; Masuda, S.; Kimura, H. A lesson from Japan: Research and development efficiency is a key element of pharmaceutical industry consolidation process. *Drug Discov. Ther.* **2014**, *8*, 57–63.

Shin, K.; Lee, D.; Shin, K.; Kim, E. Measuring the Efficiency of U.S. Pharmaceutical Companies Based on Open Innovation Types. *J. Open Innov. Technol. Mark. Complex.* **2018**, *4*, 34.

Simar, L.; Wilson, P.W. Estimation and inference in two-stage, semi-parametric models of production processes. *J. Econ.* **2007**, *136*, 31–64.

Stock, J.; Watson, M. Heteroskedasticity-Robust Standard Errors for Fixed Effects Panel Data Regression. *NBER Tech. Work. Pap.* **2006**, *323*.

Sueyoshi, T.; Goto, M. DEA radial measurement for environmental assessment: A comparative study between Japanese chemical and pharmaceutical firms. *Appl. Energy* **2014**, *115*, 502–513.

Sueyoshi, T.; Yuan, Y.; Goto, M. A literature study for DEA applied to energy and environment. *Energy Econ.* **2017**, *62*, 104–124.

Van Dijk, B. *Amadeus Database*; Bureau van Dijk Electronic Publishing: Brussels, Belgium, **2020**.

Wang, C.-N.; Nguyen, M.N.; Le, A.L.; Tibo, H. A DEA Resampling Past-Present-Future Comparative Analysis of the Food and Beverage Industry: The Case Study on Thailand vs. Vietnam. *Mathematics* **2020**, *8*, 1140.

Wei, G.-W.; Wang, J. A comparative study of robust efficiency analysis and Data Envelopment Analysis with imprecise data. *Expert Syst. Appl.* **2017**, *81*, 28–38.

White, H. A Heteroskedasticity-Consistent Covariance Matrix Estimator and a Direct Test for Heteroskedasticity. *Econometrica* **1980**, *48*, 817.

You, T.; Chen, X.; Holder, M.E. Efficiency and its determinants in pharmaceutical industries: Ownership, R&D and scale economy. *Appl. Econ.* **2010**, *42*, 2217–2241.

Zhou, Z.; Jin, Q.; Peng, J.; Xiao, H.; Wu, S. Further Study of the DEA-Based Framework for Performance Evaluation of Competing Crude Oil Prices' Volatility Forecasting Models. *Mathematics* **2019**, *7*, 827.

CHAPTER 3.

Efficiency in the CRO Industry, 2012-2020. A DEA Non-Parametric Analysis

CHAPTER 3.

Efficiency in the CRO Industry, 2012-2020.

A DEA Non-Parametric Analysis

Abstract

Outsourcing to Contract Research Organizations (CROs) has become a widespread practice by pharmaceutical and biotechnological firms seeking to reduce risks and costs associated to the development of new products. This paper analyzes empirically the efficiency of the CROs industry by looking at a sample of firms operating worldwide over the years 2012-2020.

We compute efficiency scores of the firms in the sample by means of DEA non- parametric techniques. We consider different specifications regarding inputs and outputs and obtain baseline and bootstrap estimators for efficiency. Average bootstrap efficiency in the sample is 0.665 and rather robust across specifications. Mean efficiency increases over the period 2012-2020.

The best performers in the sample are PPD Australia, Centre Recherches Biologiques and Oy Medfiles. Our results suggest that very big and very small companies outperform the rest in terms of efficiency, pointing to the coexistence of increasing returns to scale and niche competitive advantages in the industry.

3.1 Introduction

The pharmaceutical and biotechnological industry exhibits one of the highest figures of R&D intensity, after only semiconductors and communications (Lakdawalla, 2018). Wouters et al. (2020) estimate that the median research and development investment required to introduce a new drug into the market is 985.3 million dollars, while the mean amounts to 1,335.9 million dollars.

The cost of developing a new drug is substantial and has increased remarkably in the last decades. An important element of the drug value chain, clinical trials, is getting increasingly complex, long and expensive, and requires larger samples of patients (Masri, Ramirez, Popescu and Reggie, 2012; Scanell, Blanckley, Boldon and Warrington, 2012). At the same time, competition and fiscal authorities exert downward pressures on drug prices. These trends coexist with the internationalization and consolidation of the market and changes in the regulatory stance. In this scenario, it has become necessary for the pharmaceutical sector to adopt new strategies to compete successfully and survive.

One of these strategies is the outsourcing of clinical trials and other key stages of the value chain to innovation service providers, such as Contract Research Organizations (CROs). CROs offer research-based services to the pharmaceutical and biotechnological industries within the framework of a contractual relationship.

Outsourcing distributes part of the risk associated to the development of a new product between the drug developer and the innovation service provider. Outsourcing increases flexibility for drug developers and makes it possible to complete drug research projects faster and cheaper than if they were carried out internally (Masri et al., 2012). Furthermore, an appropriate R&D outsourcing strategy allows firms to specialize in core knowledge-intensive tasks (Hassanzadeh, Modarres, Nemati and Amoako-Gyampah 2014; García-Vega and Huergo, 2019), promoting an efficient allocation of resources.

Ultimately, CROs are companies providing services partly oriented to reduce costs for the pharmaceutical, medical devices and biotechnological industries (Huang, 2019). CROs manage complex networks encompassed by drug manufacturers, health authorities, ethics committees, investigational sites, doctors, patients and patient associations. Hence their competitive advantage is closely connected to their capacity to coordinate, manage and act efficiently as a hub while they integrate all product development stages into a single solution for drug manufacturers.

The issue of efficiency is hence at the core of the business model of CROs and other specialized research service firms. Despite its importance, however, we lack empirical evidence on this topic. In order to shed light on this matter, this paper computes efficiency scores by means of the DEA non-parametric bootstrap technique (Simar and Wilson, 1998, 2000, 2007) for a sample of CROs over the period 2012-2020. Moreover, it examines the profile of efficiency over time and within the sample and identifies the firms performing at the efficient frontier.

Main results show that average efficiency of CROs over 2012-2020 is 0.665 and exhibits an increasing trend over time. This figure is remarkably robust to different models and specifications. Our findings suggest as well that efficiency is larger in very big firms (in terms of turnover), pointing to the existence of increasing returns to scale, and in very small companies, suggesting niche advantages.

Literature on CROs is not abundant. Papers on this industry often approach the topic from the point of view of the advantages CROs provide for bio-pharmaceutical firms. In any event, we can relate this paper to several strands of literature. First, it is connected to contributions dealing with the economic performance of the CRO industry, such as Pichaud (2002) and Mirowsky and Van Horn (2005); Hassanzadeh et al. (2014) employ robust optimization to propose a model for selection and scheduling of drug development projects. It is also linked to articles exploring outsourcing for bio- pharmaceutical firms, as Vogel and Getz (1997); Getz and Vogel (2009); Bianchi, Cavaliere, Chiaroni, Frattini and Chiesa (2011); Lowman, Trott, Hoecht, and Sellam (2012); Gummerus, Airaksinen, Bengtström and Juppo (2016), among others. Finally, it has to do as well with non-parametric analyses of efficiency in the pharmaceutical and biotechnological industries (Mao, Li and Liu, 2014; Sueyoshi and Goto, 2014; Gascón et al, 2017; Shin, Lee, Shim and Kim, 2018; Puente, Alonso, Gascón, Ponte and de la Fuente, 2019**;** Diaz and Sanchez-Robles, 2020; Rahman, Rodríguez-Serrano and Lambkin, 2020).

To the best of our knowledge, studies about efficiency in the CRO industry are not available yet. Hence one of the contributions of the paper is to provide a first approximation to its level and evolution over 2012-2020. Moreover, this research offers insights on the industry which are enriched by the close interaction of academics and practitioners. Third, it adds up to the (still scarce) literature on the CRO sector.

The results discussed here may be of interest for CRO managers, customers, investors, analysts and other stakeholders. They can also benefit health care authorities and academics, not only since they increase our understanding of the CRO and bio- pharmaceutical industries but also because their outsourcing model might be successfully exported to other R&D intensive sectors (Mirowsky and Van Horn, 2005) suggest.

The structure of the paper is as follows: Section 3.2 provides an overview of the CRO industry. Section 3.3 discusses the data and methodology employed. Section 3.4 summarizes the main result of the empirical analysis. Section 3.5 offers some concluding remarks.

3.2 An Overview of the CRO Industry

Some ideas about the CRO industry may be useful to understand the context of our analysis. CROs emerged in the late 1970s as service companies which offered support to the pharmaceutical industry in the development of new drugs (Mirowski and Van Horn, 2005; Marsi et al., 2012). Until that moment, pharmaceutical companies had to accomplish internally both the development of new products and the enlargement of therapeutic indications for existing drugs. This constraint was especially limiting for small or medium size firms with no internal R&D capabilities.

Initially CROs focused on pre-clinical investigation and clinical trials, but gradually their portfolio of services expanded to cover nowadays all stages of drug development (Figure 3.1). In fact, the market can be classified in four categories of services, in decreasing order of relative size: clinical, (the lion's share with 66.9% of the market in 2018), discovery (including pre-discovery or molecular modeling), pre-clinical and laboratory services (Fortune, 2021). CROs may also offer post-marketing surveillance. The number of new products in development by CROs has almost tripled in 20 years and has accelerated in the past decade.

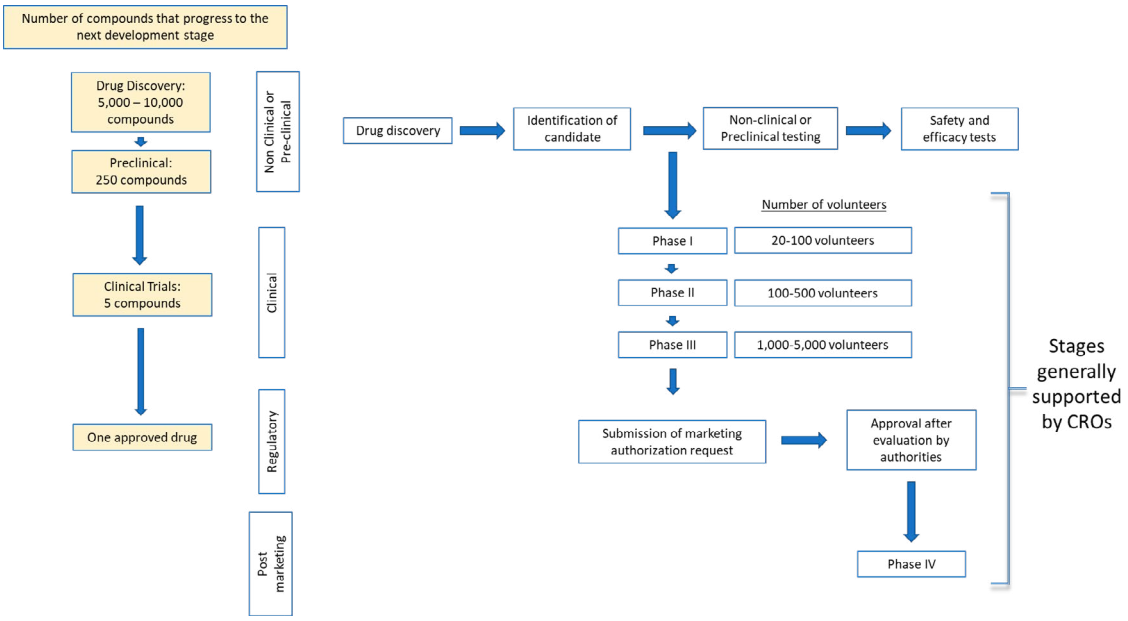

Figure 3.1. Stages of drug development
Source: European Medicines Agency and own elaboration

The number of CROs has grown steadily in recent decades, with new firms being created every year. Although the market is undergoing consolidation, it is still quite fragmented. There are two big categories of players in CRO industry: very big companies (top 10% CROs account for approximately 50% of the market) and small niche companies. The sector encompasses also medium size firms.

Big companies usually offer a full package of high value-added services, of different types: externalizations *full service*, partial services and functional service provisions of specialized personnel. They usually invest strongly in computer technology and have a broad regional coverage that facilitates the management of clinical trials in several countries when required.

Small CROs are typically niche companies specialized in specific phases of the drug development cycle, certain services like data management, specific therapeutic areas or the development of specific products like medical devices.

Outsourcing to CROs provides clear upsides to drug developers (Piachaud, 2002; Vogel and Getz, 1997):

a. Delegation of noncore activities: thus drug developers can instead specialize and focus on their core capacities. For example, CROs have ample expertise in dealing with Ethics Committees, IRBs (Institutional Review Boards), US Independent Ethics Committees and regulatory agencies. This is particularly convenient for small and medium size bio-pharmaceutical companies, where is only a limited amount of resources capable of accomplishing these activities. The same happens with regards to other specialized tasks, as data management, statistics and medical writing, among others. Some evidence suggests that CROS in China have successfully helped pharmaceutical firms handle government regulations and understand price rules, thus acting as catalysts for their modernization (Shi et al., 2014).
b. Cost efficiency: by working with CROs drug developers have the possibility to cut direct employee costs and reduce substantially the time and disbursements associated to hiring, training and firing staff.
c. Global coverage: clinical trials are often conducted in several countries or regions in order to access enough patients and engage with various medical communities and regulatory agencies. Pharmaceutical companies of small or medium size and new biotechnological firms usually lack expertise on foreign relations and regional regulatory differences; hence they profit from full-service providers coordinating clinical research across national boundaries and providing cross-cultural expertise. An example is the development of Covid-19 vaccines. Pfizer and BioNTech worked with the CRO ICON plc, which was able to engage with 153 research sites in US, Europe, South Africa and Latin America and recruit more than 44.000 clinical trial participants over four months (ICON, 2021). Although it is feasible that Pfizer had the resources necessary to manage the clinical trials, it most probably profited from the outsourcing to ICON.
d. Reduced time to market, which may be key in order to build a competitive and/or a first mover advantages and is especially relevant in R&D projects (Piachaud, 2002). CROs can accelerate the selection of research sites, reduce the timeframes necessary to obtain ethic and regulatory approvals of new studies and expedite the recruitment of patients.

In our view, these ideas point to two particularly relevant features in the interaction between customers and CROs. First, outsourcing to CROs allows a reallocation and redistribution of part of the risk associated to the launching of a new remedy. The drug developer or sponsor keeps the *project risk*, inextricably linked to the final outcome, i.e. success or failure, of the new product. This risk is quite severe, since typically for 250 compounds in the preclinical stage, five are selected for clinical trials and only one is approved (Figure 3.1).

By means of outsourcing, however, the drug developer transfers to the service provider the *operational risk*, associated to the day-to-day management of the clinical trials or service contracted in terms of protocol design, site selection, patient recruitment and data gathering and analysis. This day-to-day management is rather challenging. As Figure 3.1 conveys, the number of patients required in each stage of the drug development process varies remarkably. This entails, in turn, a different size of the workforce managing the process (more modest in Phase I and larger in Phase III) in each step. It would be very onerous for the drug developer to plan, recruit, train and adjust the optimal number of employees for each stage. A cheaper and more flexible strategy is to transfer this task to the service provider by means of outsourcing. CROs supply extra capacity when the pharmaceutical or biotechnological company has not enough internal resources, thus transforming fixed into variable costs and minimizing idle inhouse resources.

Since CROs operate on a contractual basis, the final outcome of the clinical stage, whether the new drug is deemed ready for the market or not, is not as critical as it is for the drug developer[1]. What is key for CROs, though, is the sound management of the project. Lack of compliance or delays in the delivery of the main milestones often entails penalties, whereas the achievement of timely results may be associated to incentive payment and bonuses (Russell, 2016).

Second, as discussed above, CROs coordinate and integrate different and complex activities, very often across countries. They handle and process large amounts of patients and data, and help sponsors deal with agencies and regulations. Hence they act as complex hubs for information, data and knowhow. In order to generate value for their customers CROs must carry out all these processes and operations efficiently and smoothly.

1 Obviously the final outcome is not irrelevant, either, for the CRO. If the new drug succeeds, the CRO may still cooperate in the launching and post marketing stages, thus capitalizing the knowhow acquired in the previous stages.

3.3 Methodology and Data

3.3.1 Model

Efficiency analyses usually work with microeconomic data on inputs and outputs from a set of decision-making units (DMUs), typically firms, plants or other types of organizations. There are two main ways to carry out the assessment. The Stochastic Frontier Analysis (SFA) estimates a production function statistically and computes inefficiency measures by looking at the deviations of individual DMUs from the function.

The non-parametric Data Envelopment Analysis (DEA), instead, does not assume a particular functional form between inputs and outputs. DEA designs and solves an optimization problem subject to a number of constraints by means of linear programming. This optimization problem may be formulated as the search for the maximum output attainable given a fixed quantity of inputs (output orientation) or, alternatively, as the search for the minimum amount of inputs necessary to produce a particular level of output (input orientation).

In practice, DEA searches for the most efficient DMUs in a set, which register an efficiency of 1 by definition. Next, it computes the distance of the rest of DMUs to the most efficient units and translates this information to efficiency scores[2].

More formally, suppose there are N DMUs indexed by j, (j = 1, …, N), and a technology T which transforms inputs into outputs:

$$T = \{(x,y) : x \text{ produces } y\}$$

Where x_j is a vector of m inputs and y_j is a vector of s outputs for DMU j.

$$x_j = (x_{1j}, \dots, x_{mj}) \in R^m$$
$$y_j = (y_{1j}, \dots, y_{sj}) \in R^s$$

The feasible set in this problem can be defined as the production possibility frontier P(x) or, alternatively, the input requirement set L(y):

$$P(x) \equiv \{ y: (x, y) \in T\}$$
$$L(x) \equiv \{ x: (x, y) \in T\}$$

2 Productivity and efficiency are very related concepts although theoretically different. See Raa (2010) for a discussion.

For the more general technology,

$$T = \left\{(x, Y) : \sum_{j=1}^{N} x_j \lambda_j \leq x, \sum_{j=1}^{N} y_j \lambda_j \geq y, \lambda \in \Lambda\right\}$$

Where

$$\lambda = (\lambda_1, \lambda_2, \ldots, \lambda_n) \in R^n$$

$$\Lambda_c = \{\lambda : \lambda \geq 0\}$$

$$\Lambda_v = \left\{\lambda \sum_{j=1}^{N} \lambda_j = 1, \lambda, \geq 0\right\}$$

Λ_c corresponds to the constant returns of scale case, whereas Λ_v represents variable returns to scale.

For the input oriented DEA, the goal is to find

$$\min \theta$$

$$\text{s. t. } (\theta x_j, y_j) \in T$$

Where θ is the efficiency score for DMU j.

In this paper we have chosen to work with the input-oriented DEA and variable returns to scale, as we shall detail below.

3.3.2 **Data**

We have worked with detailed micro data for a sample encompassed by global CROs over the period 2012-2020. The data have been gathered from the Orbis database (Van Dijk, 2021), which has rich economic and financial information disaggregated at the firm level. Gascón et al. (2017) and Rahman et al. (2020) are other examples of papers employing analogous databases.

It is a common practice for global CROs operating in Europe and Asia to establish affiliates per country. We have included the holding, consolidated company in the sample when available. If not, we have considered the affiliated.

In accord with other contributions, the outputs in our analysis are turnover and net income. The input proxying for capital is total assets. The input labor can be measured in units (number of employees) or in monetary value (total cost of employees); we have employed both types of measures to capture labor, which is thus proxied by the number of employees and the total cost of employees. Data for this last variable, though, is available for a smaller subset of companies.

It might be argued that these variables are very general and can be employed in many sectors. This is of course true. Nonetheless, they capture rather accurately the nature of the production process as allocating an accumulable (capital) and a non-accumulable factor (labor) in order to elaborate and sell a good or service; in absence of other variables, they are a reasonable approximation to the production function of CROs. It would have been interesting to use proxies of R&D, but these data were not available.

Figure 3.2 and Table 3.1 display trends over time and summary statistics for selected variables. Variables have been deflated with the Consumer Index Price for G20 (OECD, 2022). Average figures increase over time, pointing to an expansion of the activity in the industry, but the performance of the variables is not uniform. Average real turnover increases 76 per cent between 2012 and 2020. The number of employees increases 114 per cent over the period. The figures for real assets and real income are 159 and 186 per cent, respectively. All magnitudes have grown over time, but the growth of inputs has been faster than the growth in real turnover. Notwithstanding this asymmetry, real income has increased substantially.

Figure 3.2. Evolution over time, selected variables, 2012-2020

Notes: averages computed across DMUs. Average real turnover, average real assets and average real income in thousand dollars, deflated with the Consumer Index Price for G20, OECD.

Table 3.1. Summary statistics, selected variables, 2012-2020

	Mean	Std. Dev.	Min	Max	Growth 2012-20
Real turnover	313,131.91	729,817.22	1,607.45	4,305,538.5	76%
Employees	2,021.309	4,516.834	15	24,310	114%
Real assets	415,852.76	1,083,350.1	2,637.919	7,225,184.5	159%
Real income	14,901.538	61,726.613	-25,2171.16	344,370.16	186%

3.4 Results

3.4.1 Average Efficiency: Levels and Trends

The basic DEA framework does not consider explicitly the potential presence of measurement errors or sample bias in the data. Typically, this approach regards as unknown the efficient frontier and the underlying data generating process (DGP) of the efficiency scores. In a series of influential papers, Simar and Wilson (1998, 2000, 2007) and Daraio and Simar (2007) develop a strategy to handle these issues. They design several bootstrapping tools which, by means of many repetitions, provide approximations to the unknown distribution of efficiency and enable the computation of bias-corrected efficiency scores. Their methodology also provides standard errors and confidence intervals of the efficiency scores at a specific significance level 1-α.

We have employed both the basic DEA framework with no bootstrapping and the Simar-Wilson bootstrap approach to compute and compare radial efficiency scores for the firms in our sample. We have obtained efficiency scores for each firm and year in our sample over the period 2012-2020[3]. We have worked in a variable returns to scale, input orientation framework. The assumption of variable returns to scale is more flexible than the alternative, constant returns to scale. Furthermore, since the CRO industry has an important technological component, the hypothesis of variable returns to scale seems appropriate. The input orientation approach is intuitively more appealing, in our view, and closer to the firms' reality than output orientation[4]. The number of bootstraps replications in the general case has been 200. α is 5 per cent.

In order to check the robustness of the results, we have designed and estimated five models under alternative specifications (Table 3.2). In Model 1, the baseline, the output is turnover and the inputs are number of employees and total assets, proxying for labor and capital, respectively. Model 2 works with the same inputs and adds an additional output, net income, to total revenue. In Model 3 we replace the units (number of employees) measure for labor with the monetary value measure. Hence Model 3 considers total cost of employees and fixed assets as inputs and turnover as output. Model 4 encompasses total employee costs and total assets as inputs and turnover and net income as outputs. Finally, Model 5 reproduces Model 4, but performs 1000 bootstrap replications.

We are constrained by the availability of data in the design of these models. For example, it would have been interesting to capture the R&D of the companies, but we have not found data on the usual proxies of R&D, patents or R&D expenditure, for CROs.

3 The software employed for this exercise is the DEA toolbox for Matlab, (Alvarez et al., 2020).

4 According to our experience, strategies intending to increase efficiency in firms usually explore ways to reduce costs, rather than to expand output.

Table 3.2. Computation of efficiency, inputs and outputs

Model	Inputs	Outputs	Observations
1	# of employees Total assets	Turnover	249
2	# of employees Total assets	Turnover Net income	245
3	Total employee cost Total assets	Turnover	184
4	Total employee cost Total assets	Turnover Net income	184
5	Total employee cost ** Total assets	Turnover Net income	184

Notes: **: model with 1,000 bootstrap replications.

We compute four estimators of efficiency for each model: the basic estimator without bootstrapping, $\hat{\theta}$, the bootstrap estimator $\hat{\theta}_b$, and the upper and lower bounds of its 95% confidence Interval, $\hat{\theta}_b^U$ and $\hat{\theta}_b^L$ respectively. Hence we get a total number of 20 estimators of efficiency.

Table 3.3 summarizes some descriptive statistics of the efficiency estimators obtained from Models 1 to 5. The average bootstrap efficiency for all firms in our sample over 2012-2020 in the baseline Model 1 is 0.665. This means that a better reallocation of resources would enable firms to produce the same amount of output with 33.5% less of inputs, on average. In other words, firms should reduce their input consumption 33.5% on average to reach the efficient frontier and mimic the production conditions of the best performers in the sample. The median of the efficiency estimator is slightly higher than the mean, 0.732.

The mean of the basic DEA model, 0.783, is larger than the mean of the bootstrap estimator. This is consistent with the claim that the basic DEA model introduces some upward bias in the efficiency scores (Simar and Wilson, 1998). The standard deviation of the bootstrap estimator is also below the standard deviation of the basic DEA estimator, which is reasonable since the bootstrap technique smooths the data by repeated sampling and gives more weight to non-extreme values.

The means for the lower and higher confidence Intervals are 0.568 and 0.771 respectively. The sixth column of Table 3.2 informs about the maximum values reached by the efficiency scores in the sample. The basic DEA model assigns an efficiency score of 1 to the DMUs on the frontier, this is why the maximum for this estimator is 1. This is not the case for the bootstrap estimator, though. In the bootstrap efficiency framework, some DMUs may theoretically approach an efficiency score of 1, but this occurs with 0 probability; it is no surprise, then, that the highest level of bootstrap efficiency is 0.887.

The second panel of Table 3.3 displays the descriptive statistics for Model 2, in which two outputs, turnover and net income, have been considered. The inputs are the same as in Model 1, number of employees and total assets. The mean bootstrap efficiency is 0.686, slightly above but very close to that of Model 1. Now the best performer attains an efficiency score of 0.907. Model 3 (third panel) replaces the number of employees with the total labor cost to proxy for labor; the proxy for capital is the same as in Models 1-2, total assets. Only one output, turnover, is considered now. The mean bootstrap efficiency score diminishes somehow to 0.624.

Model 4 (fourth panel) includes total labor cost and total assets as inputs and turnover and net income as outputs. The mean bootstrap efficiency is 0.637 for this model. Model 5 is the same as Model 4, but with 1,000 bootstrap replications. As the comparison between Model 4 and Model 5 implies, the descriptive statistics are almost identical in both cases, only varying the third decimal occasionally. Therefore the gain from performing 1000 bootstrap replications instead of 200 is almost inexistent for this sample, whilst the cost in computer's time is non-negligible.

Table 3.3. Efficiency scores, descriptive statistics

Variables	Obs	Mean	Std.Dev.	Min	Max	Median
Model 1						
$\hat{\theta}^{1}$	249	.783	.232	.17	1	.846
$\hat{\theta}^{1}_{b}$	249	.665	.186	.134	.887	.732
$\hat{\theta}^{1}_{L}$	249	.568	.156	.106	.791	.618
$\hat{\theta}^{1}_{U}$	249	.771	.228	.167	.997	.834
Model 2						
$\hat{\theta}^{2}$	245	.803	.228	.168	1	.915
$\hat{\theta}^{2}_{b}$	245	.686	.185	.14	.907	.776
$\hat{\theta}^{2}_{L}$	245	.579	.152	.121	.828	.617
$\hat{\theta}^{2}_{U}$	245	.794	.225	.165	.997	.910
Model 3						
$\hat{\theta}^{3}$	184	.757	.262	.167	1	.826
$\hat{\theta}^{3}_{b}$	184	.624	.205	.131	.898	.707
$\hat{\theta}^{3}_{L}$	184	.527	.173	.101	.827	.57
$\hat{\theta}^{3}_{U}$	184	.743	.257	.165	.994	.817

Variables	Obs	Mean	Std.Dev.	Min	Max	Median
Model 4						
$\hat{\theta}^{4}$	184	.779	.254	.167	1	.870
$\hat{\theta}^{4}_{b}$	184	.637	.197	.133	.882	.718
$\hat{\theta}^{4}_{L}$	184	.532	.163	.101	.792	.572
$\hat{\theta}^{4}_{U}$	184	.764	.249	.164	.995	.857
Model 5						
$\hat{\theta}^{5}$	184	.779	.254	.167	1	.870
$\hat{\theta}^{5}_{b}$	184	.638	.197	.132	.881	.72
$\hat{\theta}^{5}_{L}$	184	.533	.163	.104	.798	.576
$\hat{\theta}^{5}_{U}$	184	.765	.249	.164	.993	.858

Table 3.4 displays the correlation coefficients between and within estimators. Panel A shows the correlation coefficients between the mean bootstrap efficiencies in the five models. The correlation between the estimators from Models 1 and 2 (the baseline model and the specification with turnover and net income as output) is almost 0.9. Instead, the correlation between Models 1 and 3 (the baseline and the specification with total employee costs proxying for labor) is smaller, 0.726. The correlation for Models 1 and 4 is 0.709. Models 4 and 5, where the only difference is the number of repetitions, exhibit a correlation of 0.999.

Panel B in Table 3.4 details the correlations between the four types of efficiency estimators computed for Model 1 (the corresponding correlations for Models 2-5 are in Appendix 2). The correlations within Model 1 estimators are quite high, larger than 0.94 in all cases. The correlation between efficiency scores obtained with and without bootstrap is at least 0.98 in all cases, slightly above this figure for the upper bound confidence interval (0.999) and slightly below for the lower bound (0.94-0.95). This suggests that the bias induced by the basic DEA estimator is moderate.

Table 3.4. Efficiency estimators, correlations.

3.4. A. Matrix of correlations, mean bootstrap efficiency estimators across models, Models 1-5

Variables	Model 1	Model 2	Model 3	Model 4	Model 5
Model 1	1.000				
Model 2	0.899	1.000			
Model 3	0.726	0.714	1.000		
Model 4	0.709	0.744	0.968	1.000	
Model 5	0.711	0.745	0.969	0.999	1.000

3.4. B. Matrix of correlations, mean efficiency estimators computed by Model 1

	$\hat{\theta}^1$	$\hat{\theta}^1_b$	$\hat{\theta}^1_L$	$\hat{\theta}^1_U$
$\hat{\theta}^1$	1.000			
$\hat{\theta}^1_b$	0.986	1.000		
$\hat{\theta}^1_L$	0.954	0.987	1.000	
$\hat{\theta}^1_U$	0.999	0.987	0.955	1.000

Notes: All correlation coefficients significant at 99%. For within correlations from Models 2-5 see Appendix 2.

Summing up, our findings suggest that bootstrap efficiency in the sample is 0.665 when averaged over firms and over time. It is slightly lower if labor is proxied by employee cost, and slightly higher if net income is added as an output. According to our estimates, therefore, the potential reduction of inputs by companies in our sample lies between 31.4% and 35.8%. Since the main messages from the baseline case Model 1 carry over to the rest, the results are rather robust to alternative specifications of inputs and outputs.

These results are not very far from those obtained with similar data for a sample of CROs operating in Europe (Díaz and Sanchez-Robles, 2021). The average efficiency in that case in the basic DEA model under the Model 1 specification was 0.716. Now it is 0.783. This is reasonable since the sample employed for this paper includes CROs from US, whose efficiency is slightly above that of European parent and subsidiary firms. The medians, anyhow, are quite close: 0.738 for the European firms and 0.732 for the more general sample.

Figure 3.3 displays the evolution over time of average (over firms) bootstrap efficiency computed according to Model 1. Mean efficiency exhibits an increasing profile and grows 20% between the beginning and end of the period. It peaks in 2014 and decreases until 2016, when it recovers and rises again.

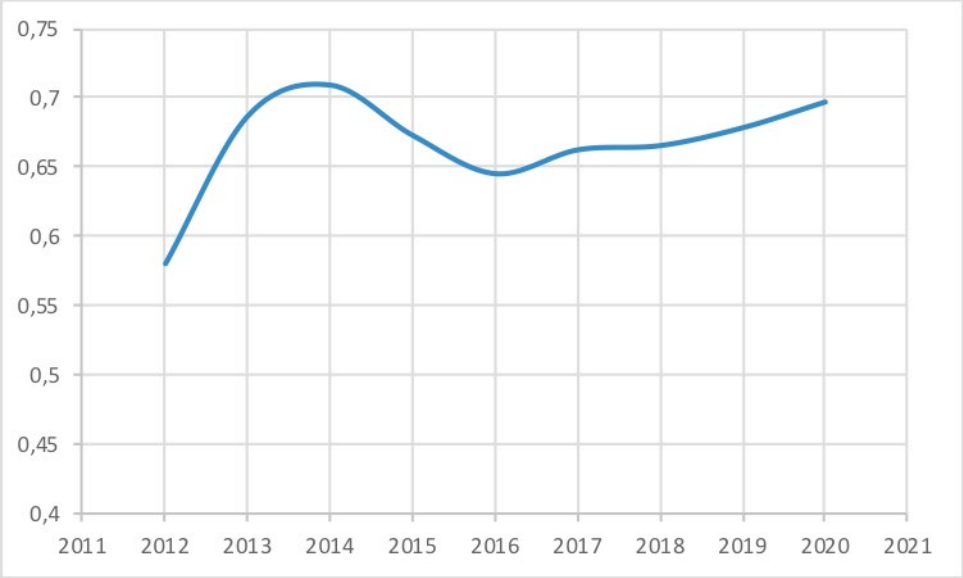

Figure 3.3. Average bootstrap efficiency over time, Model 1, 2012-2020

Note: efficiency computed according to Model 1.

3.4.2 Best Performers

This empirical exercise allows to characterize the best performers in terms of efficiency. Table 3.5 shows descriptive statistics of bootstrap efficiency scores of the best performers according to Model 1. Rankings according to Models 2-5 are very similar. Best performers are defined as those with average bootstrap efficiency equal to or larger than 0.75. Appendix 3 shows descriptive statistics for the efficiency scores of all DMUs in the sample.

The Top 3 performers are PPD Australia, Centre Recherches Biologiques and Oy Medfiles, with average bootstrap efficiencies of 0.82, 0.817 and 0.81 respectively. Figure 3.4 represents the evolution over time of bootstrap efficiency for these three companies. The three of them, and in particular PPD Australia, display remarkable stability in terms of efficiency, as showed by their small standard deviation over the period, and register in every year very high efficiency scores. The efficiency of Centre Recherches and Oy exhibits an increasing trend over the period.

Table 3.5. Average efficiency scores of best performers, Model 1, 2012-2020

DMU	Obs	Mean	St.dev.	Min	Max
C. RECHERCHES BIOLOGIQUES	**8**	**.817**	**.040**	**.737**	**.871**
CMIC	9	.790	.088	.656	.887
GKM GESELLSCHAFT	4	.798	.106	.639	.865
ICON ESPAÑA	9	.755	.067	.662	.845
IMM RECHERCHE	5	.783	.046	.708	.831
MEDPACE HOLDINGS	5	.76	.128	.534	.837
OY MEDFILES	**9**	**.810**	**.051**	**.732**	**.866**
PPD AUSTRALIA	**7**	**.82**	**.012**	**.805**	**.841**
SOIKEN HOLDINGS	9	.77	.114	.496	.879
SYNEOS	9	.78	.048	.665	.823
TFS	7	.76	.091	.621	.834

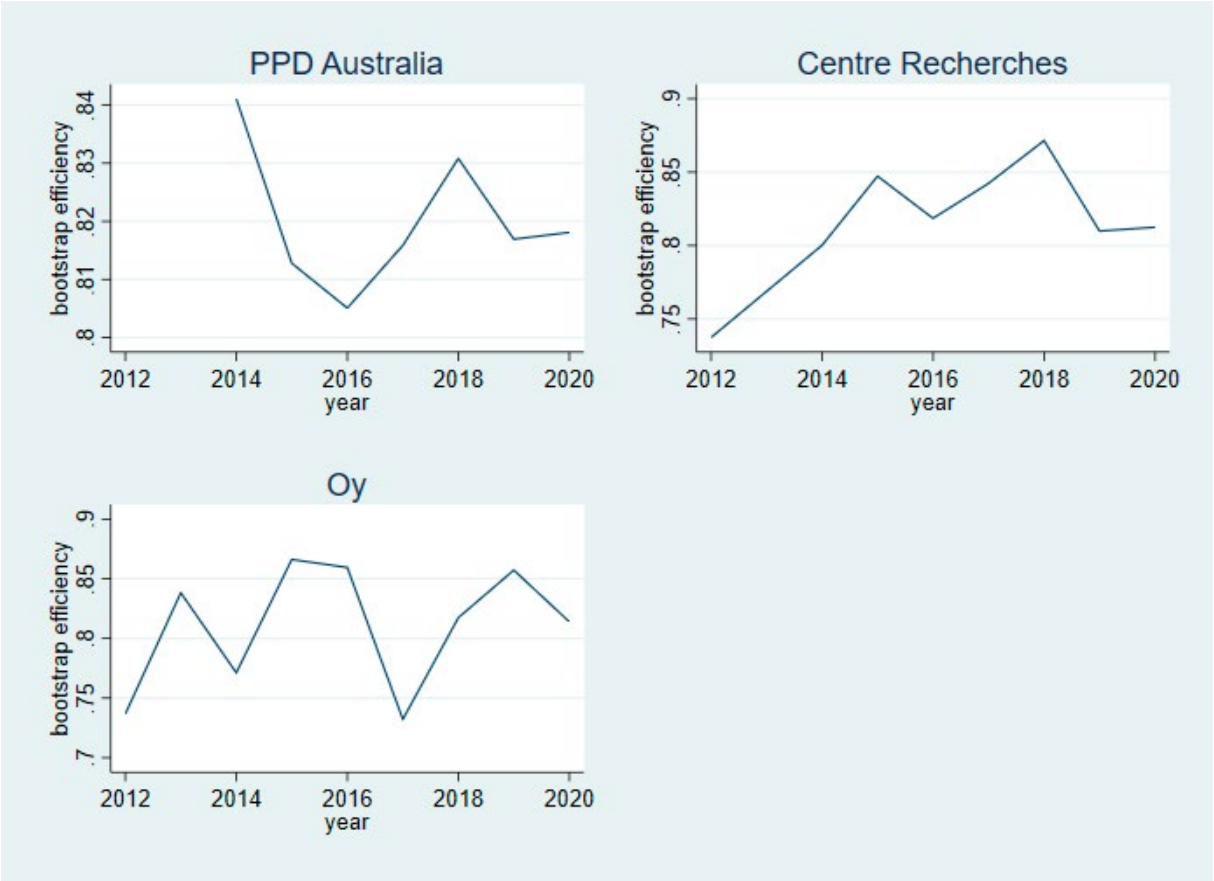

Figure 3.4. Efficiency over time, best performers

Note: bootstrap efficiency, computed according to Model 1.

Efficiency displays a remarkable degree of persistence over time, as Figure 3.5 indicates. The correlation between efficiency in t and efficiency in t-1 is 0.69, significant at 99%.

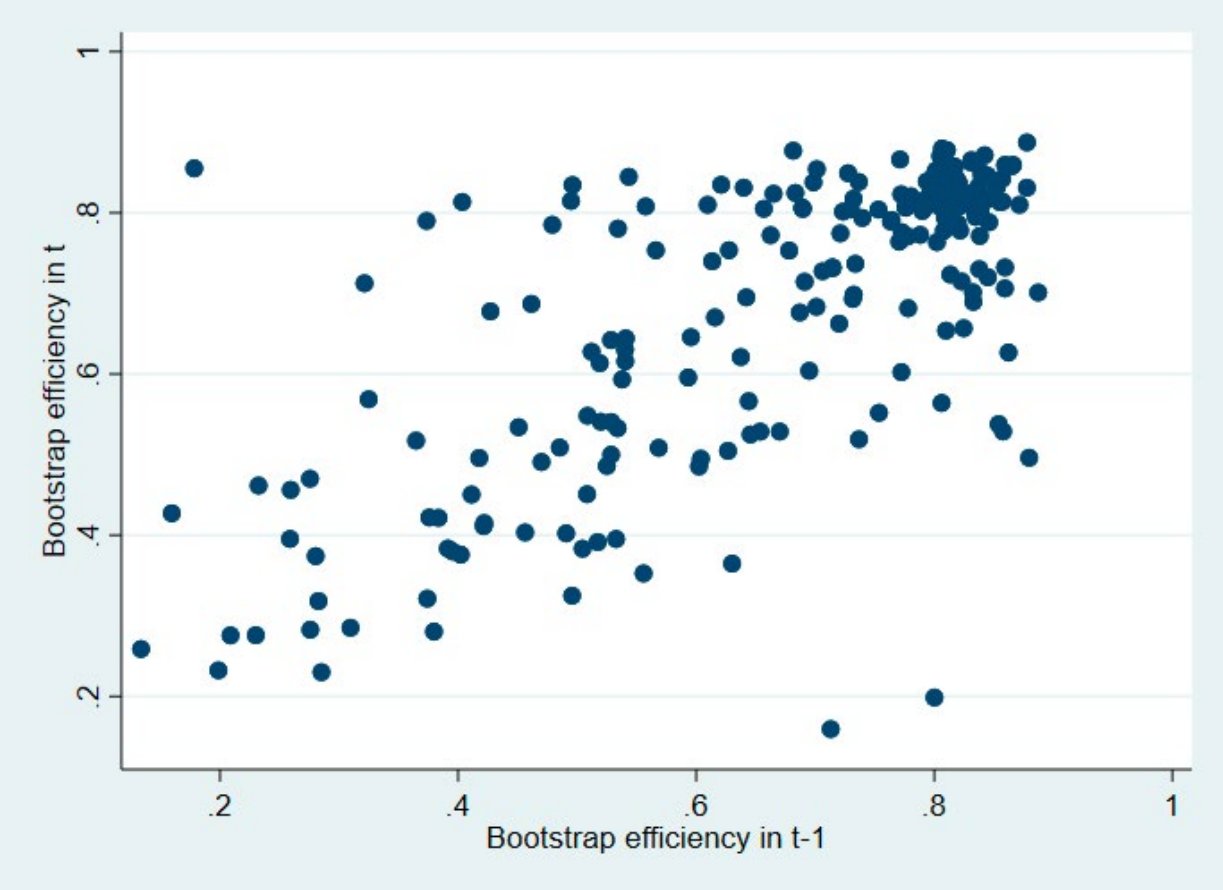

Figure 3.5. Persistence of efficiency
Note: Efficiency computed according to Model 1.

This fact suggests that efficiency may be associated to structural or fundamental features of CROs, as for example size. In order to test this hypothesis, we have divided the sample in four categories of size, very big, big, small and very small, according to their level of turnover. The thresholds for these categories are determined by the 75th, 50th and 25th percentiles of turnover. Table 3.6 summarizes the distribution of bootstrap efficiency (Model 1) by size category. The last column informs about the Krishnamoorthy and Yu (2004) test of equality of means for each category and the rest of the sample, where the null hypothesis is the equality of means between the two groups.

The average efficiency for very big and very small firms is above the global mean. The difference is almost of six points for very small firms, and the means test rejects the null hypothesis of equality of means for these companies. The gap between very big firms and the rest is smaller, though, and in this case the hypothesis of equality of means can not be rejected at conventional

levels. Big and small firms, instead, exhibit efficiency levels below the global mean, and in both cases the means test is significant. As Table 3.6 suggests, small and very small firms conform more homogeneous categories, according to their smaller standard deviation of efficiency, than very big and big companies.

Table 3.6. Mean efficiency by size

	Mean	Standard deviation	P value of test
Very big	0.676	0.214	0.536
Big	0.619	0.204	0.0416**
Small	0.629	0.155	0.01*
Very small	0.723	0.154	0***
Whole sample	0.665	0.186	

Notes: *: significant at 90%. **: significant at 95%. ***: significant at 99%. The last column reports the p value of the Krishnamoorthy and Yu (2004) test of equality of means

While this evidence is still tentative and preliminary, and will be explored in further research, Table 3.6 conveys some interesting messages. The good performance in terms of efficiency of very big firms suggests the existence of increasing returns to scale in a particular domain of the production function. These increasing returns may be related to two main reasons. First, size allows large companies to optimize their investments in technology and other state-of-the-art infrastructure (for data gathering and data management, for example) since they can distribute the associated costs among a higher number of projects, reducing average costs.

Second, it is a common practice for drug developers to establish long term relationships with one or several large CROs (Gummerus et al., 2016). This reduces transaction and search costs for both partners and makes it easier for them to accommodate to each other. In particular, it significantly reduces the costs associated to marketing and commercial strategies of CROs, thus improving their performance and efficiency. These agreements are usually more common in very big CROs because of reputation and solvency considerations. Medium size companies, instead, do not profit from these advantages.

Table 3.6 also suggests the potential existence of competitive advantages associated to specific niches of activity and high levels of specialization which are exploited by very small firms.

3.5 Concluding Remarks

In the last decades, an important part of the R&D activity of pharmaceutical and biotechnological firms has experienced profound changes. Mounting costs of product development, the need for flexibility and the challenges brought about by a scenario where global markets are increasingly important have prompted a sustained trend of outsourcing of tasks and processes. The main beneficiaries of this behavior are CROs and other innovative service providers, whose competitive advantage hinges on their capacity to efficiently coordinate and manage flows of information between drug manufacturers, health authorities, ethics committees, investigational sites, doctors and patients.

This paper explores empirically the level, time profile and basic features of efficiency in a sample of CROs over 2012-2020. Our main findings may be summarized as follows:

1. The CRO industry features an average bootstrap efficiency of 0.665, rather robust to different specifications. According to our estimates, therefore, the potential reduction of inputs by companies in order to reach the efficient frontier is on average 33.5%.

2. Efficiency displays an increasing trend over 2012-2020.

3. The best performers in the sample are PPD Australia, Centre Recherches Biologiques and Oy Medfiles, with average efficiencies of 0.82, 0.817 and 0.81 respectively.

Efficiency scores for the firms in our sample show persistence over time, thus implying that efficiency is related to structural factors. Although this issue will be explored more thoroughly in further research, our investigation offers some preliminary evidence suggesting an association between efficiency and size (measured with respect to turnover). Very large firms exhibit average levels of efficiency above the sample mean, which suggests the presence of increasing returns to scale in the industry, probably associated to the superior capacity of larger firms to adopt state-of-the-art technologies in the field of information gathering and analysis and to engage in long term commercial associations with partners. In turn, the presence of scale economies may imply that more mergers and acquisitions among big firms will take place in the future, as companies try to profit from the increasing returns to scale in production.

Very small firms also outperform the rest in terms of efficiency, suggesting that there are as well competitive advantages linked to niches.

The analysis condensed in this paper is limited by the sample and variables available in our data set. Further research covering other samples of firms and alternative variables could help shed more light on this sector; this is already in our agenda.

Appendix 1. Stages of drug development

Drug development can be divided into the following phases:

1. Drug discovery: a biological target associated with the disease or condition to be treated is identified; subsequently, experimental methods for determining the ability of chemical compounds to interact with this target are developed.

2. Non-clinical or Pre-clinical research, designed to provide information on a drug candidate´s efficacy and safety before it is tested in human subjects. It generally consists of in-vitro and in-vivo models.

3. Clinical Research or Clinical Trials, set up to answer specific research questions. The clinical stage of drug development is in turn divided into four different phases:

    a. Phase I, intended to determine safety in humans and to gather information on dosage.

    b. Phase II, where additional safety data, preliminary efficacy and adverse effects information are collected.

    c. Phase III, which determines the drug´s efficacy and monitors adverse reactions in a higher number of participants than the previous two phases. Long-term or rarer side effects that may have gone undetected in Phase I and Phase II studies are usually detected in this phase.

    d. Phase IV or post-commercialization studies. The purpose of these studies is to obtain additional information about the long-term risks and benefits of a drug once it is commercialized and used more widely.

Appendix 2. Correlations within models

Matrix of correlations Model 2

Variables	(1)	(2)	(3)	(4)
(1) Basic DEA model	1.000			
(2) Bootstrap	0.987	1.000		
(3) Lower bound, CI	0.945	0.980	1.000	
(4) Higher bound, CI	1.000	0.988	0.946	1.000

Matrix of correlations Model 3

Variables	(1)	(2)	(3)	(4)
(1) Basic DEA model	1.000			
(2) Bootstrap	0.980	1.000		
(3) Lower bound, CI	0.948	0.988	1.000	
(4) Higher bound, CI	1.000	0.983	0.950	1.000

Matrix of correlations Model 4

Variables	(1)	(2)	(3)	(4)
(1) Basic DEA model	1.000			
(2) Bootstrap	0.982	1.000		
(3) Lower bound, CI	0.943	0.984	1.000	
(4) Higher bound, CI	0.999	0.983	0.944	1.000

Matrix of correlations Model 5

Variables	(1)	(2)	(3)	(4)
(1) Basic DEA model	1.000			
(2) Bootstrap	0.982	1.000		
(3) Lower bound, CI	0.942	0.984	1.000	
(4) Higher bound, CI	1.000	0.983	0.944	1.000

Notes: all values significant at 99%.

Appendix 3. Efficiency by DMU (Model 1)

DMU	Obs	Mean	St.dev.	min	Max
ACLARIS	4	.494	.256	.159	.713
BIOCLINICA INC	1	.274	.	.274	.274
C. RECHERCHES BIOLOGIQUES	8	.817	.040	.737	.871
CHILTERN INT.	7	.615	.237	.259	.852
CMED	9	.456	.088	.364	.630
CMIC	9	.790	.088	.656	.887
COVANCE INC	2	.747	.037	.721	.774
CROMSOURCE S.R.L	9	.641	.131	.485	.854
CROWN CRO OY	3	.836	.014	.824	.852
GENSCRIPT	6	.283	.031	.230	.318
GEORGE CLINICAL	6	.680	.208	.383	.877
GKM GESELLSCHAFT	4	.798	.106	.639	.865
ICON UK	8	.382	.095	.208	.490
ICON ESPAÑA	9	.755	.067	.662	.845
IMM RECHERCHE	5	.783	.046	.708	.831
INVITES BIOCORE	8	.628	.132	.499	.857
IQVIA SPAIN	8	.754	.058	.691	.837
KCR S.A.	6	.618	.127	.479	.785
LABCORP SARL	8	.742	.120	.543	.846
LABCORP UK	8	.357	.167	.133	.712
LINICAL CO	9	.469	.078	.324	.568
MEDPACE HOLDINGS	5	.760	.128	.534	.837
NAMSA	5	.583	.114	.485	.772
NOVOTECH	2	.454	.143	.352	.555
OY MEDFILES	9	.810	.051	.732	.866
PIVOTAL SL	9	.65	.110	.494	.814
PPD AUSTRALIA	7	.82	.012	.805	.841
PPD BULGARIA	9	.603	.245	.198	.838
PPD GERMANY	8	.731	.231	.178	.859
PPD POLAND	5	.668	.099	.519	.739
PRA	8	.752	.156	.373	.857
QPS AUSTRIA	6	.753	.115	.557	.876
SCANTOX	5	.604	.095	.519	.753
SOIKEN HOLDINGS	9	.77	.114	.496	.879
SYNEOS	9	.78	.048	.665	.823
TFS	7	.76	.091	.621	.834

References

Álvarez, I., Barbero, J. and Zofío Prieto, J. 2020. A DEA toolbox for MATLAB. *Journal of Statistical Software* (Online) 95, 3.

Bianchi, M., Cavaliere, A., Chiaroni, D., Frattini, F. and Chiesa, V. 2011. Organisational modes for Open Innovation in the bio-pharmaceutical industry: An exploratory analysis. *Technovation* 31, 1, 22-33.

Daraio, C. and Simar, L. 2007. Conditional nonparametric frontier models for convex and nonconvex technologies: a unifying approach. *Journal of productivity analysis* 28 1, 13-32.

Díaz, R. F. and Sanchez-Robles, B. 2020. Non-Parametric Analysis of Efficiency: An Application to the Pharmaceutical Industry.*Mathematics* 8, 9, 1522.

Fortune, 2021. Fortune Business Insights. https://www.fortunebusinessinsights.com/industry- reports/contract-research-organization-cro-services-market-100864

García-Vega, M. and Huergo, E. 2019. The role of international and domestic R&D outsourcing for firm innovation. *Journal of Economic Behavior & Organization* 157, 775-792.

Gascón, F., Lozano, J., Ponte, B. and de la Fuente, D. 2017. Measuring the efficiency of large pharmaceutical companies: an industry analysis. *The European Journal of Health Economics* 18, 5, 587- 608.

Getz, K. A. and Vogel, J. R. 2009. Successful outsourcing: tracking global CRO usage. *Applied Clinical Trials* 18, 6, 42.

Gummerus, A., Airaksinen, M., Bengtström, M. and Juppo, A. 2016. Outsourcing of Regulatory Affairs Tasks in Pharmaceutical Companies—Why and What? *Journal of Pharmaceutical Innovation* 11, 1, 46-52.

Hassanzadeh, F., Modarres, M., Nemati, H. R. and Amoako-Gyampah, K. 2014. A robust R&D project portfolio optimization model for pharmaceutical contract research organizations. *International Journal of Production Economics 158*, 18-27.

Huang, J. 2019. Contract Research Organizations Are Seeking Transformation in the Pharmaceutical Value Chain. *ACS Medicinal Chemistry Letters* 10, 684−686.

Icon, 2021. https://www.iconplc.com/news-events/press-releases/icon-pfizer-biontech/

Krishnamoorthy, K. and Yu, J. 2004. Modified Nel and Van der Merwe test for the multivariate Behrens– Fisher problem. *Statistics & probability letters* 66, 2, 161-169.

Lakdawalla, D.N. 2018. Economics of the pharmaceutical industry. *Journal of Economic Literature* 56, 2, 397-449.

Lee, C., Lee, J. and Kim, T. 2009. Innovation policy for defense acquisition and dynamics of productive efficiency: A DEA application to the Korean defense industry. *Asian Journal of Technology Innovation* 17, 2, 151-171.

Lowman, M., Trott, P., Hoecht, A. and Sellam, Z. 2012. Innovation risks of outsourcing in pharmaceutical new product development. *Technovation* 32, 2, 99-109.

Mao, Y.; Li, J. and Liu, Y. 2014. Evaluating business performance of China's pharmaceutical companies based on data envelopment analysis. *Studies on Ethno-Medicine* 8, 51–60.

Masri, M. D., Ramirez, B., Popescu, C. and Reggie, E. M. 2012. Contract research organizations: an industry analysis. *International Journal of Pharmaceutical and Healthcare Marketing* 6, 4, 336-350.

Piachaud, B. S. 2002. Outsourcing in the pharmaceutical manufacturing process: an examination of the CRO experience. *Technovation 22*, 2, 81-90.

OECD. 2022. Https://stats.oecd.org/Index.aspx?-DataSetCode=G20_PRICES.

Puente, F.J., Alonso, S., Gascón, F; Ponte, B and Fuente, D. 2019. A model for the strategic management of innovation and R&D at pharmaceutical firms through the analysis of clinical trials. International Conference on Industrial Engineering and Industrial Management, Servicio de Publicaciones de la Universidad de Oviedo 137-138. http://hdl.handle.net/10651/51580.

Rahman, M., Rodríguez-Serrano, M. Á. and Lambkin, M. 2020. Advertising efficiency and profitability: evidence from the pharmaceutical industry. *Industrial Marketing Management* 89, 619-629.

Raa, T.T. 2010. Efficiency measures for industrial organization. *Indian Economic Review* 161-192.

Russell, S. 2016. The Opportunity in Sharing Risk: A Productive Trend in Clinical Trials. https://www.drugdiscoverytrends.com/the-opportunity-in-sharing-risk-a-productive-trend-in-clinical-trials/

Shin, K.; Lee, D.; Shin, K. and Kim, E. 2018. Measuring the Efficiency of U.S. Pharmaceutical Companies Based on Open Innovation Types. *Journal of Open Innovation: Technology, Market and Complexity* 4, 3, 34.

Simar, L. and Wilson, P. W. 1998. Sensitivity analysis of efficiency scores: How to bootstrap in nonparametric frontier models. *Management science* 44, 1, 49-61.

Simar, L. and Wilson, P. W. 2000. A general methodology for bootstrapping in non-parametric frontier models. *Journal of applied statistics* 27, 6, 779-802.

Simar, L. and Wilson, P. W. 2007. Estimation and inference in two-stage, semi-parametric models of production processes. *Journal of econometrics* 136, 1, 31-64.

Sueyoshi, T. and Goto, M. 2014. DEA radial measurement for environmental assessment: A comparative study between Japanese chemical and pharmaceutical firms. *Applied Energy* 115, 502–513.

Shi, Y. Z., Hu, H. and Wang, C. 2014. Contract Research Organizations (CROs) in China: integrating Chinese research and development capabilities for global drug innovation. *Globalization and health* 10, 1, 1-6.

Van Dijk, B. 2022. *Orbis database*. Bureau van Dijk Electronic Publishing.

Vogel, J.R. and Getz, K.A. 1997. Factors driving the increased use of outside contractors in drug development. *Clinical Research and Regulatory Affairs* 14, 3 and 4, 177–190.

Wouters, O. J., McKee, M. and Luyten, J. 2020. Estimated research and development investment needed to bring a new medicine to market, 2009-2018. *Journal of the American Medical Association* 323, 9, 844- 853.

CHAPTER 4.

The Impact of Covid-19 on Biopharmaceutical Stock Market Returns

CHAPTER 4.

The Impact of Covid-19 on Biopharmaceutical Stock Market Returns

Abstract

We analyze the stock market performance of a group of pharmaceutical and biotechnological companies during particular stages of the Covid-19 pandemic. First we examine long run trends by looking at the data on share values since 2011. Next we focus on the short term impact of Covid-19 related news on the share prices. By means of event analysis we look at two types of episodes: news related to the expansion of the pandemic and information about the development of Covid-19 vaccines.

Our findings suggest that most of the biopharmaceutical companies analyzed have not exhibited large abnormal returns, either positive or negative, over 2020 and 2021. This is surprising since market volatility in the US has been quite high since the inception of the pandemic. The only exceptions are two small biotechnological firms, Moderna and Novavax, which experienced high positive abnormal returns that have been gradually exhausted in the case of Novavax.

Regarding the information on the vaccine, positive announcements about Phase III clinical trials results have had impact on the share prices of Pfizer, Moderna and Novavax, but not of Johnson and Johnson and AstraZeneca. Approvals from regulatory agencies seem to have been already discounted by the stock markets and have not affected prices. News about a potentially large purchase of Moderna vaccines, however, have generated large positive gains for this company. Moreover, the announcements made by the European regulatory agency have not impacted US stock markets.

4.1 Introduction

The Covid-19 pandemic has impacted the economy activity substantially. All industries, from agriculture and energy to manufacturing, transportation and health, have been affected. The recovery has started; nonetheless, the pre-pandemic level/growth of GDP is not expected to resume until 2023 -depending on the countries- because war in Ukraine has compromised the economic scenario.

The pharmaceutical and biotechnological industries have also adjusted their activity. The firms in these sectors not only have adapted their processes to continue manufacturing and distributing medicines but have also undertaken the development of new drugs and biotechnological products, thus playing a key role in the management of the pandemic. A relevant number of pharmaceutical companies have devoted significant efforts to the development of vaccines, diagnostic tests and treatments to prevent and fight coronavirus.

Vaccination is widely regarded as an effective and cheap health strategy to prevent and deal with infectious diseases (Bloom et al., 2017; Remy et al., 2014). Hence it is understandable that the urgency to fight Covid-19 has reunited governments, regulatory agencies, investors and pharmaceutical companies in the search of vaccines against Covid.

Before they are approved by regulatory agencies and can be marketed, all drugs follow a long and complex path, with different sets of testing (in vitro, in animals and finally in humans) [1]. The development of vaccines, therefore, usually takes several years. A number of Covid-19 vaccines, however, took less than one year to arrive to the market. At the end of December 2020 vaccination against Covid-19 had started in a number of countries with the Pfizer-BioNTech and Moderna vaccines. Other vaccines, like those from AstraZeneca/Oxford and Johnson & Johnson (J&J), were approved by regulatory agencies and reached markets (see Appendix 1 for details).

The experience since 2020 shows that vaccines have been key in order to reduce the transmission, incidence and mortality associated to Covid-19. Phase III trials already showed high levels of effectiveness of several Covid vaccines; real world studies from different countries confirmed this efficacy. For example, Pardo Seco et al. (2022) show that the Pfizer vaccine reduces infections in all age categories, prevents hospitalization for the disease and diminishes mortality. Zheng et al. (2021) explore 51 records in a meta-analysis and conclude that the effectiveness of Covid vaccines is high according to real world results. Zheng et al. (2022), in another meta-analysis, show the effectiveness of vaccines in the prevention of variants of concern of the original Covid-19.

1 Clinical trials are a key step in the development of a new drug or remedy. They are required by regulatory agencies in order to prove the safety and efficacy of new molecular entities such as vaccines. For a description of the stages involved in the development of new drugs and the role of clinical trials see Díaz and Sanchez-Robles (2021).

Covid vaccines have thus accomplished important outcomes in terms of public health. They have also registered record production schedules. At this point it is unclear if they have also entailed large profits for vaccine developers.

On a priori grounds it might seem that vaccines are a very profitable line of business for pharmaceutical or biotechnological companies, because of the large turnover implied by programs of massive vaccinations in many countries. Historically, however, vaccines have entailed typically low returns for manufacturers, partly because many times people need only one (or just a few) dose of a vaccine, whereas other drugs are prescribed and used over a course of a treatment or even long periods of time (see Bloom et al., 2017, for a discussion).

In this paper we analyze the stock market performance of a group of pharmaceutical and biotechnological companies with activity in the main stock exchange markets. First, and in order to get some background, we examine the long run trends of equity values by looking at the data since 2011. Next we focus on the short term impact of Covid-19 related news on the share prices. By means of event analysis we look at two types of episodes: news related to the expansion of the pandemic and information about the development of Covid-19 vaccines.

Our results suggest that most of the biopharmaceutical companies analyzed have not exhibited abnormal returns over 2020 and 2021, i.e. their behavior has not departed much from that of the Dow Jones.

More in particular, we find that the impact of the first months of the pandemic on the returns of the pharmaceutical companies has been modest. No abnormal returns, either positive or negative, are detected in general. This is surprising since market volatility in the US has been quite high since the inception of the pandemic (Baker et al., 2020). The only exceptions are the two small biotechnological firms, Moderna and Novavax, which experienced high positive abnormal returns over these months.

Regarding the information on the vaccine, positive announcements about Phase III clinical trials results have impacted the share prices of Pfizer, Moderna and Novavax, but not of Johnson and Johnson and AstraZeneca. Approvals from regulatory agencies seem to have been already discounted and have not affected share prices. News about a potentially large purchase of Moderna vaccines, however, have generated large positive share values increases for this company and Pfizer Finally, the announcements made by the European regulatory agency have not influenced US stock markets.

The paper is related to several strands of literature. First, it is connected to articles exploring the impact of R&D news on pharmaceutical stock prices, as Pérez-Rodríguez and Valcárcel (2012) or De Schrijver (2013).

Our investigation is also linked to papers investigating the effects of different episodes from the Covid pandemic on stock prices. Heyden and Heyden (2021) perform an event study of US

and European stocks during the beginning of the COVID-19 pandemic and argue that stocks reacted significantly and negatively to the announcement of the first death in a given country. Baker et al. (2020) show that at the beginning the US stock markets reacted to the apparition of new cases and deaths everywhere, and later on they were very sensitive to lockdowns and restrictions to activity.

Events with high impact and low probability of happening, such as the Covid-19 pandemic, may be overstated by the public opinion, leading to irrational behavior (Blendon et al., 2004; Ichev and Marinč, 2018). Zaremba et al. (2020) suggests the presence of this effect in the COVID-19 pandemic. They show that government interventions (as, for example, information campaigns and cancellations of public events) have increased the volatility of stock markets. Haroon and Rizvi (2020) provide evidence as well about the impact of panic related to Covid-19 on volatility.

Alam et al. (2021) look at the effect of the announcements of the Covid 19 pandemic on eight industries in Australia, suggesting a positive impact on the food, healthcare, pharmaceuticals and telecommunications industries, and a negative impact on energy and real estate. Behera and Rath (2021) report that the pharmaceutical sector in India as a whole has enjoyed average abnormal returns, but the evidence is mixed concerning individual firms.

Contributions exploring the effects of Covid-19 vaccines on share values are scarce so far. One exception is Alcaide et al. (2022), who explore the impact of the announcement of the results of the Pfizer vaccine on technological firms included in Nasdaq. Zhang (2021) analyzes the impact of news about Covid-related research (i.e. effectiveness of the Pfizer, Moderna, and Johnson & Johnson's vaccines).

Piñeiro-Chousa et al. (2021) explore the performance before and after Covid of Pfizer and Moderna and find different behaviors across them and over time. According to their results, Moderna is perceived by investors as an attractive choice. Pfizer, instead, has been heavily influenced by the negative market sentiment. Furthermore, Pfizer has been more affected by market volatility than Moderna.

Our paper is also closely related to Hwang (2013), who suggests that the results of Phase III clinical trials significantly impact the stock market prices of pharmaceuticals and biotechnologicals.

4.2 Some Background. R&D and Vaccines in the Pharmaceutical and Biotechnological Industries

The pharmaceutical industry is a highly research-intensive industry. The 15 largest pharmaceutical companies invested a record $133 billion in 2021 in R&D expenditure, an increase of 44% since 2016 (IQVIA, 2022). The new medicines, medical devices or biotechnological products -including vaccines- resulting of such investment fuel in turn future revenues and bring about improvements in the life expectancy and health of the general population. The efficient use of research and development resources to develop as many novel active substances (NASs) as possible positions the companies better to innovate and compete (Schuhmacher et al., 2021).

In this context, pharmaceutical companies which invest in clinical trials to develop new products are a fundamental piece for the progress of medicine (Qiu et al. 2021). Clinical trials are required by regulatory agencies in order to prove the safety and efficacy of new molecular entities, such as vaccines.

The investment in R&D is currently strong. A record 84 NASs were initially launched globally in 2021, double the number of five years ago, and reflecting the strength of the biomedical innovation system to discover, develop and receive regulatory approval for new therapies (IQVIA, 2022).

4.2.1 Covid-19 Pandemic – Some Remarkable Landmarks in the Search of a Vaccine

As suggested above, the development of Covid-19 vaccines has been unusually fast, taking less than a year. Wuhan Municipal Health authorities reported to the WHO on December 31, 2019 the first cases of pneumonia related to a novel coronavirus. They had occurred between December 12 and December 29. The virus was named 2019-nCoV by WHO. On January 11, 2020 the Chinese authorities reported the first death caused by the new coronavirus.

The virus spread quickly to Europe, US and the rest of the world. On March, 11 2020 the WHO declared the novel coronavirus outbreak to be a pandemic, being the first one caused by a coronavirus.

The pharmaceutical and biotechnological industries together with Governments, regulatory authorities and public health systems started soon to work on the development and deployment of diagnostics, treatments and vaccines to contain the spread and the effects of the disease caused by the coronavirus. On February 25, 2020 the NIH[2] announced that a clinical trial to evaluate the

2 A part of the U.S. Department of Health and Human Services and the largest biomedical research agency in the world.

safety and effectiveness of the antiviral drug remdesivir in adults diagnosed with coronavirus had started at the University of Nebraska Medical Center in Omaha (NIH, 2020). The US Food and Drug Administration issued an emergency-use authorization for remdesivir in hospitalized patients with severe Covid-19, becoming the first authorized therapy drug for Covid-19.

On May 4, 2020 world leaders pledged a total of $8 billion for the development of treatments and vaccines against the novel coronavirus.

On July 27, 2020, a vaccine being developed by the Vaccine Research Center at the National Institutes of Health's National Institute of Allergy and Infectious Diseases, in partnership with the biotechnology company Moderna, entered Phase III testing.

On August 11, 2020 in a live teleconference, President Putin announced that Russia had approved a coronavirus vaccine for public use before completion of Phase III trials, which usually precedes approval[3]. The vaccine, named Sputnik-V, was developed by the Moscow-based Gamaleya Institute with funding from the Russian Direct Investment Fund (RDIF).

On December 2, 2020 the British Medicines and Healthcare products Regulatory Agency (MHRA) approved the use of Pfizer-BioNTech *Comirnaty* vaccine, becoming the first Occidental regulatory agency to approve a vaccine against Covid-19. This vaccine was also granted an emergency approval by FDA on December 11, 2020.

Other vaccines like AstraZeneca/Oxford *Vaxzevria*, ModeRNA *Spikevax* and Johnson&Johnson/Janssen Covid-19 vaccine followed soon and were approved by subsequent regulatory agencies (see Appendix 1 for details).

4.2.2 The Development of Vaccines

Before they are granted the regulatory approval and can be administered in humans, vaccines need to follow, as any other drug or biotechnological product, the general development pathway from in-vitro studies to Phase III clinical trials. Nowadays the whole development process takes between 4 and 7 years (AEMPS[4], 2022).

The development of Covid-19 vaccines is an exceptional case in history. The vaccine developed by Pfizer and BioNtech moved from proof of concept to the first emergency approval from a regulatory authority in only 10 months. This is explained by several factors that contributed to shorten the timelines:

3 https://www.cnn.com/2013/01/03/world/europe/vladimir-putin---fast-facts/index.html

4 Spanish Regulatory Agency *(Agencia Española del Medicamento y Productos Sanitarios)*

1) R&D incentives: the effort, collaboration and financial support from the different stakeholders involved in the development process (Forman et al., 2021).

2) Parallel undertaking of the different phases of clinical trials: previous clinical trials with other coronavirus vaccines had made available some data that helped to move quickly into early phases of Covid-19 clinical trials. While studies on phase I-II were still running, phase III studies were already being implemented.

3) Fast approvals from regulatory authorities: once the clinical trials were concluded and the clinical study dossier prepared, it was necessary for new vaccines to be approved by the relevant health assessment bodies. The regulators made their top priority to evaluate the clinical data and grant the emergency/final approval for the vaccines to be administered to the population.

4) Technological factors (AEMPS, 2022). Covid-19 vaccine developers are applying the existing knowledge about vaccines already in production. Some Covid-19 vaccines are based on the novel mRNA technology which facilitates the production of high volumes at a high speed in comparison with other types of vaccines and improves the product stability. Other Covid-19 vaccines are based in existing technologies which has also helped to produce high volumes.

5) Deployment and administration: plants were already prepared and started manufacturing the new vaccines even before they were fully tested and approved at their own risk, i.e. if the vaccine candidate would not have successfully gone through the development phases, it would have been a vain effort. The logistics of the distribution and administration of the vaccines to the population in every country was a tremendous effort facilitated by governments and local health systems.

4.3 A First Look at the Data: Share Prices over the Long and Medium Run

In this section we carry out an exploratory, descriptive analysis in order to ascertain the general profiles and long and medium run trends over time of a group of pharmaceutical companies. In particular, we focus on the publicly traded Covid-19 vaccine manufacturers. We compare these companies with the top 10 pharmaceutical companies (according to their revenues in 2020) in order to ascertain i. whether they have experienced a better behavior in the stock market and ii. the impact on their share prices of some of the most relevant landmarks of the pandemic since it started in December 2019.

As of April 20, 2022 10 vaccines have been granted emergency use by WHO (WHO, 2022)[5]. Six of them are produced by publicly traded pharmaceutical or biotechnological companies: *Nuvaxovid* from Novavax, *Spikevax* from Moderna, *Comirnaty* from Pfizer, *Ad26.COV2.S* from Johnson & Johnson/Janssen, *Vaxzevria* from Oxford/AstraZeneca and *Covilo* from Sinopharm.

Two of these six manufacturers, Pfizer and Johnson & Johnson, belong to the top 10 pharmaceutical companies according to revenues in 2020 (see Table 4.1).

Johnson & Johnson is a US manufacturer of medical devices, pharmaceuticals and other consumer goods, ranking 36 on the 2021 Fortune 500 list of largest U.S. companies corporations by revenue. Janssen Pharmaceuticals is the pharmaceutical arm of J&J. At the beginning of the Covid pandemic J&J committed around $1 billion into a vaccine. In the first quarter of 2021 vaccine sales reached $100 million (Berkeley Lovelace, Jr. 2022), less than 1% of the total revenue.

Founded in 1849 in New York, Pfizer is a large pharmaceutical firm with ample expertise in the development and manufacturing of drugs. In recent years it has undergone a restructuration, whereby the company is focusing on the development of new compounds. The company has designed and produced the Covid-19 vaccine in collaboration with BioNTech, a German biotech company.

AstraZeneca is a British-Swedish pharmaceutical and biotechnological company, the result of the 1999 merger between the Swedish Astra AB and the British Zeneca Group. It is one of the world´s largest pharmaceutical companies. AstraZeneca developed the COVID-19 vaccine in United Kingdom jointly with Oxford University. This vaccine has side effects in younger individuals which, although rare, have prompted several countries to limit its use to the elderly population

Moderna was founded in 2010 in Cambridge (Mass). The covid vaccine is the first product of the company with approval from regulatory agencies. Since Moderna had no previous expertise in marketing vaccines, the collaboration with NIH might have been key for its success.

Novavax is a small US biotechnological firm, with previous work on vaccines for respiratory syndrome (MERS), SARS and Ebola. Anyhow, the company has not brought to the market any product yet. Novavax was the first company to announce the development of a vaccine for Covid, as early as January 21, 2020. This attracted investment from private investors and the government. In February 2021 Novavax issued a press release announcing a 95,6% efficacy of the Covid vaccine, according to Phase III clinical trials. However, the company did not provide at that time underlying data or publications about the results of Phase III[6]. Their production plans experienced a delay,

5 In May 2022 a new vaccine from CanSinoBIO was granted the emergency use by WHO; therefore the total number of vaccines approved at this point (early October 2022) is 11.

6 In October 2021 Novavax produced a preprint showing a 90% efficacy in Phase III clinical trials in US and Mexico.

maybe because of lack of expertise in massive production. It has been argued that the Novavax vaccine arrived to the market too late, when middle-high income countries had already purchased their samples (Tinari and Riva, 2021).

Table 4.1. Top 10 pharmaceutical companies by revenues in 2020

Company	Total revenues in 2020 (US$ billion)
1. Johnson & Johnson	56.10
2. Pfizer	51.75
3. Roche	49.23
4. Novartis	47.45
5. Merck & Co.	46.84
6. GlaxoSmithKline	44.27
7. Sanofi	40.46
8. AbbVie	33.26
9. Takeda Pharmaceuticals	30.52
10. Shanghai Pharmaceuticals Holding	26.69

Top 10 pharmaceutical companies by revenues in 2020 – Source: https://www.pharmaceutical-technology.com/features/top-ten-pharma-companies-in-2020/

Our sample in this section, therefore, is made up by the top 10 pharmaceuticals plus the four vaccine manufacturers not included in top 10 by revenues (see Appendix 2).

We have gathered the historical monthly share price data from Yahoo Finance (https://finance.yahoo.com) to track the evolution of each company taking into account the share value at the beginning of the month. In this section we focus on two subperiods: the first one goes from July 2011 to December 2021; the second, from the start of the pandemic in December 2019 to December 2021.

We have considered the share price in the primary stock market of operation for each company (Table 4.2). To facilitate the comparison, we have converted the currency of origin to US$ when necessary. Also for comparison purposes we index the shares price to 100 at the beginning of both subperiods.

Table 4.2. Companies and main stock markets of operation

Company	Main stock market and currency
Johnson & Johnson	NYSE - US$
Pfizer	NYSE - US$
Roche	Swiss Stock Market – CHF
Novartis	NYSE - US$
Merck & Co.	NYSE - US$
GlaxoSmithKline	LSE – GBP
Sanofi	Paris Euronext - EUR
AbbVie	NYSE - US$
Takeda Pharmaceuticals	NYSE - US$
Shanghai Pharmaceuticals Holding	Shanghai Stock Exchange – CNY
AstraZeneca	LSE – GBP
ModeRNA	Nasdaq - US$
Novavax	Nasdaq - US$
Sinopharm	HKSE - HK$

AbbVie and Moderna did not trade publicly for the whole period of analysis, so we have considered their shares value since February 2013 for the first company and since January 2019 for the second.

4.3.1 Results for 2011-2021

Figures 1-3 display the performance from July 2011 to December 2021 of the top 10 pharmaceutical companies. We include also the Dow Jones for comparison.

In general Pfizer, Roche, Merck & Co, Novartis (until 2016) and AbbVie perform better than the Dow Jones. Moderna quotes below the Dow Jones until 2020 while AstraZeneca does slightly better since 2020.

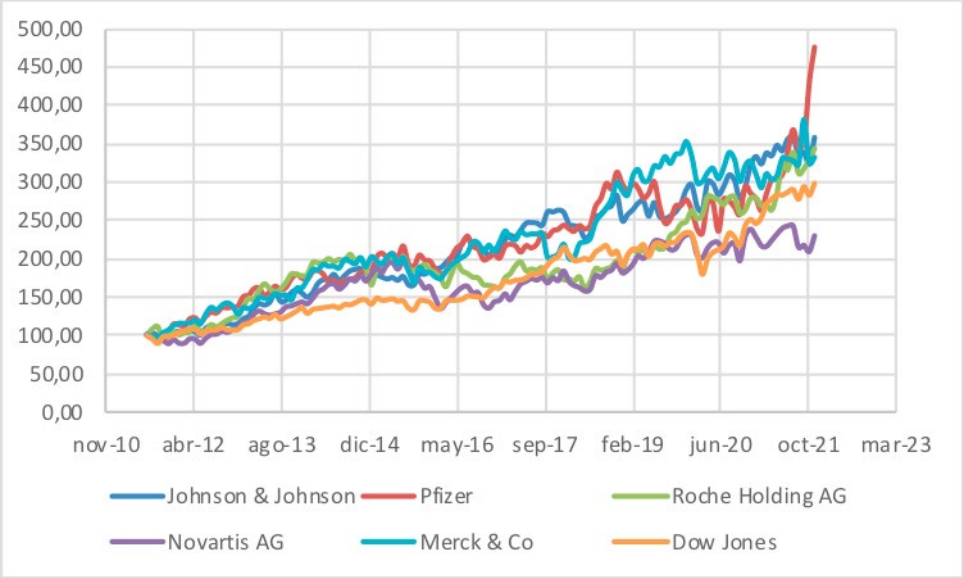

Figure 4.1. J&J, Pfizer, Roche, Novartis and Merck vs Dow Jones, Jul 2011-2021

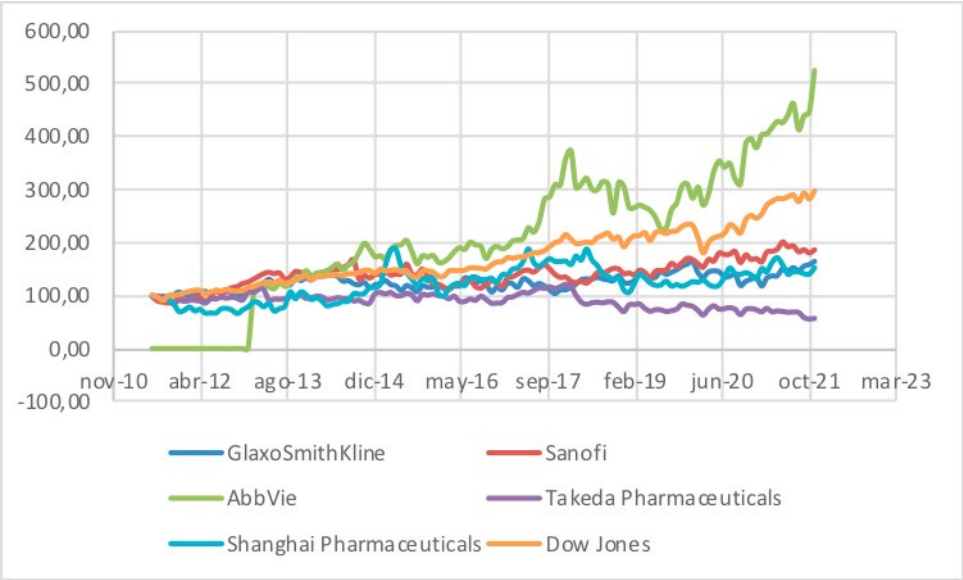

Figure 4.2. GSK, Sanofi, AbbVie, Takeda and Shanghai Pharmaceuticals vs Dow Jones, Jul 2011-2021

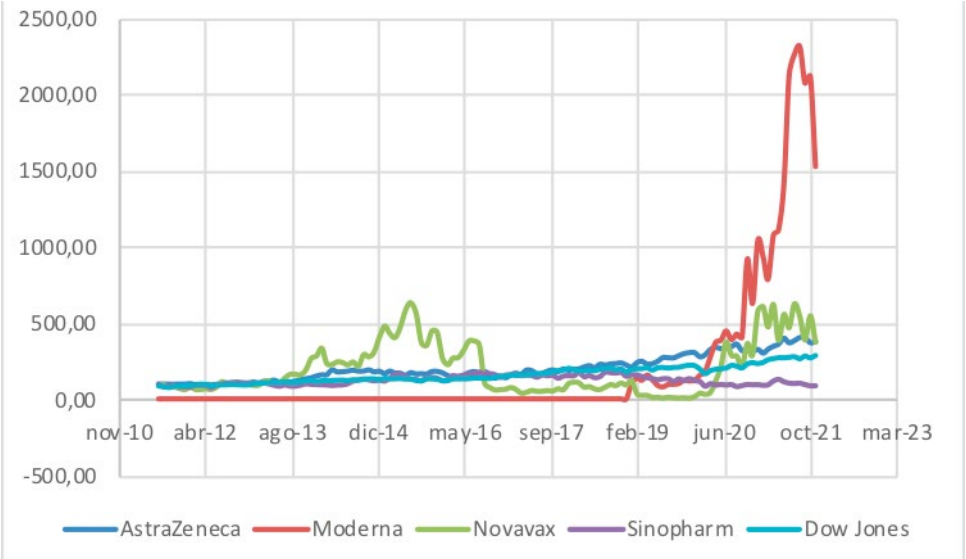

Figure 4.3. AstraZeneca, Moderna, Novavax and Sinopharm vs Dow Jones, Jul 2011-2021

4.3.2 Changes in Value over the Pre-Pandemic Period (July 2011 – December 2019)

Table 4.3 summarizes the total increase in the share value of top pharmaceutical companies since July 2011 to December 2019. To ease the comparison we have indexed the share value in July 2011 to 100. The behavior has not been homogeneous. While most firms registered positive increases until December 2019 (month in which the first cases of Covid-19 infection were reported in China), there is one company, Takeda Pharmaceuticals, whose share value decreased by 18% in the period July 2011-Dec 2019. Other companies from the top 10, as Shanghai Pharmaceuticals, GSK, Sanofi and Novartis, showed positive increases during this period but lower than the Dow Jones (DJ) average increase which was 135%. The largest increases in share values over this period correspond to Merck (351,43%), AbbVie (310%), J&J (288,8%) and Pfizer (276,66%).

The other companies considered in this analysis, i.e. the four manufacturers of Covid-19 vaccines that do not belong to the top 10 pharma companies (AstraZeneca, Moderna, Novavax and Sinopharm) also had a heterogeneous behavior before the pandemic started. The share value of the only traditional company in this group, AstraZeneca, performed better than the Dow Jones average (with a growth over the period of the share value of 203%), while the other three had modest increases, significantly smaller in any case than the Dow Jones index. It must be taken into account that Moderna is only trading publicly since January 2019, i.e. 11 months before the first cases of the pandemic were reported. Its share price experienced a decreasing trend in mid-2019 and recovered thereafter. It is remarkable that the share value of Novavax grew quite significantly

until 2015, but it decreased between 2015 and 2019. Novavax actually was the worst performing company of the group in terms of share value, with a decrease of 89% between July 2011 and December 2019. This explains its high standard deviation during this period.

Table 4.3. Total increase in value, top companies and Dow Jones, July 2011-December 2019

	Stock value jul-11	Stock value Dec-19	Growth Jul 11-Dec 19	Average monthly growth	Standard deviation
Johnson & Johnson	100,00	288,80	189%	189,07	56,17
Pfizer	100,00	276,66	177%	197,98	53,86
Roche Holding AG	100,00	248,46	148%	172,25	35,02
Novartis AG	100,00	229,34	129%	154,28	35,87
Merck & Co	100,00	351,43	251%	198,63	61,35
GlaxoSmithKline	100,00	160,74	61%	122,54	13,15
Sanofi	100,00	171,11	71%	133,40	19,17
AbbVie	NA	310,54	211%	210,39	66,23
Takeda Pharmaceuticals	100,00	82,21	-18%	95,27	11,19
Shanghai Pharmaceuticals	100,00	121,31	21%	117,34	32,65
AstraZeneca	100,00	302,98	203%	168,38	50,51
Moderna	NA	117,83	18%	111,66	22,38
Novavax	100,00	10,64	-89%	170,26	147,39
Sinopharm	100,00	141,94	42%	134,08	32,19
Dow Jones	100,00	235,02	135%	154,88	39,37

Note: Total increase of share value per company and Dow Jones between July 2011 and December 2019 with total growth in this period (%), average monthly growth and standard deviation. Own elaboration.

4.3.3 Results for 2019-2021

Figure 4.4-4.6 display the behavior of the selected companies and the Dow Jones from December 2019 to December 2021. Most of the pharmaceutical firms trade below the Dow Jones, except for Pfizer and Roche over the whole subperiod and AbbVie and Shanghai until June 2021. Moreover, the biotechnologicals Novavax and Moderna exhibit a remarkable performance, outperforming the Dow Jones since the beginning of the pandemic.

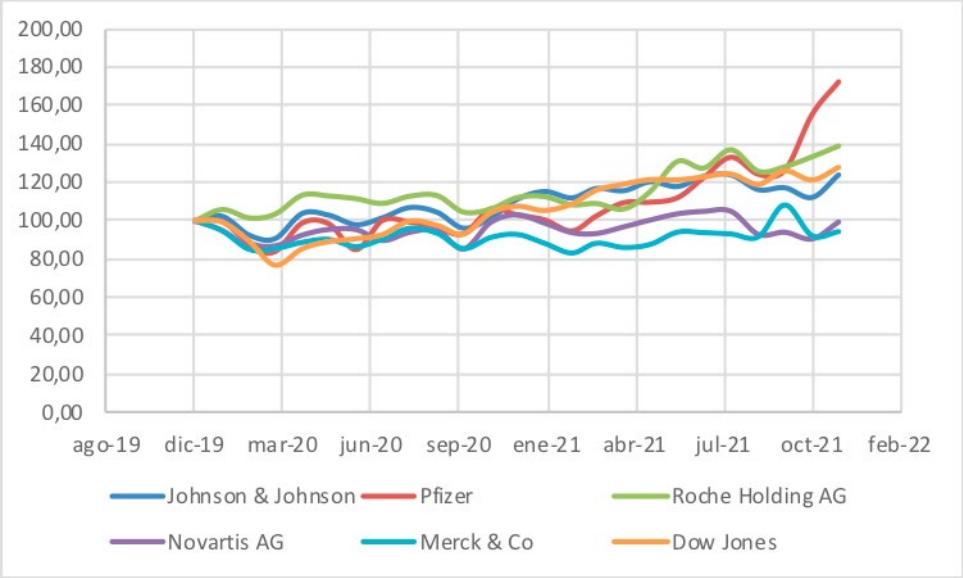

Figure 4.4. J&J, Pfizer, Roche, Novartis and Merck vs Dow Jones, Dec 2019-2021

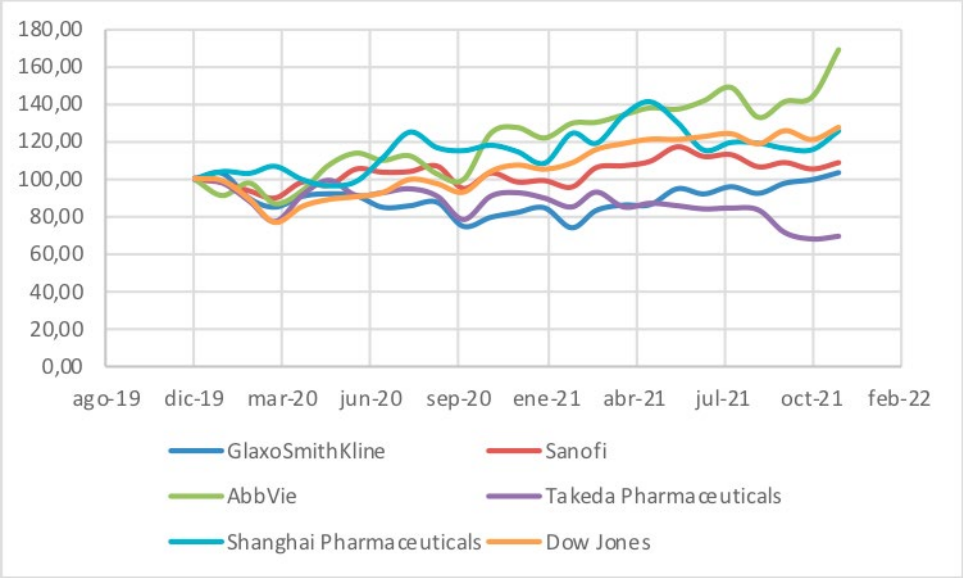

Figure 4.5. GSK, Sanofi, AbbVie, Takeda, Shanghai Pharmaceuticals vs Dow Jones, Dec 2019-2021

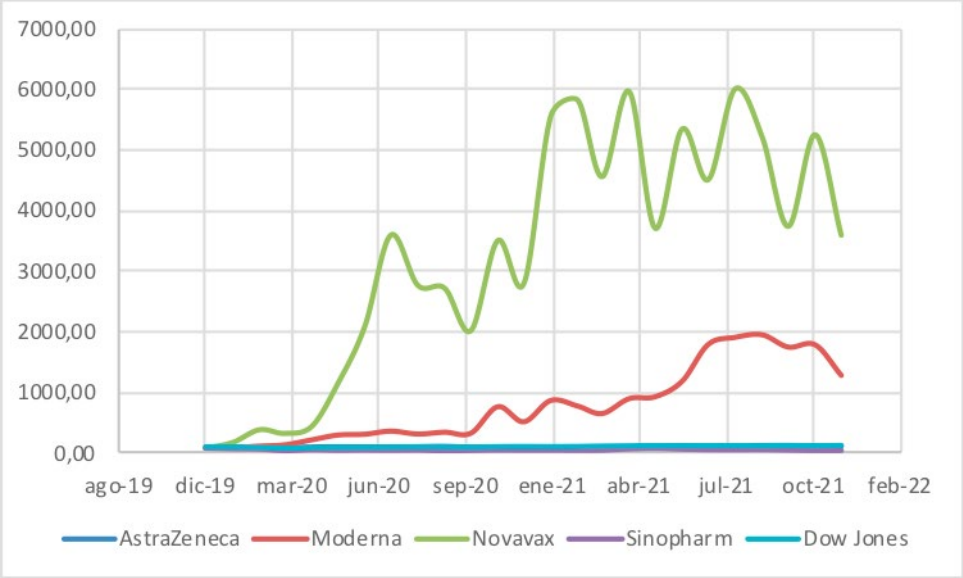

Figure 4.6. AstraZeneca, Moderna, Novavax & Sinopharm vs Dow Jones, Dec 2019-2021

4.3.4 Changes in Share Values over the Pandemic (December 2019 – December 2021)

The pandemic affected the share value of the top 10 big pharmas differently as expected. While most of them displayed a positive behavior, the share value of Novartis, Merck and Takeda decreased over time. The average growth of the Dow Jones in this period was 27%, which is remarkable. Some big pharma companies, as Pfizer, Roche and AbbVie, behaved even better (the growth of the share value was 72% for Pfizer, 38% for Roche and 69% for AbbVie).

The two Covid-19 vaccine manufacturers of the top 10 group had a different behavior. The growth of J&J was 24% -just below the DJ index- while Pfizer´s growth was well above, 72%.

Regarding the Covid-19 vaccine manufacturers which are not among the top ten big pharmas, the share price of AstraZeneca grew slightly below the DJ average (24 vs 27% respectively) and that of Sinopharm slightly above the DJ index (36 vs 27% respectively). The cases of Moderna and Novavax are impressive as their share value growth in this period were 1,198% and 3,495% respectively.

Table 4.4. Total increase in value of top 10 companies, Covid vaccine manufacturers and Dow Jones, December 2019-December 2021

	dec-19	dec-21	Total growth	Average monthly growth	Standard deviation
Johnson & Johnson	100,00	123,50	23,50%	108,73	9,85
Pfizer	100,00	171,81	71,81%	108,30	20,87
Roche Holding AG	100,00	138,30	38,30%	114,94	11,24
Novartis AG	100,00	99,57	-0,43%	96,12	5,46
Merck & Co	100,00	94,18	-5,82%	91,07	5,44
GlaxoSmithKline	100,00	103,06	3,06%	89,42	7,77
Sanofi	100,00	109,19	9,19%	103,69	6,70
AbbVie	100,00	169,13	69,13%	121,70	20,90
Takeda Pharmaceuticals	100,00	69,08	-30,92%	86,48	8,64
Shanghai Pharmaceuticals	100,00	125,37	25,37%	115,03	11,23
AstraZeneca	100,00	123,68	23,68%	112,03	11,56
Moderna	100,00	1298,47	1198,47%	802,98	630,16
Novavax	100,00	3594,72	3494,72%	3254,53	1983,70
Sinopharm	100,00	63,68	-36,32%	73,82	10,82
Dow Jones	100,00	127,33	27,33%	106,05	14,68

Note: Total increase of share value per company and Dow Jones between December 2019 and December 2021 with total growth in this period (%), average monthly growth and standard deviation. Own elaboration.

These results suggest a different behavior of the share value of traditional big pharmaceutical companies which invested on the development of a Covid-19 vaccine (Pfizer, J&J, AstraZeneca and Sinopharm) and of small/non-traditional Covid-19 manufacturers (Moderna and Novavax).

The share price of Pfizer, J&J, AstraZeneca and Sinopharm increased since the start of the pandemic; however, these companies have other products in the market[7]. Thus this performance should not be seen as a sole consequence of the investment in a Covid-19 vaccine and the associated expectations. In other words, the development of vaccines t does not seem to be a definitive factor that made the companies outperform behave better than the Dow Jones or their competitors.

7 In 2020 the financial results of Pfizer could have been negatively affected by the decrease in the demand for treatments other than Covid. The spinoff of Upjohn (its generic line of business), which later on merged Mylan, could also have had an unfavourable impact on its share value.

The situation of Moderna and Novavax is quite different than the aforementioned traditional companies. In their case being a Covid-19 manufacturer has clearly had a large impact on the company share value.

The event study discussed in the next section complements this analysis and sheds some light on this issue.

4.4 Event Study

4.4.1 Theoretical Framework

In this section of the paper we discuss the results of an event study. The event study is a widely used methodological tool which formally examines market reactions to information events, in the form of excess or abnormal returns (AR). Information events may be market-wide or firm specific. The underlying assumption is the efficiency of financial markets whereby new information quickly translates to stock prices. Excess returns are usually computed with respect to an index of the stock market.

More formally, we define the return in t of firm j as

$$R_{jt} = \frac{P_{jt} - P_{jt-1}}{P_{jt-1}} 100 \quad (1)$$

Where P_{jt} is the price of the stock of firm j in t.

We compute the excess returns (ER) for each firm j in time t according to equation (2):

$$ER_{jt} = R_{jt} - \beta_j R_{mt} \quad (2)$$

Where ER_{jt} is the excess return for firm j in time t, R_{jt} is the return for company j at t, R_{mt} is the return for the market at t and b_j the correlation between the return of j and the return of the market at t. b_j is estimated by OLS over the estimation window. Notice that our baseline model to compute the excess return is the market or Single Index Model (Brenner, 1979; Sorokina, Booth and Thorton, 2013), the most widely accepted model (Armitage, 1995), in accord with Alcaide et al. (2020) and Zhang (2021) who employ this model as well. Its main drawback is that it assumes a constant risk-free rate, but this is not very problematic for this investigation because it is likely to affect the pharmaceuticals and the market similarly.

Define an event window as the time between t_1 and t_2. Equation (3) provides the CAAR or cumulative average abnormal returns over the event window:

$$CAAR_j(t_1, t_2) = \sum_{t=t_1}^{t_2} AR_{jt} \qquad (3)$$

For $t_1 < t_2$.

Next, statistic tests (parametric and no parametric) may be computed to check if excess returns for the event window are zero (usually the null hypothesis) or significantly different from 0. Parametric tests assume that AR follow a normal distribution while non parametric tests are not grounded on this analysis.

4.4.2 Model Specification

We consider for the event analysis nine pharmaceuticals quoted in the NYSE. They are chosen based on their market capitalization. Six of them belong to the top 10 (as detailed in Table 4.1); we have added the other three vaccine developers not in the top 10: Moderna, Novavax and AstraZeneca. We work only with companies operating in NYSE or Nasdaq to ease comparisons -although they might not be the main stock market where they operate- and eliminate other potential influences on the share value linked to idiosyncratic features of other countries. The focus on US stock markets seems appropriate since they are the primary markets for four vaccine developers, Pfizer, Moderna, J&J and Novavax. Sinopharm, however, is excluded from the sample because it is not traded in NYSE or Nasdaq.

We capture the performance of the stock market with the Dow Jones. We work with closing prices.

We measure time in days. We work with a time-symmetric event window of three days before and after the event (-3,3). We consider the three days previous to the event to account for potential leaks of information and the three days after to include potential delays. We use a small window to disentangle and isolate the impact of different causes of price variations and distinguish between factors, partially at least. Furthermore, new information reflects into prices very quickly, especially so if related to Covid vaccines; these news travelled especially fast because of the stress posed by the pandemic. Hwang (2013) employs an event window of two trading days before the event date and one day after.

To compute the correlation between individual stocks and the market we define an estimation window which starts on June 6, 2019 and ends one month before the event. Hence we prevent the overlapping of the estimation window and the event window.

We distinguish two types of events and hence two subperiods: the first focuses on the expansion of the pandemic and the Covid announcements and covers the first five months of the pandemic. The second expands around the completion and approval of vaccines, from November 2020 to April 2021.

4.4.3 Covid Announcements

We have selected 10 relevant events over the first months of the pandemic related to different announcements of news on Covid with big media impact. Five of these events represent advancements in the fight with the pandemic, as a potential vaccine and a treatment for Covid and aid packages. Six events are associated to the expansion of Covid, travel restrictions, new deaths and the delay in Olympics (there is one day with a positive and a negative event). Table 4.5 details the cumulative average abnormal returns for top pharmaceuticals and vaccine developers corresponding to these events.

Table 4.5. Cumulative average abnormal returns, top pharmaceuticals and vaccine developers, January-June 2020

	21/1	14/2	25/2	29/2	8/3	13/3	24/3	01/5	11/5	27/5
Pfizer	0.71	**-4.97***	4.55	**8.53*****	4.78	**11.81*****	**-10*****	2.6	0.34	**-8.5****
P value	0.81	0.08	0.17	0.001	0.11	0.0036	0.002	0.48	0.93	0.03
Moderna	5.72	**-24.7*****	**47.8*****	**15.87****	-1.98	**46.43*****	-13.02	-0.01	**24.95***	-18.33
P value	0.52	0.005	0	0.048	0.83	0.0001	0.19	0.99	0.07	0.18
J&J	1.48	-2.68	-3.84	-0.4	2.78	**7.47****	-13.52	-3.03	-0.13	-3.66
P value	0.63	0.36	0.25	0.88	0.35	0.039	0	0.37	0.97	0.34
AbbVie	-5.21	-1.35	5.63	3.95	**10.42****	2.39	-6.87	2.23	6.32	-4.34
P value	0.32	0.78	0.31	0.37	0.04	0.69	0.18	0.65	0.20	0.38
AstraZeneca	-2.51	-3.26	-5.48	2.95	3.93	-3.76	1.87	**5.83***	0.6	-1.38
P value	0.45	0.31	0.14	0.31	0.24	0.35	0.56	0.09	0.87	0.72
Merck	-4.43	-4.41	2.4	3.91	**8.93*****	3.58	**-5.3***	**-7.13****	3.76	0.2
P value	0.16	0.14	0.49	0.15	0.005	0.35	0.09	0.026	0.28	0.96
Novartis	-0.4	-1.59	**-8*****	0.09	**4.26***	1.35	0.75	-3.3	0.32	-2.28
P value	0.87	0.5	0.0034	0.97	0.08	0.65	0.75	0.2	0.9	0.42
Sanofi	-4.51	-1.89	-0.81	3.3	1.7	5.17	-4.66	-1.49	-2.15	0.29
P value	0.16	0.58	0.83	0.28	0.63	0.22	0.19	0.67	0.56	0.94
Novavax	**67.97*****	13.69	**63.4*****	**35.39****	-14.6	-17.67	29.01	-22.18	**74.66*****	-6.09
P value	0.0001	0.38	0	0.015	0.5	0.51	0.19	0.35	0.002	0.8
Expected sign of event	+/-	-	+	-	-	+	-	+	+	-

Notes: CAARs in per cent. window: (-3, 3). Model: SIM. Diagnostic test: normality. *: significant at 90%. **: significant at 95%. ***: significant at 99%.

On January 20 a report from WHO confirmed the existence of Covid cases in Japan, South Korea and Thailand. Moreover, China reported 139 new cases of the disease and a third death. On January 21 Novavax announced the ongoing development of a vaccine for the coronavirus. January 21 is the first day of market operation after this announcement (on January 20 the NYSE market was closed due to the Martin Luther King commemoration). On that date Novavax experienced a high CAAR, of almost 68% and statistically significant. No other share price was significantly affected, which implies that the information from China and WHO did not impact the share value of pharma companies, whereas the Novavax announcement about the vaccine did raise the expectation of investors about this company achieving solid financial results.

On February 14 the market reacted negatively to the first death from Covid-19 in Europe, a Chinese tourist visiting France (Heyden and Heyden, 2021). Moderna experienced a negative and significant CAAR of almost 25%. The rest of the firms in the sample registered negative CAARs, although non-significant. The exception is again Novavax, with positive (but again not statistically significant) abnormal returns.

On February 25 the NIH announced the start of clinical trials of the antiviral drug remdesivir in adults diagnosed with coronavirus. Remdesivir was developed by Gilead and first used in 2009 against Ebola. Pfizer announced an alliance with Gilead to manufacture the drug on August 7, 2020. Moderna and Novavax registered positive and significant CAARs of 48 and 63.43%, respectively while Novartis suffered a small fall.

On February 29 a patient died of coronavirus in the Seattle area (state of Washington). For almost two months, this is considered the first Covid-19 death in United States, until autopsy results announced April 21 revealed two earlier deaths in California. Pfizer registered a positive and significant CAARs of 8,53%, and Moderna and Novavax got as well positive and significant CAARs, although smaller than those of February 25.

March 8 saw travel restrictions in Italy, with positive and significant abnormal returns for AbbVie, Merck and Novartis.

On March 13 President Trump announced a 50 billion dollars package of resources to fight the pandemic, with positive and significant reactions for Pfizer, Moderna and J&J (but not for Novavax).

March 24 was the day of the announcement of the delay of the Olympics until 2021. Pfizer suffered a big fall which led to a significant CAAR of -10%.

FDA authorized remdesivir on May 1. On this date Astra Zeneca and Merck registered a positive and negative CAAR, respectively.

On May 11 the Trump administration announced a 11 billion dollars package for Covid Testing. Moderna and Novavax exhibited positive and significant CAARs, of 24% and almost 75%, respectively.

Data about more than 100.000 deaths in US due to Covid 19 were disclosed on May 27. Regarding the shares of the firms in our sample, there was only a negative and significant CAAR for Pfizer.

Figure 4.7 summarizes this information by displaying the net sum of the significant CAARs detailed in Table 4.5 associated to these ten events for each company. This indicator can be understood as an approximation to the abnormal gains or losses induced by the first months of the pandemic. The company exhibiting the larger positive CAAR, and thus the bigger total gain in the first five months of the pandemic is Novavax, with 241,42%. Moderna is second, with 110,29%. The rest register only moderate variations, positive for AstraZeneca, AbbVie and J&J and negative for Novartis, Merck and Pfizer.

There is not a clear pattern of impact on companies by type of events. There are positive CAARs associated to news conveying both therapeutic advancements and the expansion of the virus. Aid packages though are linked to positive CAARs.

We can partially conclude, then, that in general the impact of Covid news on the share prices of pharma companies is moderate and perhaps lower than expected at the beginning of the pandemic, despite the large levels of volatility displayed by the US stock market over that period (Baker et al., 2020). There are only two companies experiencing high and significant CAARs, Novavax and Moderna. Donatelli et al. (2017) show that the impact of positive and negative investor sentiment triggered by diseases is larger on small pharmaceutical and biotechnological companies than on big biopharmas. One potential explanation, therefore, for the high CAARs of these small size companies is favorable investor sentiment towards them.

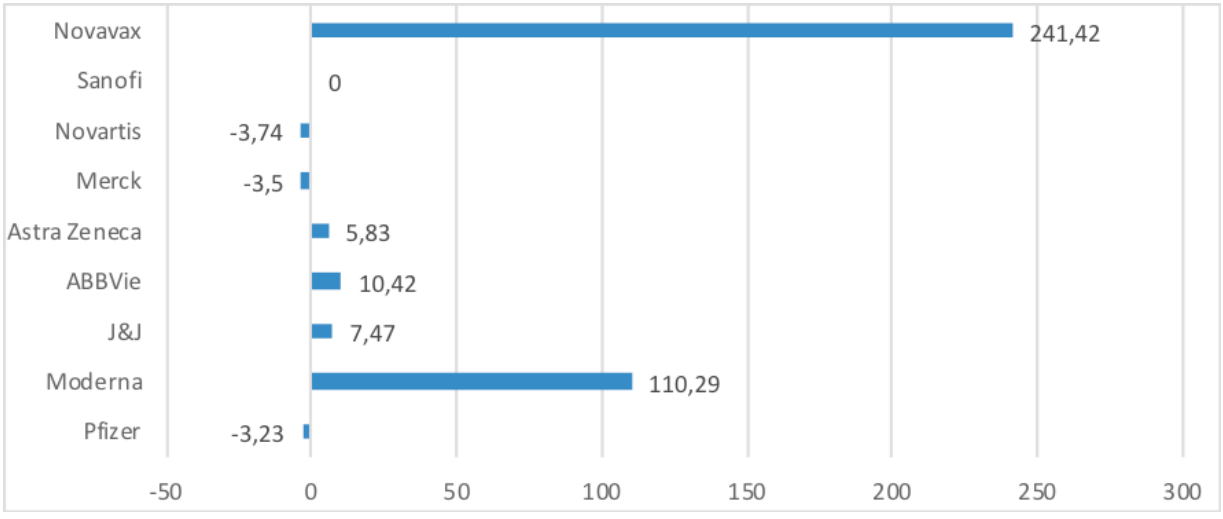

Figure 4.7. Net abnormal results (%), Covid-19 announcements

Note: Net abnormal results are computed as the sum of the CAARs displayed in Table 4.5. Only significant CAARs as considered.

4.4.4 Vaccine Landmarks

Next we consider some events linked to announcements related to Covid-19 vaccines.[8] Table 4.6 details the CAARs for the firms in our sample for several event windows linked to the development of vaccines.

On November 9 Pizer announced the excellent preliminary results of the Phase III clinical trials for its vaccine, with a 90% effectiveness. Pfizer, J&J, and Moderna registered positive CAARs, but none of them was significant. On November 11 Pfizer announced an agreement with the EU whereby the company would supply 200 million doses (the EU got also an option for 100 million additional doses).[9] No positive reaction was detected for Pfizer on that date; Moderna, however, did get a positive and significant CAAR of 28.55%. On Sunday November 15 an independent data and safety monitoring board overseeing the Phase III trials of the Moderna vaccine disclosed a preliminary review stating a 94% effectiveness. On November 16 Moderna enjoyed a 16,96% CAAR but it was not significant. No significant CAARs are found on that date for the companies in the sample. On November 18 Pfizer informed about the end of Phase III trials, with no repercussions, either, probably because they were anticipated by the market.

On November 25 Moderna announced an agreement with the European Union to sell 80 million doses of its vaccine, provided it received regulatory approval. This prompted large, positive and significant CAARs for this firm on November 25, 27 and 28 (on November 26 the market did not operate because of Thanksgiving). It seems that the news were leaked before the announcement of November 25 since on 23 and 24 November CAARs were positive and significant too.

Pfizer also exhibited positive and significant CAARs on November 25, 27 and 28, although smaller than those of Moderna. These dates brought about as well large and positive CAARs for Novavax, but they were not significant (the CAAR on November 24 could be considered as almost marginally significant, with a p value of 0.11). This suggests the presence of some interest still among the investors for Novavax, but considerably smaller than at the beginning of the pandemic.

Our hypothesis for the outcomes following the announcement of the Phase III results are as follows. Announcements from Pfizer and Moderna were close in time, only one week apart. Moderna, though, attracted more attention from investors than Pfizer because Pfizer displayed a more diversified sales composition and hence the estimated relative impact was larger for Moderna than for Pfizer.

8 In this subsection we focus on positive events because share prices are more correlated with development progress than with negative episodes (Zhang, 2013).

9 Agreements between the UE and J&J, AstraZeneca and Sanofi were already in place.

It is also possible that some investors reallocated their portfolios and shifted from Pfizer to Moderna on these days, since the share value of Pfizer experienced upward and downward fluctuations. Moreover, the announcement of the agreement between Moderna and the EU had positive spillover effects on Pfizer.

No positive effects are detected, however, either for Moderna or Pfizer around the dates of the FDA emergency approvals; this is in accord with Pérez-Rodríguez and Valcárcel (2012). Paradoxically Pfizer registered a negative and significant CAAR on December 11, the date of the Emergency Use Authorization by FDA for US. The Emergency Use Authorization for Moderna was issued on December 18. No significant CAARs for other companies in the sample are found on this date.

On January 6, 2021 the EMA approved the use of the Moderna vaccine in Europe. There are no companies with significant CAARs on that date, not even Moderna. It is thus feasible that the EMA authorization was already discounted by the stock market

On January 29 J&J and Novavax disclosed the results from the Phase III clinical trials, with 66% efficacy for J&J and 89,3% efficacy for Novavax. Novavax registered a large positive and significant CAAR of 71.9%. Instead, Astra Zeneca and Pfizer, with vaccines already in the market and therefore being competitors of J&J and Novavax, documented negative CAARs, marginally significant in the case of Astra Zeneca. The CAAR for J&J was negative but not significant. Novartis registered a negative and significant CAAR on that date.

On February 27**,** the FDA issues the Emergency Use Authorization in the US for the J&J vaccine but no significant CAARs are detected at that point, either, in line again with Pérez-Rodríguez and Valcárcel (2012).

We have also tested the impact on the US stock market of other announcements by EMA about Covid-19 vaccines. For example, on March 19 EMA issued recommendations about embolic and thrombotic events in the AstraZeneca vaccine. On April 7 the Safety Committee of EMA concluded that blood clots were rare side effects of the AstraZeneca vaccine. On April 20 EMA warned about potential clots in the J&J vaccine. No significant CAARs are detected on these dates, suggesting that the announcements by the European Regulatory Agency do not bring about noticeable effects in the US stock markets.

It follows from this analysis that the US stock markets correctly anticipated the success of Moderna and Pfizer (although proportionately smaller in the case of the second), channelling investment to these companies. Furthermore, over the end of 2020 and the beginning of 2021 markets progressively lost interest in Novavax. Finally, the shares of Astra Zeneca and Johnson and Johnson did not attract much attention, in line with the more discreet performance of their vaccines in the market.

Table 4.6. Cumulative average abnormal returns, top pharmaceuticals and vaccine developers, November 2020-April 2021

	9.11.20	10.11.20	11.11.20	12.11.20	16.11.20	19.11.20	23.11.20	24.11.20
Pfizer	0.69	-0.09	-0.9	1.09	1.79	-2.04	2.46	4.76
P value	0.86	0.98	0.82	0.78	0.65	0.60	0.53	0.22
Moderna	21.04	21.77	**28.55****	22.22	16.96	6.8	**28.04****	**51.09*****
P value	0.14	0.13	0.04	0.11	0.23	0.63	0.047	0.0003
J&J	3.56	3.52	3.93	1.42	1.6	-6.37*	-4.89	-2.83
P value	0.3	0.31	0.25	0.68	0.64	0.06	0.15	0.41
AbbVie	6.53	0.3	0.53	2.57	0.23	2.18	4.1	4.55
P value	0.15	0.95	0.9	0.57	0.96	0.63	0.36	0.31
AstraZeneca	5.67	-0.11	-2.16	-4.95	5.95	**-9.6****	-6.1	-3.46
P value	0.19	0.98	0.62	0.25	0.167	0.03	0.15	0.41
Merck	0.34	-3.32	-4.21	-2.16	1.6	-3.41	-3.11	-0.69
P value	0.92	0.36	0.24	0.55	0.65	0.34	0.38	0.85
Novartis	2.36	-0.84	-0.97	-1.19	2.76	0.43	2.64	4.97
P value	0.44	0.78	0.75	0.69	0.36	0.89	0.38	0.1
Sanofi	3.61	-3.09	-3.16	-1.54	0.35	-4.58	0.29	-1.82
P value	0.35	0.42	0.41	0.69	0.93	0.23	0.93	0.63
Novavax	-0.2	1.39	-11.38	-5.12	2.7	-8.93	23.48	37.21
P value	0.99	0.95	0.63	0.82	0.91	0.7	0.31	0.111

Notes: CAARs in per cent. window: (-3, 3). Model: SIM. Diagnostic test: normality. *: significant at 90%. **: significant at 95%. ***: significant at 99%.

Figure 4.8 summarizes the total impact of these events, employing the same methodology as in Figure 4.7. Only the value shares of Moderna, Novavax and (to a lesser extent) Pfizer register high and positive increases as a result of announcements about the vaccines.

It is interesting to notice, though, that the total impact on Moderna is much higher now than that of Novavax, suggesting that the stock markets gradually realized that the positive expectations about the Novavax vaccine were not going to materialize in the end.

AstraZeneca, instead, experiences a combined decrease of almost 25% while the value share of J&J falls 6,37%.

25.11.20	27.11.20	28.11.20	11.12.20	18.12.20	06.01.21	29.01.21	27.02.21	19.03.21	07.04.21	20.04.21
7.55*	**9.27****	**10.45*****	**-8.52****	-5.1	0.98	-6.1	2.41	3.09	0.96	3.56
0.052	0.017	0.004	0.029	0.2	0.80	0.14	0.52	0.44	0.81	0.37
38.87***	**35.21*****	**32.26****	-17.95	-20.14	1.92	8.3	-16.34	-12.44	2.74	5.06
0.006	0.012	0.013	0.2	0.15	0.89	0.56	0.21	0.38	0.84	0.72
-1.15	-0.48	2	0.21	1.12	0.14	-2.99	-2.1	2.8	-3.2	2.61
0.73	0.89	0.53	0.95	0.74	0.97	0.37	0.48	0.4	0.33	0.42
2.68	2.05	1.61	-1.52	-2.13	0.88	-3.16	0.79	-4.81	-1.98	3.84
0.55	0.65	0.7	0.73	0.64	0.85	0.49	0.84	0.28	0.65	0.38
-3.78	-5.64	-3.74	**-7.21***	-3.96	-1.68	**-7.68***	-4.1	1.69	-2.22	3.82
0.37	0.19	0.34	0.09	0.36	0.7	0.086	0.31	0.7	0.61	0.37
0.17	0.1	1.1	-3.43	-1.48	3.4	-4.24	-0.84	2.41	-2.34	1.43
0.96	0.97	0.74	0.32	0.68	0.34	0.22	0.79	0.48	0.49	0.67
2.76	3.05	4.02	-0.6	-3.1	-1.79	**-9.2*****	1.9	2.93	0.91	1.21
0.36	0.32	0.15	0.84	0.31	0.56	0.002	0.5	0.34	0.76	0.69
-1.48	-1.66	0.45	-6.16	0.8	-2.78	-5.37	-1.52	1.56	0.18	2.08
0.7	0.66	0.9	0.1	0.84	0.47	0.16	0.67	0.68	0.96	0.58
28.82	30.03	23.29	-7.36	-7.58	-8.62	**71.9*****	-32.06	-13.24	-10.06	-2.61
0.21	0.2	0.28	0.75	0.74	0.7	0.001	0.12	0.56	0.66	0.9

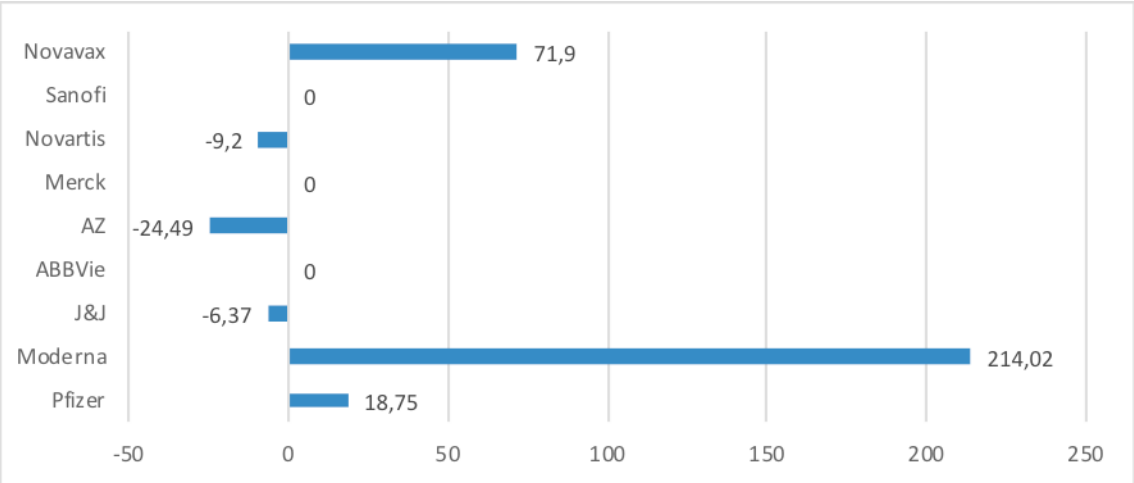

Figure 4.8. Net abnormal results (%), vaccine announcements

Note: Net abnormal results are computed as the sum of the CAARs displayed in Table 4.5. Only significant CAARs are considered.

4.5 Concluding Remarks

In this paper we analyze the performance of share prices of a group of pharmaceutical and biotechnological companies over some specific stages of the Covid pandemic.

Our investigation suggests that, except for Novavax and Moderna, pharma companies did not experience clear gains or losses due to the pandemic in its first five months.

As far as the information related to vaccines development is concerned, we find that results from Phase III clinical trials have had positive impacts on share prices in the cases of Pfizer and Moderna. Anyhow, the key event in terms of positive returns has been the order of 80 billion doses of vaccines placed by the EU to Moderna. Our results suggest that these announcements triggered large CAARs in the stock market for this biotechnological and for Pfizer. Instead, communications from the European regulatory agency do not seem to affect the US markets.

By and large, the analysis of share values suggests that biopharmaceutical firms have faced heterogeneous outcomes in the stock markets from their investment in vaccines. We can distinguish three main cases.

First, there are two instances of very successful strategies in vaccine development, one from a traditional pharma company, Pfizer, and another from a young biotechnological, Moderna. Stock markets have acknowledged these performances with positive reactions to their announcements and increases in the value of their shares, rather dramatic in the case of Moderna.

Two other traditional pharmaceuticals, Johnson and Johnson and Astra Zeneca, have been less successful. Their vaccines have been approved by regulatory authorities and marketed but achieved only modest results. The reaction of stocks markets to news from these companies has been small. One potential explanation for this fact is that the stock markets anticipated that the impact of the revenues proceeding from the vaccine on the total revenues would be limited as they had other products in their portfolio.

Finally, there is a biotechnology, Novavax, whose vaccine arouse great expectations at the beginning of the pandemic; its achievements, though, were ultimately disappointing. Stock markets reacted accordingly, and investors gradually adjusted their forecasts, triggering downward corrections in the price of the stock.

Technological factors, and in particular the adoption of mRNA technology, seems to have played an important role in the sound performance of Pfizer and Moderna regarding vaccine development. The thorough exploration of this issue, though, is left as an interesting avenue for future research.

APPENDIX 1

Main landmarks related to coronavirus pandemic

December 31, 2019 - Cases of pneumonia detected in Wuhan, China, are first reported to WHO. During this reported period, the virus is unknown. The cases occur between December 12 and December 29, according to Wuhan Municipal Health.

January 7, 2020 - Chinese authorities confirm that they have identified the virus as a novel coronavirus, initially named 2019-nCoV by WHO.

January 11, 2020 - The Wuhan Municipal Health Commission announces the first death caused by the coronavirus. A 61-year-old man, exposed to the virus at the seafood market, died on January 9 after respiratory failure caused by severe pneumonia.

January 20, 2020 - China reports 139 new cases of the sickness, including a third death. On the same day, WHO's first situation report confirms cases in Japan, South Korea and Thailand.

January 21, 2020. Novavax announces that it is developing a vaccine for the coronavirus.

January 30, 2020 - The United States reports its first confirmed case of person-to-person transmission of the coronavirus. On the same day, WHO determines that the outbreak constitutes a Public Health Emergency of International Concern (PHEIC).

February 2, 2020 - A man in the Philippines dies from the coronavirus -- the first time a death has been reported outside mainland China since the outbreak began.

February 11, 2020 - WHO names the coronavirus Covid-19.

February 14, 2020 - A Chinese tourist who tested positive for the virus dies in France, becoming the first person to die in the outbreak in Europe. On the same day, Egypt announces its first case of coronavirus, marking the first case in Africa.

February 25, 2020 - The NIH announces that a clinical trial to evaluate the safety and effectiveness of the antiviral drug remdesivir in adults diagnosed with coronavirus has started at the University of Nebraska Medical Center in Omaha. The first participant is an American who was evacuated from the Diamond Princess cruise ship docked in Japan.

February 25, 2020 - In an effort to contain the largest outbreak in Europe, Italy's Lombardy region press office issues a list of towns and villages that are in complete lockdown. Around 100,000 people are affected by the travel restrictions.

February 26, 2020 - CDC officials say that a California patient being treated for novel coronavirus is the first US case of unknown origin. The patient, who didn't have any

relevant travel history nor exposure to another known patient, is the first possible US case of "community spread".

February 29, 2020 - A patient dies of coronavirus in Washington state. For almost two months, this is considered the first death due to the virus in the United States, until autopsy results announced April 21 reveal two earlier deaths in California.

March 8, 2020 - Italian Prime Minister Giuseppe Conte signs a decree placing travel restrictions on the entire Lombardy region and 14 other provinces, restricting the movements of more than 10 million people in the northern part of the country.

March 9, 2020 - Conte announces that the whole country of Italy is on lockdown.

March 11, 2020 - WHO declares the novel coronavirus outbreak to be a pandemic. WHO says the outbreak is the first pandemic caused by a coronavirus. In an Oval Office address, Trump announces that he is restricting travel from Europe to the United States for 30 days in an attempt to slow the spread of coronavirus. The ban, which applies to the 26 countries in the Schengen Area, applies only to foreign nationals and not American citizens and permanent residents who'd be screened before entering the country.

March 13, 2020 - Trump declares a national emergency to free up $50 billion in federal resources to combat coronavirus.

March 24, 2020 - Japan's Prime Minister Shinzo Abe and International Olympic Committee (IOC) president Thomas Bach agree to postpone the Olympics until 2021 amid the outbreak.

March 25, 2020 - The White House and Senate leaders reach an agreement on a $2 trillion stimulus deal to offset the economic damage of coronavirus, producing one of the most expensive and far-reaching measures in the history of Congress.

April 8, 2020 - China reopens Wuhan after a 76-day lockdown.

April 28, 2020 - The US passes one million confirmed cases of the virus, according to Johns Hopkins.

May 1, 2020 - The US Food and Drug Administration issues an emergency-use authorization for remdesivir in hospitalized patients with severe Covid-19. FDA Commissioner Stephen Hahn says remdesivir is the first authorized therapy drug for Covid-19.

May 4, 2020 - During a virtual pledging conference co-hosted by the European Union, world leaders pledge a total of $8 billion for the development and deployment of diagnostics, treatments and vaccines against the novel coronavirus.

May 11, 2020 - Trump and his administration announce that the federal government is sending

$11 billion to states to expand coronavirus testing capabilities. The relief package signed on April 24 includes $25 billion for testing, with $11 billion for states, localities, territories and tribes.

May 23, 2020 - China reports no new symptomatic coronavirus cases, the first time since the beginning of the outbreak in December.

May 27, 2020 - Data collected by Johns Hopkins University reports that the coronavirus has killed more than 100,000 people across the US, meaning that an average of almost 900 Americans died each day since the first known coronavirus-related death was reported nearly four months earlier.

June 9, 2020: Publication of information on the agreement between AstraZeneca and Vanderbilt University for pairs of monoclonal antibodies.

June 11, 2020 - The US passes 2 million confirmed cases of the virus, according to Johns Hopkins.

Main landmarks related to vaccine developments

January 21, 2020. Novavax announces that it is developing a vaccine for the coronavirus.

July 27, 2020. The *Spikevax* vaccine developed by the NIH Vaccine Research Center in partnership with Moderna started Phase III clinical trials.

November 9, 2020: Pfizer announces that covid vaccine has 90% effectiveness, according to an efficacy analysis conducted by an external and independent group of experts, the Data Monitoring Committee, from the phase three clinical study.

November 16, 2020. Promising Interim Results from Clinical Trial of NIH-Moderna COVID-19 Vaccine, according to an interim analysis of an independent data and safety monitoring board overseeing the Phase III trials.

November 18, 2020. Pfizer and BioNTech announce the end of the Phase III study of COVID-19 vaccine candidate, meeting all primary efficacy endpoints.

November 25, 2020. Moderna announces that the European Commission is purchasing 80 million doses of its vaccine, contingent upon regulatory approval.

December 11, 2020: The FDA issues the Emergency Use Authorization in the US for the Pfizer-BioNTech vaccine

December 18, 2020: The FDA issues the Emergency Use Authorization in the US for the Moderna vaccine

December 21, 2020: The EMA approves the use of the Pfizer-BioNTech vaccine in Europe

December 30, 2020: The UK NHS approves the use of AstraZeneca/Oxford University vaccine in the UK

January 6, 2021: The EMA approves the use of the Moderna vaccine in Europe.

January 29, 2021: The EMA provides the marketing authorization for the AstraZeneca vaccine

February 27, 2021: The FDA issues the Emergency Use Authorization in the US for the Jansen vaccine (Johnson & Johnson).

March 19, 2021: EMA issues recommendations about embolic and thrombotic events in the AstraZeneca vaccine

April 7, 2021. The Safety Committee of EMA concludes that blood clots are rare side effects of the AstraZeneca vaccine

April 20, 2021: EMA warns about clots in the Jansen vaccine

June 7, 2022: Publication of the vote of the FDA Committee regarding the Novavax vaccine

APPENDIX 2

Top 10 pharmaceutical companies:

Top 10 pharmaceutical companies by revenues in 2020	Do they produce a Covid-19 vaccine?	Date in which the Emergency Use Listing (EUL) was granted by the WHO for their Covid-19 vaccine
1. Johnson & Johnson/Janssen	YES	12 Mar 2021
2. Pfizer	YES	31 Dec 2020
3. Roche	NO	Not applicable
4. Novartis	NO	Not applicable
5. Merck & Co.	NO	Not applicable
6. GlaxoSmithKline	NO	Not applicable
7. Sanofi	NO	Not applicable
8. AbbVie	NO	Not applicable
9. Takeda Pharmaceuticals	NO	Not applicable
10. Shanghai Pharmaceuticals Holding	NO	Not applicable

Other manufacturers with a Covid-19 vaccine validated by WHO:

	Date in which the Emergency Use Listing (EUL) was granted by the WHO for their Covid-19 vaccine
AstraZeneca	16 Feb 2021
ModeRNA	30 Apr 2021
Novavax	20 Dec 2021
Sinopharm	07 May 2021

Source: WHO (2022)

APPENDIX 3

Monthly evolution of the stock price, July 2011 – December 2021

	Johnson & Johnson	Pfizer	Roche Holding AG	Novartis AG	Merck & Co	GlaxoSmithKline	Sanofi	AbbVie
jul-11	100,00	100,00	100,00	100,00	100,00	100,00	100,00	NA
aug-11	101,56	98,60	107,79	95,52	96,98	97,27	91,76	NA
sep-11	99,18	92,87	110,73	91,13	95,81	99,51	89,63	NA
oct-11	100,27	101,17	94,02	92,27	102,30	99,99	88,04	NA
nov-11	100,78	105,42	97,87	88,43	106,01	102,83	90,25	NA
dec-11	103,07	114,81	104,05	93,42	111,79	107,78	97,35	NA
jan-12	103,59	113,54	100,03	88,82	114,84	103,28	92,87	NA
feb-12	102,28	112,11	102,99	89,07	114,54	102,24	92,98	NA
mar-12	104,58	121,42	103,82	94,59	115,23	104,61	98,55	NA
apr-12	103,22	122,76	114,70	94,18	119,06	106,74	97,64	NA
may-12	98,98	117,24	104,36	88,82	114,03	109,06	91,82	NA
jun-12	108,16	124,52	105,76	95,42	126,68	105,59	98,06	NA
jul-12	110,82	130,15	113,47	100,06	135,49	109,24	111,51	NA
aug-12	107,95	129,17	110,52	100,73	132,05	105,33	106,57	NA
sep-12	111,33	135,78	114,85	104,57	138,34	108,77	111,08	NA
oct-12	114,41	135,89	119,33	103,21	141,30	106,98	116,34	NA
nov-12	112,65	136,70	122,34	105,92	137,18	102,97	118,67	NA
dec-12	114,25	138,26	124,24	108,05	126,77	104,39	124,17	NA
jan-13	120,47	150,39	137,10	115,77	135,21	114,43	127,01	NA
feb-13	124,04	152,21	147,94	115,73	133,59	111,02	131,92	100,00
mar-13	133,94	160,49	146,41	126,23	138,18	113,77	137,28	110,46
apr-13	140,02	161,66	158,83	130,69	148,35	124,43	142,34	124,73
may-13	138,29	151,43	166,79	127,15	147,41	131,78	144,99	116,70
jun-13	142,11	157,06	160,48	125,29	146,62	125,67	142,54	113,01
jul-13	154,76	163,91	156,00	126,88	153,44	127,58	143,85	124,33
aug-13	143,02	159,48	160,30	129,31	150,64	123,84	132,42	117,55
sep-13	144,57	162,42	168,45	135,92	151,66	121,61	136,27	123,40
oct-13	154,44	173,50	179,45	137,41	144,93	134,12	146,51	133,66
nov-13	157,86	179,38	179,23	140,19	160,16	129,64	144,68	134,87
dec-13	153,81	174,50	177,39	142,42	160,87	134,70	143,67	147,00
jan-14	148,57	173,19	179,38	140,10	171,80	130,73	136,84	137,04

Takeda Pharmaceuticals	Shanghai Pharmaceuticals	AstraZeneca	Moderna	Novavax	Sinopharm	Dow Jones
100,00	100,00	100,00	NA	100,00	100,00	100,00
100,42	96,59	99,44	NA	98,93	82,71	95,64
98,42	92,27	98,84	NA	85,56	91,55	89,87
93,38	92,10	98,46	NA	84,49	94,57	98,45
85,00	84,85	99,44	NA	73,80	81,31	99,20
91,87	70,52	99,36	NA	67,38	82,46	100,61
90,29	72,77	102,02	NA	80,75	81,35	104,03
93,83	79,03	94,36	NA	67,91	93,39	106,66
91,67	71,69	98,63	NA	67,38	95,97	108,80
90,50	74,59	95,81	NA	72,73	90,07	108,81
86,54	67,46	94,08	NA	67,91	77,75	102,06
94,58	67,91	97,46	NA	83,42	94,27	106,07
94,75	67,74	104,01	NA	119,25	102,06	107,13
97,63	75,50	101,61	NA	109,09	110,26	107,80
96,21	76,39	106,22	NA	115,51	111,24	110,66
97,71	73,18	104,74	NA	112,30	116,61	107,85
95,63	66,72	107,98	NA	98,93	107,66	107,27
92,50	73,37	105,90	NA	101,07	108,55	107,91
107,08	79,11	112,51	NA	95,72	106,23	114,14
107,58	88,09	106,32	NA	97,33	109,59	115,74
113,54	87,24	116,54	NA	121,93	111,96	120,05
113,58	79,43	119,64	NA	125,67	103,10	122,21
92,38	85,42	124,46	NA	102,14	93,86	124,48
94,08	71,34	112,23	NA	109,63	87,13	122,78
93,83	75,97	119,37	NA	143,85	95,97	127,64
94,83	80,49	113,00	NA	168,45	88,00	121,96
98,83	106,92	119,50	NA	168,45	88,09	124,59
100,83	94,56	128,53	NA	165,78	95,14	128,02
101,46	107,00	133,94	NA	198,93	104,42	132,47
95,92	102,07	140,55	NA	273,80	100,80	136,51
96,79	93,02	151,72	NA	290,91	99,06	129,28

	Johnson & Johnson	Pfizer	Roche Holding AG	Novartis AG	Merck & Co	GlaxoSmithKline	Sanofi	AbbVie
feb-14	154,70	182,93	194,91	147,38	184,83	138,86	139,94	142,84
mar-14	166,14	184,51	194,09	155,72	184,12	137,33	143,40	144,21
apr-14	171,32	179,69	194,64	159,24	191,41	139,98	148,07	146,12
may-14	171,61	170,21	199,74	164,95	189,12	139,80	149,65	153,80
jun-14	178,19	172,01	196,14	165,81	189,09	137,36	150,71	159,77
jul-14	170,47	166,34	198,75	159,24	186,86	128,41	153,60	148,16
aug-14	176,67	171,84	196,92	164,55	197,96	129,50	159,64	157,67
sep-14	182,77	172,89	205,32	172,41	195,22	123,50	167,87	164,75
oct-14	184,81	175,11	197,79	169,77	192,20	121,65	132,50	181,00
nov-14	185,62	182,13	199,68	177,02	200,36	125,86	138,83	198,85
dec-14	180,47	183,70	186,47	169,71	188,39	115,97	134,65	188,04
jan-15	172,83	184,29	165,48	178,40	201,48	121,28	140,95	173,42
feb-15	176,92	202,40	185,90	187,55	195,66	124,13	141,57	175,15
mar-15	174,84	206,98	186,47	180,61	192,12	129,73	147,31	169,48
apr-15	172,40	201,86	191,58	191,73	200,68	122,14	139,99	187,20
may-15	174,04	206,74	203,61	193,48	205,16	119,59	141,90	194,38
jun-15	170,61	201,14	190,41	185,21	191,82	110,99	142,25	196,13
jul-15	175,43	216,31	202,32	195,40	200,17	120,24	160,19	204,37
aug-15	164,52	193,28	187,27	183,10	182,82	115,46	142,23	183,53
sep-15	164,67	189,89	184,28	173,12	167,68	108,40	140,50	160,01
oct-15	178,22	204,46	188,76	170,32	187,17	119,51	150,90	175,12
nov-15	178,59	198,11	191,90	160,54	181,52	116,82	137,12	172,58
dec-15	182,53	196,73	185,23	162,05	180,87	117,65	122,73	175,82
jan-16	185,59	185,82	181,18	146,85	175,01	120,04	122,89	162,94
feb-16	186,96	180,82	173,26	133,93	173,42	114,36	117,34	163,78
mar-16	193,67	182,45	163,16	141,75	182,74	112,96	113,48	171,31
apr-16	200,61	201,35	179,54	148,66	191,07	119,24	121,43	182,94
may-16	201,70	213,60	193,89	155,58	196,01	119,85	124,76	190,55
jun-16	218,66	218,68	183,84	161,45	200,72	134,67	128,56	187,46
jul-16	225,75	229,11	180,36	162,92	206,04	130,58	130,22	200,54
aug-16	215,13	216,13	175,62	154,14	220,55	125,94	118,42	195,79
sep-16	214,37	212,11	174,41	154,51	219,21	128,54	115,78	192,65
oct-16	210,49	198,58	165,76	138,97	207,77	122,56	122,44	170,38
nov-16	201,98	201,27	164,85	134,55	216,51	107,96	128,86	187,42
dec-16	210,52	205,43	163,25	142,53	208,30	117,36	125,50	193,03

Takeda Pharmaceuticals	Shanghai Pharmaceuticals	AstraZeneca	Moderna	Novavax	Sinopharm	Dow Jones
100,00	96,05	159,61	NA	342,25	97,55	134,41
98,75	90,34	159,78	NA	242,25	96,19	135,53
93,13	81,01	191,08	NA	234,22	92,42	136,54
94,42	83,38	178,67	NA	251,87	95,36	137,67
96,88	85,38	179,97	NA	247,06	97,17	138,57
95,25	89,12	183,36	NA	232,09	105,15	136,40
95,13	89,96	189,37	NA	250,80	124,48	140,81
90,58	103,66	183,23	NA	222,99	130,49	140,35
91,87	102,71	184,03	NA	299,47	139,33	143,21
86,92	104,59	191,22	NA	285,56	132,89	146,82
86,42	115,18	178,82	NA	317,11	126,32	146,77
104,50	115,08	182,62	NA	417,65	130,46	141,35
107,00	121,93	167,62	NA	489,30	124,84	149,32
104,33	155,56	183,24	NA	442,25	145,65	146,39
107,04	183,63	171,16	NA	413,37	169,81	146,92
101,13	186,75	169,81	NA	481,28	170,27	148,32
100,92	154,21	157,12	NA	595,72	158,53	145,10
105,38	143,05	173,33	NA	644,92	138,61	145,68
102,25	130,94	165,30	NA	575,94	136,52	136,11
91,13	118,98	166,78	NA	378,07	126,06	134,11
103,21	132,15	164,46	NA	360,96	149,31	145,46
101,83	128,11	180,76	NA	457,75	151,41	145,92
104,29	135,19	181,72	NA	448,66	144,66	143,50
100,92	103,79	171,97	NA	275,40	126,49	135,60
99,54	99,90	154,17	NA	233,16	131,69	136,01
95,08	113,48	145,87	NA	275,94	162,91	145,64
99,83	121,20	150,00	NA	280,21	154,77	146,37
89,88	122,68	156,10	NA	325,67	167,06	146,48
89,75	119,12	172,92	NA	388,77	171,74	147,65
94,46	132,98	180,10	NA	391,44	176,89	151,79
91,96	134,59	173,98	NA	365,78	187,26	151,53
99,83	130,45	180,95	NA	111,23	175,48	150,77
93,54	130,35	160,58	NA	81,28	177,83	149,40
86,17	132,29	138,46	NA	64,71	170,53	157,48
86,58	125,37	152,28	NA	67,38	150,63	162,75

	Johnson & Johnson	Pfizer	Roche Holding AG	Novartis AG	Merck & Co	GlaxoSmithKline	Sanofi	AbbVie
jan-17	206,93	200,69	161,47	144,65	221,02	111,95	119,71	188,38
feb-17	223,31	215,80	174,77	152,96	234,85	124,49	134,77	192,55
mar-17	229,09	218,58	179,84	145,33	226,55	123,45	136,88	202,89
apr-17	227,10	216,72	190,41	156,22	223,83	117,11	141,80	205,32
may-17	235,89	208,61	195,44	165,83	233,82	132,84	147,79	207,61
jun-17	244,94	216,69	184,14	169,28	230,16	129,00	149,06	228,02
jul-17	245,73	213,92	186,19	172,79	231,09	120,00	145,57	219,85
aug-17	245,09	218,82	184,72	170,94	231,02	123,97	153,00	238,93
sep-17	242,25	232,55	187,70	174,11	231,63	119,54	158,84	281,95
oct-17	259,76	228,39	173,24	167,47	200,73	111,76	151,43	286,36
nov-17	259,61	236,20	181,23	174,00	201,39	105,09	141,09	309,67
dec-17	261,93	238,10	184,98	170,27	205,03	112,09	135,45	309,00
jan-18	259,07	243,49	172,40	182,64	217,73	112,12	136,11	358,56
feb-18	243,49	238,69	173,40	169,04	199,24	117,26	128,52	372,75
mar-18	241,78	235,46	170,46	163,97	200,16	122,88	126,12	304,59
apr-18	238,65	242,89	175,88	161,22	218,22	131,29	128,44	310,70
may-18	225,69	238,38	160,99	156,66	220,67	132,74	125,00	321,69
jun-18	230,63	243,05	169,70	158,81	225,00	132,36	133,17	301,24
jul-18	251,88	267,50	186,58	176,38	246,06	135,44	143,89	299,87
aug-18	256,01	278,16	184,59	174,51	256,22	132,79	143,86	315,25
sep-18	264,37	297,75	186,53	181,13	264,99	130,67	147,75	310,66
oct-18	267,85	290,93	189,40	183,86	276,84	129,31	152,11	255,70
nov-18	281,07	312,35	196,52	192,42	298,39	138,29	151,16	312,95
dec-18	248,49	297,19	185,34	180,40	287,37	126,40	142,53	306,04
jan-19	256,25	289,02	204,44	183,99	281,89	124,98	143,65	266,54
feb-19	263,11	297,73	211,72	191,79	307,87	130,20	140,16	266,28
mar-19	270,96	291,68	207,92	202,11	314,99	142,17	149,00	270,82
apr-19	273,69	278,91	210,90	199,17	300,12	139,27	144,74	266,78
may-19	254,21	285,16	202,95	207,42	302,03	134,40	134,65	261,20
jun-19	271,82	300,16	215,52	221,16	319,72	135,99	147,06	247,61
jul-19	254,14	269,12	212,30	221,81	318,56	146,39	148,33	226,84
aug-19	250,51	246,32	214,31	218,25	331,91	141,58	149,34	227,26
sep-19	254,39	251,28	230,01	210,48	323,12	145,33	161,59	261,76
oct-19	259,62	268,35	234,45	211,78	334,85	150,03	155,95	275,00
nov-19	270,34	269,40	245,08	223,56	336,86	156,72	163,05	307,70

Takeda Pharmaceuticals	Shanghai Pharmaceuticals	AstraZeneca	Moderna	Novavax	Sinopharm	Dow Jones
87,42	138,86	140,35	NA	70,05	167,71	163,58
97,04	139,34	160,23	NA	80,75	168,99	171,39
98,50	149,49	170,04	NA	68,45	169,56	170,16
103,46	151,96	163,04	NA	43,85	164,02	172,45
107,38	163,65	189,91	NA	49,20	166,92	173,01
105,92	187,21	186,26	NA	61,50	165,26	175,81
110,83	161,99	166,48	NA	55,61	153,20	180,27
115,71	155,13	168,82	NA	56,15	167,46	180,74
115,38	161,90	183,50	NA	60,96	163,21	184,51
118,00	168,78	191,03	NA	58,29	165,84	192,51
115,29	163,81	180,92	NA	72,73	145,66	199,88
118,54	163,59	197,35	NA	66,31	160,37	203,56
122,92	164,48	188,68	NA	108,02	163,67	215,34
118,58	157,97	194,76	NA	116,04	163,67	206,12
101,71	173,52	198,29	NA	112,30	185,59	198,49
88,37	166,48	210,67	NA	83,42	156,31	198,98
84,17	187,10	218,78	NA	87,17	164,70	201,07
87,08	166,56	206,16	NA	71,66	148,99	199,88
88,33	156,34	227,83	NA	67,91	156,78	209,29
86,96	141,55	223,70	NA	83,42	188,59	213,82
89,04	136,29	229,91	NA	100,53	185,40	217,89
87,92	130,90	232,41	NA	94,12	182,70	206,83
78,33	132,76	236,54	NA	110,70	186,76	210,31
70,08	110,93	222,97	NA	98,40	159,26	192,10
83,21	106,29	209,62	100,00	125,13	169,27	205,87
83,58	124,02	239,07	136,14	37,97	168,55	213,42
84,88	140,03	246,84	122,59	29,41	157,92	213,52
76,17	133,16	229,04	156,81	28,34	148,86	218,99
70,71	124,06	232,00	125,18	15,19	142,45	204,35
73,75	119,36	247,83	88,19	15,67	133,44	219,05
73,33	119,98	270,95	78,92	11,52	141,35	221,23
70,25	126,95	270,16	94,76	15,96	140,45	217,43
71,67	117,97	269,58	95,90	13,42	121,72	221,66
74,87	120,63	283,60	100,90	11,15	139,57	222,73
84,58	117,52	297,00	122,65	12,97	128,27	231,00

	Johnson & Johnson	Pfizer	Roche Holding AG	Novartis AG	Merck & Co	GlaxoSmithKline	Sanofi	AbbVie
dec-19	288,80	276,66	248,46	229,34	351,43	160,74	171,11	310,54
jan-20	294,74	262,96	262,81	228,91	332,40	165,05	168,57	284,16
feb-20	266,25	238,40	252,18	203,36	297,86	143,99	160,87	304,67
mar-20	261,27	232,83	257,00	199,70	299,33	136,72	154,38	270,83
apr-20	298,95	273,64	281,13	212,67	311,22	145,75	168,94	292,20
may-20	296,38	272,42	280,13	219,44	316,63	147,92	165,89	334,33
jun-20	282,14	235,59	276,64	219,22	303,34	146,20	180,92	354,21
jul-20	292,43	277,23	270,60	206,17	317,25	136,59	178,07	342,41
aug-20	307,78	274,92	279,82	216,01	337,14	137,82	178,68	349,73
sep-20	300,68	266,99	280,56	218,27	327,97	140,81	183,65	319,86
oct-20	276,91	258,11	259,65	195,98	299,53	120,53	163,25	310,76
nov-20	292,20	293,75	263,56	227,98	320,16	128,12	177,22	387,10
dec-20	320,06	285,15	278,08	237,01	325,77	132,19	169,11	396,61
jan-21	331,75	278,10	279,30	227,07	309,36	136,11	170,32	379,33
feb-21	322,25	262,26	268,94	215,63	291,50	119,39	164,46	403,46
mar-21	336,32	283,71	270,49	214,55	309,44	133,99	182,32	405,26
apr-21	333,00	302,66	263,56	222,53	301,67	138,44	184,05	417,54
may-21	346,34	303,29	285,73	230,73	307,30	138,75	188,07	429,06
jun-21	339,22	309,68	323,99	238,20	330,03	152,15	201,36	426,94
jul-21	354,58	338,54	315,64	241,20	329,01	147,82	192,47	440,81
aug-21	356,49	367,62	338,85	241,20	326,53	153,84	194,14	462,90
sep-21	334,52	343,21	311,47	213,50	321,48	148,29	183,01	413,42
oct-21	337,38	349,03	317,36	216,06	380,24	156,76	186,90	439,48
nov-21	322,99	428,75	329,97	208,07	323,50	159,80	181,00	447,17
dec-21	356,67	475,34	343,62	228,35	330,97	165,65	186,82	525,22
Total growth	257%	375%	244%	128%	231%	66%	87%	425%
Average	213,07	217,52	194,13	166,81	221,51	126,44	141,83	248,60
Standard deviation	71,88	67,95	56,40	41,74	73,11	15,25	25,04	96,94

Takeda Pharmaceuticals	Shanghai Pharmaceuticals	AstraZeneca	Moderna	Novavax	Sinopharm	Dow Jones
82,21	121,31	302,98	117,83	10,64	141,94	235,02
80,12	126,25	302,77	123,55	20,37	127,62	232,69
72,08	125,12	276,06	156,20	42,78	119,90	209,25
63,25	129,55	288,92	180,42	36,31	87,42	180,49
74,75	121,12	323,90	277,05	48,48	105,26	200,49
81,25	117,17	336,72	370,48	123,10	95,54	209,03
74,71	119,87	330,03	386,81	222,86	99,45	212,57
75,83	134,77	334,11	446,39	382,62	95,73	217,64
77,54	151,41	342,56	390,90	295,03	98,95	234,12
74,33	141,49	358,41	426,20	289,71	84,32	228,78
64,12	139,55	316,67	406,45	215,80	91,89	218,24
74,29	142,97	319,00	920,12	372,99	99,36	244,08
75,83	138,97	311,21	629,34	298,16	97,60	252,05
73,46	131,51	324,11	1043,13	590,75	98,22	246,91
69,62	150,56	300,35	932,59	618,26	94,10	254,73
76,08	144,28	325,62	788,86	484,79	97,30	271,60
69,58	162,16	344,38	1077,23	633,50	124,69	278,96
71,21	170,76	358,71	1114,52	394,71	136,70	284,35
70,12	157,51	396,41	1415,54	567,67	119,61	284,13
68,75	139,94	367,14	2130,12	479,49	109,07	287,69
69,13	144,82	381,58	2269,22	637,81	106,74	291,20
68,25	144,34	401,25	2318,43	554,30	108,28	278,71
58,42	141,01	400,63	2079,58	397,94	99,15	294,98
55,63	140,18	367,69	2123,07	557,83	90,22	283,97
56,79	152,09	374,74	1530,00	382,54	90,39	299,25
-43%	52%	275%	1430%	283%	-10%	199%
90,58	121,71	201,25	691,00	206,46	128,21	172,97
14,29	31,25	83,16	728,30	175,45	31,92	53,67

APPENDIX 4

Monthly evolution of the stock price, December 2019 – December 2021

	Johnson & Johnson	Pfizer	Roche Holding AG	Novartis AG	Merck & Co	GlaxoSmithKline	Sanofi	AbbVie
dec-19	100,00	100,00	100,00	100,00	100,00	100,00	100,00	100,00
jan-20	102,06	95,05	105,78	99,81	94,59	102,68	98,52	91,51
feb-20	92,19	86,17	101,50	88,67	84,76	89,58	94,02	98,11
mar-20	90,47	84,16	103,44	87,07	85,18	85,06	90,23	87,21
apr-20	103,51	98,91	113,15	92,73	88,56	90,68	98,73	94,09
may-20	102,62	98,47	112,75	95,68	90,10	92,03	96,95	107,66
jun-20	97,70	85,15	111,34	95,59	86,31	90,96	105,74	114,06
jul-20	101,26	100,21	108,91	89,89	90,28	84,98	104,07	110,26
aug-20	106,57	99,37	112,62	94,18	95,93	85,74	104,43	112,62
sep-20	104,11	96,50	112,92	95,17	93,32	87,60	107,33	103,00
oct-20	95,88	93,30	104,50	85,45	85,23	74,99	95,41	100,07
nov-20	101,18	106,18	106,08	99,40	91,10	79,71	103,57	124,65
dec-20	110,82	103,07	111,92	103,34	92,70	82,24	98,83	127,72
jan-21	114,87	100,52	112,41	99,01	88,03	84,68	99,54	122,15
feb-21	111,58	94,79	108,24	94,02	82,95	74,28	96,11	129,92
mar-21	116,45	102,55	108,87	93,55	88,05	83,36	106,56	130,50
apr-21	115,31	109,40	106,08	97,03	85,84	86,13	107,56	134,46
may-21	119,93	109,63	115,00	100,60	87,44	86,32	109,91	138,17
jun-21	117,46	111,93	130,40	103,86	93,91	94,66	117,68	137,48
jul-21	122,78	122,37	127,04	105,17	93,62	91,96	112,49	141,95
aug-21	123,44	132,88	136,38	105,17	92,91	95,71	113,46	149,06
sep-21	115,83	124,05	125,36	93,09	91,48	92,26	106,96	133,13
oct-21	116,82	126,16	127,73	94,21	108,20	97,52	109,23	141,52
nov-21	111,84	154,97	132,80	90,72	92,05	99,42	105,78	144,00
dec-21	123,50	171,81	138,30	99,57	94,18	103,06	109,19	169,13
Total growth	23,50%	71,81%	38,30%	-0,43%	-5,82%	3,06%	9,19%	69,13%
Average	108,73	108,30	114,94	96,12	91,07	89,42	103,69	121,70
Standard deviation	9,85	20,87	11,24	5,46	5,44	7,77	6,70	20,90

Takeda Pharmaceuticals	Shanghai Pharmaceuticals	AstraZeneca	Moderna	Novavax	Sinopharm	Dow Jones
100,00	100,00	100,00	100,00	100,00	100,00	100,00
97,47	104,07	99,93	104,86	191,46	89,91	99,01
87,68	103,14	91,11	132,57	402,01	84,47	89,04
76,94	106,79	95,36	153,12	341,21	61,59	76,80
90,93	99,84	106,91	235,12	455,53	74,16	85,31
98,83	96,58	111,14	314,42	1156,78	67,31	88,94
90,88	98,81	108,93	328,27	2094,22	70,06	90,45
92,25	111,09	110,28	378,83	3595,48	67,44	92,61
94,32	124,81	113,06	331,75	2772,36	69,71	99,62
90,42	116,63	118,30	361,71	2722,36	59,41	97,35
78,00	115,04	104,52	344,94	2027,89	64,74	92,86
90,37	117,86	105,29	780,88	3505,03	70,00	103,86
92,25	114,56	102,71	534,10	2801,76	68,76	107,25
89,36	108,40	106,97	885,28	5551,26	69,20	105,06
84,69	124,11	99,13	791,46	5809,80	66,30	108,39
92,55	118,93	107,47	669,48	4555,53	68,55	115,57
84,64	133,67	113,66	914,21	5953,01	87,85	118,70
86,62	140,76	118,39	945,86	3709,05	96,30	120,99
85,30	129,84	130,84	1201,33	5334,42	84,27	120,90
83,63	115,36	121,18	1807,77	4505,78	76,84	122,42
84,09	119,38	125,94	1925,82	5993,47	75,20	123,91
83,02	118,98	132,43	1967,59	5208,79	76,29	118,59
71,06	116,24	132,23	1764,88	3739,45	69,86	125,51
67,66	115,56	121,36	1801,79	5241,96	63,56	120,83
69,08	125,37	123,68	1298,47	3594,72	63,68	127,33
-30,92%	25,37%	23,68%	1198,47%	3494,72%	-36,32%	27,33%
86,48	115,03	112,03	802,98	3254,53	73,82	106,05
8,64	11,23	11,56	630,16	1983,70	10,82	14,68

References

AEMPS. 2022. *Desarrollo de vacunas*. https://www.aemps.gob.es/la-aemps/ultima-informacion-de-la-aemps-acerca-del-covid%E2%80%9119/vacunas-contra-la-covid%E2%80%9119/desarrollo-de-vacunas/).

Alam, M. M., Wei, H. and Wahid, A. N. 2021. COVID-19 outbreak and sectoral performance of the Australian stock market: An event study analysis. *Australian economic papers* 60, 3, 482-495.

Alcaide, M. Á., De la Poza, E. and Olmeda, N. G. 2022. How has the announcement of the Covid-19 pandemic and vaccine impacted the market? *Economic Research-Ekonomska Istraživanja*, 1-17.

Armitage, S. 1995. Event study methods and evidence on their performance. *Journal of economic surveys* 9, 1, 25-52.

Baker, S. R., Bloom, N., Davis, S. J., Kost, K. J., Sammon, M. C. and Viratyosin, T. 2020. *The unprecedented stock market impact of COVID-19*. -National Bureau of Economic Research Working Paper 26945.

Behera, C. and Rath, B. N. 2021. The COVID-19 pandemic and Indian pharmaceutical companies: An event study analysis. *Bulletin of Monetary Economics and Banking, Special* Issue 2021, 1-14.

Berkeley Lovelace, Jr., 2021. "Johnson & Johnson reports $100 million in quarterly sales from Covid vaccine". *CNBC*. Retrieved April 29, 2021

Bloom, D. E., Canning, D. and Weston, M. 2017. The value of vaccination. In Stevens, P. (ed.), *Fighting the diseases of poverty*, Routledge, 214-238.

Brenner, M. 1979. The sensitivity of the efficient market hypothesis to alternative specifications of the market model. *The Journal of Finance* 34, 4, 915–929. https://doi.org/10.1111/j.1540-6261.1979.tb03444.x

De Schrijver, J. 2013. *Analysis of stock market reactions to FDA and EMEA announcements*. Ghent University.

Díaz, R. F. and Sanchez-Robles, B. 2020. Non-Parametric Analysis of Efficiency: An Application to the Pharmaceutical Industry. *Mathematics* 8, 9, 1522.

Donadelli, M., Kizys, R. and Riedel, M. 2017. Dangerous infectious diseases: Bad news for Main Street, good news for Wall Street? *Journal of Financial Markets* 35, 84-103.

Forman, R., Shah, S., Jeurissen, P., Jit, M. and Mossialos, E. 2021. COVID-19 vaccine challenges: What have we learned so far and what remains to be done? *Health Policy* 125, 5, 553-567.

Goodell, J. W. 2020. COVID-19 and finance: Agendas for future research. *Finance Research Letters* 35, 101512. https://doi.org/10.1016/j.frl.2020.101512

Haroon, O. and Rizvi, S.A.R. 2020. COVID-19: media coverage and financial markets behavior—a sectoral inquiry. J. of Behavioural and Experimental Finance 27, 100343. https://doi.org/10.1016/j.jbef.2020.100343.

Heyden, K. J. and Heyden, T. 2021. Market reactions to the arrival and containment of COVID-19: an event study. *Finance Research Letters* 38, 101745.

Hwang, T. J. 2013. Stock market returns and clinical trial results of investigational compounds: an event study analysis of large biopharmaceutical companies. *PloS one* 8, 8, e71966.

Ichev, R. and Marinč, M. 2018. Stock prices and geographic proximity of information: Evidence from the Ebola outbreak. *International Review of Financial Analysis* 56, 153-166.

IQVIA. 2022. *Global Trends in R&D.* Institute for Human Health Science, February. https://www.iqvia.com/insights/the-iqvia-institute/reports/global-trends-in-r-and-d-2022

NIH. 2020. *NIH clinical trial of remdesivir to treat COVID-19 begins.* https://www.nih.gov/news-events/news-releases/nih-clinical-trial-remdesivir-treat-covid-19-begins

Pardo-Seco, J., Mallah, N., López-Pérez, L.R., González-Pérez, J.M., Rosón, B., Otero-Barrós, M.T., Durán-Parrondo, C., Rodríguez-Tenreiro, C., Rivero-Calle, I., Gómez-Carballa, A., Salas, A. and Martinón-Torres, F. 2022. Evaluation of BNT162b2 Vaccine Effectiveness in Galicia, Northwest Spain. International Journal of Environmental Research and Public Health 19, 4039. https://doi.org/10.3390/ijerph19074039.

Perez-Rodriguez, J. V. and Valcarcel, B. G. 2012. Do product innovation and news about the R&D process produce large price changes and overreaction? The case of pharmaceutical stock prices. *Applied economics* 44, 17, 2217-2229.

Piñeiro-Chousa, J., Lopez-Cabarcos, M.A., Quiñoá-Piñeiro, L. and Pérez Pico, A. 2022. US biopharmaceutical companies' stock market reaction to the COVID-19 pandemic. Understanding the concept of the 'paradoxical spiral' from a sustainability perspective. Technological Forecasting & Social Change 175, 121365.

Qiu, T., Wang, Y., Liang, S., Han, R. and Toumi, M. 2021. The impact of COVID-19 on the cell and gene therapies industry: disruptions, opportunities, and future prospects. *Drug Discovery Today* 26, 10, 2269-2281.

Remy, V., Largeron, N., Quilici, S. and Carroll, S. 2015. The Economic Value of Vaccination: Why Prevention Is Wealth. Journal of market access & health policy 3, 1, 29284.

Schuhmacher, A., Wilisch, L., Kuss, M., Kandelbauer, A., Markus Hinder, M. and Gassmann, O. 2021. R&D efficiency of leading pharmaceutical companies – A 20-year analysis. Drug Discovery Today 26, 8, 1784-1789.

Sorokina, N., Booth, D. E. and Thornton Jr, J. H. 2013. Robust Methods in Event Studies: Empirical Evidence and Theoretical Implications. *Journal of Data Science* 11.

Thakor, R.T., Anaya, N., Zhang, Y., Vilanilam, C., Siah, K.W., Wong, C.H. and Lo, A.W. 2017. Just how good an investment is the biopharmaceutical sector? Nature Biotechnology 35, 12, 1149–1157. https://doi.org/10.1038/nbt.4023.

United Nations, 2015. Transforming our world: the 2030 agenda for sustainable Development. New York.

WHO. 2022. Coronavirus disease (Covid-19): Vaccines. https://www.who.int/news-room/questions-and-answers/item/coronavirus-disease-(covid-19)-vaccines?gclid=CjwKCAjwve2TBhByEiwAaktM1AeIM1Gorz0_0pncPAqXqpVMmhkQmrKHFRQpzQCY0P55lAAlge_8HxoCZ9IQAvD_BwE&topicsurvey=v8kj13)

Zaremba, A., Kizys, R., Aharon, D. Y. and Demir, E. 2020. Infected markets: Novel coronavirus, government interventions, and stock return volatility around the globe. *Finance Research Letters* 35, 101597.

Zeng, B., Gao, L., Zhou, Q., Yu, K. and Sun, F. 2022. Effectiveness of COVID-19 vaccines against SARS-CoV-2 variants of concern: a systematic review and meta-analysis. *BMC medicine* 20, 1, 1-15.

Zhang, L. C. 2021. *Event study: The influence of COVID-19 research and development news on pharmaceutical and biotech companies*. Working paper, University of Michigan–Ann Arbor.

Zheng, C., Shao, W., Chen, X., Zhang, B., Wang, G. and Zhang, W. 2022. Real-world effectiveness of COVID-19 vaccines: a literature review and meta-analysis. *International Journal of Infectious Diseases* 114, 252-260.

CHAPTER 5.

Conclusiones

CHAPTER 5.
Conclusiones

5.1 Conclusiones y trabajo futuro

Los objetivos planteados en la presente tesis son los siguientes:

1. Evaluar el nivel de eficiencia de las empresas farmacéuticas y biotecnológicas principalmente productoras de remedios frente a aquellas que, además, realizan I+D. Se ha considerado para ello una muestra de empresas del sector en Europa.

2. Determinar la eficiencia de las empresas especializadas en el desarrollo clínico de nuevos tratamientos o CROs como un actor decisivo a la hora de aportar valor e influir en el uso de los recursos internos de las empresas farmacéuticas y biotecnológicas.

3. Analizar la evolución en bolsa de las empresas que han desarrollado una vacuna contra el virus Covid-19 y determinar si ello ha tenido alguna influencia en su comportamiento en el mercado de valores frente a sus competidores.

Los resultados del análisis de la eficiencia de las empresas farmacéuticas y biotecnólogicas principalmente productoras frente a aquellas que además realizan I+D muestran que las primeras son más eficientes en el uso de sus recursos. Es posible concluir además que el nivel de eficiencia de la industria farmacéutica europea es moderado y que la tendencia es decreciente durante el periodo 2010-2018. Se observa además una relación entre el tamaño de las empresas y la eficiencia, resultando las empresas muy grandes o muy pequeñas más eficientes que aquellas con un tamaño mediano o pequeño. Estos resultados sugieren que las empresas del sector se benefician de economías de escala -empresas muy grandes- o de altos niveles de especialización -empresas muy pequeñas-, factores ambos que acontecen en menor medida en empresas de tamaño medio.

La eficiencia de las CROs, a diferencia de lo que sucede con las empresas farmacéuticas y biotecnológicas, crece a lo largo del periodo considerado. Los datos sugieren que las CROs con más éxito son aquellas de mayor tamaño, con acceso a las últimas tecnologías y alianzas comerciales estables. Se concluye por ello que la tendencia actual de consolidación de empresas del sector mediante fusiones y adquisiciones continuará en el futuro.

En general, la comparación de los resultados de los capítulos 3 y 4 pone de manifiesto diferencias notables entre los sectores farmacéutico y biotecnológico, por una parte, y de las CROs por otra en la última década.

Las empresas farmacéuticas y biotecnológicas registran niveles medios de eficiencia reducidos. Además, la eficiencia es decreciente en el tiempo. En cambio, las CROs alcanzan un nivel medio de eficiencia más alto y que aumenta a lo largo del periodo analizado. Aunque no se pueden realizar comparaciones estrictamente cuantitativas entre los niveles medios de eficiencia porque están referidos a muestras diferentes, sí puede realizarse una valoración cualitativa. El subsector de las CROs, de acuerdo con nuestro análisis, resulta ser más dinámico, competitivo y homogéneo que el sector constituido por farmacéuticas y biotecnológicas. Además, que el primero presente una distancia media a la frontera formada por las empresas más eficientes menor que en el caso de las segundas es consistente con el hecho de que el mercado de ensayos clínicos es relativamente reciente, globalizado y acostumbrado a trabajar con márgenes escasos, mientras que el mercado de productos farmacéuticos es más maduro.

El análisis del precio de las acciones muestra que las compañías biofarmacéuticas tuvieron un comportamiento variado tras su inversión en el desarrollo de vacunas para tratar el virus Covid-19. Es posible distinguir tres situaciones diferenciadas: i) Pfizer y Moderna han visto su inversión en la vacuna recompensada por el mercado y han reaccionado positivamente a los anuncios sobre los distintos hitos de la pandemia. En cualquier caso no es descartable que en el caso de Pfizer otros factores hayan influido en dicho éxito; ii) Johnson&Johnson y AstraZeneca han tenido resultados más modestos en bolsa. Una posible explicación es que el impacto de los ingresos por las vacunas haya quedado diluido puesto que el portfolio de productos comercializados por ambas es muy amplio; iii) Novavax no ha visto recompensada en bolsa su inversión en el desarrollo de la vacuna. Esta compañía mostró una evolución positiva al principio de la pandemia pero su valoración empeoró significativamente después. Es posible que los inversores no hayan visto reflejadas las expectativas en unos mejores resultados financieros tras la comercialización de la vacuna y hayan reaccionado de manera negativa, vendiendo sus acciones de la empresa.

Como posibles acciones para complementar el presente trabajo se sugiere lo siguiente:

- Paper 1 (Chapter 2) - Ampliar el horizonte temporal para la evaluación de la eficiencia de las empresas farmacéuticas/biotecnológicas según se vayan publicando nuevos datos.

  Adicionalmente en el Stage 1 se ha utilizado la técnica no-paramétrica DEA pero la utilización de técnicas paramétricas como el SFA podría resultar útil para confirmar si los datos de eficiencia obtenidos son sensibles a la técnica empleada.

  Sería asimismo interesante analizar cuáles son las características de los países que influyen positiva o negativamente en el nivel de eficiencia. Esto podría hacerse mediante la introducción de variables macroeconómicas e institucionales en los modelos del Stage 2.

- Paper 2 (Chapter 3) – La investigación está limitada por la muestra de empresas y variables disponibles en el conjunto analizado. Una investigación adicional con otra muestra de empresas y variables alternativas podría arrojar más luz sobre la eficiencia del sector de las CROs.

- Paper 3 (Chapter 4) - Ampliar el horizonte temporal para la evaluación de la cotización en bolsa de las empresas productoras de una vacuna para tratar el virus Covid-19 con el objetivo de discernir a largo plazo si la inversión en dicha vacuna tiene efectos adicionales.

  Asimismo, dado que las empresas que mostraron mejor comportamiento en bolsa en el periodo de pandemia, Pfizer y Moderna, utilizan la tecnología mRNA en sus vacunas, se sugiere explorar si este hecho tiene alguna relación con dicho éxito.

APÉNDICE A.
Publicaciones

APÉNDICE A

Publicaciones

This thesis has led to the following publication:

Díaz, Ricardo F. and Sánchez-Robles, Blanca (2020) "Non-Parametric Analysis of Efficiency: An Application to the Pharmaceutical Industry". In *Mathematics*.