QUADERNO

"PHARMA 4.0: OPPORTUNITÀ E VINCOLI DELLA DIGITALIZZAZIONE DELL'INDUSTRIA FARMACEUTICA"

"PHARMA 4.0: OPPORTUNITIES AND CONSTRAINTS OF THE PHARMACEUTICAL INDUSTRY DIGITALIZATION"

Pharma 4.0: a new perspective of opportunities and constraints

Pharma 4.0: nuove prospettive di opportunità e vincoli

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Industry 4.0: the concept is not new, yet 4.0 opens a brand-new perspective: everybody is involved, with new technologies.

Pharma 4.0 is no exception in this perspective, with its own features and aims. In this frame, are regulations a constraint? Well, looking at trend of the last fifteen years, Authorities have been opening doors to change and innovate, with new technologies and new attitude. Pharma 4.0 sort of gathers them all.

Have a good Pharma 4.0 trip.

Key words: Industry 4.0

Industria 4.0: il concetto non è nuovo, ma 4.0 apre una nuova prospettiva: tutti sono coinvolti, con nuove tecnologie.

Pharma 4.0 non fa eccezione in questa prospettiva, con le sue caratteristiche e scopi. In questo quadro, le normative sono un vincolo? Bene, guardando le tendenze degli ultimi quindici anni, le autorità hanno aperto le porte al cambiamento e all'innovazione con nuove tecnologie e nuovi atteggiamenti. Piuttosto Pharma 4.0 li riunisce tutti.

Buon viaggio con Pharma 4.0.

Parole chiave: *Industry 4.0*

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Introduction

With an inspired term, Industry 4.0 indicates the big change that, starting from industry, is underway in many sectors of our XXI century activities.

The term recalls the previous Industrial Revolutions, which were each a consequence of wide technological, organizational and social leaps through technological innovation and new production models (Fig. 1).

A first leap was in the early XIX century, with the introduction of machines to take over the manual productions also thanks to new energy sources, symbolized by the textile industry in United Kingdom.

A second leap a century later, with overwhelming innovations in many fields, led to the first, shy signals of globalization and what we call the mass production, especially symbolized by Fordism in manufacturing.

With the technological and social acceleration that we all recognize, a third symbolic leap is considered to be the diffusion and fusion of informatics and automation in the seventies-eighties of the XX century.

Whatever our interpretation is, all these transitions have at least four elements in common:

1) *leap in productivity*, whatever leap might mean in the different situations, e.g., increased volumes, enlarged product selections, higher quality and standards, stricter adherence between supply and demand;
2) *impacts on employment*, at least in terms of substitution of existing jobs with new ones. This fact, by itself, has always been an issue since the first Luddite opposition;
3) new attitude in the consumers, who change their own demand, once acknowledged the new supply, that is taken for granted from that moment on;
4) new behaviour of the manufacturer, who on one hand invests in the change, on the other hand adapts to the change, with no actual way back.

None of these elements is unrelated to our current Fourth Revolution. Indeed, the ongoing 4.0 transition looks

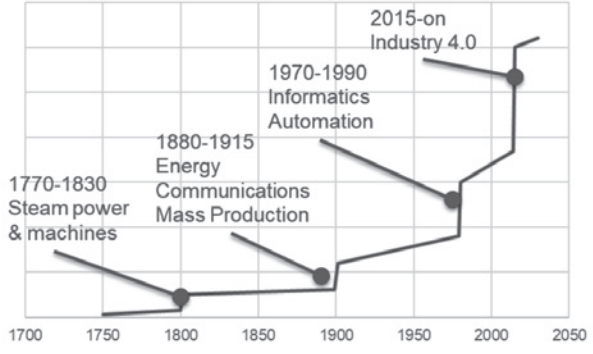


Figure 1.
Industrial revolutions: a view.

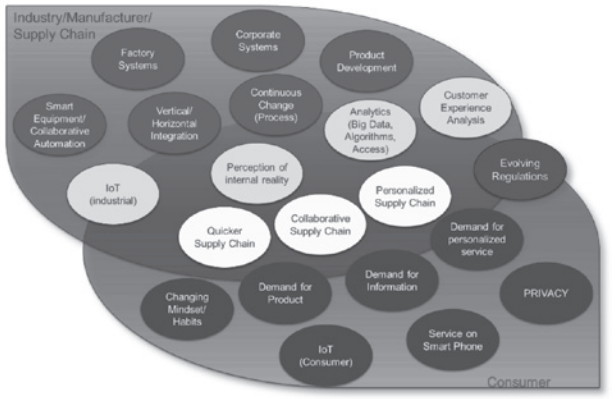


Figure 2.
Industry 4.0: everybody is involved, and connected.

even bigger, due to the new importance of technologies, such as robotics and artificial intelligence, and the wide potential of this change to all the activity sectors in a globalized world. Deep analyses are underway by governments and analysts.

From a manufacturing perspective, two aspects of the fourth revolution deserve to be underlined: the extent of involvement of all parts, from Industry to the Consumer, and the extent of the identification between product and information, well beyond the usual combination of production/distribution cycle and information flow.

In other words, in the Industry 4.0 scenario everybody is involved, in a sort of total connection. Besides, the Consumer increasingly asks for information in a product and asks for products from information, with increasing awareness, with increasing global attitude (Fig. 2).

Is everything new?

Not exactly. Of course, we can observe this developing scenario from an historical, common sense perspective: every revolution, of every kind, somehow results from a previous evolutionary path that moved to its tipping point. Yet, the ongoing revolution comes also from the practical observation of facts, attempts and trends in the last three decades, also confirmed by major analysts. Let us provide two illustrative examples.

In Italy, a dedicated study of Assolombarda (i.e., the association of enterprises of Lombardy, Italy) in 2016 points out that, looking at the manufacturing innovation in the last years, Industry 4.0 can be considered as an evolution that has been underway in the last decades, rather than a proper revolution, suddenly triggered by the availability of new technologies.

In turn, in a dedicated article in 2015, Gartner Group (a global research and advisory firm) corroborates the idea that the concept of Industry 4.0 is not new by itself, but is rather

the latest step in a sort of dialectic development process of technologies and business processes.

So, what is new?

According to Assolombarda, there are no doubts that the recent availability and the increasing diffusion of certain enabling technologies provides new tools to manufacturing resources, boosting the renewal of the currently adopted business model.

In our opinion, what is new is the handy availability of new technologies, with costs that are more sustainable than before, allowing to speed up the improvement processes on their course, to implement a new identity between product and information, to be spread along the whole value and supply chain, with the direct, active participation of the final customer.

The consequences can be huge.

Pharma 4.0

The pharmaceutical sector (Pharma in the following) is no exception to this 4.0 reality, its new opportunities, its new identity between product and information, its new involvement of all parts.

Yet, such a sector has its own characteristics and values to drive the choices. In particular, it is characterized by an ethical dimension of the concept of quality: zero defects to be pursued in the product, the final consumer is a patient, the interrelation is strict and continue with the Regulatory Authorities throughout the entire drug life cycle for the safeguard of the patient (Fig. 3).

Also, in Pharma 4.0 not everything is new. Yet, the rapid evolution of technologies and attitudes brings important changes in the demand, in the manufacturing operations, in the interactions with the Authorities, and in the new, valuable availability of information.

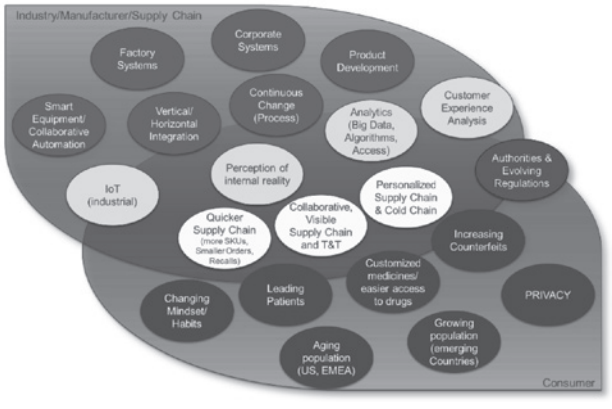


Figure 3.
Pharma 4.0: different roles and dynamics, in full connection.

What is changing in the Pharma 4.0 world

The change in the demand is the change of attitude, behaviour and involvement of the consumer/patient, and of the relationship itself between consumer/patient and industry. This is a world where the integration between information and product can bring to increase the therapeutic adherence, for example. Where the creation of personalized drugs and services can be boosted, as in the case of wearable devices. Where some important questions can be answered, such as anticounterfeiting through serialization, or adverse events reported promptly and managed via dedicated analytics technologies in the widest context of correlations.

The change in the manufacturing operations can come from lower costs and shorter time in automation and in collaborative information technology, which offer new opportunities to a reliable and secure support to actions and decisions throughout the operations. Secure and timely messaging, collaborative robotics for a new micro-logistics, reliable process data from Internet of Things are just few examples.

The change in the interaction with the Authorities is the shortening of the information distances made possible, which creates new scenarios such as Quality Metrics and risk-based inspections.

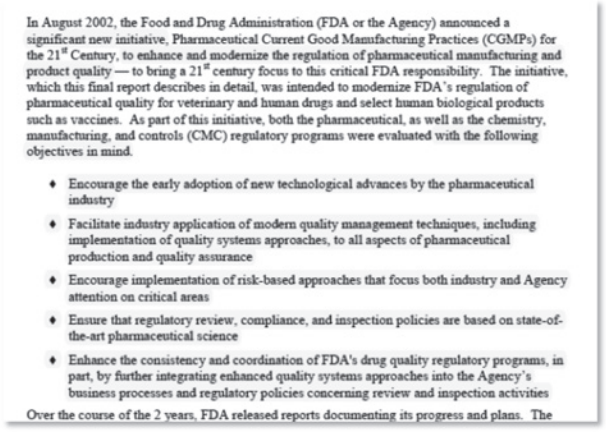
The change in the information availability is the new possibility of a fast, massive, aimed elaboration, which creates an information at hand at all process and organizational levels: predictive maintenance, predictive quality control, at last real application of PAT [1], analysis of operational scenarios among the possible examples.

Is this change sustainable for Pharma?

Pharma has been working hard on the concept of change in the last two decades. At the dawn of the third millennium the Pharma world realized that the zero-defects quality concept could not be pursued any longer with the old logics of exhaustive control, but rather through a continuous improvement process to detect, analyse, correct and prevent the issues, i.e., through the development of knowledge.

A milestone, among others, of this evolution can be considered the FDA initiative "Pharmaceutical cGMPs for the 21st century", aiming "to enhance and modernize the regulation of pharmaceutical manufacturing and product quality", stated in a Final Report in 2004. It was the opening to an evolutionary quality culture, based on state-of-the-art science, adoption of new technological advances, enhancing

[1] Process Analytical Technologies, defined by FDA as a mechanism to design, analyse, and control pharmaceutical manufacturing processes through the measurement of Critical Process Parameters which affect Critical Quality Attributes.

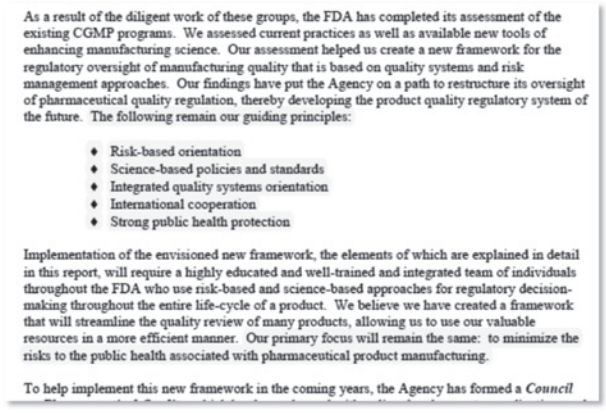


In August 2002, the Food and Drug Administration (FDA or the Agency) announced a significant new initiative, Pharmaceutical Current Good Manufacturing Practices (CGMPs) for the 21st Century, to enhance and modernize the regulation of pharmaceutical manufacturing and product quality — to bring a 21st century focus to this critical FDA responsibility. The initiative, which this final report describes in detail, was intended to modernize FDA's regulation of pharmaceutical quality for veterinary and human drugs and select human biological products such as vaccines. As part of this initiative, both the pharmaceutical, as well as the chemistry, manufacturing, and controls (CMC) regulatory programs were evaluated with the following objectives in mind.

- Encourage the early adoption of new technological advances by the pharmaceutical industry
- Facilitate industry application of modern quality management techniques, including implementation of quality systems approaches, to all aspects of pharmaceutical production and quality assurance
- Encourage implementation of risk-based approaches that focus both industry and Agency attention on critical areas
- Ensure that regulatory review, compliance, and inspection policies are based on state-of-the-art pharmaceutical science
- Enhance the consistency and coordination of FDA's drug quality regulatory programs, in part, by further integrating enhanced quality systems approaches into the Agency's business processes and regulatory policies concerning review and inspection activities

Over the course of the 2 years, FDA released reports documenting its progress and plans. The

Figure 4.
FDA Report – from executive summary page 1.



As a result of the diligent work of these groups, the FDA has completed its assessment of the existing CGMP programs. We assessed current practices as well as available new tools of enhancing manufacturing science. Our assessment helped us create a new framework for the regulatory oversight of manufacturing quality that is based on quality systems and risk management approaches. Our findings have put the Agency on a path to restructure its oversight of pharmaceutical quality regulation, thereby developing the product quality regulatory system of the future. The following remain our guiding principles:

- Risk-based orientation
- Science-based policies and standards
- Integrated quality systems orientation
- International cooperation
- Strong public health protection

Implementation of the envisioned new framework, the elements of which are explained in detail in this report, will require a highly educated and well-trained and integrated team of individuals throughout the FDA who use risk-based and science-based approaches for regulatory decision-making throughout the entire life-cycle of a product. We believe we have created a framework that will streamline the quality review of many products, allowing us to use our valuable resources in a more efficient manner. Our primary focus will remain the same: to minimize the risks to the public health associated with pharmaceutical product manufacturing.

To help implement this new framework in the coming years, the Agency has formed a *Council*

Figure 5.
FDA Report – from executive summary page 2.

communication and collaboration, ever-increasing widespread knowledge (Figs. 4-5).

From the very beginning, there was also the awareness that such a process could not even take place in a paper-based environment, but only with the systematic adoption of the information systems at their best potential.

To enable this adoption, objective criteria were needed to ensure security and reliability of the electronic data "at least" at the same level as the data on paper. FDA itself opened the way with 21CFR Part 11 "Electronic Records, Electronic Signatures", whose Final Guidance issued in August 2003 drove the path of change throughout several worldwide public initiatives and private technical developments. A path that results now in the achievements of Data Integrity concepts. Thanks to this, now the electronic data are more reliable, secure and usable than any paper-based method: now, electronic data can be valuable information.

A proper blessing to the full adoption of all the 4.0 criteria.

Then, let's act Pharma 4.0

Some basic ideas for the implementation of Pharma 4.0, starting from technology: technology is an enabler of change. As such, we must consider that in some cases technology can change completely our operational model (for example with 3D printers in the production of personalized drugs) but generally speaking may not.

Also, in this case, though, technology can help us evolve our model in modes, costs, promptness, quality, opportunity.

How to use this opportunity, and to which extent, is mainly a matter of attitude and approach: we need a method, a philosophy to drive our culture for change. This is Operational Excellence: Pharma knows it and has already experienced it with success.

Operational Excellence can be considered as the child of another Revolution, the Lean one, completed and further boosted with contributions from the best operational practices experienced worldwide in the last 30 years in all the Industry sectors.

In the last fifteen years, Pharma has approached Operational Excellence with close care and constructive humbleness, accepting the debate with the other industry sectors. This allowed Pharma to eventually realize with pragmatism that Operational Excellence is attitude and culture for the constant change, the best environment to sustain the continuous discontinuity.

In few words, what it takes now to cope with the Pharma 4.0 changes, and build further value from them is the scientific method, a focus on the involvement of the people, a conscious use of technology, and a systematic pursuing of quality and sustainability.

Vertical integration: from the process sensor to the Regulatory Authority

Starting from this culture for change, the Data Integrity principles and techniques, and determined attitude and route, we can think of pragmatic principles for a to-be process and system architecture.

The ISA-95 standard helps us design a new reference model for operations and information in the Pharma production site. It is the vertical integration to support operations and Big Data collection and elaboration (Advanced Analytics).

Looking at Figure 6, two main elements deserve a remark: the integrated domain of operational data inside the Pharma Company, from the physical process to the business management, and the increasingly leaner and integrated exchange of information with the Regulation Authorities.

Here the ISA-95 standard that, again, is not new, is our compass to design the new route to support the decisions at all levels, from the process operator to the senior manager,

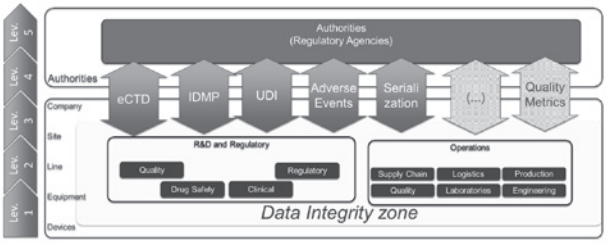


Figure 6.
Vertical integration: a model.

with the right information at the right time. In this way gaining potentials such as:

- predictive analyses (e.g. on Maintenance, Laboratories etc.);
- Product Quality Review by joining data from different sources (Labs, QA, Production);
- KPI for continuous improvement (at Company, Site, Line level with OEE);
- Quality Metrics (risk-based inspections from KPIs);
- On-Demand analytics (e.g. for an audit, which User interacted with a given Electronic Record in a QMS or LIMS);
- simulation-based decisions (e.g. what to produce where, in case of…; what in case of Batch recall etc.);
- Data Reconciliation (e.g. QMS and DSDB in case of systems not completely integrated) (Fig. 7).

Horizontal integration: the new supply chain

In a frame of full control of our newly organized information, we can look with confidence to the challenges of the new Pharma Supply Chain, which faces a complex reality where demand and relationships are changing, due to many different factors such as changing demographics in both ma-

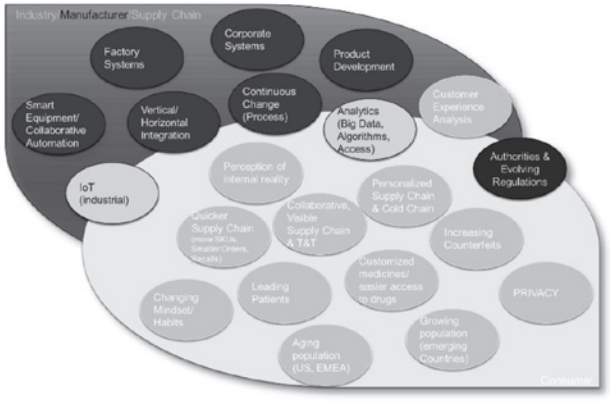


Figure 7.
Vertical integration Pharma 4.0: who is involved.

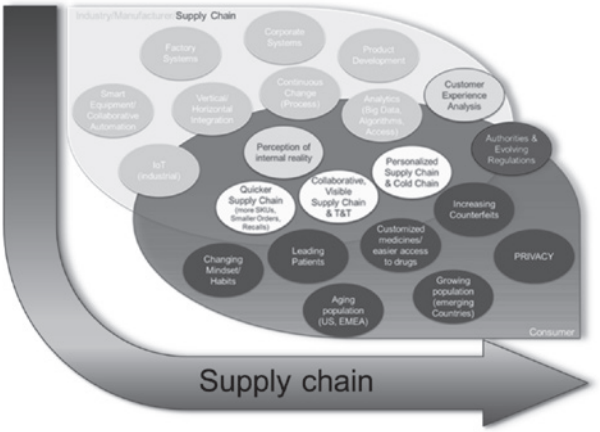


Figure 8.
Horizontal integration Pharma 4.0: who is involved.

ture and emerging Countries, change of the products (with several of them requiring specific storage and transportation and controlled room temperature), increased demand for services beyond the mere product delivery, the already cited increased awareness and new active role in the supply chain that is now played by patients and consumers, the need to respond to the serialization and traceability requirements, the consequent need of a new end-to-end supply chain visibility.

And hence the role of Pharma 4.0 technology and attitude gets central to provide near-real-time data visibility, to support the end-to-end process collaboration, to enable new models and a new potential, inaccessible so far (Fig. 8).

What's next: challenges and directions

Cultivate the culture of change and innovation, and identify key metrics aimed at the internal organization and processes: these are just two of the recommendations that Gartner Group includes in a recent paper dedicated to the state of the art of the 4.0 transformation in the industry.

In our opinion these are two important points from where to start the path to 4.0, also exchanging experiences with peers (yet another point in Gartner Group's approach to 4.0).

In a Pharma perspective just let us make explicit the quality-related metrics to be shared both internally to the Company and externally with the Regulatory Authorities, in view of the rapid process of rationalization of the information flow.

This looks to be a good starting point for Pharma. Without forgetting that Pharma has a consolidated tradition of networking to pool experiences and ideas, with several prestigious organizations. Among them, ISPE (www.ispe.org), is an organization of 40'000 Life Science professionals in the world, with aimed initiatives.

Then just let us get ready, and start acting 4.0.

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