AGENZIA ITALIANA DEL FARMACO

AIFA activities against the short supply of medicines: the Ozempic case

Domenico Di Giorgio

July 2024

AGENZIA ITALIANA DEL FARMACO

Public Declaration of transparency/interests*

The view and opinions expressed are those of the individual presenter and should not be attributed to AIFA

Interests in pharmaceutical industry	NO	Current	From 0 to 3 previous years	Over 3 preavious years
DIRECT INTERESTS:				
1.1 Employment with a company: pharmaceutical company in an executive role	X	☐	☐	☐ mandatory
1.2 Employment with a company: in a lead role in the development of a medicinal product	X	☐	☐	☐ mandatory
1.3 Employment with a company: other activities	X	☐	☐	☐ optional
2. Consultancy for a company	X	☐	☐	☐ optional
3. Strategic advisory role for a company	X	☐	☐	☐ optional
4. Financial interests	X	☐	☐	☐ optional
5. Ownership of a patent	X	☐	☐	☐ optional
INDIRECT INTERESTS:				
6. Principal investigator	X	☐	☐	☐ optional
7. Investigator	X	☐	☐	☐ optional
8. Grant or other funding	X	☐	☐	☐ optional
9. Family members interests	X	☐	☐	☐ optional

*Domenico Di Giorgio, in accordance with the Conflict of Interest Regulations approved by AIFA Board of Directors (25.03.2015) and published on the Official Journal of 15.05.2015 according to EMA policy /626261/2014 on the handling of the conflicts of interest for scientific committee members and experts. FINANCIAL STATEMENT: I am not receiving a compensation for this presentation.

Framework definition (2015): manufacturing shortages, distribution disruption, regulatory distortions in tenders

Operational Pilot Project related to the short supply of some key medicines, possibly subject to raking for export purposes:

- Involvement of all relevant stakeholders (local authorities dealing with GDPs, MAH, pharmacists and wholesalers associations; MoH traceability system, police forces)
- Definition of the different kind of «shortages» (scientific approach)

Review

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Medicine Access @ Point of Care
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Tackling distribution-related shortages of medicines: An Italian case study evaluated in the European Union framework

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Abstract

Availability of human medicines is affected by problems associated with both manufacturing and distribution-related issues. The lack of definition of "shortages" or "unavailability" of medicines in European regulation represents an obstacle to the set up of proper preventive and counteracting measures. In this review, we describe how, within this framework, Italy started a program of shared activities, involving central and local authorities, police forces, and private stakeholders' associations through an "*ad hoc technical forum*," that reduced the extent of the problem, at least in the short term, as demonstrated through some indicators defined by considering the key medicines affected by unavailability due to distribution-related issues. These measures should be strengthened and complemented with others so as to ensure their effectiveness in the long term.

Manufacturing shortages, distribution disruptions, tender (H) issues

One of the key points agreed by all stakeholders in the "Shared document on distribution of medicines" signed in 2016 (a crucial point in the Italian strategy against short supply of medicines) is the distinction between "manufacturing shortages" (CARENZE) and "distribution disruption" (INDISPONIBILITÀ): due to different roots, calling to different solutions. Later, a third "shortage" was also better defined, related to specific issues in the management of hospital tenders.

Related to manufacturing/regulatory issues; MAH have to notify it to the Agency 4 months in advance, according to art. 34, comma 6, del D.Lgs. n. 219/2006

Mainly caused by local distribution issues (GDP related), to be notified to and investigated by the Regional authorities.

Networking: TTI (National Forum on Short Supply of Medicines)

Operational forum, involving

- National (AIFA, MoH, ISS-CNS) and Regional authorities
- MAH, traders, pharmacists, distributors associations
- Technical associations (logistic, traceability, software houses, manufacturers – APIs, medicines/gases…)
- Scientific and professional associations (physicians, pharmacists, hospitals…)

Since 2015, 49 recorded meetings (generating field operations, training sessions, tools, awareness campaigns, publications, conferences, joint statements, guidelines…)

Networking: TTI (National Forum on Short Supply of Medicines)

- **AIFA**: Shortages management office (coordination) + Legal department, General directorate, Chairman of the board office, Press office
- **Ministry of Health**: GDP office, Traceability service (+ Cabinet/Press office, when needed)
- **Local Administrations**: Regional authorities (Campania, Friuli Venezia Giulia, Lazio, Liguria, Lombardia, Piemonte, Veneto), Autonomous Provinces (Trento, Bolzano)
- **Police Forces**: Carabinieri NAS
- **Technical administrations**: Poligrafico e Zecca dello Stato (traceability), SCFM (National Armed Forces manufacturing site)
- **MAH associations**: Egualia (generics), Farmindustria (branded), AIP, AIM (parallel trade)
- **Pharmacies associations**: Federfarma, Assofarm, FarmacieUnite
- **Wholesalers/distributors**: ADF, Federfarma Servizi (wholesalers), Assoram (logistic services)
- **Logistic-technical services associations**: Assosoftware (software houses association), Consorzio DAFNE (traceability)
- **Manufacturing**: Assogastecnici (medical gases), Federchimica (API manufacturers)
- **Scientific societies**: SIFO (hospital pharmacists), FOFI (federation of pharmacists professional orders), LICE, AME, AMENS, SIE (clinics - specialists), FIMMG (clinics)

The 2020 crisis: shortages management (without export ban!)

- Import authorization for structures and MAH
- Search for Italian and foreign suppliers
- Contacts with other administrations for specific issues
- Administrative and logistical support
- Support for MA holders (logistic interventions and derogations, inclusion of pharmaceutical activities in productive continuity; management procedure Medicinal Oxygen; support for exchange of critical API suppliers)
- Controlled distribution exercises (Hydroxychloroquine, Lopinavir/Ritonavir, anesthetics).
- Network operations on specific issues (eg refusals of drug distribution)
- Management of international relations (sharing of good practices in the EC network, eg on regulatory flexibility in medical gas filling; extraordinary initiatives for nonstandard cases, eg import of experimental drugs from third countries through diplomatic contacts, transport and distribution of donations from third countries, reporting to HMA/WGEO on traditional Chinese medicine products found in the distribution network)
- Contacts with foreign countries for mutual support on current and future deficiencies (support to French and Israeli contacts on midazolam supplies; discussion with EMA/Health Canada/WHO of the risks of shortages for specific drugs produced in Italy)
- Contacts with the production network for reports from Civil Protection and other administrations outside the health circuit

AIFA AND HOSPITAL SUPPLY DURING THE COVID CRISIS: THE COLLABORATION BETWEEN REGIONS, COMPANIES, AND AGENCY

Domenico Di Giorgio, Oscar Cruciani, Carla Maione, Gianluca Polifrone (AIFA), Adriano Pietrosanto (Assogenerici), Luca Paoles (Farmindustria), Verena Moser, Nadia Colangelo (Provincia Autonoma di Bolzano), Annalisa Campomori (Provincia Autonoma di Trento), Maria Rosalia Puzo (Regione Basilicata), Adele Emanuela De Francesco, Rita Francesca Scarpelli(Regione Calabria), Ugo Trama (Regione Campania), Ester Sapigni (Regione Emilia-Romagna), Paola Rossi, Laura Mattioni (Regione Friuli Venezia Giulia), Lorella Lombardozzi, Marcello Giuliani (Regione Lazio), Barbara Rebesco (Regione Liguria), Ida Fortino (Regione Lombardia), Luigi Patregnani (Regione Marche), Antonella Lavalle, Giuseppina Trofa, Maria Teresa Sisto (Regione Molise), Guendalina Brunitto (Regione Piemonte), Vito Bavaro, Paolo Stella, Francesco Colasuonno (Regione Puglia), Donatella Garau (Regione Sardegna), Pasquale Cananzi (Regione Sicilia), Claudio Marinai (Regione Toscana), Mariangela Rossi (Regione Umbria), Andrea Fadda (Regione Valle d'Aosta), Giovanna Scroccaro, Olivia Basadonna, Roberta Rampazzo (Regione Veneto), Marcello Pani (SIFO)

June 2020

CONTEXT

The current epidemic environment is marked by new therapeutic demands, a high level of dynamism in treatment scheme suggestions, both *on label* and *off label*, and specific organizational needs in the provision of care. Furthermore, the epidemic's widespread nature requires a particular timeliness in the definition and application of the provisions.

The sudden increase in demand for normally low-spread drugs, such as some antivirals (which, at the time, had not yet been evaluated in comparison to COVID therapy), triggered a backlash on the distribution network, which also concerned the territory where the availability of some of the products had encountered unexpected difficulties, at the height of the crisis, which began around mid-March. The AIFA had to respond by rapidly authorizing the import of large quantities of the products required by the protocols, which, however, gradually changed, modifying the expected needs in a sudden way.

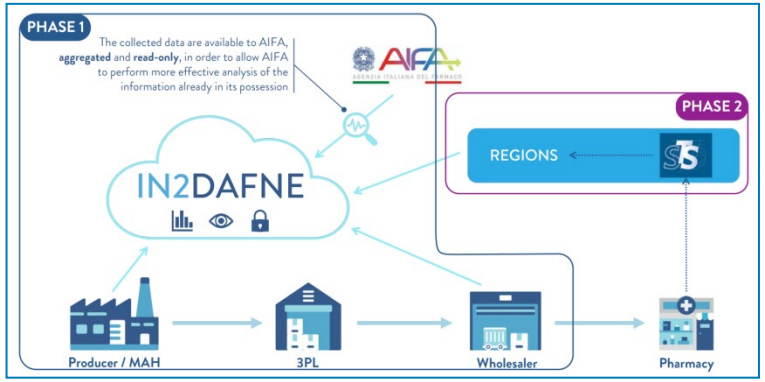
In parallel, with the increasing occupation of intensive care units, the demand for drugs such as anaesthetics, whose production has critical aspects that make it difficult to increase availability. The increase in complexity was due to an uncoordinated demand by the territory, which meant that individual hospital facilities were competing for supplies, generating problems so that the stocks of the areas still unaffected by the virus could hardly be made available to the network, in prevision of the emergency.

"COMMUNITY EXPERTS" MODEL

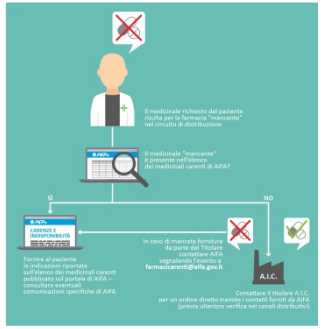
The AIFA has provided an organizational response that has proven effective in response to the new needs given by the pandemic, forming a "community of experts". An operational network that has involved the referents of the regions with the task of supervising, monitoring, and collecting timely the territory's needs, acting as transducers between them and the institutions, and allowing them to carry out timely interventions (ensuring, for example, the supply of hospitals by companies through the regions), and providing real-time support by pharmaceutical companies, interfaced with the AIFA through the network managed by the industry associations, Assogenerici and Farmindustria.

https://www.aifa.gov.it/documents/20142/1028586/AIFA_and_hospital_supply_during_the_covid_crisis.pdf

Generating and promoting good practices



Il primo portale dei farmaci indisponibili

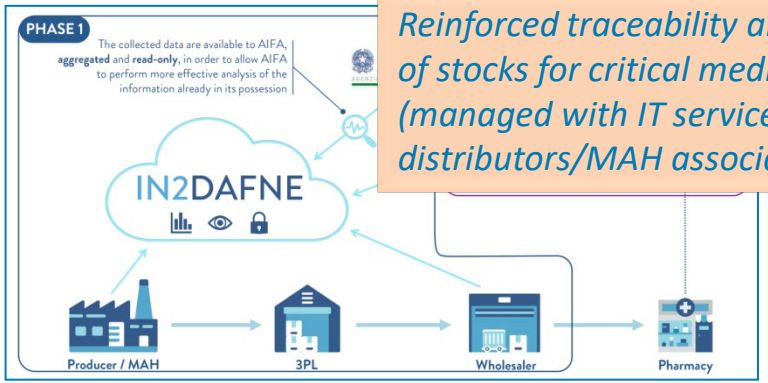


https://www.aifa.gov.it/en/farmaci-carenti

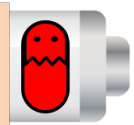
Some examples of the TTI activities and results

"Supposed shortage" of medical gases (miscommunication) managed with MAH/pharmacies

Reinforced traceability and verification of stocks for critical medicines (managed with IT services and distributors/MAH associations)



IT platform for signalling issues in availability of medicines in hospitals (related to tenders/supplier qualification), set up with the Hospital Pharmacists association, SIFO



Drugshost

Il primo portale dei farmaci indisponibili

"What to do" shortages guideline for pharmacists, developed and distributed by TTI

Webpage for patients information on shortages mitigation for epylepsy medicines (in cooperation with the relevant clinics association)

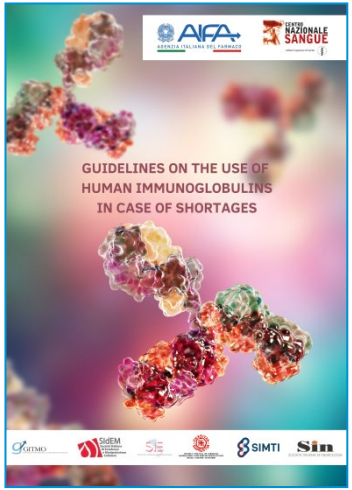
https://www.aifa.gov.it/en/il-tavolo-tecnico-indisponibilita

Good practices sharing via guidelines and EU projects

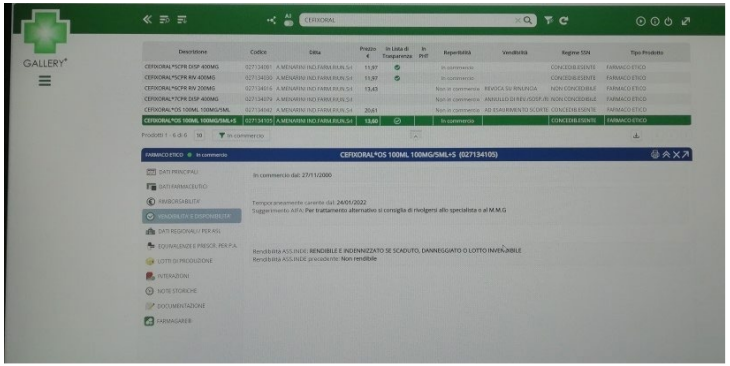
AIFA developed and coordinates the **CHESSMEN** project (EU Joint Action on Shortages), building on our previous experiences in counteracting pharmacrime (Fakeshare, Medi-Theft EC projects led by AIFA) that allowed us the in depth study of the distribution network (as the TTI was built on the Volcano Operation experience).

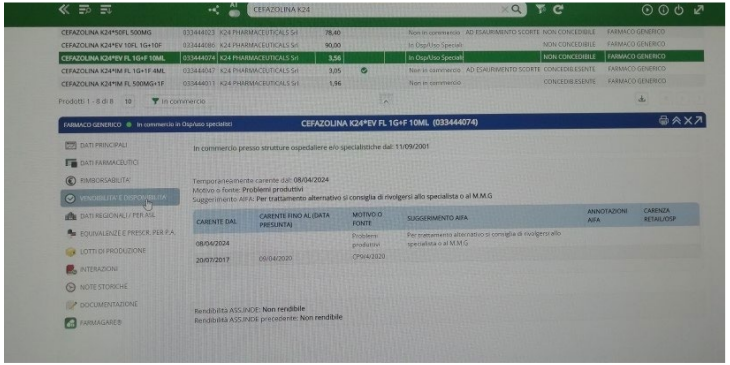
CHESSMEN will allow the sharing of **existing** and **new** good practices, from Italy and other MS, as for instance

- **FEC** - the web platform for MAH for the notification of shortages,
- **SCFM** – the National Manufacturing/Importing firm involved in shortages mitigation)
- the **IG shortages guideline**,
- the **AIFA-Regional training** on shortages
- the **software alerts on shortages** for pharmacists and physicians



Stakeholders involvement: “Shortages Alert” in pharmacy softwares





PHARMACY SOFTWARE:

- Partners, **Federfarma, AssoSoftware**
- **Status: completed** (use promotion)

PHYSICIAN SOFTWARE:

- Partners, **AssoSoftware, FIMMG, Regione Liguria**
- **Status: ongoing** (beta version)

Case study: Ozempic shortage (2023-2024)

In Italy mitigation measures granting a **centralized and controlled distribution** have been put in place from February 2023, through the involvement of all relevant stakeholders: MAH, Regional authorities, distribution network, scientific associations.

Communication – a key element in the strategy - was also managed by involving the relevant stakeholders: eg, the measure was promoted via DHPC.

NOTA INFORMATIVA IMPORTANTE CONCORDATA CON L'AGENZIA ITALIANA DEL FARMACO (AIFA)

6 Marzo 2023

COMUNICAZIONE DIRETTA AGLI OPERATORI SANITARI (DHPC)

Ozempic® (semaglutide) soluzione iniettabile in penna preriempita: stato di carenza

Gentile Professionista Sanitario,

Novo Nordisk S.p.A., rappresentante legale in Italia di Novo Nordisk A/S, in accordo con l'Agenzia Europea per i Medicinali (EMA) e con l'Agenzia Italiana del Farmaco (AIFA), desidera informarLa di quanto segue:

- l'aumento della domanda di Ozempic® ha portato a carenze che si prevede continueranno per tutto il 2023. Sebbene la fornitura continui ad aumentare, non è possibile prevedere con certezza quando risulterà sufficiente a soddisfare completamente la domanda attuale.
- Una tardiva consapevolezza della situazione di esaurimento delle scorte può comportare l'impossibilità per i pazienti di acquisire le dosi necessarie, con possibili conseguenze cliniche come l'iperglicemia.
- La invitiamo ad assicurare che i pazienti che utilizzano Ozempic® siano informati di quanto sopra e che i pazienti, a rischio di esaurimento di Ozempic®, vengano trasferiti in sicurezza ad un altro agonista del GLP-1 o ad altre idonee alternative terapeutiche in base alla Sua valutazione clinica.
- Ozempic® è indicato esclusivamente per il trattamento di adulti affetti da diabete mellito di tipo 2 non adeguatamente controllato in aggiunta alla dieta e all'esercizio fisico. Ogni altro utilizzo, inclusa la gestione del peso, rappresenta un uso off-label e attualmente mette a rischio la disponibilità di Ozempic® per la popolazione indicata.

Sintesi e informazioni di base

Ozempic® (semaglutide) è indicato in Italia per il trattamento di adulti affetti da diabete mellito tipo 2 non adeguatamente controllato in aggiunta alla dieta e all'esercizio fisico:

- come monoterapia quando l'uso di metformina è considerato inappropriato a causa di intolleranza o controindicazioni;
- in aggiunta ad altri medicinali per il trattamento del diabete.

Case study: Ozempic shortage (2023-2024)

Based on initial assessments and subsequent follow up activities, it can be confirmed that in Italy the off-label use of Ozempic is **negligible, if not completely absent**.

The impact on the shortage of Ozempic is evidently positive; currently, all dosages are (formally) declared in shortage, but only to allow the quota distribution to be managed.

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Case study: Ozempic shortage (2023-2024)

The model applied in Italy provides that:

1) the Regions purchase Ozempic packs directly from the MAH and then distribute the packs to pharmacies that dispense to patients with a reimbursable medical prescription (for strictly on-label indications). This model is called "Distribuzione per conto" (DPC), that is, distribution by pharmacies on behalf of the Regions.
2) the MAH is applying a quota to the Regions, in order to avoid hoarding phenomena; furthermore, the product is not placed in the "free" distribution channels. In the event of an emergency, pharmacies can request packages from the MAH SOS service (in 2023 the use of this service for Ozempic is negligible).

In summary: **The centralized and controlled distribution** of Ozempic in Italy has increased the availability of the medicine to patients and has made off-label use negligible (if not null).

AGENZIA ITALIANA DEL FARMACO

https://www.aifa.gov.it/crimine-farmaceutico - https://www.aifa.gov.it/en/farmaci-carenti

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