EUROPEAN COOPERATION
IN SCIENCE AND TECHNOLOGY

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Main Proposer Details

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Sub-field of Science of Department:	Health Sciences	**Core Area of Expertise:**	Medical and Health Sciences

General Features

Title: **Product shortages as risk factors for clinical and quality of life outcomes**

Acronym: **MEDICINES SHORTAGES**

Initial Idea:
In a 2013 survey, 99% of over 300 hospital pharmacist respondents from 27 countries recorded problems with medicines shortages in their hospital. Furthermore, 63% reported experiencing the problem on a weekly, sometimes daily basis.

Aside from patient welfare and safety considerations, substituting an alternative medicinal product is a cost-intensive approach compared to using the initial standard product. A simple intermediate substitution of a drug on the formulary can, in a German example, cost 1800 €, a definite substitution between 3800 € and 4690 €.

Similar long-term projections for 2050 are now also emerging in the food domain. Coping strategies for foodstuff supply may include treaties with supplier countries such as Brazil. However, this is not possible for medicines due to legal and quality aspects.

This Action is intended to make a significant contribution to strategic thinking about how to respond to product shortage problems by offering systematic sharing of research about medicine, food product and nutriceutical shortages. This includes knowledge-sharing about the extent of shortages being experienced, trends, impacts and evidence-based solutions founded upon shared research on the causational factors.

The aim of the Action is to attain constructive agreement between all participating stakeholders in areas such as definition, measurement and understanding of shortage problems. The Action is also intended to reveal any restrictive legal and economic frameworks, erroneous incentives in the supply chain, conflicts of interest, and problematic cost-benefit ratios that serve to exacerbate or create shortages.

Expertise needed for evaluation:
3.3 Health Sciences: Health services, health care research
3.3 Health Sciences: Nutrition and dietetics
3.1 Basic medicine: Pharmacology, pharmacogenomics, drug discovery and design, drug therapy
5.2 Economics and business: Business ethics
5.2 Economics and business: Strategy and management
2.6 Medical engineering: Medical engineering and technology
2.9 Industrial biotechnology: Pharmaceutical applications
3.4 Medical biotechnology: Medical biotechnology, other

Keywords:
drug, medicine, nutriceutical, shortage, availability, induced cost, outcome, risk factor, negotiated agreement, hospital, pharmacy, pharma industry, economy, manufacturing, preparation, processing, quality requirement, competent authority, FDA, EMA, health care logic, market logic, market authorisation, regulation, industrial, health, economics, public health, patient safety

Field(s) of application:
Health

Affiliations *:

Number of COST Country Institutions: 9
Number of COST International Partners: 0

Other Institutions (International Organisations, European Institutions and Agencies, European RTD Organisations): 0

**Calculations performed as per TDP Pilot Guidelines and based on users' e-COST profiles and COST Affiliation Categories*

Strategy

Objective 1 (A.5) - Type:Development of knowledge needing international coordination: new or improved theory/model/scenario/projection/simulation/narrative/methodology/technology/technique

1. Handbook, Guidelines, Best Practices, for S&T purposes.
2. Joint peer-reviewed publication , open access.
3. Stakeholders Outreach, including Unwritten Inputs and Dissemination, to business.
4. Action Science and Technology Meeting, Working Group.
5. Internal and External Communication, Conference Attendance for Action Dissemination Purposes.
6. Internal and External Communication, Virtual Network: any web-based resource needed for work coordination among Action Members.
7. Internal and External Communication, Website.
8. Science and Technology Event or Meeting, Action Workshop.
9. Science and Technology Event or Meeting, Action Conference.
10. Documents to be Used as Input to Stakeholders, to enterprises.

11. Achievement of Specific Network Features in terms of WG Composition, expertise.
12. Delivery of Written Input to a Stakeholder (excluding business enterprises), to a government body.

Objective 2 (A.6) - Type:Achievement of a specific tangible output that cannot be achieved without international coordination (e.g. due to practical issues such as database availability, language barriers, availability of infrastructure or know-how, etc.)

1. Delivery of Written Input to a Stakeholder (excluding business enterprises), to a government body.
2. Achievement of Specific Network Features in terms of WG Composition, expertise.
3. Documents to be Used as Input to Stakeholders, to enterprises.
4. Handbook, Guidelines, Best Practices, for S&T purposes.
5. Joint peer-reviewed publication , open access.
6. Stakeholders Outreach, including Unwritten Inputs and Dissemination, to business.
7. Action Science and Technology Meeting, Working Group.
8. Internal and External Communication, Conference Attendance for Action Dissemination Purposes.
9. Internal and External Communication, Virtual Network: any web-based resource needed for work coordination among Action Members.
10. Internal and External Communication, Website.
11. Science and Technology Event or Meeting, Action Conference.
12. Science and Technology Event or Meeting, Action Workshop.

Objective 3 (A.7) - Type:Input to stakeholders (e.g. standardization body, policy-makers, regulators, users) -excluding commercial applications

1. Stakeholders Outreach, including Unwritten Inputs and Dissemination, to business.
2. Action Science and Technology Meeting, Working Group.
3. Internal and External Communication, Conference Attendance for Action Dissemination Purposes.
4. Internal and External Communication, Virtual Network: any web-based resource needed for work coordination among Action Members.
5. Internal and External Communication, Website.
6. Science and Technology Event or Meeting, Action Workshop.
7. Science and Technology Event or Meeting, Action Conference.
8. Joint peer-reviewed publication , open access.
9. Handbook, Guidelines, Best Practices, for S&T purposes.
10. Delivery of Written Input to a Stakeholder (excluding business enterprises), to a government body.
11. Achievement of Specific Network Features in terms of WG Composition, expertise.
12. Documents to be Used as Input to Stakeholders, to enterprises.

Objective 4 (B.13) - Type:Bridging separate fields of science/disciplines to achieve breakthroughs that require an interdisciplinary approach

1. Delivery of Written Input to a Stakeholder (excluding business enterprises), to a government body.
2. Unpublished Aspects of Knowledge Creation, Including Experimentation and Testing, survey.
3. Achievement of Specific Network Features in terms of WG Composition, expertise.
4. Stakeholders Outreach, including Unwritten Inputs and Dissemination, to business.
5. Action Science and Technology Meeting, Working Group.
6. Internal and External Communication, Virtual Network: any web-based resource needed for work coordination among Action Members.
7. Internal and External Communication, Website.
8. Science and Technology Event or Meeting, Action Workshop.
9. Science and Technology Event or Meeting, Action Conference.

A. Challenge

Describe the challenge you would like to meet by creating a COST Action and explain why you consider it important (i.e. relevance and timeliness). The challenge is about:

a. *Explaining the problems you want to solve: the content of the challenge falls within one or more of the categories of Action objectives you selected. Any background information needed to explain or to make a convincing case for the challenge you propose needs to be given here.*
b. *Explaining why solving the proposed challenge(s) has an impact: the envisaged impact can be either on codified and tacit knowledge (for definitions see Guidelines for Proposers) or on society. Unless you selected category 6 (Achievement of a specific tangible output…), explain exclusively the content of the challenge (e.g. if you selected 'new model' explain what the model is about and why it is needed), not the form*

that the solution will take (e.g. a co-authored peer-reviewed publication where the new model will be presented).

Medicines shortages (also referred to as drug shortages) are a global phenomenon[1-3] affecting all hospital and health systems in Europe.[4] Furthermore it is a phenomenon that if left alone threatens to become a crisis in terms of delivering patient care.[5, 6] This COST Action proposal is submitted in order to facilitate exchange of research about the problem in the European context, and to support the public policy environment in developing and implementing evidence-based solutions.

THE GLOBAL AND EUROPEAN MEDICINES SHORTAGES PROBLEM

Over the past ten years, reports of medicines shortages have grown steadily. Whilst documentation of the problem is not robustly conducted at a European level (one of the challenges the Action will seek to address), evidence from the USA gives a good sense of the development. Shortages in the USA have grown by over 25%, within only a few years from 2006 (70 shortages) to 2011 (267 shortages).[4, 7, 8] In total, from 2004 to 2011, more than 1400 medicinal products were published as being in shortage in the USA.[8] The number increased from 91 reported in 2004 to 242 in 2011.[8] The average duration of a shortage increased from 139 to 242 days in the same period.[8] Substitution (62%), alternatives (25%) and compounding (2%) have been the most common methods to cope with such situations.[8]

Meanwhile, a survey conducted in 2012/2013 by the European Association of Hospital Pharmacists (EAHP) found that 99% of hospital pharmacies across more than 25 European countries were affected by medicines shortages in their hospital.[4, 9] 63% of hospital pharmacists experienced shortages on a weekly basis, sometimes with up to 3 cases per week or even daily. 77% reported that the situation was getting worse and urgently needed action.[4, 9]

In Belgium, for example some 30 drugs are regularly in short supply in community pharmacies.[10] In the Netherlands, shortages are monitored and published by the Royal Dutch Pharmacists Association (KNMP) on a website (http://www.farmanco.knmp.nl). One of the biggest Swiss university hospitals experienced 172 cases of drug shortage in 2011, i.e. 3 cases per week, with the involvement of 51 suppliers, and with multiple shortages for some products. A particular drug was out of stock between 21 and 335 days.[11] The recently published database from the European Medicines Agency (EMA) also indicates a particular shortage (Fabrazyme) first reported in 2009 that is still unresolved.[12]Drugs used in chemotherapy (including classic alkylating, anti-metabolic or topoisomerase-inhibiting anti-neoplastics) that have held a marketing authorisation for a long period and widely used vaccines are the most concerning products on the steadily growing list.[6, 13] Usually pharmaceutical expertise succeeds in finding a suitable solution in up to 90% of all cases; however, searching for a solution has to be conducted on top of the pharmacist's regular duties.[11, 14]

UNDERSTANDING THE IMPACTS OF THE SHORTAGES PROBLEM

COSTS TO HEALTH SYSTEMS: Medication is selected for the hospital formulary due to their assessed affordability and value. Therefore, any alternatives required because of shortages are generally cost-intensive compared to the usual product. For example, a simple intermediate substitution of a particular drug on a formulary can cost 1800 €, and a definite substitution can cost between 3800 € and 4690 € (figures from Germany).[11]

RISKS TO PATIENTS: Risks to patient safety are increased by substitution in the case of shortages, from the use of other excipients, different products in various concentrations, vials and outer packaging in foreign languages, or untranslated package leaflets to patients. Additional stress for healthcare professionals, associated with the heightened and unpredictable workload that accompanies medicines shortage, can also create additional risks of medication error.

DIVERSION OF HEALTHCARE PROFESSIONAL TIME: To bridge the gap arising from a case of drug shortage pharmacists and healthcare professionals are required to spend significant time in addition to their other tasks.[15]

However, the totality of the impact of shortages in Europe has not been scientifically quantified. It is an objective of this

proposed COST Action to bring together, and stimulate, such research, in order to create a better-informed policy environment, and a setting for evidence based solutions to be identified and implemented.

PAYING ATTENTION TO SMALL MARKETS AND SECONDARY SHORTAGES

Small markets are particularly sensitive to drug shortages[16] and healthcare professionals working in those countries are worried about medication shortages.[4, 9] High registration and regulatory costs for market authorisation(s) may tempt suppliers to economise in countries with low volumes of sales. This is a major problem for smaller countries within Europe and beyond. Withdrawal from the market in countries such as Austria or Switzerland may be an alert for an upcoming critical situation in the European Union. The necessity to import medication from other countries will have a significant impact on those markets as well, and may in-avertedly lead to a secondary shortage problem.

Secondary shortages can occur through the result of “panic buying”, parallel trade or an increased demand in a second product when the preferred option is in short supply itself; exemplified by influenza treatments.[17]

UNDERSTANDING THE CAUSATIONAL FACTORS

Developing and enhancing the understanding of what is causing the increase in medicines shortages will be another key objective of the proposed COST Action on the subject. The problem is generally understood to be multi-factoral[7, 19] including:

- Quality or availability problems related to active ingredients or to production processes or equipment (e.g. heparin contamination[20] and propofol case[21])
- Demand spikes (e.g. oseltamivir following flu pandemic scenarios[22])
- Unintended consequences of contracting by large buyers leading to the loss of small suppliers
- Over stocking caused by panic buying (especially when there are a lack of alternatives)
- Parallel trade of medicines[23, 24]
- Discontinuation decisions taken by industry, possible related to pricing or other macro-economic factors
- Globalisation of supply chains creating new vulnerabilities

What is missing is a balanced understanding of the extent to which these factors relate to each other. Which is quantifiably of greater causal factor than others? Which of the cited factors should policy makers address as a priority? By bringing together researchers and the principal stakeholders with access to the relevant information, the proposed COST Action will attempt to shine light on the answers to these key questions in order to prepare a reliable foundation for the development of solutions.

EXPLORING GLOBAL PRODUCTION FACTORS

Most drugs in short supply represent highly available active ingredients and the shortage may be linked to safety and quality issues.[7] Deviations from Good Manufacturing Practice (GMP) rules uncovered on inspections of production sites that then require improvements and investments in a producing plant may play an important role in decision making about maintaining production or not.[7] The risk and the consequences for the supply chain, which arises from cases of a major quality problem and paralysis of a big production plant after a merger of several smaller sites, is the more concerning, as fewer suppliers exist. The risk of affecting the global medicines supply market will be clearly higher in scenarios where one or a few large production facilities are affected as opposed to scenarios where production is conducted by many smaller sites. Other exacerbating factors might include where production is relocated into “low-cost” countries, which have less experience of achieving reliable industrial production free from major operational disruptions. The suitability and application of lean production methods for the pharmaceutical sector must also be further investigated.

To better understand the causational factors of medicines shortages, the proposed COST Action will need to examine the extent, nature and role of production problems in causing Europe's current medicines shortages problems, sharing research on the topic, and providing a platform for information to be shared.

EXPLORING ECONOMIC AND OTHER FACTORS

The impacts created by health systems' cost containment measures is another cited factor in creating medicines shortage problems.[6] Additionally, parallel trade of medicines, stock piling and demand spikes are other posited suggestions for why some medicinal products are increasingly found to be in short supply.

Alongside examination of the production problems in the pharmaceutical sector and their impacts on availability, the proposed COST Action must assist cross border examination and shared knowledge about the extent to which market forces are causing shortages, and if so how these might be addressed.

Examining the range of impacts, causes and solutions will therefore require a diverse range of specialities to be brought to bear within the Action - from health professionals, to patients, to industry experts, health economists, public policy experts and others. The authors of this proposed Action hold the ambition to achieve that aspiration.

THE NEED TO EXAMINE THE POLICY OPTIONS

In 2011, the seriousness of the situation in the USA prompted authorities in that country to intervene in the market and remind manufacturers and suppliers on their responsibilities. US President Barack Obama signed the Executive Order 13588 instructing the Food and Drug Administration (FDA) to require from manufacturers adequate advanced notice of discontinuation of certain prescription drugs and to review more quickly any modifications of the production processes of these drugs.[18] These requirements comprised an obligation to notify and inform on drug shortages to governmental agencies. However, they do not require disclosure of the reasons nor the decisions, which lead to a withdrawal of products from the market. An appropriate announcement is requested in cases where only one provider for a medically necessary active ingredient is available. The FDA has additionally created a task force for strategic planning and response to the medicines shortage problem.[18] Meanwhile its counterpart in Europe, the European Medicines Agency (EMA) has largely restricted its reflections to shortages caused by Good Manufacturing Practice (GMP) compliance problems.[12] As a result of FDA action, 38 shortages in the USA were prevented in 2010, 195 in 2011, and 150 in 2012 (up to November), but more has to be done to obtain a sustainable troubleshooting and legislation has been increased to this effect recently.[7, 18]

The proposed COST Action would draw together the actions taken by Governments and others across Europe to share solutions and identify the most efficacious responses.

STRATEGIC OBJECTIVES OF THE PROPOSED ACTION

- **Strategic objective 1: To create a research network in which all stakeholders within the medicines supply can participate, exchange information, and improve understanding.**

As a result of the globalisation of pharmaceutical production, it has become increasingly difficult to resolve medicines shortage problems on a regional/national basis alone. In order for the new Action to be successful in improving clinical, financial and life-quality outcomes, the whole global supply chain should be committed. Individuals as well as representative associations, researchers as well as practicing healthcare professionals and patients, are intended to be

integrated in the pan-European Action.

- **Strategic objective 2: To assemble, synchronise and share the existing and current knowledge about medicines shortages in Europe.**

Only with an enhanced understanding of the cross-domain nature, impact and causes of medicines shortages can a robust approach to problem solving be formed. Through conferences, online sharing tools, and other networking and exchange mechanisms, the Proposal authors are confident the suggested Action can achieve this goal.

- **Strategic objective 3: To promote stakeholder-government dialogue on the evidence, research findings and potential solutions.**

After the formation of the Managing Committee, a number of leading organisations/individuals will be contacted so that other stakeholders of the whole global supply-chain such as governments, policy-makers, regulators, and consumers are involved. The Action can then be uniquely placed to promote this much-needed dialogue at a European and international level, which is not taking place via other platforms at the current time.

- **Strategic objective 4: To create a positive environment for innovative solution identification and implementation.**

By harnessing the exchange of evidence and ideas that the proposed Action is foreseen to create, it is hoped that dialogue between stakeholders, government, and regulatory agencies can stimulate the formation of appropriate suggestions for remedial action and solutions to prevent and reverse the current growing trend of medicines shortages.

As a summary, this Action is intended to make a significant contribution to strategic thinking about how to respond to product shortage problems by offering systematic sharing of research about medicine, food product and nutriceutical shortage (defined as functional food).

This includes knowledge sharing about the extent of shortages being experienced, trends, impacts and evidence-based solutions founded upon research on the causing factors. The aim of the Action is to attain constructive agreement between all participating stakeholders in areas such as definition, measurement and understanding of shortage problems. The Action is also intended to reveal any restrictive legal and economic frameworks, erroneous incentives in the supply chain, conflicts of interest, and problematic cost-benefit ratios that serve to exacerbate or create shortages.

With a focus too on stimulating the proposition of policy solutions, it is intended that patients and healthcare systems will ultimately benefit from an improved situation of medicines supply sustainability. It is also intended that the Action will provide a tool to prevent the same errors in the food domain, which have been encountered in the pharmaceutical domain.

Ultimately the proposed **COST Action** envisages playing a significant role in:

- developing an evidence-based consensus between countries on how to fight against drug shortages;
- therein, bringing about a qualitative and quantitative improvement of the availability of drugs, foodstuff and nutriceuticals; and,
- finally, decreasing the number of shortages to exceptional incidences and to short-termed interruptions only of the supply chain by providing recommendations and solutions.

It aims in its lifetime of funding:

- to analyse the history and cases of drugs, foodstuff and nutriceuticals shortages;
- to analyse shortages' causes along the supply chain by an independent, scientific and integrating approach; and,
- to attain a constructive agreement on adequate next steps of producers, store keepers, wholesalers, hospital pharmacists, authorities and administrators.

If a COST Action can be taken into consideration, it must be the objective to attain a constructive agreement on adequate next steps of all stakeholders as well as explore legal and economic frameworks, erroneous incentives along the supply chain, conflicts of interest, and an over-all cost-benefit ratio. It is important too, to attempt to learn from the experiences within the pharma domain in order that some reasoned anticipations could be drawn for the potential threats to the food domain, where concerns about world regions resilience to access nutrition and basic foodstuffs has become more evident.

PRINCIPAL RESEARCH QUESTIONS

The **main research questions** are as follows:

- What is the scale of the problem of medicines shortages within Europe and what are the effects in providing patient care?
- Are there restrictive legal and economic frames that are producing unfavourable decisions with consequences for shortages and availability of drugs, foodstuff and nutriceuticals?
- Are there any erroneous incentives along the supply chain that promote incidences of medicines shortages?
- Are there any conflicts of interest between industrial private enterprises and public health suppliers which hinder the search of a negotiated agreement?
- Does the present analysis reveal options for finding common and consensus-enabling standards or guidelines?
- Which over-all cost-benefit and cost-risk ratios are arising from shortages if a global assessment over the whole supply-chain is conducted?

B. Added Value of Networking

Explain exactly and in practical terms why and how the pan-European coordination provided by COST would leverage non-COST funded human and physical resources (e.g. employee time; infrastructures). Explain why the same challenges could not be met at all or at the same level (in terms of scope, scale or quality) without a pan-European network.

BRINGING TOGETHER THE DIVERSE INTEREST GROUPS

In respect of the subject of the proposed Cost Action (medicines shortages), there is a diverse range of impacted stakeholders with legitimate interests in investigating, understanding and solving the difficulties. These include:

- The healthcare professional's interest in achieving the best clinical outcomes for patients (represented by physicians, pharmacists, nurses, physiotherapists, nutritionists, mid-wives, etc).
- The taxpayers' interests in achieving the best cost-benefit and cost-effectiveness ratio in the delivery of healthcare (represented by hospital administrators, politicians, governments, legal representatives, health insurance companies, etc.)
- The patients' interests in securing the best quality of life
- The manufacturer/supplier interest in achieving a profitable and sustainable return for investment of resources and capital risk

In relation to the medicines supply shortages problem in Europe there is no current forum in Europe that brings these interests together to share knowledge and research, and exchange experiences and ideas on resolution. It is hoped and intended that the proposed COST Action on medicines shortages can meet this unmet networking need.

THE 'BOTTOM UP' SOLUTIONS OPPORTUNITY OF SUCH A NETWORK

In untangling and resolving the medicines shortage problem in Europe, the diversity of interest in the subject from the full variety of stakeholders must be understood, balanced and reflected within any proposed settlement or set of solutions if unintended consequence is to be avoided. As examples:

- Understanding between payer interest and supplier of the consequences on supply chain sustainability of certain pricing and cost containment strategies;
- Appreciation between manufacturer and prescriber/dispenser/administrator of the impacts that short notice of medicines supply interruption can have in relation to the provision of high quality and safe care to the patient;
- Understanding between prescribers and dispensers of what is realistically possible in the way of sourcing alternative supply, recommending or manufacturing alternatives in the case of shortages that occur at short notice; and,
- Appreciation by policy makers of the seriousness of the medicines shortage problem from a patient care and health system sustainability perspective, and the accompanying urgency for policy development and implementation.

In line with the philosophy of the COST programme, it is by bottom up negotiation and discussion on medicines shortage solutions that more achievable and workable resolution programmes can be developed - as opposed to relying on top down created edicts that may not have benefited from stakeholder input and scrutiny. In view of no existing platform for structured and meaningful stakeholder exchange on the shortages problem currently existing, and the cited causational factors being supra national in nature, a supported COST international Action can fill the vacuum for debate that no other programme yet fills, or appears likely to.

Furthermore, a top down approach is hampered by the reality that health is a policy area for which the EU does not have direct legal competency, it being established as a reserved matter under a series of EU treaties. The need for well developed consensus is therefore heightened – this can occur through bringing together a network, such as that suggested within this Action.

BRINGING UNIQUE DISCIPLINARY INSIGHTS TOGETHER

Research in the health sector does not only happen on different levels (i.e. macro, intermediate and micro) but also in various settings (i.e. in-patient and out-patient levels, treatment and prevention, etc), in function of the perspective (i.e. medical, economic, ethics, organisational) various aspects and target groups are also in the focus (e.g. patient safety, quality of care, professional collaboration etc). Altogether this has brought about a variety of research skill sets, areas,

databases and knowledge repositories. Thus, health services research by itself and of its nature is multi- and trans-disciplinary. A new COST Action in the area of medicines shortages should aspire to integrate and reflect this diversity of expertise when investigating in full aspects such as the impact of medicines shortages, and the extent to which proposed solutions might be forecast to achieve their purpose.

The research question determines the methodology to be applied. In this shortages action, it will be rather a sequence of methodologies to be applied in order to obtain a change of the actual scene. In the beginning, the dominating question is the “why?” Literature already exists, and this will need to be reviewed completely. This first item has to be followed by a quantitative evaluation in an epidemiologic way, so that the question would be “what is theprevalence?” Also this step can be mostly derived from existing publications. However, the third step “how to improve the situation?” would require the intervention of a pan-European multi- and trans-disciplinary expert team.

BRINGING NATIONAL PERSPECTIVES AND EXPERIENCES TOGETHER

National perspectives on the nature (e.g. generics v originator etc), impact (delayed treatment, patient safety, time diversion), causation (e.g. pricing v parallel trade v small markets), and potential solutions available (e.g. regulatory v voluntary) in relation to the medicines shortage problem differ. There is a public interest in examining this difference between countries for the opportunities they afford to enhance understanding and shine a light on the transferable lessons it may provide to others.

On causation, it may be surmised that some countries in Europe have a higher vulnerability to small market shortages (e.g. Austria, Iceland, Switzerland), others to parallel export induced shortages (e.g. Programme countries such as Greece), others to pricing related shortages (e.g. those who have implemented different forms of cost containment programmes), and others to global production and quality issues. However, this remains largely assumption at the present time and to develop a better understanding the proposed COST Action should grasp the unique opportunity to bring those with strong national understanding of the problems together in order to generate a more coherent European understanding.

As an example of added value of networking **on the solutions perspective**, at national level, in some places, some moderate progress in the fight against shortages has already been achieved, such as in the case of remedial legislation in the USA focused on supply chain security[25]. However, this is not more than a first troubleshooting exercise whose sustainability is not yet warranted. In addition, it is not yet translated to other countries, thus the international dimension of potential solutions is not well known.

As another example, a promising approach of finding an agreement has recently been attained in Switzerland. The Swiss Association of Public Health Administration and Hospital Pharmacists (GSASA) has developed guidelines to cope with drug shortages[26]and, supported by the most important Swiss Associations and Federations of pharmacists (Swisspharma), physicians (FMH), and hospitals (H+), has signed an agreement with the leading associations of pharmaceutical industry (ASSGP, Intergenerica, Interpharma, Science industries, and Swiss Association of Importers of Proprietary Medicines (*VIPS*)) to readily provide pharmacies with active ingredients for individualized preparations and small scale stock production of commercially not available formulations or dosages.[27]

Alongside examination of FDASIA therefore, the proposed COST network would use the unique opportunity of an international network to draw insightful comparisons and make appropriate conclusions in order to guide improved international and national level policy making.

Other aspects of importance and value in relation to bringing together an international network through COST on medicines shortages includes enhancing the understanding of regional affordability aspects, in relation to both causation and solutions. Some regions of Europe may be able to afford certain remedial measures more than others (e.g. small-scale production), or may suffer impacts from shortages to a greater extent due to the unaffordability of alternative sources of supply. Better understanding of these aspects can bring new value to thinking about European solutions, likely only to be achievable via such an international network as offered by COST.

Members of the Network of Proposers for the ACTION have already pursued some avenues of contact with healthcare professionals, system managers, patient organisations and industry representatives in countries beyond Europe and can envisage the achievement of robust international exchange within the Action over the 4 year lifespan.

BRINGING THERAPEUTIC PERSPECTIVES TOGETHER

Shortages affect different disease conditions in different ways. For example, EAHP's 2013 survey on medicines shortages found that respondents reported oncology medicines to be among the most common in shortage, which is supported by anecdotal and evidence based reports elsewhere.[28-30] The Network of Proposers has thus had strong indicative interest in involvement from oncology professional and patient organisations to be part of the Action if approved.

Elsewhere, the impacts for rare disease patients are influenced by a set of different factors. In the first instance, diagnosis and initial treatments are provided within the hospital setting. Nonetheless patients require the stable supply of treatment and this may be provided by community care. Typical hospital preparations and/or orphan drugs that are used to treat rare diseases can become unavailable due to inability to meet the quality requirements expected from manufacturers or narrow profit margins. These products are sometimes even withdrawn from the market without being announced to pharmacies. This is due to focus being on the manufacture of medicines for which active ingredients and optimised production lanes in industry are already implemented. If any disruption occurs, it will have consequences, which may lead to the patient waiting or being unable to obtain the prescribed treatment. For similar reasons to the oncology example provided in the previous paragraph, so too the Network of Proposers has received strong positive interest from rare disease patients organisations to be involved in the potential Action.

The proposed COST Action can provide a unique way for all stakeholders in the medicines supply chain to better understand the impacts and nature of the shortages problem for different types of patients, all of which can usefully feed into the case and evidence base for solutions.

ENHANCING THE PROSPECT OF PAN-EUROPEAN SOLUTIONS

By bringing together interested observers, participants, impacted stakeholders, policy makers and payers from across Europe's diverse economic, political and health landscape with the purpose of sharing information, knowledge and ideas on the medicines shortage issues (in a manner not currently provided for) the prospect of being able to agree European level approaches towards solution are enhanced greatly. This is particularly meaningful for small countries that otherwise may face insurmountable obstacles in combatting the international factors causing the problem (production, pricing, incentives), or create the desirable support tools to alleviate the symptoms (e.g. comprehensive databases on the status of shortages).

In the view of the network of proposers, medicines shortages is a policy problem of sufficient public health concern to merit concerted pan-European action and cooperation between Governments. Compiling, sharing and analysing the evidence about shortages across countries should facilitate others to come to that understanding.

Such pan-European action could include pan-European reporting systems, definitions, targets, advice to health professionals, and clarification of ethical and legal obligations upon the manufacturers.

IN SUMMARY

In summary, it is the declared aim of the new Action to bring together ALL the primary stakeholders in the medicines supply chain process in order to find an agreement on the paths towards resolution of shortage problems across Europe.

No independent forum to achieve this currently exists, and no other pan-European mechanism for achieving this, and funding research-sharing activity, has been identified. COST therefore has enormous potential value to add in this

regard.

The alternative, of no such network, presents risks of fragmented national approaches, incoherent and trial-and-error policy responses being enacted based on incomplete policy understanding, poorly disseminated research findings, and lost opportunities to stimulate new research.

The Proposers are confident therefore that the added value of a COST Action research network on shortages can be demonstrated at an early stage, and via the breadth of anticipated participation, and the untapped desire to share information and knowledge in a coherent way via a formal network.

C. Milestones and Deliverables: contents and time frames

Describe the specific form of the activities (milestones and deliverables) needed to meet the challenge and selected as relevant to each objective: specify clearly the outputs corresponding to the achievement of your objectives and to the solution of the challenge proposed.For the main outputs, specify:

- *The means to achieve them;*
- *Their envisaged time frames.*

All milestones and deliverables should be:

- *Achievable within an Action's lifetime;*
- *Feasible in terms of content;*
- *Realistic in terms of time frame.*

At this stage, a few examples per objective (minimum 1) are sufficient, as work plans are finalized only once the COST Action starts.

REACHING CONSENSUS

For several years now countries in Europe, and elsewhere in the world, have been making steps to combat the problem of medicines supply shortages. In many countries awareness is reasonably established, at least amongst relevant health policy-making audiences. Some preliminary troubleshooting strategies include national level reporting systems or provider-user negotiated agreement.[31] Actions however are isolated and not generally coordinated between countries, or often even between relevant ministries and Government departments within a country. Furthermore, often only parts of the medicines supply chain participate in such actions.

Following systematic sharing and pooling of evidence and research, it is an ambition of the network of proposers that consensus papers, on the way forward, are signed up to by national and European Governmental and regulatory agencies, in addition to associations of health professionals, payer interest, patients and manufacturer/wholesalers. Consensus visions are set up as milestones and deliverables within the Action lifespan.

Initial scoping of interest in the proposed Action by the Network of Proposers leads to confidence that participation of such supply chain actors across Europe towards consensus agreements will be forthcoming. This is supported by knowledge of the achievement of such agreements from countries such as Switzerland, and the willingness of partners to engage in such agreements.

To achieve this consensus position deliverable, COST Action Main Milestones and Deliverables (Table 2, p14, *COST Open Call Guidelines for TDP Pilot*) 2 (Action Conference), 3 (Action Workshop), 10 (Handbook, Guidelines, Best practices) and 16 (Virtual Network) are likely to be utilised.

In timeline, **in a first phase of the Action (working packages 1 to 3)** working groups and corresponding working packages have to be built as follows:

- governmental and regulatory representatives;
- production and quality assurance specialists;
- independent (pharmaco-) economists, policy makers and deciders from enterprises, usually top managers, general directors of industrial associations;
- ethicists (with experience in ethical review boards/healthcare decisions);
- product managers, wholesaler representatives, procurement specialist in hospitals, usually hospital pharmacists;
- the most concerned clinicians (i.e. oncologists, microbiologists, immunologists, etc);

- patient organisations;
- other healthcare professionals; and,
- sociologists and other relevant disciplines.

In a second phase of the Action (working packages 4 and 5), as soon as interests of each working group will have been fixed, the new circumstances will have to be reframed and discussed on merged platforms. These will be:

- legal and governmental representatives together with production and quality assurance specialists;
- independent economists, policy makers and deciders of pharma and food industry together with health care providers and ethicists representing patients interests; and,
- supply chain managers and health care providers such as hospital pharmacists and clinicians.

In the course of these negotiations, discrepancies resistant to direct agreements may arise. In this case, the regrouped teams have to separate again and BATNAs and WATNAs (Best and Worst Alternatives to Negotiated Agreements) have to be negotiated and mediated at the round table until an agreement will have been found.

In a third phase of the Action (working packages 5 and 6), plenary meetings of all working groups will be scheduled. The findings of the merged working groups will be debated in plenary round-table meetings with all stakeholders in order find a negotiated agreement. If this fails in a first attempt, mediation will be implemented to attain a final agreement which will be a common compromise between individual best and worse alternatives to negotiated agreements (BATNA and WATNA). The Managing Committee will have to formulate on this common basis a proposal for an adoptable resolution which will be approved by the plenary assembly and be submitted not only to all involved professional associations, but also, it is hoped, to European Councils and national governments.

The situation related to foodstuff will be prospectively assessed in an own focus group as soon as clarity is obtained from the pharma supply chain. As an alternative, it may be subject for a following project separated from the medicines cases as far as GMP guidelines and quality requirements are less restricted than in pharma domain.

DATA COLLECTION AND MANAGEMENT

Data collection and management as well as statistics will be of particular importance, as only consolidated approved common data will be acceptable as a basis for negotiations.

As is the case in anaesthesia and intensive care units, better reporting systems in Europe in the area of medicines shortages may be suitable tools to promote transparency and error culture (critical incidence reporting system CIRS[32]). Incidents can be reported and are available for evaluation.

For this, a European drug shortages bank (EDSB) or European shortages prevention and availability reporting system (EU-SPARS) (denomination is still open), within which all cases of medicines, nutriceuticals, foodstuff and devices shortages should be reported is envisaged as an important deliverable. This could be an increased development from the existing EMA Shortages catalogue[12] or a bespoke product.

Such an option, which was realised and successfully installed in the eighties and nineties by the GSASA as a Clearing Centre for contested raw materials[33] has lead to a net and sustainable improvement and stabilisation on a high level of the quality of contested raw material for pharmaceutical production in hospitals. The Clearing Centre could be closed later as there were almost no more contested materials of inacceptable quality on the market. This principle of a Clearing Centre translated into a more modern reporting system will be the most promising approach to create a basis for an analysis of the shortage problem and for finding an agreement.

As dependencies and interrelations are to be examined, statistical analysis will be performed on the reported shortage data using binary logistic regression with likelihood ratio back elimination and common Odds Ratios. The assessment of the cases relies on statistical calculations using SPSS latest version. As a multivariate dependency, the probability of a

shortage can be expressed using binary regression analysis. The power analysis reveals that 200 cases with an error probability alpha of 0.05 and beta of 0.12, with a confidence interval of 95% and a Nagelkerke R^2 off 0.6 results in a power of 0.8 [34, 35]. No exclusion criteria seem to be applicable. Cases, which have been resolved in the meantime, need to be analysed too. They may help to find a coping strategy and an agreement.

To achieve this data collection and management deliverable, COST Action Main Milestones and Deliverables (Table 2, p14, *COST Open Call Guidelines for TDP Pilot*) 16 (Virtual Network), 17 (Website), 20 (Development of Software), and 21 (Database) are likely to be utilised.

Project Plan

Working Package 1: 01.01.2015 – 31.01.2015

- Tasks
  - Recruit and fix support of professional associations and of experts along the supply chain, definition of working groups, special interest groups, focus groups
    - Governmental and regulatory representatives
    - Production and quality assurance specialists
    - Independent (pharmaco-) economists, policy makers and deciders from enterprises
    - Ethicists and mediators
    - Product managers, wholesaler representatives, procurement specialist in hospitals, usually hospital pharmacists
    - The most concerned clinicians (i.e. oncologists, microbiologists, immunologists, et cetera)
    - Sociologists
  - Milestones
    - Support of associations and experts is fixed
    - Kick-off Congress and workshop programmes are announced on time
    - A draft version of the Memorandum of Understanding of the COST Action is available and sent with the Congress invitation

Working Package 2: 01.02.2015 – 30.06.2015

- Tasks
  - Kick-off congress and first meetings of working and special interest groups
  - Approval, implementation and promotion of the European medicines shortages catalogue as a reporting system
  - Development of questionnaires for retrieval of lacking data in parallel focus groups
- Milestones
  - Kick-off Congress and workshop meetings have successfully been accomplished
  - Catalogue of “to do”s of each working group is fixed
  - Approvals on strategies are obtained

Working Package 3: 01.07.2015 – 31.12.2015

- Tasks
  - Retrieval of retrospective data
  - Ongoing prospective data collection for an undetermined length of time
  - Data synchronisation and consolidation on a further annual basis
  - Elimination of multiple records (key: EAN code)
  - Statistical calculations of correlations and of dependences on a further annual basis

        - Binary logistic regression
        - Odds Ratios
    - Non-statistical analysis and assessments on a further annual basis
        - Case histories
        - Interpretation in parallel focus groups
        - Integrated interpretation
    - Organisation of the first fall symposium and workshop meetings
    - Mediation processes for working groups failing in getting agreements on their position
- Milestones
    - Collection of retrospective data on shortages is available and running stable
    - Prospective data is retrieved and consolidated
    - Each working and special interest group has found an agreement for their position in the following negotiations
    - Statistics is calculated and made available to working groups for interpretation

Working Package 4: 01.01.2016 – 31.12.2016

- Tasks
    - Merging working groups according to their interfaces along the supply chain
        - Legal and governmental representatives together with production and quality assurance specialists
        - Independent economists, policy makers and deciders of pharma and food industry together with health care providers and ethicists representing patients interests
        - Supply chain managers and health care providers such as hospital pharmacists and clinicians
    - Spring Congress and workshop meetings
    - Fall symposium and workshop meetings
    - Mediation processes for merged working groups failing in getting agreements on their common position
    - Ongoing data synchronisation, consolidation, and interpretation (including statistics) on an annual basis
    - Prospective evaluation of the situation related to foodstuff
- Milestones
    - Each merged working and special interest group has found an agreement for their position in the following plenary negotiations
    - The deductively assessed situation of food industry is fixed and further actions to anticipate shortages of the “pharma type” are defined

Working Package 5: 01.01.2017 – 31.12.2017

- Tasks
    - Development of a shortage policy
    - Pharmacoeconomical evaluation of cost – benefit per stakeholder
    - Global pharmacoeconomical evaluation
- Milestones
    - Shortage policy is developed
    - Global pharmacoeconomical assessment is done

Working Package 6: 01.01.2018 – 31.12.2018

- Tasks
    - Round-table meetings for negotiation of agreements
    - Finding BATNA and WATNA (best or worse alternatives to negotiated agreements)
    - Final reports, communications and valorisation
- Milestones
    - Agreements are negotiated OR Alternatives are found
    - End of project

D. Action structure and participation – Working Groups, management, internal procedures

Describe the Action organization in terms of Working Groups and management structure that would best help the Action meet the proposed challenge. Bear in mind that the proposed Action organization and management structure must respect COST rules. In particular:

- *Management Committee Members are nominated by the COST National Coordinators*
- *Working Group Members and Occasional Participants are decided directly by the Management Committee, but their reimbursement is constrained by budget availability*
- *Working Groups and management can be adapted by the Management Committee of the Action during an Action's lifetime.*

Reasons for medicines shortages are multi-factorial, arising from: investment decisions (or lack thereof) into the supply chain; decisions taken by multi-national enterprises; production related items including ambitious quality requirements; disruptions in logistics and the supply chain; erroneous stock management; unexpected increase in demand; export of medicines; macroeconomic impacts, and other factors.

Meanwhile, the level of access to health services and the incidence rate of medicines shortage are more generally dependent on macro factors such as financial systems, organisational processes, health technologies, individual behaviour, market structures, quality, security, efficiency and efficacy.

Gaining an enriched understanding of the medicines shortage problem therefore requires examination of the interactions between the key health service players and the population, on an intermediate level, the services and logistics management from manufacturers to providers of services, and on a micro level, the interrelation between healthcare professionals and patients.

The resilience of healthcare providers in coping with drug shortages is a crucial area for investigation if consequences such as decreased patient safety and reduced patient outcomes are to be prevented. All stakeholders acting in the medicines supply chain are envisaged to be part of a new Action. Professional associations, associations of manufacturers, pharma industry and wholesalers as well as governmental delegates have to find an agreement or resolution. As the problem is a global one, the action structure must consist of a multinational multidisciplinary approach and organisation. A resolution, or any international agreement, should be nationally adopted.

Initial private scoping of interest in the prospective Action with patient groups, other healthcare professionals (including doctors, nurses and various branches of pharmacy) and patient organisations (cancer and rare disease) has engendered a strongly positive response. Direct approaches to the pharmaceutical manufacturing and wholesale industry on the topic have not yet been made, but in view of the public activity of these interest groups in this area, we predict interest will be forthcoming if the Action is approved. Likewise, regulatory and governmental agencies such as the European Medicines Agency and DGs SANCO and ENTERPRISE, already conducting workshop and papers in this topic area, should have motive to be involved. Bespoke approaches may be required for national medicines agencies and health ministries.

In timeline, **in a first phase of the Action (working packages 1 to 3)** working groups and corresponding working packages have to be built as follows:

- governmental and regulatory representatives;
- production and quality assurance specialists;
- independent (pharmaco-) economists, policy makers and deciders from enterprises, usually top managers, general directors of industrial associations;
- ethicists (with experience in ethical review boards/healthcare decisions);
- product managers, wholesaler representatives, procurement specialist in hospitals, usually hospital pharmacists;
- the most concerned clinicians (i.e. oncologists, microbiologists, immunologists, etc);
- patient organisations;
- other healthcare professionals; and,
- sociologists and other relevant disciplines.

In a second phase of the Action (working packages 4 and 5), as soon as interests of each working group will have been fixed, the new circumstances will have to be reframed and discussed on merged platforms. These will be:

- legal and governmental representatives together with production and quality assurance specialists;
- independent economists, policy makers and deciders of pharma and food industry together with health care providers and ethicists representing patients interests; and,
- supply chain managers and health care providers such as hospital pharmacists and clinicians.

In the course of these negotiations, discrepancies resistant to direct agreements may arise. In this case, the regrouped teams have to separate again and BATNAs and WATNAs, best and worst alternatives to negotiated agreements, have to be negotiated and mediated at the round table until a agreement has been found.

In a third phase of the Action, plenary meetings of all working groups will be scheduled. This will be the second plenary assembly after the kick-off meeting. The Managing Committee will have to formulate a proposal for an adoptable resolution which will be approved by the plenary assembly and be submitted not only to all involved professional associations, but also to European Councils and national governments.

The following list describes how and in what frequencies working groups will be invited to real or virtual meetings:

		Meetings Kick-off and annual congress (spring)	Symposium (fall)	Biannual workshop	Telephone or Skype Conference	On demand
Activity	Managing Committee	X	X	X	X	X
	Working and Special Interest groups	X	X	X	X	X
	Scientific Missions	X				X
	Training					X
	Dissemination					X

This would lead to the 2015 schedule as follows:

- January, February 2014: Telephone and Skype Conferences, on demand activities (MC and WG/SIG Leaders)
- March 2015: Kick-off Congress with Keynotes, Seminars, Workshops, Special Interest Groups
- April, May, June, July, August 2014: Telephone and Skype Conferences, on demand activities (MC and WG/SIG Leaders)
- September 2014: Symposium with Workshops and Working & Special Interest Groups meetings
- October, November, December 2014: Telephone and Skype Conferences, on demand activities (MC and WG/SIG Leaders)

The Action depends on the development of a European platform and the implementation of a European shortages prevention and availability reporting system (EU-SPARS) in order to harmonise actions against shortages. This duty has to be assumed by both the Action's Managing Committee and by a nationally founded research and development group which shall give the technical support. Retrospective data will have to be retrieved eventually by the aid of national associations. Prospective data shall be reported and saved directly in the databank by users themselves. With comprehensive data only, a true analysis, prevention and anticipation of shortages can be obtained. Assessment, interpretation and policy development will be performed by focus groups.

The situation related to foodstuff will be prospectively assessed in an own focus group. It may be subject for a following project. These specific findings will be debated in reframing round-table meetings with the stakeholders in order find a negotiated agreement between manufacturers of nutritional products and consumers representatives.

Network of Proposers - Features

Countries*:

9 COST Country Institutions

- Switzerland
- Belgium
- Netherlands
- Latvia
- Austria
- Denmark
- Germany
- Italy
- Ireland

0 Near-Neighbour Country Institutions

0 COST International Partners

0 European Commission and EU Agencies

0 European RTD Organisations

0 International Organisations

** This section lists the countries of the institutions with which Proposers are affiliated. Proposers affiliated with more than one institution are asked to choose the institution that is most relevant to the Proposal. Independents are not eligible to be Proposers, as specified in the COST Guidelines for TDP Pilot.*

Number of Proposers: 11

Gender Distribution of Network of Proposers: Males 54.5%; Females: 45.5%

Average number of years elapsed since PhD graduation of Proposers***: 21.5

****This figure takes into account only those Proposers who reported holding a doctoral degree, i.e. of all Proposers. The calculation is based on the month and year in which the last doctoral degree was obtained by each Proposer.*

Number of Early Stage Researchers****: 1

*****This figure takes into account only those Proposers who reported holding a doctoral degree, for whom a maximum of 8 years elapsed between the date of in which their PhD was awarded and the date of submission of this Proposal.*

Core Expertise of Proposers: Distribution by Sub-Field of Science****:

36.4% Health Sciences
36.4% Other medical sciences
18.2% Clinical medicine
9.1% Basic medicine

*****The Core Expertise is defined by each Proposer at registration and it is the sub-field of science corresponding to the first research exertise area selected.*

Institutional distribution of Network of Proposers*****:

45.5% Higher Education & Associated Organisations
27.3% Government/Intergovernmental Organisations except Higher Education
18.2% Private Non-Profit without market revenues, NGO
9.1% Standards Organisation

Higher Education & Associated Organisations: 5

Number by Field of Science of Department/Faculty of Affiliation:
- Health Sciences : 2
- Clinical medicine : 1
- Other medical sciences : 2

Number by Type:
- Education Oriented : 4
- Research Oriented : 1

Number by Ownership:
- Fully or mostly public : 5

Government/Intergovernmental Organisations except Higher Education: 3

Number by Level:
- Central and Federal Government : 1
- Local government : 2

Number by Type:
- Other Public Non-Profit Institution : 2
- Government department or government-run general public services : 1

Private Non-Profit without market revenues, NGO: 2

Number by Type:
- Advocacy/Membership Organization : 2

Number by Level:
- International or European : 2

Standards Organisation: 1

Number by Membership type:
- With no government membership : 1

Number by Level:
- National : 1

***** *Based on contractual relationship deemed as most relevant to the Proposal by each Proposer.*

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You are free to provide bibliographic references. This section is shown to evaluators but it is optional and is not necessarily taken into account for evaluation purposes.

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Network of Proposers

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