1. Problem Statement

Global health crises, including public health emergencies of international concern, can be unpredictable, multifaceted and involve multiple stakeholders in addition to regulators. The role of health regulatory authorities (HRA) in crisis management may not be clear or can be misunderstood.

Moreover, global health crises frequently become political priorities with multiple stakeholders playing a part and competing for limited resources. Health product related activities are often fundamental to the management of the crisis.

Hence, it is important to clarify the role of regulators and to open pathways for HRA engagement in a coordinated response and communication strategy to global health crises at the international level.

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1 In the context of the ICMRA Mapping Project, participating countries agreed to conduct a preliminary mapping of the major on-going regulatory initiatives aimed at or impacting on managing of global health crises, from a regulatory perspective (EMA paper: “International Coalition of Medicines Regulatory Authorities (ICMRA) Priority Identification: Preliminary Analysis of Current Initiatives on Health Crisis Management Including Gaps, Opportunities and Challenges” (EMA/592161/2015, November 3rd 2015). The ICMRA Management Committee also provided key “probing questions” for ICMRA to address.

2 See 3.

3 In this document, health regulatory authorities refer to national regulatory authorities responsible for the regulation of medical products.

Disclaimer: This document has been endorsed as a formal ICMRA document by ICMRA members.
There are some initiatives dealing with a global health crisis at an international level, such as the Global Health Security Initiative (GSHI), the Coalition for Epidemic Preparedness Innovations (CEPI), and several WHO initiatives: R&D Blueprint, the International Health Regulations (IHR), the Emergency Use Assessment and Listing (EUAL) and the Program on Health Emergencies. Occasionally, some HRAs are called upon to contribute to the discussion. At a regional level, some initiatives are also in place, such as the EU Incident Management Plan (IMP), which involves regulators in the continuous monitoring of incidents that may have a serious impact on public health, or the African Vaccine Regulatory Forum (AVAREF), in which African regulators can share information and accelerate development of medical products towards regulatory approval, including clinical trial approvals.

However, until now, there was no global mechanism for managing a crisis focused on Health Regulatory Authorities. This framework was developed to meet the need to have better international coordination in the regulatory field.

2. Purpose

This document is a framework for the involvement of HRAs in the management of global health crises in a coordinated and consistent manner. It addresses the roles and responsibilities of HRAs in this process, as well as identifies the opportunities for international collaboration. It also establishes a Standard Operating Procedure (SOP) for HRAs dealing with global health crises, through a structure of communication among HRA’s focal points, a platform/forum for information exchange and roles of the secretariat for organizational support\(^4\) (Annex 1).

3. Defining global health crises from the health regulators’ perspective

A Public Health Emergency of International Concern (PHEIC) is defined in the WHO IHR (2005) as “an extraordinary event which is determined, as provided in these Regulations:

(i) to constitute a public health risk to other States through the international spread of disease; and

(ii) to potentially require a coordinated international response”. This definition implies a situation that is serious, unusual or unexpected; carries

\(^4\) Based on FDA paper: “ICMRA Standard Operating Procedure – Facilitating Prompt Collaboration among Heads of Regulatory Authorities”.


implications for public health beyond the affected State’s national border; and may require immediate international action.  

For this paper, and considering the HRA specificities, a global health crisis is considered as an unforeseen occurrence, or a combination of circumstances, that poses a significant public health risk to several countries and that involves the safety, efficacy, security and availability of health products (e.g. pharmaceuticals), and that potentially requires or would benefit from a coordinated international response by HRAs. A public health risk is not limited to the spread of diseases.

After assessing the event’s associated risks, if routine processes for response are not considered sufficient, therefore urgent and coordinated action is required to manage and control the situation. Since each event situation is unpredictable, dynamic and has the potential to escalate into an emergency, each ICMRA member should be prepared to act, preferably, before a crisis emerges.

3.1. Major scenarios of global health crisis related to HRA activities

Involvement of regulators in health crisis as defined above can be envisaged in three major scenarios:

**Scenario 1 - Incidents of quality or safety issues for products on the market, where such quality or safety issues have a global impact on public health.**

It is expected to have some cases that could be categorized as incidents related to quality or safety. While most the cases would be expected to be ordinary and would be addressed with existing resources and protocols each HRA already has at its disposal, there may be events of quality or safety issues that require a broader involvement and collaboration among HRAs. Only those few incidents would be categorized as a potential global health crisis in Scenario 1.

Examples might include the assessment of a worldwide incident with a medicine with potential serious adverse event, which can also lead to the lack of substitute product.

It is up to each involved HRA to assess and decide if an incident would require or benefit from broader international involvement, liaising with the concerned HRAs.

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5 WHO. IHR Procedures concerning public health emergencies of international concern (PHEIC). PHEIC Procedures
through ICMRA. On a case-by-case basis, different actions can be considered, including liaising bilaterally with HRAs, contacting WHO or its regional offices, or working through ICMRA, bringing together a group of involved HRAs, national public health organizations, or experts to deal with the incident.6

**Scenario 2 - Unavailability of products due to a crisis, where already registered products are in short supply or unavailable due to stockpiling.**

Unavailability of medical products used to prevent or treat a serious or life-threatening disease for which there is no other available source with sufficient supply of that product available, is very challenging and can easily evolve into a crisis. HRAs can play an important role to minimize negative impact on patients, healthcare facilities and clinicians. Examples in this category may include a viral pandemic where antiviral medications or vaccines are in shortage or unavailable.

In this scenario, to have an international consultation or exchange of information could be helpful. Beside possible actions listed under Scenario 1, different approaches could be applied, varying from simple consultation through email up to establishing virtual or face-to-face meetings.

**Scenario 3 - Urgent need for new medical treatments or vaccines in the face of an emerging health threat**

This applies to situations where there are true unmet needs, the demand for regulatory actions and no treatments available7. An incident will be categorized in

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6 Within the European Union (EU), the incident management plan (IMP) ensures that the concerned bodies take appropriate action whenever incidents arise concerning human medicines. The incident review network (IRN) reviews incidents in terms of their impact on public health and the measures needed to address them. The IRN decides if an incident would require/benefit from a broader international involvement.

7 World Health Organization. 2018 Annual Review of the Blueprint List of Priority Diseases: Potential to cause a public health emergency and the absence of efficacious drugs and/or vaccines, there is an urgent need for accelerated research and development for Crimean-Congo hemorrhagic fever (CCHF), Ebola virus disease and Marburg virus disease, Lassa fever, Middle East respiratory syndrome coronavirus (MERS-CoV) and Severe Acute Respiratory Syndrome (SARS), Nipah and henipaviral diseases, Rift Valley fever (RVF), Zika, Disease X. Available from:  http://www.who.int/blueprint/priority-diseases/en/
scenario 3 whenever WHO declares it a Public Health Emergency of International Concern (PHEIC).

In this Scenario, each Country’s Ministry of Health (MoH) and WHO will take measures using already established WHO-IHR mechanisms. Nationally, HRAs should provide the necessary support when requested. Additionally, in this context, it is up to HRAs to identify authorized or new medical products under assessment to participate in collaborative initiatives in the regulatory field, or to facilitate development and availability of novel technologies.

4. Principles, Roles and Responsibilities

The principles of Crisis management by ICMRA members include:

**Collaborative** – creating and sustaining broad and sincere relationships among individuals and organizations to encourage trust, advocate a team atmosphere, build consensus, exchange information and facilitate communication.

**Comprehensive** – considering all threats, phases, scenarios, stakeholders and all impacts relevant to global health crises.

**Confidential** – regarding restricted information and use secure communication channels. Depending on the type of information exchanged, *ad-hoc* confidentiality agreements may need to be established.

**Coordinated** – synchronizing the activities and communication of all relevant stakeholders to achieve a common purpose.

**Flexible** – using creative and innovative approaches to solve global health crises challenges.

**Integrated** – ensuring unity of effort and transparency at all domestic levels of government and all elements of ICMRA.

**Patient-focused** – ensuring patients’ health and wellbeing guide regulatory actions and decisions.

**Professional** – valuing a science and knowledge-based approach based on education, training and preparedness (international simulation), experience, ethical practice, public stewardship and continuous improvement.

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Progressive – anticipating future crises and taking preventive and preparatory measures against damage to global public health.

Risk-based – using sound risk management principles (hazard identification, risk analysis and impact analysis) in assigning priorities and resources.

Transparent: conducting organizational operations and decisions with accountability, trustworthiness and transparency and the goal of building and maintaining trust among ICMRA members and others involved with the coalition.

4.1 Roles and Responsibilities

ICMRA recognizes WHO as the international leader in most global public health emergencies situations. Looking for better collaboration between ICMRA members and WHO, ICMRA encourages WHO to contact ICMRA Chair or Secretariat whenever regulatory actions are required in a global health crisis.

The roles and responsibilities applicable to ICMRA members are the following:

**ICMRA Secretariat:**

- To activate and maintain contact with HRA’s designated focal points or through appropriate channels.
- To receive, coordinate and share information and requests with all ICMRA members (analysis of specific regulatory situation, international collaboration, data access and organizational information sharing, assuming necessary confidentiality agreements are established).
- To engage with WHO and other international organizations requiring or providing situational information.
- To disseminate or communicate the position of ICMRA on required issues, when agreed.
- To invite other ICMRA non-members to participate in ICMRA discussions.

**ICMRA members**

**A. Actions applicable nationally by HRAs, if appropriate:**

- To develop and implement a national plan for health emergency situations, before a crisis arises⁹.

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⁹ The Strategic Framework for Emergency Preparedness published by WHO (http://apps.who.int/iris/bitstream/10665/254883/1/9789241511827-eng.pdf) can assist the development of national plans. It is a unifying framework which identifies the principles and elements of effective country health emergency preparedness.
To provide a dedicated incident management structure.

To collaborate closely with national authorities to support disease surveillance, risk assessment, PHE preparedness and response measures (e.g. to be represented on the national Health Emergency Committee, usually coordinated by the Ministry of Health).

Share scientific information and data relating to the cause or etiology of the crisis, with a view to mitigate the risks for the population.

Facilitate multinational assessment including setting up multinational expert groups

Coordinate inspections necessary in case of quality defects, or clinical trials in emergency situations, as necessary

To prioritize and expedite the evaluation and approval of new pharmaceutical and diagnostic products, as well as vaccines and medical products needed to address public health emergencies.

To consider implementing facilitated regulatory pathways for marketing approval of drugs already approved by other HRAs.

To monitor the conduct of clinical trials in the context of the crisis.

To establish regulatory guidance for associated risks to health products related to the health threat, whenever necessary.

To provide concerned authorities with any updated information on risks associated with crisis-related health products.

To communicate to the public or specific groups (e.g. healthcare professionals, press) the rationale for apparently divergent actions taken at national level.

To strengthen the post market surveillance (quality, safety and efficacy) of health products associated with the health threat.

B. Applicable to international collaboration:

To exchange information on actions taken nationally by HRA about events with a potential to escalate into a crisis.

To provide public interest advice to support development and availability of the novel medical product, including vaccination strategies in the case of novel vaccine.

To participate in collaborative regulatory initiatives, such as WHO’s R&D Blueprint10.

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10 The R&D Blueprint was developed at the World Health Assembly in May 2016. It is a global strategy and preparedness plan that allows the rapid activation of R&D activities during epidemics. Its aim is to fast-track the availability of effective tests, vaccines and medicines that can be used to avert large scale crisis.
To explore the feasibility of cooperation among ICMRA members on the clinical and quality evaluation of novel products, to achieve faster approval at national level.

To discuss the benefit-risk profile of the novel medical product based on scientific evidence and clinical practice consideration, applicability of the result to the concerned population, and to discuss the sub-populations (if any) that would benefit from the use of the novel medical product.

To provide the post-marketing surveillance framework needed to ensure safe and effective use of the novel medical product.

To review and assess the impact of major safety issues and advise the appropriate regulatory actions to be taken to maintain the positive benefit-risk profile.

To notify ICMRA Secretariat of potential or ongoing national emergencies, especially those that may affect other countries.

To identify alternative manufacturers for the product in shortage, and to check their availability to start production.

To provide regulatory assistance on technology transfer processes, to enable other manufacturers (public or private) to start production in an expedited timeframe.

5. Communications

Communications are a key part of managing a global health crisis. Through effective communication, it is possible to provide the required information and reach stakeholders in a timely manner, be open and transparent about regulatory processes, ensure coordination of regulatory actions, and maintain confidence in the regulatory authorities during a crisis showing how international collaboration is taking place. The SOP attached provides the mechanism for ICMRA members to communicate with one another during such event. It is also recognized that communication with key stakeholders, such as the WHO (and its regional offices, when necessary), may also be required. In relation to the WHO and depending on the nature of the emergency, it is recommended to use, the secretariat of the recently updated WHO Program on Health Emergencies, or the Department of Essential Medicines and Health Products (Appendix A).

In addition, outwards communication via press releases or statements on the regulators’ websites may also be helpful. Sharing such information may be facilitated through the ICMRA secretariat in conjunction with the ICMRA communication group, as established in Appendix B, C and D.
1. Purpose

- To provide a coordinated and consistent global approach to preparing for, preventing, protecting against, mitigating, responding to, and recovering from incidents involving or impacting products regulated by ICMRA members.

- A longer-term objective is global coordination and communication between various stakeholders to expand the global reach and leverage our individual and collective responses. Special attention will be given to the communication strategy, so the coordination will be prompt and effective and contribute to the coherence of measures necessary in a crisis.

2. Definitions

- A global health crisis is considered as an unforeseen occurrence or a combination of circumstances that poses a significant public health risk to other States and that involves the safety, efficacy, security and availability of health products, and that potentially requires a coordinated international response by HRA. After assessing an event’s associated risks, routine measures are found not sufficient and therefore urgent and coordinated action is required to manage and control the situation.

- A requestor is defined as an ICMRA member, ICMRA non-member or non-HRA organization seeking to quickly bring together selected global regulatory counterparts for a discussion on a public health emergency issue.

- A principal is defined as the Head of the Regulatory Authority.

3. Communications

ICMRA members can engage in global health crisis management based on a comprehensive approach. It can encompass a range of prevention, preparedness, response and recovery actions which can be applied in a broad sense to an unknown disease outbreak or, alternatively, in a narrower context, such as the response to a specific incident of products quality or safety issues.
It is encouraged that simple mechanisms of exchange of information between requestors and ICMRA Members are adopted. ICMRA Secretariat will facilitate communication, receiving requests and forwarding to ICMRA Emergency Contact List. However, for those cases where ICMRA Chair and/or ICMRA Executive Committee foresee that the emergency notified requires or can benefit from an Emergency call among ICMRA members, the next steps below can be triggered.

Requestors can submit a Notification Form (Appendix A) to the Secretariat to notify of an emergency. The agenda for the Emergency call (Appendix B) can be submitted together or right after the Notification form.

ICMRA Secretariat will assist the requestor in alerting the ICMRA Emergency Contact List and will provide logistical support, as necessary, to ensure that prompt dialogue occurs. The ICMRA members may identify experts or a multi-disciplinary team to address in a timely and effective manner specific issues, including matters required by Non-HRA organizations.

Outcomes of the discussions and key decisions taken during the call can be forwarded to ICMRA members using a Meeting Report (Appendix C). At any time, ICMRA may need to communicate with Non-HRA organizations. This will be made according to Appendix D.

ICMRA Secretariat responsibilities on these issues may include: i) to organize ICMRA Emergency Contact List, according to the procedures agreed on this document; ii) to support ICMRA members on summarizing meeting reports; iii) to develop/organize the institutional memory of the discussions; iv) to facilitate teleconference meetings among ICMRA members, upon request; v) to facilitate communication with WHO, or other non-HRA organization.

**ICMRA Emergency Contact List**

- Each ICMRA Member should identify at least two points of contact. The Head of the Regulatory Authority him/herself may be the first one and an institutional email could be the second one. Additional contacts can be provided.
- Whenever ICMRA Secretariat contacts ICMRA Members requesting/providing information on a crisis situation, at least one of the NRA’s points of contact should confirm the receipt of the email within one working day.

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11 Whenever possible, ICMRA Secretariat should provide a virtual communication mechanism to support the expedited share of information among ICMRA members, allowing other NRAs and WHO to have access to and use information or any update as soon as it is made available.
ICMRA Emergency Contact List will be managed by the ICMRA Secretariat and regularly updated and circulated to ICMRA members.

ICMRA members are responsible for alerting the ICMRA Secretariat when their Emergency Contacts change.

ICMRA Emergency Contact List should include names, titles, organizations, email addresses, work telephone numbers, and mobile telephone numbers.

Email

During an emergency, the requestor should complete the form in Annex A and send it by email, to ICMRA Chair and ICMRA Secretariat.

The requestor will work with the ICMRA Secretariat to select a date/time, send a meeting invitation, and circulate any relevant background documents.

Teleconferences

ICMRA Secretariat and the requestor will work together to organize the emergency ICMRA teleconference, unless otherwise specified.

The requestor should provide an international teleconference number. If the requestor is unable to do so, ICMRA Secretariat will provide one.

If the requested participants are not available during the selected teleconference time, they will designate a representative to participate.

A template agenda for emergency calls is included in Appendix B.

The call leader or the ICMRA Secretariat will distribute to ICMRA Members the highlights and action items from the teleconference within 2 days of the teleconference.

The teleconference developments may be forwarded to ICMRA members using Appendix C.
4. APPENDIX A: Notification Form

Date: ____________________________  [ ] FOR ICMRA’s Crisis Management Only
(mm /dd / yyyy North American Format)  Please check the box if the provided notification
contains classified information

Initiated/Requested by: ________________
[ ] Name of ICMRA Member
[ ] Name of ICMRA non Member
[ ] Name of non-HRA organizations

Type of Regulatory Discussion to occur (please select):
[ ] Policy              [ ] Information Exchange
[ ] Technical issues    [ ] Unknown
[ ] International Collaboration

Scenario
[ ] Incidents of quality or safety issues for products
[ ] Unavailability of products
[ ] Urgent need for new health technology
[ ] Other

Specific Type of Event (multiple answers possible)

______ Chemical  ________ Outbreak
______ Biological  ________ Incidents of quality/safety issues
______ Radiological  ________ Products Shortage/Unavailability
______ Unknown  ________ Other: specify

Officials to participate (please select):
______ Senior Officials
______ International Office Officials
______ Others (please be specific)

Short description of event (provided by initiating ICMRA Member): ____________________________
____________________________________________________________________________________
____________________________________________________________________________________

Troubleshooting

____________________________________________________________________________________
____________________________________________________________________________________

ICMRA Secretariat  ICMRA Chair
Head of International Office | Policy - EU &  CEO MHRA
International Policy & Strategy  Medicines and Healthcare products
Medicines and Healthcare products Regulatory  Regulatory Agency (MHRA)
Agency (MHRA)  Tel: +4420 3080 6000
10 South Colonnade  Ian.Hudson@mhra.gov.uk
Canary Wharf  ICMRA Secretariat
London  Head of International Office | Policy - EU &
E14 4PU  International Policy & Strategy
Canary Wharf  Medicines and Healthcare products
London  Regulatory Agency (MHRA)
Tel: +44 20 3080 6311  ICMRA Secretariat
ICMRASEC@mhra.gov.uk

12 It should be used by ICMRA members or ICMRA non members, including non-HRA organizations.
5. APPENDIX B: Template Agenda for Emergency Calls

Proposed time of Teleconference:

1. Brief Summary of the Issue and Purpose of the Call
   Call leader (either the ICMRA requestor or the Secretariat)

2. Roundtable: Updates from other Countries
   All

3. Identification of:
   • additional countries ICMRA may need to talk to/coordinate with; and
   • external stakeholders ICMRA may need to talk to/coordinate with.
   All

4. Assign who will Lead the Communication Outreach to the Parties Identified in Agenda Item 3, if any
   Call leader (either the ICMRA requestor or the Secretariat)

5. Summary of the Discussion and Action Items
   Call leader (either the ICMRA requestor or the Secretariat)

6. APPENDIX C: Template Meeting Report

1. Summary of the Discussion
   Call leader (The Secretariat)

2. Main Decisions
   All

3. Next Steps
   All

4. Next Meeting (if it is the case)
   All
7. APPENDIX D: Non-HRA organizations to receive ICMRA crisis communications\textsuperscript{13}

Principles:

It is assumed that each HRA will be responsible for ensuring that ICMRA crisis communications are delivered to the relevant government agencies and health system organizations within its jurisdiction.

Based on the nature of each crisis, a judgement will be made with regard to which organizations from the following list of non-HRAs need to receive the communications issued.

The Secretariat will co-ordinate liaison between the relevant members to decide which non-HRA organizations are to be included in the communications:

- Where an incident team has been established, it will work with the Chair of the Communications Group to suggest a communication plan, which will then be agreed with the MC Chair and Vice Chairs.
- Where there is no incident team, the requesting member will work with the Chair of the Communications Group to suggest a communication plan, which will then be agreed with the MC Chair and Vice Chairs.

The non-HRA organizations should be segmented into priority stakeholder groups to reflect the relevance and perceived level of influence they may hold in relation to the specific crisis incident:

- **Priority One** stakeholders – the incident is of high relevance to these stakeholders and they will be able to influence the course of action taken, support ICMRA’s position, or enable ICMRA communications to reach a wider relevant audience. They should receive a targeted communication from ICMRA, seeking their support, and reinforced, where appropriate, by direct contact from an ICMRA member HRA or representative of the MC. This group may include the general public.
- **Priority Two** stakeholders – the incident is of intermediate relevance to these stakeholders. They will be able to either support ICMRA’s position or enable ICMRA communications to reach a wider relevant

\textsuperscript{13} This document was prepared by the ICMRA Communication Group.
audience. They should receive a generic communication from ICMRA seeking their support and inviting further engagement if required.

- **‘Priority Three’ stakeholders** - the incident is of low relevance to these stakeholders but they will enable ICMRA communications to reach a wider relevant audience. They should receive a generic communication from ICMRA for information only.

In all cases where the stakeholder is a national or regional organization, the relevant HRA(s) will take the lead in the communications approach.

**Non-HRA organizations:**

**Other international collaborative bodies for medicines regulation**
- HMA - Heads of Medicines Agencies (EU)
- ICDRA – International Conference of Drug Regulatory Authorities
- ICH – International Council for Harmonization
- IPRP – International Pharmaceutical Regulators Program
- IRCH – International Regulatory Cooperation for Herbal Medicine
- PIC/S - The Pharmaceutical Inspection Convention and Pharmaceutical Inspection Co-operation Scheme

**International collaborative bodies for the pharmaceutical industry**
- AESGP – Association of the European Self-Medication Industry
- AIPM – Association of International Pharmaceutical Manufacturers
- BIO – Biotechnology Industry Organization
- EFPIA - European Federation of Pharmaceutical Industries and Associations
- Medicines for Europe (generics, biosimilars)
- FIP – International Pharmaceutical Federation
- IPFMA - International Federation of Pharmaceutical Manufacturers & Associations
- IGPA – International Generic Pharmaceutical Alliance
- JPMA – Japan Pharmaceutical Manufacturers Association
- PhRMA – Pharmaceutical Research and Manufacturers of America
- WSMI – World Self-Medication Industry

**International regulatory and enforcement agencies**
- APEC - Asia Pacific Economic Cooperation forum
- EDQM – European Directorate for the Quality of Medicines & Healthcare
- IAMRA – International Association of Medical Regulatory Authorities
- OECD - The Organization for Economic Co-operation and Development
- ASEAN – Association of South East Asian Nations
- PAHO – Pan American Health Organization
- WHO – World Health Organization

**Global science//professional/research/academic networks**
- AAPS – American Association of Pharmaceutical Scientists
- EAPB – European Association of Pharma Biotechnology
- FIP – International Pharmaceutical Federation
- ICR - Institute of Clinical Research
- ISPE – International Society for Pharmacoepidemiology
- PDA – Parenteral Drug Association

**International patient networks**
- EPF - European Patients’ Forum
- EURORDIS- European Organisation for Rare Diseases
- IAPO - International Alliance of Patients’ Organisations
- NORD- North America Organization for Rare Diseases

**Other organizations with an interest in healthcare**
- Bill & Melinda Gates Foundation
- DIA –Drug Information Association
- RAPS – Regulatory Affairs Professionals’ Society
- TOPRA – The Organisation for Professionals in Regulatory Affairs

**Global pharma/medicines media**
- BioPharm International
- International Pharmaceutical Regulatory Monitor
- Pharmaceutical Business Review
- Pharmaceutical Engineering Magazine
- Pink Sheet
- Politico
- SCRIP Intelligence
- WorldPharma