Promoting Patient Safety: From Bench to Bedside?

First Collaborative Pharmacy Conference: Promoting Patient Safety through Pharmacy Practice, Technology & Research Conference

Mohamed Izham M.I., PhD & Husam Younes, PhD
Professors of College of Pharmacy
Sheraton Doha – Qatar
April 22-23, 2016

Disclaimer: *The presenting authors has no relationship to disclose*

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1st Collaborative Pharmacy Conference
Promoting Patient Safety through
Pharmacy Practice, Technology and Research
22 to 23 April 2016 | The Sheraton, Doha

جامعة قطر QATAR UNIVERSITY | RGU ROBERT GORDON UNIVERSITY ABERDEEN

Presentation:
Promoting Patient Safety: from Bench to Bedside

Mohamed Izham M.I., PhD & Husam Younes, PhD
Professors of College of Pharmacy

Learning Objectives

- Understand the current status of pharmaceutical regulatory environment in the region
- Understand key elements of the quality control/assurance process for pharmaceuticals
- Understand the real example(s) representing interchangeability challenges and quality of marketed medicines.

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Presentation Outline

- Current status of pharmaceutical regulatory environment
- Cases/Studies
- Recommendations

Background

- According to Hughes and Blegen (2008), lack of appropriate policies, procedures, and protocols can impact medication safety in institutional setting

(Hughes RG & Blegen MA, 2008)

Background

- **Billions of Dollars, Thousands of Lives**
  - Globalization of pharmaceutical markets and production has increased the spread and prevalence of unsafe medicines.

Background

- Two categories:
  - counterfeit medicines
    - deliberately forged and mislabeled
  - substandard medicines
    - do not meet the required quality or safety standards

(Torstensson and Pugatch 2010)

Evidence of Unsafe Medicines

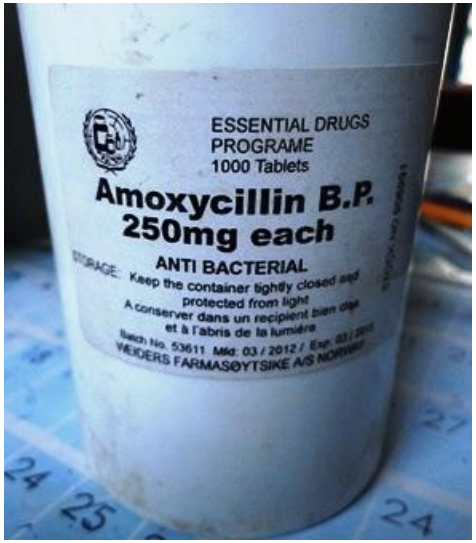
At micro level…….

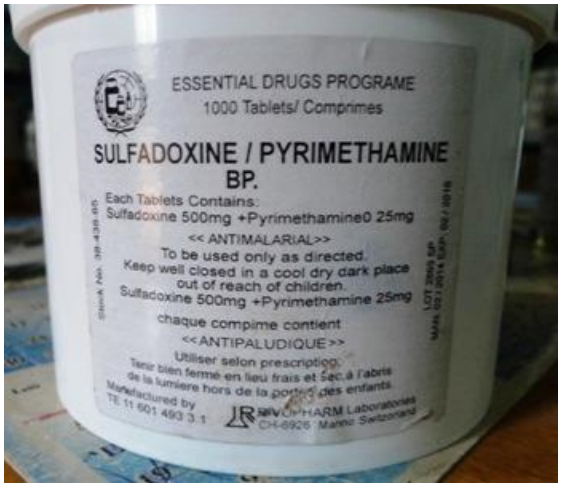
Wrong vaccines send schoolgirl into coma

Saudi Gazette Saudi Gazette – Wed, Nov 19, 2014

Saudi Gazette – Wed, Nov 19, 2014

Eg.: FALSIFIED MEDICAL PRODUCTS





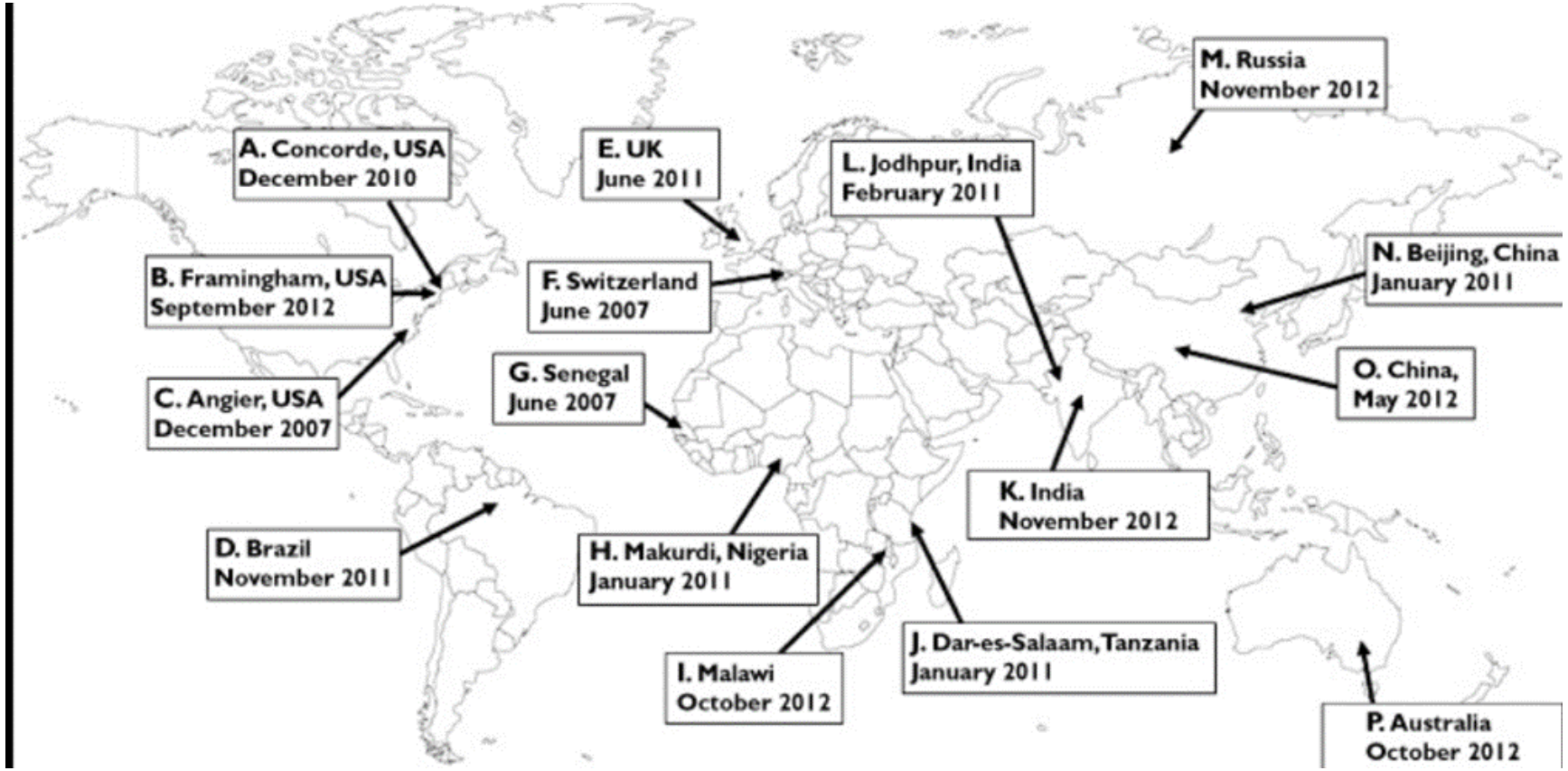
Amoxycillin B.P 250 mg (Weiders ; BN 53611)

Quinine sulphate 300 mg B.P (Remedica ; BN 44675)

Quinine sulphate 300 mg B.P (Weiders ; BN 9765)

Sulfadoxine + pyrimethamine (Rivopharm ; BN 2869 SP)

Substandard drugs: A potential crisis for public health



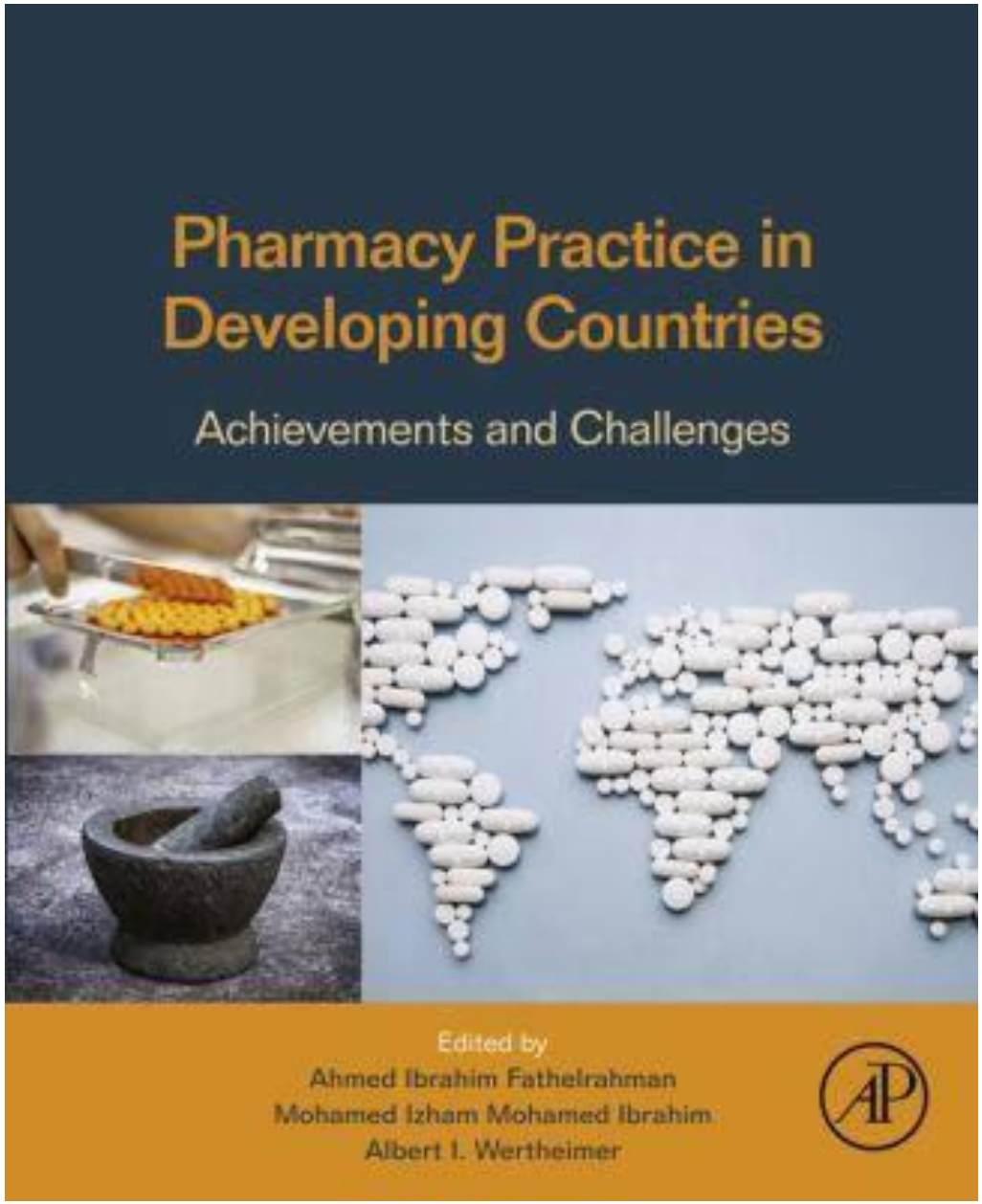
Johnston A & Holt DW, 2013

Medicines Regulatory Systems

- WHO Drug Information 2008, approximately:
  - 20 % of countries have fully operational medicines regulations
  - 50 % have regulations of varying capacity
  - 30 % have either none or very limited drug regulation

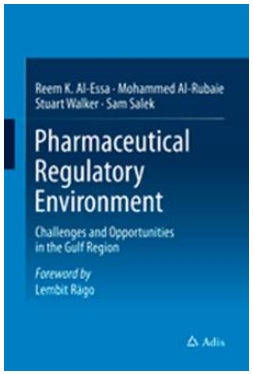
- Many developing countries are incapable of ensuring safety, efficacy and quality of the pharmaceutical products available in their markets because they are resource constrained in terms of staffing, standard systems and training

Pharmacy Practice in Developing Countries: Achievements and Challenges offers a detailed review of the history and development of pharmacy practice in developing countries across Africa, Asia, and South America. Pharmacy practice varies substantially from country to country due to variations in needs and expectations, culture, challenges, policy, regulations, available resources, and other factors.



Medicines Regulatory Systems

- The Middle East and North Africa (MENA) region comprises:
  - around 2 % of the global pharmaceutical market, with an average annual growth of 10.4 %;
  - the Arab market (22 Arab countries) comprises 1.5 %, valued at around US$6.2 billion, of which the largest market is Saudi Arabia, valued at around US$1.2 billion



(Nixon and Trombe 2013)

Table 1.2 The structure, responsibilities and scope of activities within each of the seven Gulf Cooperation Council (GCC) regulatory authorities

Country		Bahrain	Kuwait	Oman	Qatar	Saudi Arabia	UAE
Name of authority		National Health Regulatory Authority	Kuwait Drug and Food Control	The General Directorate of Pharmacy and Drug Control	The Pharmacy and Drug Control Department	Saudi Food & Drug Authority	The Registration and Drug Control Department
Independent stand-alone authority		✓	✗	✗	✗	✓	✗
Budget/GBP		NA	2 million	NA	NA	85 million	1.6 million
Fees/GBP		9	230	130	None	>5,000	NA
Scope of registration responsibilities	Medicines for human use	✓	✓	✓	✓	✓	✓
	Veterinary medicines	✗	✓	✗	✗	✓	✓
	Medical devices and in vitro diagnostics	✓	✓	✓	✓	✓	✓
	Cosmetic products	✗	✓	✗	✗	✗	✗
	Food supplements	✗	✓	✗	✗	✗	✗
	Herbal medicines	✗	✓	✗	✗	✗	✗

(continued)

Table 1.2 (continued)

Country		Bahrain	Kuwait	Oman	Qatar	Saudi Arabia	UAE
Scope of activities	Marketing authorisation	✓	✓	✓	✓	✓	✓
	Post-marketing surveillance	✓	✓	✓	✓	✓	✓
	Sample analysis	✓	✓	✓	✓	✓	✓
	Advertising control	✗	✓	✓	✗	✓	✓
	Price regulation	✓	✓	✗	✓	✓	✓
	GMP inspection	✓	✓	✗	✗	✓	✗
	Clinical trial authorisation	✗	✗	✓	✗	✓	✓

Medicines Regulatory Systems

- The initiation of the harmonization of the regulatory process in the GCC started in 1976
  - pharmaceutical companies apply satisfactory standards to guarantee manufacturing of quality, safe and effective medicines
  - standardize their regulations with regard to medicines importation practices in the Gulf states

- GCC Central Drug Registration (GCC-DR) Committee was formed in May 1999
  - all the GCC authorities are equally responsible for evaluating the quality, safety and efficacy of medicines
  - all countries provided with copies of the product registration dossier for their individual assessments

Medicines Regulatory Systems

- Mission of the GCC Central Drug Registration (GCC-DR)
  - establish central group-purchasing program
  - establish a unified Gulf Drug Registration System
  - ensure good manufacturing practices (GMPs) according to international standards
  - carry out post-marketing surveillance after registration
  - use of highly effective and safe medications to protect public health in the Gulf countries

Medicines Regulatory Systems

- A face-to-face meeting with all the Directors and General Directors of Regulatory Affairs in the Ministry of Health in the GCC states took place during the GCC-DR meetings in 2011 and 2012

(Al-Essa RK et al. 2015)

Regulatory Review Times in the Gulf Region

Table 3.1 Number of approved products for GCC in 2008, 2009 and 2010

Countries	Type of company	2008	2009	2010
		Approved products	Approved products	Approved products
Bahrain	Gulf	**5**	5	51
	Arab non-Gulf	**25**	37	42
	Asian	**7**	2	19
	International	**50**	105	62
	Total	**87**	**149**	**174**
Kuwait	Gulf	81	51	43
	Arab non-Gulf	94	38	46
	Asian	17	3	5
	International	224	106	116
	Total	**416**	**198**	**210**
Oman	Gulf	52	37	56
	Arab non-Gulf	15	25	29
	Asian	15	5	12
	International	89	105	81
	Total	**171**	**172**	**178**
Qatar	Gulf	56	57	134
	Arab non-Gulf	39	13	11
	Asian	1	0	0
	International	107	30	62
	Total	**203**	**100**	**207**
Saudi Arabia	Gulf	150	91	16
	Arab non-Gulf	25	52	19
	Asian	0	0	0
	International	134	132	57
	Total	**309**	**275**	**92**

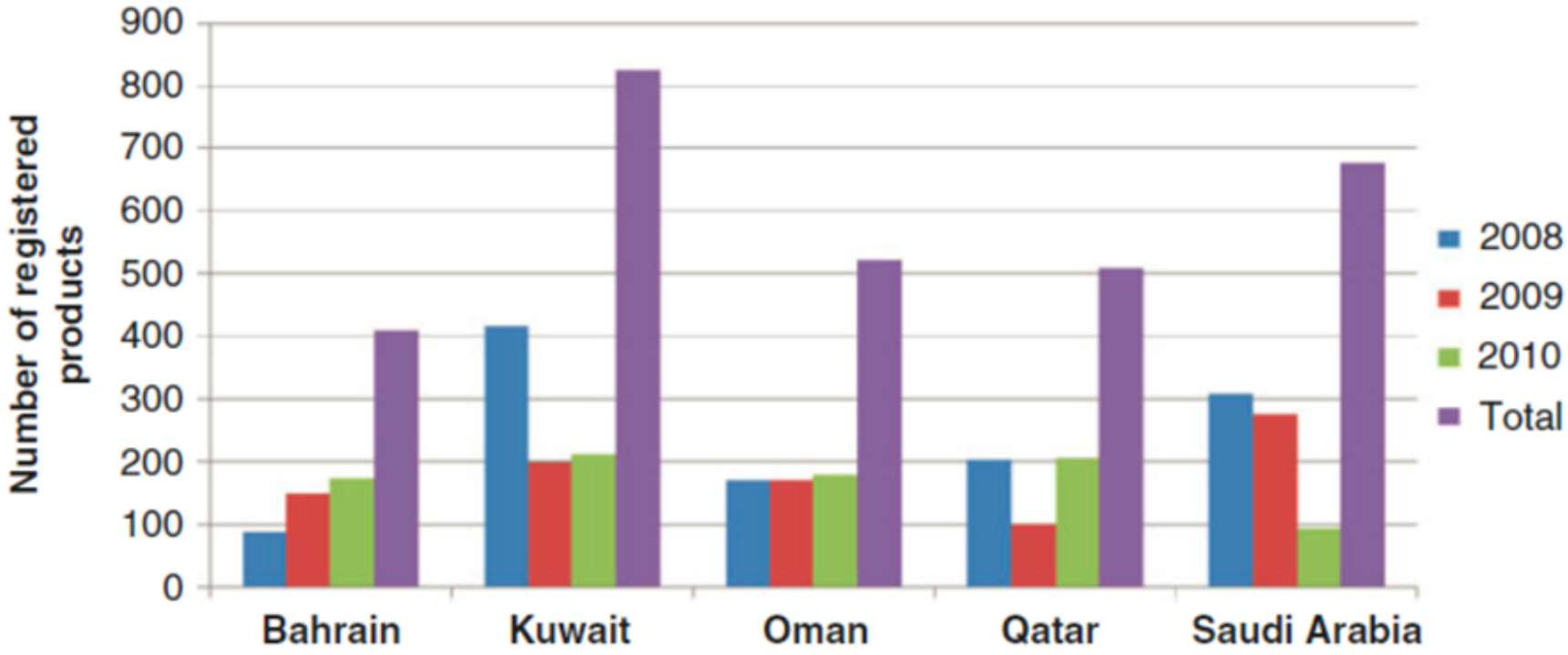


Fig. 3.1 Number of approved products by five regulatory authorities (2008–2010)

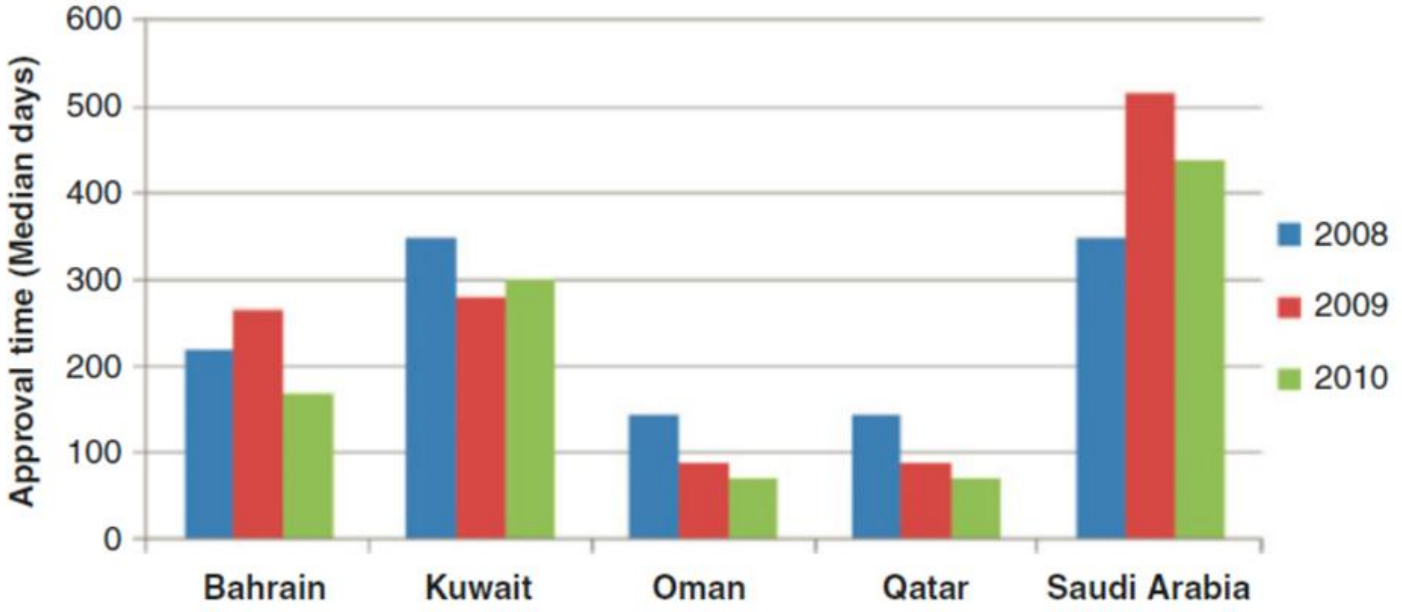


Fig. 3.2 Median approval times for all products (2008–2010)

The median approval time for all approved products in the GCC states ranged from 69 days in Oman and Qatar in 2010 to 515 days in Saudi Arabia in 2009

Qatar also experienced a decrease in the registration period for the three years: 143 days in 2008 and 69 days in 2010

Quality Measures in the Gulf Regulatory Practices

Table 4.2 Measures used to achieve quality in the GCC review processes

Quality measure	Bahrain	Kuwait	Oman	Qatar	Saudi Arabia	UAE
Quality policy	✓	✓	✗	✗	✗	✓
Good review practice (GRP)	✓	✗	✗	✗	✗	✗
Standard operating procedures (SOPs)	✓	✗	✓	✓	✗	✓
Assessment templates	✓	✓	✗	✗	✓	✓
Internal peer reviews	✓	✗	✓	✗	✓	✓
External peer reviews	✗	✗	✓	✗	✗	✓
Shared/joint reviews	✓	✓	✓	✓	✓	✓

Table 4.3 Quality audit and feedback activities carried out to improve the quality of the assessment and registration process in the GCC states

Activities that bring improvement in the review process	Bahrain	Kuwait	Oman	Qatar	Saudi Arabia	UAE
Reviewing assessors' feedback and taking necessary action	✓	✓	✗	✓	✓	✓
Reviewing stakeholders feedback and taking necessary action	✓	✓	✓	✓	✓	✗
Using an internal tracking system to monitor (e.g. consistency, timeliness, efficiency and accuracy)	✓	✓	✓	✗	✓	✗
Carrying out internal audits and using findings to improve the system	✓	✗	✓	✓	✓	✗
Having external quality audits by an accredited certification body to improve the system	✗	✗	✓	✗	✗	✗
Having a 'post-approval' discussion with the sponsor to provide feedback on the quality of the dossier and obtain the company's comments	✓	✓	✗	✗	✗	✓

The Current Status of the Common Technical Document

- The most significant regulatory initiative that the GCC member states have proactively implemented as part of their goal to standardize their regulatory systems is the Common Technical Document

- Pharmacovigilance (PV) and medicines communication has also been an important initiative by the GCC countries, but it has not yet been fully regulated to reach the European or US standards

Table 5.3 Overall SWOT analysis for the GCC regulatory authorities

Strengths	**Weaknesses**
Experienced regulatory staff	Shortage of experts in CTD evaluation
Well-established authorities	Lack of training and educational programmes
Existing legislations and regulations	
Active cooperation between the authorities	
Opportunities	**Threats**
Working in collaboration with regional and international agencies	High staff turnover
Emerging technologies seeking new modern drug approval processes, e.g. e-CTD	Increased number of substandard and counterfeit medicines

ttp://www.un.org/africarenewal/magazine/may-2013/counterfeit-drugs-raise-africa%E2%80%99s-temperature

The Current Status of Drug Safety and Pharmacovigilance

- Although an awareness of the important role of drug safety monitoring (pharmacovigilance) in the Gulf states has dramatically improved in recent years, communication of medicines benefits and harms between the various stakeholders, such as regulatory authorities, pharmaceutical industry, healthcare professionals and consumers, lags far behind

- According to Harrison-Woolrych (2012):
  - core of successful risk management lies in effective risk communication
    - PV activities,
    - risk management plans (RMPs) and
    - risk minimization activities

- Current Pharmacovigilance Practices in the Gulf Region

Table 6.1 Current initiative of pharmacovigilance in each Gulf states

Questions	Bahrain	KSA	Kuwait	Oman	Qatar	UAE
Do you have a PV department?	No	Yes	Yes	Yes	No	Yes
How many people employed in the PV department	NP	14	3	3	NA	2
To whom does the PV department report?	NP	Vice President of Drug Affairs	Head of Registration Department who reports to the Registration and Release Superintendent	Director of Drug Control	NA	Director of Department
Do you collaborate with other authorities within the region?	NP	No	Yes	Yes	Yes	Yes
Do you work with the industry?	NP	Yes	Yes	Yes	Yes	Yes

KSA Kingdom of Saudi Arabia, *NP* not provided

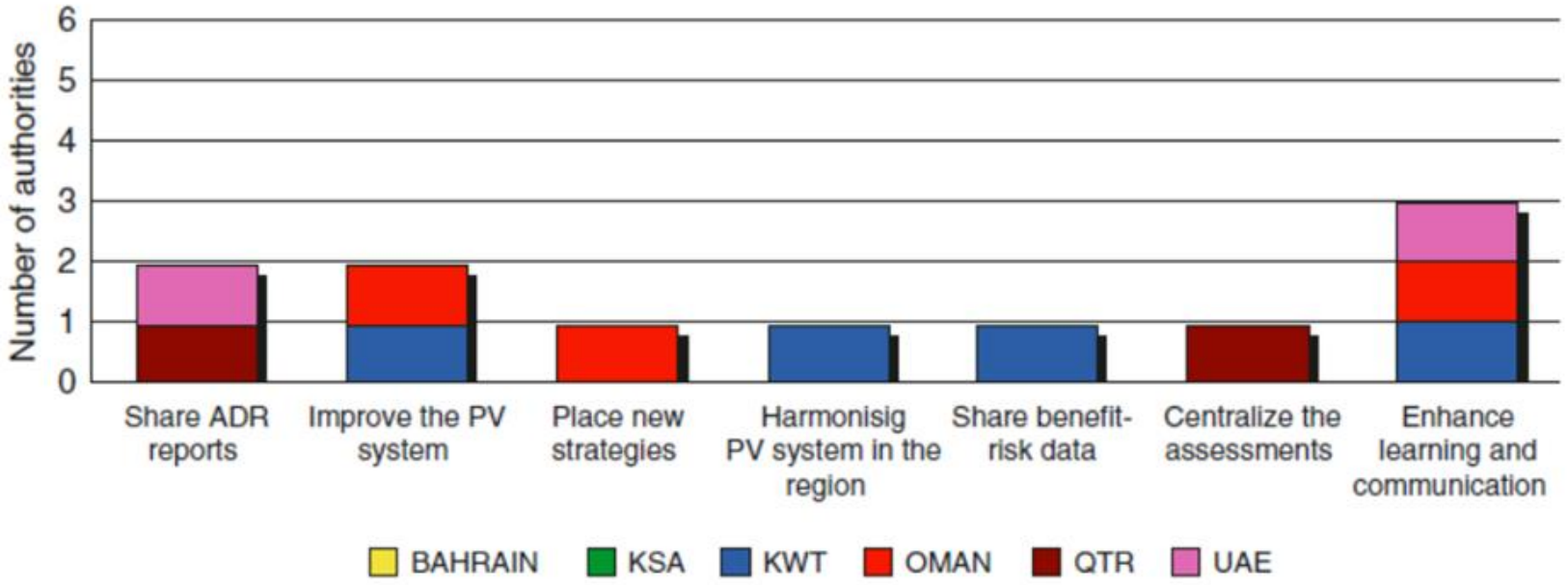


Fig. 6.1 Purpose of collaborative efforts between the GCC regulatory authorities

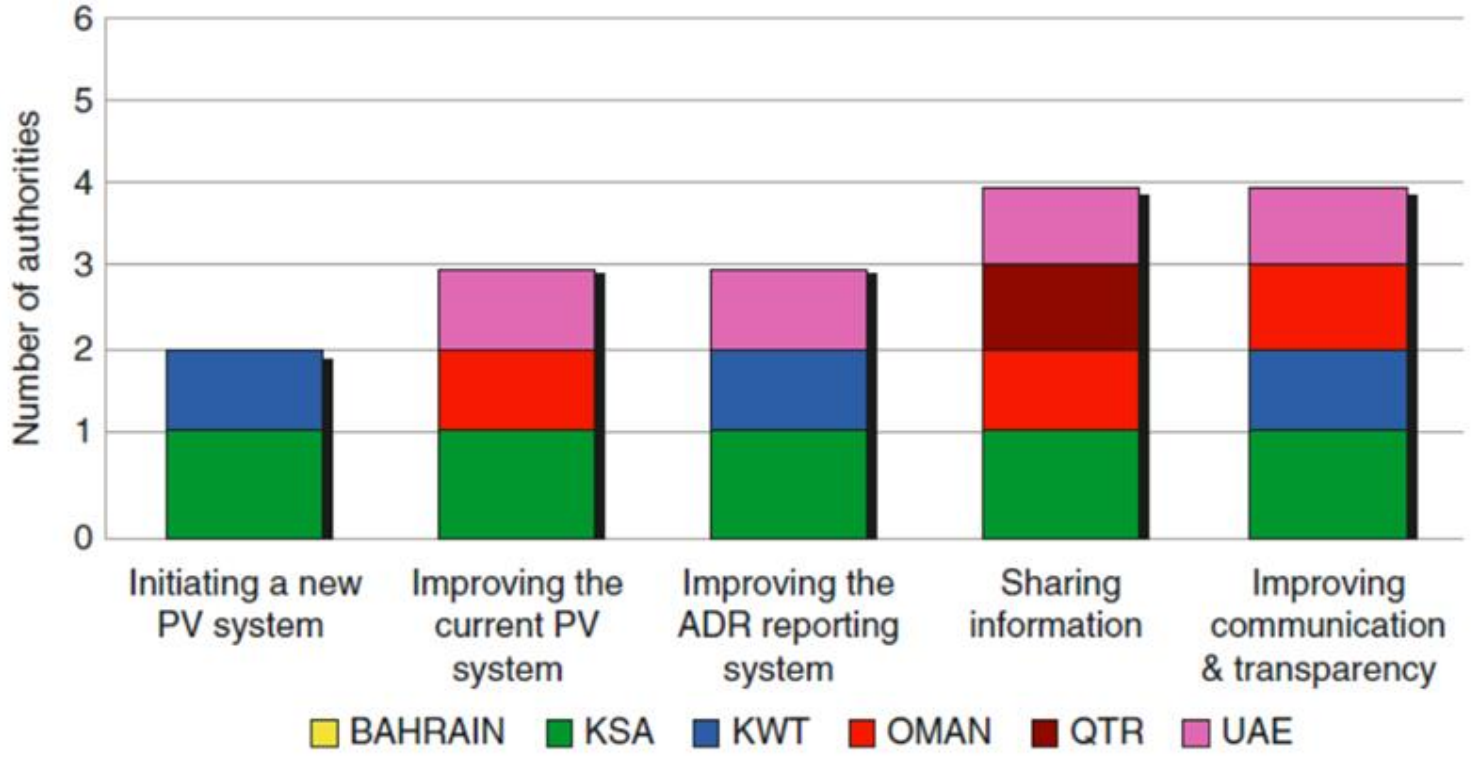


Fig. 6.2 Reasons for working with the pharmaceutical industry

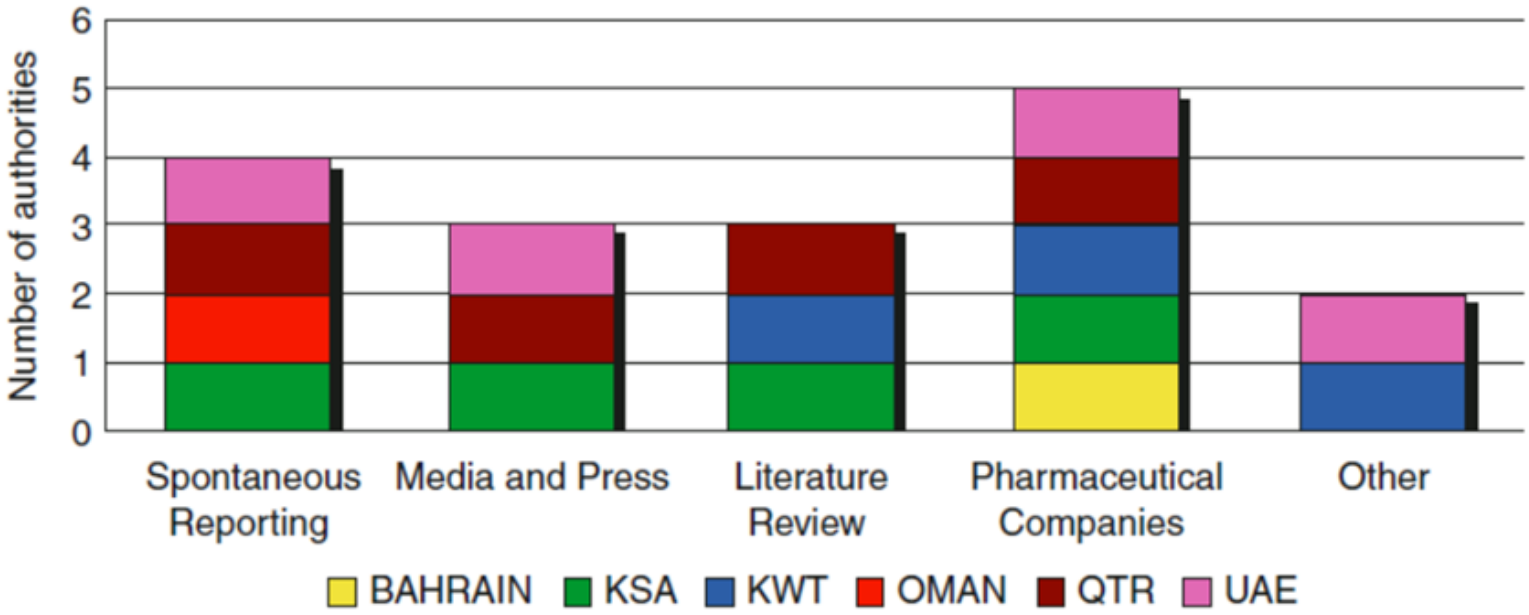


Fig. 6.3 Methodology for collecting adverse drug reaction reports by the GCC regulatory authorities

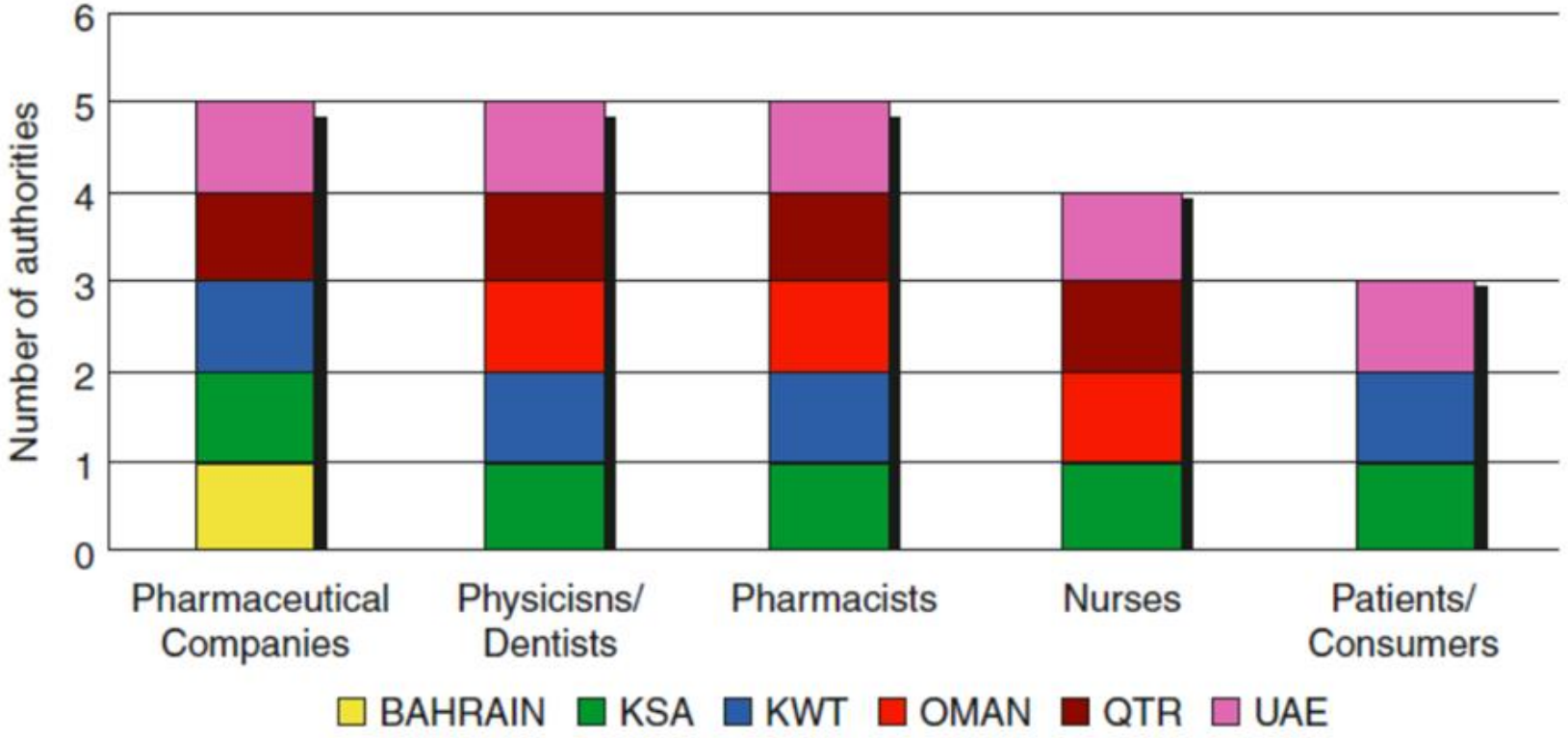


Fig. 6.4 Adverse drug reaction reporters to the GCC regulatory authorities

Table 6.2 Management of the adverse drug reaction reporting system in each Gulf state

Question	Bahrain	KSA	Kuwait	Oman	Qatar	UAE
Do you have a standard reporting form?	No	Yes	Yes	Yes	Yes	Yes
Who evaluates adverse drug reaction reports?	NP	Internal Assessor	Internal Assessor	Internal Assessor	Committee	Internal Assessor Committee
Authorities views on the role of industry in reporting adverse drug reactions?	NP	Mandatory	Mandatory	Mandatory	Mandatory	Mandatory

KSA Kingdom of Saudi Arabia, *NP* not provided

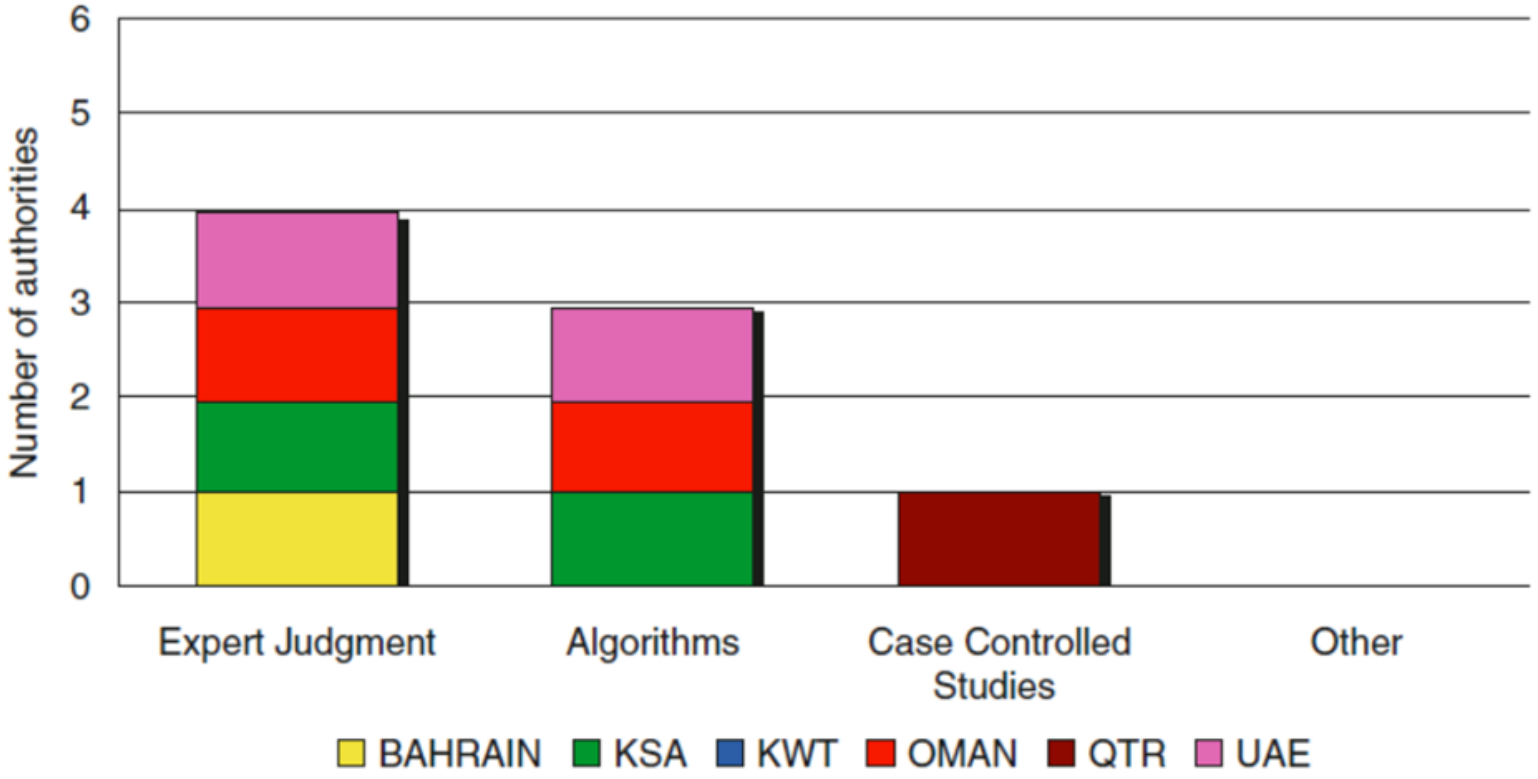


Fig. 6.5 Causality assessment methods adopted in the Gulf region

Table 6.3 Status of benefit-risk assessment and communication in the Gulf

Question	Bahrain	KSA	Kuwait	Oman	Qatar	UAE
Are you aware of the PBRER?	Yes	Yes	Yes	Yes	Yes	Yes
Is it of value to review adverse drug reactions without looking at the benefits of the medicines?	NP	No	No	No	No	No
Should there be benefit-risk assessment in the post-marketing period of medicines?	NP	Yes	Yes	Yes	Yes	Yes
Do you have a benefit-risk assessment framework for the regulatory review phase?	NP	No	No	No	No	Yes as per EMA
Would you be interested in being provided with a framework?	NP	Yes	Yes	Yes	Yes	NA
Do you have a plan to initiate a framework for benefit-risk assessment?	NP	Yes[a]	No	Yes	No	NA
Do you have an established mechanism for communicating the outcome of the reported adverse drug reactions?	NP	Yes	Yes	Yes	Yes	Yes

KSA Kingdom of Saudi Arabia, *NP* not provided

[a]A new department for benefit-risk assessment will function next year (2015) in Saudi Arabia and will implement a new framework for this activity

* periodic benefit-risk evaluation reports (PBRERs)

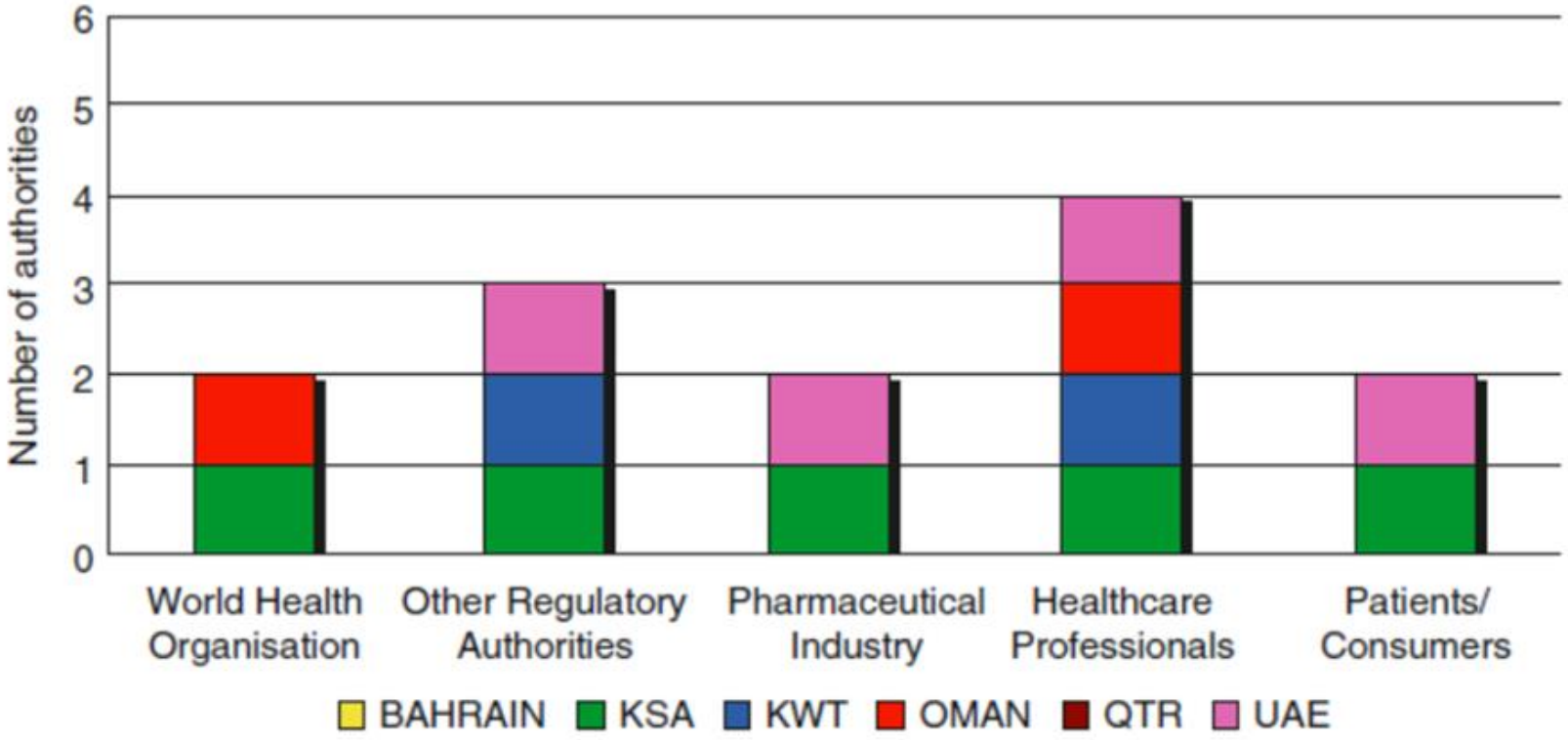


Fig. 6.6 Sectors receiving adverse drug reaction from the GCC regulatory authorities

Table 6.4 Regulators' views on the driving forces for effective pharmacovigilance systems in the Gulf region

Country	Drivers for effective PV system
Bahrain	Not provided
KSA	1. Highly skilled staff
	2. Financial support
	3. Administrative support
Kuwait	1. Raising awareness about healthcare professionals and patients about the importance of appropriate reporting
	2. Experts and well-trained staff for effective evaluation of reports
Oman	1. Public awareness about the PV system
	2. Coordinated multidisciplinary efforts amongst healthcare professionals
	3. Continuing education programmes with IT support
Qatar	1. National awareness on adverse drug reactions
	2. Encourage patients and healthcare professionals to report all types of adverse drug reactions
	3. Comply with international standards and ensure appropriate monitoring system for adverse drug reaction reporting
	4. Ensuring safety of available medications in the country
UAE	1. Importance of patient safety and evaluation of drug safety
	2. Governmental health recommendations and strategies to provide patients with best service through benefit-risk evaluation
	3. PV is about benefit-risk evaluation, which aims at providing the best treatment

KSA Kingdom of Saudi Arabia

Table 6.5 Regulators' views on the obstacles for effective pharmacovigilance system in the Gulf region

Country	Obstacles to effective PV system
Bahrain	1. Limited staff number
	2. Budget
KSA	1. Underreporting
	2. Many pharmaceutical companies in the region have not yet developed systems of PV
	3. Limited collaborations from some of the government sectors
Kuwait	1. Lack of proper reporting (number and quality of reports are low)
	2. Lack of qualified human resources
Oman	1. Lack of awareness amongst reporters
	2. Misconception about adverse drug reaction reporting within the private sector
	3. Staff has limited background knowledge and exposure to PV
	4. Back up of IT support
Qatar	1. Underreporting from healthcare professionals and society
	2. Lack of trained and competent staff
	3. Limited awareness about the PV system
	4. Lack of time amongst healthcare professionals
UAE	1. Underreporting (healthcare professionals are too busy)
	2. Lack of educational programmes in the area of reporting for consumers and healthcare professionals
	3. Lack of IT support for electronic reporting provided for healthcare professionals
	4. Shortage of qualified PV officers in industry and key areas

KSA Kingdom of Saudi Arabia

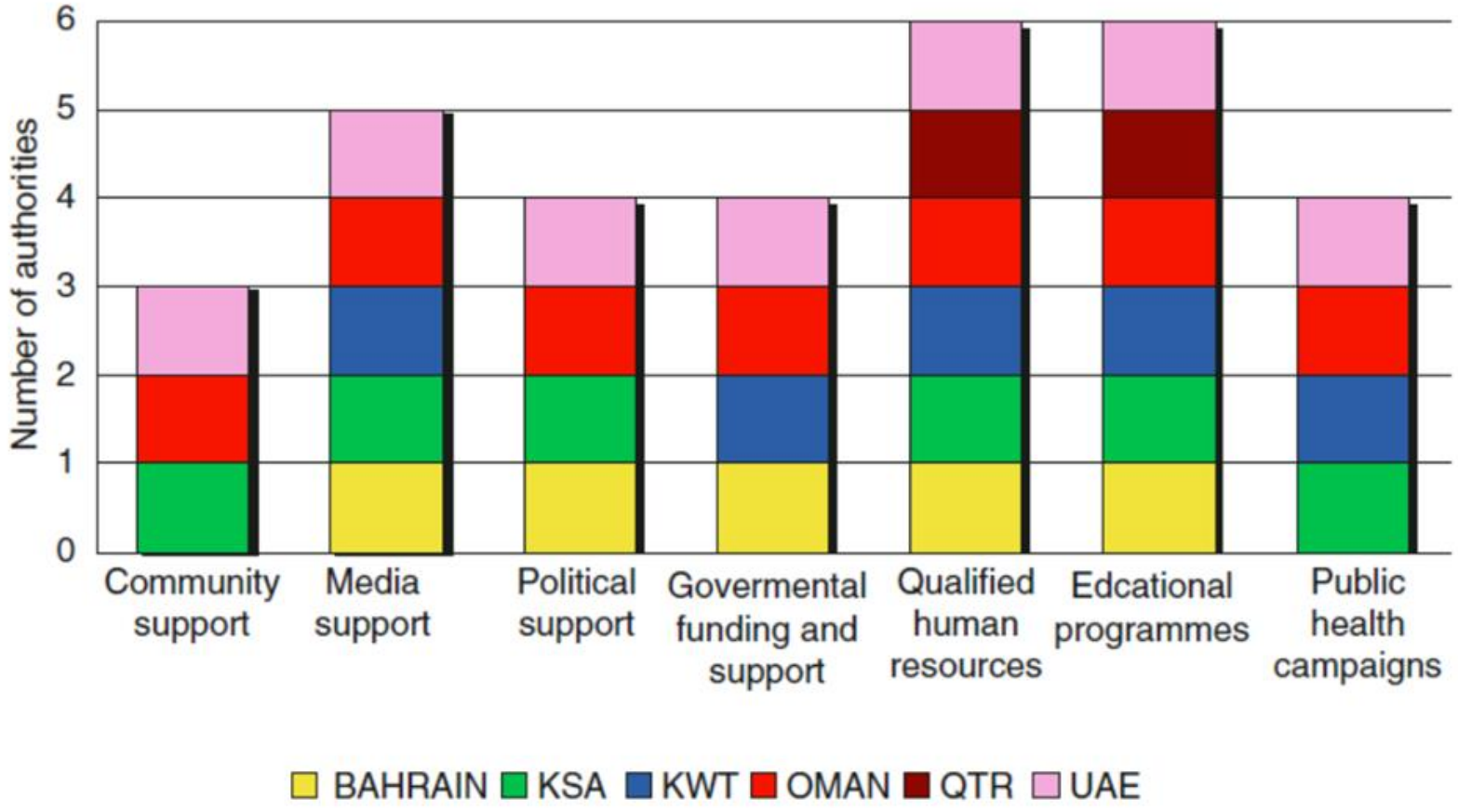


Fig. 6.7 Requirements for a successful PV system in the Gulf states

Pharmaceutics & Polymeric Drug Delivery Research Laboratory (PPDDRL)

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Industrial Pharmacy & Biopharmaceutics

- Sustained/Controlled release of conventional dosage forms
- Transdermal Drug Delivery
- Pharmacokinetics
- Pharmaceutical Analysis & Quality Control

Poly (diol-tricarballylate) Biodegradable Elastomers

Polymeric Drug Delivery For Therapeutic Proteins

- Characterization and Biocompatibility
- Drug Delivery in Cancer Therapy (IL-2)
- Targeted Nanoparticles
- Other...

Tissue Engineering

- Cartilage Repair
- Cardiovascular Applications
- Other...

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QC History/Evolution

- **1900's- Adulterated Food**
  - First purity laws enacted
- **1930's- Sulfanilimide Elixir**
  - Drugs had to be proven safe
- **1960's- Thalidomide**
  - Drugs had to be proven safe and effective through clinical trials
- **1980's- Tylenol Incidence**
  - Controlled Inspection

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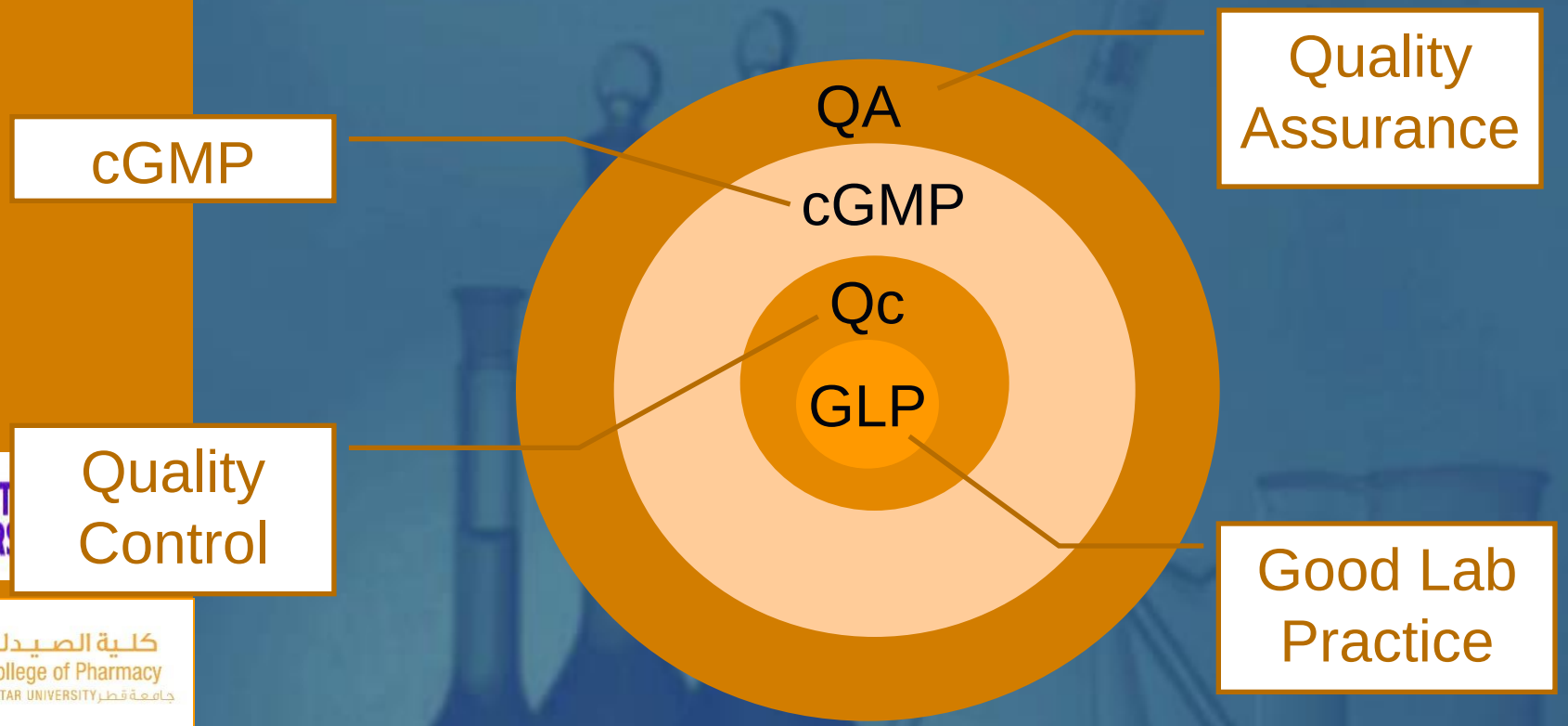
Pharmaceuticals Quality Management



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Why QC is important?

- They are enforced by laws
- Ensure good quality of Pharmaceutical products
- Reduce final product rejects & recalls
- Ensure Satisfied customers
- Maintain manufacturing consistency
- Company image and reputation

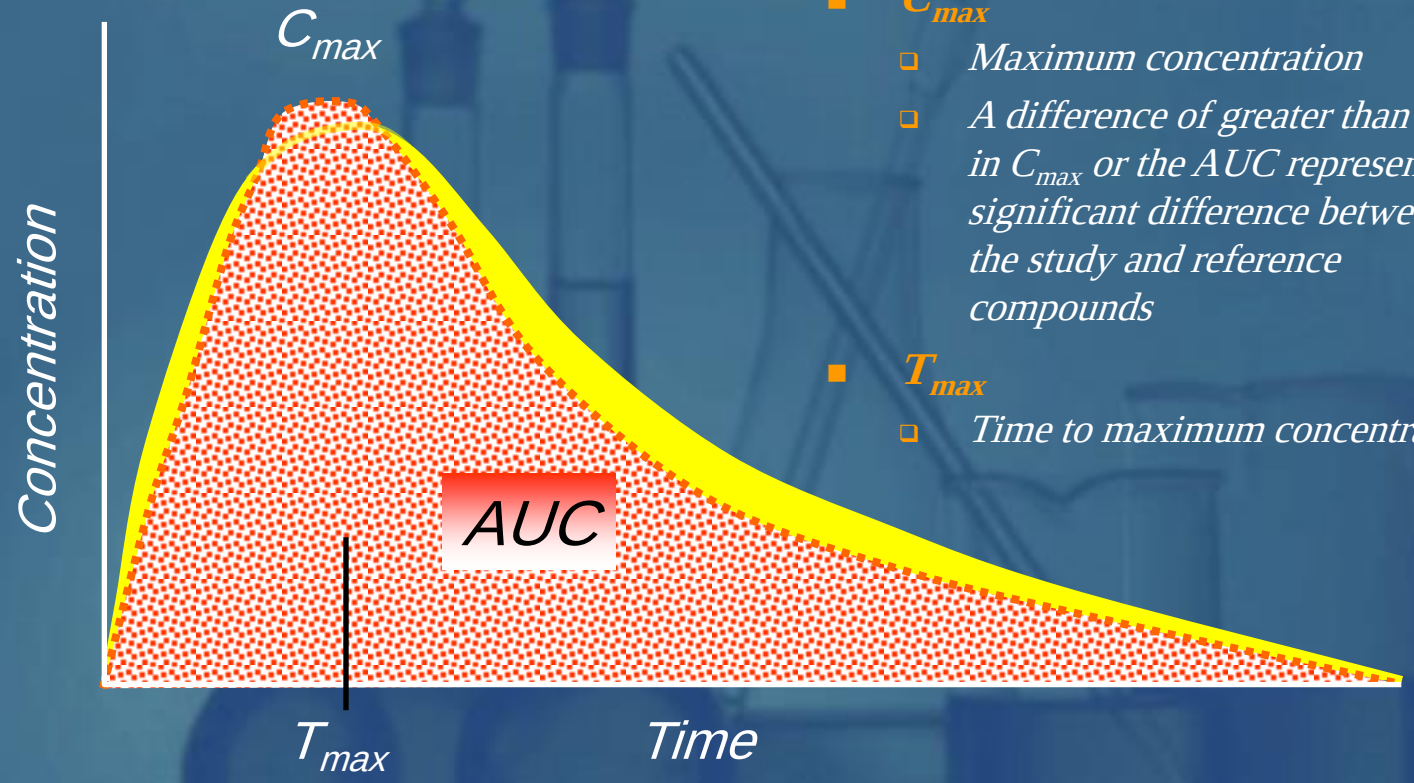
Key Quality Terms

- **CHANGE CONTROL**
  - written procedure that describes the action to be taken if a change is proposed to facilities, etc. used in fabrication, packaging, and testing of drugs or any change that may affect quality or support system operation
- **DEVIATION**
  - Planned or unplanned temporary departure from an approved process, specification or procedure with the ***potential*** to impact product quality

Generic Versus Brand

- **Bioequivalence Studies**

Bioavailability/Bioequivalence Studies



- ***AUC***
  - *Area under the concentration-time curve*
- ***C_{max}***
  - *Maximum concentration*
  - *A difference of greater than 20% in C_{max} or the AUC represents a significant difference between the study and reference compounds*
- ***T_{max}***
  - *Time to maximum concentration*

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Compendial Testing of Solid Dosages

- **Content Analysis**
  - Dose accuracy and confirmation
- **Dissolution Testing**
  - *in vitro – in vivo* correlation
  - Possible representation of bioavailability
- **Similarity Factor Analysis**
  - Confirm similarity in behavior and release pattern

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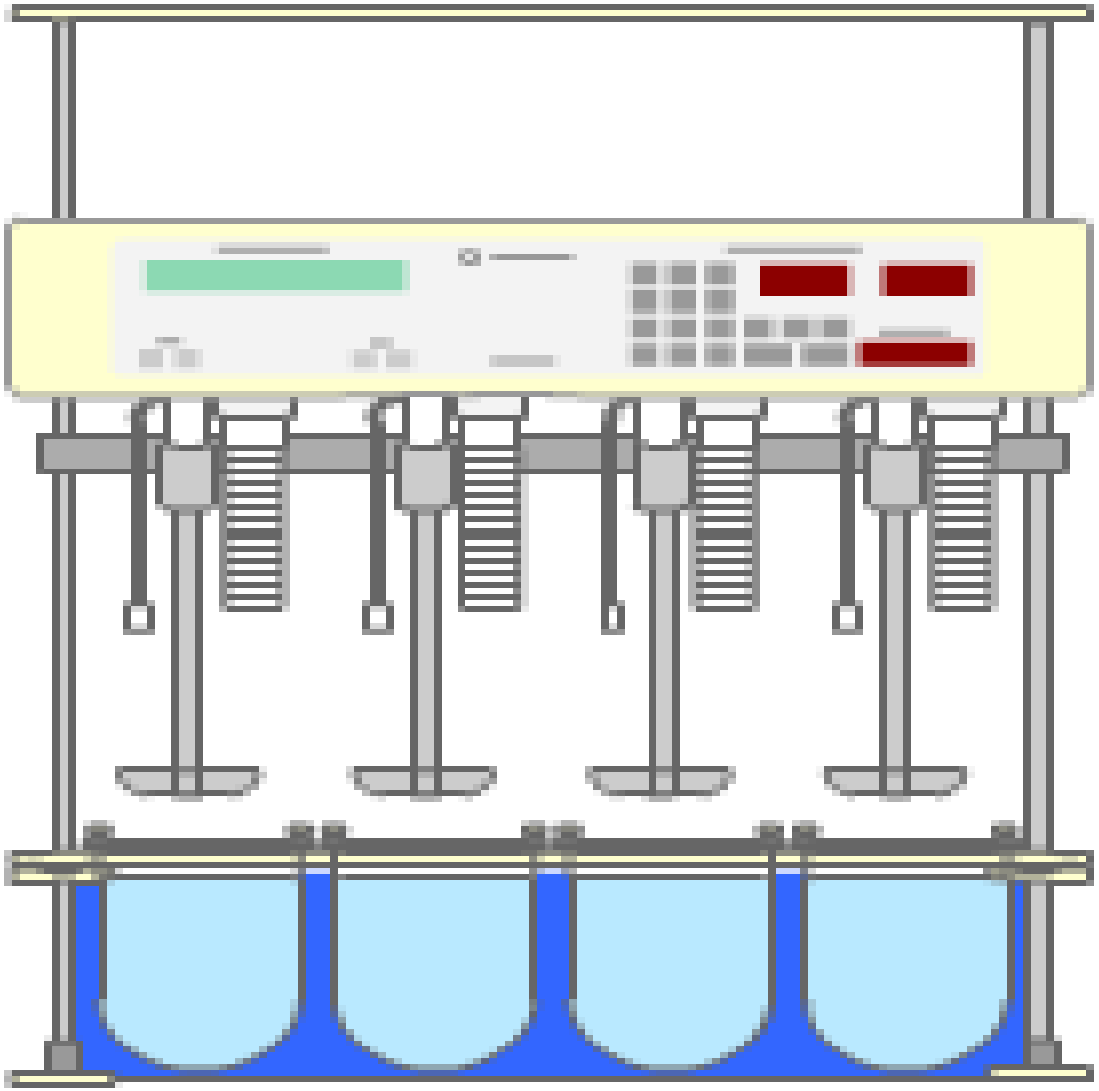
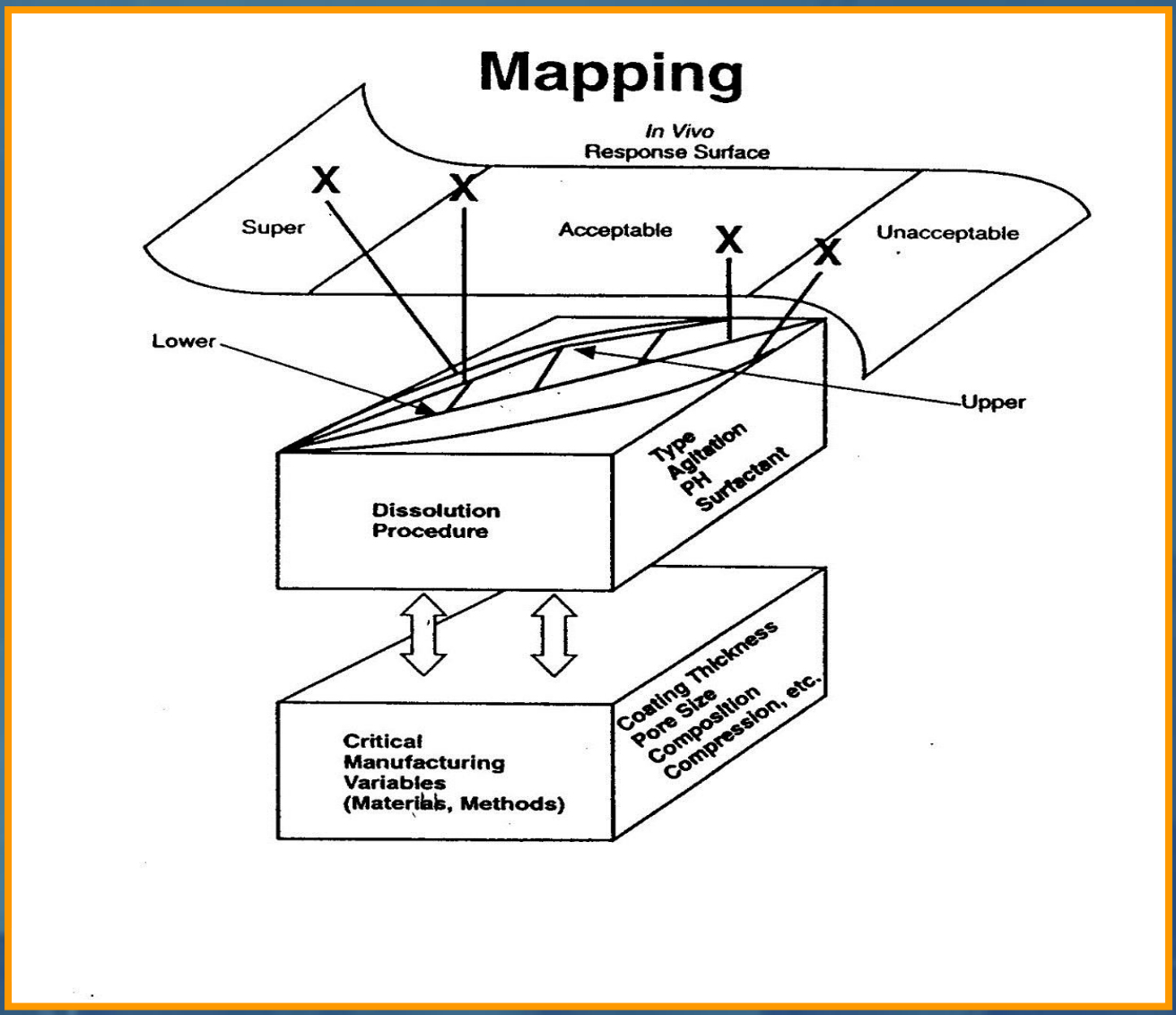
Dissolution Testing



Mapping Concept



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Interchangeable Drug Products

- Pharmaceutical equivalents or pharmaceutical alternatives that are therapeutic equivalents and have the same route of administration of the reference and fall within the conditions of use for that reference product.

Pharmaceutical Equivalents

- Drug products that contain the identical amounts of the identical medicinal ingredients, in comparable dosage forms, but do not necessarily contain the same non-medicinal ingredients.

Pharmaceutical Alternatives

- Drug products that contain the same or similar amount(s) of the same or similar medicinal ingredient(s) (e.g., different salts, esters, complexes, or solvates of the same therapeutic (active) moiety), in comparable dosage forms, but do not necessarily contain the same non-medicinal ingredients.

Therapeutic Equivalents

- Pharmaceutical equivalents or pharmaceutical alternatives that have been shown to be bioequivalent to a reference product as demonstrated by bioavailability (based on same molecular species), pharmacodynamic, or clinical studies. and have been deemed to have the same safety and efficacy profile as the reference product.

Metformin Study: What to look for?

- According to the USP 39, Not less than 70% of the label amount of Metformin HCl dissolved in 45 min.
- According to the USP 39, Metformin HCl tablet should not contain less than 95% and not more than 105% of active ingredient.
- According to the FDA and ICH guidance, dissolution curves of any 2 drugs could be considered similar or equivalence, if the f2 value greater than 50 (50-100).

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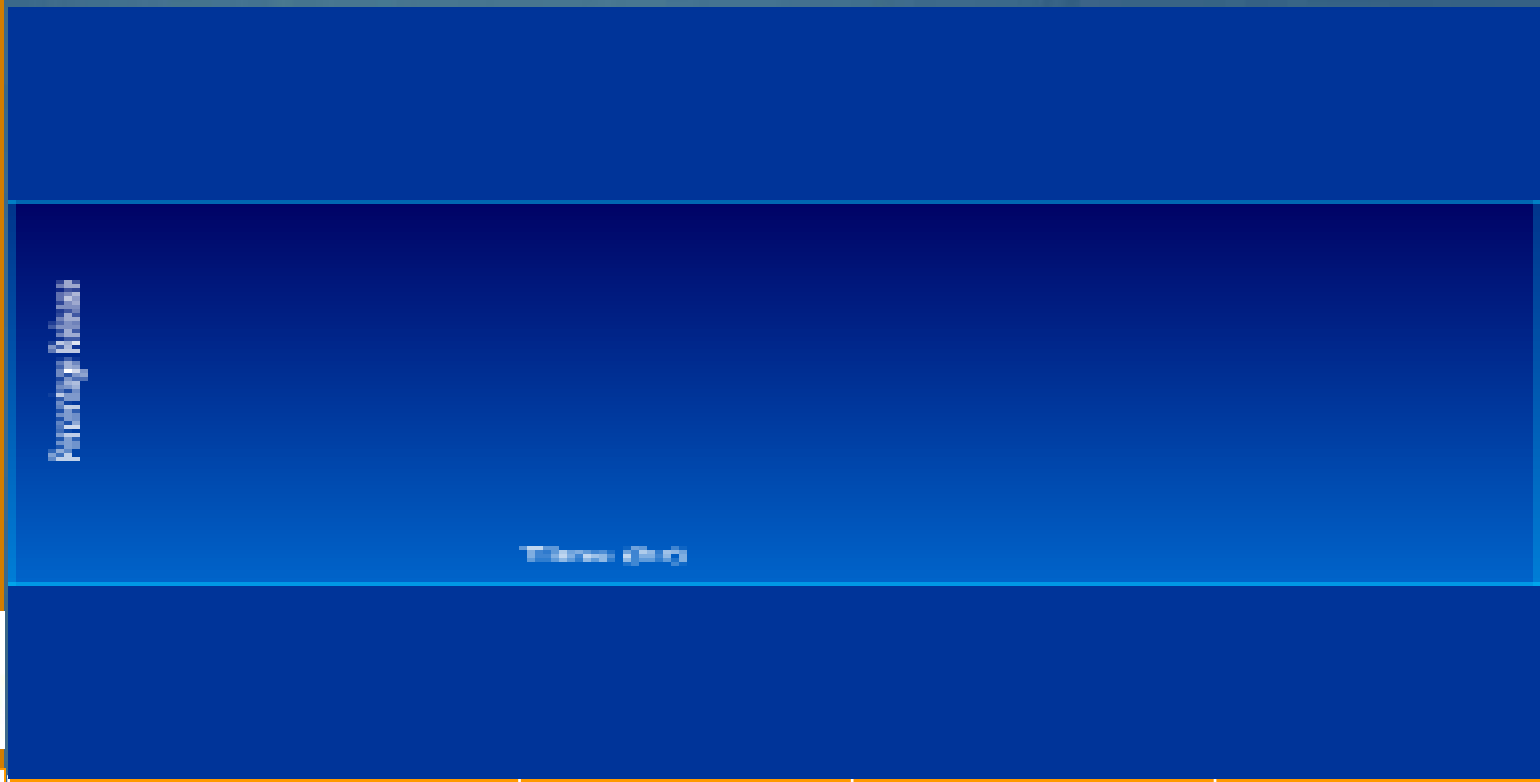
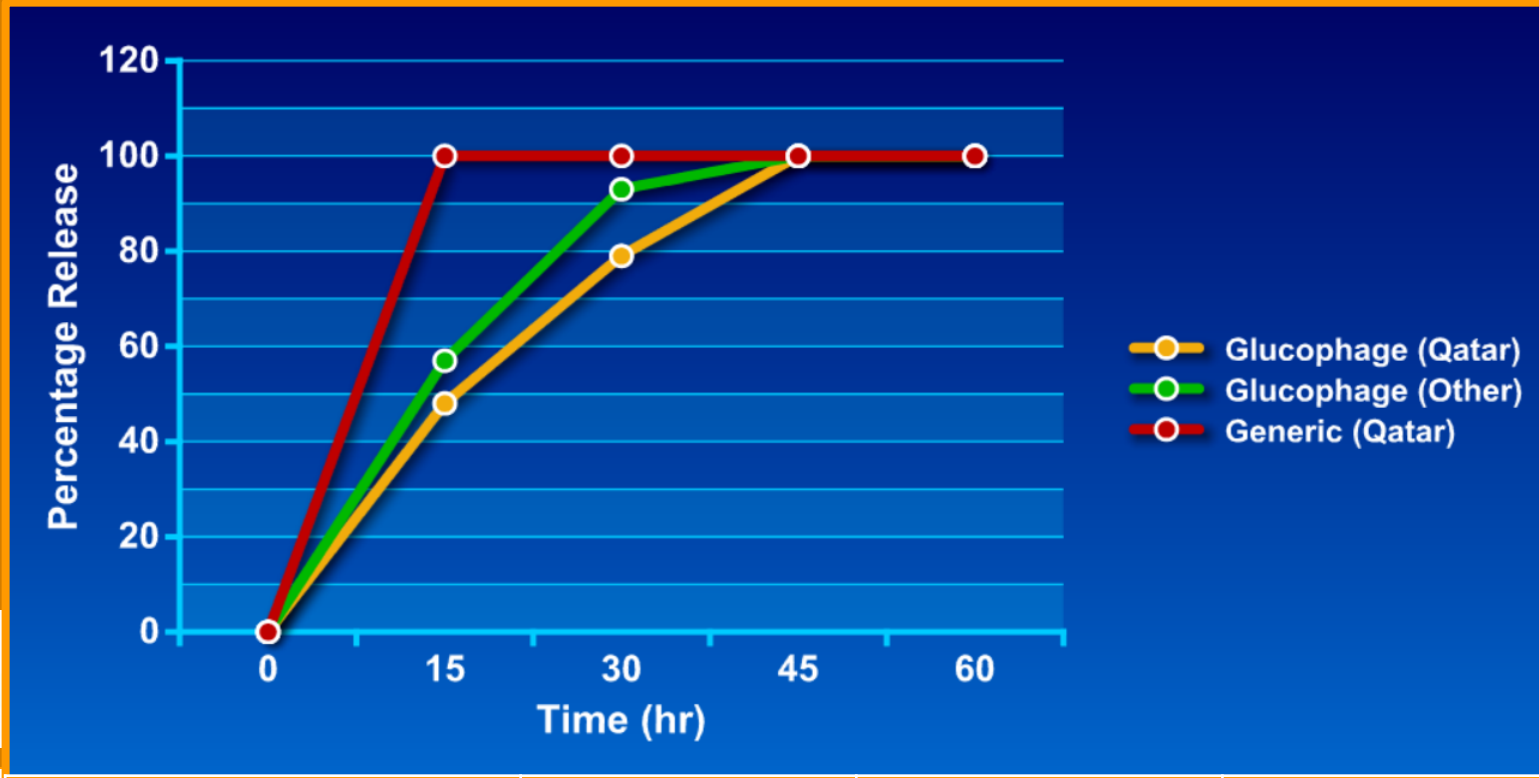
Metformin Compendial Testing



	Glucophage (Qatar)	Glucophage (Other)	Generic (Qatar)
% Content	97.9	96.6	102
Similarity Factor (f2)		88	32

Metformin Compendial Testing



	Glucophage (Qatar)	Glucophage (Other)	Generic (Qatar)
% Content	97.9	96.6	102
Similarity Factor (f2)		88	32

Preliminary Studies of QC for Metformin

Product No.	P#1	P#2	P#3	P#4	P#5	P#6	P#7	P#8	P#9	P#10
% Content	92.7	99.8	89.5	94.9	96.6	110	**92.8**	98.8	102.1	97.6
f_2	68	**33**	53	51	88	37	65	**39**	**32**	56

Drug Name	Country of Manufacturing / purchase
Diaphage®	Jordan
Diamet®	Jordan
Glucophage®	Oman
Glymet®	Jordan
Diamet®	Palestine
Glucomet®	Palestine
Glucophage®	Thailand
Miformin®	Thailand
Metaphage®	Qatar
Glucophage®	Qatar

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Conclusions & Recommendations

- Post marketing random sampling and testing is a must
- *In vitro* similarity and testing confirmation does not always guarantee similar in vivo results unless strong (level A) vitro-in vivo correlation is established
- Similarity factor and release pattern should be considered in certain cases of pharmaceuticals.

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Recommendations

1. Networking – are we working in silo? Should we be working in silo? It's vital that team members step out of their silos and start working together

2. Looking collectively at risk

3. Establish a successful medication safety program for the country

4. More researches are needed

Preventing medication errors and promoting medication safety are shared responsibility

We need to get away from the traditional culture of Blame and Shame


Arigato
Mahalo
Grazie
Spasiba
THANK YOU
Thoinks
Moite
Gracias
Merci
Danke
Shukran