Utrecht WHO Winter Meeting 2019

Wednesday 9 - Thursday 10 January 2019

Utrecht - WHO Collaborating Centre for Pharmaceutical Policy and Regulation

Utrecht, The Netherlands

Venue: Faculty Club Helios

Programme Meeting report

WHO Collaborating Centre for Pharmaceutical Policy and Regulation

Utrecht University

Utrecht - WHO Winter Meeting 2019

Wednesday 9 January - Thursday 10 January

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Utrecht - WHO Collaborating Centre for
Pharmaceutical Policy and Regulation
Utrecht, The Netherlands

WHO Collaborating Centre for Pharmaceutical Policy and Regulation

Utrecht University

General Information

Venue
Faculty club 'Helios'
Kanunnikenzaal
Achter de Dom 7a
3512 JN Utrecht
Phone: +31 30 253 9911

Date

Wednesday 9 January – Thursday 10 January, 2019

For all practical matters during the meeting, please contact:

Tom Jacobs (uu.who.wintermeeting@gmail.com)
Mobile: +31 (0)6 345 612 79

Rianne van den Ham (H.A.vandenHam@uu.nl)
Mobile: +31 (0)6 289 631 99

Organizing Committee

Utrecht - WHO Collaborating Centre for Pharmaceutical Policy and Regulation

- Rianne van den Ham
- Tom Jacobs
- Aukje Mantel
- Bert Leufkens

Department of Essential Medicines and Health Products

- Verica Ivanovska

Welcome

We are delighted to welcome all of you in Utrecht to the 2019 edition of the Utrecht - WHO Collaborating Centre for Pharmaceutical Policy and Regulation Winter Meeting. It has been a tradition now for more than 10 years to start the New Year with this exciting event. We are pleased to see that so many colleagues and friends with a wide range of professional backgrounds, organisations and countries are joining us in this tradition.

The meeting will start on Wednesday with researchers who will discuss their ongoing or planned work in oral presentations. Presentations and discussions are organized in different thematic sessions related to regulatory science, access to medicines and pharmaceutical pricing and reimbursement. We sincerely hope that these discussions will contribute to bringing pharmaceutical policy analyses and evidence-based policy making on pharmaceuticals to a higher level. At the end of the first day one of the Centre's PhD students, Haggar Hilda Ampadu, will defend her thesis entitled *"Evolving national pharmacovigilance systems in Africa"*. You are invited to witness this special event.

We have chosen *"Access to medicines for children: Clinical, policy and regulatory aspects"* as central theme for the second day. When it comes to improve access to efficacious, safe and affordable medicines for children, one runs into many clinical, policy and regulatory debates. While nobody will be against improving access to our beloved little ones, the road towards innovative and sustainable access scenarios for pharmacotherapy in children is rather bumpy and long. Children are not just young adults is a widely accepted notion, but to translate this notion into action, reaching out and building sustainable paediatric therapy systems, requires excellent science, but also vision and leadership. All this makes access to medicines for children a powerful, cross-cutting learning device for pharmaceutical policy and regulation. Invited speakers will present their views on the various angles of this topic. Participants are strongly invited to share their own experiences and views.

We would like to thank all of you for your contributions in advance and hope that you will enjoy this edition of the meeting!

On behalf of the Organizing Committee,

Bert Leufkens, Aukje Mantel-Teeuwisse, Tom Jacobs and Rianne van den Ham

WHO Collaborating Centre for Pharmaceutical Policy and Regulation

Utrecht University

Winter meeting 9 + 10 January 2019

Time schedule Wednesday 9 January 2019

Venue: Faculty club 'Helios', Kanunnikenzaal, Achter de Dom 7a, Utrecht

Presentations of ongoing pharmaceutical policy analyses

09:30 - 10:00 Registration, coffee

10:00 - 10:15 Welcome and introduction to the winter meeting
Bert Leufkens (UU) and **Aukje Mantel** (UU)

10:15 - 12:00 Paper presentations - parallel sessions
1a - **Regulation á la carte** (Kanunnikenzaal)
1b - **Ensuring access to the essentials** (Belle van Zuylenzaal)

12:00 - 13:00 Lunch break

13:00 - 14:15 Paper presentations - parallel sessions
2a - **Is the price right?** (Kanunnikenzaal)
2b - **To regulate or not?** (Belle van Zuylenzaal)

14:15 - 14:45 Coffee/tea break

14:15 - 15:45 Paper presentations
3 - **Spotlight session**

15:45 - 16:15 Coffee/tea break

16:15 - 17:15 Thesis defence: Evolving national pharmacovigilance systems in Africa
Hilda Ampadu (UU)

17:15 - 18:30 Reception with drinks and snacks

Time Schedule Thursday 10 January 2019

Venue: Faculty club 'Helios', Kanunnikenzaal, Achter de Dom 7a, Utrecht

Access to medicines for children: Clinical, policy and regulatory aspects

09:30 - 10:00 Coffee, registration new participants

10:00 - 10:10 Welcome and introduction to the meeting
Bert Leufkens (UU) and **Verica Ivanovska** (WHO)

10:10 - 10:40 Medicines use in children and adolescents
Rob Heerdink (UIPS)

10:40 - 11:10 10 years Priority Medicines for Children
Benien van Vingerhoed-van Aken (ZonMW)

11:10 - 11:30 Coffee break

11:30 - 12:00 Pediatric formularies and off-label use
Tjitske van der Zanden (Erasmus MC)

12:00 - 12:30 Antibiotic use in children: a global picture
Verica Ivanovska (WHO)

12.30 - 13:40 Lunch break

13.40 - 14.00 Meyler Award ceremony for best pharmacovigilance student paper
Chantal Kats (UU)

14:00 - 14:30 The 1000 days children health model
Johan Garssen (UIPS/Danone)

14.30 - 15.00 Importance of clinical pharmacology research in children
Catherijne Knibbe (LACDR)

15:00 - 15:30 Wrap up and meeting closure

15:30 - 16:00 Coffee/tea break

16:15 - 17:00 Inaugural lecture: Zorgen om met geneesmiddelen
Please note that the lecture is in Dutch
Aukje Mantel (UU)

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Presentations of ongoing pharmaceutical policy analyses

Parallel session 1a - Wednesday 9 January 2019
10:15 - 12:00

REGULATION À LA CARTE

Session Chairs: **Helga Gardarsdottir + Alex Dodoo**

Nr	Presenter	Title
1	**Opalska**	Assessment of the regulatory actions taken by the European network between 2007-2017 on well-known antibiotics.
2	**Bhrilikova**	Registration of essential medicines in Kenya, Tanzania, and Uganda.
3	**Mustafa**	Assessment of Pharmaceuticals Benefits Package of the National Health Insurance Fund, Sudan, 2003-2016.
4	**Peeters**	Effects Of Regulatory Major Objections On Reimbursement Decisions In Europe.
5	**Glerum**	Drug Switching in the Netherlands Quantified: An Observational Cohort Study.

Parallel session 1b - Wednesday 9 January 2019
10:15 - 12:00

ENSURING ACCESS TO THE ESSENTIALS

Session Chairs: **Aukje Mantel-Teeuwisse + Wilbert Bannenberg**

Nr	Presenter	Title
6	**Kong & Warren**	Linking Global Health Prioritisations to Access to Medicine: from Pipeline to Portfolio.
7	**Tordrup**	Resource needs for viral hepatitis elimination through universal health coverage: Projections in 67 low-income and middle-income countries, 2016-2030.
8	**Costa**	Sickle Cell Disease: a well-known inherited disease offers lessons on how to improve access to essential medicines in low resourced settings.
9	**Iyengar**	Rapid assessment of essential medicines situation in refugee settlements in Cox's Bazaar, Bangladesh.
10	**Samukange**	Selection of Blood, Blood Components and Blood Products as Essential Medicines in 105 Low and Middle-Income countries.

Parallel session 2a - Wednesday 9 January 2019
13:00 – 14:15

IS THE PRICE RIGHT?

Session Chairs: **Wim Goettsch + Luc Besançon**

Nr	Presenter	Title
11	**Kibira**	Contribution of the Global Fund's Private Sector Copayment Mechanism towards ensuring universal access to quality assured antimalarial medicines in Uganda.
12	**Atikeler**	Cost of unlicenced and orphan medicines in Turkey, Kazakhstan and Poland.
13	**Fradi**	An analysis of the Tunisian medicines price policy.
14	**Pyo**	Generic price and uptake level comparison across OECDs and its corresponding generic pricing policies.

Parallel session 2b - Wednesday 9 January 2019
13:00 – 14:15

TO REGULATE OR NOT?

Session Chairs: **Marieke de Bruin + Bert Leufkens**

Nr	Presenter	Title
15	**Kalf**	Patient Reported Outcome Measures In Health Technology Decision Making.
16	**Millard**	The Use of Surrogate Endpoints in Current Drug Approval Pathways.
17	**Alsamil**	Reporting of quality attributes in similarity assessments of recombinant therapeutic proteins in scientific publications: a systematic review.
18	**Druedahl**	Medicines authority regulators and industry perspectives on the European regulation of biosimilars.

Plenary Session - Wednesday 9 January 2019
14:45 - 15:45

SPOTLIGHT SESSION

Session Chair: **Rianne van den Ham + Fatima Suleman**

Nr	Presenter	Title
19	**Chepynoga**	Combining availability and affordability dimensions of access to medicines in a single SDG indicator: a methodology proposed to identify how many medicines are accessible.
20	**Holz**	Pharmaceutical price negotiations in Mexico – a policy mechanism towards access to innovative medicines.
21	**Coppens**	Scientific publication and presentation of results at conferences in the field of gene and cell based therapies: a cohort analysis of clinical trials in the Netherlands between 2007- 2017.

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Short biography of speakers on 10 January 2019

Prof. dr. H. (Bert) G. Leufkens

Dr Leufkens is professor of Pharmaceutical Policy and Regulatory Science at Utrecht University. During the mid-80s he worked at Leiden University and was a Fulbright Fellow at the University of Minnesota (US). In 1997 he was appointed as full professor at Utrecht University. From 2003-2005 he was the Scientific Director of the Utrecht Institute for Pharmaceutical Sciences (UIPS), and during 2006-2007 head of the Department of Pharmaceutical Sciences of the Faculty of Science in Utrecht. Dr Leufkens is research and policy-wise active at several (inter) national platforms on drug safety, pharmaceutical policy and regulatory science (e.g. past-member EMA Pharmacovigilance Working Party 2005-2009, chair of Dutch Medicines Evaluation Board (MEB) 2007-2017, past-member of the EMA CHMP 2009-2015, past-President of ISPE, since 2008 Scientific Director of the Utrecht WHO Collaborating Centre for Pharmaceutical Policy and Regulation. He is affiliate professor at the Faculdade de Farmácia da Universidade de Lisboa and the Copenhagen Centre for Regulatory Science (CORS). He is (co) author of ›500 papers in peer reviewed journals, book chapters and research reports.

Benien Vingerhoed-van Aken

Benien Vingerhoed-van Aken PhD is Program Manager at The Netherlands Institute for Health Research and Development (ZonMw). She initiated the ZonMw Rational Pharmacotherapy Program, and heads the department responsible for funding and monitoring approximately 200 researchprojects, patientregistries and projects focussed on clinical practice. The mission of this subsidy program is to ensure that (existing) medication is deployed in a more effective, safe and efficient manner, to enhance the quality of pharmacotherapeutic care for patients and to improve cost-efficiency in care and/or for society. Dr Vingerhoed holds a Medical Biology degree from the University of Utrecht and completed her PhD in experimental internal medicine at the Academic Medical Centre in Amsterdam. She worked for ten years in international clinical trial management of phase I-III studies in various diseases at the Center for Human Drug Research (CHDR), Organon and Centocor.

Email: vingerhoed@zonmw.nl

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Prof. dr. Catherijne A.J. Knibbe

Professor Catherijne Knibbe is clinical pharmacologist-hospital pharmacist in the St. Antonius Hospital in Nieuwegein/Utrecht and professor of Individualized Drug Treatment at the Cluster of Systems Bioedicine & Pharmacology of the LACDR, Leiden University, the Netherlands. She leads a research group in which advanced statistical techniques are used to individualise drug therapy in special patient populations such as children and neonates, pregnant women and morbidly obese children and adults, mainly supported by ZonMw and NWO. She has supervised 17 PhD theses, is currently supervising 10 PhD students and 2 Post Docs, and is co-author of over 180 international peer-reviewed publications and contributions to books. She combines her research group with combines clinical responsibilities in patient care in the Department of Intensive Care/Anesthesiology.

Knibbe is supervisor of the Clinical Pharmacology training program, co-supervisor of the Hospital Pharmacy training program in the St Antonius Hospital, member of the Central Committee of Research Involving Human Subjects (the 'CCMO'), member of certification committee of the Dutch Society of Clinical Pharmacology & Biopharmacy, chair of the Concilium Hospital Pharmacy of the Dutch Society of Hospital Pharmacy, member of the NWO/ZonMW committee Innovational Research Incentives Scheme (VIDI), external European Expert for Paediatric Medicines/ European Medicines Agency and has been member of the national Committee of State 'Doek' involving medical-ethical aspects of (non-therapeutic) research in children.

Prof. dr. Johan Garssen

Johan Garssen is Professor of Immunopharmacology at Utrecht University, where he's also Head of the Division Pharmacology at the Utrecht Institute for Pharmaceutical Sciences. At Nutricia-Research, after several functions as from 2002, Johan is currently R&I Director Immune in the Global ELN Centre of Excellence Utrecht.

He studied medicine and biology at the Free University, Amsterdam, the Netherlands. He specialized in immunology, pharmacology and biochemistry and finished both studies in 1987 cum laude. He is registered as immunologist and pharmacologists. He finished his PhD thesis at the University of Utrecht in 1991 on the role of T cells in respiratory allergy, an immunopharmacological approach. This PhD programme and a postdoc period was partly performed at Yale University, New Haven, USA.

After the postdoc period he became senior scientist and head immunobiology at the National Institute of Public Health in the Netherlands. There he coached many research projects, both preclinical as well as clinical research, in the field of immunomodulation induced by a.o. nutritional ingredients, drugs and environmental agents.

Johan Garssen published over 700 peer reviewed papers in the field of "immunomodulation" and has his professorship/chair since 2006. He is editorial board member for several journals and has contributed to various grants, a.o. NWO, EU, NIH, STW, Bill Gates, EDB, RAAK-PRO, children hospital innovation grants. Board/Faculty member of Eureka, an international society for translational medicine, and member of several medical and animal ethical committees.

Dr E.R. (Rob) Heerdink

Dr E.R. (Rob) Heerdink PhD is an associate professor of Clinical Pharmacoepidemiology at the Utrecht Institute for Pharmaceutical Sciences, Utrecht University and professor of Innovation of Pharmaceutical Care at the University of Applied Sciences Utrecht. He is principal investigator of the Centre for Clinical Therapeutics. His research is driven by questions from clinical practice and spans from traditional pharmaco-epidemiological methods to systems pharmacy research into context related aspects of pharmacotherapy. He has published over 250 peer-reviewed articles on topics including (psychiatric) pharmacotherapy, drug exposure patterns, adherence and the relation between pharmaceutical care and clinical outcomes and has served as co-promotor for over 30 PhD students. Dr Rob Heerdink is a founding and honorary member of the European Society for Patient Compliance and Persistence (Espacomp).

Verica Ivanovska

Verica Ivanovska is a Technical Officer at the WHO HQ Department of Essential Medicines and Health Products. She currently works with the Innovation, Access and Use team on issues related to surveillance of antimicrobial use. Verica's broader research interest comprises pharmaceutical policy analysis, access and use of medicines, medicines for children, priority setting in health care and medical anthropology. She has contributed to three WHO publications (Medicines use in primary care in developing and transitional countries - 2009, Priority medicines for Europe and the world – 2013, and WHO Global report on the surveillance of antimicrobial consumption - 2018) and has published her research in international peer-reviewed journals. Along with her WHO affiliation, Verica has been an assistant professor at the Faculty of Medical Sciences in Stip, Macedonia, and a member of the executive committee of the European Drug Utilization Research Group. Verica is a pharmacist with a Master degree in public health (Glasgow University, UK) and a PhD degree from the Division of Pharmacoepidemiology and Clinical Pharmacology (Utrecht University, the Netherlands).

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Tjitske van der Zanden

Tjitske van der Zanden is the technical director of the Dutch Paediatric Pharmacotherapy Expertise Network, that publishes the Dutch Paediatric Formulary (www.kinderformularium.nl). Originally trained as a nurse and a clinical research coordinator, she worked on several paediatric clinical studies at the ErasmusMC-Sophia Childrens Hospital in Rotterdam, before she joined the Dutch Paediatric Formulary as a projectmanager from the very start in 2005. As a projectmanager and later on the technical director Tjitske is responsible for the technical development and maintenance as well as the contents (dosing information) of the Dutch Paediatric Formulary. In 2016 she started her PhD on 'Optimal dosing and drug use in paediatric patients' at the Radboud UMC in Nijmegen. Her Phd specifically aims at disseminating the knowledge that was gained by the development of the Dutch Paediatric Formulary to address and ultimately improve (off-label) drug use in children.

List of participants UU-WHO winter meeting 9 + 10 January 2019

(as of 3 Januaryy 2019)

Name	Institution
Aileen Yang	Student
Aleksandra Opalska	EC
Alex Dodoo	ACC for Pharmacovigilance & Surveillance
Alex Kong	Access to Medicine Foundation
Ali Akbar	Eu2P
Ali Alsamil	UIPS/UU
Allyson Pollock	Institute of Health and Society, Newcastle University
Ana Paula Dresch	MSF Belgium
Anne Fleur Donker	Utrecht University
Anne Taams	Utrecht University
Armina Padmasawitri	Utrecht University
Aukje Mantel-Teeuwisse	Utrecht University, WHO Collaborating Centre for Pharmaceutical Policy & Regulation
Benien Vingerhoed-van Aken	ZonMw
Bert Leufkens	Utrecht University, WHO Collaborating Centre for Pharmaceutical Policy & Regulation
Catherijne Knibbe	Leiden University
Chantal Kats	Utrecht University
Claudia Nannei	World Health Organization
Colin Millard	Newcastle University UK
Daniela Moye Holz	UMCG, University of Groningen
David Tordrup	UU / Triangulate Health Ltd
Delphi Coppens	Utrecht University
Denis Kibira	UU / HEPS Uganda
Doerine Postma	UU / KNMP
Elizabeth, Henehan	Boston University School of Public Health
Emma Bernsen	Universiteit Utrecht
Enrico Costa	Dept of Pharmacy - University Hospital of Verona
Enver Kagan Atikeler	Turkish Medicines and Medical Devices Agency
Eugène van Puijenbroek	Lareb
Fatima Suleman	University of KwaZulu-Natal/Utrecht University

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Freek de Haan	Copernicus Institute of Sustainable Development (UU)
Gaby Ooms	HAI
Giovanni Tafuri	Zorginstituut Nederland
Hanneke Dominicus	CARED foundation
Heine van Wieren	Tagliente
Helga Gardarsdottir	Utrecht University, WHO Collaborating Centre for Pharmaceutical Policy & Regulation
Helle Christiansen	Institut for Pharmacy, Copenhagen Centre for Regulatory Science
Hend El Tayebi	German University in Cairo
Hilda Ampadu	UU / ACC for Pharmacovigilance & Surveillance
Ines Fradi	Faculty of Pharmacy, University of Monastir, Tunisia
Isam Mustafa	National Health Insurance Fund
Jan Hendriks	UCAB
Joan Deckers	Medicines Evaluation Board (MEB)
Johan Garssen	Utrecht University
Junhee Pyo	UU/IQVIA
Kashi Barbara Carasso	Hera
Kasper Blom	Utrecht University
Kateryna Chepynoga	World Health Organization
Katrina Perehudoff	Dalla Lana School of Public Health
Kees van Grootheest	Lareb
Kevin Klein	Utrecht University / Exon Consultancy
Koray Parmaksiz	ESHPM, Erasmus University Rotterdam
Leila-Sophie Otten	Utrecht University
Louise Druedahl	Copenhagen Centre for Regulatory Science, University of Copenhagen
Lourens Bloem	Utrecht University, Dutch Medicines Evaluation Board
Luc, Besançon	Pharmacy and Consulting
Luigi Angelillo	Santen
Margo Warren	Access to Medicine Foundation
Marie Elske Gispen	University of Groningen
Marieke de Bruin	Copenhagen Centre for Regulatory Science
Nelleke Duijm	Copenhagen University, Department of Pharmacy
Niels Peeters	Utrecht University
Olaf Klungel	Universiteit Utrecht
Per Sindahl	Danish Medicines Agency
Peter Reijnders	Reijnders Regulatory Affairs Consultancy

Petra Sevcikova	Newcastle University, UK
Pieter Glerum	CBG-MEBP
Rachel Kalf	Utrecht University
Rianne van den Ham	Utrecht University, WHO Collaborating Centre for Pharmaceutical Policy & Regulation
Rick Vreman	Utrecht University
Rob Heerdink	Universiteit Utrecht
Shuichi Jack Suzuki	Former WHO Intern (currenly Eli Lilly)
Sibren van den Berg	Utrecht University
Sini Eskola	EFPIA/UU PhD for professionals
Surasak Saokaew	School of Pharmaceutical Sciences, Universtiy of Phayao
Swathi Iyengar	WHO - Headquarters
Teresa Leonardo Alves	RIVM
Tjitske van der Zanden	The Netherlands paediatric formulary
Tom Jacobs	Utrecht University, WHO Collaborating Centre for Pharmaceutical Policy & Regulation
Verica Ivanovska	World Health Organization
Washington Samukange	UU / Paul Ehrlich Institut
Wilbert Bannenberg	Hera
Wim Goettsch	Division of PECP, UIPS, UU
Wim Scholten	Willem Scholten Consultancy
Yared Santa-Ana-Tellez	Foundation for the Promotion of Health and Biomedical Research of Valencia Region
Yiyi Zhang	Utrecht University
Zuzana Kusynova	International Pharmaceutical Federation (FIP)

WHO Collaborating Centre for Pharmaceutical Policy and Regulation

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Overview abstracts 6 January 2019

WHO Collaborating Centre for Pharmaceutical Policy and Regulation

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1 Assessment of the regulatory actions taken by the European network between 2007-2017 on well-known antibiotics.

Aleksandra Opalska[1,2], Marcel Kwa[3], Bert Leufkens[1], Helga Gardarsdottir[1,4]

1. Division Pharmacoepidemiology and Clinical Pharmacology, Utrecht Institute for Pharmaceutical Sciences, Faculty of Science, Utrecht University, Utrecht, The Netherlands
2. Directorate-General for Health and Food Safety, European Commission
3. Department of Pharmacovigilance, Medicines Evaluation Board, Utrecht, The Netherlands
4. Department of Clinical Pharmacy, Division Laboratories, Pharmacy and Biomedical Genetics, University Medical Center Utrecht, Utrecht, The Netherlands

Background:
Antimicrobial resistance is one of the most important challenges facing modern clinical practice. As part of the strategy to counter antimicrobial resistance, the European Medicine Agency (EMA) set out to regulate and promote the appropriate use of antibiotics by healthcare professionals and patients by means of a referral procedure (Article 30 & 31) where product information of antibiotics is re-evaluated and harmonized.
The objective of this study is to provide an overview of changes in the Summary of Product Characteristics (SmPCs) of antibiotics that underwent a referral procedure between 2007-2017.

Methods:
Publicly available information on regulatory procedures and assessment reports from the European Commission community register of medicinal products and the EMA database were used to identify antibiotics that underwent Article 30 or 31 referral procedures. Changes in the relevant sections of the SmPCs were assessed. A change was defined as any modification related to restriction of a therapeutic indication from the SmPCs during the referral procedure. Modifications made in the section 4.1. therapeutic indications were stratified by type into: removal relating to group of infections versus one disease and removal involving treatment versus prophylaxis.

Interim results:
Thirteen antibiotics from five different classes underwent a referral procedure during the study period 2007-2017. Most included cephalosporins (31%), followed by penicillins (23%), fluoroquinolones (15%), carbapenems (15%) and glycopeptide (15%). The referral procedure resulted in change of the SmPCs' section 4.1. therapeutic indications for almost all antibiotics (92%). In total, there were 61 changes applied to section 4.1. of which 43% (26/61) were classified as a changes involving a group of indications (e.g. upper respiratory tract infections) and 57% (35/61) as a disease specific (e.g. acute sinusitis). Most (92%, 55/61) of the changes in section 4.1 involved antibiotics used for treatment and only 10% (6/61) involved prophylactic therapy.

Conclusions:
Therapeutic indications were restricted in section 4.1 for almost all antibiotics that underwent the referral procedure. Most involved disease specific and applied to antibiotic treatment of infection, and not prophylactic therapy. Further research is needed to examine the impact on antimicrobial resistance.

2 Registration of essential medicines in Kenya, Tanzania, and Uganda

P. Brhlikova, A. Green, E. Rainey, S. Whiteman, C. Mellor, R. Lyus, G. Hillsmith, A. Homes, S. Musa, C. Brown, R. Walker, A.M. Pollock

Institute of Health and Society, Newcastle University, Newcastle upon Tyne, UK

Background:
Despite international efforts to improve the availability of selected priority medicines and vaccines, low- and middle-income countries struggle to ensure access to a broader set of essential medicines as specified by their national essential medicines lists (EML). Although barriers to registration of generics and novel essential medicines have been researched, the extent to which essential medicines are registered is unknown as are the links between local production and their availability.(Wirtz et al. 2017) This study examines registration of essential medicines in Kenya, Tanzania, and Uganda. These countries are members of East African Community (EAC), which launched the EAC Medicines Registration Harmonization project in 2012 and formulated a regional pharmaceutical manufacturing plan of action (2012-16) to promote access to affordable quality essential medicines in the EAC.

Methods:
We compared the National Drug Registers of Kenya, Tanzania, and Uganda (February 2018) with the respective national EML valid at that time (Kenya v. 2016, Tanzania v. 2017, Uganda v. 2016) to determine the registration status of essential medicines and to identify those essential medicines which are manufactured locally.

Results:
About one third of registered products in Kenya (28%), Tanzania (33%), and Uganda (38%) correspond to essential medicines. A significant proportion of essential medicines do not have any equivalent product registered; 31% (211/675) in Kenya, 44% (353/803) in Tanzania, 37% (243/661) in Uganda. Up to 17% of registered products are manufactured in the EAC: 17% (1020/6150), 10% (410/3956), and 11% (433/4009) of products registered in Kenya, Tanzania and Uganda respectively. Of the products sourced from the region, 29% (300/1020) in Kenya, 41% (167/410) in Tanzania, and 43% (186/433) in Uganda are medicines listed in the corresponding national EML.

Conclusions:
A significant proportion of essential medicines do not have any equivalent products registered in the EAC countries and therefore cannot be available at all times. Registration of essential medicines needs to be prioritised at national and regional level and local manufacturing of missing essential medicines promoted through the regional manufacturing plan.

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3 Assessment of Pharmaceuticals Benefits Package of the National Health Insurance Fund, Sudan, 2003-2016

I.M. Mustafa

National Health Insurance Fund, Sudan

Background:
The Health Insurance Schemes have a potential role in improving accessibility to medicines especially for chronic medications. A comprehensive Pharmaceutical Benefits Package is the key factor for reducing the financial burden of purchasing medicines from out-of- pocket of patients.
The National Health Insurance Fund, Sudan (NHIF) is aiming at achieving the Universal Population Coverage by the end of 2020, however more than 40% of the population is poor and suffer from Catastrophic Health Expenditure. The objective of the study was to assess the changes of the Pharmaceutical Benefits Package of NHIF from 2003 to 2018 especially for the medicines used for cardiovascular diseases, diabetes, central nervous system and antibiotics. The second objective was to compare between the NHIF lists, the Sudan Essential Medicines lists and the World Health Organization's (WHO) Model lists of Essential Medicines.

Methods:
Study design: An observational descriptive study.
Setting and study population: Pharmaceutical Benefits lists of the NHIF for the years 2003, 2007, 2012, 2014 and 2018 were analysed in Excel. The WHO recent Medicines lists and Sudan Essential Medicines list of 2016 were used for comparison. The methodologies used for update of NHIF lists over years were assessed.

Results:
The expansion of the NHIF Lists was significant in which the number of dosage forms in 2003 was 330 and increased to 513, 590, 603 and 690 in the years 2007, 2012, 2016 and 2018 respectively. The medicines used for cardiovascular diseases increased by 43 while those for diabetes increased by five, central nervous system by 13.

Conclusion: the trends of expansion of the NHIF Medicines lists over time shown in the study, reflects the development of the scheme, however effective implementation and us of pharmaco-economic evaluation tools are needed .

4 Effects Of Regulatory Major Objections On Reimbursement Decisions In Europe

Lourens T. Bloem, PharmD[1,2], Rick A. Vreman, PharmD[1,3], Niels W.L. Peeters[1], Jarno Hoekman, PhD[4], Hubert G.M. Leufkens, PhD[1], Olaf H. Klungel, PhD[1,5], Aukje K. Mantel-Teeuwisse, PhD[1]

1. Division of Pharmacoepidemiology and Clinical Pharmacology, Utrecht Institute for Pharmaceutical Sciences, Utrecht University, Utrecht, The Netherlands
2. Dutch Medicines Evaluation Board, Utrecht, The Netherlands
3. National Health Care Institute, Diemen,The Netherlands
4. Innovation Studies, Copernicus Institute of Sustainable Development, Utrecht University, Utrecht, The Netherlands
5. Julius Center for Health Sciences and Primary Care, University Medical Center Utrecht, Utrecht, The Netherlands

Background:
To enhance timely access to medicines, the European Medicines Agency (EMA) may accept less conclusive clinical evidence with a higher level of uncertainty at time of marketing authorization (MA). How this affects reimbursement recommendations remains unknown. We aimed to (i) determine whether the existence of major clinical objections (MOs) regarding phase III data during the MA procedure as a measure for uncertainty is associated with negative reimbursement recommendations, and (ii) identify differences in clinical studies used for decision-making by EMA and reimbursement agencies.

Methods:
For a cohort of innovative medicines that received MA (2009 & 2010, excluding vaccines) we identified all publicly available initial reimbursement recommendations in England, France, the Netherlands and Scotland. Risk ratios (RRs) and 95% confidence intervals (CI) were calculated overall and per jurisdiction for the association between MOs identified in MA dossiers (Putzeist et al, 2012) and negative reimbursement recommendations. Data on clinical studies were extracted from reimbursement dossiers and EMA's public assessment reports (EPARs).

Results:
For 35 medicines, 109 reimbursement recommendations were made, of which 43 percent were negative. The presence of clinical MOs was associated with an increased, although non-significant, risk for a negative reimbursement recommendation: 1.4 (95% CI 0.9 to 2.3). For England, France, the Netherlands and Scotland, the RRs were 0.6, 1.5, 2.1 and 1.1, respectively (all non-significant). The proportion of studies in the EPAR also used for reimbursement recommendations varied from 24 (England) to 55 (France) percent. The proportion of studies used for reimbursement decision-making that were not included in the EPAR varied from 13 (France) to 55 (England) percent.

Conclusions:
Acceptance of uncertainties by regulators may be associated with negative reimbursement recommendations. This study suggests different considerations regarding clinical evidence between regulators and reimbursement authorities. Many studies in the EPAR are not used for reimbursement recommendations, and vice versa.
Words: 300/300

Declaration of funding: None. Brief description:
This study assesses the relation between uncertainty in clinical evidence used for regulatory decision-making (measured in major objections raised by the EMA) and reimbursement recommendations (measured by proportion of negative recommendations). Results show that acceptance of uncertainties by regulators may be associated with negative reimbursement recommendations, which indicates that different considerations regarding clinical evidence exist between regulators and reimbursement agencies.

5

Drug Switching in the Netherlands Quantified: An Observational Cohort Study

P.J. Glerum[1,2], M. Maliepaard[1,3], V. de Valk[4], D.M. Burger[5], C. Neef[2]

1. Medicines Evaluation Board, Utrecht, The Netherlands
2. Department of Pharmacology and Toxicology, CARIM, Maastricht University, The Netherlands
3. Department of Pharmacology and Toxicology, Radboud University Medical Centre, Nijmegen, The Netherlands
4. National Health Care Institute, Diemen, The Netherlands
5. Department of Pharmacy, Radboud University Medical Centre, Nijmegen, The Netherlands

Background:
The debate on drug switching would benefit from research into related adverse drug reactions (ADRs). However, such investigations are hampered by the absence of data on the population at risk – the actual number of patients who receive different formulations of their prescribed medication. Here, we provide a qualitative and quantitative description of drug switching in the Netherlands.

Methods:
We conducted a retrospective cohort study of patients prescribed drugs for chronic use whose medication was changed to another drug formulation, using information from a nationwide health insurance claims database.

Results:
There were numerous drug switches, with a peak in the period January to March, which is most likely explained by the Dutch Preference Policy. In some months 3 in every 5 repeat prescriptions were filled with a product from another manufacturer. Most (80.3%) drug switches were between two generic products; 7.1% of the switches concerned a brand-name drug being replaced by a generic product, 3.5% a switch from a generic to a brand-name product, and 9.1% a switch between two brand-name products. A large proportion (9.5%) of all switches involved a product obtained from parallel import. The high switch rates can be explained by switching between the numerous formulations containing the same active substance produced by different manufacturers.

Conclusions:
Overall, this study provides a unique characterization of the frequency of drug switches in the Netherlands. These data will facilitate future analysis of reported ADRs related to switching between drug formulations.

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Linking Global Health Prioritisations to Access to Medicine: from Pipeline to Portfolio

A.C. Kong and M.E. Warren

Access to Medicine Foundation, Amsterdam, The Netherlands

Background/Research Question:
A diverse cast of global health players influenced by the United Nations Sustainable Development Goals play critical roles in defining global disease priorities, and promoting the availability and access of vital health products for these diseases to patients living in low- and middle-income countries (LMICs). The 2018 Access to Medicine Index examines the role of pharmaceutical companies in increasing access to medicine. Through this work, we sought to investigate if and how companies are influenced by the global health community and how they respond to corresponding priorities.

Methods:
Data was collected from 20 of the largest global pharmaceutical companies through a questionnaire and publicly available information. Research and development (R&D) projects and marketed products were considered based on product type (e.g. medicines, vaccines and diagnostics) and disease target. Seventy-seven diseases, conditions and pathogens, including infectious diseases, non-communicable diseases and conditions such as maternal haemorrhage, were in scope for the 2018 Index. R&D projects were assessed on their alignment with priority R&D product gaps, identified by the World Health Organization (WHO) and Policy Cures Research to guide R&D for urgently needed products for patients in LMICs, and the access plans developed for these projects. Marketed products were assessed based on product-specific access initiatives (i.e. equitable pricing strategies, non-exclusive voluntary licences or structured donation programmes).

Results:
1,314 eligible R&D projects and 1,036 marketed products were included for analysis by the Index. Twenty-three percent (n=298) of the R&D projects in the collective company pipeline targets priority product gaps, but the majority (54%) of these projects focus on five diseases: malaria, HIV/AIDS, tuberculosis, Chagas disease and leishmaniasis. Access planning during R&D disproportionately favours priority R&D projects, with 57% of these projects having access plans in place, compared to 4.2% for all other R&D projects. Of the 1,036 marketed products from the 20 companies assessed, 53 products were determined to be critical candidates for companies' access initiatives; these products are on-patent, first-line therapies listed on the 2017 WHO Model List of Essential Medicines for diseases in scope. Of these 53 products, those with access initiatives (n=37) are predominantly (73%) for the treatment of HIV/AIDS or hepatitis C or are preventative vaccines. These products are linked to significant donor funding or attention.

Conclusions:
Both R&D and access initiatives for R&D projects and marketed products are heavily influenced by donor priorities and funding. This has created a distinct focus on products targeting key diseases aligned with global health funding priorities while the development and deployment of products targeting other critical diseases is limited. To address these disparities and to advance access to medicine, a concerted effort to expand areas of focus is required from both the industry and the global health organisations who motivate them.

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7 Resource needs for viral hepatitis elimination through universal health coverage: Projections in 67 low-income and middle-income countries, 2016-2030

David Tordrup[1], Yvan Hutin[2], Karin Stenberg[3], Jeremy Lauer[3], David Hutton[4], Mehlika Toy[5], Nick Scott[6], Marc Bulterys[2], Andrew Ball[2] and Gottfried Hirnschall[2]

1. WHO Collaborating Centre for Pharmaceutical Policy and Regulation, University of Utrecht, Netherlands
2. Global Hepatitis Programme, WHO, Geneva, Switzerland
3. Department of Health Systems Governance and Financing, WHO, Geneva Switzerland
4. Dept. of Health Management and Policy, School of Public Health, University of Michigan, United States
5. Stanford University, United States
6. Burnet Institute, Melbourne, Australia

Background:
In 2016, the World Health Assembly adopted the global health sector strategy on viral hepatitis that has the goal of eliminating viral hepatitis as a public health threat by 2030 (-90% incidence, -65% mortality). However, the 2017 WHO estimate for the cost projections of strengthening health systems and advancing universal health coverage to achieve the health-related Sustainable Development Goals (SDGs, WHO SDG investment scenarios) did not include resource needs estimates for the scaling up of testing and treatment for HBV and HCV infections.

Methods:
We completed the 2017 WHO cost projections of the health-related SDGs and modelled the implementation of WHO recommendations for the testing and treatment of HBV and HCV infection. We quantified additional requirements in terms of commodities (e.g., diagnostic tests, medicines), health worker time and programme support across 67 low- and middle-income countries. We considered a flatline scenario, a progress scenario that scaled up the WHO recommended interventions and an ambitious scenario where the service coverage of diagnosis and treatment were scaled to levels needed to reach hepatitis elimination by 2030. Cost of commodities were based on best available prices of generic medicines and diagnostics in 2018. We estimated total costs and the additional investment needed over the projection of the 2016 baseline cost.

Results:
The 67 countries considered (2015 population: 5.6 billion) accounted for 230 million persons living with HBV (90% of the world's total) and 52 million persons living with HCV infections (73% of the world's total). The preliminary analysis shows, under the progress scenario, 2,400 million and 850 million persons would be initially tested for HBV and HCV infection, for a cumulative number of persons treated of 24 and 34 million, respectively, by 2030, and an additional cost of USD 27 billion. Under the ambitious elimination scenario, 5,502 million and 6,129 million persons would be initially tested for HBV and HCV infection, for a cumulated number of persons treated of 32 and 62 million, respectively, and an additional cost of USD 59 billion. By 2030, elimination would avert 4.5 million premature deaths and lead to a gain of 51.5 million healthy life years. Price of HCV medicines and HBV DNA testing had the largest impact on the hepatitis price tag.

Conclusions:
Scaling up of HBV and HCV testing and treatment to reach elimination would add 1.5% to the ambitious health-care strengthening scenario, avert an additional 4.6% premature deaths and add an additional 9.6% healthy life years in 2016-2030. Further efforts are needed to ensure that all countries can access HCV medicines and HBV DNA testing at prices compatible with the coverage requirements needed to reach elimination.

8 Sickle Cell Disease: a well-known inherited disease offers lessons on how to improve access to essential medicines in low resourced settings

E.Costa[1,2], E.Kaale[3], P.Tibalinda[3], J.Makani[4], H.G.M. Leufkens[1], L.Luzzatto[4]

1. WHO Collaborating Centre for Pharmaceutical Policy and Regulation, Utrecht University, The Netherlands
2. Department of Pharmacy, Azienda Ospedaliera Universitaria Integrata di Verona, Italy
3. School of Pharmacy, Muhimbili University of Health and Allied Sciences, Dar-es-Salaam, Tanzania
4. Department of Haematology, Muhimbili University of Health and Allied Sciences, Dar-es-Salaam, Tanzania

Background:
Sickle cell disease (SCD) is a group of inherited disorders characterised by the presence of a unique abnormal haemoglobin, which confers to red blood cells the tendency to become sickle-shaped when deoxygenated. Signs and symptoms (i.e., anaemia, painful crisis and infections) usually begin in early childhood. The greatest burden of SCD is borne by people in sub-Saharan Africa. Up to now only one drug, hydroxyurea (HU) has shown efficacy for amelioration of symptoms. However, its use remains largely suboptimal in low-income countries. An international and multidisciplinary collaboration between haematologists and pharmacists aims to: A) pilot production of HU as galenic at local level; B) assess the availability and affordability of HU in Africa; C) strengthen global pharmaceutical policies to improve the access to HU globally.

Methods:
A) a local production was implemented in Tanzania; B) a preliminary survey to assess costs and availability of HU in Tanzania was carried out; later, , a survey on HU availability and affordability among African countries will be carried out according to WHO-HAI methodology; C) a HU global initiative is to be planned.

Results:
A) 3,690 capsules were produced in 7 lots for 41 patients (45 days of therapy per patient at therapeutic dose). Raw materials represent 27% of the budget, while personnel costs 40%. HU from HASTE would cost 0,18 USD per gram, 5-10 times cheaper than the ones on Tanzanian retail market. B) Local survey in Dar es Salaam: HU at a dose of 1 G per day costs approximately 35 USD per month. Costs and availability of HU can differ among i) African countries, ii) urban and rural pharmacies, iii) the population income. C) As Global Fund supports AIDS, TBC and malaria drugs, collaboration among institutions and pharmaceutical industry ought to supports HU affordability.

Conclusions:
Our preliminary analysis has revealed that the price of HU for the majority of Tanzanian SCD patients is too high to fit into their budget. On the other hand, compounding HU in Africa is feasible and affordable. Moreover, investing in the expertise of healthcare personnel can improve pharmaceutical know-how in Africa, an important first step to improving pharmaceutical policies.

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Access to Medicines in Rohingya Refugee Camps

Swathi Iyengar[1,2]

1. Postgraduate Student, Division of Pharmacoepidemiology & Clinical Pharmacology, Utrecht Institute for Pharmaceutical Sciences, Utrecht University, Utrecht, Netherlands
2. Technical Officer, Innovation, Access, and Use, Essential Medicines & Health Products, Access to Medicines, Vaccines, and Pharmaceuticals, World Health Organization, Geneva, Switzerland

Background:
In 2018, approximately one million Rohingyas have fled violence in Myanmar's Rakhine State and crossed into Cox's Bazar, Bangladesh – one of the country's poorest districts. The provision of health services to this vulnerable population in the refugee camps has necessitated the procurement and supply of essential medicines on an emergency basis, through different actors and using different mechanisms. However, the rapid influx of medicines from various sources and the limited regulatory oversight increases the risk of substandard or falsified medicines becoming available in the local market, as well as increases the complexity of supply, distribution, and storage systems.

Methods:
To better understand these supply system and access issues, a rapid assessment of the Rohingya camps was conducted in October 2018 over ten days. Facilities were chosen randomly by camp area and included a total of 43 health posts, primary health centers, field hospitals, and unregistered drug shops. The assessment was composed of a semi-structured interview of key informants in health facilities and use of a customized mobile application to collect product information on a core set of tracer medicines required to treat critical illnesses within the camp. Product information included availability, length of stockout where applicable, price, brand, manufacturer, manufacturing origin. The semi-structured interview included questions on disposal, dispensing, record-keeping, procurement methods, and finally recommendations to improve access.

Results:
All health facilities, except for unregistered drug shops, provided medicines for free inside the camp area. Unregistered drug shops are selling the products at the maximum retail price allowed by Bangladesh's Directorate General of Drug Administration. Although 70% of health facilities do not have pharmacists, experienced medical personnel such as nurses, midwives, or medical assistants are dispensing products when pharmacists are not available. Stockouts were mainly noted among anti-infectives, oral rehydration salts, and analgesics when during outbreaks. At the time of the assessment, anti-infectives and child health products, such as ORS and zinc, were frequently available in the facilities surveyed. Products for mental health and products for non-communicable disease management had low availability or were often not offered in health posts and primary care facilities. Other aspects assessed included sourcing and storage: 75% of the products found in health facilities were locally manufactured, and only 20% of facilities surveyed providing products requiring cold storage had proper cold storage environments. Based on these findings, the following recommendations were made: 1) improve storage conditions at health facilities or modify procurement to match environmental constraints; 2) consider a central mechanism to establish a list of "prequalified" local suppliers with trusted quality; 3) establish "minilabs" in the camps to allow the drug regulatory authority to screen for potentially substandard and falsified products; 4) begin providing essential NCD medicines at health post and primary health care levels to support continuity of treatments for patients.

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Selection of Blood, Blood Components and Blood Products as Essential Medicines in 105 Low and Middle-Income countries

Washington T. Samukange[1,2], Helga Gadarsdottir[1], Hubert G.M. Leufkens[1] and Aukje K. Mantel-Teeuwise[1]

1. Division of Pharmacoepidemiology & Clinical Pharmacology, Utrecht Institute for Pharmaceutical Sciences (UIPS), Utrecht, the Netherlands
2. Paul Ehrlich Institut, Langen, Germany

Background:
Blood products of human origin are used as treatment options for several diseases including some rare diseases like haemophilia. Where they are available, they are often the only existing treatment option. We studied the alignment of national essential medicines lists (NEMLs) with the WHO Model list for the selection and factors associated with inclusion of blood products of human origin.

Methods:
NEMLs from all low and middle-income countries (LMICs) were studied for inclusion of blood products of human origin. Data obtained from 105 NEMLs were compared to the WHO Model list. The results were analysed by WHO region, income level, and year of NEML update. Non-parametric tests were used to compare differences among groups.

Results:
The median number of blood products of human origin on the NEMLs was four (range: 0 -10). The most frequently selected blood products were immunologicals, available in over 70% of the NEMLs studied. Blood and blood components were the least selected products on NEMLs, found on less than 15% of the NEMLs. Nine countries did not have any blood products on their NEMLs. The number of products on recently updated NEMLs differed significantly with older NEMLs (P = 0·045). There was no relationship between the number of blood products selected and a country's income (P = 0·288).

Conclusions:
Alignment of NEMLs with the WHO EM list varied greatly for different groups of blood products. Reliance on evidence, particularly for rare diseases is recommended for selection and inclusion of blood products on NEMLs.

11 Contribution of the Global Fund's Private Sector Copayment Mechanism towards ensuring universal access to quality assured antimalarial medicines in Uganda.

Denis Kibira[1], Anthony Ssebagereka[1], Jimmy Opigo[2], Henry Katamba[2]

1. Coalition for Health Promotion and Social Development
2. National Malaria Control Program, Ministry of Health, Uganda

Background:
Malaria is the single largest cause of illness in Uganda. Uganda contributed 17% of the total malaria cases in the East and Southern Africa sub region in 2016 with pregnant women and children being the most affected. The private sector plays a substantial role in Uganda's health system, providing health services to approximately half of the population. Under the Private sector copayment mechanism, Quality Assured Artemisinin-based Combination Therapies (QAACTs) are procured from pre-qualified manufacturers through a financing model offering a 70% subsidy by the Global Fund. The ultimate goal is to increase availability and affordability of QAACTs in the private sector. The aim of this assessment was to track the availability, prices and affordability of co-paid QAACTs between October 2016 and December 2017.

Methods:
A standardized methodology co-developed by WHO and HAI was adapted to assess the availability, prices and affordability of co-paid QAACTs. Data was collected from 495 Private-For-Profit healthcare facilities in 23 districts among six regions of Uganda (Central, Northern, West Nile, Western, South-Western and Eastern over five quarterly rounds. Affordability was assessed based on the wage of the lowest paid unskilled government worker.

Results:
The median availability of co-paid QAACTs among private healthcare facilities increased from 87% to 97%. Overall median retail prices for co-paid QAACTs by pack price were UGX 4000, 3000, 2500 and 1500 for the 6x4, 6x3, 6x2 and 6x1 pack sizes respectively.
On average, the lowest paid unskilled government worker would have to spend 68% of his daily wage on co-paid QAACTs, and (100%) of his daily wage on management (both diagnosis and treatment) of uncomplicated malaria.

Conclusion:
The availability of co-paid QAACTs increased. Prices of co-paid QAACTs were marginally affordable.
Malaria stakeholders should consolidate these gains made.

12 Cost of unlicenced and orphan medicines in turkey, kazakhstan and poland

E.K. Atikeler[1], A. Baran[2], K. Gaitova[3], H.G. Leufkens[1], Czech M[4], W. Goettsch[1]

1. Utrecht Institute for Pharmaceutical Sciences, Utrecht University, Utrecht, The Netherlands
2. Medical University of Warsaw, Warsaw, Poland
3. Republican Center for Health Development of Ministry of Health Kazakhstan, Astana, Kazakhstan
4. The Institute of Mother and Child, Warsaw, Poland

Background:
As a result of Turkey's healthcare reforms initiated in 2003 access to medicines increased rapidly that enlarged the public medicine expenditure. Simultaneously, costs of unlicenced or unmarketed licenced medicines became greater. The goal of this study was to describe the impact of direct imported medicines on the total public medicine expenditure. The results were compared with Kazakhstan and Poland.

Methods:
The reimbursement system of Turkey was assessed focusing on the mechanism of direct imported medicines. The Medicines Bringing From Abroad (MBFA) list and sales data from Turkish Pharmacist Association (main provider for direct import medicines in Turkey) were used for the study. The sales data of 10 selected for the study products that contribute to the highest expenditure in Turkey were obtained from Polish and Kazakhstan Ministry of Health.

Results:
The direct imported medicines constitute to the 8% of the total public pharmaceutical spendings in Turkey. In contrast ,this was only possible for orphan medicines in Kazakhstan. In Poland the analyzed products are reimbursed (5 out of 10) within Drug Programmes. In addition a target import and special named patient program exist for life saving therapies. The study shown that 9 products had an orphan indication and contributed to 500 million € costs in Turkey for the year 2017. The public expenditure were lower in Kazakhstan and Poland.

Conclusions:
Direct import of medicines has quite significant impact on the total costs for medicines in Turkey. Other countries in the region, such as Kazakhstan and Poland, that do not use the system of direct import for all medicines have much lower number of patients and associated costs for these products. There is a need to introduce new policy concerning the use of unlicenced medicines for instance by creating HTA Agency. In addition solutions for providing orphan drugs to patients should be created to ensure a sustainable and fair access to therapies on future.

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An analysis of the Tunisian medicines price policy

I. Fradi[1], N. Ghozzi[2], S. Miled[2], K. Souissi[3]

1. Faculty of Pharmacy, University of Monastir, Tunisia
2. Directorate of Pharmacy and Medicines, Ministry of Health, Tunisia
3. Tunisian Central Pharmacy

Background:
The price of medicines constitutes an important lever of health policy as it influences the access of patients to treatment. In Tunisia, the price negotiation is made by different actors in the process, including the Ministry of Health, the Ministry of Trade and the Ministry of social affairs as well as the National Health Insurance Fund and the Tunisian Central Pharmacy which intervenes in the supply of the medicine onto the territory. Recently, higher prices in Tunisia than those applied in the benchmark countries has been noticed for several medicines. The aim of this study is to analyze and explain the origin of that differences in prices.

Methods:
A comparative study of the public prices applied in Tunisia and other countries (France and Morocco) was conducted on 92 reference medicines. Comparison was made by converting the prices in local currency to either the same currency (Euro) or to international dollars using purchasing power parity (PPP) exchange rates. Then, inter-countries price comparison was made for generics of the reference products that had higher prices in Tunisia.

Results:
Using the same currency, the prices of 54 (from the 92) were higher in Tunisia than in France. On the other hand, when PPP exchange rates were used 89 medicines had higher prices in Tunisia. Higher prices of reference products impacted significantly those of the corresponding generics. It seems that the difference in price is more important for the strong dosages because of applying the same price for different dosages in France when the price is rising with the dosage in Tunisia. In comparison with Moroccan prices higher values were observed for 10 Tunisian specialties when Euro is used (44 using PPP).

Conclusions:
This analysis highlights the importance of updating the price of medicines in order to reduce the price of mature products and enable the introduction of innovative ones. Benchmarking constitute an important tool not only when setting the initial price of the reference medicines but also throughout the hole life of the Drug and to set the price of generics. Finally, recommendations on updating the rules of price negotiations were issued.

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Generic price and uptake level comparison across OECDs and its corresponding generic pricing policies

Junhee Pyo, MS B.Pharm

Utrecht University, IQVIA

Background:
Generics play an important role in cost saving for both payer and patient meanwhile ensuring a broad access to medicine. Differences in national generic pricing policies result in different level of its price to further impact on the generic uptake level. This study aims to compare generic price across OECD countries, and investigate national generic pricing policy and generic uptake.

Method:
We have selected 20 generic prescription molecules of each ATC class in a global level according to their sales volumes. Ex-factory price of these molecules with same strength and formula for each ATC across countries have been retrieved from IQVIA Health global database (MIDAS) of annually averaged price in 2017. Generic prices were compared as (1) median price level across countries, and (2) on a relative scale setting the highest country's price level at 1.00. The generic uptake proportion was calculated as the volume uptake proportion compared to the original drug's sales volume. Generic policy measures were collected from the literature search of government and OECD documents.

Result:
We extracted 125 common medicinal products, defined by molecule, strength and formulation, which are present as generics in more than 75% OECD countries. Among OECDs, New Zealand (0.11 as a relative scale when Mexico's set to 1.00), Turkey (0.14), Netherlands (0.17), Norway (0.17), UK (0.21), Poland (0.22), Slovakia (0.22) and Sweden (0.23) ranked as lower price countries of 25th percentile. Mexico (1.00), Switzerland (0.85), Korea (0.67), Japan (0.66), China (0.57), Ireland (0.55), France (0.53) and Canada (0.47) ranked as higher price countries of 75th percentile. The generic price level was reversely associated to the generic uptake proportion compared to original medicines. Lower price level countries widely adopted therapeutic reference pricing rule, generic substitution and incentives to prescriber and pharmacist to achieve generic efficiency.

Conclusion:
Within OECDs, a wide variation of generic price level has been observed and a national generic pricing level reversely associated with the extent to generic uptake. Lower price level countries widely adopted the generic enhancing policy.

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15 Patient Reported Outcome Measures In Health Technology Decision Making

R.R.J. Kalf [a,b], R. Vreman [b], D. Delnoij [a, c], M.L. Bouvy [b], W.G. Goettsch [a, b]

a. Zorginstituut Nederland, Eekholt 4, 1112 XH Diemen, the Netherlands
b. University Utrecht, Department of Pharmacoepidemiology and Clinical Pharmacology, Utrecht, the Netherlands
c. Erasmus University Rotterdam, The Erasmus School of Health Policy & Management, Rotterdam, the Netherlands

Background:
Regulatory bodies and Health Technology Assessment (HTA) agencies request clinical outcome measures to support their assessments for marketing authorisation, and pricing and reimbursement decisions. It is of additional value when these outcome measures actually matter to patients. We assessed the extent to which regulators and HTA require outcome measures that matter to patients, as defined by the International Consortium for Health Outcomes Measurement (ICHOM), in pharmaceutical decision-making.

Methods:
ICHOM guidelines for oncological indications were selected. We identified publicly available regulatory and HTA assessment guidelines from the website of the Food and Drug Administration (FDA), European Medicines Agency (EMA), European Network for Health Technology Assessment (EUnetHTA), the Dutch National Health Care Institute (ZIN), the National Institute for Health and Care Excellence (NICE), and Institute for Quality and Efficiency in Health Care (IQWiG).

Results:
Of the fifty-one guidelines identified, twenty-four were included in the analysis. The FDA and EMA provided cancer specific guidelines for marketing assessments, as well as guidelines for lung cancer, breast cancer, and prostate cancer. All HTA agencies provided general assessment guidelines. ICHOM guidelines suggest which outcome measures to collect, when to do so and how to report them, while guidelines from regulators and HTA are more general. ICHOM suggests more patient reported outcome measures in disease-specific guidelines as compared to regulators. NICE and ZIN request that quality of life is collected using the EQ-5D, while ICHOM suggests disease-specific quality of life questionnaires.

Conclusions:
ICHOM stresses the importance of disease-specific outcome measures. This is supported by regulators by publishing disease-specific guidelines in some instances, such as breast cancer and lung cancer. On the other hand, HTA often request generic outcome measures to allow comparisons between indications. Disease-specific outcome measures could, however, be used to identify whether the outcomes of a new treatment actually matter to patients.

16 The Use of Surrogate Endpoints in Current Drug Approval Pathways

Colin Millard

Institute of Health and Society, Newcastle University

Background:
A major challenge in clinical trials is to establish clinically meaningful endpoints. Ideally the primary endpoint of the trial should be a clinical endpoint, ‘a characteristic or variable that reflects how a patient feels, functions, or survives’. There are a number of disadvantages to using clinical endpoints in clinical trials. Where disease progress is slow, measuring the clinical endpoint can take a long time; it can take decades for cervical cancer to develop following HPV infection, or for morbidity or death related to diabetes. In addition, to achieve statistical validity, trials using clinical endpoints require a large sample; this combined with the long duration makes trials based on clinical endpoints costly. To overcome these problems sponsors have increasingly used intermediate biomarkers as surrogates for clinical endpoints. This paper assesses the role of surrogate endpoints in current FDA and EMA drug approval procedures and the degree to which evidence derived from them provides accurate safety and efficacy measures.

Methods:
Review of the academic literature on surrogate endpoints and review of FDA and EMA expedited drug approval pathways.

Results:
The FDA has developed four schemes to expedite the approval of drugs for serious diseases and unmet medical needs. The EMA currently has 5 expedited drug approval programmes. Although surrogate endpoints can be used as evidence in all of these programmes, in some they are the major source of evidence. A large number of drugs have now been approved through existing expedited programme using surrogate measures.

Conclusion:
Clinical trials using surrogate endpoints introduce an element of uncertainty because claims about therapeutic efficacy are based on extrapolations from effects on surrogate markers. Predictions based on these extrapolations can lead to both overestimations and underestimations of the effect of an intervention on a clinical endpoint. This study concludes that surrogate markers should only be used when there is sufficient evidence that they can be used to predict clinical outcomes and that confirmatory trials are undertaken in a timely fashion to confirm the benefit to risk profile of the approved drug.

17 Reporting of quality attributes in similarity assessments of recombinant therapeutic proteins in scientific publications: a systematic review

Alsamil A. M[1,3], Giezen, T.[2], Leufkens, H.G.M.[1], Gardarsdottir, H.[1,4,5]

1 Division of Pharmacoepidemiology and Clinical Pharmacology, Utrecht Institute of Pharmaceutical Sciences, Faculty of Science, Utrecht University, Utrecht, the Netherlands
2 Stichting Apotheek der Haarlemse Hospitals, Haarlem, the Netherlands
3 Products Evaluation Directorate, Drug sector, Saudi Food and Drug Authority, Riyadh, Saudi Arabia
4 Department of Clinical Pharmacy, Division Laboratory and Pharmacy, University Medical Center Utrecht, Utrecht, the Netherlands
5 Department of Pharmaceutical Sciences, University of Iceland, Reykjavik, Iceland

Background:
The analytical similarity assessment is the most sensitive tool to detect potential differences between a biosimilar and an authorized reference medicinal product. As more biosimilars are being developed and entering the market, the availability of similarity assessment data in the public domain is increasing.
Objective: To identify and describe structural and functional quality attributes (QAs) that are reported in scientific publications of similarity assessments.

Method:
English-full-text articles published between 1 January 2017 and 31 July 2018 that presented similarity assessments of biosimilars were identified in PubMed and EMBASE. Information on publication and product characteristics as well as type of reported QA, were registered. The QAs assessed were divided into structural and functional attributes, and further into different sub-categories.

Result:
45 analytical similarity assessments for 40 biosimilars (currently 12 approved and 28 unapproved) were identified from 31 scientific publications. The assessments included 107 QAs, (77.0% structural, 23.0% functional) for which large differences were found regarding type and number of QAs reported among molecules and therapeutic classes. The QAs underneath physicochemical properties and post-translation modifications (82.0%), primary structures and biological activities (80.0%) and higher order structures (67.0%) sub-categories were most often assessed. The QAs reported in the assessments for monoclonal antibodies (56.0%) were two folds higher than hormones (18.0%), although the quantity of QAs reported within sub-categories was doubled in rituximab than infliximab assessments.

Conclusion:
Most of assessments included structural QAs; however, the QAs reported differ between publications, even for the same molecules. The assessments data availability escalates knowledge about key quality attributes to facilitate decision-making on analytical similarity.

18 Medicines authority regulators and industry perspectives on the European regulation of biosimilars

L.C. Druedahl[1,2], Marieke De Bruin[1], Marco van de Weert[3], Timo Minssen[4], Hans Hoogland[5], Anna Birna Almarsdóttir[2]

1 Copenhagen Centre for Regulatory Science, Department of Pharmacy, Faculty of Health and Medical Sciences, University of Copenhagen, Denmark.
2 Social and Clinical Pharmacy, Department of Pharmacy, Faculty of Health and Medical Sciences, University of Copenhagen, Denmark.
3 Protein Formulation and Biophysics, Department of Pharmacy, Faculty of Health and Medical Sciences, University of Copenhagen, Denmark.
4 Centre for Advanced Studies in Biomedical Innovation Law (CeBIL), Faculty of Law, University of Copenhagen, Denmark.
5 LEO Pharma A/S, Ballerup, Denmark.

Background:
Biosimilar medicinal products (biosimilars) have been authorized in Europe since 2006. For approving a proposed biosimilar, the product needs to be assessed as highly similar in terms of quality, safety and efficacy to an already approved biological medicinal product. Earlier studies mention incentives for introducing biosimilars to include fostering competition as means to decrease health care costs while maintaining incentives for innovation of new biologic treatments. However, it is unknown how stakeholders (medicines authority regulators and the pharmaceutical industry) perceive the incentives for introducing biosimilars and whether the current structure of the regulation of biosimilars fulfills these incentives. Therefore, the aim of this study was to evaluate whether the European regulation of biosimilars is working as intended.

Methods:
Purposive convenience sampling was used to recruit participants for qualitative individual interviews. Eligible participants were medicines authority regulators with experience with the European regulation of biosimilars or representatives from pharmaceutical companies with marketing authorization for either an originator biologic or a biosimilar medicinal product in the European Union. An inductive content analysis was applied.

Results:
Preliminary results include perceived implications of the European regulation of biosimilars on public health and innovation; appropriateness of the regulatory assessment of biosimilarity exercise vs. manufacturing change comparability exercise; and biosimilarity as a moving target.

19 Combining availability and affordability dimensions of access to medicines in a single SDG indicator: a methodology proposed to identify how many medicines are accessible

K. Chepynoga, C. Nannei

Department of Essential Medicines and Health Products, World Health Organization, Geneva, Switzerland

Background:
Measurement of access to medicines is a high priority for the global development agenda given access is an integral part of universal health coverage (UHC) and an indispensable element of delivery of quality health care. Access to medicines is a multidimensional concept that is composed of the availability of medicines and the affordability of their prices. Information on these two dimensions has been analyzed independently since 2001, hence not providing a composite evaluation of overall access to medicines. In particular, ensuring one of the dimensions (e.g. availability) does not necessarily indicate the realization of the other (e.g. affordability) and vice versa. With the new Sustainable Development Goal (SDG) indicator on access to medicines, these two dimensions are combined into a single number.

Methods:
The new indicator reads: proportion of health facilities with a core set of relevant essential medicines available and affordable on a sustainable basis. Technically availability and affordability of medicines are converted in binary format and a medicine is considered accessible when simultaneously available and affordable. Medicines are weighted in the basket according to the burden of the corresponding condition(s). Weighted proportion of the accessible medicines is then computed on a facility level. Next, the surveyed facilities are categorized as facilities that have essential medicines simultaneously available and affordable versus facilities that do not, applying a threshold of 80% to the overall basket. Finally a ratio of the health facilities with accessible medicines over the total number of the surveyed health facilities is computed.

Results:
The proposed methodology was tested in ten LIC and LMIC which were captured by a pilot data survey in 2016 using the WHO Medicines Price and Availability Monitoring mobile application tool. These computations allowed for testing the indicator and results varied from 0 to 69%.

Conclusions:
The proposed methodology is recommended to allow evaluation of access to medicines on a national level. However, various levels of disaggregation of the indicator are allowed (across facility type [pharmacy/hospital], geography [rural/urban areas], therapeutic group [chronic/acute diseases] and access “dimension” [availability/affordability]), making it sensible to changes in policies and therefore implementing corrective measures for poor access.

20 Pharmaceutical price negotiations in Mexico – a policy mechanism towards access to innovative medicines

D.D. Moye Holz, J.P. van Dijk, S.A. Reijneveld, H.V. Hogerzeil

Department of Community and Occupational Medicine,
University Medical Center Groningen, University of Groningen, the Netherlands

Background:
In 2008, the Mexican government implemented price negotiations to improve access to innovative medicines, promote price uniformity across public health institutions, improve procurement efficiency and obtain savings in the pharmaceutical expenditure. This strategy applies only for public procurement prices of patented medicines included in the national formulary. We analyzed the impact of price negotiations in the price of innovative medicines and their accessibility in the public sector in Mexico.

Methods:
We retrieved the public procurement prices and volume of eight selected innovative medicines (using cancer medicines as example). We analyzed price changes and trends. We used drug utilization research methods to assess the use, as proxy of access, of these medicines from 2010-2016.

Results:
From 2010 to 2016, negotiated prices of selected patented cancer medicines decreased in US dollars, while they remain almost constant for most medicines when expressed in national currency. The price decreases for most medicines in comparison to the previous year ranged approximately from 2% - 40%. For all medicines, prices did not become uniform - all medicines showed different procurement prices across and within health institutions. The use of innovative medicines supplied in the public sector increased, suggesting better access. However, we found that use (i.e. access) was better in social health institutions than at the ministry of health’s facilities. As well, the central region of the country used (i.e. access) more innovative medicines than the other regions.

Conclusions:
The establishment of price negotiations seems to have led to reduced prices and an increase in the volume of medicines procured in the public sector. However, medicine procurement by public hospitals should be monitored to ensure that negotiated prices benefit all institutions. Although use and access to innovative medicines has increased over the years, their access is unequal across health insurances and geographic regions. Further efforts should be in place to guarantee equal access to innovative medicines in Mexico.

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Scientific publication and presentation of results at conferences in the field of gene and cell based therapies: a cohort analysis of clinical trials in the Netherlands between 2007-2017

D.G.M. Coppens[1], H. Gardarsdottir[1], C.A. van den Bogert[1], M.L. De Bruin[1,2], H.G.M. Leufkens[1], J. Hoekman[1,3]

1 Utrecht Institute for Pharmaceutical Sciences, Utrecht University, Utrecht, The Netherlands, 2 Copenhagen Centre for Regulatory Science, University of Copenhagen, Copenhagen, Denmark, 3 Innovation Studies Group, faculty of Geosciences, Utrecht University, Utrecht, The Netherlands

Background:
The novelty and heterogeneity of technologies, and scientific and technological uncertainties within the gene and cell based therapies (GCT) field demand timely publication of trial results. The aim of this study is to investigate the occurrence and determinants of publication in a cohort of GCT trials (2007-2017) on two publication outcomes: publication in scientific literature, and presentation of results at conferences.

Methods:
A GCT trial cohort was created using the Dutch registry for clinical trials. We defined candidate determinants related to sponsor, product, and trial characteristics, and duration of follow-up. We performed a search for publications that matched trials. Associations between sponsor plus other determinants and the two outcomes of publication were calculated as crude and adjusted odds ratios (OR), and 95% confidence intervals (CI).

Results:
The overall publication rate in scientific literature is 29% of GCT trials that were authorized between 2007-2017. Results show associations between publicly sponsored trials compared to privately sponsored trials (adjusted OR 2,1; 95% CI 0,7 – 6,8), trials that are targeting other disease areas than oncology (adjusted OR 2,6; 95% CI 1,0 – 6,9), and trials with more than 5,5 years follow-up compared to less than 5,5 years of follow-up (adjusted OR 5,5; 95% CI 2,1 – 14,5). , and publication in scientific literature. The overall rate of presenting results at conferences is 27% of GCT trials that were authorized between 2007-2017. Results show that public sponsors are less likely to present results at conferences compared to private sponsors (adjusted OR 0,1; 95% CI 0,0 – 0,4). Trials for GCTs with lymphocytes (adjusted OR 5,0; 95% CI 1,0 – 24,3), dendritic cells (adjusted OR 4,9; 95% CI 0,9 – 27,8), and vectors for gene delivery (adjusted OR 2,0; 95% CI 0,4 – 9,4) as active substance, compared to stem cells and other somatic cells, are more likely to be presented at conferences.

Conclusions:
Public sponsors are more likely to publish results in scientific literature, whereas private sponsors are more likely to present findings at conferences. The rather limited publication rates show that reporting of GCT trial results needs to be improved.

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