EUROPEAN MEDICINES AGEN
SCIENCE MEDICINES HEA

proving Regulatory Reviews
A considerations

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an Medicines Agency

edback on EPARs

- riability in the presentation
- ck of clarity
- e total CHMP effort is much larger than reflected in tl AR
- R balance most difficult part to write
- Too shy about value judgements
- Unclear intellectual process
- Variable level of detail

March 2008 CHMP: Reflection paper on benefit-risk assessment methods with two main recommendatio

1. Revise the benefit-risk balance section of the CH
   Assessment Report template
   - Structured list of benefit and risk criteria
   - Guidance
   - Improve consistency, transparency and communication of B/R

2. Research methodologies of benefit-risk balance
   - Involving experts, assessors, and specialists i
     Decision Theory

nefit-Risk Methodology Project

e:

velopment and testing of tools and processes for balancing
tiple benefits and risks as an aid to informed regulatory
isions about medicinal products

eframe:

009 – 12/2011 » Main research

012 – 12/2012 » Pilot phase + initial implementation

013 - … » Part of core business + continuous research

In this presentation:

- **Coordinating different inputs**
- **Maintaining independence**
- **Improving decision making**
- **Improving Report Writing**
- **Accurate reflection in product information**

MA evaluation process is a choir with any singers

- Rapporteur/coRapporteur
- Peer reviewer
- PRAC
- EMA secretariat (paediatric, geriatric, RMP, quali review)
- Scientific Advisory Groups

uild a strong and transparent Conflict o
nterest policy

Helps to build trust to public and colleagues

Network of 3500 experts. Public.

Risk levels and tasks

Can be found on our website

mitation: expertise in very

What makes a good regulatory decision?

- Take the “right” decision - and do it in a rational, predictable way (avoid Type I and Type II errors)
- Justify/explain the decision
- Communicate the decision (+justification + explanation) to external stakeholders
- Provide more detail than just “yes/no” (qualitative to quantitative)

ackground

o good-enough definition of benefit-risk in legislation

HMP audit in November 2004: Need for a more
ystematic approach that will improve consistency of B/
nalyses

MA/CHMP Working Group set up in May 2006

enefit-Risk Methodology Project

Work Packages:

: Describe current practice of B-R assessment

: Assess applicability of current tools for regulatory B-R assessment

: Develop and field test tools and processes to emonstrate their usefulness

: Synthesize information from the field test and evelop a B-R tool box for everyday use.

: Develop a training package for regulatory assessors

Benefit-Risk assessment
From art to science

oals to achieve:

- Justify / explain decision
- Implicit criteria -> Explicit criteria
- Enhance predictability and auditablity of regulatory decisions
- Enhance communication to outside worl
- Qualitative -> Quantitative

Benefit-Risk assessment
Art or science?

Ingredients of regulatory decisions:

Data (incidences)

Uncertainty

Values (utilities/disutilities)

Decisions driven by:

probability of event x “value” of event

-> “**expected utilities**”

Whose values should count?

t is increasingly difficult to bring new drugs to market…

but it will be even harder to keep them on the market

Drugs (and regulators) become victims of the Efficacy-Effectiveness gap

se study: Acomplia rimonabant mg

un 2006: approved for obesity and over-weight patients.

"effect was moderate and of clinical elevance for 20-30% of patients")

se study: Acomplia rimonabant
mg

an 2009: marketing authorisation withdraw
n light of post-approval data

"new data indicated a shorter duration of treatment in h lif
nd a reduced beneficial effect…

sk of experiencing the adverse mental effects are higher in
atients with comorbidity")

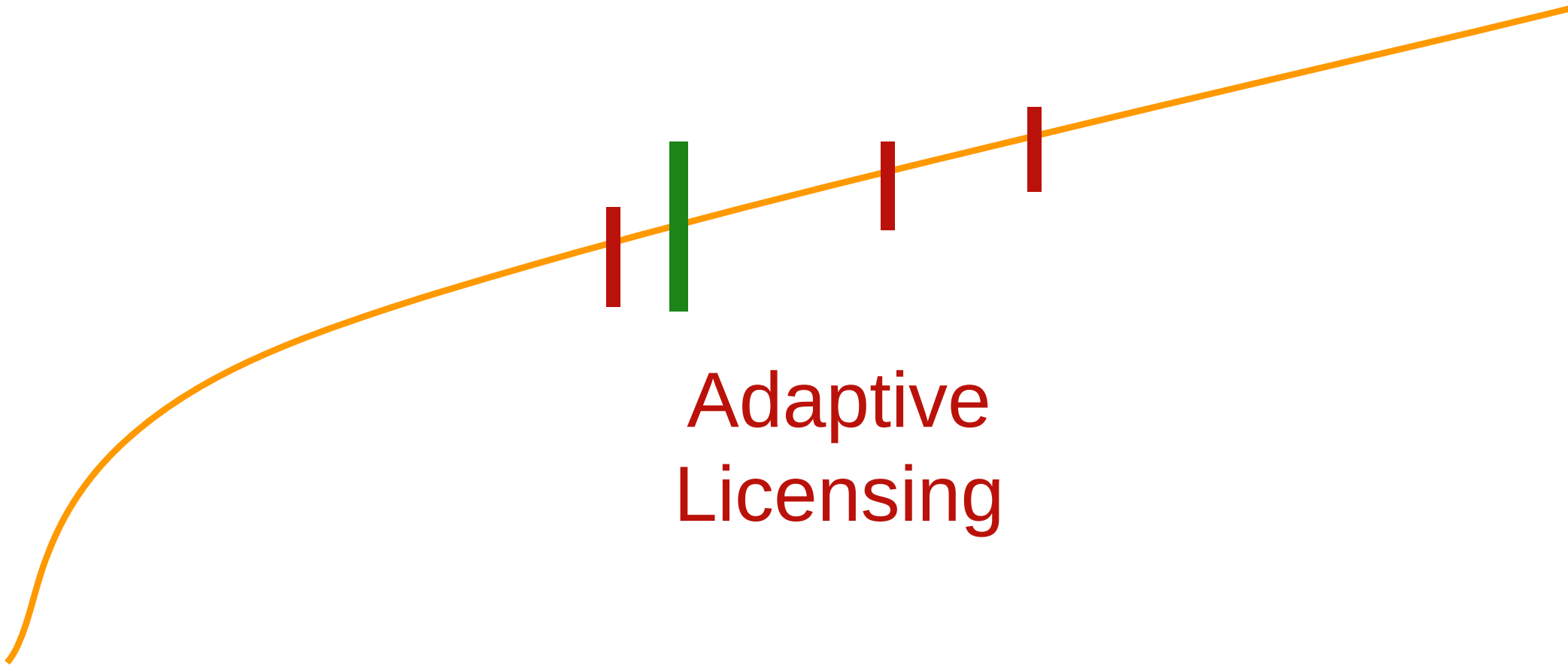
Sources of variability contributing to poor performance in real world

Biology

Behavior

Genomics	Environment	Physician prescribing	Patient adherence
nt' s genomic up	Co-morbidity, baseline severity of disease, altered physiological states, external factors	Inappropriate prescribing, prescribing to non-responders, medication errors	Poor adherence t prescribed drug regimen, non-persistence; "dru holidays"

Current model of licensing
“The Magic Moment”



Adaptive
Licensing

Adaptive Licensing ...

is a prospectively planned, adaptive
pproach to regulation of drugs. Through
erative phases of information gathering
llowed by regulatory evaluation and
ction, adaptive licensing seeks to align
egulatory market access of a new drug
ith emerging information on benefits
nd harms.

Adaptive Licensing scenarios – "design factors"

- broaden treatment-eligible population
- reduce uncertainty around endpoint
- reduce uncertainty around study design
- reduce statistical uncertainty
- ensure effectiveness
- address rare AEs

aptive Licensing – what conditions ust be in place to make it work?

anage concerns over lowered standards?

ommitment from industry to conduct "stage n+1 udies" ?

ignment between regulatory – payers – escribers?

fferent reward/incentive structure warranted?

pable under current regulatory framework?

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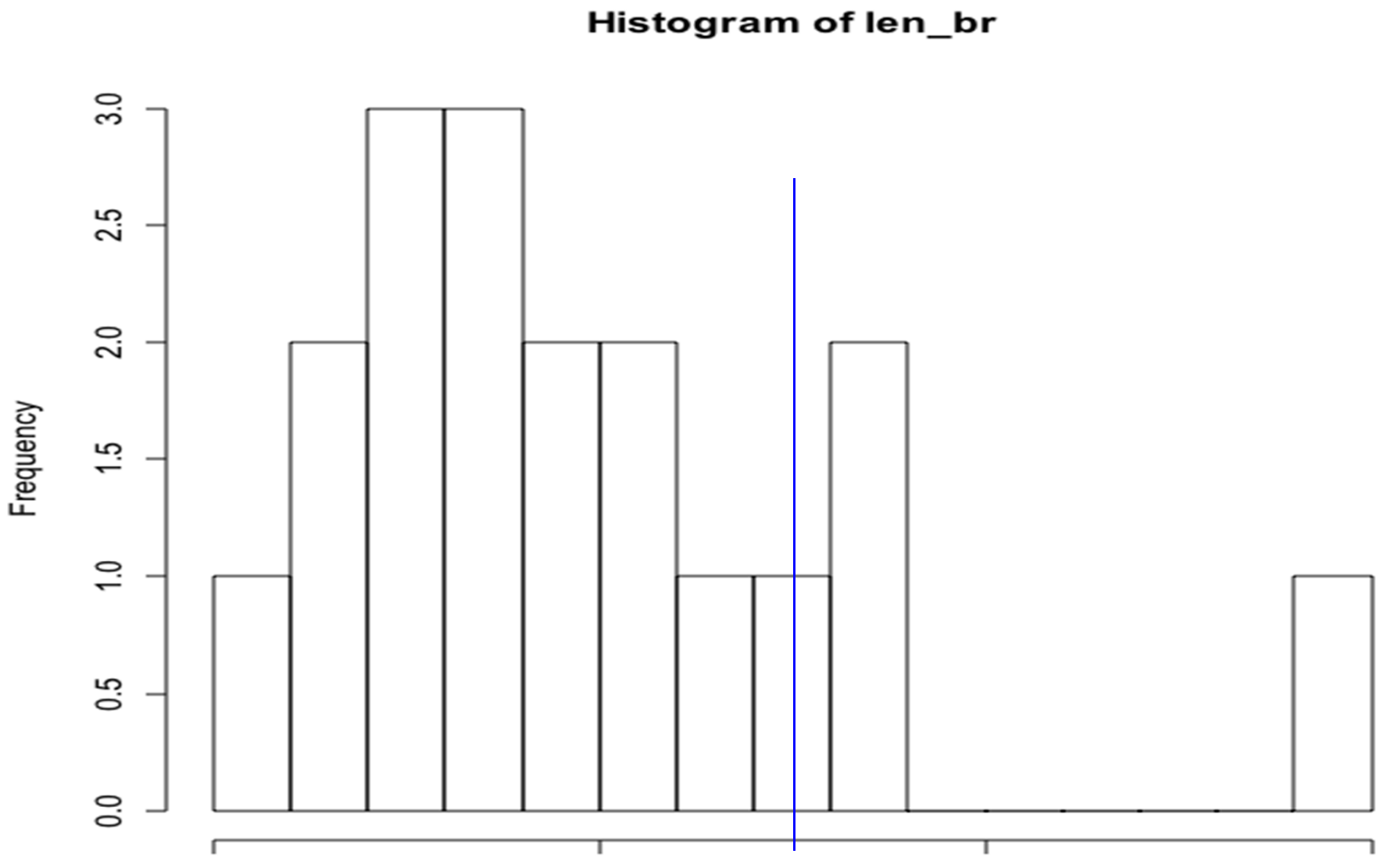
ed to satisfy multiple readers

MP Peers	Clear, brief, multiple views
er EMA Committees	COMP, CAT, PDCO, PRAC ...
H, competitors	Constructive criticism, attention to confidentiality
lth Care professionals	Scientifically rigorous, rational than emotional
ents, public, media	Avoid jargon Political correctness
yers	What is the legal basis? Are legal requirements fulfilled? Support CHMP Opinion (SmPC)
bodies	Help relative effectiveness assessment

ngth In Words Of BR Balance Section in EPAR (20
mple of 20 EPARS)



neral Principles

plain how the data fulfil the legal requirements

Justify Opinion (explicitly)

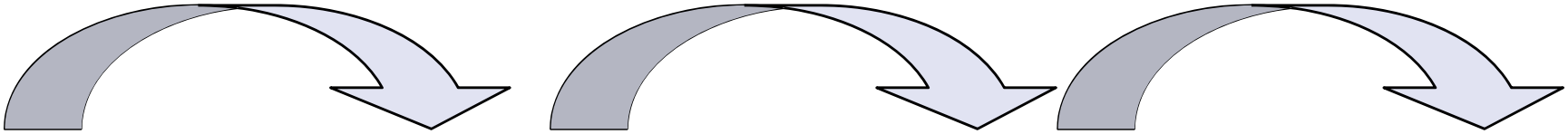
tinguish between data submitted and CHMP conclusions

Reference any statement

e style of Scientific Publication

(Introduction) (Methods) (Results) (Discussion)

IRD



Introduction - Methods - Results - Discussi

rive for clarity

e concise

stinguish between data submitted and CHMP conclusions

Reference any statement

troduction

sent the nature and scope of problem

State the objectives, and requirements

ate the principal results)

ate the principal conclusion)

tch out

General statements not based on data (use references)

Statements about benefits of other products, medical need, relative effectiveness

sults

-select results (important and new results)

vide the big picture, then present the details

concise

"Results are in Tables 1-4 and Figures 3-6"

tch out

Representative data not listings: "*The fool collects facts the wise man selects them*" (J.W. Powell)

Avoid Redundancy

"It is clearly shown by the data in Table 1 that nafcill inhibited the growth of *N. gonorrhoea*"

"Nafcillin inhibited the growth of *N. gonorrhoea* (Tabl 1)"

scussion

e core of the report

w conclusions from the data

Summarise evidence for each conclusion

Explain the logic (Why? How much?)

Make sure message is crystal clear

Stick to your topic: **do the data fulfil the legal requirements?**

tch out

Don’ t copy from MAA

Too long and verbose, repeat results, irrelevant

Too short, only conclusive statement

The “squid technique”, doubtful about the facts or reasoning retreat behind a cloud of ink (D.Savile)

scribing cause-effect relationships

ifficult to prove cause-effect relationships, a matter of
dgement

"The study **demonstrates** the efficacy of doxorubicin"

"In the study, an improvement in survival was **observed** for doxorubicin. On the basis of all data submitted, the **CHMP concluded** that efficacy had b established according regulatory standards."

nefit-Risk Assessment Template

efits

eneficial effects

ncertainty in the knowledge about the benefits

ks

nfavourable effects

ncertainty in the knowledge about the risks

ance

mportance of favourable and unfavourable effects

enefit-risk balance

cussion on the benefit-risk assessment

clusions

here?

ogle “CHMP templates”

w.ema.europa.eu

Regulatory

Human medicines

- Pre-authorisation
  - Assessement templates and guidance
- Post-authorisation
  - Assessement templates

e-Authorisation Templates and Guidance

plates and guidance documents as of September 2010

dance (PDF) Downloads	**Template (Word) Downloads**
AR Overview Guidance	D80 AR Overview Template
AR Quality Guidance	D80 AR Quality Template
AR Non-Clinical Guidance	D80 AR Non-Clinical Template
AR Clinical Guidance	D80 AR Clinical Template
	D120, D150, D180, Re-examination…

The pitfalls of too many templates?

nefit-Risk Assessment section

efits

Beneficial effects

Uncertainty in the knowledge about the benefits

s

Unfavourable effects

Uncertainty in the knowledge about the risks

ance

mportance of favourable and unfavourable effects

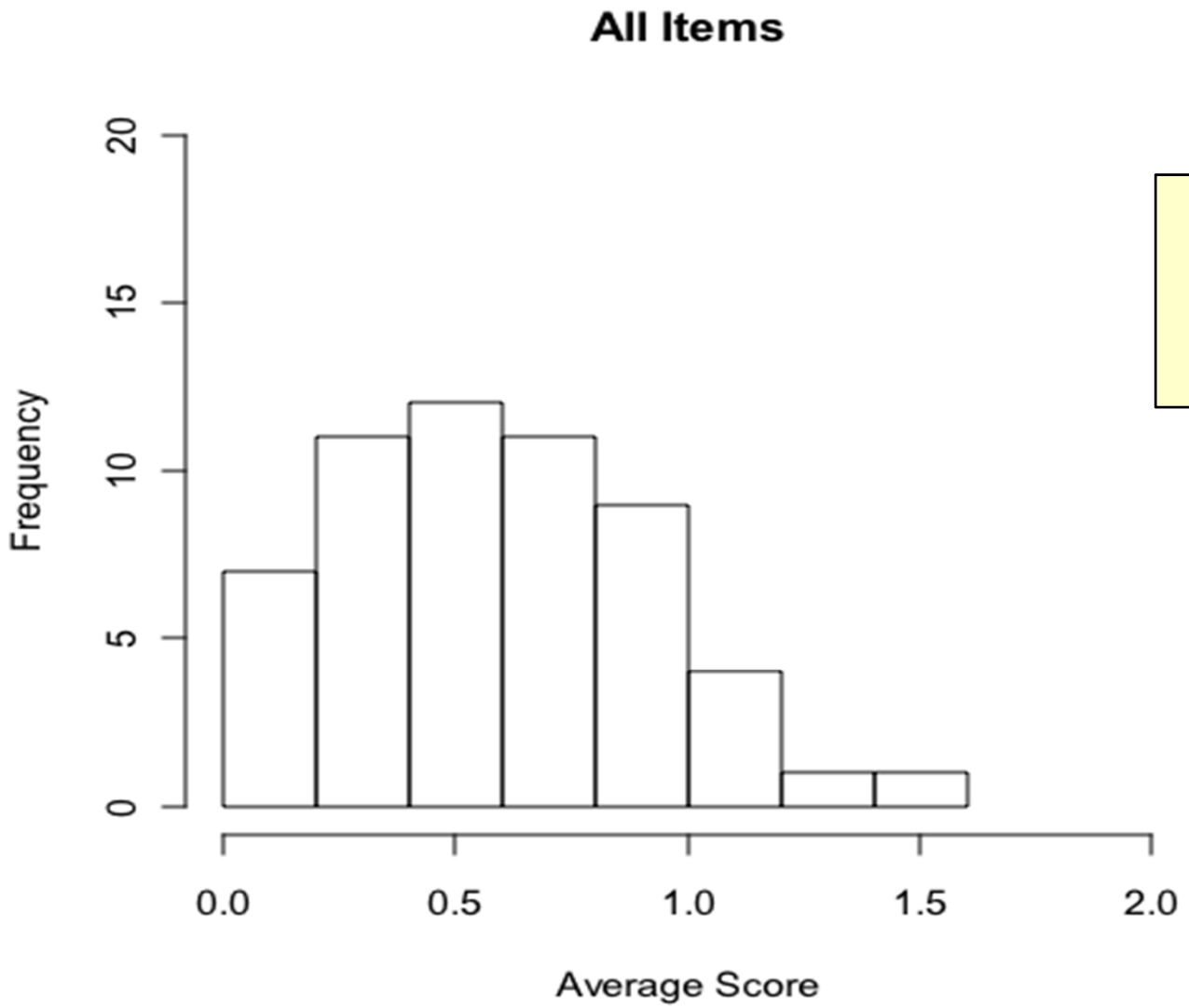
Benefit-risk balance

cussion on the benefit-risk assessment

clusions

0=Not covered
1=Partly covered
2=Fully covered

verall Compliance



0=Not covered
1=Partly covered
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ummary

HMP AR Template Guidance
- Distinguish Data from Interpretation
- Discussion, Benefit-Risk balance

elevance
- What is the legal basis?
- Are legal requirements fulfilled?
- Support CHMP Opinion (SmPC)

ndependence
- CHMP takes responsibility for own statements
- Don’ t copy/paste whole sections from MAA

IMP AR and SmPC

ntroduction

Claimed and approved indication (4.1), posology (4.2)

Quality

Qualitative And Quantitative Composition (2), Pharmaceutical form (3)

Non-Clinical

Discussion (5.3 Preclinical safety data, 4.3, contraindications, 4.5 Interactions, 4.6 Pregnancy and lactation, 5.1 Pharmacodynamic properties)

HMP AR and SmPC

nical Pharmacology

Discussion (5.2 Pharmacokinetic properties)

nical efficacy

Discussion (4.2, dosing in special populations; 5.1 Pharmacodynamic proper

nical Safety

Subheadings… (4.8 Undesirable effects, 4.9 Overdose)

Discussion (4.3, contraindications , 4.4 special warnings, 4.7 Effects on abili
drive and use machines)

nd don't forget the package leaflet!

Thank you for your attention

h acknowledgement and special thanks to:

ns Georg Eichler

ncesco Pignatti

olaos Zafiropoulos