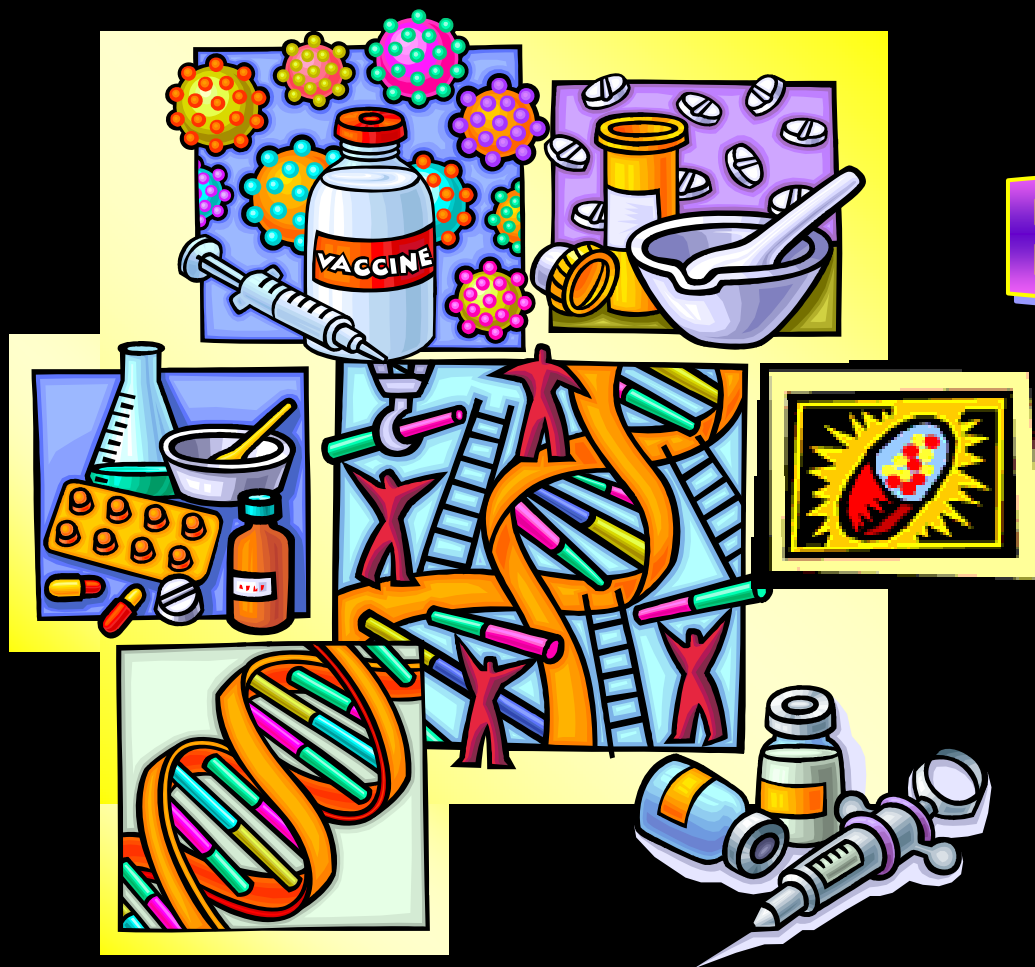


Biosimilares; VI EAMI Octubre 2006 - Lisboa

Biosimilares

Aspectos regulatorios



Sol Ruiz, PhD
AEMPS



Sunny

Bobby Hebb

Track Listings

1. Sunny - Bobby Hebb
2. Sunny - Arthur Lyman Group
3. Sunny - Georgie Fame
4. Sunny - Booker T. & The MG's
5. Sunny - Dusty Springfield
6. Sunny - John Schroder Orchestra
7. Sunny - Robert Mitchum
8. Sunny - Stan Kenton
9. Sunny - Herbie Mann & Tamiko Jones
10. Sunny - Stanley Turrentine
11. Sunny - Andy Williams
12. Sunny - The Ventures
13. Sunny - Cher
14. Sunny - Jimmy Smith
15. Sunny - Wilson Pickett
16. Sunny - Nancy Wilson

Vol. 1

Track Listings

1. Sunny - James Brown And Dee Felice Trio Feat
2. Sunny - Chris Montez
3. Sunny - Les McCann
4. Sunny - Shirley Bassey
5. Sunny - Jose Feliciano
6. Sunny - The Four Tops
7. Sunny - Marian Love
8. Sunny - The Walker Brothers
9. Sunny - Paul Kuhn
10. Sunny - Trini Lopez
11. Sunny - Young Holt Trio
12. Sunny - Marvin Gaye
13. Sunny - The Electric Flag
14. Sunny - Leonard Nimoy
15. Sunny - Ella Fitzgerald
16. Sunny - Gary Lewis And The Playboys
17. Sunny - Brother Jack McDuff And David Newman

Vol. 2

Biológicos

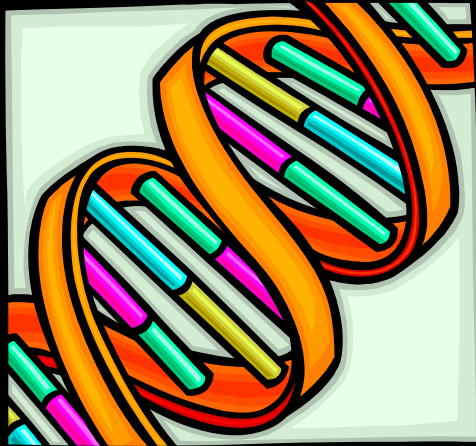
Características



debido a su complejidad no puede ser completamente caracterizado mediante técnicas analíticas solamente

calidad determinada por la combinación de análisis físico-químicos y biológicos, además del proceso de producción y su control (controles en proceso)

la actividad biológica e inmunogenicidad dependen de todas las "características estructurales"



Productos biotecnológicos

- proteínas y glicoproteínas
- moléculas grandes y complejas
- microheterogeneidad inherente debido a modificaciones post-traduccionales



Producto Químico

estructura molecular bien definida, 'fácil' de caracterizar

el perfil de impurezas depende de las vías de síntesis y de degradación

seguridad y eficacia independientes del origen del producto

Producto Químico



Producto Biológico



specs biotech

ICH Q6B



comparabilidad; proceso secuencial

CALIDAD
SEGURIDAD
EFICACIA

comparabilidad

1

Cambio en un proceso de producción determinado

- ↘ desarrollo
- ↘ después de la autorización

2

Nueva autorización de comercialización

- ↘ comparación frente a un producto de referencia

cambios en el proceso de producción

1

Cambio en un proceso de producción determinado

- ↘ desarrollo
- ↘ después de la autorización



EMA/CPMP/BWP/3207/00 Rev 1

Guía sobre Comparabilidad

tipo de modificación

No clasificación *a priori* de cambios en mayores o menores

Un cambio aparentemente menor puede tener un impacto en la calidad, seguridad y eficacia

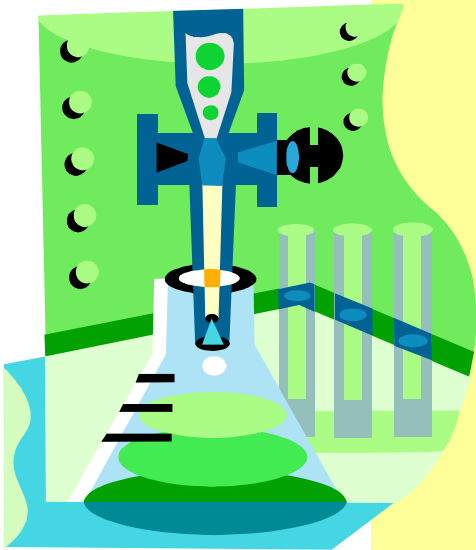
El fabricante debe valorar las consecuencias del cambio



EMA/CPMP/BWP/3207/00 Rev 1

Guía sobre Comparabilidad

comparabilidad; análisis paso a paso



CARACTERIZACIÓN

PROCESO DE FABRICACIÓN

DATOS DE LIBERACIÓN DE LOTES

ESTABILIDAD

DATOS PRECLÍNICOS/CLÍNICOS

MANUFACTURING PROCESS

Design
Process
Control

Expression system

- *MCB / WCB*

Fermentation / culture process

- *site/facility, scale, equipment, cell culture conditions, raw materials...*

Purification process

- *site/facility, scale, equipment, purification protocol, column/resin, reagents...*

Other

- *batch definition*
- *shelf-life*
- *storage conditions...*

examples

- generation of a new WCB; new MCB (increased yield)
- substitution of FBS by a serum-free culture medium; or by irradiated FBS
- scale increase: changes in stability observed after an increase from 1200 L to 2000 L
- alternative manufacturing facility (alternate process???)

MANUFACTURING PROCESS

Drug Product

Formulation and filling

- *site/facility*
- *scale*
- *manufacturing protocol*
- *equipment*
- *excipient*

Other

- *batch definition*
- *shelf-life*
- *container/closure system*
- *storage conditions...*

examples

- change in formulation: elimination of HSA, change in buffer composition and presentation (freeze-dried to solution).

EPO, beta IFN

- alternative supplier of PEG (different impurity profile, different reactivity)

comparabilidad

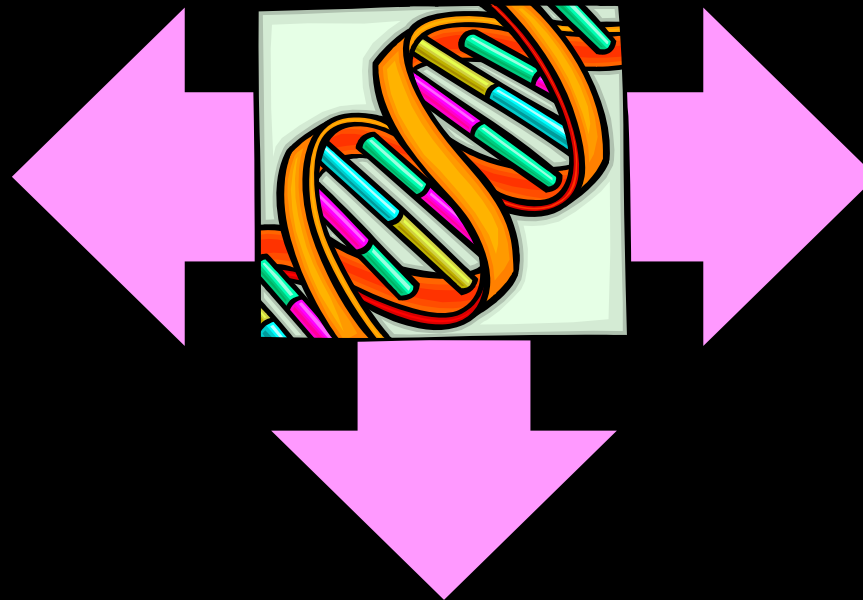
2

Nueva autorización de comercialización

↘ comparación frente a un producto de referencia

Biological / Biotech Products

source
materials



production
process &
purification

characterization

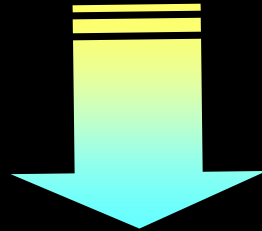
Comparability to a reference product

Independent development will result in inherent differences in:

- source materials, expression systems, culture process details
- purification process (scheme, scale, operation...)
- IPC, test methods, specifications...

Comparison based on a pharmacopoeial monograph is not sufficient

Comparability to a reference product



preclinical and/or clinical studies

depending on the

- nature of the drug substance and formulation
- complexity of its molecular structure
- differences with the reference product

Medicamentos Biosimilares;

guías / directrices europeas

antes...

QUALITY

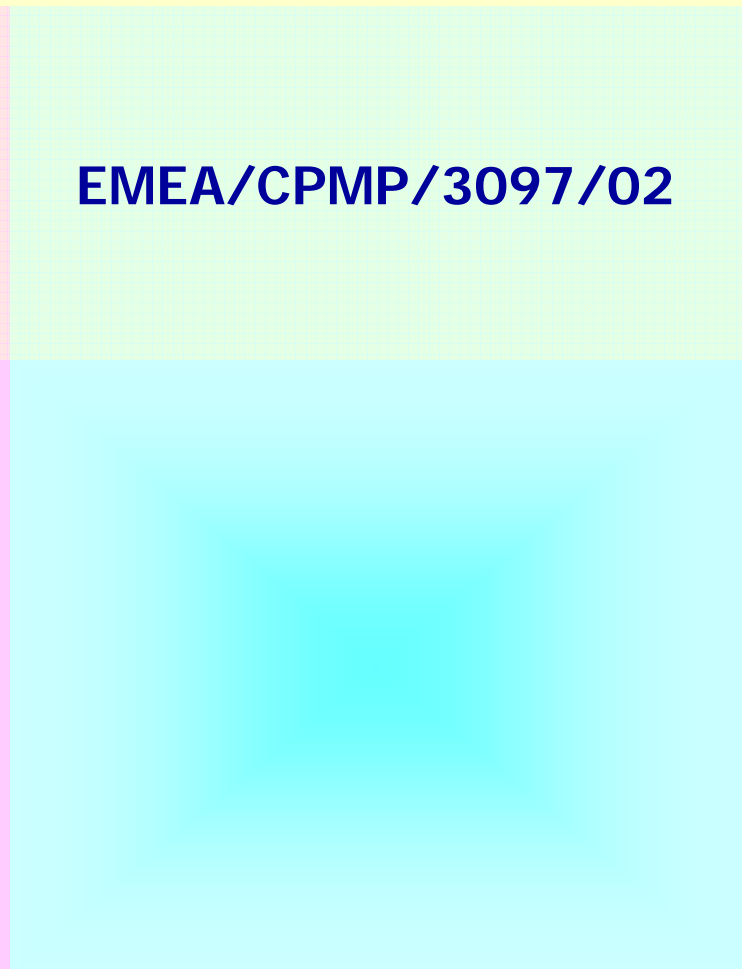
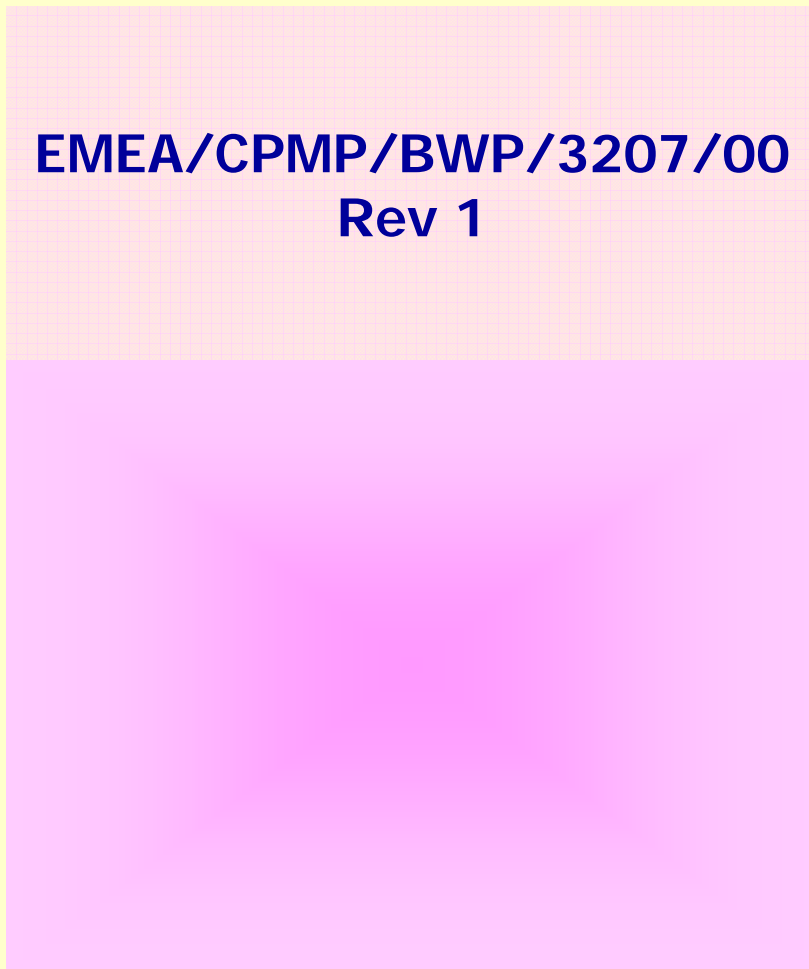
CLINICAL

**Changes
in a given
manufacturing
process**

**EMA/CPMP/BWP/3207/00
Rev 1**

EMA/CPMP/3097/02

**New
manufacturing
process**



Biosimilar medicinal products

Concept Papers (i.e. documents that will be developed as guidelines)

[CHMP/146710/2004](#) Similar Biological Medicinal Products containing **Recombinant Human Insulin** - Annex to the Guideline for the Development of Similar Biological Medicinal Products containing Biotechnology Derived Proteins as Active Substance (non) Clinical Issues (*Released for consultation by CHMP November-2004*)

[CHMP/146701/2004](#) Similar Biological Medicinal Products containing **Recombinant Granulocyte-Colony Stimulation Factor** - Annex to the Guideline for the Development of Similar Biological Medicinal Products containing Biotechnology Derived Proteins as Active Substance (non) Clinical Issues (*Released for consultation by CHMP November-2004*)

[CHMP/146489/2004](#) Similar Biological Medicinal Products containing **Recombinant Human Growth Hormone** - Annex to the Guideline for the Development of Similar Biological Medicinal Products containing Biotechnology Derived Proteins as Active Substance (non) Clinical Issues (*Released for consultation by CHMP November-2004*)

[CHMP/146664/2004](#) Similar Biological Medicinal Products containing **Recombinant Human Erythropoietin** - Annex to the Guideline for the Development of Similar Biological Medicinal Products containing Biotechnology Derived Proteins as Active Substance (non) Clinical Issues (*Released for consultation by CHMP November-2004*)

Biosimilar medicinal products

Guidelines

[EMA/CHMP/42832/05](#) Guideline on Similar Biological Medicinal Products containing Biotechnology-Derived Proteins as Active Substance: **Non-Clinical and Clinical Issues** (CHMP released for consultation May 2005)

[EMA/CHMP/94528/05](#) Annex Guideline on Similar Biological Medicinal Products containing Biotechnology-Derived Proteins as Active Substance: Non-Clinical and Clinical Issues - Guidance on Similar Medicinal Products containing **Somatropin** (CHMP released for consultation May 2005)

[EMA/CHMP/32775/05](#) Annex Guideline on Similar Biological Medicinal Products containing Biotechnology-Derived Proteins as Active Substance: Non-Clinical and Clinical Issues - Guidance on Similar Medicinal Products containing **Recombinant Human Insulin** (CHMP released for consultation May 2005)

[EMA/CHMP/49348/05](#) Guideline on Similar Biological Medicinal Products containing **Biotechnology-Derived Proteins** as Active Substance: **Quality Issues** (CHMP released for consultation March 2005)

[CPMP/437/04](#) Guideline on **Similar Biological Medicinal Products** (*Released for consultation by CHMP November-2004*)

Biosimilar medicinal products

Adopted Guidelines

[CPMP/3097/02](#) Note for Guidance on Comparability of Medicinal Products containing Biotechnology-derived Proteins as Drug Substance - **Non Clinical and Clinical Issues** (*CPMP adopted December 2003*)

[CPMP/BWP/3207/00 Rev.1](#) Guideline on Comparability of Medicinal Products containing **Biotechnology-derived Proteins** as Active Substance - **Quality Issues** (*CPMP adopted December 2003*)

International Conference on Harmonization (ICH)

Quality - Adopted Guidelines

[Topic Q5E](#), Step 4 Note for Guidance on Biotechnological/Biological Products Subject to changes in their Manufacturing Process (CPMP/ICH/5721/03 final approval by CHMP December 2004)

QUALITY

CLINICAL

**Changes
in a given
manufacturing
process**

ICH Q5E

EMA/CPMP/3097/02

**New
manufacturing
process**

**Guideline on similar
biological products
containing
biotechnology-derived
proteins as active
substance: Quality
issues**

**Product-specific
guidelines**

Guideline on Similar Biological Products (CPMP/437/04)

**new manufacturing
process**



Product-specific guidelines

insulin

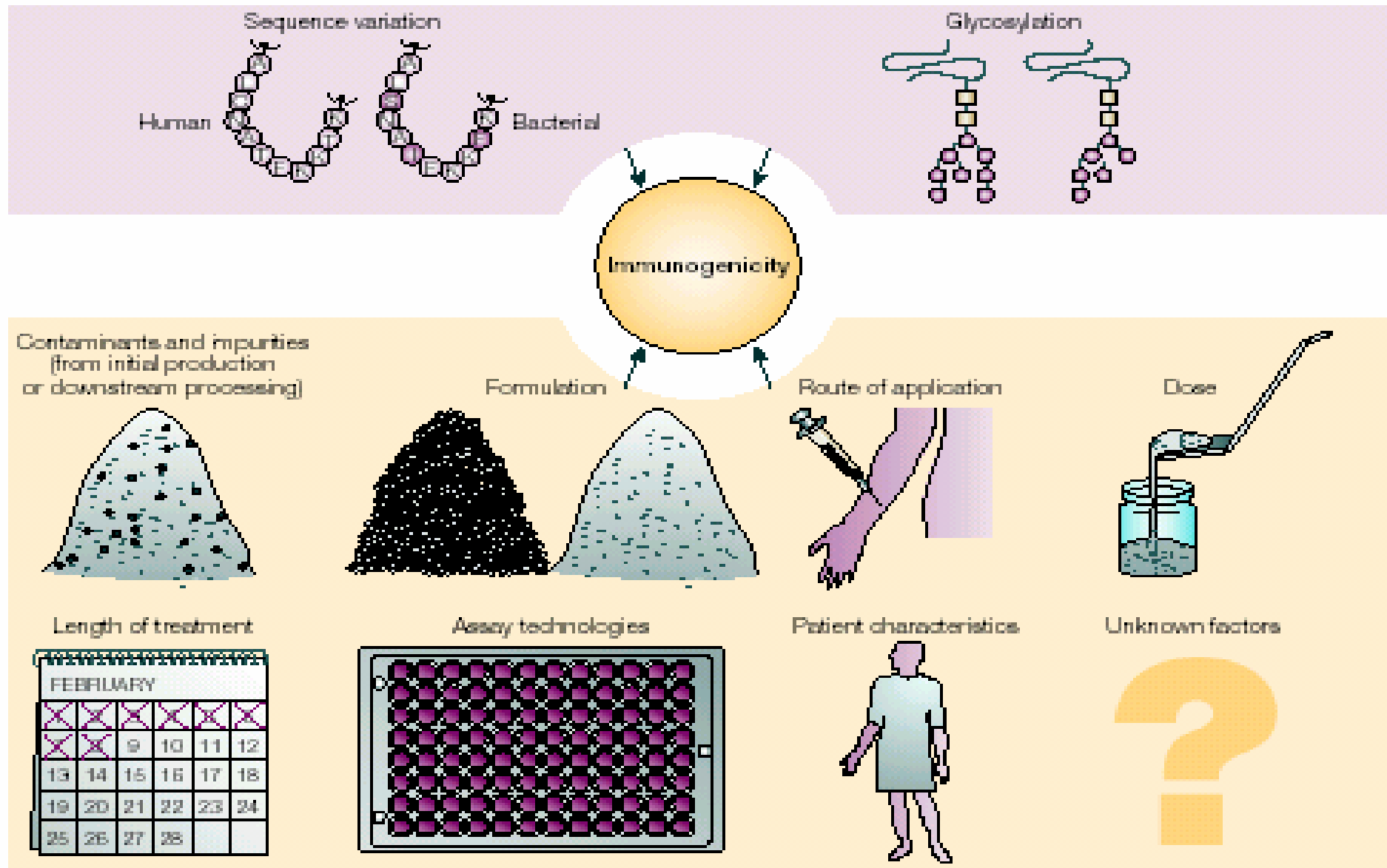
EPO

somatropin

G-CSF

Factors affecting immunogenicity

Schellekens, NRDD 2002



A suggestion of storms ahead

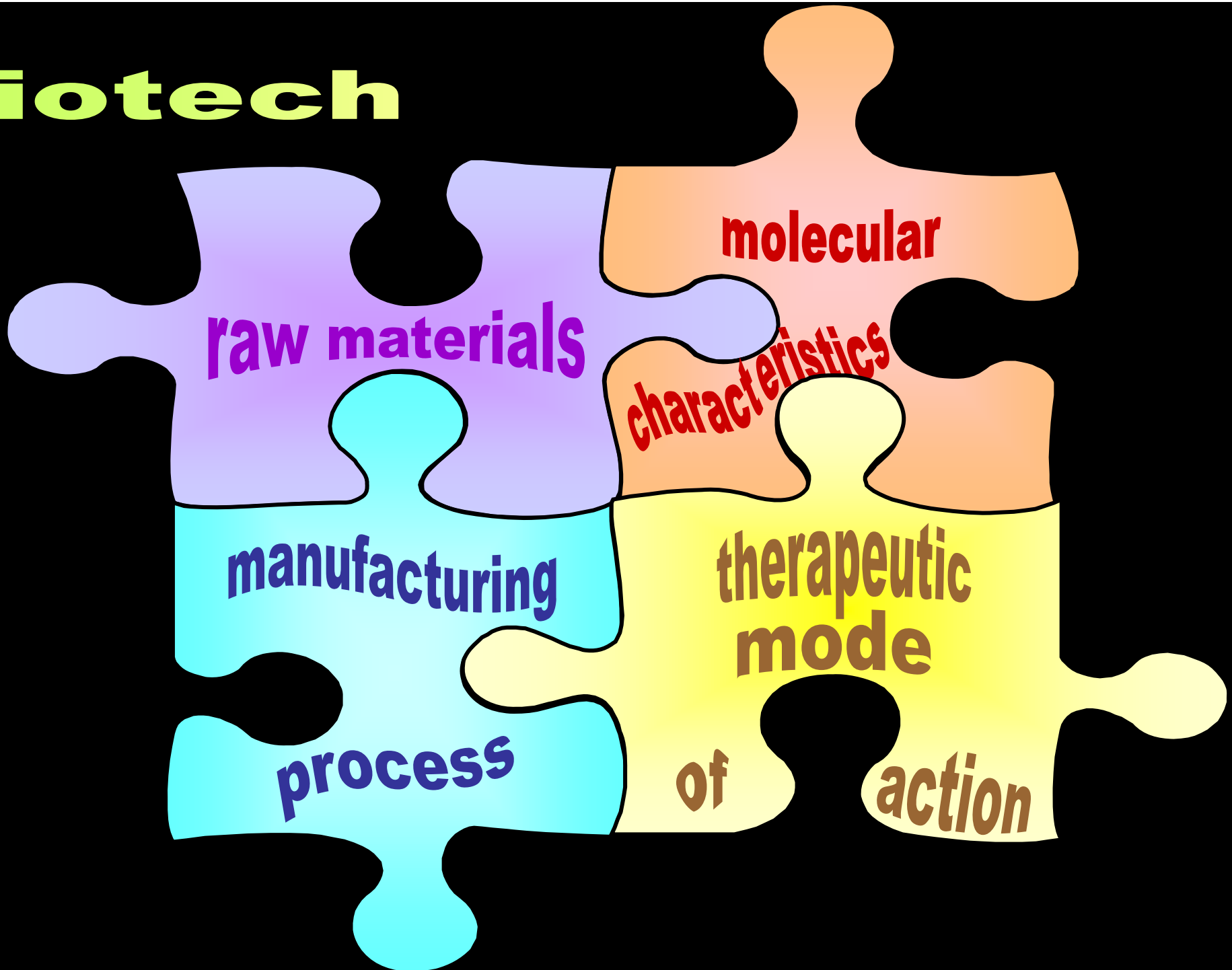
Although the numbers affected might seem insignificant when compared with the 3 million patients who are treated with epoetin each year, the relative sudden appearance of a serious adverse effect for a tried-and-tested product reminds us that much remains to be discovered about the immunogenicity of biopharmaceuticals

Adam Smith

Nature Reviews Drug Discovery, April 2002

Biotech

U
—
a
c
—
o
—
o
—
o
—
i



Biosimilares; VI EAMI Octubre 2006 - Lisboa



Gracias !