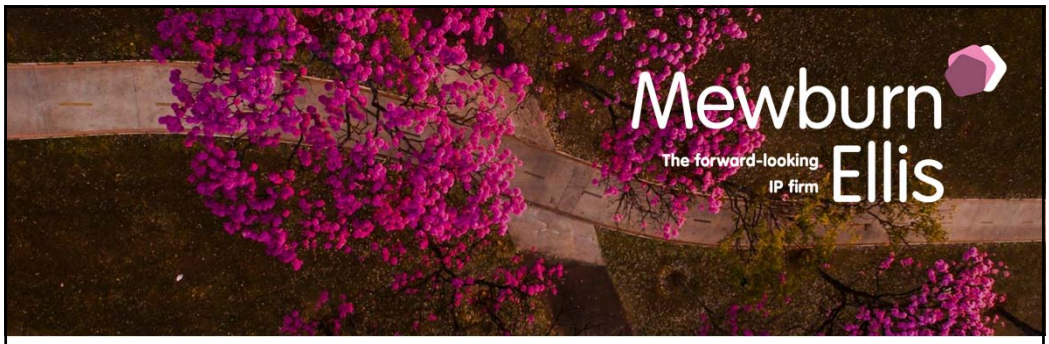
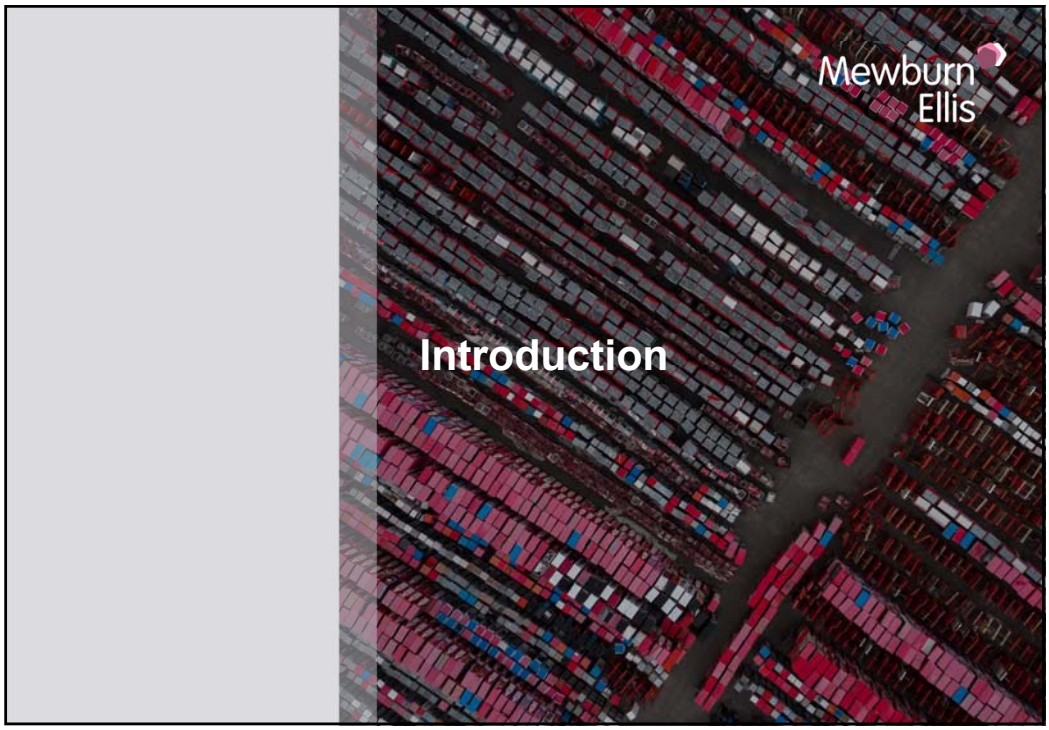


Antibody patenting practice at the EPO

Chris Denison
March 2021

1



2

Today we will cover:

- Overview of antibody patenting practice at the EPO
  - Focus on drafting tips, in light of prosecution experience
  - Now tied in to new section in EPO examination guidelines, in force 1 March 2021
  - Available at: https://www.epo.org/law-practice/legal-texts/guidelines.html
- Some other comments on the new guidelines
- A suggestion for when we don't have comparative data that the examiner wants to see

3

Our experience

- Mewburn Ellis has long and deep experience in drafting, prosecuting, defending and opposition antibody patent applications, for the entire range of clients from academic institutions and start-ups to multinational pharmaceutical companies
- Including many blockbuster drugs

4

Broad principles of EPO practice

- EPO does not recognise structural non-obviousness*
  - An antibody is not inventive simply because its sequence could not be predicted in advance
  - GL G-II, 5.6.2 ¶4: "If a novel antibody binds to the same antigen as known antibodies, inventive step is not acknowledged solely on the basis that the novel antibody is structurally different from the known antibodies. Arriving at alternative antibodies by applying techniques know[n] in the art is considered to be obvious to the skilled person. The fact that the structure of the thus obtained alternative antibodies, i.e. their amino acid sequences, is not predictable is not a reason for considering these antibodies as non-obvious (see T 605/14, section 24; T 187/04, section 11)."

* Important caveat: this lecture is based our typical experiences of EPO prosecution; there are always exceptions.

5

Broad principles of EPO practice

- For a technical effect to support inventive step, it must be obtained across the scope of the claim
  - Any change to a CDR can result in the loss of binding to the target (even though many in fact won't), and any change to a variable domain can result in a change of binding affinity, and related properties
  - Undefined / unrestricted sequence variation is usually not permitted

6

Broad principles of EPO practice

- Antibody development is a mature field.
- Many technologies are now routine and cannot establish inventive step on their own
  - When an antibody with particular functional properties has been disclosed, it is generally routine to produce further antibodies with similar properties, if the screens are adequately described
    - e.g. affinity, cross-reactivity or selectivity, neutralisation
  - Some improvements are also routine – e.g. humanisation, affinity maturation
- Presumptions can be rebutted with evidence of difficulty
  - G-II, 5.6.2, ¶5:

    Nevertheless, antibodies can be inventive if the application overcomes technical difficulties in producing or manufacturing the claimed antibodies.

7

Broad principles of EPO practice

- Relevant to inventive step, and also breadth of claim
- A written description of multiple antibodies is not generally a requirement for a broad claim
  - Though it can help persuade the examiner that the properties are reproducible

8

Two scenarios

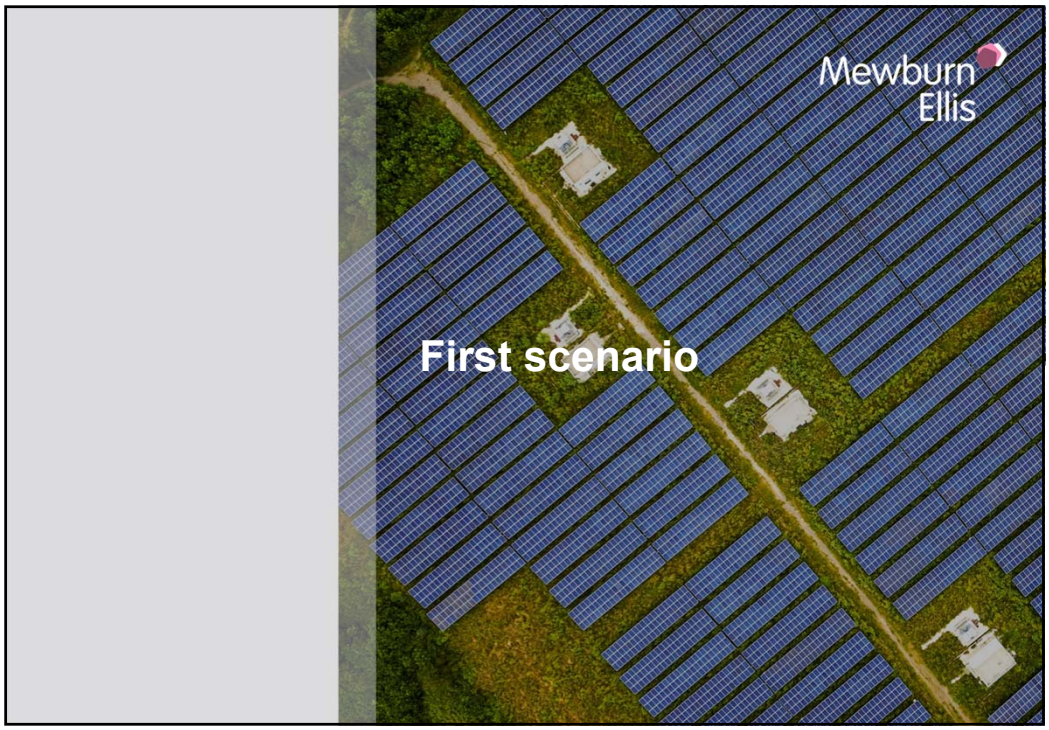
- These principles result in two typical scenarios
- First scenario:
  - Antibodies that bind to or do something new, e.g.:
    - Antibodies to a new target
    - Antibodies to a known target with unexpected functions/activities/properties
  - In principle, can support broad claims, not necessarily limited by antibody sequence
  - Definition by target: G-II, 5.6.1.2
    - NB no sequence variation in definition of the target!
  - Definition by target + function: G-II, 5.6.1.3
    - Rather problematic section; will return later

9

Two scenarios

- Second scenario:
  - Target and antibodies to it are known
  - Invention resides in the development of an improved or optimised antibody
  - Examiners will expect narrow, sequence-based definitions which can cause problems as the antibodies are further developed
  - Key message of the talk: with good drafting and suitable underlying data, some breadth can be retained

10



11

First scenario: new target

- New gene products are now typically rare
- BUT a new target does not need to be a new gene product as such
  - Newly identified processed forms of known protein
    - Typically reveal new epitopes
  - Newly identified quaternary structures, e.g. heterodimers when only homodimers were known
  - Other newly identified epitopes on known proteins, e.g. epitopes newly identified on tumour cell surface antigens.
- In these cases, individual prior art antibodies may inherently bind to the new target, as well as the known protein.
- Consider including reference examples showing that any reproducible prior art (e.g. commercially available) antibodies do not bind to the new target.

12

First scenario: new target

- Careful thought to fallback positions can permit broad sub-generic claims even if individual prior art antibodies accidentally anticipate:
  - Lack of cross-reactivity with known forms (e.g. unprocessed protein / homodimers)
  - Human or humanised antibodies (can avoid accidental anticipation by research antibodies)
  - Binding affinity for new target
  - Relative binding affinities for known protein and new target
  - Additional functional properties (e.g. prevents interaction of newly identified processed form with another protein)

13

First scenario: new target

- Consider including data to support an argument that antibodies to the new target are a novel and inventive selection from general teachings in the prior art
  - e.g. a panel of antibodies is raised against known target A; of these, only a small fraction are able to bind to new target A'
  - Or additional steps are needed to arrive at antibodies to new target A'
  - Post-filing data should also be admissible

14

First scenario: new function

- Antibodies to known targets but having new functions
- In principle, can also support broad claims, defined in terms of the target + function
- Wide variety of possible functions, which can be defined either positively or negatively, often in combination:
  - Cross-reactivity or lack of cross-reactivity with other proteins, resulting in a different effect from known antibodies
  - Effect antibody binding has on target cells
  - Modulation of other interactions e.g. ligand-receptor interactions (e.g. binds to R and prevents R-L1 interaction but not R-L2 interaction, where L1 and L2 were thought to bind to the same region of R)

15

First scenario: new function

- Generally acknowledged at G-II, 5.6.1.3, ¶1:

  In addition to the functional definition by the antigen it binds to, claims directed to antibodies can be further characterised by functional features defining further properties of the antibodies; for example, the binding affinity, neutralising properties, induction of apoptosis, internalisation of receptors, inhibition or activation of receptors (c.f. e.g. T 299/86, Reasons 3 - 6, and T 1300/05, Reasons 4 - 7).
- But expect careful scrutiny from the examiner.
  - Very common for the examiner to object that a sequence-based definition is required
  - The examiner will need to be convinced that prior art antibodies to the same target do not inherently have the same functions
  - The Guideline continues with a passage that is difficult to understand, and potentially problematic

16

First scenario: new function – the new guideline

- G-II, 5.6.1.3, ¶2:

  If an antibody is claimed exclusively by functional features and the prior art discloses in an enabling manner an antibody directed to the same antigen using an immunisation and screening protocol that arrives at antibodies having the claimed properties, it has to be assumed that the prior-art antibody inherently displays the same functional properties as the claimed antibody, which thus lacks novelty (cf. G-VI, 6). [Bit about unusual parameters] In both these cases the burden of proof of novelty resides with the applicant

- What does it mean by "an immunisation and screening protocol that arrives at antibodies having the claimed properties"?
  - Presumably the properties needn't be explicitly disclosed in the prior art, or there would be no need to resort to inherency and presumption.
  - But if not, how is it assessed?
  - Need the properties be displayed by all antibodies produced by the method? Or only some?

17

First scenario: new function – the new guideline

- This seems like a badly paraphrased version of the general section of the guidelines on implicit disclosure (G-VI, 6), to which it refers
- G-VI, 6 seems to apply a different standard:

  [Lack of novelty] may be implicit in the sense that, in carrying out the teaching of the prior-art document, the skilled person would inevitably arrive at a result falling within the terms of the claim. An objection of lack of novelty of this kind is raised by the examiner only where there can be no reasonable doubt as to the practical effect of the prior teaching

  - Compare with "has to be assumed" and reversal of the burden of proof in the new guideline
- Functional features are already often hotly contested. We expect the new guideline will not change this.
  - May further encourage examiners to demand proof that all possibly relevant prior art antibodies are outside the scope of claims defined by function.

18

First scenario: new function

- Carefully chosen fallback positions can be useful to avoid objections based on accidental anticipations and presumed properties of prior art antibodies, without necessarily losing commercially relevant scope
  - e.g. human/humanised
  - Minimal structural characterisation, e.g. a single CDR, in line with T 617/07 (cited in the case law book)
- Again, it can be useful to provide data to show that antibodies to the target do not necessarily display the claimed functional properties
  - Supports novel selection

19

First scenario: new function

- Very importantly, unless they are common general knowledge, the application must contain clear descriptions of:
- How to reproduce antibodies meeting the functional criteria
  - e.g. suitable screens or library panning protocols
- How to determine, unambiguously, whether the functional criteria are met or not
  - Tempting to refer to several techniques, but this can be problematic if they lead to different results
- Needs a good story to explain the technical contribution that is made by the unexpected function, e.g. unexpected role in disease
  - As well as establishing inventive step, this is very helpful to avoid common objections that the claim merely defines the antibody in terms of a result to be achieved.

20

21

Second scenario

Mewburn Ellis

- Most cases nowadays fall into the second scenario
  - Target and antibodies to it are known
  - Desirable functional properties of antibodies are known, e.g. inhibition of receptor-ligand interaction; agonism of receptor; binding to tumour antigen
- Typical cases involve the provision or development of an antibody, often highly engineered, with advantageous or optimised properties compared to prior art antibodies.
- Two main challenges:
  - Assumption that antibodies must be narrowly defined structurally
  - Assumption that many techniques are both routine as such and can be routinely combined in antibody development.

22

First challenge

- Examiners often start from the assumption that the claims should be narrowly defined by sequence, e.g. all 6 CDRs, or even both variable domains
- This is a consequence of two basic points:
  - The technical effect must be obtained across the scope of the claims
  - Any change to CDRs can dramatically affect or even abolish antibody binding and framework changes can dramatically affect affinity

23

First challenge

- Whether examiner is likely to require all 6 CDRs or both variable domains depends on nature of technical effect being considered for inventive step.
- Property related to the epitope (e.g. blocking R-L interaction) → 6 CDRs
  - In a claim to an antibody against the target (i.e. implicitly retaining binding to the target) FR changes might affect affinity but they are unlikely to change the epitope significantly
- Property related to affinity → full variable domains
- Borne out by the new guidelines

24

Guidelines – 6 CDRs

- G-II, 5.6.1.1 Definition by structure of the antibody

  Since the three CDRs of each of the variable domains of the light and heavy chains are normally responsible for binding to the antigen, the conventional antibody, in order to be uniquely defined by its structure only and have its characteristic binding specificity, needs to be defined by at least these six CDRs to fulfil the requirements of Art. 84.

  …

  If a conventional antibody is defined by fewer than the sequences of the six CDRs, the claim will be objected to under Art. 84 because it lacks an essential technical feature.

  A claim to an antibody defined by its structure by fewer than six CDRs will be considered to fulfil the requirements of Art. 84 only if it is experimentally shown that one or more of the six CDRs do not interact with the target epitope or if it concerns a specific antibody format allowing for epitope recognition by fewer CDRs.

25

Guidelines – full variable domains

- G-II, 5.6.2 Inventive step of antibodies, ¶3:

  If the surprising technical effect involves the binding affinity, the structural requirements for conventional antibodies inherently reflecting this affinity must comprise the six CDRs and the framework regions because the framework regions also can influence the affinity.

26

First challenge – suggestions for retaining scope

- Mutational analysis / consensus sequences / modelling of the binding interface can identify which residues (and even which CDRs) are critical and which are not
  - Can allow wild-carding of residues within CDRs and/or specifying fewer than all CDRs (latter acknowledged in the guidelines at G-II, 5.6.1.1, ¶4)
  - Potentially allowing a fully structural definition that still permits some variation from the exemplified antibody sequence(s)
  - But this depends on having the data at the time of filing
- More generally applicable: a combination of (1) structural definitions that permit some sequence variation and (2) functional definitions that correspond to the technical effect
  - This combination permits some sequence variation while ensuring that the technical effect is attained across the scope of the claim

27

Combination of structural and functional features

- Endorsed by guidelines
- G-II, 5.6.1.4 Definition by functional and structural features

  Antibodies can also be defined by both functional properties and structural features. It is possible to claim an antibody characterised by the sequences of both variable domains or CDRs with less than 100% sequence identity when combined with a clear functional feature.
- Should avoid problematic guideline G-II, 5.6.1.3, ¶2, which refers to claims defined exclusively by functional features
- But still requires careful drafting

28

Combination of structural and functional features

- The functional feature(s) should be included as a generally applicable feature of the invention, which can be combined with the structural definitions of the antibody without adding matter
- Don't just rely on disclosure of the functional feature in the examples – probably not generalisable
- Try to identify what is advantageous about the antibodies of the invention and include:
  1. Generalised statements that the antibodies of the invention preferably have these advantageous functional features; and
  2. Claims to the functional feature, with an appropriate dependency structure that provides explicit combinations with claims directed to structural definitions.

29

Combination of structural and functional features

- The specification must disclose how the functional feature can be unambiguously assessed
  - This is something that is commonly lacking in many applications that we see
  - If giving alternative methods, consider how to deal with an objection that these yield inconsistent results. As determined by any of the methods? Or state a preferred method?
- Take care with permitted sequence variation: % identity can be meaningless for short CDRs
  - At least 95% sequence identity to a 7 residue CDR arguably requires complete identity, because 6/7 identical residues is ~86% identity.
- Where an effect results from a particular residue or mutation, provide basis for keeping that residue invariant
  - "Wherein residue x is amino acid y"

30

Second challenge

- The assumption that many forms of optimisation are now routine as such and may be routinely combined.
- Types of engineering that are likely to be considered routine include:
  - Affinity maturation.
  - Immunogencity reduction (humanisation / human).
  - Bi- and multi-specific formats.
  - Fc effector function engineering.
  - FcRn half-life engineering.
  - Conjugation, e.g. ADCs.
  - Production compatibility.
  - Glycosylation engineering.
- Application of any of these techniques alone is generally unlikely to justify inventive step for the resultant antibody. More is usually needed.

31

Second challenge – suggestions

- Inventive step can arise from unexpected results / effectiveness compared to expected improvements
  - Some examiners set a low bar for this – can be worth a try!
    - Especially recently - some surprisingly soft allowances
    - Poor drafting of the new guidelines may be responsible: G-II, 5.6.2 Inventive step of antibodies, ¶1:

      Examples of surprising technical effects when compared to known and enabled antibodies are, for example, an improved affinity, an improved therapeutic activity, a reduced toxicity or immunogenicity, an unexpected species cross-reactivity or a new type of antibody format with proven binding activity.
    - Implication that any improvements are inventive?
    - Don't expect all examiners to take this approach!

32

Second challenge – suggestions

- Inventive step can arise from combinations of multiple improvements and/or constraints
  - Improving property x without adversely affecting property y
  - Simultaneously improving properties x and y.
- Can be supported by the argument that any change (especially in CDRs) can markedly reduce affinity or even abolish antigen binding
- Conversely this can make it difficult to retain wide scope for sequence variation, especially involving the mutated residues that provided the improvements
  - Need careful drafting to balance extent and location of sequence variation in the claims.

33

Second challenge – suggestions

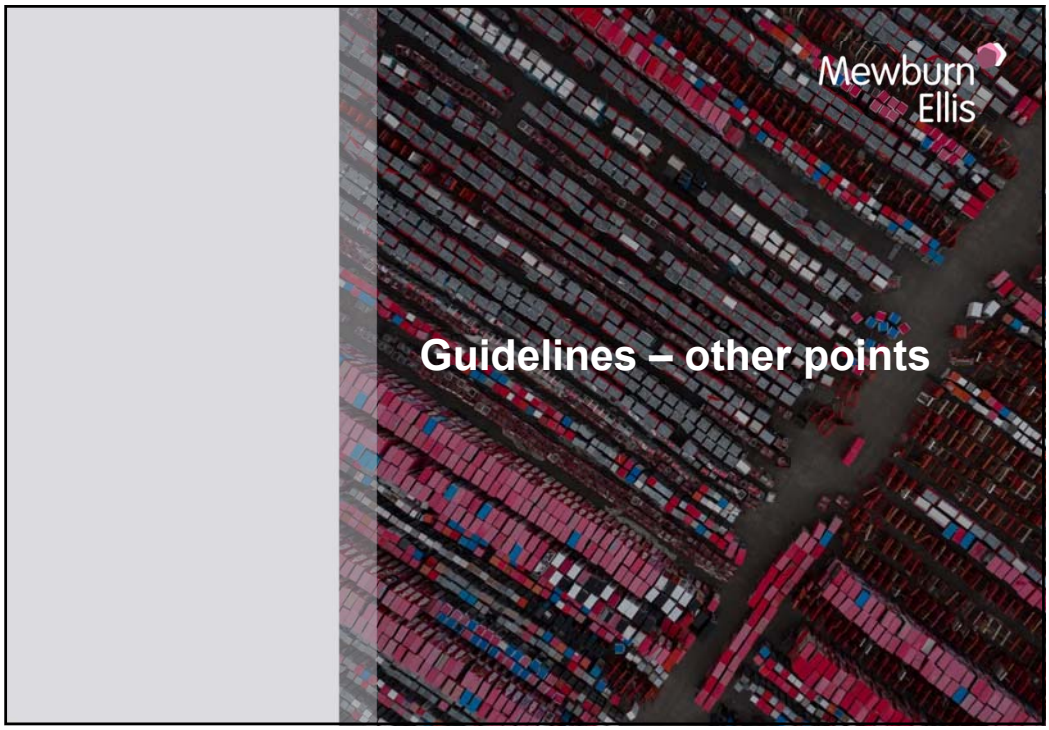
- Examples (based on experience, but simplified):
  - Prior art antibodies bind human target strongly and cyno target weakly; improving affinity for cyno without reducing affinity for human might confer inventive step in the context of those specific antibodies (whereas broad claims simply to cross-reactive antibodies will probably not be permitted).
  - Antibody has a CDR residue that causes production problems. Several mutants are tried. As expected, most result in reduced affinity but one surprisingly also increases affinity as well as avoiding the production problem.
  - Antibody has multiple residues that cause production problems. Several mutants are tried for each residue. Certain combinations have much less deleterious effect on binding than the majority.

34

Second challenge – suggestions

- Therapeutic antibodies each follow a unique path that may involve several, but not all, of the kinds of engineering mentioned above
- So it can be useful to tell a good technical story about the multiple problems solved in developing the antibody, along with data to support that those problems have been solved, and that other approaches did not solve the problem (commensurate with the scope of the claims).
- Comparative data can be invaluable when there is close prior art, especially own earlier antibodies.

35



36

Other points in the new Guidelines

- G-II, 5.6.1.6 discusses definition by the epitope
- No great surprises
- Refers back to controversial guideline on functional features
  - Implication that burden of proof is on applicant to establish that the epitope distinguishes the claim from known antibodies to the same target
  - But it is rarely the case that there is no reasonable doubt that the prior art antibodies will bind the same epitope (as in G-VI, 6)
- Emphasises need to define the epitope clearly
  - Particularly for discontinuous epitopes
  - Must explain how binding to the epitope is determined, as well as what the epitope is

37

Other points in the new Guidelines

- Nothing on cross-competing antibodies
  - Examiners typically take the view that cross-competing antibodies do not necessarily share the inventive properties of a reference antibody
  - Likely to need at least an additional functional limitation based on the inventive properties
  - But, not unusual for claims to slip through without it

38

Other points in the new Guidelines

- G-II, 5.6.2 Inventive step, ¶2:

  If inventive step relies on an improved property versus the enabled antibodies of the prior art, the main characteristics of the method for determining the property must also be indicated in the claim or indicated by reference to the description (F-IV, 4.11.1).

- Seems wrong in the case of an antibody for which the improvement is inherent from a structural definition.
  - e.g. antibody defined by complete VH and VL domains with surprisingly improved affinity over the prior art
  - Should not be necessary to specify in the claim how affinity is determined.
- Should apply only when the improved property is used to define the scope of the claim?
  - e.g. to exclude non-inventive embodiments encompassed by a partial structural definition.

39

Other points in the new Guidelines

- Just poor drafting?
  - Next paragraph (¶3) goes on to discuss the need for complete variable domains in a structural definition of an antibody that is inventive because of binding affinity.

40

41

Lack of comparative data

- Often the application does not provide comparative data with the closest prior art as identified by the examiner
- Applicants can be unwilling to generate such data
- Typical objection: in the absence of data showing an unexpected effect compared to the closest prior art, the claimed antibody is merely one among a multitude of equally obvious solutions to the technical problem of providing an alternative to the prior art antibody

42

Lack of comparative data

- An argument that we have successfully deployed recently:
- Comparative data show that the antibody has particularly good properties compared with a panel of other antibodies (e.g. from the development of a clinical lead)
- So it goes beyond being merely one among a multitude of equally obvious solutions:
  - It is inventive among the multitude of alternatives to the prior art, even if there are no data that it is better than the prior art
- Likely to be effective only when the comparative data concern a property about which the closest prior art is silent
  - Unless comparative data reflect difficulty reproducing prior art

43

44

Summary

- In appropriate cases, it is still possible – but challenging – to get broad, functionally defined antibody claims at the EPO
- If defining antibodies only by structure, it is common that little or no sequence variation from the exemplified antibodies will be permitted
- Good practice to include:
  - Stand-alone functional definition(s) of the antibody
  - Structural definitions that permit some sequence variation, explicitly combined with functional definition(s), and (if applicable) any specific engineered features
  - Stand-alone structural definitions, especially if there is any doubt about reproducibility of the tests for functional features. But sequence variation is unlikely to be allowed without specific supporting data. Nevertheless, picture claims also have value
- Don't just rely on the functional feature being disclosed in the examples

45

Summary

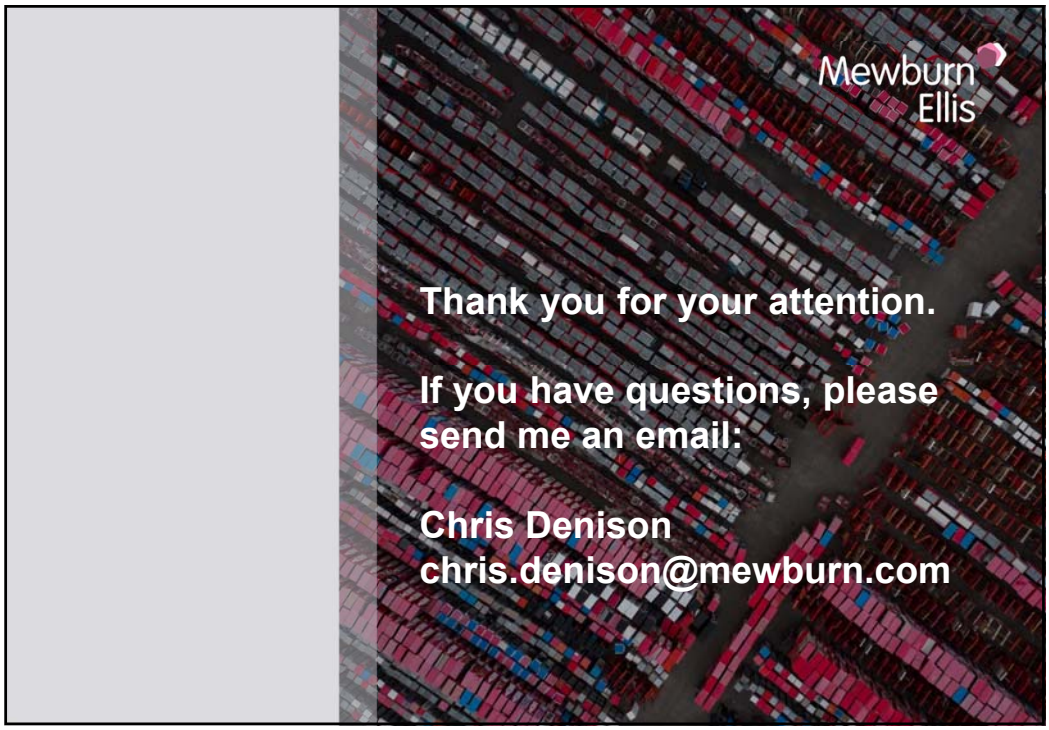
- Describe how the functional feature can be clearly and unambiguously assessed.
- Take care with drafting sequence variation.
- Provide basis for keeping engineered residues invariant, if using structural definitions that permit sequence variation
- Include a technical story to support inventive step
  - Why the functional features are advantageous, especially if it is an unexpected advantage
  - Problems that the antibody has been engineered to overcome, difficulties that were encountered
- Don't despair if you can't get comparative data for the closest prior art

46

Summary

- We are always happy to discuss the EP perspective when you are drafting at the US provisional / PCT stage.
- Applications drafted with EP requirements in mind typically do well in other jurisdictions
  - Positive IPRP from the EPO can be very helpful
  - Consider filing Demand for IPE

47



48